
# รายงานฉบับสมบูรณ์

# การจัดการความรู้เพื่อส่งเสริมเวชศาสตร์อิงหลักฐานในประเทศไทย

ศาสตราจารย์นายแพทย์วิษณุ ธรรมลิขิตกุล

สัญญาเลขที่ RTA 478005

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**ศาสตราจารย์นายแพทย์วิษณุ ธรรมลิขิตกุล**

**ภาควิชาอายุรศาสตร์และสถานส่งเสริมการวิจัย**

**คณะแพทยศาสตร์ศิริราชพยาบาล**



**สนับสนุนโดยสำนักงานกองทุนสนับสนุนการวิจัย**

(ความเห็นในรายงานนี้เป็นของผู้วิจัย สกว.ไม่จำเป็นต้องเห็นด้วยเสมอไป)

# กิตติกรรมประกาศ

คณะผู้วิจัยขอขอบคุณสำนักงานกองทุนสนับสนุนการวิจัยที่สนับสนุนทุนเมธีวิจัยอาวุโส ระหว่าง พ.ศ. 2547 ถึง พ.ศ. 2550 เรื่อง การจัดการความรู้เพื่อส่งเสริมเวชศาสตร์อิงหลักฐานในประเทศไทย

## บทคัดย่อ

โครงการที่ได้รับทุนเมธีวิจัยอาวุโสของสำนักงานกองทุนสนับสนุนการวิจัยระหว่าง พ.ศ. 2547 ถึง พ.ศ. 2550 เรื่อง การจัดการความรู้เพื่อส่งเสริมเวชศาสตร์อิงหลักฐานในประเทศไทย ได้เน้นเรื่องการจัดการความรู้ ซึ่งหมายถึงกระบวนการเชิงรุกอย่างเป็นระบบในการนำความรู้ที่มีอยู่แล้ว หรือสร้างความรู้ที่เกี่ยวข้องเพื่อนำมาใช้ในระบบบริการสุขภาพเพื่อให้วิธีบริการสุขภาพเป็นบริการสุขภาพที่อิงหลักฐาน อันจะทำให้บริการสุขภาพนั้นมีคุณภาพ มีประสิทธิภาพ และเป็นธรรม กระบวนการทำงานของคณะผู้วิจัย คือ 1) สร้างหรือพัฒนานักวิจัยทั้งอาจารย์แพทย์ แพทย์ประจำบ้าน นักศึกษาแพทย์ และนักศึกษาระดับบัณฑิตศึกษาให้มีทักษะในการทำวิจัยที่มีคุณภาพทั้งการวิจัยปฐมภูมิและการวิจัยทุติยภูมิ 2) ทำวิจัยเพื่อสร้างความรู้ที่สามารถนำไปประยุกต์ใช้เป็นนโยบายสุขภาพและวิธีปฏิบัติของบริการสุขภาพ และ 3) นำความรู้ที่มีอยู่แล้วมาประยุกต์ให้เป็นนโยบายและวิธีบริการสุขภาพเพื่อพัฒนาคุณภาพ ประสิทธิผล ประสิทธิภาพ และความเป็นธรรมของบริการสุขภาพ ผลได้ที่สำคัญจากโครงการนี้ คือ 1) สร้างและพัฒนานักวิจัยที่มีคุณภาพจำนวน 39 คน 2) ผลงานวิจัยที่มีคุณภาพที่ได้รับการตีพิมพ์เผยแพร่จำนวน 40 เรื่อง และ 3) นำผลงานวิจัยอย่างน้อย 10 เรื่องไปใช้เป็นนโยบายสุขภาพและวิธีปฏิบัติของบริการสุขภาพ ผลลัพธ์และผลกระทบที่สำคัญจากโครงการนี้คือปัญหาสุขภาพที่สำคัญของประเทศไทยหลายเรื่องลดลง และการประหยัดทรัพยากรสุขภาพในการแก้ปัญหาสุขภาพที่สำคัญของประเทศไทยหลายเรื่อง



**คำหลัก**

การจัดการความรู้ เวชศาสตร์อิงหลักฐาน การวิจัย การใช้ผลงานวิจัย

**ABSTRACT**

The project funded by Thailand Research Fund (Senior Researcher Scholar 2004 - 2007) entitled “Knowledge Management to Promote Evidence-Based Health Policy and Practice in Thailand” focused on knowledge management which is defined as an active and systematic process of utilizing the existing knowledge and/or generating relevant knowledge for setting healthcare policy and practice in order to establish or enhance quality, efficiency and equity in health care. Such active and systematic processes included knowledge translation and knowledge generation of research evidence relevant to local health problems in Thailand. The activities of the study team included 1) building & strengthening capacity of clinical researchers, graduates and post graduates in conducting high quality primary clinical as well as secondary research (systematic review, meta-analysis), 2) generating high quality clinical evidence leading to establishing knowledge-based health policy and clinical practice in Thailand, and 3) translating valid, relevant and applicable health knowledge to healthcare policy and practice in order to improve or enhance quality, effectiveness, efficiency and equity in health care. The outputs of the project were: 1) capacity of 39 Thai researchers was built or strengthened, 2) 40 high quality clinical research publications, and 3) 10 relevant clinical evidences were implemented in health policy and/or clinical practice in Thailand. The outcomes and impacts of the project were alleviation of several important health burdens in Thais as well as financial impact on healthcare budget for several important health burdens in Thais.

**Key Words**

Knowledge Management, Evidence-Based Medicine, Knowledge Generation,
Knowledge Translation

## ผลงานที่ได้จากโครงการ

**ผลงานตีพิมพ์ในวารสารวิชาการนานาชาติ / หนังสือ / สิทธิบัตร**

**งานวิจัยที่ได้รับการตีพิมพ์ (ภายใต้ทุนสนับสนุนของ สกว.)**

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**การพัฒนานักวิจัย**

ภายใต้การสนับสนุนทุนวิจัยจาก สกว. คณะผู้วิจัยได้พัฒนานักวิจัยร่วมในโครงการ ดังนี้

**1. อาจารย์แพทย์ แพทย์ประจำบ้าน แพทย์ประจำบ้านต่อยอด**

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แพทย์หญิงศรีเพชรัตน์ เมฆวิวัฒนวงศ์
แพทย์หญิงภาศรี มหารมย์
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แพทย์หญิงจินตนา หล่อสุทธิธรรม
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นายแพทย์สุรชัย ลิ้มตังตุรกุล
แพทย์หญิงณัฏฐกานต์ สุวรรณศักดิ์ศรี
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แพทย์หญิงภิญโญ รัตนาอัมพวัลย์
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แพทย์หญิงฉันทนา หมอกศิริพงษ์
แพทย์หญิงวิลาวัณย์ แสงศิรินาคะกุล
แพทย์หญิงนิธิอาภา บำรุงศรี
นายแพทย์ชาติชาย สามัคคีนิช
แพทย์หญิงหัสญา ตันติพงศ์
นายแพทย์ทรงยศ ใจยินดี
แพทย์หญิงปวีณา อุดมวิบูลย์ชัย
นายแพทย์เอกพันธ์ อนันตนิตย์

**2. นักศึกษาปริญญาโทและปริญญาเอก**

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นายสุรศักดิ์ เสาแก้ว
นส.ราตรี แมนไธสง
นส.เกศนภา ถาวร
นายปิยะเมธ ดิลกธรสกุล
นส.รสรินทร์ สรวมศิริ
นายนริศร นางาม

**การนำผลจากโครงการไปใช้ประโยชน์**

คณะผู้วิจัยขอเสนอตัวอย่างของการนำผลจากโครงการไปใช้ประโยชน์ ดังนี้

***1. การรักษาโรคติดเชื้อจากแบคทีเรียดื้อยาต้านจุลชีพด้วย Colistin***

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โรคติดเชื้อที่เกิดในผู้ป่วยที่รับไว้รักษาในโรงพยาบาลศิริราชพบประมาณร้อยละ 8 โดยเชื้อแบคทีเรียที่ก่อให้เกิดโรคติดเชื้อในโรงพยาบาลที่พบบ่อยที่สุดได้แก่ *A.baumannii* ซึ่งเชื้อนี้ดื้อต้านจุลชีพทุกขนานทั้ง Beta-Lactams, Aminoglycosides และ Fluoroquinolones เพิ่มจากร้อยละ 4 เมื่อ พ.ศ. 2541 เป็นร้อยละ 57 ใน พ.ศ. 2546 ผู้ป่วยเหล่านี้มักได้รับการรักษาด้วยยาต้านจุลชีพหลายขนานร่วมกัน (เช่น Meropenem ร่วมกับ Netilmicin ร่วมกับ Cefoperazone/ Sulbactam) โดยมีค่าใช้จ่ายเฉพาะยาต้านจุลชีพประมาณวันละ 6,000 บาท ผู้ป่วยที่ติดเชื้อดื้อยาดังกล่าวเสียชีวิตร้อยละ 80

ศาสตราจารย์นายแพทย์วิษณุ ธรรมลิขิตกุลได้วิจัยปัจจัยเสี่ยงของการติดเชื้อดื้อยา *A.baumannii* ทำให้ทราบว่าปัจจัยเสี่ยงของการติดเชื้อดื้อยาดังกล่าว คือ การมีสายหรือท่อต่างๆ ในร่างกาย และการได้รับยาต้านจุลชีพมาก่อน ซึ่งปัจจัยเหล่านี้มักแก้ไขไม่ได้ เพราะผู้ป่วยเหล่านี้เจ็บป่วยรุนแรงและจำเป็นต้องได้รับการรักษาดังกล่าว

การสืบค้นวิธีรักษาโรคติดเชื้อดื้อยาดังกล่าวพบว่ายา Colistin ซึ่งเป็นยาต้านจุลชีพเก่าตั้งแต่ พ.ศ. 2490 แต่หยุดใช้ไปเนื่องจากมีพิษและมียาขนานอื่นทดแทนได้ ถูกนำกลับมาใช้รักษาการติดเชื้อดื้อยานี้ได้ผลปานกลาง การวิจัยของศาสตราจารย์นายแพทย์วิษณุ ธรรมลิขิตกุล ทำให้ทราบว่าเชื้อ *P.aeruginosa* และ *A baumannii* ที่ดื้อยาต้านจุลชีพทุกขนานซึ่งแยกได้จากผู้ป่วยที่รับไว้รักษาที่โรงพยาบาลศิริราชทุกสายพันธุ์ไวต่อยา Colistin แต่ยา Colistin ไม่มีจำหน่ายในประเทศไทย หากมีผู้ป่วยติดเชื้อดังกล่าวและรับผิดชอบค่ายาได้ ผู้ป่วยต้องไปซื้อยาจากต่างประเทศซึ่งมีค่าใช้จ่ายสูงมาก และไม่เป็นธรรมกับผู้ป่วยที่ไม่สามารถรับผิดชอบค่าใช้จ่ายได้ ศาสตราจารย์นายแพทย์วิษณุ ธรรมลิขิตกุลได้ติดต่อกับบริษัทยาทั้งบริษัทยาข้าม

ชาติและบริษัทยาภายในประเทศให้นำยาดังกล่าวมาจำหน่ายในประเทศไทย แต่ไม่มีบริษัทใดประสงค์จะนำยาดังกล่าวมาจำหน่ายในประเทศไทย

ศาสตราจารย์นายแพทย์วิษณุ ธรรมลิขิตกุลได้ทบทวนตำรับยาของสำนักงานคณะกรรมการอาหารและยา กระทรวงสาธารณสุข พบว่าบริษัทแอตแลนติคเคยผลิตยา Colistin ซึ่งมียาชา Dibucaine เป็นส่วนผสมอยู่ด้วยเมื่อ 30 ปีก่อน แต่ได้เลิกผลิตนานแล้ว ศาสตราจารย์นายแพทย์วิษณุ ธรรมลิขิตกุลจึงติดต่อบริษัทแอตแลนติคและชี้แจงความจำเป็นของยาดังกล่าวให้ผู้บริหารของบริษัททราบ ซึ่งบริษัทแอตแลนติคก็ได้ผลิตยา Colistin อีกครั้ง แต่ยานี้ต้องขึ้นทะเบียนใหม่กับสำนักงานคณะกรรมการอาหารและยา กระทรวงสาธารณสุข เพราะต้องเปลี่ยนสูตรตำรับเป็นยา Colistin เดี่ยว ศาสตราจารย์นายแพทย์วิษณุ ธรรมลิขิตกุล ได้ประสานงานกับสำนักงานคณะกรรมการอาหารและยาในการขึ้นทะเบียนยา Colistin โดยใช้เวลาประมาณ 8 เดือน จนได้รับทะเบียนยาเมื่อ พ.ศ. 2547

ศาสตราจารย์นายแพทย์วิษณุ ธรรมลิขิตกุลได้ทดสอบฤทธิ์การทำลายเชื้อด้วยยา Colistin ที่ผลิตภายในประเทศไทยพบว่า ยาดังกล่าวมีฤทธิ์ต่อเชื้อดื้อยาดีมาก และได้ประเมินประสิทธิผลและความปลอดภัยของยา Colistin ที่ผลิตภายในประเทศไทยในการรักษาผู้ป่วยในโรงพยาบาลศิริราชจำนวน 93 รายที่ติดเชื้อ *P.aeruginosa* และ *A.baumannii* ที่ดื้อยาต้านจุลชีพทุกขนาน พบว่ากลุ่มผู้ป่วยที่ได้รับการรักษาด้วยยา Colistin มีอัตราหายจากการติดเชื้อและอัตราที่เชื้อหมดไปจากร่างกายมากกว่ากลุ่มผู้ป่วยที่ได้รับการรักษาด้วยยาอื่น อัตราตายของกลุ่มผู้ป่วยที่ได้รับการรักษาด้วยยา Colistin ก็ลดลงจากกลุ่มผู้ป่วยที่ได้รับการรักษาด้วยยาอื่นร้อยละ 50 นอกจากนี้ พิษและผลข้างเคียงของยาในกลุ่มผู้ป่วยที่ได้รับยา Colistin ยังน้อยกว่ากลุ่มที่ได้รับยาอื่น แสดงว่ายา Colistin ที่ผลิตภายในประเทศไทยมีประสิทธิผลและปลอดภัยในการรักษาการติดเชื้อดื้อยา

ผลการวิจัยดังกล่าวทำให้โรงพยาบาลศิริราชบรรจุยา Colistin อยู่ในรายการยาของโรงพยาบาลศิริราชตั้งแต่เดือนมีนาคม พ.ศ. 2548 และบริษัทแอตแลนติคจำหน่ายยา Colistin ทั่วประเทศตั้งแต่เดือนพฤษภาคม พ.ศ. 2548 โดยมีค่าใช้จ่ายประมาณวันละ 400 บาท ซึ่งน้อยกว่าการรักษาด้วยยาอื่นหลายขนานร่วมกันประมาณ 10 - 20 เท่า

ผลได้และผลกระทบจากการวิจัยเพื่อพัฒนาการรักษาโรคติดเชื้อที่ดื้อยาต้านจุลชีพด้วยยา Colistin คือ

- บทความตีพิมพ์ในวารสารการแพทย์ 3 เรื่อง
- ผลงานวิจัยได้รับรางวัล 1 รางวัล
- มียา Colistin ใช้ในประเทศไทยสำหรับรักษาโรคติดเชื้อดื้อยาทุกขนานเป็นครั้งแรก
- ผู้ป่วยหายจากการติดเชื้อดื้อยามากขึ้นโดยโอกาสที่ผู้ป่วยเสียชีวิตจากการติดเชื้อดื้อยาลดลงร้อยละ 50 จึงช่วยชีวิผู้ป่วยได้ปีละหลายร้อยราย

- ค่าใช้จ่ายในการรักษาการติดเชื้อดื้อยาลดลง 10 - 20 เท่า โดยโรงพยาบาลศิริราชประหยัดค่ายาต้านจุลชีพสำหรับรักษาการติดเชื้อดื้อยามากกว่า 20 ล้านบาทในปี พ.ศ. 2549 และ พ.ศ. 2550

- ประหยัดค่าใช้จ่ายการรักษาโรคติดเชื้อดื้อยาทั้งประเทศปีละหลายร้อยล้านบาท

- ส่งเสริมอุตสาหกรรมผลิตและจำหน่ายยาภายในประเทศไทย

- ยา Colistin ได้รับการบรรจุให้อยู่ในบัญชียาหลักแห่งชาติตั้งแต่ พ.ศ. 2551 ทำให้ผู้ป่วยทุกคนสามารถได้รับการรักษาด้วยยา Colistin อย่างทั่วถึง การวิจัยเรื่องนี้จึงนำไปสู่ค้นพบยาที่ใช้รักษาโรคที่มีอัตราตายสูงที่เป็นธรรม (equity) กับคนไทยทุกคนเพราะเป็นยาที่อยู่ในบัญชียาหลักแห่งชาติ

**2. การป้องกันปอดอักเสบติดเชื้อที่สัมพันธ์กับเครื่องช่วยหายใจด้วย 2% Chlorhexidine**

**ผลงานวิจัย**

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ปอดอักเสบติดเชื้อที่สัมพันธ์กับเครื่องช่วยหายใจ (Ventilator-Associated Pneumonia, VAP) เป็นการติดเชื้อในโรงพยาบาลที่พบบ่อยที่สุด อัตราการเกิด VAP ในผู้ป่วยที่รับไว้รักษาในโรงพยาบาลศิริราชมีประมาณ 14 ครั้งต่อ 1,000 วันของการใช้เครื่องช่วยหายใจ การเกิด VAP 1 ครั้งทำให้ผู้ป่วยอยู่โรงพยาบาลนานขึ้น 13 วัน เสียค่ายาต้านจุลชีพ 13,200 บาท และมีโอกาสเสียชีวิต 20% - 50%

มาตรการป้องกัน VAP มีหลายมาตรการ ซึ่งโรงพยาบาลศิริราชได้นำมาใช้แล้ว มาตรการหนึ่งที่น่าสนใจว่าอาจมีประสิทธิผลในการป้องกัน VAP คือ การทำความสะอาดช่องปากผู้ป่วยที่ได้รับท่อช่วยหายใจด้วย 2% Chlorhexidine เพราะกลไกการเกิดปอดอักเสบมักเกิดจากเชื้อโรคในช่องปากผู้ป่วยเล็ดลอดลงสู่ปอด แต่ยังไม่เคยมีหลักฐานว่าการทำความสะอาดช่องปากผู้ป่วยที่ได้รับท่อช่วยหายใจด้วย 2% Chlorhexidine สามารถป้องกัน VAP ได้ ดังนั้น ศาสตราจารย์นายแพทย์วิษณุ ธรรมลิขิตกุล จึงดำเนินการวิจัยเพื่อพัฒนาการป้องการ VAP ดังนี้

1. ประสานงานกับฝ่ายเภสัชกรรม โรงพยาบาลศิริราช เพื่อพัฒนาสูตรและผลิต 2% Chlorhexidine สำหรับทำความสะอาดช่องปากเนื่องจากวิธีการนี้เป็นนวัตกรรม จึงยังไม่มีน้ำยานี้จำหน่ายในประเทศใด

2. ทดสอบฤทธิ์การทำลายเชื้อก่อโรคที่พบบ่อยของการติดเชื้อในโรงพยาบาลด้วย 2% Chlorhexidine ที่เตรียมโดยฝ่ายเภสัชกรรม พบว่าน้ำยานี้ทำลายเชื้อได้ดี

3. วิจัยประสิทธิผลของการทำความสะอาดช่องปากผู้ป่วยที่มีท่อช่วยหายใจด้วย 2%

Chlorhexidine เปรียบเทียบกับน้ำเกลือในผู้ป่วย 207 คนที่รับไว้รักษาที่โรงพยาบาลศิริราช และได้รับท่อช่วยหายใจ โดยใช้รูปแบบการวิจัย Randomized Controlled Trial พบว่าอัตราการเกิด VAP ในกลุ่มที่ได้รับ 2% Chlorhexidine ลดลง 67%

ผลได้และผลกระทบจากการวิจัยเพื่อพัฒนาการป้องกันปอดอักเสบติดเชื้อที่สัมพันธ์กับเครื่องช่วยหายใจด้วยน้ำยา 2% Chlorhexidine คือ

-โรงพยาบาลศิริราชมอบหมายให้ฝ่ายเภสัชกรรมผลิตน้ำยา 2% Chlorhexidine สำหรับทำความสะอาดช่องปากผู้ป่วยทั่วไปของโรงพยาบาลศิริราชเนื่องจากน้ำยานี้ไม่มีจำหน่ายในประเทศไทย

-โรงพยาบาลศิริราชเปลี่ยนนโยบายการทำความสะอาดช่องปากผู้ป่วยที่มีท่อช่วยหายใจจากน้ำเกลือเป็น 2% Chlorhexidine ตั้งแต่เดือนตุลาคม 2550

-อัตราการเกิด VAP ตั้งแต่เดือนมกราคม ถึงธันวาคม พ.ศ. 2551 คือ 7 – 10 ครั้งต่อ 1,000 วันของการใช้เครื่องช่วยหายใจ ซึ่งลดลงจากเดิม จึงลดอัตราป่วยจาก VAP ได้ และประหยัดค่าใช้จ่ายของ VAP ได้

-เนื่องจากน้ำยานี้ยังไม่มีจำหน่ายในประเทศไทย จึงได้แจ้งให้เอกชนที่สนใจผลิตภัณฑ์ดังกล่าวผลิต 2% Chlorhexidine เพื่อจำหน่ายให้สถานพยาบาลอื่น ซึ่งจะช่วยลดปัญหาการติดเชื้อในโรงพยาบาลได้ ขณะนี้เอกชนได้ผลิตน้ำยาดังกล่าวและกำลังขอรับทะเบียนยาจากสำนักงานคณะกรรมการอาหารและยา กระทรวงสาธารณสุข

**3. การป้องกันการติดเชื้อในกระแสเลือดที่สัมพันธ์กับการใส่สายสวนหลอดเลือดดำส่วนกลางด้วยน้ำยา 2% Chlorhexidine ใน 70% Alcohol**

**ผลงานวิจัย**

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การติดเชื้อจากการใส่สายสวนหลอดเลือด (Catheter-Associated Blood Stream Infections, CA-BSI) ในผู้ป่วยที่รับไว้รักษาในโรงพยาบาลศิริราชมีประมาณ 5 ครั้งต่อ 1,000 วันของการคาสายสวน การติดเชื้อ CA-BSI 1 ครั้งทำให้ผู้ป่วยอยู่โรงพยาบาลนานขึ้น 15 วัน เสียเงินค่ายาต้านจุลชีพ 10,753 บาท และมีโอกาสเสียชีวิต 10% แนวทางปฏิบัติการใส่สายสวนหลอดเลือดของโรงพยาบาลศิริราชแนะนำให้ทำความสะอาดผิวหนังบริเวณที่ใส่สายสวนด้วย 10% Povidone Iodine

ผลงานวิจัย Meta-analysis ของ randomized controlled trials เปรียบเทียบการใช้น้ำยา 10% Povidone Iodine กับ 2% Chlorhexidine ทำความสะอาดผิวหนังก่อนใส่สายสวนหลอดเลือดพบว่าอุบัติการของ CA-BSI ลดลง 50% และการวิเคราะห์ความคุ้มค่าของการใช้ 2% Chlorhexidine แทน 10% Povidone Iodine ก็พบว่าคุ้มค่า

ศาสตราจารย์นายแพทย์วิษณุ ธรรมลิขิตกุลจึงวิจัยเพื่อพัฒนาการป้องกันการติดเชื้อในกระแสเลือดที่สัมพันธ์กับการใส่สายสวนหลอดเลือดดำส่วนกลางด้วยน้ำยา 2% Chlorhexidine ใน 70% Alcohol โดยวิเคราะห์ความคุ้มค่าว่า หากศิริราชจะผลิต 2% Chlorhexidine ใน 70% Alcohol และนำ 2% Chlorhexidine ใน 70% Alcohol มาใช้แทน 10% Povidone Iodine สำหรับทำความสะอาดผิวหนังก่อนใส่สายสวนจะคุ้มค่าหรือไม่ ซึ่งพบว่าการใช้ 2% Chlorhexidine ใน 70% Alcohol มีความคุ้มค่า

ดังนั้น ศาสตราจารย์นายแพทย์วิษณุ ธรรมลิขิตกุลจึงประสานงานกับฝ่ายเภสัชกรรม โรงพยาบาลศิริราชเพื่อเตรียม 2% Chlorhexidine ใน 70% Alcohol เนื่องจากน้ำยานี้ไม่มีจำหน่ายในประเทศไทย และได้ทดสอบฤทธิ์การทำลายเชื้อก่อโรคที่พบบ่อยของการติดเชื้อในโรงพยาบาลด้วย 2% Chlorhexidine ใน 70% Alcohol ที่เตรียมโดยฝ่ายเภสัชกรรม พบว่าน้ำยานี้ทำลายเชื้อได้ดี

ศาสตราจารย์นายแพทย์วิษณุ ธรรมลิขิตกุลจึงนำ 2% Chlorhexidine ใน 70% Alcohol ที่เตรียมโดยฝ่ายเภสัชกรรม ไปใช้กับผู้ป่วยที่หออภิบาลในโรงพยาบาลศิริราช พบว่าอุบัติการของ CA-BSI ในกลุ่มที่ได้ 2% Chlorhexidine ใน 70% Alcohol ลดลง 43%

ผลได้และผลกระทบจากการวิจัยเพื่อพัฒนาการป้องกันการติดเชื้อในกระแสเลือดที่สัมพันธ์กับการใส่สายสวนหลอดเลือดดำส่วนกลางด้วยน้ำยา 2% Chlorhexidine ใน 70% Alcohol คือ

-โรงพยาบาลศิริราชมอบหมายให้ฝ่ายเภสัชกรรมผลิตน้ำยา 2% Chlorhexidine ใน 70% Alcohol สำหรับใช้กับผู้ป่วยทั้งโรงพยาบาล

-โรงพยาบาลศิริราชเปลี่ยนนโยบายจากการใช้ 10% Povidone Iodine ทำความสะอาดผิวหนังเป็น 2% Chlorhexidine ใน 70% Alcohol ตั้งแต่เดือนพฤศจิกายน 2549

-อัตราการเกิด CA-BSI ระหว่างเดือนมกราคม พ.ศ. 2550 ถึงสิงหาคม 2551 คือ 0.5 - 3 ครั้งต่อ 1,000 วันของการคาสายสวนหลอดเลือดซึ่งลดลงจาก 5 - 7 ครั้งต่อ 1,000 วันของการคาสายสวนในช่วงก่อนมกราคม พ.ศ. 2550

-เนื่องจากน้ำยานี้ยังไม่มีจำหน่ายในประเทศไทย จึงได้แจ้งให้เอกชนที่สนใจผลิตภัณฑ์ดังกล่าวผลิต 2% Chlorhexidine ใน 70% Alcohol เพื่อจำหน่ายให้สถานพยาบาลอื่น ซึ่งจะช่วยลดปัญหาการติดเชื้อในโรงพยาบาลได้ ขณะนี้เอกชนกำลังการขอขึ้นทะเบียนผลิตภัณฑ์ 2% Chlorhexidine ใน 70% Alcohol กับสำนักงานคณะกรรมการอาหารและยา กระทรวงสาธารณสุข

**4. การแพทย์แผนไทยและสมุนไพร**

**ปัญหาและความสำคัญของการแพทย์แผนไทยและสมุนไพรไทย**

ยาจากสมุนไพรไทยเป็นการรักษาโรคโดยอาศัยภูมิปัญญาท้องถิ่นซึ่งมีความสำคัญต่อคนไทยมานานกว่าร้อยปี หน่วยงานต่างๆ ทั้งภาครัฐและเอกชนได้พยายามส่งเสริมให้บุคลากรสาธารณสุขและสถานพยาบาลต่างนำสมุนไพรไทยไปใช้รักษาผู้ป่วย แต่ไม่ประสบความสำเร็จ เนื่องจากปัจจัยสำคัญ คือ ผู้ประกอบวิชาชีพเวชกรรมไม่มั่นใจสรรพคุณของสมุนไพรเพราะไม่มีหลักฐานจากการวิจัยทางคลินิกสนับสนุน ดังนั้น สมุนไพรจึงมีการใช้ในวงแคบเฉพาะผู้ที่ศรัทธาในสมุนไพรและผู้ที่ใช้สมุนไพรตามการโฆษณาสรรพคุณของสมุนไพรเหล่านั้น (Jiaranaikajorn T, Panthawangkul J, Thamlikitkul V. Use of alternative medicine among medical patients at Siriraj Hospital. Siriraj Hospital Gaz 2002;45:603-10) ทำให้ผู้ที่ควรได้รับสมุนไพรที่มีประโยชน์ไม่ได้รับสมุนไพรดังกล่าว ส่วนผู้ที่ไม่ควรได้รับสมุนไพรที่ไม่มีประโยชน์หรือสมุนไพรที่อาจเป็นโทษก็สิ้นเปลืองค่าใช้จ่ายในการใช้สมุนไพรที่ไม่มีสรรพคุณจริงและอาจเกิดพิษจากการใช้สมุนไพรที่ไม่ปลอดภัย การวิจัยเกี่ยวกับสมุนไพรจำนวนมากที่ได้รับการสนับสนุนจากหน่วยงานวิจัยก็มักวิจัยฤทธิ์ของสารสกัดสมุนไพรชนิดในห้องปฏิบัติการ หรือวิจัยความเป็นพิษของสารสกัดสมุนไพรในสัตว์ทดลอง โดยสมุนไพรส่วนมากที่มีผลการศึกษาจากห้องปฏิบัติการและสัตว์ทดลองไม่ถูกนำมาวิจัยในคนอย่างเหมาะสมเพื่อพัฒนาเป็นผลิต ภัณฑ์สุขภาพต่อไป จึงทำให้การลงทุนวิจัยเกี่ยวกับสมุนไพรเป็นการลงทุนที่ไม่คุ้มค่า ดังนั้น ศาสตราจารย์นายแพทย์วิษณุ ธรรมลิขิตกุล และ รองศาสตราจารย์ ดร. ณธร ชัยญาคุณาพฤกษ์ จึงเน้นการวิจัยเกี่ยวกับสมุนไพรไทย 3 ด้าน คือ ก.) นำสมุนไพรที่มีผลงานวิจัยพื้นฐานด้านการออกฤทธิ์และความปลอดภัยแล้วมาวิจัยในคนเพื่อพิสูจน์ประสิทธิผลและความปลอดภัย(Translational Research) ข.) ทำวิจัยประเภททุติยภูมิ คือ meta-analysis เกี่ยวกับประสิทธิภาพและความปลอดภัยของสมุนไพร และ ค.) นำสมุนไพรที่มีการใช้มายาวนานหรือสมุนไพรที่มีการกล่าวอ้างสรรพคุณต่างๆ มาวิจัยในคนเพื่อยืนยันประสิทธิผลและความปลอดภัย ก่อนที่จะสนับสนุนให้มีการใช้ในการบริการสุขภาพ การผลิตจำหน่าย และการปลูกต่อไป

**ตัวอย่างการใช้ผลงานวิจัยการแพทย์แผนไทยและสมุนไพร**

**ผลงานวิจัย**

Kuptniratsaikul V, Thanakhumtorn S, Chinswangwatanakul P, Wattanamongkonsil L, **Thamlikitkul V**. Efficacy and safety of *Curcuma domestica* extracts in patients with knee osteoarthritis**.** J Altern Complement Med 2009;15:891-7.

คนไทยอายุมากว่า 60 ปีประมาณร้อยละ 40 มีโรคข้อเข่าเสื่อม ผู้ป่วยโรคนี้มีอาการปวดเข่า และใช้เข่าในการประกอบกิจวัตรประจำวันและการทำงานอย่างลำบาก การรักษาผู้ป่วยข้อเข่าเสื่อมนอกจากการฝึกกำลังกล้ามเนื้อต้นขาให้แข็งแรงแล้ว ผู้ป่วยส่วนมากได้รับยาประเภท Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) ยาดังกล่าวมีผลข้างเคียงทำให้กระเพาะอาหารอักเสบ มีแผลที่กระเพาะอาหาร และเลือดออกจากกระเพาะอาหาร

ผลงานวิจัยพื้นฐานทั้งการศึกษาในห้องปฏิบัติการและสัตว์ทดลองแสดงว่าสารสกัดขมิ้นมีฤทธิ์ต้านการอักเสบด้วยกลไกหลายชนิด รวมทั้งยับยั้งเอนไซม์ Cyclooxygenase-2 (COX-2) ด้วย และอาสาสมัครสุขภาพแข็งแรงที่ได้รับสารสกัดขมิ้นขนาด 8,000 มิลลิกรัมติดต่อกัน 3 เดือนก็ไม่มีผลข้างเคียง เนื่องจากสารที่มีฤทธิ์ยับยั้ง COX-2 สามารถนำมาใช้เป็นยาต้านการอักเสบได้ แต่การสืบค้นข้อมูลแล้วไม่พบผลงานวิจัยการรักษาโรคข้อเสื่อมด้วยสารสกัดขมิ้น

ศาสตราจารย์นายแพทย์วิษณุ ธรรมลิขิตกุลจึงประสานกับองค์การเภสัชกรรมผลิตสารสกัดขมิ้นและกรมพัฒนาการแพทย์แผนไทยและการแพทย์ทางเลือก กระทรวงสาธารณสุขเพื่อทำวิจัยต่อยอดจากการวิจัยพื้นฐานและการวิจัยทางคลินิกระยะที่ 1 ด้วยการวิจัยทางคลินิกระยะที่ 3 ในผู้ป่วยข้อเข่าเสื่อมจำนวน 107 คน โดยแบ่งผู้ป่วยเป็น 2 กลุ่ม กลุ่มหนึ่งได้รับยา Ibuprofen ส่วนอีกกลุ่มหนึ่งได้รับสารสกัดขมิ้นนาน 6 สัปดาห์ (ผลงานวิจัย 2.1.1.) พบว่าอาการปวดเข่าและการทำงานของเข่าในผู้ป่วยที่ได้รับสารสกัดขมิ้นดีขึ้นมากภายหลังการรักษา และผลการรักษาดังกล่าวไม่แตกต่างจากการรักษาด้วย Ibuprofen โดยผลการรักษาในกลุ่มสารสกัดขมิ้นมีแนวโน้มดีกว่ากลุ่ม Ibuprofen มีผู้ป่วย 1 รายที่ได้รับ Ibuprofen มีเลือดออกจากกระเพาะอาหาร ผลงานวิจัยนี้แสดงว่าสารสกัดขมิ้นมีประสิทธิผลและปลอดภัยในการรักษาโรคข้อเข่าเสื่อมไม่แตกต่างจากยากลุ่ม NSAIDs

ผลได้และผลกระทบจากการวิจัยเพื่อพัฒนาการรักษาโรคข้อเข่าเสื่อมด้วยสารสกัดขมิ้น คือ

-บทความตีพิมพ์ในวารสารการแพทย์ 1 เรื่อง

-ผู้ป่วยโรคข้อเข่าเสื่อมสามารถใช้สารสกัดขมิ้นเป็นทางเลือกในการรักษาโรคข้อเข่าเสื่อม

-องค์การเภสัชกรรมกำลังพิจารณาเพิ่มข้อบ่งใช้ของสารสกัดขมิ้นสำหรับรักษาข้อเข่าเสื่อมออกจำหน่าย

**การใช้ผลงานวิจัยการแพทย์แผนไทยและสมุนไพรเพื่อรักษาอาการที่พบบ่อย**

ศาสตราจารย์นายแพทย์วิษณุ ธรรมลิขิตกุล และ รองศาสตราจารย์ ดร. ณธร ชัยญาคุณาพฤกษ์ ได้ประสานกับหน่วยงานที่เกี่ยวข้องทั้งหน่วยงานที่ให้ทุนสนับสนุนการวิจัยสมุนไพร (เช่น กรมวิทยาศาสตร์การแพทย์ กระทรวงสาธารณสุข, กรมพัฒนาการแพทย์แผนไทยและการแพทย์ทางเลือก กระทรวงสาธารณสุข, หน่วยงานที่สนใจการวิจัยสมุนไพร และบุคลากรที่สนใจการวิจัยสมุนไพรในการประเมินประสิทธิผลและความปลอดภัยของสมุนไพรหลายชนิดด้วยการวิจัยทางคลินิกระยะที่ 2 และ 3 และ meta-analysis โดยมีผลงานวิจัยบางส่วนก็พบว่าสมุนไพรบางชนิดมีประโยชน์และปลอดภัยซึ่งนำไปสู่การรับสมุนไพรดังกล่าวไว้ในรายการยาสมุนไพรตามบัญชียาหลักแห่งชาติ ส่วนสมุนไพรบางชนิดก็ไม่พบว่ามีประโยชน์ และอาจมีผลข้างเคียงที่รุนแรงได้ โดยสมุนไพรที่มีการวิจัยและได้เผยแพร่ไปยังหน่วยงานที่เกี่ยวข้องและสังคมแล้ว เช่น

- ว่านหางจระเข้ (*Aloe vera*) รักษาแผลจากความร้อน (burn)
- ยาธาตุอบเชย (Cinnamon Stomachic Mixture) รักษาท้องอืดเฟ้อ (dyspepsia)
- รางจืด (*Thunbergia lauriforia*) ลดระดับแอลกอฮอร์ในเลือด
- การนวดแบบราชสำนัก บรรเทาอาการปวดเมื่อย
- สารสกัดเถาวัลย์เปรียง (Derris scandens) รักษาข้อเข่าเสื่อม
- ขิง (ginger) รักษาอาการคลื่อไส้อาเจียน
- บอระเพ็ด (*Tinospora crispa*) ไม่พบประสิทธิผลในการรักษาโรคเบาหวานและมีผลข้างเคียงต่อตับ
- ปัญจขันธ์ (*Gymnostemma pentaphylum*) ไม่พบประสิทธิผลในการรักษาไขมันในเลือดสูง
- ใบหม่อน (*Morus alba*) ไม่พบประสิทธิผลในการรักษาเบาหวาน
- แมงลักคา (*Hyptis suaveolens*) ไม่พบประสิทธิผลในการรักษาไข้หวัดใหญ่

**5. การนำผลงานวิจัยเรื่องอื่น ๆ ไปใช้ประโยชน์** เช่น

**ผลงานวิจัย**

- **Thamlikitkul V**, Indranoi A. Switching from heparinized saline flush to normal saline flush for maintaining peripheral venous catheter patency. Int J Qual Health Care 2006;18:183-5.

- งานวิจัยถูกนำไปใช้เป็นแนวทางในการเปลี่ยนพฤติกรรมการใช้น้ำเกลือแทนเฮปพารินในการป้องการการอุดตันของข็มให้สารน้ำเข้าสู่หลอดเลือดดำ

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- Thavorn K, Chaiyakunapruk N. A cost-effectiveness analysis of a community-based smoking cessation program in Thailand. Tobacco control 2008;17:177-82.

- งานวิจัยถูกนำไปใช้ประกอบการพิจารณาการผลักดันให้มีการเบิกจ่ายการให้บริการเลิกบุหรี่ในระดับชาติ โดยผู้บริโภคผลงานวิจัยโดยตรงคือสถาบันหลักประกันสุขภาพแห่งชาติ

**ผลงานวิจัย**

- Chirakup S, Chaiyakunapruk N et al. Cost-effectiveness analysis of thiazolidinediones in uncontrolled type 2 diabetic patients receiving sulfonylureas and metformin in Thailand Value in Health 2008;11 (suppl 1):S43-51.

- งานวิจัยถูกนำไปใช้ประกอบการพิจารณายานี้ในคณะกรรมการพิจารณาบัญชียาหลักแห่งชาติ และเป็นข้อมูลประกอบการประชุมเกี่ยวกับการเพิกถอนทะเบียนตำรับยา rosiglitazone ในประเทศไทยด้วย

**รางวัล**

1. รางวัลผลงานวิจัยของนักศึกษาแพทย์ในการประชุม Asian Medical Students' Association จากผลงานวิจัย เรื่อง Effectiveness of the royal Thai traditional massage for relief of muscle pain

2. รางวัลผลงานวิจัยแพทย์ประจำบ้านต่อยอดในการประชุมวิชาการประจำปีของราชวิทยาลัยอายุรแพทย์แห่งประเทศไทย เรื่อง Efficacy and safety of colistin (colistimethate sodium) for therapy of infections caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in Siriraj Hospital, Bangkok, Thailand

3. รางวัลผลงานวิจัยแพทย์ประจำบ้านในการประชุมวิชาการประจำปีของราชวิทยาลัยอายุรแพทย์แห่งประเทศไทย เรื่อง Development of appropriate procedure for inflation of endotracheal tube cuff in intubated patients

4. รองศาสตราจารย์ ดร. ณธร ชัยญาคุณาพฤกษ์ ได้รับรางวัล ดังนี้

- นักวิจัยดีเด่นของมหาวิทยาลัยนเรศวร 3 ปี (2007, 2008, 2009)
- รับรางวัล *William Rutala Award* จาก *American Professional in Infection Control*
- รางวัล Nagai Research award 2 ปี (2006, 2008)
- โปสเตอร์ดีเด่นในงานประชุมวิชาการ เช่น The 5th Asian Conference Pharmacoepidemiology, The jointed Annual Scientific Meeting of Department of Medical Sciences and the 10th Annual National Cancer Institute
- รางวัลผลงานวิจัย Routine to Research

**การเชื่อมโยงทางวิชาการกับนักวิชาการอื่นทั้งในและต่างประเทศ**

- นักวิจัยในเครือข่ายของ Asian Network for Surveillance of Resistant Pathogens Asian Network (ANSORP)
- นักวิจัยในเครือข่ายของ International Clinical Epidemiology Network (INCLEN) โดยเฉพาะโครงการ Knowledge Plus Project
- นักวิจัยจากมหาวิทยาลัย Pittsburgh และมหาวิทยาลัย Colorado ประเทศสหรัฐอเมริกา และมหาวิทยาลัย Monash ประเทศออสเตรเลีย

**การได้รับทุนอื่น ๆ จากทั้งในและต่างประเทศ**

- ทุนวิจัยจากสำนักงานคณะกรรมการวิจัยแห่งชาติ (วช.)
- ทุนวิจัยจากกระทรวงสาธารณสุข
- ทุนวิจัยจากมูลนิธิ Rockefeller
- ทุนวิจัยจาก National Institute of Health (NIH) ประเทศสหรัฐอเมริกา โครงการวิจัยเภสัชจลนศาสตร์ของยา Colistin ร่วมกับมหาวิทยาลัย Pittsburgh และมหาวิทยาลัย Colorado ประเทศสหรัฐอเมริกา และมหาวิทยาลัย Monash ประเทศออสเตรเลีย

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# ผลงานตีพิมพ์ในวารสารและหนังสือ
# (ภายใต้ทุนสนับสนุนของสำนักงานกองทุนสนับสนุนการวิจัย)

International Journal of Infectious Diseases (2004) 8, 47–51

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# Implementation of clinical practice guidelines for upper respiratory infection in Thailand

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Received 13 August 2002; received in revised form 11 March 2003; accepted 2 April 2003
**Corresponding Editor:** Michael Whitby, Brisbane, Australia

**KEYWORDS**
Clinical practice guidelines;
Implementation;
Upper respiratory infection

**Summary** *Objective:* To determine the effectiveness of implementing clinical practice guidelines (CPG) on antibiotic prescribing for adults with upper respiratory infection (URI) in terms of the changes in diagnosis and prevalence and patterns of antibiotic prescribing.

*Methods:* The CPG on antibiotic treatments for adults with URI published in the Annals of Internal Medicine 2001; 134: 479–52 were considered to be of high quality and applicable to Thai patients. A one-page clinical practice protocol in Thai was prepared from these guidelines. The dissemination strategy provided CPG and clinical practice protocol to 12 general practitioners in Siriraj Social Security Program in Bangkok during interactive educational meetings in April 2001. The information on 837 URI episodes from January to March (pre-CPG phase) and 774 URI episodes during May to July (post-CPG phase) were extracted from the patients' medical records. Telephone follow up for patients without antibiotics in the post-CPG phase was also attempted.

*Results:* Changes in the post-CPG period included (1) The diagnosis of URI was used less frequently whereas the diagnosis of common cold, pharyngitis and acute bronchitis were used more frequently ($p < 0.05$). (2) Antibiotic use fell from 74.0% to 44.1% ($p < 0.001$). (3) Fewer prescriptions for amoxicillin, roxithromycin, co-trimoxazole and doxycycline, and more for penicillin V ($p < 0.05$). Patients ($n = 97$) not given antibiotics reported recovery in 83.5% and improvement in 16.5%.

*Conclusion:* A locally prepared clinical practice protocol based on US CPG for appropriate antibiotic use for URI combined with interactive educational meetings is effective in promoting appropriate diagnosis and antibiotic therapy in an ambulatory setting in a tertiary care hospital in Thailand.



## Introduction

The prevalence of penicillin-resistant *Streptococcus pneumoniae* in Thailand increased to 42% in 2000.[1,2] Overuse of antibiotics for minor respiratory infections is found to be an important factor for the

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1201-9712/$30.00 
doi:10.1016/j.ijid.2003.09.001

selection of resistant strains.[3–6] Antibiotics are prescribed to 51–76% of adults with upper respiratory infections (URI) in the United States.[7,8] We found that antibiotics were prescribed to 80% of adults with URI who visited the Social Security Program at Siriraj Hospital, Bangkok, Thailand in the year 2000. It seems reasonable that reducing the use of unnecessary antibiotics could decrease or at least halt the development of drug-resistant streptococci.[9–11] Effective interventions are needed in view of the high rates of antibiotic resistance and use in Thailand and other countries.

The objective of this study was to determine the effectiveness of a simple one-page clinical practice protocol and US CPG for appropriate antibiotic use for URI combined with interactive educational meetings with general practitioners to improve the diagnosis and the use of antibiotics for adults with URI.

## Methods

The study was approved and endorsed by Faculty of Medicine Siriraj Hospital, Mahidol University. It was conducted at Siriraj Hospital in Bangkok, a 2000-bed tertiary care university hospital. There are about 80,000 adult outpatient visits annually to the Social Security Program in the hospital clinic. URI accounts for about 5% of these visits. The key recommendations presented in position papers on appropriate antibiotic use for URI in adults (Ann Intern Med 2001; 134: 479-529) were used to prepare a one-page clinical practice protocol in the Thai language (Figure 1).

The first part of the protocol emphasizes an importance for the diagnosis of specific clinical syndromes, i.e., common cold, rhinitis, non-specific upper respiratory tract infections, pharyngitis, tonsillitis, sinusitis, rhinosinusitis and acute bronchitis.

Clinical Practice Protocol on Antibiotic Use in Adults with Upper Respiratory Infections (URI) *

This protocol is intended for guiding general practitioners in making diagnoses and prescribing antibiotics for adults with upper respiratory infections in ambulatory care.

An adult who has no chronic or serious underlying diseases and presents to ambulatory care with symptoms and/or signs of upper respiratory infections should receive a more specific diagnosis of 'common cold' or 'rhinitis' or 'rhinopharyngitis' or 'pharyngitis' or 'tonsillitis' or 'sinusitis' or 'acute bronchitis' depending on his/her major symptoms and signs.
A diagnosis of 'URI' should be avoided.

The recommended treatments for each clinical syndrome of upper respiratory infections are:

Common cold/rhinitis/non-specific upper respiratory tract infections
- Symptomatic therapy such as an antipyretic should be given
- An antibiotic is not necessary since this syndrome is almost always caused by viruses.

*Pharyngitis/tonsillitis*
- Symptomatic therapy such as an antipyretic should be given
- An antibiotic should not be given routinely since most of the cases are caused by viruses. An antibiotic should be given to the patient who has at least three of the following criteria: fever, tonsillar exudate, tender anterior cervical lymphadenopathy, no cough. The antibiotic of first choice is penicillin V since group A streptococcus has not been resistant to penicillin. Erythromycin should replace penicillin V for the patient allergic to penicillin.

Sinusitis/rhinosinusitis
- The patient with mild symptoms should receive symptomatic therapy such as an antipyretic. An antibiotic may not be given
- The patient with severe symptoms or persistent symptoms longer than seven days should receive an antibiotic. The antibiotic of first choice is amoxicillin.

Acute bronchitis
- The patient should receive symptomatic treatment such as an antipyretic
- A β-agonist inhaler may relieve the symptoms
- An antibiotic is not necessary since this syndrome is usually caused by viruses.

* This protocol is modified from Principles of Appropriate Antibiotic Use for Treatment of Acute Respiratory Tract Infections in Adults: Background, Specific Aims, and Methods. *Annals of Internal Medicine* 2001;**134**:479–529

**Figure 1** Translation into English from Thai of the Clinical Practice Protocol.

The second part focuses on the antibiotics recommended for each clinical syndrome. The clinical practice protocol and US CPG were presented to 12 general practitioners who provided care for the Social Security Program. Two sessions of interactive educational meeting were organized in April 2001. Each session lasted 1.5 hours.

One of the investigators (VT) presented the current situation on antibiotic use for adults with URI at the ambulatory care service of Social Security Program and the necessity for change. The rationale for a separate diagnosis of each clinical URI syndrome and the principles for prescribing antibiotics for each clinical syndrome were then explained. Evidence for each recommendation in the CPG was clarified. The physicians agreed to adhere to the clinical practice protocol.

Sample size was based on the following considerations. The antibiotic prescription rate for adults with URI at the ambulatory care service of Social Security Program at Siriraj Hospital in 2000 was approximately 80%. It was hypothesized that antibiotic prescriptions could be reduced to 50% or less. For a 5% type I error and 20% type II error, 50 episodes of URI for each general practitioner were required. Therefore at least 600 episodes of URI for each period were needed. The medical records of the patients who attended ambulatory care service from January to March 2001 (pre-CPG period) and May to July 2001 (post-CPG period) were retrieved. The inclusion criteria were that:

- The adult patients had no underlying diseases and that they received care from the participating general practitioners.
- Information was extracted on diagnoses and antibiotic prescriptions.
- The clinical outcomes for patients who received no antibiotics during the post-CPG period were assessed by telephone interviews at seven days following their visits.
- The data were analyzed by descriptive statistics. All comparisons were performed by a chi-square test using Epi-Info version 6. All statistical tests were 2-sided and considered significant at $p < 0.05$.

## Results

The URI clinical syndromes identified by general practitioners during the two study periods are shown in Table 1. The diagnosis of URI was significantly reduced and pharyngitis, the common cold and bronchitis were diagnosed more often during the post-CPG period compared to the pre-CPG period. Time series analysis of clinical syndromes of URI revealed no significant difference among the months during each period. The antibiotic prescription rates were 74.0% in the pre-CPG period and 44.1% in the post-CPG period ($p < 0.001$, RR 0.6 with 95% CI 0.55–0.65).

The antibiotics prescribed during each period are shown in Table 2. There was a significant reduction in use of amoxicillin, co-trimoxazole, roxithromycin and doxycycline; and penicillin V was prescribed significantly more often during the post-CPG period compared with the pre-CPG period. Time series analysis of antibiotic prescription rates revealed no significant difference among the months during each period. Co-trimoxazole is not recommended in the URI antibiotic guidelines, nevertheless it accounted for 22.3% of the patients' prescriptions during the pre-CPG period and 17.1% during the post-CPG period. The correlation between the clinical syndromes of URI and antibiotic prescribing is shown in Table 3. The antibiotic prescription rate for the common cold was significantly less than for all other clinical syndromes of URI for both periods. The antibiotic prescription rates for URI, bronchitis and the common cold were significantly less during the post-CPG period when compared with those during the pre-CPG period.

Telephone interviews at seven days post-visit were attempted for 192 patients who received no antibiotics during the post-CPG period. Of these

**Table 1** Clinical syndromes of URI made by general practitioners.

| Clinical syndrome | Pre-CPG period (837 episodes) | Post-CPG period (774 episodes) | *p* | Relative risk (95% confidence interval) |
|---|---|---|---|---|
| URI | 720 (86.0%) | 242 (31.1%) | <0.001 | 0.36 (0.33-0.40) |
| Pharyngitis | 49 (5.9%) | 192 (24.8%) | <0.001 | 4.24 (3.2-5.7) |
| Bronchitis | 38 (4.5%) | 99 (12.8%) | <0.001 | 2.6 (1.8-3.7) |
| Tonsillitis | 24 (2.9%) | 17 (2.2%) | 0.5 | 0.8 (0.4-1.4) |
| Common cold | 5 (0.6%) | 223 (28.8%) | <0.001 | 48 (20-116) |
| Sinusitis | 1 (0.1%) | 1 (0.1%) | 1 | |

**Table 2** Antibiotic prescriptions made by general practitioners.

| Antibiotic | Pre-CPG period (837 episodes) | Post-CPG period (774 episodes) | *p* | Relative risk (95% confidence interval) |
|---|---|---|---|---|
| Amoxicillin | 289 (34.5%) | 108 (14%) | <0.001 | 0.45 (0.37-0.55) |
| Cotrimoxazole | 187 (22.3%) | 132 (17.1%) | 0.01 | 0.76 (0.62-0.93) |
| Roxithromycin | 79 (9.4%) | 22 (3%) | <0.001 | 0.3 (0.19-0.48) |
| Doxycycline | 21 (2.5%) | 4 (0.5%) | 0.01 | 0.21 (0.07-0.6) |
| Penicillin V | 16 (1.9%) | 72 (9.3%) | <0.001 | 4.87 (2.86-8.29) |
| Cefuroxime | 11 (1.3%) | 0 | | |
| Erythromycin | 3 (0.4%) | 2 (0.3%) | | |
| Spiramycin | 6 (0.7%) | 0 | | |
| Co-amoxiclav* | 1 (0.1%) | 0 | | |
| Lincomycin | 3 (0.4%) | 1 (0.1%) | | |
| Cephalexin | 2 (0.2%) | 0 | | |
| Norfloxacin | 1 (0.1%) | 0 | | |

* Amoxicillin-clavulanate.

**Table 3** Prevalence of antibiotic prescribing in each clinical syndrome of URI.

| Clinical syndrome | Prevalence of antibiotic prescription | |
|---|---|---|
| | Pre-CPG phase (%) | Post-CPG phase (%) |
| URI | 73 | 49 |
| Pharyngitis | 81 | 78 |
| Tonsillitis | 92 | 94 |
| Bronchitis | 74 | 40 |
| Common cold* | 20 | 10 |

* $p < 0.01$ when compared with other clinical syndromes.

97 (50.5%) were contacted after two attempts. Eighty-one (83.5%) of patients reported URI recovery, 16 (16.5%) reported that they had much improved.

## Discussion

Clinical practice guidelines are tools for changing clinicians' behaviour. Success in promoting more appropriate healthcare behaviour in clinicians depends on the quality and relevance of clinical practice guidelines and the effectiveness of the strategy used to disseminate the information. It was found that the URI CPG published in the Annals of Internal Medicine to be of a high quality according to Shaneyfelt's criteria[12] and relevant to clinical practice in Thailand. They are however in English and are much too long and detailed to be useful for busy practitioners. It was felt that only a few key points were needed to construct a practical protocol. Two main issues were focused upon: diagnosis and antibiotic prescribing for healthy adults with URI. It was elected to use interactive educational meetings for this study because it has been demonstrated to be an effective dissemination strategy.[13,14]

The intervention used in the study was effective in changing clinicians' behaviour in the diagnosis and treatment of URI patients. Similar results have been obtained by different interventions.[15,16] It is believed that a major factor contributing to the success of the current intervention was the substantial increase in the diagnosis of the common cold. Most of the clinic physicians agreed that antibiotics are not needed for this condition. A relatively small proportion of the patients were diagnosed with pharyngitis or tonsillitis, but antibiotic prescription rates for these two syndromes were still high (78–94%). This appears to be excessive since only up to 30% of the healthy adults with pharyngo-tonsillitis were found to have a positive throat culture for *Streptococcus pyogenes* (Thamlikitkul V, unpublished data). Use of rapid diagnostic methods for this bacterium should help reduce rate of antibiotic use, but may not reduce costs.

Co-trimoxazole is not recommended in the URI antibiotic guidelines. Nevertheless it accounted for 22.3% of the patients' prescriptions during the pre-CPG period and 17.1% during the post-CPG period. This is explained by the use of this drug by one senior clinician for almost all his patients with URI. He did not change his prescribing behaviour after receiving the intervention. When this practitioner's practice was excluded, the

antibiotic prescription rates were reduced from 66.8% to 34.2% for the pre-CPG period and post-CPG period respectively ($p < 0.001$). He has now retired.

Several issues continue to be of concern. First, although the antibiotic prescription rates fell from 74.0% to 44.1%, they still remained high in the post-CPG period. Ideally the antibiotic prescription rate for healthy adults with URI should not exceed 10%, since more than 90% are not caused by bacteria. Given the uncertainty of clinical findings in differentiating bacterial from viral infection in pharyngitis and tonsillitis, the antibiotic prescription rate would be expected to exceed 10% for these conditions, but a 44.1% use during the post-CPG period still appears to be excessive. Second, although the selection of antibiotics during the post-CPG period tended to be more appropriate, the choice made by the general practitioners needs to be improved. Third, this intervention was successful for at least a three-month period. In order to maintain the effectiveness of our intervention, all general practitioners have been reminded every six months since January 2002. The prevalence of antibiotic prescribing in 100 consecutive adult patients with URI in June 2002 was 41%. Finally, evidence-based clinical practice guidelines may need to be shown to be safe as well as effective under field conditions. It was found that virtually all patients who did not receive antibiotics during the post-CPG period had improved and none required readmission.

## Acknowledgements

The authors would like to thank Mrs Kornthip Prasarnkul, Mr Somchart Maneenoi, Ms Wilawan Achawakulthep, Ms Orasa Bumrungpak and Ms Pacharin Tubwiroj for their technical support; Dr Supachai Ratanamaneechat and Dr Piyasakon Sakonsatayatorn for their administrative assistance; and Dr Calvin M Kunin for his reviewing of the manuscript.

Grant Support: By contract RTA/05/2544 from the Thailand Research Fund and International Clinical Epidemiology Network (INCLEN) Trust. Both are non-for-profit organizations. Dr Visanu Thamlikitkul is a recipient of Senior Researcher Scholar from the Thailand Research Fund.

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# Randomized Controlled Trial of *Tinospora crispa* for Additional Therapy in Patients with Type 2 Diabetes Mellitus

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*A randomized double blind placebo controlled trial was conducted to determine the efficacy of Tinospora crispa as additional treatment in patients with type 2 diabetes mellitus who did not respond to oral hypoglycemic drugs and refused insulin injection. Twenty patients were allocated to receive Tinospora crispa powder in capsule form at a dosage of 1 gram thrice daily for 6 months. Twenty patients received a placebo. The main outcomes were changes in fasting plasma glucose, glycosylated hemoglobin and insulin levels. The baseline characteristics of the patients in both groups were not significantly different. There were no significant changes in fasting plasma glucose, glycosylated hemoglobin and insulin levels among the patients within the group and between groups. Two patients who received Tinospora crispa showed marked elevation of liver enzymes that returned to normal after discontinuing Tinospora crispa. Moreover, patients in the Tinospora crispa group had significant weight reduction and cholesterol elevation while taking Tinospora crispa. It is concluded that there is no evidence to support the use of Tinospora crispa 3 grams a day for additional therapy in patients with type 2 diabetes mellitus who did not respond to oral hypoglycemic drugs. The patients receiving Tinospora crispa may have an increased risk of hepatic dysfunction.*

**Keywords :** *Tinospora crispa, Diabetes mellitus*

***J Med Assoc Thai 2004; 87(5): 543-6***

*Tinospora crispa* is a medicinal plant used as a remedy for patients with diabetes mellitus in Malaysia[1]. *Tinospora crispa* was found to have an anti-hyperglycemic effect in animals[2-4]. The hypoglycemic effect of *Tinospora crispa* is mediated by increasing insulin secretion from isolated rat and human islets of Langerhans[3]. *Tinospora crispa* is commonly used in diabetic patients in Thailand as well. Toxicological study of crude extract of *Tinospora crispa* revealed no obvious adverse effects[5]. However, animals of both sexes receiving the highest dose of *Tinospora crispa* extract had significantly higher alkaline phosphatase (ALP) levels, alanine aminotransferase (ALT) levels and liver weights than those of the water control and tragacanth control groups. Histopathological study of the liver indicated that male rats receiving the highest dose of the extract had significantly higher incidence of bile duct proliferation and focal liver cell hyperplasia than the two control groups. Blood chemistry studies revealed that both male and female rats receiving 1.28 g/kg. body weight of the extract had significantly higher cholesterol levels but significantly lower glucose levels than those of water control and tragacanth control groups. To our knowledge, there has been no controlled clinical trial of *Tinospora crispa* in patients with diabetes mellitus.

The objective of the study was to determine the efficacy of *Tinospora crispa* in patients with type 2 diabetes mellitus who did not respond to oral hypoglycemic drugs and refused insulin injection.

## Patients and Method

The study was a randomized double blind placebo controlled trial conducted at Siriraj Hospital.

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The study was approved by the Institutional Review Board of the Faculty of Medicine Siriraj Hospital. The eligible study subjects were patients with type 2 diabetes mellitus older than 35 years who had received an adequate dose of oral hypoglycemic agents for at least 2 months and still had a glycosylated hemoglobin of greater than 8.5% and refused insulin injection. Patients with liver disease, heart disease, renal impairment or those who previously received traditional medicine were excluded. Eligible patients were randomly allocated to the study group or the control group. All subjects received oral hypoglycemic agents. The study group received additional *Tinospora crispa* powder in a capsule form at a dosage of 1 gram thrice daily for 6 months. *Tinospora crispa* powder was prepared by the Department of Medical Sciences, Ministry of Public Health. The control group was given placebo in an identical capsule to be taken in the same fashion as the study drug. Compliance with the medication was made by a pill count at each visit. The patients were interviewed, examined and blood was taken for complete blood count, fasting plasma glucose, liver enzyme profile and renal function at entry and every month during the study. Blood for glycosylated hemoglobin and insulin determination was collected at enrollment and every 2 months during the study.

A sample size of 16 patients per group was estimated according to the assumption that baseline mean glycosylated hemoglobin was 10% with a standard deviation of 2% and post treatment mean glycosylated hemoglobin in *Tinospora crispa* group was 8% or less with type I error 5% and type II error 20%. The data were analyzed by descriptive statistics, student t test, repeated measure ANOVA and chi-square test where appropriate. A p value of $\leq 0.05$ indicates a statistically significant difference.

**Results**

There were 40 eligible patients. Twenty patients were in the study group and 20 in the control group. The baseline characteristics of the patients between the two groups were not significantly different as shown in Table 1. Six patients (3 in the *Tinospora crispa* group and 3 in the control group) were withdrawn from the study. One patient in the *Tinospora crispa* group had to receive insulin due to having active pulmonary tuberculosis. Two patients in the *Tinospora crispa* group had elevation of liver enzymes (SGOT and SGPT of greater than 200 u/L.) more than 3 times the baseline values after receiving it for 2 and 5 months. Liver enzymes in the aforementioned 2 patients returned to normal (less than 30 u/L.) after discontinuing *Tinospora crispa* for one month. One of them had evidence of hepatitis C infection. Two patients in the control group had to receive insulin due to having a subdural hematoma and being treated with prednisolone for Bell's palsy. One patient in the control group had to leave the study due to difficulty in returning to the clinic for follow up. Therefore, the authors were able to follow 34 patients until the end of the study. Fasting plasma glucose, glycosylated hemoglobin and insulin levels of the patients in both groups during 6 months were

**Table 1.** Baseline characteristics of the patients in the study

| Characteristic | *Trinospora Crispa* Group(N=20) | Placebo Group(N=20) | P value |
|---|---|---|---|
| Gender, Male : Fema | 7 : 13 | 5 : 15 | 0.7 |
| Mean age, year (SD) | 58.4 (9.2) | 59.1 (10.7) | 0.8 |
| Mean body weight, kg (SD) | 60.8 (10.0) | 58.9 (10.0) | 0.5 |
| Mean BMI, kg./m$^2$ (SD) | 27 (5.5) | 26 (5.1) | 0.7 |
| Mean FPG, mg/dL. (SD) | 214.9 (45.5) | 227.3 (73.4) | 0.5 |
| Mean glycosylated Hb, % (SD) | 10.4 (1.6) | 10.0 (1.2) | 0.4 |
| Mean insulin level, uu/ml. (SD) | 17.9 (9.5) | 17.8 (13) | 0.9 |
| Mean hematocrit, % (SD) | 38.7 (3.3) | 39.7 (2.7) | 0.3 |
| Mean WBC (SD) | 7,971 (2,072) | 7,368 (1,586) | 0.3 |
| Mean BUN, mg./dL. (SD) | 15.1 (5.2) | 15.6 (4.9) | 0.8 |
| Mean creatinine, mg/dL. (SD) | 1.0 (0.3) | 1.0 (0.2) | 0.6 |
| Mean cholesterol, mg/dL (SD) | 233.6 (51.9) | 218.2 (31.7) | 0.7 |
| Mean triglyceride, mg/dL (SD) | 204.8 (127.2) | 183.9 (75.3) | 0.5 |
| Mean SGOT, u/L (SD) | 28.36 (12.8) | 25.8 (9.8) | 0.4 |
| Mean SGPT, u/L (SD) | 30.3 (15) | 27.5 (17.3) | 0.6 |
| Mean bilirubin, mg/dL (SD) | 1.33 (0.26) | 1.58 (0.27) | 0.4 |

not significantly different as shown in Fig. 1 and Fig. 2. At the end of the study, all patients in the *Tinospora crispa* group had glycosylated hemoglobin values greater than 8.5% compared with 71% of the patients in the control group ($p = 0.04$). The body weight of the patients significantly decreased (approximately 2 kilograms) and the patients' cholesterol levels significantly increased (approximately 30 mg./dL.) after taking *Tinospora crispa*. Changes in hematocrit, white blood cells, triglyceride, renal function and liver profile of the remaining patients were not observed.

## Discussion

This study was unable to demonstrate the efficacy of *Tinospora crispa* for therapy in patients with type 2 diabetes who did not respond to oral hypoglycemic drugs since there were no significant changes in fasting plasma glucose or glycosylated hemoglobin between those collected at baseline and during the study period in either group. Therefore, there is no evidence to support the use of *Tinospora crispa* in diabetic patients. However, there may be several explanations for being unable to detect any efficacy of *Tinospora crispa* in the present study. The authors recruited only type 2 diabetic patients who did not respond to an adequate dose of oral hypoglycemic agents. The insulin levels in the blood samples of the patients taking *Tinospora crispa* in the present study were not increasing. If the mechanism of action of *Tinospora crispa* is to stimulate insulin secretion, it is very unlikely that *Tinospora crispa* will be efficacious in these patients. A study that includes patients with mild diabetes who have never received oral hypoglycemic agents should be conducted in order to determine the efficacy of *Tinospora crispa*. Small sample size was not an explanation since 16 patients per group should be sufficient to detect the effect of at least 2% difference in glycosylated hemoglobin between the groups and there was no trend for any reduction in fasting plasma glucose or glycosylated hemoglobin in 17 patients who received *Tinospora crispa* for 6 months. In addition, all patients in the Tinospora crispa group still had glycosylated hemoglobin greater than 8.5% compared with 71% of those in the placebo group. An inadequate dosage or inadequate active ingredients of *Tinospora crispa* used in the study might explain the study results. A treatment duration of 6 months should be long enough to see the effect of treatment and this should not be the reason for negative results. Compliance with the medication was found to be satisfactory. Contamination was unlikely since this study included only patients who did not receive other traditional medicines. Co-intervention was considered insignificant since this study was double-blinded. *Tinospora crispa* is a well known appetite stimulant due to its bitterness and the patients in this group might consume more food after taking *Tinospora crispa* leading to uncontrolled diabetes and weight reduction. An explanation for the increase in cholesterol after taking *Tinospora crispa* is unclear. This observation was also found in animals[5]. Two patients (10%) who received *Tinospora crispa* at a dosage of 3 grams a day developed liver dysfunction and the study medication had to be discontinued. Although one patient had underlying chronic hepatitis, this

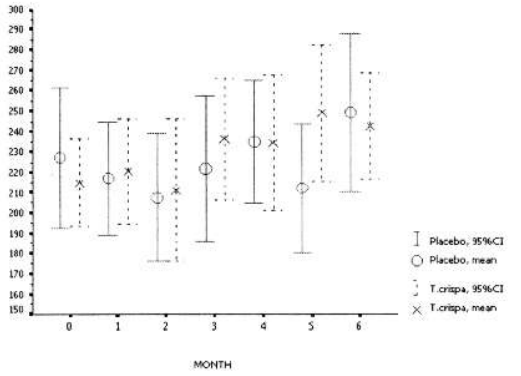


**Fig. 1** Fasting plasma glucose in patients taking *Tinospora crispa* (X) and taking placebo (O)

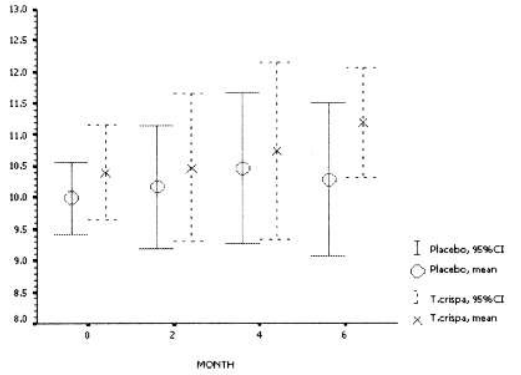


**Fig. 2** Glycosylated hemoglobin in patients taking *Tinospora crispa* (X) and taking placebo (O)

observation suggests that hepatic dysfunction is an adverse effect of *Tinospora crispa*, and patients wanting to take *Tinospora crispa* and health care personnel who want to provide *Tinospora crispa* to the patients should be aware of this effect.

**Acknowledgements**

The authors wish to thank the Department of Medical Sciences, Ministry of Public Health for preparing the medications and supporting the study. Dr. Visanu Thamlikitkul is a senior researcher scholar, a recipient of the Thailand Research Fund.

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## *ประสิทธิผลของบอระเพ็ดในการรักษาผู้ป่วยเบาหวาน*

***ชวัญญา แสงสุวรรณ, สุทธิพล อุดมพันธุรัก, สาธิต วรรณแสง , วิษณุ ธรรมลิขิตกุล***

*คณะผู้วิจัยได้ศึกษาประสิทธิผลของการรักษาโรคเบาหวานในผู้ใหญ่ที่ไม่ตอบสนองต่อการรักษาด้วยยารับประทานและไม่ยินยอมรับการรักษาด้วยอินสุลินจำนวน 40 คนโดยแบ่งผู้ป่วยออกเป็น 2 กลุ่มแบบสุ่ม ผู้ป่วยจำนวน 20 คนได้รับการรักษาเดิมที่เคยได้รับร่วมกับบอระเพ็ดขนาด 1 กรัมรับประทานวันละ 3 ครั้งติดต่อกันนาน 6 เดือน ส่วนผู้ป่วยอีก 20 คนได้รับการรักษาเดิมที่เคยได้รับร่วมกับยาหลอก ลักษณะของพื้นฐานและความรุนแรงของโรคในผู้ป่วยทั้งสองกลุ่มไม่แตกต่างกัน ผลการศึกษาพบว่าระดับน้ำตาลในพลาสมาและระดับของ glycosylated hemoglobin ภายหลังได้รับบอระเพ็ดไม่ลดลงจากระดับก่อนได้รับบอระเพ็ด และไม่น้อยกว่ากลุ่มที่ได้รับยาหลอก ผู้ป่วย 2 ราย (ร้อยละ 20) ที่ได้รับบอระเพ็ดมีผลทางข้อนที่ตับ ผู้ป่วยที่ได้รับบอระเพ็ดมีน้ำหนักตัวลดลงและมีระดับโคเลสเตอรอลในเลือดเพิ่มขึ้น การศึกษานี้แสดงว่าบอระเพ็ดไม่มีประสิทธิผลในการรักษาโรคเบาหวานในผู้ใหญ่ที่ไม่ตอบสนองต่อการรักษาด้วยยารับประทานและไม่ยินยอมรับการรักษาด้วยอินสุลินโดยอาจมีผลข้างเคียงต่อตับ*

# The Effect of *Thunbergia lauriforia Linn.* on Blood Alcohol Concentration after Consumption of Beer

Siriwan Sasithonrojanachai*
Suthipol Udompanthurak†
Visanu Thamlikitkul‡

**Abstract** **Blood alcohol concentration was determined by alcohol breath test in nine adult healthy subjects after taking a bottle (630 ml) of Thai beer with an alcohol concentration of 8 per cent (vol/vol) and after taking 1.8 grams of *Thunbergia lauriforia Linn.* prior to consumption of Thai beer at the same concentration and amount. The concentration of alcohol in the blood after taking *Thunbergia lauriforia Linn.* was found to be statistically significantly lower (by 11.7 per cent) than that when was consumed alone.**

***(Intern Med J Thai 2004; 20:27-29)***

***Key words:*** ***Thunbergia lauriforia Linn.*, blood, alcohol**

Traffic accidents comprise one of the leading causes of death in Thailand and alcohol consumption has been found to be a major risk factor for road accidents[1-4]. There have been extensive campaigns against drunk drivers and breath testing in drivers has been officially employed since 1996. A blood alcohol concentration of 50 mg% or more is considered illegal for driving vehicles. In the year 2000, there was a claim publicized in the newspapers that taking *Thunbergia lauriforia Linn.* at the same time as alcohol could decrease the absorption of alcohol and therefore prevent testing positive on an alcohol breath test. *Thunbergia lauriforia Linn.* is a medicinal plant widely used in Thailand. The main chemical ingredients in this plant are flavonoids such as apigenin, cosmosin and delphinidin[5]. *Thunbergia lauriforia Linn.* has been found to produce the effect of anti-intoxication by organophosphate insecticides in animals[6,7]. To our knowledge, there is no information about the effect of *Thunbergia lauriforia Linn.* on alcohol absorption in human subjects.

The objective of the study was to determine the effect of *Thunbergia lauriforia Linn.* on blood alcohol concentration after consumption of beer in healthy adult volunteers.

## SUBJECTS AND METHODS

The subjects were nine healthy adult volunteers, seven men and two women, average age 34.3 years (SD 7

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years), average height 165.9 cm (SD 6.5 cm) and average body weight 63.3 Kg (SD 10.3 Kg). They drank a bottle (630 ml) of Thai beer with an alcohol concentration of 8 per cent (vol/vol) on an empty stomach within 30 minutes. Blood alcohol concentration was measured by alcohol breath test every 15 minutes after commencing beer consumption for 180 minutes or until alcohol was undetectable. Several weeks later the same subjects took 1.8 grams of *Thunbergia lauriforia Linn.* dried leaf powder capsules orally prior to drinking the same amount of beer. Blood alcohol concentration was measured by alcohol breath test every 15 minutes after commencing alcoholic beverage consumption for 180 minutes or until alcohol was undetectable. The subject was instructed to thoroughly rinse the oral cavity with water to remove any residual alcohol in the oral cavity before measuring. All alcohol breath tests were performed using an Intoxilyser (model Alco-sensor IV, Intoximeters Inc., MO). The blood alcohol concentrations of the subjects in both experiments were analyzed by descriptive statistics and multiple regression analysis. A $p$ value of 0.05 or less was considered statistically significant.

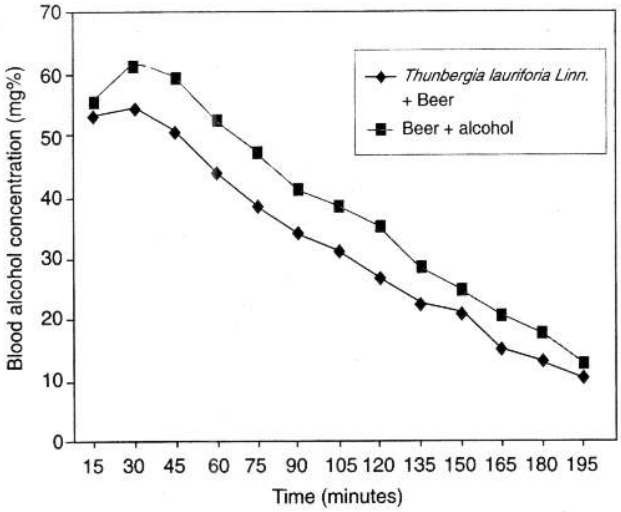


**Fig. 1.** Blood alcohol concentration time curves after beer consumption alone and consumption *Thunbergia lauriforia Linn.* and beer.

## RESULTS

The blood alcohol concentration-time curves for both experiments are shown in Figure 1. The mean peak alcohol concentration in the blood of the subjects after beer consumption was 61.6 mg% (SD 10.2 mg%) at 30 minutes whereas that of the subjects who took of *Thunbergia lauriforia Linn.* prior to beer consumption was 54.4 mg% (SD 8.6 mg%). Consumption of *Thunbergia lauriforia Linn.* along with beer can reduce peak blood alcohol concentration by 11.7 per cent. The difference in blood alcohol concentration time curves between the two experi-ments was statistically significant ($p < 0.001$). No subjects reported any adverse reactions to *Thunbergia lauriforia Linn.*.

## DISCUSSION

This study used an alcohol breath test to determine blood alcohol concentration since it had been demonstrated that the alcohol level measured by breath test was highly correlated with that directly measured from blood with a correlation coefficient of 0.987 ($p = 0.001$)[8]. The results of the study revealed that taking *Thunbergia lauriforia Linn.* at a dosage of 1.8 grams just prior to alcohol consumption could reduce the peak blood alcohol concentration. This effect is likely to be due to a decrease in absorption of alcohol from the gastrointestinal tract. However, the effect of *Thunbergia lauriforia Linn.* is quite minimal since it could only reduce the blood alcohol concentration by 11.7 per cent which might not be clinically important if a large amount of alcohol is consumed. The effect of a larger dose of *Thunbergia lauriforia Linn.* on blood alcohol concentration is unknown. It should be mentioned that our experiment was not performed in the subjects after taking meals instead of taking *Thunbergia lauriforia Linn.*; therefore, the findings observed in this study could be due either to a direct effect of *Thunbergia lauriforia Linn.* or a non-specific effect similar to taking alcohol after a meal.

## ACKNOWLEDGEMENTS

*The authors would like to thank the Department of Medical Sciences, Ministry of Public Health for supplying the Thunbergia lauriforia Linn. capsules for the study.*

*Dr. Visanu Thamlikitkul is a recipient of a grant from the Thailand Research Fund as Senior Researcher Scholar.*

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**บทคัดย่อ** **ประสิทธิผลของสมุนไพรรางจืดต่อระดับของแอลกอฮอร์ในเลือดภายหลังการดื่มเบียร์**

**ศิริวรรณ ศศิธรโรจนชัย*, สุทธิพล อุดมพันธุรัก† , วิษณุ ธรรมลิขิตกุล‡**

**ภาควิชานิติเวชศาสตร์, †สถานส่งเสริมการวิจัย และ ‡ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล, กรุงเทพฯ ๑๐๗๐๐*

คณะผู้วิจัยได้ศึกษาผลของการรับประทานสมุนไพรรางจืดต่อระดับของแอลกอฮอร์ในเลือดโดยให้อาสาสมัครที่มีสุขภาพแข็งแรงจำนวน ๘ คนดื่มเบียร์ไทย ๑ ขวด (๖๓๐ มล.) แล้ววัดระดับของแอลกอฮอร์ในเลือดจากการตรวจระดับแอลกอฮอร์จากลมหายใจเปรียบเทียบกับการรับประทานรางจืดในขนาด ๑.๘ กรัมก่อนดื่มเบียร์ในขนาดเดียวกัน พบว่าระดับของแอลกอฮอร์ในเลือดในช่วงที่ได้รับรางจืดร่วมด้วยต่ำกว่าระดับของแอลกอฮอร์ในเลือดในช่วงที่ไม่ได้รับรางจืดอย่างมีนัยสำคัญทางสถิติแต่ความแตกต่างนี้มีขนาดน้อยเพียงร้อยละ ๑๑.๗.

***(วารสารอายุรศาสตร์แห่งประเทศไทย ๒๕๔๗; ๒๐:๒๗-๒๙)***


***คำสำคัญ:*** **สมุนไพรรางจืด, แอลกอฮอล์, เบียร์**

Original Article

# *In Vitro* Activity of Telithromycin Against *Streptococcus pneumoniae* Isolated from Patients in Siriraj Hospital

**Somporn Srifeungfung, Ph.D.***
**Visanu Thamlikitkul, M.D.****

**ABSTRACT**

Seventy-one isolates of *Streptococcus pneumoniae* from different patients in different departments in Siriraj Hospital during 2002 and 2003 were tested for susceptibility to penicillin, clindamycin, tetracycline, erythromycin, vancomycin and telithromycin. Thirty-one isolates (43.7%) of *S. pneumoniae* were susceptible to penicillin, 5 (7%) were intermediately resistant to penicillin, and 35 (49.3%) were highly resistant to penicillin. The susceptibility of *S. pneumoniae* to clindamycin, tetracycline, erythromycin and vancomycin was 74.6 percent, 42.3 percent, 59.2 percent, and 100 percent, respectively. All isolates were susceptible to telithromycin. Telithromycin could be an alternative oral therapy for infections caused by drug-resistant *Streptococcus pneumoniae* in Thailand. (*J Infect Dis Antimicrob Agent 2004;21:79-81.*)

## INTRODUCTION

*Streptococcus pneumoniae* is a common cause of community-acquired respiratory tract infections in Thailand. The prevalence of drug-resistant *Streptococcus pneumoniae* (DRSP) has been increasingly reported over the past two decades,[1-7] thus a development of new antibiotics for treating these infections is urgently needed. Telithromycin is a ketolide, which is a 14-membered ring semi-synthetic macrolide. Telithromycin is active against DRSP including penicillin-resistant and macrolide-resistant *S. pneumoniae*.[8-10] Efficacy and safety of oral telithromycin at 800 mg once daily for 5 to 10 days has been demonstrated in community-acquired pneumonia, acute exacerbations of chronic bronchitis, acute sinusitis and pharyngitis/tonsillitis.[8,9] Telithromycin has been available in Europe for the aforementioned indications for several years and it has been available in USA since April 2004. The objective of this study was to determine the *in vitro* activity of telithromycin against *S. pneumoniae* isolated from Thai patients hospitalized to a tertiary care hospital in Bangkok.

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Received for publication: July 15, 2004.

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**Keywords:** *Streptococcus pneumoniae*, susceptibility, penicillin, erythromycin, clindamycin, tetracycline, telithromycin, vancomycin

## MATERIALS AND METHODS

### *Streptococcus pneumoniae* Isolates

Seventy-one isolates of *S. pneumoniae* were from sputum (40), blood (20) and others (11) from different patients in different departments in Siriraj Hospital during July 2002 and March 2003. Identification of *S. pneumoniae* was performed by using standard microbiological method (morphology and optochin susceptibility as shown by a zone of inhibition ≥ 14 mm in diameter). They were stored at -70 C in 5 percent trypicase soy broth plus 20 percent (V/V) glycerol until the time that the susceptibility test was conducted.

### Susceptibility Test

The susceptibility to penicillin was performed by E-test using a 90-mm agar plate containing cation-adjusted Mueller Hinton agar with 5 percent sheep blood.[11] The susceptibility of *S. pneumoniae* to erythromycin, clindamycin, telithromycin, vancomycin, and tetracycline was performed by disk diffusion according to the National Committee for Clinical Laboratory Standards (NCCLS) 2002 procedures.[12] *S. pneumoniae* ATCC 49619 was used as quality control strain in every batch tested. All plates were incubated at 35 C in 5 percent $CO_2$ for 20-24 hours. Interpretation of the test results for "sensitive" or "intermediate" or "resistant" to erythromycin, clindamycin, telithromycin, vancomycin, and tetracycline was made according to the criteria in Table 1.[12]

## RESULTS

Thirty-one strains (43.7%) of *S. pneumoniae* had a penicillin MIC of ≤0.06 (sensitive), 5 (7%) had a MIC of >0.06 - 1 (intermediate), and 35 (49.3%) had a MIC of >1 mg/L (resistant). The susceptibility of *S. pneumoniae* to clindamycin, tetracycline, erythromycin, vancomycin, and telithromycin was 74.6 percent, 42.3 percent, 59.2 percent, 100 percent, and 100 percent, respectively.

## DISCUSSION

Our results indicate that the prevalence of penicillin- and macrolide-resistant *S. pneumoniae* in patients attending Siriraj Hospital during 2002 and 2003 was quite high. This observation is similar to those reported elsewhere.[2] Patients suspected of having infections caused by DRSP may need an antibiotic that can overcome the resistance mechanism. Risk factors for acquiring DRSP have been identified. The major risk factor for acquisition of penicillin-resistant *S. pneumoniae* in Thai patients was a recent antibiotic use.[3,4] Antibiotics active against DRSP are limited and few are available in an oral form. New generation of fluoroquinolones (levofloxacin, moxifloxacin,

**Table 1. Criteria for interpretation of zone diameters of studied antibiotics against *S. pneumoniae*.**

| Antibiotic | Disk Content | Zone Diameter (mm) | | |
|---|---|---|---|---|
| | | Resistant | Intermediate | Sensitive |
| Telithromycin | 15 μg | ≤16 | 17-20 | ≥21 |
| Erythromycin | 15 μg | ≤15 | 16-20 | ≥21 |
| Clindamycin | 2 μg | ≤15 | 16-18 | ≥19 |
| Tetracycline | 30 μg | ≤18 | 19-22 | ≥23 |
| Vancomycin | 30 μg | - | - | ≥17 |

gatifloxacin), linezolid and telithromycin are shown to be effective in therapy of DRSP infections. In our study, telithromycin is active against all 71 isolates of *S. pneumoniae*. Telithromycin should have a role for treatment of *S. pneumoniae* infections in Thai patients especially in outpatient care settings.

**ACKNOWLEDGEMENT**

The author would like to thank Aventis Pharma for supplying the telithromycin disks. Dr. Visanu Thamlikitkul is a recipient of the Senior Researcher Scholar, Thailand Research Fund.

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# EPIDEMIOLOGY OF EXTENDED-SPECTRUM BETA-LACTAMASE PRODUCING GRAM-NEGATIVE BACILLI AT SIRIRAJ HOSPITAL, THAILAND, 2003

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**Abstract.** A cross-sectional study was conducted from August to September, 2003 to determine the prevalence and risk factors in acquiring extended-spectrum beta-lactamase (ESBL) producing gram-negative bacilli (GNB) in patients admitted to Siriraj Hospital and the outcomes of these infections. Of 346 isolates of gram-negative bacteria in 249 patients, 102 isolates from 87 patients were colonization only, but 244 isolates from 162 patients were infections. The common GNB were *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Enterobacter cloacae*. The overall prevalence of ESBL producers was 30.1%. *K. pneumoniae* had a very high prevalence of ESBL producers (56.9%). The urinary tract was the most common site for ESBL- producing GNB infections. Nosocomial infections, duration from admission to infection, peripheral line, urinary catheterization, nasogastric tube insertion and previous use of beta-lactams, cephalosporins and fluoroquinolones were associated with acquiring ESBL-producing GNB infections. ESBL-producing GNB were significantly more resistant to antimicrobial agents. More than 80% of ESBL-producing GNB were susceptible to carbapenems. Mortality in patients infected with ESBL-producing GNB (41.3%) was significantly higher than those infected with non- ESBL-producing GNB (19.8%).

## INTRODUCTION

Bacteria can be resistant to antimicrobial agents by various mechanisms. Beta-lactamase production is the most important mechanism for bacterial resistance to beta-lactam antibiotics and many beta-lactamases have been identified. Since *Klebsiella pneumoniae* with ESBL production was first isolated from the University Hospital in Frankfurt, Germany in 1983 (Knothe *et al*, 1983), many outbreaks caused by multi-resistant strains have been reported all over the world. In Asia, ESBL-producing bacteria have been reported in China (Jacoby and Medeiros, 1991, Cheng and Chen, 1994), Japan (Yagi, *et al*, 2000), Singapore (Jacoby and Medeiros, 1991), Korea (Kim *et al*, 1998) and Thailand (Chanawong *et al*, 2001). In Thailand, Asawapokee *et al* (1994) reported that the prevalence of ESBL-producers in *K. pneumoniae* was 39% in 1994 and in *E. coli* 10% in 1996.

ESBLs are plasmid-mediated enzymes that hydrolyze broad-spectrum beta-lactams and are strongly inhibited by clavulanate. ESBLs are transmitted by plasmids among bacteria and difficult to detect by routine antimicrobial susceptibility tests. Furthermore, antibiotics such as trimethoprim-sulfamethoxazole, aminoglycosides and fluoroquinolones (Martinez-Martinez *et al*, 1998) are often co-transferred on a resistance plasmid, resulting in multiple drug resistance. Thus clinical treatment failure occurs frequently, especially when inappropriate antimicrobial therapy is used to treat infections caused by ESBL- producing organisms. Therefore, if infections with ESBL-producing organisms can be predicted by the clinical characteristics of patients, this may lead to a better selection of antibiotics and may improve the outcome of infections.

The objectives of this study were to deter-

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mine the prevalence of ESBL-producing GNB, the risk factors for infections with ESBL-producing GNB, antibiotic susceptibility patterns of ESBL-producing GNB, and the outcomes of patients infected with ESBL-producing GNB.

## MATERIALS AND METHODS

The study protocol was approved by the Ethics Committee on Human Research at Siriraj Hospital. From August to September 2003, all isolates of GNB from clinical specimens collected from patients admitted to Siriraj Hospital were identified and tested for the existence of ESBL as well as their susceptibility to antibiotics. ESBL was determined according to the criteria of the National Committee for Clinical Laboratory Standards (2000) by means of a disk diffusion method. A combination disk diffusion method was performed using a ceftazidime disc (30 μg) and a ceftazidime/clavulanate disk (30/10 μg) placed onto Muller-Hinton agar containing GNB and incubated for 24 hours. ESBL production was indicated if the diameter of the inhibition zone around the ceftazidime/clavulanate disk was ≥5 mm greater than the diameter of the inhibition zone around the ceftazidime disk. All patients older than 15 years, from whom GNBs were isolated, were prospectively followed. All relevant information on demographics, risk factors for infection, type of infection, antibiotic therapy and outcomes, were collected from the patients and their medical records. Statistical analysis was performed using SPSS. Chi-square, Fisher's exact test, and Student's *t*-test were used where appropriate. All statistical tests were two-sided, and $p<0.05$ was considered significant.

## RESULTS

During the study period, 346 isolates of GNB from 249 patients were suitable for analysis. Of the 346 isolates of GNB, 244 isolates from 162 patients were infections, 102 isolates from 87 patients were colonizations. The prevalence of ESBL-producing GNB is shown in Table 1. The overall prevalence of ESBL producers was 30.1%. *K. pneumoniae* had a very high prevalence of ESBL production (56.9%). Of the 162 patients who had GNB infections, 31.5 % were infected with ESBL-producing GNB and 68.5% were infected with non-ESBL-producing GNB. The characteristics of the patients infected with ESBL-producing GNB and non-ESBL-producing GNB are shown in Table 2. The characteristics

Table 1
Prevalence of ESBL producers in 346 isolates of GNB.

| Gram-negative bacilli | ESBL negative N (%) | ESBL positive N (%) | Total N (%) |
|---|---|---|---|
| *Escherichia coli* | 70 (66.7) | 35 (33.3) | 105 (30.3) |
| *Klebsiella pneumoniae* | 22 (43.1) | 29 (56.9) | 51 (14.7) |
| *Pseudomonas aeruginosa* | 50 (79.4) | 13 (20.6) | 63 (18.2) |
| Nonfermentative gram-negative bacilli | 23 (74.2) | 8 (25.8) | 31 (9.0) |
| *Enterobacter cloacae* | 13 (54.2) | 11 (45.8) | 24 (6.9) |
| *Salmonella* spp | 2 (66.6.0) | 1 (33.3) | 3 (0.9) |
| *Aeromonas hydrophila* | 1 (100.0) | 0 (0.0) | 1 (0.3) |
| *Acinetobacter baumannii* | 41 (93.2) | 3 (6.8) | 44 (12.7) |
| *Haemophilus influenzae* | 2 (100.0) | 0 (0.0) | 2 (0.6) |
| *Serratia marcescens* | 3 (100.0) | 0 (0.0) | 3 (0.9) |
| *Providentia stuatii* | 0 (0.0) | 1 (100.0) | 1 (0.3) |
| *Morganella morganii* | 0 (0.0) | 2 (100.0) | 2 (0.6) |
| *Vibrio* spp | 1 (100.0) | 0 (0.0) | 1 (0.3) |
| *Proteus mirabilis* | 14 (93.3) | 1 (6.7) | 15 (4.3) |
| Total | 242 (69.9) | 104 (30.1) | 346 (100.0) |

Table 2
Characteristics of the patients infected with ESBL-producing GNB and non-ESBL-producing GNB.

| Characteristic | ESBL | | p-value |
|---|---|---|---|
| | Negative 111 patients | Positive 51 patients | |
| Male | 58 (52.3%) | 25 (49.0%) | 0.83 |
| Mean age (SD), years | 59.5 (18.8) | 60.9 (20.4) | 0.68 |
| Type of ward | | | |
| General ward | 69 (62.2%) | 37 (72.5%) | 0.44 |
| Private ward | 36 (32.4%) | 12 (23.5%) | |
| ICU | 6 (5.4%) | 2 (3.9%) | |
| Department | | | |
| Medicine | 59 (53.2%) | 29 (56.9%) | 0.79 |
| Other departments | 52 (46.8%) | 22 (43.1%) | |
| Underlying diseases | | | |
| Diabetes mellitus | 31 (27.9%) | 12 (23.5%) | 0.69 |
| Hypertension | 36 (32.4%) | 11 (21.6%) | 0.22 |
| Heart diseases | 20 (18.0%) | 8 (15.7%) | 0.89 |
| COPD | 9 (8.1%) | 3 (5.9%) | 0.75 |
| Chronic renal failure | 8 (7.2%) | 5 (9.8%) | 0.55 |
| Chronic liver disease | 4 (3.6%) | 4 (7.8%) | 0.26 |
| Cerebrovascular disease | 19 (17.1%) | 9 (17.6%) | 1.00 |
| Malignancy | 33 (29.7%) | 21 (41.2%) | 0.21 |
| Neutropenia | 6 (5.4%) | 2 (3.9%) | 1.00 |
| HIV infection | 5 (4.5%) | 0 | 0.33 |
| Others | 100 (90.1%) | 50 (98.0%) | 0.11 |
| Site of infections | | | |
| Respiratory tract | 52 (46.8%) | 23 (45.1%) | 1.00 |
| Urinary tract | 65 (58.6%) | 36 (70.6%) | 0.26 |
| Skin and soft tissue infection | 20 (18.01%) | 8 (15.7%) | 0.92 |
| Gastrointestinal tract | 16 (14.4%) | 6 (11.8%) | 0.87 |
| CNS infection | 1 (1%) | 0 | 1.00 |
| Bone and joint infection | 3 (2.7%) | 0 | 0.56 |
| Primary bacteremia | 11 (9.9%) | 3 (5.9%) | 0.56 |
| Nosocomial infections | 60 (54.1%) | 39 (76.5%) | 0.01 |
| Median duration from admission to infection (interquartile range), days | 4 (13) | 13 (25) | 0.01 |
| Kanofky performance status score (median) | 60 | 50 | <0.001 |
| Presence of central intravenous line | 12 (10.8%) | 7 (13.7%) | 0.79 |
| Presence of peripheral venous line | 67 (60.4%) | 43 (84.3%) | 0.004 |
| Parenteral nutrition | 4 (3.6%) | 2 (3.9%) | 1.00 |
| Mechanical ventilation | 23 (20.7%) | 15 (29.4%) | 0.31 |
| Endotracheal intubation | 23 (20.7%) | 15 (29.4%) | 0.31 |
| Tracheostomy | 7 (6.3%) | 4 (7.8%) | 0.74 |
| Urinary catheterization | 54 (48.6%) | 37 (72.5%) | 0.01 |
| Nasogastric tube insertion | 33 (29.7%) | 28 (54.9%) | 0.004 |
| Gastrostomy/jejunostomy | 2 (1.8%) | 0 | 1.00 |
| Peritoneal dialysis | 3 (2.7%) | 4 (7.8%) | 0.21 |
| Hemodialysis | 2 (1.8%) | 2 (3.9%) | 0.59 |
| Decubitus ulcer | 8 (7.2%) | 8 (15.7%) | 0.16 |
| Chemotherapy | 5 (4.5%) | 4 (7.8%) | 0.46 |
| Immunosuppressive agents | 17 (15.3%) | 7 (13.7%) | 0.98 |
| Other invasive procedures/surgery | 25 (22.5%) | 17 (33.3%) | 0.21 |
| Previous antibiotic treatment | 36 (32.4%) | 32 (62.7%) | 0.001 |
| Previous beta-lactam treatment | 28 (25.2%) | 26 (51.0%) | 0.002 |
| Previous cephalosporin treatment | 20 (18.0%) | 21 (41.2%) | 0.003 |
| Previous carbapenem treatment | 6 (5.4%) | 6 (11.8%) | 0.2 |
| Previous aminoglycoside treatment | 7 (6.3%) | 7 (13.7%) | 0.19 |
| Previous fluoroquinolone treatment | 5 (4.5%) | 12 (23.5%) | 0.001 |

Table 3
Antibiotic susceptibility patterns of ESBL-producing GNB and non-ESBL-producing GNB.

| Antibiotic | ESBL-negative Number susceptible/ total tested isolates (%) | ESBL-positive Number susceptible/ total tested isolates (%) | p-value |
|---|---|---|---|
| Ampicillin | 25/197 (12.7%) | 1/90 (1.1%) | 0.003 |
| Cefazolin | 96/195 (49.2%) | 2/88 (2.3%) | <0.001 |
| Amikacin | 182/241 (75.5%) | 64/103 (62.1%) | 0.017 |
| Gentamicin | 150/241 (62.2%) | 29/103 (28.2%) | <0.001 |
| Cotrimoxazole | 73/242 (30.2%) | 17/102 (16.7%) | 0.014 |
| Amoxicillin/clavulanate | 81/199 (40.7%) | 3/93 (3.2%) | <0.001 |
| Ampicillin/sulbactam | 91/199 (45.7%) | 8/91 (8.8%) | <0.001 |
| Cefotaxime | 122/242 (50.4%) | 2/103 (1.9%) | <0.001 |
| Ceftriaxone | 122/242 (50.4%) | 2/103 (1.9%) | <0.001 |
| Ceftazidime | 179/242 (74.0%) | 5/104 (4.8%) | <0.001 |
| Sulbactam/cefoperazone | 180/239 (75.3%) | 44/104 (42.3%) | <0.001 |
| Norfloxacin | 35/80 (43.8%) | 2/30 (6.7%) | 0.001 |
| Ciprofloxacin | 123/240 (51.3%) | 19/104 (18.3%) | <0.001 |
| Cefpirome | 173/237 (73%) | 26/104 (25.0%) | <0.001 |
| Cefepime | 186/240 (77.5%) | 50/104 (48.1%) | 0.006 |
| Imipenem | 185/240 (77.1%) | 94/104 (90.4%) | 0.019 |
| Meropenem | 181/237 (76.4%) | 90/102 (88.2%) | <0.001 |
| Tazobactam/piperacillin | 182/240 (75.8%) | 54/104 (51.9%) | <0.001 |

found to be significantly associated with the acquisition of ESBL-producing organisms were nosocomial infections, duration of hospitalization prior to infections, presence of peripheral intravenous catheter, insertion of urinary catheter, insertion of a nasogastric tube, prior use of beta-lactams, cephalosporins or fluoroquinolones within the previous 3 months, and lower Karnofsky performance status score. The antibiotic susceptibility patterns for ESBL-producing GNB and non-ESBL-producing GNB are shown in Table 3. ESBL-producing GNB were significantly more resistant to antimicrobial agents except for the carbapenems. About 90% of ESBL-producing GNB were susceptible to carbapenems compared with 77% in non-ESBL-producing GNB. The mortality rate in patients infected with ESBL-producing organisms was 43.1% compared to 19.8% in patients with non-ESBL-producing GNB (p=0.008).

## DISCUSSION

Earlier studies on the prevalence of ESBL-producing organisms in eight medical centers in Thailand showed that the prevalence of ESBL-producing *E. coli* and *K. pneumoniae* during 1996-1999 was 15.7% and 45.6%, respectively (Biedenbach *et al*, 1999). The annual reports of ESBL-producing organisms at another university hospital in Thailand revealed that the prevalence of ESBL-producing *K. pneumoniae* increased from 10.2% in 1998 to 46.5% in 2001. The present study observed that an overall prevalence of ESBL-producing gram-negative bacteria was 30.1% and the prevalence of ESBL-producers in *E. coli*, *K. pneumoniae* and *Enterobacter cloacae* increased to 33.3%, 56.9% and 45.8%, respectively. The prevalence of ESBL-producing *E. coli* and *K. pneumoniae* in our study was higher than in previous studies from the same institution and different institutions in Thailand. This observation indicated that ESBL production has played an important role in the resistance mechanism of GNB in Thailand, especially in tertiary care institutions. Previous studies suggested that urinary catheters, nasogastric tubes, central venous catheters, arterial cath-

eters, endotracheal tubes, ventilators, total parenteral nutrition and emergency abdominal surgery were related to colonization or infection with ESBL-producing organisms (Lautenbach *et al*, 2001; Nathisuwan *et al*, 2001; Ho *et al*, 2002; Kang *et al*, 2004a,b). Our study found that the factors significantly associated with the acquisition of ESBL-producing GNB were nosocomial infections, longer durations of hospitalization prior to infection, presence of peripheral intravenous catheters, urinary catheters, nasogastric tubes, prior uses of beta-lactams, cephalosporins or fluoroquinolones within the previous 3 months and a lower Kanofsky performance status score. Our study did not observe any correlation between co-morbid conditions of the patient and the acquisition of organisms with ESBL-production as reported by others (Lin *et al*, 2003). Our study showed that the Karnofsky performance status score was lower in the group with ESBL-producing GNB infections. One study also showed that patients with fecal colonization of ESBL-producing *K. pneumoniae* had a higher clinical severity score on admission (Pena *et al*, 1997). We found that nosocomial infection was a significant risk factor and the longer the patients were hospitalized, the more likely they were to be colonized and infected with ESBL-producing GNB. Paterson *et al* (1997) found that 31% of patients with ESBL-producing *K. pneumoniae* had received a third generation cephalosporin within the 14 days preceding bacteremia compared with 3% in the control group. The widespread use of third generation cephalosporins is believed to be the major cause of the mutation in these enzymes that have led to the emergence of ESBL-producing bacteria (Rice *et al*, 1990; Naumovski *et al*, 1992). An association between fluoroquinolones and the emergence of ESBL production has also been observed (Paterson *et al*, 2000). A possible explanation for the co-existence of these two resistance mechanisms is that they were transferred on the same plasmid. The study of plasmid-mediated ciprofloxacin resistance has recently been reported (Martinez-Martinez *et al*, 1998).

In our study, prior use of beta-lactams or fluoroquinolones was associated with infections caused by ESBL-producing GNB. Prior use of aminoglycosides was also found more often in patients infected with ESBL-producing GNB, though it did not reach a significant level due to the small sample size. Our findings confirmed an association between antimicrobial use and the emergence of ESBL-producing GNB. The ESBL-producing GNB in our series was significantly less susceptible to all antimicrobial agents when compared with non- ESBL-producing GNB, except for carbapenems. This may be explained by the fact that ESBL was not detected in most strains of *Acinetobacter baumannii* (93%), and the prevalence of carbapenem resistant *Acinetobacter baumannii* was high. Of 55 strains which were ESBL-negative and carbapenem-resistant, 12 were *Pseudomonas aeruginosa*, 8 were non-fermenters and 35 were *Acinetobacter baumannii*. Carbapenem is the most active and reliable treatment regimen for infections caused by ESBL-producing GNB (Paterson *et al*, 2004a,b; Kang *et al*, 2004a,b). Mortality in patients infected with ESBL-producing GNB was high (41.3%), even in patients who received carbapenems. This observation can be explained by a high prevalence of imipenem-resistance (5 of 16 strains) and delayed treatment (3 patients received carbapenem treatment 72 hours after the onset of infection). Therefore, infections caused by ESBL-producing GNB have become more important in Thailand due to limited effective antibiotics and high mortality. Pena *et al* (1998) reported a significant role in rigorous restriction of oxyimino-âlactam use in the management and successful control of a large nosocomial ESBL-producing *K. pneumoniae* outbreak. The New York Hospital also found a decrease in the rate of ESBL-producing *K. pneumoniae* upon a shift in antibiotic utilization from cephalosporins to other antibiotics (Rahal *et al*, 1998). However, with the limitation of healthcare costs, along with a limited number of broad spectrum antibiotics, cephalosporins remain the most common empiric antibiotics for Thai patients. The results from our study may be useful for selecting empiric antibiotics active against ESBL-producing GNB if the patient has the aforementioned factors associated with infection caused by ESBL-producing GNB.

## ACKNOWLEDGEMENTS

The authors would like to thank Mr Suthipol Udompunthurak for his statistical analysis and The Thailand Research Fund for supporting the study. Dr Visanu Thamlikitkul is a recipient of the Senior Researcher Scholarship of the Thailand Research Fund.

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# Health Knowledge Management

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Health research findings should be appropriately utilized and ultimately have impact on policy, practice and patients' outcomes. The key messages from the 2004 *World Report on Knowledge for Better Health* are biomedical discoveries cannot improve people's health without research to find out how to apply them specifically within different health systems, population groups, and diverse political and social contexts; and, a stronger emphasis should be placed on translating the knowledge into actions to improve health thereby bridging the gap between what is known and what is actually being done.[1] Knowledge translation has been a concern and the strategies for bridging the gap between practice and evidence were proposed.[2-5] In this respect, knowledge management has become an important strategy to ensure that knowledge produced by the health research system will be used to improve health.

The author has received a funding support from the Thailand Research Fund for the project entitled "Health Knowledge Management to Promote Evidence-Based Health Policy & Practice," since 2001. Over the past five years, the author has gained experiences on health knowledge management. This article is intended to illustrate the concept and the framework of knowledge management the author accomplished from organizing the aforementioned project.

Health knowledge management is an active and systematic process of utilizing the existing knowledge to generate or enhance quality, efficiency, and equity in health care through evidence-based health policy and practice. Knowledge is practically classified into three main categories as depicted for "Knowledge Iceberg" in Fig 1. The tip of the iceberg above the water level is explicit knowledge; the parts of the iceberg beneath the water are tacit knowledge and undocumented knowledge or nature or truth, which has an endless base. Only a very small amount of the explicit knowledge and the tacit knowledge have been utilized. Therefore, the strategies of health knowledge management are:- 1) to translate the explicit knowledge and the tacit knowledge to policy and practice; 2) to transform the tacit knowledge to the explicit knowledge; and 3) to discover undocumented knowledge or nature or truth. The steps of knowledge management are: knowledge identification, knowledge validation, knowledge synthesis, knowledge translation, knowledge generation, and knowledge sharing. The important steps are knowledge translation and knowledge generation. Knowledge translation is an application of knowledge within a complex system of interactions among researchers and stakeholders, including users, to accelerate the capture of the benefits of research. Knowledge generation in the context of health knowledge management is the organization of research for which the hypothesis and study design are developed specifically to answer the questions faced by decision makers and health practitioners. This kind of knowledge generation is called practical or pragmatic research or user-driven or policy-driven research.[6]

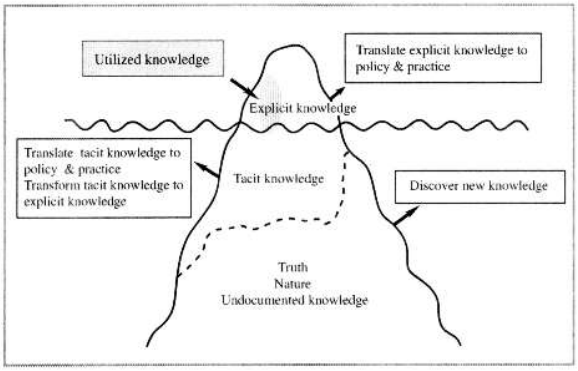


Fig 1. Knowledge iceberg and knowledge management strategies

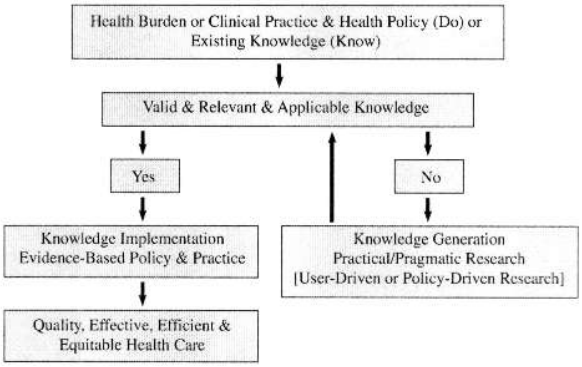


Fig 2. Framework of health knowledge management

An overall framework of health knowledge management is shown in Fig 2. The starting point could be a health burden or a current policy or practice or an existing knowledge. If it is a health burden or a current policy or practice, the relevant information are identified and retrieved. Then the existing knowledge or the retrieved information is assessed for its validity, relevancy and applicability. If the existing knowledge is valid, relevant and applicable, knowledge implementation should be attempted through evidence-based health policy and practice in order to achieve healthcare service which is effective, efficient and equitable. On the other hand, if the existing knowledge is invalid or not relevant or not applicable, a user-driven or policy-driven research should be carried out in order to achieve valid, relevant and applicable knowledge before implementing it.

The main contributing factors for the presence of the gap between knowledge and action for health are:-1) most researchers have not been systematically involved in the implementation of their own findings; 2) policy makers, practitioners and consumers may not be well equipped to implement research findings into policy and decision making. Therefore, a "convenor" or "knowledge manager" or "knowledge broker," whose job is to translate research findings into an accessible form that can be used by policy-makers and others and who can, if necessary, organize policy-driven or user-driven research becomes vital. The responsible institutions should invest more resources in promoting professional communicators or intermediaries in order to narrow the gap between what we have the knowledge to do and what is actually done as well as on developing a culture where decisions taken by policy-makers, health professionals and the public are based on evidence.

Dr. Visanu Thamlikitkul is a senior researcher who received a grant from the Thailand Research Fund.

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International Journal for Quality in Health Care 2006; Volume 18, Number 3: pp. 183–185 10.1093/intqhc/mzi107

## Quality in Practice

# Switching from heparinized saline flush to normal saline flush for maintaining peripheral venous catheter patency

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## Abstract

**Background.** The practice of using heparinized saline as a flush fluid for maintaining peripheral venous catheter patency of hospitalized patients in Siriraj Hospital in Bangkok, Thailand is not evidence-based.

**Objective.** To switch from heparinized saline flush to normal saline flush for maintaining peripheral venous catheter patency in the patients hospitalized to medical wards.

**Methods.** Study sites were 10 medical wards containing 240 beds. The interventions included (i) disseminating evidence-based clinical practice policy on using flush fluid for maintaining peripheral venous catheter patency to responsible personnel, (ii) reminding the prescribers on using normal saline flush instead of heparinized saline flush, (iii) providing technical advice on using normal saline flush to nurses who encountered peripheral venous catheter clot while using normal saline flush, (iv) confirming a necessity of heparinized saline flush order with the prescriber, and (v) setting up a regulation on marking a special symbol on heparinized saline flush prescription if one really needed heparinized saline flush. The information on using flush fluids was collected from the physicians' order sheets in the medical records at baseline, every 2–4 weeks during the intervention periods, and at 6 months after launching intervention.

**Results.** All hospitalized patients in medical wards who had peripheral venous catheter locks received heparinized saline flush in February 2005. The practice was totally switched to normal saline flush in June and November 2005.

**Conclusion.** The key features critical to success of this implementation are dissemination of evidence-based clinical practice policy and a regulation of having prescriber mark a specific sign right after the heparinized saline flush order.

**Keywords:** heparinized saline flush, normal saline flush, peripheral venous catheter patency

Siriraj Hospital is a tertiary care university hospital in Bangkok, Thailand. The capacity of the hospital is 2300 beds; 2200 beds in 111 general wards and 135 beds in 10 intensive care units. The total number of personnel is approximately 10 000, in which 1300 are physicians (700 faculty and 600 residents) and 4200 are nurses. There are approximately 1 000 000 outpatient visits and 100 000 in-patients per year. Up to 75% of the patients admitted to Siriraj Hospital require a peripheral intravenous catheter to provide access for administration of drugs and fluids. Maintenance of the patency of indwelling peripheral intravenous catheters could be done by continuous drip of the fluid via the catheter or connecting the catheter with a device called intravenous catheter lock. The intravenous catheter lock has advantage for the patient to move around without carrying the fluid bottle. However, indwelling peripheral intravenous catheter lock requires a periodical flush with fluid to prevent a clot. The work instruction regarding the use of flush fluid for maintaining peripheral venous catheter patency was prepared in 2001 and was revised in 2003. Both versions of the work instruction recommended heparinized saline as a flush fluid. A survey on the use of the fluids for flushing peripheral venous catheter locks was conducted on 7 September 2004. There were 2021 hospitalized patients on that day. Three hundred and thirty-five patients (16.6%) received peripheral venous catheter locks; 88.7% of them received heparinized saline as a flush fluid, whereas 11.3% received normal saline. In addition to several known disadvantages of using heparin for flushing peripheral venous catheter locks, e.g. bleeding, abnormal coagulation test results, thrombocytopenia, and drug interaction, the cost of heparin used for this purpose was estimated to be 2.4 million baht (US$60 000) per year. The evidence from three meta-analyses found no

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significant difference in the incidence of catheter clotting and phlebitis between peripheral venous catheters flushed with normal saline and those flushed with 10 or 50 units per milliliter of heparinized saline [1–3]. Therefore the use of heparinized saline as a flush fluid for peripheral venous catheter lock in Siriraj Hospital is not evidence-based and this practice should be corrected. Normal saline should replace heparinized saline for maintaining peripheral venous catheter patency in more than 95% of hospitalized patients with peripheral venous catheter locks. We are certain that the existing evidence to be used for forming change strategies is valid, relevant, and applicable to our situation for several reasons. In addition to the aforementioned meta-analyses, two randomized controlled studies conducted by the nurses in Siriraj Hospital and Ramathibodi Hospital in Bangkok also observed similar findings as reported in the meta-analyses [4,5]. Many hospitals in Thailand use normal saline as a flush fluid for peripheral venous catheter locks. Moreover, three patient-care areas in Siriraj Hospital have used normal saline flush for maintaining peripheral venous catheter patency for many years without any problems.

The objective of the study was to change an opinion-based health service to an evidence-based health service on the use of fluid flush for maintaining peripheral venous catheter patency for patients hospitalized to medical wards in Siriraj Hospital.

## Methods and resul.ts

Study sites were 10 medical wards containing 240 beds. The information on using flush fluids was collected from the physicians' order sheets in the medical records of all hospitalized patients with peripheral venous catheter locks in medical wards by the author (AI). The author (AI) also interviewed the nurses responsible for caring for peripheral venous catheter locks. The baseline information gathered on 18 February and 25 February 2005 revealed that all of the patients with peripheral venous catheter locks received heparinized saline flush, as summarized in Table 1. Evidence-based clinical practice policy on maintaining peripheral venous catheter patency with normal saline flush was prepared. It was one-page document containing a significance of the guideline, the evidence, the recommendation, and the grade of recommendation and references. The evidence-based clinical practice policy was disseminated to medical residents and nurses stationed in all medical wards in March 2005. The information on flush fluid use gathered on 25 April and 4 May 2005 found that heparinized saline flush was used in about one-third of the patients as summarized in Table 1. The main reasons for using heparinized saline are as follows: (i) heparinized saline flush was ordered by the final year medical students who were not aware of the clinical practice policy; (ii) some residents still ordered heparinized saline flush because they were so familiar with this prescription that they thought this device was called 'heparin lock' even though they did not originally intend to use heparin; and (iii) some nurses in some wards felt that the peripheral venous catheters clotted more often when they used normal saline flush so they returned to use heparinized saline flush. Hence, additional measures were employed on 12 May 2005. The author (VT) distributed the clinical practice policy to the final year medical students. The medical residents were reminded to adhere to normal saline flush instead of heparinized saline flush. The author (VT) asked the chief nurse to convince the nurses who complained of experiencing clot more often that this was due to the technique of flushing peripheral venous catheter lock and to inform them the appropriate technique. The information on using flush fluids gathered on 18 May 2005 found that heparinized saline flush was used in about one-fourth of the patients as summarized in Table 1. The main reasons for using heparinized saline flush are as follows: (i) heparin was ordered by a new batch of final year medical students who were not aware of the clinical practice policy; (ii) some residents still ordered heparinized saline flush because they were so familiar with this prescription and they thought that this device was called 'heparin lock' even though they did not originally intend to use heparin; and (iii) some nurses in some wards felt that the catheters clotted more often when they used normal saline flush. Hence, more additional measures were employed on 26 May 2005. The author (VT) called on the meeting with the nurses from all medical wards. During the meeting, the evidence and the advantages of using normal saline flush were reemphasized. The nurses from patient-care areas who had used normal saline flush for many years were invited to join the meeting, and they shared their experiences of using normal saline flush with the nurses from medical wards. It was agreed that if any nurse received an order of heparinized saline flush from the in-charge physician, she would ask the prescriber if he/she really needed heparin. The author (VT) also circulated the clinical practice policy to the new batch of the final year medical students rotating to medical wards. It was decided that it would be difficult and time consuming for monitoring and circulating the clinical practice policy to the responsible personnel and reminding the prescribers. Therefore a regulation on marking a specific sign right after the order of heparinized saline flush was set. If the

**Table 1** The use of flush fluids for maintaining peripheral venous catheter patency of hospitalized patients in medical wards

| Date | Patients who received heparinized saline flushes, *n* (%) | Patients who received normal saline flushes, *n* (%) |
|---|---|---|
| 18 February 2005 | 90 (100) | 0 |
| 25 February 2005 | 64 (100) | 0 |
| 25 April 2005 | 23 (34.3) | 44 (65.7) |
| 4 May 2005 | 23 (32.9) | 47 (67.1) |
| 18 May 2005 | 21 (23.3) | 69 (76.7) |
| 6 June 2005 | 1 (1.6) | 61 (98.4) |
| 20 June 2005 | 0 | 56 (100) |
| 30 June 2005 | 0 | 66 (100) |
| 30 November 2005 | 0 | 105 (100) |

prescriber really wanted to use heparinized saline flush, one must write '*' right after the order, otherwise the nurse would use normal saline flush even if the order read heparinized saline flush without '*'. This regulation was notified to medical residents, final year medical students rotating to medical wards, and the responsible nurses. The information on flush fluids use gathered on 6 June, 20 June and 30 June, and 30 November 2005 found that normal saline flush totally replaced heparinized saline flush as summarized in the Table 1.

## Discussion

Health research findings should be appropriately utilized and ultimately have impact on policy, practice, and patients' outcomes. The key messages from the 2004 *World Report on Knowledge for better Health* are (i) biomedical discoveries cannot improve people's health without the study to find out how to apply them specifically within different health systems, population groups, and diverse political and social contexts; (ii) and stronger emphasis should be placed on translating knowledge into actions to improve health thereby bridging the gap between what is known, and what is actually being done [6]. Knowledge translation has been a concern, and the strategies for closing the gap between practice and evidence were proposed [7–9]. The interventions we used to switch from heparinized saline flush to normal saline flush for maintaining peripheral venous catheter patency included educational interventions and administrative interventions. We believed that the key features critical to success of this implementation were dissemination of evidence-based clinical practice policy and a regulation of having prescriber mark '*' right after the heparinized saline flush order. Our successful knowledge translation confirms the observation that getting research findings to practice needs multifaceted interventions. In addition to promoting an evidence-based health service by switching from heparinized saline flush to normal saline flush for maintaining peripheral venous catheter patency in our institution, this change also has an impact on enormous saving resources of the patients, the hospital, and the responsible people.

It is hoped that the aforementioned case study would encourage responsible health care institutions to pay more attention on narrowing the gap between the knowledge which we have and what is actually done as well as on developing a culture where decisions taken by policy-makers, health professionals, and the public are based on evidence.

## Acknowledgements

The authors thank The Thailand Research Fund for supporting the study.

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**Accepted for publication 3 February 2006**

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2006, p. 1555–1557 Vol. 50, No. 4
0066-4804/06/$08.00+0 doi:10.1128/AAC.50.4.1555–1557.2006


# In Vitro Activity of Tigecycline against *Burkholderia pseudomallei* and *Burkholderia thailandensis*

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Received 23 August 2005/Returned for modification 31 October 2005/Accepted 10 January 2006

**Investigation of the in vitro activity of tigecycline against *Burkholderia pseudomallei* and *Burkholderia thailandensis* revealed that the inhibition zone diameters of tigecycline against all isolates were ≥20 mm and that the $MIC_{50}$ values were 0.5 and 1 μg/ml and the $MIC_{90}$ values were 2 and 1.5 μg/ml for *B. pseudomallei* and *B. thailandensis*, respectively.**

*Burkholderia pseudomallei*, a gram-negative bacterium, causes in humans and animals a disease called melioidosis (22). The bacterium is a soil organism found mainly in Southeast Asia and northern Australia. Recently, two distinct biotypes of *B. pseudomallei* strains have been defined based on their ability to assimilate L-arabinose and their difference in pathogenicity (2, 7, 17, 23). Both biotypes have been found in soil of areas where melioidosis is endemic in Thailand (20, 21). The $Ara^+$ *B. pseudomallei* is much less virulent than $Ara^-$ *B. pseudomallei* (2, 17). However, $Ara^+$ *B. pseudomallei* has been reported to cause disease in humans (11). Subsequently, a distinct new species, *Burkholderia thailandensis*, was proposed for the $Ara^+$ *B. pseudomallei* strain (3). *B. pseudomallei* is usually resistant to many antibiotics. Antibiotics currently recommended for therapy of melioidosis are ceftazidime, imipenem, meropenem, amoxicillin/clavulanate, cefoperazone/sulbactam, trimethoprim-sulfamethoxazole, doxycycline, and chloramphenicol (22). The development of resistance of *B. pseudomallei* to these antibiotics was recognized (6, 8, 19, 24), and hence a search for new agents effective against *B. pseudomallei* is needed.

Tigecycline is a glycylcycline antibiotic that shows promising activity against a wide range of organisms (25). Tigecycline is active against gram-positive cocci, including methicillin-resistant staphylococci, penicillin-resistant *Streptococcus pneumoniae*, and vancomycin-resistant enterococci. Tigecycline is also active against many gram-negative bacilli, including those resistant to multiple antibiotics as well as anaerobes. However, the activity of tigecycline against *B. pseudomallei* has not been reported. The present study was undertaken to explore the activity of tigecycline against *B. pseudomallei* and *B. thailandensis*.

One hundred twenty-six strains of *B. pseudomallei* and *B. thailandensis* were selected from our collection. One hundred two strains of *B. pseudomallei* were isolated from different infected patients, and 24 strains of *B. thailandensis* were isolated from 23 soil samples collected from different sites and from one infected patient. All *Burkholderia* species were identified with the API 20NE (bioMerieux, France). *B. pseudomallei* and *B. thailandensis* were differentiated by the arabinose assimilation test (20). In vitro susceptibilities were determined by Kirby-Bauer disk diffusion, Etest, and MicroScan. Paper disks containing tigecycline at 15 μg per disk (Becton Dickinson), Etest strips (AB Biodisk), and gram-negative MicroScan MIC panels (Dade Behring Inc.) were provided by Wyeth Research. Susceptibility testing was done by direct colony suspension according to guidelines suggested by CLSI (4). Quality control was performed by testing the susceptibility of *Escherichia coli* ATCC 25922 as recommended by Wyeth Research.

The distribution of inhibition zone diameters of tigecycline against *B. pseudomallei* and *B. thailandensis* is shown in Table 1. All strains had an inhibition zone diameter of ≥20 mm. The $MIC_{50}$ and $MIC_{90}$ values of tigecycline as determined by Etest are shown in Table 2. The $MIC_{50}$ values were 0.5 and 1 μg/ml for *B. pseudomallei* and *B. thailandensis*, respectively. The $MIC_{90}$ values were 2 and 1.5 μg/ml for *B. pseudomallei* and *B. thailandensis*, respectively. There was a significant correlation between inhibition zone diameters and MICs from Etest ($P < 0.001$; $r = -0.68$). The mean inhibition zone diameters of the strains with MIC of 3, 2, 1.5, 1. 0.75, and 0.5 μg/ml were 20, 21.8, 22.6, 23.5. 24.4, and 26.7 mm, respectively. The correlation of MICs determined by Etest and MicroScan was satisfactory, as shown in Table 3. Thirty-two strains (50%) had identical MICs determined by Etest and MicroScan, whereas another 50% had a difference in MICs of 0.25 to 0.5 μg/ml.

The MICs of tigecycline for *B. pseudomallei* and *B. thailandensis* observed in our study were higher than those for *S. pneumoniae*, *Staphylococcus aureus*, *Enterococcus* spp., and non-ESBL-producing *Enterobacteriaceae* (1). However, they were comparable to the MICs of tigecycline for *Acinetobacter* spp., *Enterobacter aerogenes*, and ESBL-producing *Klebsiella pneumoniae* (1). The breakpoints for inhibition zone diameter and MIC of tigecycline against *B. pseudomallei* and *B. thailandensis* are not available. The breakpoint of doxycycline against *B. pseudomallei*, adapted from data compiled by the National Committee for Clinical Laboratory Standards for similar organisms to be used for susceptibility testing, was 4 μg/ml (15). The U.S. FDA-approved breakpoints of tigecycline against *Enterobacteriaceae* to be used by local laboratories were an inhibition zone diameter of ≥19 mm and a MIC of ≤2 μg/ml (4). With the aforementioned breakpoints used to determine susceptibility of *Burkholderia* spp. to tigecycline, all isolates of *B. pseudomallei* and *B. thailandensis* were susceptible to tige-

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TABLE 1. Distribution of tigecycline susceptibility as determined by disk diffusion for *B. pseudomallei* and *B. thailandensis*

| Organism (no. of isolates) | No. (%) of isolates for which the inhibition zone diameter (mm) was: | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 30 |
| *B. pseudomallei* (102) | 12 (11.8) | 16 (15.7) | 26 (25.5) | 21 (20.6) | 2 (2) | 24 (23.5) | | | | 1 (1) |
| *B. thailandensis* (24) | | 1 (4.2) | 3 (12.5) | 5 (20.8) | | 13 (54.2) | 1 (4.2) | | | 1 (4.2) |

cycline according to the inhibition zone diameter criteria and 98% of *B. pseudomallei* isolates and all *B. thailandensis* isolates were susceptible to tigecycline according to the MIC criteria. The MICs determined by Etest were significantly correlated with the inhibition zone diameters and the MICs determined by MicroScan. Therefore, disk diffusion and Etest methods are reliable for determination of susceptibility of tigecycline against *B. pseudomallei* and *B. thailandensis*.

Pharmacokinetic and pharmacodynamic studies of tigecycline in healthy subjects after a 100-mg loading dose given intravenously followed by 50 mg every 12 h have been reported (5, 12–14, 18). The mean maximum concentration ($C_{max}$), the mean time to maximum concentration, the mean minimum concentration ($C_{min}$), the mean area under the curve, and the mean half-life of tigecycline in serum were 0.72 μg/ml, 0.52 h, 0.1 μg/ml, 1.73 μg · h/ml, and 15 h, respectively. These profiles were favorable for many organisms, such as *S. pneumoniae*, *Chlamydia pneumoniae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, and *Haemophilus influenzae*, since the $MIC_{90}$ values of tigecycline for such organisms were very low. The mean $C_{max}$ of tigecycline in serum (0.72 μg/ml) after the conventional dose of tigecycline (100-mg loading dose followed by 50 mg every 12 h) was above the MICs of tigecycline for only 6% of *B. pseudomallei* and *B. thailandensis* isolates. However, it was found that tigecycline had a large volume of distribution (7 to 10 liters/kg), indicating extensive distribution into the tissues (13). In addition, the mean $C_{max}$, the mean time to maximum concentration, the mean $C_{min}$, the mean area under the curve, and the mean half-life of tigecycline in the alveolar cells were 15.2 μg/ml, 2 h, 6.4 μg/ml, 134 μg · h/ml, and 23.7 h, respectively (5). These observations imply that tigecycline accumulates in the cells and could be effective for infections caused by intracellular organisms. The mean $C_{max}$ and the mean $C_{min}$ of tigecycline in the alveolar cells were much higher than the MICs for all isolates of *B. pseudomallei* and *B. thailandensis*. Therefore, tigecycline should be a suitable antibiotic for therapy of melioidosis, since *B. pseudomallei* is an intracellular bacterium (9, 10, 16). This hypothesis needs further investigation by conducting clinical trials on therapy of melioidosis with tigecycline.

TABLE 2. MICs of tigecycline for *B. pseudomallei* and *B. thailandensis* as determined by Etest

| Organism (no. of isolates) | MIC (μg/ml) | | |
|---|---|---|---|
| | Range | For 50% of isolates | For 90% of isolates |
| *B. pseudomallei* (102) | 0.5–3 | 0.5 | 2 |
| *B. thailandensis* (24) | 0.5–1.5 | 1 | 1.5 |

TABLE 3. Correlation between MICs determined by Etest and MicroScan

| MIC (μg/ml) determined by MicroScan | No. of strains with the following MIC (μg/ml) determined by Etest: | | | | |
|---|---|---|---|---|---|
| | 0.50 | 0.75 | 1.00 | 1.50 | 2.00 |
| 0.50 | 1 | 1 | 1 | | |
| 0.75 | | | | | |
| 1.00 | 1 | 2 | 22 | 24 | |
| 1.50 | | | | | |
| 2.00 | | | | 3 | 9 |

We thank Wyeth Research for providing tigecycline susceptibility disks, Etest strips, and gram-negative MicroScan tests.

We thank the Thailand Research Fund for supporting the study.

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# Bridging the gap between knowledge and action for health: case studies

Visanu Thamlikitkul[a]

**Abstract** Biomedical discoveries could improve people's health only if they are suited to the diverse political and social contexts, health systems and population groups. Knowledge generated through evidence-informed health policy and practice when applied to the local situation enhances the quality and efficiency of health care. This article describes four case studies on bridging the gap between knowledge and action for health in a tertiary care hospital in Bangkok, Thailand. Gaps between knowledge and action for health are classified into "know–do" and "do–know" gaps with knowledge implementation and knowledge generation being the key measures for bridging the gap.

Bulletin of the World Health Organization 2006;84:603-607.

*Voir page 606 le résumé en français. En la página 606 figura un resumen en español.*

يمكن الاطلاع على الملخص بالعربية في صفحة 606.

## Introduction

Health research findings impact policy, practice and patient outcomes if they are appropriately translated into healthcare practice. The 2004 *World report on knowledge for better health* stated that biomedical discoveries could improve people's health only if they are applied specifically to diverse political and social contexts, health systems and population groups. The report laid a strong emphasis on translating knowledge into action to improve health thereby bridging the gap between what is known and what is actually done.[1] Knowledge translation has been a cause for concern and strategies for bridging the gap between practice and evidence have been proposed.[2–5]

I describe four case studies chosen to illustrate how to bridge the gap between knowledge and action for health according to the framework in Siriraj Hospital, Bangkok where the "Knowledge Management to Promote Evidence-Informed Health Care Policy and Practice in Thailand" project has been conducted since 2001. The concept and the framework for knowledge management was based on my experiences at Siriraj Hospital over the first two years of the project (Fig. 1).[6]

Siriraj Hospital is a tertiary-care university hospital in Bangkok, Thailand with 2335 beds (2200 beds in 111 general wards and 135 beds in 10 intensive care units); approximately 10 000 personnel of which 1300 are physicians (700 faculty members and 600 residents) and 4200 are nurses; with around 1 000 000 outpatient visits and 100 000 inpatients per year.

I have classified the gaps between knowledge and action for health into "know–do" and "do–know" gaps with knowledge implementation and knowledge generation being the key measures for bridging the gap between knowledge and action for health.

## Case Studies

### Knowledge implementation for bridging the "do–know" gap

#### *Heparinized saline flush and peripheral venous catheter patency*

Many hospitalized patients require a peripheral intravenous catheter for the administration of drugs and fluids. The patency of indwelling peripheral intravenous catheters is maintained by a continuous drip of fluid via the catheter or by connecting the catheter to an intravenous catheter lock (IV lock). The IV lock is advantageous as the patient can move around without carrying the fluid bottle. However, an indwelling IV lock has to be periodically flushed with fluid to prevent clots.

The work instruction for the flush procedure in Siriraj Hospital (prepared in 2001 and revised in 2003) recommends using heparinized saline as flush fluid. A September 2004 survey, on the use of fluids for flushing peripheral intravenous catheters, found that the majority of the patients with IV lock received heparinized saline (89%) as flush fluid while the remaining (11%) received normal saline.[7] This occurred despite the known disadvantages of using heparin for flushing IV locks and the high cost of using heparin — an estimated 2.4 million baht (US$ 60 000) per year. Evidence from three meta-analyses found no significant difference in the incidence of catheter clot and phlebitis between peripheral intravenous catheters flushed with normal saline and those flushed with 10 units per ml or 50 units per ml of heparinized saline.[8–10] Results from two randomized controlled studies conducted by nurses at Siriraj Hospital and Ramathibodi Hospital in Bangkok reported findings similar to those from the meta-analyses.[11,12] Therefore, the practice of using heparinized saline as flush fluid for maintaining peripheral intravenous catheter patency of hospitalized patients in Siriraj Hospital was not evidence-based and had to be corrected. Many hospitals in Thailand use normal saline as flush fluid for IV lock and three patient-care areas in Siriraj Hospital have used normal saline flush for maintaining peripheral intravenous catheter patency for many years without any problems.

The knowledge management project at Siriraj introduced five knowledge

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Ref. No. **05-023622**

(*Submitted: 2 May 2005 – Final revised version received: 25 February 2006 – Accepted: 16 March 2006*)

implementation strategies/interventions for switching from heparinized saline flush to normal saline flush in 10 medical wards containing 240 beds.

1. Disseminating evidence-based clinical practice policy on using flush fluid for maintaining peripheral intravenous catheter patency to responsible personnel.
2. Reminding prescribers to use normal saline flush instead of heparinized saline flush.
3. Providing technical advice to nurses on using normal saline flush in the event of peripheral intravenous catheter clot.
4. Confirming the necessity of using heparinized saline flush with the prescriber.
5. Setting up a regulation that if the prescriber really wanted to use heparinized saline flush: an asterix should be placed next to the prescription otherwise the nurse would use normal saline flush. This regulation was added because many prescribers called the IV lock "heparin lock" and prescribed "heparin lock" even though they did not intend to use heparin.

The information on using flush fluids was collected from physicians' order sheets in the medical records at baseline in February 2005, and then every two to four weeks during the intervention period up to June 2005 and six months after implementing the interventions. All hospitalized patients in medical wards who had IV locks received heparinized saline flush at baseline. After knowledge interventions 1–4 were applied, from March to May 2005, in 75% of the patients with IV locks flush fluid was switched to normal saline. Normal saline flush completely replaced the practice of using heparinized saline flush after the inclusion of administrative intervention 5 from June to November 2005. The hospital administrator subsequently adopted these strategies as a policy for the entire hospital in January 2006. In addition to the publication of this observation[7] and its policy implications, this knowledge implementation resulted in enormous savings in terms of resources for the patients and the hospital.

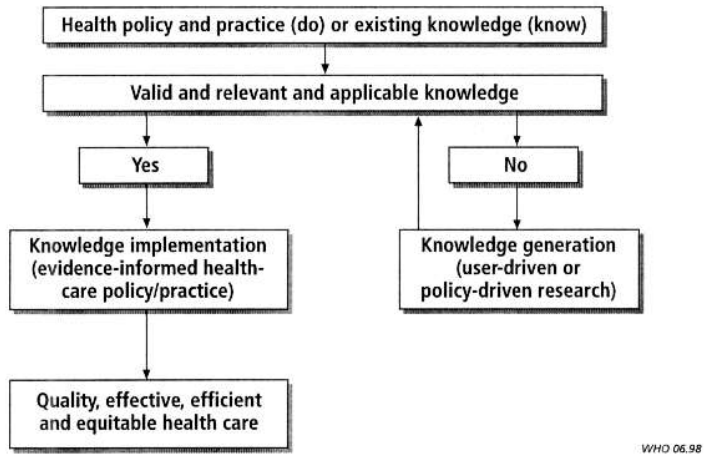
## Knowledge generation for bridging the "do–know" gap: *Urinary drainage bag change regimen*

Urinary tract infection (UTI) is a common complication among patients with an indwelling urethral catheter. Each change of the urinary drainage bag predisposes the patient to developing UTI, and increases personnel time, expense and plastic waste. During the preparation meeting for Siriraj Hospital's accreditation in August 2001, there was a conflict between the nurse practitioners and the infection control committee regarding the frequency of urine bag changes for patients with short-term urinary catheter. The nurses' guideline recommended a urine bag change every three days but the infection control committee said it should not be changed on such a routine basis.

A review of the literature showed only one relevant study that compared urine bag changing regimens in 12 elderly long-term urinary catheterized patients.[13] The study found no significant clinical or microbiological differences between patients who had a daily urine bag change and those who had a weekly bag change. This study, however, was not applicable to Siriraj Hospital because it was conducted on long-term catheterized elderly patients. A guideline for preventing infections associated with the insertion and maintenance of short-term indwelling urethral catheters in acute care recommended that urinary drainage bags should be changed when clinically indicated, without any supporting evidence.[14] In this respect, neither the nurses' guideline nor the infection control committee's recommendation were based on valid evidence.

A randomized controlled trial on the incidence of UTI, among hospitalized patients with short-term indwelling urethral catheters, which compared a three-day urinary drainage bag change to a no-change found no significant difference in the incidence of UTI between the two groups.[15] This result was adopted as a policy endorsed by the Dean of Faculty of Medicine, Siriraj Hospital for the entire hospital from February 2002 and disseminated to infection control nurses during the national workshop on prevention and control of nosocomial infections in July 2002. In addition to a publication[15] and policy implications, it saved on costs, personnel time and plastic waste.

Fig. 1. **Framework for bridging the gap between knowledge and action for health**




## Knowledge implementation for bridging the "know–do" gap *Semi-recumbent positioning to prevent ventilator/associated pneumonia*

Pneumonia is a common complication among patients on a respirator, causing high mortality and morbidity. While there is evidence that the supine position is a risk factor for ventilator-associated pneumonia (VAP),[16–18] a clinical study revealed that the semi-recumbent position prevented VAP with a relative risk reduction of 76% (95% confidence interval (CI): 27–93%) and number-needed-to-treat (NNT) of four.[19] An evidence-based clinical practice guideline recommends the semi-recumbent position as an intervention to prevent VAP.[20] These findings were valid, relevant and applicable to the

patients in Siriraj Hospital. A survey of the body position of patients on respirators in 14 medical wards of Siriraj Hospital during February–March 2003 showed that only 17% of the patients were in semi-recumbent position. A total of 27% of the residents and nurses in 14 medical wards recommended the semi-recumbent position for patients on respirators. However, the reasons for this response were not based on evidence for pneumonia prevention from the literature but mainly physiological, such as better lung expansion, better oxygenation and decreased intra-thoracic pressure.

The knowledge management project at Siriraj developed and executed strategies for knowledge implementation in the target populations — residents and nurses. These were:

1. informing the target population about the evidence during a quality improvement conference meeting in July 2003;
2. disseminating a one-page clinical practice policy in Thai containing information on the significance of the problem, the evidence, recommendation, grade of recommendation, contraindications for and warnings about the semi-recumbent position and the relevant references;
3. creating awareness among health-care personnel by placing a specific sign at the patient's bed. The front side of the sign would read, "This patient should be placed in a semi-recumbent position", while the back of the sign contained "indications, contraindications and warnings about the semi-recumbent position".

Because this was a no-cost simple intervention, a compliance rate greater than 90% was expected. However, a survey in July–August 2003, after the implementation of the aforementioned strategies, revealed that only 41% of patients on respirators in the 14 medical wards were placed in the semi-recumbent position, significantly higher than 17% at baseline ($P$ <0.005), but the compliance was considered unsatisfactory. Therefore, additional strategies, such as feedback of observations to nurses, a reminder system and increasing awareness were implemented. Repeat surveys during November–December 2003 and March–April 2004 revealed that 56% and 76% of the patients on respirators in 14 medical wards, respectively, were placed in the semi-recumbent position. A survey of 739 adult patients on respirators in all intensive care units during October and December 2003 revealed that 68% of them were placed in a semi-recumbent position. The incidence of VAP per 1000 ventilation days decreased from 11.3 during January–December 2002 to 9.2 and 9.4 during October–December 2003 and January–June 2004, respectively. This decrease was not large because compliance with the semi-recumbent position was still modest. The lessons learned from these attempts showed that knowledge translation strategies are not easy even for implementing a simple and free intervention.

### Knowledge generation for bridging the "know–do" gap

#### *Antibiotic prophylaxis for preventing infection in cancer patients*

The majority of patients who receive chemotherapy for the treatment of cancer develop neutropenia and thus are susceptible to bacterial infections. Bacterial flora in the oral cavity and gut of chemotherapy-induced neutropenic patients themselves cause these infections. Reports from two meta-analyses, which determined the efficacy of oral prophylactic antibiotics in afebrile neutropenic patients due to cancer chemotherapy, showed that oral prophylactic antibiotics, fluoroquinolones and cotrimoxazole, decreased bacteraemia and infection-related mortality due to bacterial causes during neutropenic episodes.[21,22] Although, evidence from these meta-analyses was valid and relevant to Thai patients, the issue of applicability was a concern. Most of the primary studies included in the meta-analyses were conducted in developed countries, where antibiotics are not available without prescription. In Thailand, however, antibiotics can be purchased without prescription, and fluoroquinolones and cotrimoxazole are commonly given to patients with acute diarrhoea and upper respiratory infections. Fluoroquinolones are also used as a growth stimulator in the shrimp industry in Thailand, and thus commonly available. Moreover, it is not known if bacterial flora in the oral cavity and gut of Thai patients who have cancer chemotherapy-induced neutropenia are susceptible to fluoroquinolones and cotrimoxazole, and whether they should receive such antibiotics.

This situation led the way for knowledge generation on the susceptibility of bacteria isolated from the oral cavity and gut of Thai patients with cancer chemotherapy-induced neutropenia. A study to determine the susceptibility of bacteria colonized in the oral cavity and/or gut of 140 Thai patients with cancer chemotherapy-induced neutropenia to oral antibiotics available in Thailand is currently being conducted. Preliminary results suggest that bacterial flora isolated from some patients are resistant to many oral antibiotics. By the end of 2006 it will be confirmed whether oral antibiotics would be beneficial for Thai patients before knowledge implementation of "to use" or "not to use" oral prophylactic antibiotics in Thai patients with cancer chemotherapy-induced neutropenia takes place.

## Conclusions and recommendations

The gap between what we know and what we practice, i.e. the know–do gap, is mentioned in the literature, and translating research findings into practice by knowledge implementation has been attempted. The case studies described in this article found that another category of gap — the do–know gap, i.e. the gap between what we practice and what we know, is also common in health-care systems in developing countries. Knowledge generation is also an important measure to bridge the gap between knowledge and action for health and it is hoped that the above-mentioned case studies will encourage responsible institutions in developing countries to invest more resources in promoting professional communicators or intermediaries to narrow the gap as well as develop a culture where decisions taken by policy-makers, health professionals and the public are based on evidence. ■

### Acknowledgements

I thank the Thailand Research Fund, the International Clinical Epidemiology Network (INCLEN) Trust and the Faculty of Medicine Siriraj Hospital for supporting the activities and research mentioned in this article. I also thank Mary Ann Lansang and Somsak Chunharas for reviewing the manuscript and providing valuable comments and suggestions.

**Funding:** The author received grant for the work as a Senior Researcher Scholar of the Thailand Research Fund.

**Competing interests:** none declared.

## Résumé

### Combler le fossé entre savoir et action en faveur de la santé : études de cas

Les découvertes dans le domaine biomédical ne peuvent déboucher sur des améliorations en matière de santé publique que si elles sont adaptées aux divers contextes politiques et sociaux, systèmes de santé et groupes de population. Les connaissances acquises à travers l'application à la situation locale de politiques et de pratiques sanitaires s'inspirant d'éléments factuels permettent d'améliorer la qualité et l'efficacité des soins de santé prodigués. L'article présente quatre études de cas examinant comment établir un pont entre les connaissances et les interventions en faveur de la santé dans un hôpital dispensant des soins tertiaire de Bangkok en Thaïlande. Les ponts à établir entre connaissances et interventions sanitaires sont répartis en deux catégories, «savoir-faire» et «faire-savoir», la mise en œuvre des connaissances et la génération de données étant des mesures clés pour créer de tels liens.

## Resumen

### Cerrar la brecha entre los conocimientos y la acción sanitaria: estudios de casos

Los descubrimientos biomédicos sólo redundan en mejoras de la salud de las personas cuando están adaptados a los diversos contextos políticos y sociales, sistemas de salud y grupos de población. Los conocimientos que generan las políticas y prácticas sanitarias basadas en la evidencia cuando se aplican a la situación local fomentan la calidad y eficiencia de la atención sanitaria. En este artículo se describen cuatro estudios de casos sobre la manera de corregir la brecha existente entre los conocimientos y la acción sanitaria en un hospital de atención terciaria de Bangkok, Tailandia. Las brechas teórico-prácticas en materia de salud son de dos tipos: «conocimientos-acción» y «acción-conocimientos», y las soluciones para corregirlas radican en la aplicación de conocimientos y la generación de conocimientos, respectivamente.

## ملخص

### رأب الفجوة بين المعارف والعمل من أجل الصحة: دراسة حالات

لا يمكن للمكتشفات الطبية والبيولوجية أن تحسِّن من حياة الناس ما لم تكن متناسبة مع السياق السياسي والاجتماعي ومع النظم الصحية ومع المجموعات السكانية. وتتولَّد المعارف من خلال السياسات والممارسات الصحية المسندة بالبيِّنات، وإثر تطبيقها على الوضع المحلي فإنها ستعزِّز الجودة والفعالية في الرعاية الصحية. ويصف هذا المقال أربع دراسات للحالات حول رأب الفجوة بين المعارف والعمل من أجل الصحة في إحدى مستشفيات الرعاية الثالثية في بانكوك في تايلاند. فالفجوات بين المعارف والعمل من أجل الصحة تصنَّف إلى فجوات المعرفة للعمل وفجوات العمل للمعرفة، ويبقى كل من تنفيذ المعارف وتوليدها الوسيلتين الأكثر أهمية في رأب هذه الفجوة.

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Original Article

# In Vitro Activity of Tigecycline Against Methicillin-Resistant *Staphylococcus aureus* Isolated from the Patients at Siriraj Hospital

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**ABSTRACT**

An in vitro activity study of tigecycline against 51 clinical isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) from different patients hospitalized at Siriraj Hospital, Bangkok, Thailand from 2002 to 2004 was performed by the disk diffusion method and E-test. All isolates had an inhibition zone of ≥ 20 mm, with the $MIC_{50}$ and $MIC_{90}$ of 0.125 and 0.25 mg/L, respectively. The study results indicated that all MRSA isolates tested were susceptible to tigecycline. (*J Infect Dis Antimicrob Agents 2006; 23:1-4.*)

## INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most common causes of infections in hospitalized patients. The prevalence of MRSA among *S. aureus* isolates from hospitalized patients at Siriraj Hospital from January to May 2005 was 51.5 percent.[1] The common sites of MRSA infections were the skin and skin structures, the lower respiratory tracts, and the blood stream. Antibiotics currently used for therapy of MRSA infections include glycopeptides, fluoroquinolones, co-trimoxazole, fosfomicin, fusidic acid, and linezolid. However, these antibiotics had considerable drawbacks including the possibility of toxicity, emergence of resistance, and high monetary cost. Therefore, a search for any new agents effective against MRSA is ongoing.

Tigecycline is a glycylcycline antibiotic that shows a promising activity against a wide range of organisms.[2-4] Tigecycline is active against gram-positive cocci including methicillin-resistant staphylococci, penicillin-resistant *Streptococcus pneumoniae*, and vancomycin-resistant enterococci.

The objective of the study was to determine an in vitro activity of tigecycline against MRSA clinical isolates from Thai patients.

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Received for publication: October 27, 2005.

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**Keywords:** Tigecycline, Methicillin-Resistant *Staphylococcus aureus*

## MATERIALS AND METHODS

### MRSA Isolates

Fifty-one clinical isolates of MRSA from different infected patients hospitalized at Siriraj Hospital, Bangkok, Thailand from 2002 to 2004 were included. They were isolated from the lower respiratory tract (N=15), the pus (N=16), the blood (N=10), and the other specimens (N=10). All isolates had oxacillin minimum inhibitory concentration (MIC) of >4 mg/L and vancomycin MIC of <4 mg/L. Forty-six isolates were vancomycin-susceptible MRSA, and 5 isolates were vancomycin-hetero-resistant MRSA. Vancomycin-susceptible MRSA and vancomycin hetero-resistant MRSA were determined by a one-point population analysis and confirmed by a population analysis.[5,6]

### Tigecycline Susceptibility Study

The methodology for susceptibility testing was done by direct colony suspension according to the guidelines recommended by the Clinical and Laboratory Standards Institute (CLSI).[7] The test isolate was grown overnight on blood agar at 35°C, and the colonies were picked and suspended in sterile normal saline equivalent to a 0.5 McFarland standard. The suspension was used to inoculate on Mueller-Hinton agar. The paper discs containing tigecycline 15 μg per disk (Becton Dickinson, USA) and E-test strips (AB BIODISK, Sweden) were placed according to manufacturer's recommendation. The agar plates were incubated at 35°C for 18 hours before the inhibition zone and MIC results were read. Quality control was performed by testing the susceptibility of *S. aureus* ATCC 29213 as recommended by Wyeth Research, USA.

## RESULTS

The MIC of tigecycline against *S. aureus* ATCC 29213 was 0.064 mg/L which was within the reference range of 0.03-0.25 mg/L. A distribution of inhibition zone diameters of tigecycline against 51 MRSA isolates by the disk diffusion method is shown in Table 1. The inhibition zone of tigecycline against all isolates of MRSA was ≥20 mm. A distribution of MICs of tigecycline against 51 MRSA isolates by the E-test is shown in Table 2. The $MIC_{50}$ and $MIC_{90}$ values were

**Table 1. Distribution of inhibition zone diameter of tigecycline against methicillin-resistant *Staphylococcus aureus* (MRSA).**

| Organism (No. of isolates) | Number of isolates with diameter of inhibition zone (mm) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 30 |
| All MRSA (N=51) | 4 | 7 | 9 | 11 | 2 | 13 | 3 | | 1 | 1 |
| Vancomycin-susceptible MRSA (N=46) | 2 | 7 | 9 | 8 | 2 | 13 | 3 | | 1 | 1 |
| Vancomycin-hetero-resistant MRSA (N=5) | 2 | | | 3 | | | | | | |

**Table 2. Distribution of MICs of tigecycline against MRSA.**

| Organism (No. of isolates) | Number of isolates with MIC (mg/L) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0.032 | 0.064 | 0.094 | 0.125 | 0.19 | 0.25 | 0.5 |
| All MRSA (N=51) | 2 | 6 | 12 | 17 | 7 | 6 | 2 |
| Vancomycin-susceptible MRSA (N=46) | 2 | 6 | 12 | 15 | 5 | 5 | 1 |
| Vancomycin-hetero-resistant MRSA (N=5) | | | | 2 | 2 | 1 | |

0.125 and 0.25 mg/L, respectively. Susceptibility profiles of tigecycline against vancomycin-susceptible MRSA and vancomycin-hetero-resistant MRSA were not significantly different.

## DISCUSSION

According to the US Food and Drug Administration (FDA)-approved breakpoints of the inhibition zone of ≥19 mm and MIC of <0.5 mg/L indicating the susceptibility of *S. aureus* to tigecycline[8], all studied isolates of MRSA in one study were considered susceptible to tigecycline. These observations confirmed the worldwide data on in vitro susceptibility of tigecycline against MRSA.[9-14] Tigecycline was found to be effective and safe for treating patients with complicated intra-abdominal infections and complicated skin and skin-structure infections.[15-19] Tigecycline has been approved by the US FDA for treating patients with the aforementioned infections. However, the existing evidence proving the effectiveness of treating MRSA infections with tigecycline remains limited. Tigecycline may prove to be an important antibiotic for treatment of MRSA infections in Thailand in the near future once more clinical information on use of tigecycline in treating of MRSA infections becomes available.

## ACKNOWLEDGEMENT

The authors thank Wyeth Research for providing tigecycline susceptibility discs and E-test strips and the Thailand Research Fund for supporting the study.

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Original Article

# In Vitro Activity of Colistin and Tigecycline Against Extended-Spectrum-Beta-Lactamase (ESBL)-Producing *Escherichia coli* and *Klebsiella pneumoniae* Isolated from Patients in Siriraj Hospital

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**ABSTRACT**

An in vitro activity study of colistin and tigecycline against extended-spectrum-beta-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae* isolated from the patients hospitalized at Siriraj Hospital from 2004 to 2005 was conducted by the disk diffusion method and E-test. An in vitro activity of colistin revealed that 1) all 100 isolates had an inhibition zone of ≥11 mm, 2) the minimal inhibitory concentration $MIC_{50}$ and $MIC_{90}$ of colistin against 50 isolates of ESBL-producing *E. coli* were 0.5 mg/L and 1 mg/L, respectively, and 3) the $MIC_{50}$ and $MIC_{90}$ of colistin against 50 isolates of ESBL-producing *K. pneumoniae* were 0.5 mg/L and 0.5 mg/L, respectively. An in vitro activity of tigecycline revealed that 1) the $MIC_{50}$ and $MIC_{90}$ of tigecycline against 63 isolates of ESBL-producing *E.coli* were 0.5 mg/L and 1 mg/L, respectively, and 2) the $MIC_{50}$ and $MIC_{90}$ of tigecycline against 42 isolates of ESBL-producing *K. pneumoniae* were 1.5 mg/L and 2 mg/L, respectively. The study results indicated that ESBL-producing *E. coli* and *K. pneumoniae* isolated from the patients in Siriraj Hospital were susceptible to colistin and tigecycline. (*J Infect Dis Antimicrob Agents 2006;23:21-4.*)

## INTRODUCTION

The prevalence of extended-spectrum-beta-lactamase (ESBL)-producing organisms and their antimicrobial resistance patterns may vary between geographic areas. The prevalence of ESBL-producing *E. coli* and *K. pneumoniae* causing infections,

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Received for publication: December 9, 2005.

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**Keywords:** colistin, tigecycline, ESBL, *Escherichia coli*, *Klebsiella pneumoniae*

especially hospital-acquired infections, in Thailand has been increasing. The prevalence of ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* isolated from the patients of Siriraj Hospital in 2003 was 56.9 percent and 33.3 percent, respectively.[1] ESBL-producing *E. coli* and *K. pneumoniae* are usually more resistant to antibiotics than ESBL-non-producing strains. They are usually resistant to most beta-lactams including penicillins and cephalosporins. The choice of antibiotic therapy for ESBL-producing *E. coli* and *K. pneumoniae* is, therefore, limited. The most effective antibiotic for severe infections caused by such organisms is a carbapenem, and as a result, any new agents effective against ESBL-producing *E. coli* and *K. pneumoniae* are sought after.

Colistin has been shown to be active and effective against multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* including those isolated from Thai patients.[2,3] Tigecycline is a glycylcycline antibiotic that shows promising activity against a wide range of organisms.[4] Tigecycline is active against many Gram-negative bacilli including those resistant to multiple classes of antibiotics.

The objective of the study was to determine an in vitro activity of colistin and tigecycline against ESBL-producing *E. coli* and *K. pneumoniae* isolated from the patients hospitalized at Siriraj Hospital from 2004 to 2005.

## MATERIALS AND METHODS

The studied organisms were 113 and 92 strains of ESBL-producing *E. coli* and *K. pneumoniae* isolated from different patients hospitalized at Siriraj Hospital from 2004 to 2005. The method for detection of ESBL-producers was the double-disk diffusion as recommended by the Clinical and Laboratory Standards Institute (CLSI).[5] The susceptibility of colistin was determined by the disk diffusion test, using a 10-μg colistin sulfate disk, and the minimal inhibitory concentration (MIC) was determined by the E-test method for 50 isolates of ESBL-producing *E. coli* and 50 isolates of ESBL-producing *K. pneumoniae*. A quality control was performed by testing the susceptibility of *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853. The MIC of tigecycline was determined by the E-test method for 62 and 42 isolates of ESBL-producing *E. coli* and *K. pneumoniae*, respectively. Quality control was performed by testing the susceptibility of *E. coli* ATCC 25922. The methodology for susceptibility testing was done by direct colony suspension as recommended by the CLSI.[5] The test isolate was grown overnight on blood agar at 35°C, and colonies were picked to suspend in sterile normal saline equivalent to a 0.5 McFarland standard. The suspension was used to inoculate on Mueller-Hinton agar, and the E-test strip was placed according to the manufacturer's recommendation. The agar plates were incubated at 35°C for 18 hours before the inhibition zone and the MIC results were read.

## RESULTS

The inhibition zones of colistin against *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were both 12 mm, and their MICs were both 0.25 mg/L. The MIC of tigecycline against *E. coli* ATCC 25922 was 0.12 mg/L. All aforementioned values were within reference limits. An in vitro activity of colistin revealed that 1) all isolates had an inhibition zone of ≥ 11 mm, 2) the $MIC_{50}$ and $MIC_{90}$ of colistin against ESBL-producing *E. coli* were 0.5 mg/L and 1 mg/L, respectively, and 3) the $MIC_{50}$ and $MIC_{90}$ of colistin against ESBL-producing *K. pneumoniae* were 0.5 mg/L and 0.5 mg/L, respectively. An in vitro activity of tigecycline revealed that 1) the $MIC_{50}$ and $MIC_{90}$ of tigecycline against ESBL-producing *E.coli* were 0.5 mg/L and 1 mg/L,

respectively and 2) the $MIC_{50}$ and $MIC_{90}$ of tigecycline against ESBL-producing *K. pneumoniae* were 1.5 mg/L and 2 mg/L, respectively.

## DISCUSSION

The susceptibility breakpoints of colistin against Gram-negative bacilli are the inhibition zone of ≥ 11 mm, and the MIC of ≤ 2 mg/L, whereas the susceptibility breakpoint of tigecycline against Enterobacteriaceae is the MIC of ≤ 2 mg/L. Therefore, nearly all strains of ESBL-producing *E. coli* and *K. pneumoniae* isolated from the patients hospitalized at Siriraj Hospital from 2004 to 2005 were susceptible to colistin and tigecycline. Our observations on susceptibility of ESBL-producing *E. coli* and *K. pneumoniae* to colistin and tigecycline were similar to several reports from other countries.[6-8] However, clinical studies on efficacy of colistin and tigecycline for infections caused by ESBL-producing *E. coli* or *K. pneumoniae* are needed before they can be recommended in clinical practice. In addition, there are two different bases between colistin used in an in vitro susceptibility (colistin sulfate) and in clinical indications (sodium colistimethate). Even though sodium colistimethate, after intravenous administration, will dissociate into colistin sulfate, conclusion from most studies between correlation of in vitro susceptibility and clinical outcome cannot be drawn. Colistin and tigecycline may prove to be important antibiotics for treatment of ESBL-producing *E. coli* and *K. pneumoniae* infections in Thailand in the near future once more clinical information on colistin and tigecycline therapy of such infections becomes available.

## CONCLUSION

Colistin and tigecycline are found to be active against ESBL-producing *E. coli* and *K. pneumoniae* isolated from Thai patients. Both antibiotics have a potential for being alternative therapy for infections caused by ESBL-producing *K. pneumoniae* and *E. coli* in the near future.

## ACKNOWLEDGEMENT

The authors thank Atlantic Co. Ltd for providing colistin disks and E-test strips, Wyeth Research for providing tigecycline E-test strips, and The Thailand Research Fund for supporting the study.

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# Effectiveness of the Royal Thai Traditional Massage for Relief of Muscle Pain

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## ABSTRACT

**Objective:** To determine the effectiveness of Thai traditional massage for muscle pain relief.
**Methods:** Adults with muscle pain in the neck and/or shoulder and/or back without organic causes that needed specific treatment who attended the Ayuraved Clinic during April to May 2004 received royal Thai traditional massage performed by experienced personnel. An effectiveness of royal Thai traditional massage was determined by pain relief assessed by visual analog scale
**Results:** There were 115 participants; 88 (76.5%) were females. The mean age of the participants was 47.9 years; 45.2% of them had shoulder pain, 40.9% back pain and 26.1% neck pain. The median duration of the symptom was 4 months. The mean pain scores of the participants before and after the royal Thai traditional massage were 7.0 and 3.2, respectively ($p<0.001$). The participants who had a pain score < 3 before and after the royal Thai traditional massage were 3.5% and 79.1%, respectively ($p<0.001$). Adverse effects of the massage were not observed.
**Conclusion:** Royal Thai traditional massage is probably effective in relieving muscle pain of the neck, shoulder and back.

**Keywords:** Royal Thai traditional massage; Muscle pain; Myalgia

**Siriraj Med J 2006;58: 702-704**
***E-journal: http://www.sirirajmedj.com***

Muscle pain is a common complaint of individuals presented to general medical practitioners. The causes of muscle pain are usually related to occupation or bad posture, without any specific organic diseases. These patients usually receive non-steroidal anti-inflammatory agents (NSAIDs) for symptomatic relief. This mode of therapy may lead to side effects such as gastritis, peptic ulcer and upper gastro-intestinal bleeding. In addition, a long-term use of NSAIDs, especially COX-2 inhibitors, is costly. Thai traditional massage has been used to relieve muscle pain in Thai people for centuries. The maneuver may be an appropriate alternative therapy in modern medicine for relieving muscle pain. A meta-analysis of randomized controlled trials of massage therapy in various conditions revealed that its single dose had insignificant effect on immediate pain whereas multiple-doses were found effective[1]. The aforementioned meta-analysis was not applicable to our setting in Thailand for two reasons. First, the massage used in the included studies was not Thai traditional massage. Second, the study patients had a wide variety of pain, including labor, post-operative and cancer pain. Therefore, the present study was carried out to determine whether a single session of the royal Thai traditional massage (RTTM) was effective in reliving muscle pain.

## MATERIALS AND METHODS

This was an experimental self-controlled study at the Ayurved Clinic, Siriraj Hospital and Ayurved School, Phaholyotin Campus, Bangkok, from April to May, 2004. The study was approved by the Ethics Committee on Human Research, Faculty of Medicine Siriraj Hospital, Mahidol University.

### *Participants*

The participants were adults, older than 18 years, who had muscle pain either in the neck, shoulder or back and agreed to participate in the study. A participant would be excluded if s/he had an organic cause of muscle pain that needed specific treatment, skin lesion at the massagesite or had been receiving massage. Sample size estimation was based on a pilot study of 14 subjects with muscle pain. The mean pain score before RTTM was 7 and the mean pain score after RTTM was $\leq 3$.

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TABLE 1. Study participants' characteristics

| | |
|---|---|
| Total | 115 |
| Males | 27 (23.5%) |
| Females | 88 (76.5%) |
| Age (Years) | |
| Mean ± SD | 47.9 ± 13.8 |
| Body weight (Kg.) | |
| Mean ± SD | 61.2 ± 10.9 |
| Site of pain | |
| Shoulder | 52 (45.2%) |
| Back | 47 (40.9%) |
| Neck | 30 (26.1%) |
| Others | 9 (7.8%) |
| Duration of pain | |
| Mean | 1.8 years |
| Median | 4 months |
| Range | 1day to 20 years |
| Duration of pain | |
| Acute pain (≤6 months) | 66 (57.4%) |
| Mean | 1 month |
| Median | 14 days |
| Range | 1 day to 6 months |
| Chronic pain (> 6 months) | 49 (42.6%) |
| Median | 12 months |
| Range | 8 months to 20 years |
| History of prior treatment | |
| Yes | 93 (80.9%) |
| Modern medicine | 56 (60.2%) |
| Current treatment | |
| Yes | 45 (39.1%) |
| Modern medicine | 26 (57.8%) |

Approximately, 80% of the subjects had a mean pain score after RTTM ≤3. The aim of the study was to detect any response (mean pain score after massage ≤3) of 80% ± 10% with 5% type I error (2-sided). Therefore, the appropriate sample size was 108.

### *Intervention*

The massage maneuver used in this study was the Royal Thai Traditional Massage. The practitioners were experienced personnel at the Ayurved Clinic, Siriraj Hospital, and the Ayurved School, Phaholyotin Campus, Bangkok. They used only palms and fingers to compress the area where the clients complained of having pain for 40 to 45 minutes. There was no bone and joint manipulation during the massage procedures.

### *Main Outcome Measurement*

Each participant was asked to provide demographic and relevant clinical data to the study team before receiving the massage. The severity of pain was also assessed by each participant using a visual analog scale of 0 to 10 where 0 was "no pain" and 10 was "unbearable pain". The pain severity was reassessed by each participant immediately after finishing the massage, using the identical scale.

TABLE 2. Effectiveness of the royal Thai traditional massage in 115 participants

| | Pain score Mean ± SD (Range) |
|---|---|
| Before massage | 7.0 ± 1.9 (3 - 10) |
| After massage | 3.2 ± 1.2 (0 - 7) |
| | **Participants with pain score ≤3** |
| Before massage | 4 / 115 (3.5%) |
| After massage | 91 / 115 (79.1%) |

### *Data Analysis*

The data were entered into SPSS for Windows. The data were analyzed by descriptive statistics, paired student t-test and chi-square statistics where appropriate.

## RESULTS

In total, there were 115 participants. The characteristics of the studied participants are shown in Table 1. Most participants were middle-aged females. The common sites of pain were shoulder(s), back and neck. The median duration of the symptom was 4 months. Fifty-seven percent of the subjects had muscle pain for less than 6 months. Most subjects had used modern medicine for the treatment of their muscle pain. The effectiveness of RTTM is shown in Table 2. The mean pain scores of the participants before and after RTTM were 7.0 and 3.2, respectively ($p<0.001$). Subjects who had a pain score of ≤3 before and after RTTM were 3.5% and 79.1%, respectively ($p<0.001$). The response rates in participants with shoulder, back and neck pain were 82.7%, 74.5% and 76.7%, respectively ($p=0.6$). The response rates in participants with acute pain and chronic pain were 83.3% and 73.5%, respectively ($p=0.3$). Adverse effects of the massage were not observed.

## DISCUSSION

We found that RTTM was safe and effective in relieving muscle pain of the shoulder(s), back and neck. The differences in the effectiveness of RTTM among various sites of pain or between acute and chronic pain were not observed. The explanations for pain relief achieved by the massage included the gate control theory of pain reduction,[2] promotion of parasympathetic activity,[2] influence on body chemistry, e.g., an increase in serotonin levels,[3] a release of endorphins,[4] mechanical effects to promote circulation of blood and the lymph[5]. The magnitude of the effects of treatment in our study was quite obvious. A mean decrease in the pain score was 4 and the response rate (pain score of ≤3) after the massage (79.1%) was much higher than that before the massage (3.5%). Since our study is a self-controlled study and there was no concurrent control group, a portion of the responses observed after massage could be due to placebo effect or Hawthorne effect.[6] The Hawthorne effect is often mentioned as a possible explanation for positive results in intervention studies. It is used to cover many phenomena, not only unwittingly confounding variables under study by the study itself, but also behavioral change due to an awareness of being observed, active compliance with the supposed wishes of researchers because of special attention received, or positive response to the stimulus being introduced. Therefore, the effectiveness and efficiency of RTTM should be confirmed in a randomized controlled study.

## ACKNOWLEDGEMENTS

The authors would like to thank Dr. Tawee Laohapand, Dr. Pravit Akarasereenont, Dr. Pongparadee Chaudakshetrin, Aurmpon Suwantrai, and Sroisri Aiumponchai for their valuable advices and the Thailand Research Fund for supporting the study.

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## บทคัดย่อ

# ประสิทธิผลของการนวดแผนไทยแบบราชสำนักในผู้ที่มีอาการปวดกล้ามเนื้อ


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**วัตถุประสงค์:** เพื่อทราบประสิทธิผลของการรักษาผู้ที่มีอาการปวดกล้ามเนื้อบริเวณไหล่ หลัง และคอด้วยการนวดแผนไทยแบบราชสำนัก

**วิธีการ:** ผู้ที่มีอาการปวดกล้ามเนื้อบริเวณไหล่ หลัง และคอจำนวน 115 คนได้รับการนวดแผนไทยแบบราชสำนักที่คลินิกอายุรเวท โรงพยาบาลศิริราช และโรงเรียนอายุรเวท พหลโยธิน ระหว่างเดือนเมษายนถึงพฤษภาคม พ.ศ. 2547 ประเมินประสิทธิผลของการรักษาโดยสอบถามความรุนแรงของอาการปวดก่อนและหลังการรักษาด้วยการนวด ด้วยคะแนนความรุนแรงของอาการปวดตั้งแต่ 0 (ไม่ปวด) จนถึง 10 (ปวดมากที่สุดจนทนไม่ได้)

**ผลการศึกษา:** ผู้ป่วยจำนวน 115 คน เป็นหญิง 88 คน (ร้อยละ 76.5) อายุเฉลี่ย 47.9 ปี ผู้ป่วยร้อยละ 45.2, 40.9 และ 26.1 มีอาการปวดไหล่ หลัง และคอตามลำดับ ระยะเวลาที่มีอาการเฉลี่ย 4 เดือน คะแนนความรุนแรงของอาการปวดโดยเฉลี่ยก่อนการนวดมีค่า 7 และคะแนนความรุนแรงของอาการปวดโดยเฉลี่ยภายหลังการนวดมีค่า 3 ($p<0.001$), ผู้ที่มีอาการปวดกล้ามเนื้อก่อนได้รับการนวดมีคะแนนความรุนแรงของอาการปวดเท่ากับหรือน้อยกว่า 3 (ปวดเล็กน้อย) เพียงร้อยละ 3.5 ในขณะที่คะแนนความรุนแรงของอาการปวดเท่ากับหรือน้อยกว่า 3 ภายหลังได้รับการนวดมีเพิ่มขึ้นเป็นร้อยละ 79.1 ($p<0.001$), ไม่พบผลข้างเคียงและภาวะแทรกซ้อนจากการนวด

**สรุป:** การนวดแผนไทยแบบราชสำนักน่าจะมีประสิทธิผลในการรักษาผู้ที่มีอาการปวดกล้ามเนื้อบริเวณไหล่ หลัง และคอ

# Cost-Effectiveness Analysis of Chlorhexidine Gluconate Compared with Povidone-Iodine Solution for Catheter-Site Care in Siriraj Hospital, Thailand

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***Background:*** *Catheter-related bloodstream infections (CRBSI) are an important cause of patient morbidity, mortality, and increased health care costs. Use of an antiseptic solution for skin disinfection at the catheter insertion site helps prevent catheter-related infections. In Thailand, povidone-iodine solution is the most commonly used agent for this purpose. However, the results of several studies including a meta-analysis indicated that the use of chlorhexidine gluconate is more effective than the use of povidone-iodine as an antiseptic for preventing CRBSI. This study evaluated the cost-effectiveness of chlorhexidine gluconate versus povidone-iodine for catheter-site care using the Siriraj Hospital perspective.*

***Material and Method:*** *We used a decision analytic modeling for estimating the cost-effectiveness of antiseptic solutions. The CRBSI rate was obtained from the Center for Nosocomial Infection Control at Siriraj Hospital, while the efficacy of cholorhexidine compared to povidone-idone was based on a meta-analysis. The cost of managing infections was derived from the Thai Drug Related Group (DRG). A series of sensitivity analyses were performed. Since the time horizon of the analysis was less than 1 year, there was no need for discounting.*

***Results:*** *We found that the use of chlorhexidine, rather than povidone iodine, for central catheter site care resulted in a 1.61 % decrease in the incidence of CRBSI, a 0.32 % decrease in the incidence of death, and savings of 304 baht per catheter used. For peripheral catheter site care, the results were similar, although the differences were smaller.*

***Conclusion:*** *Use of chlorhexidine gluconate in place of the current standard solution for vascular catheter site care is a cost-effective method of improving patient safety in Siriraj Hospital.*

***Keywords:*** *Cost effectiveness, Chlorhexidine gluconate, Povidone-iodine, Catheter-related bloodstream infections*

***J Med Assoc Thai 2006; 89 (Suppl 5) : S94-101***
***Full text. e-Journal:*** *http://www.medassocthai.org/journal*

Intravascular catheters are commonly used in caring for hospitalized patients but can lead to catheter-related bloodstream infection CRBSI[1], particularly the central-line catheter[2]. Bloodstream infections related to the use of catheters are an important cause of morbidity, mortality, and increased duration of hospitalization and health care cost[2-6]. In Thailand, these infections result in an increased duration of hospitalization of 15 days and the additional cost of antibiotics for one episode of CRBSI was approximately 10,753 baht[7]. In addition, CRBSI has been associated with mortality of 12% - 25%[8-13]. Nowadays, there are several procedures, which help to prevent these infections, such as performing catheter insertion at the subclavian site, maximizing sterile barriers and avoiding the use of antibiotic ointment[14-15]. Moreover, disinfecting the skin at the catheter insertion site with antiseptic

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solution helps to prevent these infections as well, and povidone iodine is the agent most commonly used in several countries including Thailand for this purpose[16-18].

A recent meta-analysis and cost-effectiveness study[19-20] found that the use of chlorhexidine gluconate in place of the current standard solution for vascular catheter site care is a simple and cost-effective method of improving patient safety in the hospital setting. In addition, guidelines of the Infectious Diseases Society of America, and the Centers for Disease Control and Prevention (CDC) recommend the use 2% of chlorhexidine gluconate as an antiseptic for the prevention of catheter-related infections[21-22]. Because of these recommendations, Siriraj Hospital intends to switch from povidone iodine to chlorhexidine gluconate for skin disinfection at the catheter insertion site. However, the cost of chlorhexidine is more than povidone iodine and information on the cost-effectiveness of this switch is needed prior to implementing this intervention. Therefore, we evaluated the cost-effectiveness of the use of both antiseptics for vascular catheter site care for endorsing the policy on using chlorhexidine instead of povidone iodine for skin disinfection at the catheter insertion site of the patients in Siriraj Hospital.

## Material and Method

### *Decision analysis model*

A decision analytic model was developed to evaluate the outcomes associated with the use of chlorhexidine gluconate versus povidone iodine solutions for catheter site care as shown in Fig. 1[23]. Either solution could be used at the time that an intravascular catheter was inserted and then every 48–72 hr to clean the insertion site. Patients with a catheter could have one of the following outcomes: 1) CRBSI, defined as isolation of the identical pathogen from a peripherally obtained blood culture and from a colonized catheter; 2) local catheter-related infection, defined as the presence of purulence or signs of inflammation (e.g., erythema, tenderness, and induration) within two cm of the catheter exit site[24]; 3) catheter colonization without bloodstream infection or local catheter-related infection; and 4) no colonization or infectious complications. Colonization of the catheter was defined as growth of microorganisms from a catheter segment using quantitative (>1000 cfu/mL)[25] or semiquanti-

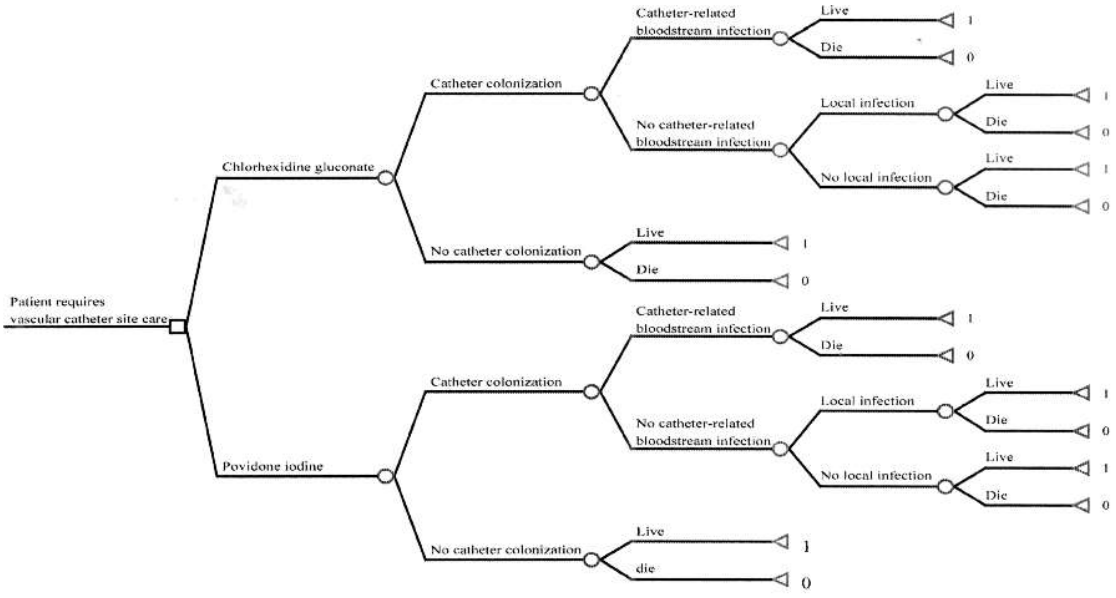


**Fig. 1** Decision tree comparing the use of chlorhexidine gluconate with the use of povidone iodine for vascular catheter site care

tative (>15 cfu)[26] culture techniques. CRBSI was associated with a risk of dying. We assumed that local or systemic catheter-related infections did not occur without preceding catheter colonization. We performed the analysis using the hospital perspective; the time horizon was the period of hospitalization.

The hypothetical cohort in the decision analysis model included hospitalized patients requiring either a peripheral or central vascular catheter for short-term use (average duration, <10 days). Because the risk of CRBSI differs for central and peripheral venous catheters[24], we analyzed these cohorts separately. We considered "central vascular catheters" to include central venous, peripherally inserted central venous, pulmonary arterial, and hemodialysis catheters and introducer sheaths, whereas "peripheral vascular catheters" included peripheral venous and peripheral arterial catheters.

***Likelihood of events***

The probabilities of clinical events used in the decision analysis model are shown in Table 1. The probabilities of CRBSI with povidone iodine (the baseline risk) for central line were derived from Siriraj Hospital[7] and the study of Thongpiyapoom and colleagues[27]. The probabilities of catheter colonization were obtained from the literature[20]. The probability of CRBSI with chlorhexidine gluconate was determined by multiplying the probability of CRBSI when povidone iodine was used by the summary risk ratio of CRBSI when chlorhexidine gluconate was used, based on the results of the recently published meta-analysis[19].

The probability of catheter colonization when chlorhexidine gluconate was used was similarly derived (Table 1). All probabilities of clinical events for peripheral line were based on the study of Chaiyakunapruk and colleague[19]. These probabilities were similarly

**Table 1.** Probabilities of clinical events and comparison of the costs associated with chlorhexidine gluconate and povidone iodine solutions for vascular catheter site care

| Probability of clinical event or cost | Base-case value (range) | | Reference(s) |
|---|---|---|---|
| | Central line | Peripheral line | |
| Catheter-related bloodstream infection | | | |
| Probability when povidone iodine solution is used, % | 3.16 (0.9–3.5) | 0.92 (0.00-2.32) | [7,27] |
| Risk ratio for chlorhexidine gluconate solution* | 0.49 (0.28-0.88) | 0.49 (0.28-0.88) | [19] |
| Catheter colonization | | | |
| Probability when povidone iodine solution is used, % | 18.09 (10.10–26.08) | 7.91 (5.53-10.28) | [19] |
| Risk ratio for chlorhexidine gluconate solution* | 0.49 (0.31-0.77) | 0.49 (0.31-0.77) | [19] |
| Probability of death attributable to CRBSI, % | 20.0 (4.40–25.0) | 1.12 (0.47-2.11) | [8-13,27,29-33] |
| Probability of local infection if colonization occurs, % | 20.0 (0.00–40.0) | 20.0 (0.00-40.0) | [28] |
| Cost in Thailand in 2005, Baht | | | |
| Cost of 10% povidone iodine | 22.39 (11.86-27.99) | 3.73 (1.87-4.66) | [7] |
| Cost of 1% chlorhexidine gluconate | 25.80 (13.67-30.96) | 4.3 (2.15-5.16) | [7] |
| Cost associated with CRBSI per case | 27,341.09 (18,907.60-53,127.34) | 27,341.09 (18,907.60-53,127.34) | [34-35] |
| Cost of managing local infection per case | 10,756.66 (8,770.56-18,694.45) | 10,756.66 (8,770.56-18,694.45) | [34-35] |

* To introduce a correlation between the probabilities of events in each treatment arm, the probability associated with the use of a chlorhexidine gluconate solution was calculated by multiplying the risk ratio by the probability associated with the use of povidone iodine solution. In the base case for the chlorhexidine arm, the probabilities that a catheter-related bloodstream infection would occur were 1.55% and 0.45% for central and peripheral lines, respectively, and the probabilities of catheter colonization were 8.86% and 3.88%

derived as central line (Table 1). We estimated that 20% of the colonized catheters were associated with local signs of infection[28]. All probabilities were calculated separately for central and peripheral catheter models. The probability of death attributable to CRBSI for a central venous catheter was calculated based on data from studies published elsewhere, which report excess mortality of 4%–25%. We used a 20 % attributable mortality for the base-case scenario and explored a range from 4% to 25% in sensitivity analyses because several studies in 2003-2004 found that the range of mortality rate was 22% to 25%[8-13,27,29-33] and a study in Thailand[27] reported a mortality rate of 20%. For patients with peripheral vascular catheters, we estimated an attributable mortality due to CRBSI of 1.12% (range, 0.47%-2.11%)[32].

***Costs***

We estimated the cost of antiseptic solution based on the total amount of solution used multiplied by the cost of the solution per ml. The total amount of solution used for the central line was estimated as 10 ml for clean skin at insertion on the first day, and 20 ml per day for 7.9 days while the amount of solution for the peripheral line was estimated as 5 ml per day for 5.6 day for clean skin at insertion (Table1).

Direct medical costs for patients with CRBSI were estimated based on data of the Thai Diagnosis Related Group (DRG) in year 2002-2003[34]. These medical costs were determined by multiplying the relative weight (RW) by cost per relative weight of these diseases. We used 16,000 Baht as cost per relative weight for university hospital in the year 2003 for calculation[34]. We estimated the relative weight for treatment of CRBSI as a septicemia adult, with moderate complication while the relative weight for treatment of a local infection was estimated as a minor skin disorder, with mild to moderate complication of Thai DRG[35]. These relative weights were 1.6547 and 0.6510, respectively[34]. For sensitivity analysis, we varied the cost of managing septicemia ranging from the treatment cost for septicemia without complication to those for patients with catastrophic complications. Likewise, we ranged the cost of managing local infection using the cost for minor skin disorder without complication and with catastrophic complication. All costs were adjusted to Thai baht in the year 2005.

***Outcome assessment and sensitivity analyses***

Outcomes calculated were the incidence of CRBSI, the incidence of death attributable to CRBSI, and the direct medical costs. The mean expected value for the differences in the incidence of death, the incidence of CRBSI, and the direct medical costs were determined. To assess uncertainty associated with the results, we conducted a series of one-way sensitivity analyses to evaluate the effect of varying individual parameters on the outcomes. To further test the robustness of the results, we set all parameters in the model to favor chlorhexidine gluconate in a best-case scenario and to favor povidone iodine in a worst-case scenario (Table 2).

**Table 2.** Results of decision analysis comparing chlorhexidine gluconate and povidone iodine solutions for vascular catheter site care in Thailand in 2005

| Cathether type | Direct medical cost, Baht | Incidence of CRBSI, % | Incidence of death due to CRBSI, % |
|---|---|---|---|
| Central line | | | |
| Chlorhexidine gluconate solution | 251.07 | 1.55 | 0.31 |
| Povidone iodine solution | 555.57 | 3.16 | 0.63 |
| Difference | -304.49 | -1.61 | -0.32 |
| Best-case scenario | -1740.48 | -2.52 | -0.63 |
| Worst-case scenario | 13.56 | -0.11 | -0.005 |
| Peripheral line | | | |
| Chlorhexidine gluconate solution | 92.09 | 0.45 | 0.005 |
| Povidone iodine solution | 192.23 | 0.92 | 0.01 |
| Difference | -100.15 | -0.47 | -0.005 |
| Best-case scenario | -632.35 | -1.67 | -0.47 |
| Worst-case scenario | 3.29 | 0.00 | 0.00 |

*Main assumptions in the analysis*

There were several main assumptions in our analysis: 1) the relative risk of death due to CRBSI was the same for central and peripheral vascular catheters; 2) the relative risks for CRBSI and catheter colonization for chlorhexidine gluconate, compared with povidone iodine, were the same in central and peripheral vascular catheters; 3) the cost of CRBSI was independent of survival outcome; 4) catheter colonization without local infection had no costs or adverse outcomes; 5) catheter-site erythrema without evidence of local infection did not affect survival outcome or cost; 6) the costs of medical care per case for all complications were the same in central and peripheral vascular catheters.

**Results**

*Costs and outcomes*

In the base-case analysis, use of chlorhexidine gluconate rather than povidone iodine for central line catheter site care led to an absolute decrease in the incidence of CRBSI of 16 cases/1000 catheters, and a decrease in the incidence of death attributable to CRBSI of 3 cases/ 1000 catheters (Table 2). In addition to these clinical benefits, use of chlorhexidine gluconate resulted in expected cost savings of 304.49 Baht for each catheter used, compared with the use of povidone iodine. Use of chlorhexidine gluconate rather than povidone iodine for peripheral line catheter site care led to an absolute decrease in the incidence of CRBSI of 5 cases/ 1000 catheters, and a decrease in the incidence of death attributable to CRBSI of 0.05 cases/1000 catheters. In addition to these clinical benefits, use of chlorhexidine gluconate resulted in expected cost savings of 13.56 Baht per catheter used, compared with the use of povidone iodine.

*Sensitivity analyses*

The use of chlorhexidine gluconate for central catheter site care resulted in cost-savings in most of the one-way sensitivity analyses as shown in Table 2. The cost of CRBSI was the most influential parameter in the model. Other influential parameters included the reduction in risk of CRBSI for chlorhexidine gluconate, the probability of death due to CRBSI, and the baseline risk of CRBSI. The use of chlorhexidine gluconate resulted in a dominant strategy in best-case but not in the worst-case scenario. In the worst case scenario, using chlorhexidine gluconate resulted in an increase of total medical costs of 18 Baht, while the incidence of CRBSI (decrease 0.11%) and death (decrease 0.005%) remained diminished. The threshold analysis indicated that the use of chlorhexidine gluconate would still provide cost-savings unless the cost of chlorhexidine gluconate exceeded 196.6 baht per 100 ml.

For peripheral vascular catheters, use of chlorhexidine gluconate for insertion site care was again found to be the best strategy in all one-way sensitivity analyses. The baseline risk of catheter-related bloodstream infection was the most influential parameter in the model. When the base-case scenario parameters were used in calculations, the use of chlorhexidine gluconate would save 100.15 Baht, and it still save cost as long as the cost of chlorhexidine gluconate was less than 373 Bath per 100 ml. In the worst-case scenario, use of chlor-hexidine gluconate resulted in an increase in direct medical costs of 3.29 Baht. However, it did not result in increases of the incidence of CRBSI and death due to CRBSI.

**Discussion**

To the best of our knowledge, this is the first study that has been performed to evaluate the cost-effectiveness of chorhexidine gluconate compared with povidone-iodine solution for catheter-site care in Thailand. Our analysis found that using of chlorhexidine gluconate for catheter site care reduces the incidence of CRBSI and decreases health care costs as shown by a prior study[20]. Our analysis was conducted from the perspective of the health care provider, rather than from that of society as a whole, as recommended by previous guidelines[39]. However, from a societal perspective, including indirect costs, such as time lost from work, the analysis would result in even greater cost savings for the chlorhexidine gluconate strategy.

Our analysis suggests that use of chlorhexidine gluconate for patients requiring short-term vascular catheterization, either with central or peripheral catheters, likely results in reductions of the incidence of CRBSI and health care costs. These results held true over a wide range of clinical and economic assumptions. This unusual combination of clinical benefits and decreased costs makes chlorhexidine gluconate attractive for routine use for both central and peripheral vascular catheter site skin care. Although, this study was conducted from the perspective of a university hospital, we believe that the use of chlorhexidine gluconate instead of povidone iodine could be generalized to general and other hospitals in Thailand, especially in university hospital where it may save more than our results because the actual cost of managing

septicemia and local infection might be higher than in other hospitals

The results from this study led to the production of 2% chlorhexidine gluconate in 70% alcohol by Siriraj Hospital Pharmacy Department and the implementation of using 2% chlorhexidine gluconate in 70% alcohol instead of 10% povidone iodine for catheter-site care of the patients hospitalized in three intensive care units (ICU) in Siriraj Hospital since January 2006. The preliminary results of this implementation from January to March in 70 patients revealed that the incidence of CRBSI was 3 per 1000 catheter days, which is less than the incidence of CRBSI observed in the same ICUs, 5 per 1000 catheter days, in the year 2005.

**Conclusions**

Our cost-effectiveness analysis shows that using chlorhexidine gluconate rather than povidone iodine for vascular catheter site disinfection in hospitalized patients requiring short-term vascular access is likely to result in decreased morbidity, mortality, and health care costs in the Thailand hospital setting. In addition, this simple method can be relatively easily implemented to improve patient safety, and, thus, should perhaps take priority in efforts to prevent vascular catheter–related infection.

**Acknowledgements**

The authors thank the Thailand Research Fund for supporting the study and infection control nurses at the Center for Nosocomial Infection Control, Siriraj Hospital for providing some data.

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## ต้นทุน-ประสิทธิผลของ คลอเฮ็กซิดีน กลูโคเนท เปรียบเทียบกับ โพวิโดน ไอโอดีน สำหรับทำลายเชื้อที่ผิวหนังบริเวณที่ใส่สายสวนหลอดเลือดที่โรงพยาบาลศิริราช

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*ผู้ป่วยที่ได้รับการคาสายสวนในหลอดเลือดเสี่ยงต่อการติดเชื้อในกระแสเลือด น้ำยาทำลายเชื้อที่ผิวหนังบริเวณที่ใส่สายสวนหลอดเลือดของผู้ป่วยไทยที่ใช้กันทั่วไปคือโพวิโดน ไอโอดีน มีหลักฐานจากการวิจัยในต่างประเทศที่แสดงว่า คลอเฮ็กซิดีน กลูโคเนท ลดโอกาสติดเชื้อในกระแสเลือดได้มากกว่าโพวิโดน ไอโอดีนและคุ้มค่ากว่า การศึกษานี้จึงต้องการทราบต้นทุน-ประสิทธิผลของ คลอเฮ็กซิดีน กลูโคเนท เปรียบเทียบกับ โพวิโดน ไอโอดีน สำหรับทำลายเชื้อที่ผิวหนังบริเวณที่ใส่สายสวนหลอดเลือดที่โรงพยาบาลศิริราชโดยอาศัยข้อมูลจากโรงพยาบาลศิริราชและข้อมูลอื่นที่เกี่ยวข้องจากฐานข้อมูลต่าง ๆ ในประเทศไทยและต่างประเทศในกรณีที่ไม่มีข้อมูลในประเทศไทยซึ่งพบว่าคลอเฮ็กซิดีน กลูโคเนท มีต้นทุน-ประสิทธิผลดีกว่าโพวิโดน ไอโอดีนทั้งการคาสายสวนหลอดเลือดส่วนกลางและสายสวนหลอดเลือดส่วนปลาย ดังนั้นจึงควรใช้คลอเฮ็กซิดีน กลูโคเนทสำหรับทำลายเชื้อที่ผิวหนังบริเวณที่ใส่สายสวนหลอดเลือดแทนโพวิโดน ไอโอดีน*

# In Vitro Activity of Tigecycline against Clinical Isolates of Multidrug-Resistant *Acinetobacter baumannii* in Siriraj Hospital, Thailand

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*In vitro activity of tigecycline against 148 strains of Acinetobacter baumannii isolated from different patients hospitalized at Siriraj Hospital, Bangkok, Thailand during 2002 to 2005 was conducted. These isolates were resistant to beta-lactams, aminoglycosides and fluoroquinolones. In vitro susceptibilities were determined by Kirby-Bauer disk diffusion, E-test and broth microdilution methods. The $MIC_{50}$ and $MIC_{90}$ values of tigecycline against A. baumannii determined by the broth microdilution method were 0.5 and 1 mg/L respectively. The MICs of tigecycline determined by E-test were 4-fold higher than those from the broth microdilution method. An inhibition zone of $\geq$13 mm was well correlated with a tigecycline MIC of $\leq$ 2 mg/L and had a sensitivity of 99% and a specificity of 100%. The study results indicated that 97.3% of MDR A. baumannii strains isolated from the patients hospitalized at Siriraj Hospital were susceptible to tigecycline. Tigecycline may prove to be an important antibiotic for treatment of multidrug-resistant A. baumannii infections in Thailand in the near future.*

**Keywords:** *Tigecycline, Acinetobacter baumannii*

***J Med Assoc Thai 2006; 89 (Suppl 5): S102-5***
***Full text. e-Journal:*** *http://www.medassocthai.org/journal*

*Acinetobacter baumannii* has emerged as a worldwide problem in causing infections in hospitalized patients[1-3]. *A. baumannii* is one of the most common causative pathogens in nosocomial pneumonia, bacteraemia, urinary tract infections, and skin and soft tissue infections, and the mortality associated with these infections is high. The incidence of infections caused by multidrug-resistant (MDR) pathogens, particularly *Acinetobacter baumannii* and *Pseudomonas aeruginosa,* in Thailand has dramatically increased[4]. A prospective study of 208 clinical isolates of *A. baumannii* recovered from patients in Siriraj Hospital from January to December 2002 revealed that 86 strains (41.3%) were isolated from infected patients and the remaining 58.7% were colonizers[5]. In this study, 57% of *A. baumannii* isolates were resistant to all antimicrobial agents available in Thailand including beta-lactams, aminoglycosides and fluoroquinolones, and the overall mortality rate of the patients infected with pandrug-resistant *A. baumannii* was 79%[5]. The study of 104 clinical isolates of *A. baumannii* from 100 hospitalized patients at Maharaj Nakorn Chiang Mai Hospital, Thailand also observed that 46% of the isolates were pandrug-resistant and the overall mortality was 52%[6]. The only available antibiotic effective for treating infections caused by *A. baumannii* resistant to all beta-lactams,aminoglycosides and fluoroquinolones is colistin[7], hence a search for new agents effective against MDR *A. baumannii* is needed.

Tigecycline is a glycylcycline antibiotic that shows promising activity against a wide range of organisms including multi-drug resistant gram positive cocci and gram negative bacilli[8]. The objective of the study was to determine in vitro activity of tigecycline against clinical isolates of MDR *A. baumannii* in

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Siriraj Hospital, Thailand.

**Material and Method**

One hundred and forty-eight strains of *A. baumannii* isolated from different infected patients hospitalized at Siriraj Hospital, Bangkok, Thailand during 2002 to 2005 were included. These isolates were resistant to all beta-lactams, aminoglycosides, and fluoroquinolones. In vitro susceptibilities of MDR *A. baumannii* to tigecycline were determined by Kirby-Bauer disk diffusion, E-test, and broth microdilution methods. Paper disc containing tigecycline 15 μg per disk (Becton Dickinson, USA), E-test strips (AB BIODISK, Sweden) and gram negative MicroScan MIC panels (Dade Behring Inc., USA) were provided by Wyeth Research. The methodology for susceptibility testing was done by direct colony suspension according to guidelines suggested by CLSI [9]. Quality control was performed by testing the susceptibility of *E. coli* ATCC 25922 as recommended by Wyeth Research.

**Results**

A distribution of inhibition zone diameters of tigecycline against *A. baumannii* is shown in Table 1. The $MIC_{50}$ and $MIC_{90}$ values of tigecycline against *A. baumannii* determined by E-test were 2 and 4 mg/L respectively. The $MIC_{50}$ and $MIC_{90}$ values of tigecycline against *A. baumannii* determined by the broth microdilution method were 0.5 and 1 mg/L respectively. There was a significant correlation between inhibition zone diameters and MICs determined by the broth microdilution method ($p<0.001$, $r = -0.8$), and between MICs of tigecycline determined by E-test and MICs determined by the broth microdilution method ($p<0.001$, $r=0.9$). The accuracy of the inhibition zone diameter of ≥13 mm in predicting susceptibility of *A.baumannii* to tigecycline is shown in Table 2. If the MIC of tigecycline at ≤2 mg/L was considered as a breakpoint for tigecycline susceptibility, the inhibition zone diameter of ≥13 mm had a sensitivity of 99% and a specificity of 100% in predicting the susceptibility of *A.baumannii* to tigecycline and 97.3% of MDR *A.baumannii* were susceptible to tigecycline.

**Discussion**

The previous studies on the in vitro activity of tigecycline against *A.baumannii* by the broth microdilution method revealed that the $MIC_{50}$ and the $MIC_{90}$ for tigecycline were 0.5-1 and 2 mg/L respectively, and more than 90% of these isolates had MICs ≤2 mg/L and were considered susceptible to tigecycline[10, 11]. Carbapenem-resistant *A. baumannii* isolates were still susceptible to tigecycline with comparable MICs to the aforementioned values[12, 13]. However, in vitro activity of tigecycline against *A. baumannii* by the agar dilution method observed that the $MIC_{50}$ and the $MIC_{90}$ for tigecycline against *A.baumannii* were 8 and 8 mg/L respectively[14]. These findings implied that the different methods of in vitro susceptibility testing of tigecycline against *A. baumannii* might yield different results. The breakpoints for the inhibition zone diameter and MIC of tigecycline against *A.baumannii* are not available. The US FDA-approved breakpoints of tigecycline against Enterobacteriaceae to be used by the local laboratory were inhibition zone diameter ≥19 mm and a MIC≤2 mg/L[9]. The previous studies on in vitro activity of tigecycline against *A. baumannii* used such a MIC breakpoint[10-14]. It is not known if the testing methods used in general microbiology laboratories, disk diffusion and E-tests, are accurate in predicting the MICs of tigecycline against *A. baumannii*.

The $MIC_{50}$ and the $MIC_{90}$ of tigecycline against *A. baumannii* determined by the broth microdilution method observed in our study were similar to those reported in the literature[10-13] and 97.3% of MDR *A. baumannii* isolated from the hospitalized patients at Siriraj Hospital were susceptible to tigecycline. However, our findings indicated that there was a discrepancy in the susceptibility results of tigecycline against *A. baumannii* for the different

**Table 1.** Distribution of the inhibition zone diameter of tigecycline against 148 isolates of MDR *A. baumannii*

| Inhibition Zone Diameter (mm) | Number of Isolates (%) |
|---|---|
| 11 | 1 (0.7) |
| 12 | 4 (2.7) |
| 13 | 4 (2.7) |
| 15 | 8 (5.4) |
| 16 | 11 (7.4) |
| 17 | 20 (13.5) |
| 18 | 34 (23.0) |
| 19 | 21 (14.2) |
| 20 | 17 (11.5) |
| 21 | 16 (10.8) |
| 22 | 8 (5.4) |
| 23 | 3 (2.0) |
| 26 | 1 (0.7) |

**Table 2.** Accuracy of the inhibition zone diameter of ≥13 mm in predicting the susceptibility of *A.baumannii* to tigecycline

| | MIC (MicroScan) ≤ 2 mg/L | MIC (MicroScan) > 2 mg/L |
|---|---|---|
| Inhibition Zone Diameter ≥13 mm | 143 | 0 |
| Inhibition Zone Diameter <13 mm | 1 | 4 |

methods of testing. The MICs determined by E-test were usually 4-fold higher than those determined by the broth microdilution method and E-test might not be an accurate method for in vitro susceptibility testing of tigecycline against *A. baumannii*. Moreover, our study also observed that the US FDA-approved breakpoint of tigecycline against Enterobacteriaceae, to be used by the local laboratory, of an inhibition zone diameter ≥19 mm, was not applicable to tigecycline against *A. baumannii*. The breakpoint for an inhibition zone diameter ≥13 mm was more accurate in predicting susceptibility of *A.baumannii* to tigecycline with a sensitivity of 99% and a specificity of 100%. Our findings of good in vitro activity of tigecycline against MDR *A. baumannii* warrant a clinical study to prove its efficacy and to determine whether such proposed breakpoint and testing methods are valid.

**Acknowledgements**

We wish to thank Wyeth Research for providing E-test strips and MicroScan gram negative panels for tigecycline susceptibility test and The Thailand Research Fund for supporting the study.

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## การทดสอบฤทธิ์ของ tigecycline ต่อ Acinetobacter baumannii ที่ดื้อยาต้านจุลชีพหลายขนานที่แยกได้จากผู้ป่วยในโรงพยาบาลศิริราช

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ผู้วิจัยได้ทดสอบฤทธิ์ของ tigecycline ต่อ Acinetobacter baumannii ที่ดื้อยาต้านจุลชีพหลายขนานที่แยกได้จากผู้ป่วยของโรงพยาบาลศิริราชระหว่าง พ.ศ. 2545 ถึง พ.ศ. 2548 จำนวน 148 สายพันธุ์ด้วยวิธี disk diffusion และวัด minimum inhibitory concentration (MIC) ด้วย E-test และ broth microdilution พบว่า 1) ค่า $MIC_{50}$ และ $MIC_{90}$ ของ tigecycline ต่อ A. baumannii ที่ดื้อยาต้านจุลชีพหลายขนานที่ทดสอบด้วยวิธี broth microdilution เท่ากับ 0.5 มก./ล. และ 1 มก./ล. ตามลำดับ 2) ค่า $MIC_{50}$ และ $MIC_{90}$ ของ tigecycline ต่อ A. baumannii ที่ดื้อยาต้านจุลชีพหลายขนานที่ทดสอบด้วยวิธี E-test มีค่ามากกว่าค่า MIC ที่ได้จากวิธี broth microdilution ประมาณ 4 เท่า 3) เส้นผ่านศูนย์กลางของ inhibition zone ของ tigecycline $\geq$13 มม.เป็นค่าที่เหมาะสม สำหรับพิจารณาความไวของ A. baumannii ต่อ tigecycline หากใช้เกณฑ์ MIC$\leq$2 มก./ล. ในการระบุว่า A. baumannii ไวต่อ tigecycline โดยมีความไวร้อยละ 99 และความจำเพาะร้อยละ 100, 4) Acinetobacter baumannii ที่ดื้อยาต้านจุลชีพหลายขนานร้อยละ 97.3 ไวต่อ tigecycline ดังนั้น tigecycline น่าจะมีประโยชน์ในการรักษาโรคติดเชื้อ Acinetobacter baumannii ที่ดื้อยาต้านจุลชีพหลายขนานในประเทศไทย

# Epidemiology of *Staphylococcus aureus* Infections and the prevalence of Infection Caused by Community-Acquired Methicillin-Resistant *Staphylococcus aureus* in Hospitalized Patients at Siriraj Hospital

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**Background:** *The CA-MRSA infections have emerged in many parts of the world over the past decade. To our knowledge, the prevalence of CA-MRSA infections in Thai patients is unknown.*
**Objective:** *To determine an epidemiology of Staphylococcus aureus (S. aureus) infections in hospitalized patients in Siriraj Hospital and the prevalence of infections caused by community-acquired methicillin-resistant S. aureus (CA-MRSA).*
**Material and Method:** *The study was carried out at Siriraj Hospital from January to May 2005. The eligible patients were hospitalized patients whom S. aureus were isolated from their clinical specimens submitted to Department of Microbiology. S. aureus isolate was classified into infection or colonization. S. aureus infections were further classified into methicillin-resistant S. aureus (MRSA) or methicillin-sensitive S. aureus (MSSA) infections, and hospital-acquired (HA) or community-acquired (CA) infections. CA-MRSA infection is defined as infection caused by MRSA isolated from the patient within 72-hour of hospitalization and has no features of HA MRSA infections.*
**Results:** *There were 669 S. aureus isolates from 448 patients. Two hundred and sixty two patients (58.5%) were MSSA whereas 186 (41.5%) were MRSA infections. CA-MRSA was found in three isolates (0.9% of total MRSA) from two patients.*
**Conclusion:** *The prevalence of CA-MRSA infections in hospitalized patients in Siriraj Hospital was uncommon and these patients could probably be HA MRSA infections.*

**Keywords:** *Prevalence, Staphylococcus aureus, Methicillin-resistant, Community-acquired, Cross sectional study, Cohort study,Thailand*

***J Med Assoc Thai 2006; 89 (Suppl 5): S106-17***
***Full text. e-Journal:*** *http://www.medassocthai.org/journal*

The penicillinase-stable beta-lactams such as cephalosporins, methicillin and nafcillin became available in the late 1950s[1]. Ironically, the first methicillin-resistant *Staphylococcus aureus* (MRSA) was described at about the same time[2, 3]. The prevalence of MRSA progressively increased thereafter[4, 5]. A survey of the National Nosocomial infections Surveillance System reported that the hospital prevalence MRSA increased from 2.1% in 1975 to 35% in 1991[6]. It is currently as high as 70% in certain centers, but great geographic variations exists. The data from the SENTRY Antimicrobial Surveillance Program during 1997 and 1999 revealed that the MRSA prevalence varied as follows: Western Pacific region, 46%; United States, 34.2%; Latin America, 34.9%; Europe, 26.3%; Canada, 5.7%. Moreover, a variation of MRSA varied greatly among countries within a region. In European centers, the percentages of MRSA varied from less than 2% in the Netherlands to 54.4% in Portugal. In Western

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Pacific countries, MRSA ranged from 23.6% (Australia) to more than 70% in Japan and Hong Kong[7]. In Thailand, from a survey of 32 hospitals (1998-2001), the MRSA ranged from 24-36%. MRSA has traditionally been considered a healthcare-associated pathogen in patients with established risk factors[8-10]. MRSA has become a major cause of hospital-acquired (HA) infections over the past decade.[11]

MRSA is an emerging community pathogen. It was first reported in the early 1990s among closed communities of Aborigines in Western Australia[12]. Fatal community-acquired MRSA (CA-MRSA) infections were reported in USA in 1999[13]. Outbreaks of CA-MRSA infections in healthy children, adolescents, and adults were described worldwide[13-25]. CA-MRSA infections tend to occur in younger persons than do hospital-acquired MRSA (HA-MRSA) infections. They often cause sporadic cases of skin and soft tissue infections but cases of necrotizing pneumonia were also reported[26]. CA-MRSA was found to be associated with virulent strains producing Panton-Valentine leucocidin (PVL) and a variety of other exotoxins[27]. It showed resistance to methicillin, which is encoded by the *mecA* gene, mostly found on the type IV staphylococcal cassette chromosome (SCC)[16]. The spread of CA-MRSA strains was not limited to the community and might also be seen in the hospital setting[28]. A recent meta-analysis reported a pooled MRSA colonization prevalence rate of 1.3% in 10 studies testing a total of 8,350 persons in the community, whereas the respective prevalence rate was 0.2% in studies excluding persons exposed to healthcare services[29]. In this meta-analysis, it was also found that MRSA colonization was more frequent among persons in the community from whom cultures were obtained in the healthcare setting compared with those screened outside the healthcare setting[29]. Studies from some states in USA showed an increase in the number of CA-MRSA clinical isolates during the past decade[15, 21, 23], whilst this number remained stable in other states[14]. Factors that might facilitate the spread of CA-MRSA within hospitals included admission of unrecognized carriers from the community, prolonged asymptomatic colonization, inadequate laboratory identification and report, and inadequate adherence to hand hygiene and contact precaution measures.

The CA-MRSA infections have emerged in several parts of the world over the past decade. An emergence of CA-MRSA was reported from Taiwan with relatively high incidence (25-75%)[30, 31] whereas a true CA-MRSA infection was very rare in Singapore[32,33]. To our knowledge, a prevalence of CA-MRSA infections in Thailand is unknown. This study determines an epidemiology of *S. aureus* infections in hospitalized patients in Siriraj Hospital and the prevalence of infections caused by CA-MRSA.

## Material and Method

### *Subjects and Study Procedures*

The study was approved by the Ethics Committee on Human Research of Faculty of Medicine Siriraj Hospital. This cross sectional study was carried out from January 1 to May 31, 2005 at Siriraj Hospital, a 2,000-bed tertiary care university hospital in Bangkok, Thailand. The eligible patients were hospitalized patients whom *S. aureus* were isolated from their clinical specimens submitted to Department of Microbiology. *S. aureus* isolates were classified into infection or colonization. *S. aureus* infections were further classified into MRSA or MSSA; and nosocomial, HA or community-acquired (CA) infections. CA is defined as infection caused by MRSA isolated from the patient within 72-hour of hospitalization and has no features of HA MRSA infections, history of hospitalization, surgery, dialysis, or residence in a long-term care facilities within one year of the MRSA culture date or a permanent indwelling catheter or percutaneous medical device (e.g. tracheostomy tube, gastrostomy tube, or urethral catheter) present at the time of cultures, a known positive culture for MRSA prior to the study period or who had been discharged from an acute care hospital within 10 days. Nosocomial infection is the infection occur-

**Table 1.** Classification of cases with *S. aureus* isolated from their clinical specimens

| Classification of cases | | No. of cases (%) |
|---|---|---|
| MSSA* | | 262 (100) |
| | Community-acquired | 68 (26.0) |
| | Nosocomial | 117 (44.7) |
| | Healthcare-associated | 77 (29.4) |
| MRSA** | | 186 (100) |
| | Community-acquired | 2 (1.1) |
| | Nosocomial | 154 (82.8) |
| | Healthcare-associated | 30 (16.1) |
| Total | | 448 (100) |

* Methicillin-Sensitive *Staphylococcus aureus*
** Methicillin-Resistant *Staphylococcus aureus*

ring in the patient who has been hospitalized for more than 72-hour or who had been discharged from an acute care hospital within 10 days. The isolates that are neither CA nor nosocomial-acquired therefore, belong to the "healthcare-associated" setting and are classified as HA infections. The medical records of the eligible subjects were reviewed. The relevant information regarding clinical data and microbiological data of each

**Table 2.** Demographics of 446 cases with *S. aureus* isolated from their clinical specimens

| Demographic data | | Type of *S. aureus* | | p |
|---|---|---|---|---|
| | | MSSA (N=262) | MRSA (N=184) | |
| Age | Mean (yr.) | 44.9 | 55.3 | <0.001 |
| | Standard Deviation(yr.) | 27.3 | 24.0 | |
| | Minimum (d.) | 1 | 7 | |
| | Maximum (yr.) | 93.0 | 95.0 | |
| Gender | Male | 129 (49.2%) | 99 (53.8%) | 0.39 |
| Nationality | Thai | 251 (95.8%) | 179 (97.3%) | 0.57 |
| | Others | 11 (4.2%) | 5 (2.7%) | |
| Location of the residence | Central | 218 (83.2%) | 152 (82.6%) | 0.72 |
| | Northeast | 17 (6.5%) | 12 (6.5%) | |
| | South | 11 (4.2%) | 8 (4.3%) | |
| | North | 7 (2.7%) | 2 (1.1%) | |
| | Others | 9 (3.5%) | 10 (5.5%) | |
| Occupation | Nursing home | 1 (0.4%) | 0 | NA* |
| | Government employee | 15 (5.7%) | 12 (6.5%) | |
| | Farmer | 7 (2.7%) | 6 (3.3%) | |
| | Student | 28 (10.7%) | 10 (5.4%) | |
| | Employee | 46 (17.6%) | 21 (11.4%) | |
| | Free | 13 (5.0%) | 16 (8.7%) | |
| | None | 150 (57.2%) | 117 (63.5%) | |
| | Others | 2 (0.8%) | 2 (1.1%) | |
| Living arrangement | Private | 257 (98.1%) | 181 (98.4%) | 1.0 |
| | Nursing home | 5 (1.9%) | 3 (1.6%) | |

* Not available

**Table 3.** Clinical data of 446 patients

| Clinical data | | Type of *S. aureus* | | p |
|---|---|---|---|---|
| | | MSSA (N=262) | MRSA (N=184) | |
| Ward | Medicine | 105 (40.1%) | 118 (64.1%) | <0.001 |
| | Surgery | 87 (33.3%) | 48 (26.1%) | |
| | OB&GYN | 7 (2.7%) | 1 (0.5%) | |
| | Pediatrics | 38 (14.5%) | 10 (5.4%) | |
| | EENT | 16 (6.1%) | 6 (3.2%) | |
| | Others | 9 (3.5%) | 1 (0.5%) | |
| History of healthcare-associated conditions | | 158 (60.3%) | 145 (78.8%) | <0.001 |
| Catheter or device | | 42 (16.0%) | 40 (21.7%) | 0.16 |
| Prior presence of MRSA | | 2 (0.8%) | 14 (7.6%) | <0.001 |
| Hospitalization > 72 h* | | 108 (41.2%) | 142 (77.2%) | <0.001 |
| Prior hospitalization | | 150 (57.3%) | 145 (79.2%) | <0.001 |

*Hospitalization more than 72 hours or who had been discharged from an acute care hospital within 10 days

**Table 4.** Underlying medical conditions of 446 patients

| Underlying diseases / conditions | | Type of *S. aureus* MSSA(N=262) | MRSA (N=184) | p |
|---|---|---|---|---|
| Pulmonary diseases | COPD | 4 (1.5%) | 14 (7.6%) | 0.06 |
| | Bronchial asthma | 4 (1.5%) | 1 (0.5%) | |
| | ILD | 2 (0.8%) | 0 | |
| | Prior pneumonia | 1 (0.4%) | 0 | |
| | Others | 14 (5.3%) | 16 (8.7%) | |
| Neoplastic diseases | | 57 (21.8%) | 45 (24.5%) | 0.58 |
| Liver diseases | Cirrhosis | 11 (4.2%) | 17 (9.2%) | 0.07 |
| | Chronic active hepatitis | 1 (0.4%) | 1 (0.5%) | |
| | Others | 4 (1.5%) | 3 (1.6%) | |
| Heart diseases | CHF | 5 (1.9%) | 4 (2.2%) | 0.13 |
| | CAD | 24 (9.2%) | 25 (13.6%) | |
| | Valve replacement | 1 (0.4%) | 2 (1.1%) | |
| | Congenital heart diseases | 7 (2.7%) | 3 (1.6%) | |
| | Others | 8 (3.1%) | 9 (4.9%) | |
| Neurologic diseases | Stroke | 22 (8.4%) | 19 (10.3%) | 0.01 |
| | TIA | 1 (0.4%) | 0 | |
| | Cerebral palsy | 1 (0.4%) | 0 | |
| | Bed-ridden status | 8 (3.1%) | 14 (7.6%) | |
| | Others | 14 (5.3%) | 18 (9.8%) | |
| Renal diseases | Azotemia | 7 (2.7%) | 14 (7.6%) | 0.13 |
| | Chronic kidney disease | 15 (5.7%) | 10 (5.4%) | |
| | HD via catheter | 15 (5.7%) | 9 (4.9%) | |
| | HD via AVF | 9 (3.4%) | 7 (3.8%) | |
| | Peritoneal dialysis | 2 (0.8%) | 3 (1.6%) | |
| | Others | 2 (0.8%) | 4 (2.2%) | |
| Diabetes mellitus | | 55 (21.0%) | 53 (28.8%) | 0.07 |
| High alcohol intake | | 16 (6.1%) | 16 (8.7%) | 0.20 |
| Smoking | | 25 (9.5%) | 19 (10.3%) | 0.60 |
| Neutropenia | | 5 (1.9%) | 13 (7.1%) | 0.01 |
| Splenectomy | | 1 (0.4%) | 1 (0.5%) | 1.0 |
| Metabolic disorder | | 2 (0.8%) | 4 (2.2%) | 0.24 |
| Recent operation | | 15 (5.7%) | 15 (8.2%) | 0.52 |
| Implanted devices | Pacemaker | 0 | 1 (0.5%) | 0.03 |
| | Others | 13 (5.0%) | 19 (10.3%) | |
| Recent corticosteroid | | 8 (3.1%) | 17 (9.2%) | 0.02 |
| Immuno-suppressives | | 21 (8.0%) | 22 (12.0%) | 0.28 |
| Others | | 111 (42.4%) | 83 (45.1%) | 0.63 |

subject were retrieved and entered into the structured case record forms.

***Data Analysis***

Data were expressed as percentage and mean ± SD for nominal and continuous variables, respectively. Analyses were performed using SPSS 13.0 (SPSS Inc, Chicago, Illinois). Nominal variables were compared by Chi-square test or Fisher's Exact test and continuous variables were compared by two-tailed unpaired t-test or Mann-Whitney U test as appropriate. The statistically significant factors were confirmed by the multivariate analysis using a forward likelihood logistic regression model. A p- value < 0.05 was considered significant.

**Results**

From January 1 to May 31, 2005, 669 *S. aureus* isolates from 448 patients were enrolled. Two hundred and sixty two patients (58.5%) were MSSA whereas

186 (41.5%) were MRSA. CA-MRSA was found in three isolates (0.9% of total MRSA) from two patients as shown in Table 1.

***Description of CA-MRSA patients***

***Case 1***

A 46-year old Thai male presented with a three-month history of fever, malaise, weight loss, and hematemesis. He came to community hospital as an outpatient three times within three weeks. His underlying medical conditions included liver cirrhosis, hepatitis C infection, heavy alcoholic drinking, and smoking. He was admitted to general medical ward with dyspnea. He received endotracheal tube, nasogastric tube, and urethral catheter. Chest radiography revealed bilateral reticulonodular with patchy infiltration. MRSA was isolated from the sputum on the second day of hospitalization. Sputum examination was positive for acid fast bacilli. He was empirically treated with ceftriaxone, amikacin, and ciprofloxacin. He also received anti-tuberculosis drugs. He had clinical improvement and left the hospital six days after admission.

***Case 2***

A 52-year old female presented with chronic ulcer of her left leg. She had wound dressing at a community clinic everyday for two weeks and she took penicillin V 2 grams per day for two weeks. She was admitted to surgery ward for wound debridement and she was found to have diabetes mellitus. MRSA was isolated from pus and tissue on the first and second day of admission. She received ceftriaxone and clindamycin, wound debridement and diabetic control. She was improved and left the hospital seven days after admission.

***MSSA and MRSA patients***

The demographics of the patients who had

**Table 5.** Previous medical history of antibiotics use in 446 patients

| Antibiotic | Type of *S. aureus* | | |
|---|---|---|---|
| | MSSA (N=262) | MRSA (N=184) | p |
| Prior antibiotics use | 74 (28.2%) | 135 (73.4%) | <0.001 |
| Cephalosporins | 25 (9.5%) | 82 (44.6%) | <0.001 |
| Penicillins | 31 (11.8%) | 40 (21.7%) | 0.07 |
| Aminoglycosides | 6 (2.3%) | 23 (12.5%) | <0.001 |
| Quinolones | 6 (2.3%) | 28 (15.2%) | <0.001 |
| Macrolides | 2 (0.8%) | 3 (1.6%) | 0.65 |
| Tetracyclines | 0 | 1 (0.5%) | 0.42 |
| Carbapenems | 3 (1.1%) | 27 (14.7%) | <0.001 |
| Glycopeptides | 3 (1.1%) | 13 (7.1%) | 0.002 |
| Miscellaneous | 13 (5.0%) | 56 (30.4%) | <0.001 |

**Table 6.** Predisposing factors of 446 patients

| Risk factors | Type of *S. aureus* | | |
|---|---|---|---|
| | MSSA (N=262) | MRSA (N=184) | p |
| Arterial catheter | 11 (4.2%) | 6 (3.3%) | 0.80 |
| Central venous catheter | 16 (6.1%) | 30 (16.3%) | <0.001 |
| Double lumen catheter | 15 (5.7%) | 15 (8.2%) | 0.41 |
| Endotracheal tube | 62 (23.7%) | 75 (40.8%) | <0.001 |
| Tracheostomy | 11 (4.2%) | 25 (13.6%) | <0.001 |
| Urethral catheter | 88 (33.6%) | 104 (56.5%) | <0.001 |
| Nasogastric tube | 70 (26.7%) | 104 (56.5%) | <0.001 |
| Surgical intervention | 127 (48.5%) | 98 (53.3%) | 0.37 |
| Others | 33 (12.6%) | 32 (17.5%) | 0.20 |

**Table 7.** Category of infections of 446 patients

| Type of infection | | Type of *S. aureus* MSSA (N=262) | MRSA (N=184) | p |
|---|---|---|---|---|
| Infective endocarditis | Native valve | 1 (0.4%) | 0 | 1.0 |
| Soft tissue infection | Abscess | 50 (19.1%) | 10 (5.4%) | <0.001 |
| | Cellulitis | 6 (2.3%) | 0 | |
| | Necrotizing fasciitis | 3 (1.1%) | 1 (0.5%) | |
| | Others | 19 (7.3%) | 9 (4.9%) | |
| Orthopedic infection | COM* | 7 (2.7%) | 2 (1.1%) | 0.80 |
| | AOM** | 2 (0.8%) | 0 | |
| | Surgical site infect | 3 (1.1%) | 4 (2.2%) | |
| | Others | 2 (0.8%) | 2 (1.1%) | |
| Respiratory tract infection | CAP*** | 22 (8.4%) | 10 (5.4%) | 0.03 |
| | HAP**** | 20 (7.6%) | 39 (21.2%) | |
| | Lung abscess | 0 | 1 (0.5%) | |
| | Empyema | 2 (0.8%) | 2 (1.1%) | |
| | Others | 6 (2.3%) | 0 | |
| Urinary tract infection | | 5 (1.9%) | 3 (1.6%) | 1.0 |
| Primary bacteremia | | 23 (8.8%) | 9 (4.9%) | 0.17 |
| Other infections | | 23 (8.8%) | 22 (12.0%) | 0.35 |
| Colonization | | 75 (28.6%) | 74 (40.2%) | 0.01 |

* Chronic osteomyelitis
** Acute osteomyelitis
*** Community-acquired pneumonia
**** Hospital-acquired pneumonia

**Table 8.** Source of clinical specimens containing *S. aureus*

| Specimen | Type of *S. aureus* MSSA (N=262) | MRSA (N=184) |
|---|---|---|
| Blood | 36 (13.7%) | 17 (9.2%) |
| Joint fluid | 5 (1.9%) | 2 (1.1%) |
| Pleural fluid | 2 (0.8%) | 1 (0.5%) |
| Peritoneal fluid | 0 | 1 (0.5%) |
| Pus | 99 (37.8%) | 39 (21.2%) |
| Sputum | 82 (31.3%) | 93 (50.5%) |
| Bronchial fluid | 1 (0.4%) | 2 (1.1%) |
| Urine | 13 (5.0%) | 7 (3.8%) |
| Others | 24 (9.2%) | 22 (12.0%) |

MRSA infections were not significantly different from those who had MSSA except MRSA patients were older: 55.3 years vs 44.9 years as shown in Table 2. The variables that were significantly different between MRSA and MSSA patients are shown in Table 3 to 12. They were: 1) clinical data on type of wards (p<0.001), history of healthcare-associated factors (p<0.001), prior MRSA culture (p<0.001), hospitalization more than 72 hours or who had been discharged from an acute care hospital within 10 days (p<0.001), prior hospitalization (p<0.001); 2) underlying medical conditions on neurologic diseases (p=0.01), neutropenia (p=0.01), implanted devices (p=0.03), and recent corticosteroids (p=0.02); 3) previous history of prior antibiotic use (p<0.001), cephalosporin use (p<0.001), aminoglycoside use (p<0.001), quinolone use (p<0.001), carbapenem use (p<0.001), glycopeptide use (p=0.002), miscellaneous antibiotics (p<0.001); 4) predisposing factors on central venous catheter, endotracheal tube, tracheostomy, urethral catheter, and nasogastric tube (p<0.001); 5) category of infection on soft tissue infection (p<0.001), respiratory tract infection (p=0.03), and colonization (p=0.01); 6) clinical evaluation of infections on duration of fever (p<0.001), duration of admission (p<0.001), admission to ICU (p=0.04), and duration from hospitalization until death (p=0.03); 7) initial antibiotic regimen on number of initial antibiotics regimen (p<0.001), fourth generation cephalosporin use (p=0.003), penicillins use (p<0.001), quinolones use (p=0.001), carbapenems use (p<0.001), glycopeptides use (p<0.001), and miscellaneous use (p=0.006); 8) outcome on early outcome (p<0.001), complication (p=0.002), overall outcome (p<0.001), and cause of overall death (p<0.001). Six

**Table 9.** Clinical outcomes of infections

| Duration (day) | Type of *S. aureus* | | p |
|---|---|---|---|
| | MSSA (N=262) | MRSA (N=184) | |
| Duration of fever | 113 (43.1%) | 121 (65.8%) | <0.001 |
| Mean | 4.39 | 6.56 | |
| Standard Deviation | 9.26 | 7.24 | |
| Range | 1-90 | 1-35 | |
| Duration of symptom | 230 (87.8%) | 161 (87.5%) | 0.96 |
| Mean | 28.34 | 9.99 | |
| Standard Deviation | 242.72 | 15.10 | |
| Range | 1-3650 | 1-120 | |
| Duration of hospitalization | 262 (58.5%) | 184 (41.1%) | <0.001 |
| Mean | 28.62 | 47.82 | |
| Standard Deviation | 36.01 | 52.53 | |
| Range | 1-213 | 1-348 | |
| Admission to ICU | 45 (17.2%) | 65 (35.3%) | 0.04 |
| Mean | 13 | 28 | |
| Standard Deviation | 20 | 45 | |
| Range | 1-101 | 1-348 | |
| Duration from admission to death | 50 (19.1%) | 77 (41.8%) | 0.03 |
| Mean | 18.21 | 18.60 | |
| Standard Deviation | 33.20 | 17.38 | |
| Range | 1-211 | 1-72 | |

variables associated with mortality were surgical wards, respiratory infections, use of endotracheal tube, category of *S. aureus*, indwelling urethral catheter, and having implanted devices as shown in Table 13.

**Discussion**

The recent report on *S. aureus* concluded that CA-MRSA in Thailand was extremely rare[34]. There was a report from a hospital in Thailand describing a child who had CA-MRSA infection[35]. He presented with submandibular lymphadenitis and MRSA was isolated from pus collected from incision and drainage of the lymph node on admission day. The molecular type of this isolate of MRSA was unknown. Our data suggests that the prevalence of CA-MRSA infections in hospitalized patients in Siriraj Hospital was uncommon, and both patients who met criteria of CA-MRSA infections could probably be HA MRSA infections since both of them had history of hospital visits just prior to their hospitalizations. Moreover, the antibiotic susceptibility profiles of MRSA isolated from both patients were multi-drug resistant. The universal definition of CA-MRSA has not been established and acceptable. In fact, the previous review revealed that at least eight different definitions have been used to classify MRSA infections as community acquired[29]: 1) isolation of MRSA within 24 h of admission, 2) isolation of MRSA within 24 h of admission, with other exclusions, 3) presence of MRSA at or within 48 h of admission, 4) isolation of MRSA within 48 h of admission, with other exclusions, 5) isolation of MRSA within 48–72 h of admission, 6) isolation of MRSA within 72 h of admission, 7) isolation of MRSA within 72 h of admission, with other exclusions, 8) isolation of MRSA from a patient from a community clinic or facility. An observation of a very low prevalence of CA-MRSA might not be valid since we did not include out-patients who could have minor *S. aureus* infections and these patients might have CA-MRSA infections. A recent outpatient visit within 12 months was found to be the risk factors for MRSA acquisition[29]. Other risk factors were recent hospitalization, recent nursing home admission, chronic illness, injection drug use, and close contact with a person with risk factor(s) for MRSA acquisition.

**Table 10.** Initial antibiotic regimens of 446 patients

| Initial antibiotic regimen | | Type of *S. aureus* MSSA (N=262) | MRSA (N=184) | p |
|---|---|---|---|---|
| Number of initial antibiotic regimens | Monotherapy | 147 (56.1%) | 76 (41.3%) | <0.001 |
| | Duotherapy | 72 (27.5%) | 77 (41.8%) | |
| | Triple therapy | 9 (3.4%) | 11 (6.0%) | |
| | > 3 antibiotics | 1 (0.4%) | 4 (2.2%) | |
| | No treatment | 33 (12.6%) | 16 (8.7%) | |
| First generation cephalosporin | | 17 (6.5%) | 4 (2.2%) | 0.06 |
| Second generation cephalosporins | | 2 (0.8%) | 0 | 0.51 |
| Third generation cephalosporins | | 90 (34.4%) | 62 (33.7%) | 0.97 |
| Fourth generation cephalosporins | | 7 (2.7%) | 18 (9.8%) | 0.003 |
| Penicillins | | 84 (32.1%) | 27 (14.7%) | <0.001 |
| Aminoglycosides | | 29 (11.1%) | 17 (9.2%) | 0.64 |
| Quinolones | | 14 (5.3%) | 27 (14.7%) | 0.001 |
| Macrolides | | 5 (1.9%) | 2 (1.1%) | 0.70 |
| Tetracyclines | | 2 (0.8%) | 1 (0.5%) | 1.0 |
| Carbapenems | | 7 (2.7%) | 38 (20.7%) | <0.001 |
| Glycopeptides | | 21 (8.0%) | 37(20.1%) | <0.001 |
| Miscellaneous | | 43 (16.4%) | 51 (27.7%) | 0.006 |
| Susceptible to initial antibiotics | Susceptible to all antibiotics | 66 (25.2%) | 18 (9.8%) | NA* |
| | Susceptible to some antibiotics | 19 (7.3%) | 2 (1.1%) | |
| | Resistant to all antibiotics | 3 (1.1%) | 36 (19.6%) | |
| | Unknown | 174 (66.4%) | 128 (69.6%) | |

* Not available

**Table 11.** Outcomes of 446 patients

| Outcome | | Type of *S. aureus* MSSA (N=262) | MRSA (N=184) | p |
|---|---|---|---|---|
| Early outcome * | Improve | 202 (77.1%) | 92 (50.0%) | <0.001 |
| | Failure | 51 (19.5%) | 78 (42.4%) | |
| | Death | 9 (3.4%0 | 14 (7.6%) | |
| Cause of early death** | Death | 9 (3.4%) | 14 (7.5%) | 0.21 |
| | Uncontrolled *S. aureus* infection | 4 (1.5%) | 10 (5.4%) | |
| | Other | 5 (1.9%) | 3 (1.6%) | |
| | Unknown | 0 | 1 (0.5%) | |
| Complication | Uncontrolled *S. aureus* infection | 9 (3.4%) | 21 (11.4%) | 0.002 |
| | Unrelated to *S. aureus* infection | 72 (27.6%) | 77 (41.8%) | |
| Overall outcome | Improve | 202 (77.1%) | 101 (54.9%) | <0.001 |
| | Failure | 46 (17.6%) | 75 (40.8%) | |
| | Undetermine | 14 (5.3%) | 8 (4.3%) | |
| Cause of death | Death | 50 (19.1%) | 77 (41.8%) | <0.001 |
| | Uncontrolled *S. aureus* infection | 8 (3.1%) | 19 (10.3%) | |
| | Other | 42 (16.0%) | 57 (31.0%) | |
| | Unknown | 0 | 1 (0.5%) | |

* Outcome within 3-5 days of treatment
** Death within 72 hours

**Table 12.** Susceptibility of *S. aureus* to initial antibiotic regimen of 448 cases

| Antibiotic | Type of *S. aureus* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | MSSA (N=262) | | | MRSA (N=184) | | | CA-MRSA (N=2) | | |
| | S* | R** | I*** | S* | R** | I*** | S* | R** | I*** |
| Ampi/amoxy | 18.2% | 81.8% | 0 | 0 | 100% | 0 | 0 | 0 | 0 |
| Cefazolin | 100% | 0 | 0 | 0 | 100% | 0 | 0 | 0 | 0 |
| Chloramphenicol | 96.6% | 3.4% | 0 | 92.3% | 6.7% | 0 | 0 | 100% | 0 |
| Cotrimoxazole | 99.4% | 0.6% | 0 | 13.1% | 85.9% | 1.0% | 0 | 100% | 0 |
| Erythromycin | 91.4% | 7.4% | 1.2% | 1.1% | 98.9% | 0 | 0 | 100% | 0 |
| Gentamicin(10mcg) | 98.2% | 1.8% | 0 | 8.1% | 91.9% | 0 | 0 | 100% | 0 |
| Methicillin | 100% | 0 | 0 | 0 | 100% | 0 | 0 | 100% | 0 |
| Amoxy/clavulanate | 100% | 0 | 0 | 0 | 100% | 0 | 0 | 0 | 0 |
| Ampi/sulbactam | 100% | 0 | 0 | 0 | 100% | 0 | 0 | 0 | 0 |
| Cefoxitin | 100% | 0 | 0 | 0 | 100% | 0 | 0 | 0 | 0 |
| Ceftazidime | 100% | 0 | 0 | 0 | 100% | 0 | 0 | 0 | 0 |
| Ceftriaxone | 100% | 0 | 0 | 0 | 100% | 0 | 0 | 0 | 0 |
| Netilmycin | 100% | 0 | 0 | 0 | 100% | 0 | 0 | 0 | 0 |
| Ofloxacin | 100% | 0 | 0 | 0 | 100% | 0 | 0 | 0 | 0 |
| Tetracycline | 59.7% | 40.3% | 0 | 12.9% | 87.1% | 0 | 0 | 100% | 0 |
| Ciprofloxacin | 80.6% | 5.0% | 14.4% | 1.0% | 99.0% | 0 | 0 | 100% | 0 |
| Clindamycin | 94.8% | 4.5% | 0.7% | 8.6% | 91.4% | 0 | 0 | 100% | 0 |
| Fosfomycin | 100% | 0 | 0 | 87.7% | 9.2% | 3.1% | 100% | 0 | 0 |
| Fusidic acid | 100% | 0 | 0 | 91.8% | 6.1% | 2.1% | 100% | 0 | 0 |
| Vancomycin | 100% | 0 | 0 | 100% | 0 | 0 | 100% | 0 | 0 |
| Teicoplanin | 100% | 0 | 0 | 100% | 0 | 0 | 100% | 0 | 0 |
| Linezolid | 100% | 0 | 0 | 100% | 0 | 0 | 100% | 0 | 0 |
| Rifampicin | 100% | 0 | 0 | 46.2% | 53.8% | 0 | 50% | 50% | 0 |

* Sensitive, ** Resistant, *** Intermediate

**Table 13.** Variables associated with mortality by logistic regression

| Variable | p | Adjusted OR | 95% CI for OR |
|---|---|---|---|
| Ward | | | |
| Medicine | 0.001 | 3.4 | 1.7-6.8 |
| Others | 0.40 | 0.7 | 0.3-1.7 |
| Respiratory infection | <0.001 | 3.2 | 1.8-5.7 |
| Retain endotracheal tube | 0.001 | 2.8 | 1.5-5.2 |
| Category of *S. aureus* | 0.004 | 2.1 | 1.3-3.6 |
| Urethral catheter | 0.01 | 2.2 | 1.2-4.0 |
| Implanted devices | 0.21 | 4.6 | 1.3-16.9 |

MRSA colonization can persist for months to years[9,36], and one study reported an estimated half-life of MRSA colonization of 40 months among patients known to be colonized with MRSA who were admitted to a university hospital[36]. The majority of colonized patients remained completely asymptomatic. Therefore, acquisition of MRSA, whether it occurs in the hospital or in the community, frequently goes unrecognized unless clinical infection develops. Given the duration for which colonization with MRSA can persist, an infection may develop in a setting different from that in which the organism was initially acquired. Thus, in the absence of more epidemiological data, such as the results of surveillance cultures documenting time of acquisition, the true site of acquisition of MRSA is rarely known with certainty. The commonly used term "CA-MRSA" implies that it is known that the organism was acquired in the community. It appears, however, that this term is often used to refer to the detection of colonization or infection in the community, rather than to actual acquisition of MRSA in the community. The term "community-onset" MRSA (CO-MRSA), which simply describes the patient's location at the time of identification of MRSA, would be more technically correct than the currently used "CA-MRSA", which implies that the site of MRSA acquisition is known[29]. When a patient with nosocomially acquired MRSA spreads the

organism to multiple members of the patient's household or community, this should not be called "community acquisition".

In this study, we found that the patients who had MRSA isolated from their clinical specimens were significantly associated with health care-associated risk factors, prior antibiotic use, and predisposing factors when compared with those with MSSA. These observations were similar to the previous study[8-10]. MRSA patients were also associated with longer duration of fever, longer duration of hospitalization[9, 37], more frequent admission to ICU[9, 37] and higher mortality than MSSA patients. Most MRSA isolates were susceptible to several antimicrobial classes (including chloramphenicol, fosfomycin, and fusidic acid) and treatment of MRSA infections may not routinely require glycopeptides. CA-MRSA poses important challenges for public health officials. Surveillance data are needed to determine the geographic distribution of cases and to monitor the emergence of this important problem in the community. In addition, local information is needed to direct clinical decisions about treatment. However, public health resources for establishing new surveillance systems are limited. Creative approaches to surveillance, such as tracking infections from sentinel hospitals in areas that serve high-risk communities or performing periodic cross-sectional surveys, should be considered.

## Conclusion

The prevalence of CA-MRSA infections in hospitalized patients in Siriraj Hospital was uncommon. These patients could probably be health care-associated MRSA infections. All CA-MRSA should be confirmed by molecular analysis.


## Acknowledgments

The authors wish to thank Mr. Suthipol Udompunturak for statistical analyses, and The Thailand Research Fund and the Asian Network for Surveillance of Resistant Pathogens (ANSORP) for supporting the study.


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## ระบาดวิทยาของการติดเชื้อ *Staphylococcus aureus* และความชุกของ *community-acquired methicillin-resistant Staphylococcus aureus* ในผู้ป่วยที่รับไว้รักษาในโรงพยาบาลศิริราช

**ศรีเพชรรัตน์ เมฆวิวัฒน์วงศ์, สมพร ศรีเฟื่องฟุ้ง, กุลกัญญา โชคไพบูลย์กิจ, ดรินทร์ โล่ห์ศิริวัฒน์, วิษณุ ธรรมลิขิตกุล**

*ผู้วิจัยศึกษาผู้ป่วยที่รับไว้รักษาในโรงพยาบาลศิริราชที่แยกเชื้อ Staphylococcus aureus จากสิ่งส่งตรวจของผู้ป่วยระหว่างเดือนมกราคมถึงพฤษภาคม พ.ศ. 2548 เพื่อทราบระบาดวิทยาของการติดเชื้อ S. aureus และความชุกของการติดเชื้อ S. aureus ที่เกิดในชุมชน พบว่าจากจำนวนเชื้อ 669 สายพันธุ์ที่แยกได้จากผู้ป่วย 448 คน เชื้อจากผู้ป่วย 262 คน (ร้อยละ 58.5) เป็นเชื้อ MSSA ส่วนเชื้อจากผู้ป่วย 186 คน (ร้อยละ 41.5) เป็นเชื้อ MRSA ความชุกของการติดเชื้อ S. aureus ที่เกิดในชุมชนพบเพียง 3 สายพันธุ์จากผู้ป่วย 2 คนเท่านั้น ผู้ป่วยที่ติดเชื้อ MRSA มีลักษณะที่แตกต่างจากผู้ป่วย MRSA คือ 1) ผู้ติดเชื้อ MRSA มีอายุมากกว่า 2) ผู้ติดเชื้อ MRSA เป็นผู้ป่วย อายุรกรรม เคยรับการรักษาที่สถานพยาบาล เคยมีการติดเชื้อ MRSA เคยอยู่โรงพยาบาลมาก่อน และอยู่ในโรงพยาบาลนานกว่า 72 ชั่วโมง 3) ผู้ติดเชื้อ MRSA มีโรคปอดเรื้อรัง โรคระบบประสาท เม็ดเลือดขาวในเลือดต่ำ มีอุปกรณ์การแพทย์อยู่ในร่างกาย ได้รับคอร์ติโคสเตียรอยด์ และยาต้านจุลชีพ 4) ผู้ติดเชื้อ MRSA มีอุปกรณ์การแพทย์สอดใส่เข้าสู่ร่างกาย 5) ผู้ติดเชื้อ MRSA มีปอดอักเสบ การติดเชื้อที่ผิวหนังและเนื้อเยื่อใต้ผิวหนัง และ colonization 6) ผู้ติดเชื้อ MRSA มีเชื้อ S. aureus ในเสมหะ 7) ผู้ติดเชื้อ MRSA มีไข้นานกว่าอยู่โรงพยาบาลนานกว่า และอยู่ในหออภิบาลนานกว่า 8) ผู้ติดเชื้อ MRSA ได้รับการรักษาด้วยยาต้านจุลชีพหลายขนาน เชื้อ MRSA ทุกสายพันธุ์ไวต่อ vancomycin, teicoplanin และ linezolid ผู้ติดเชื้อ MRSA มีอัตราความล้มเหลวต่อการรักษา และอัตราการตายสูงกว่าผู้ติดเชื้อ MSSA ปัจจัยที่สัมพันธ์กับอัตราตายจากการติดเชื้อ S. aureus คือ ผู้ป่วยอายุรกรรม ปอดอักเสบ มีการติดเชื้อ MRSA และได้รับอุปกรณ์การแพทย์สอดใส่เข้าสู่ร่างกาย*

# Implementation of Clinical Practice Policy on the Continuous Intravenous Administration of Amphotericin B Deoxycholate

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**Background:** *Systemic fungal infections have significantly increased. The mainstay of treatment is amphotericin B deoxycholate. A limitation of using amphotericin B includes infusion-related reactions and nephrotoxicity. A continuous infusion of amphotericin B was found to reduce nephrotoxicity and infusion-related reactions.*
**Objective:** *To implement clinical practice policy on the continuous intravenous administration of amphotericin B in the patients hospitalized in general medical wards at Siriraj Hospital.*
**Method:** *A one-page evidence-based clinical practice policy on continuous intravenous administration of amphotericin B was prepared and disseminated to all general medical wards in Siriraj Hospital. The information on the patients who received amphotericin B treatment between March 2004 and March 2006 was collected. The data were analyzed using descriptive statistics, univariate analysis and multiv ariate analysis as appropriate. A p-value of $< 0.05$ was considered statistically significant.*
**Results:** *Of 166 courses of amphotericin B treatment in 148 patients, 102 courses (61.4%) were given continuous intravenous administration of amphotericin B (CI group) and 64 courses (38.6%) were given conventional 4-to 6-hour intravenous administration (RI group). The mean age of the patients in the CI group was significantly greater than that in the RI group. The CI group had more patients with neutropenia with persistent fever whereas the RI group had more patients with HIV/AIDS and cryptococcal meningitis. The incidence of amphotericin B-related nephrotoxicity was 27.5% in the CI group compared with 39.1% in the RI group ($p=0.164$). Chills were observed in 6.9% of the patients in the CI group compared with 26.6% in the RI group ($p=0.001$). Overall mortality at the end of therapy was significantly higher in the CI group. However, most of the deaths in the CI group were unrelated to fungal infections or amphotericin administration.*
**Conclusion :** *Continuous infusion of amphotericin B was associated with a decrease in infusion-related reactions and tended to have less nephrotoxicity than those in the 4-to 6-hour infusion group.*

**Keywords :** *Continuous-infusion, Amphotericin B, Nephrotoxicity, Infusion-related reactions*

***J Med Assoc Thai 2006; 89 (Suppl 5): S118-24***
***Full text. e-Journal:*** *http://www.medassocthai.org/journal*

Systemic fungal infections have significantly increased over the past 30 years[1-4]. Systemic opportunistic fungal infections constitute a leading cause of morbidity and mortality in neutropenic patients[5]. In addition, HIV-infected patients often have a variety of fungal infections, especially those who have CD4+ T lymphocyte counts of <50 cells/μL[6,7]. The common causative agents in HIV-infected patients include *Cryptococcus neoformans*, *Histoplasma capsulatum*, and *Penicillium maneffei* [8].

The mainstay of treatment for these patients is amphotericin B deoxycholate despite it being associated with significant drug-related adverse effects, especially infusion-related reactions, [9-11] and nephrotoxicity [12,13]. Over the past few years, several randomized trials revealed different strategies to reduce AmB-induced renal toxicity. These strategies included sodium supplementation,[14,15] concurrent administration of low-dose dopamine,[16] correction of potassium depletion[17] and slow infusion rates. Many recent

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clinical trials of new antifungal agents have observed better outcomes and lower drug-related toxicity[18-22]. However, amphotericin B remains a cornerstone of antifungal therapy for patients with opportunistic fungal infections. Recently, continuous infusion of amphotericin B has been found to reduce the incidence of nephrotoxicity and infusion-related reactions, compared with traditional administration of the same amount of the drug over 4–6 h[23-26] as well as the results from local randomized controlled study conducted at Ramathibodi Hospital [27]. This mode of administration of amphotericin B seems to be effective in reducing the adverse effects of amphotericin B [28] and is feasible in our setting. This prompted us to implement clinical practice policy based on continuous intravenous administration of amphotericin B deoxycholate in the patients hospitalized in the general medical wards at Siriraj Hospital.

## Material and Method

A one-page evidence-based clinical practice policy on continuous intravenous administration of amphotericin B containing a description of the problem of using amphotericin B, recommendation on using continuous intravenous administration of amphotericin B, grade of recommendation and references was prepared. The clinical practice policy on continuous intravenous administration of amphotericin B was circulated to 10 general medical wards at Siriraj Hospital in March 2004. The decision to use continuous infusion or 4-to 6-hour infusion of amphotericin B was made by the responsible attending physicians. The use of medications to prevent infusion-related reactions was decided by attending physicians. The study was approved by the ethics committee on human research of the Faculty of Medicine, Siriraj Hospital. We collected the information on the patients who received amphotericin B who had serum creatinine <3 mg/dl. The patients who needed amphotericin B could receive a continuous infusion (CI group) or 4-to 6-hour infusion (RI group) of amphotericin B. In the patients who received continuous infusion of amphotericin B, amphotericin B at the appropriate dosage was added in 500 ml of 5% glucose without any additives and given intravenously as a continuous infusion over 24 hours. Medications to prevent any infusion-related reaction and intravenous saline were administered whenever appropriate.

Infusion-time was recorded in all cases. All infusion-related conditions were recorded including chills, nausea, vomiting, and phlebitis. Serum creatinine was measured at least twice a week and creatinine clearance (CrCl) was calculated by the Cockcroft-Gault formula[29]. Renal impairment was defined as a doubling of baseline serum creatinine and was calculated as a creatinine ratio (peak serum creatinine during amphotericin B administration/baseline serum creatinine).

The number of patients required for this study was assessed by the assumption that a rate of renal impairment in the CI group was 20% $\pm$ 7.5%. That was clinically less than 40% observed in hospitalized patients in the Department of Medicine who received 4-hour amphotericin B infusions in 2002, where 110 courses of CI would be needed at the two-sided significance level of 5%. Multivariate logistic regression analysis was used to adjust for potential confounding variables with regard to renal impairment and outcome. A Mann-Whitney U-test was used for median comparisons.

## Results

### *Baseline characteristics*

Of 166 courses of amphotericin B treatment in 148 patients, 102 courses (61.4%) in 91 patients were given by continuous intravenous administration of amphotericin B (CI group) and 64 courses (38.6%) in 57 patients were given by conventional 4-to 6-hour intravenous administration (RI group). The demographics of the patients in both groups are shown in Table 1. There were no significant differences in gender, duration of treatment or total dose of amphotericin B. However, the patients in the CI group were older than those in RI group (40 (15-74) vs 36 (16-68) years, $p$ = 0.03) and had less HIV/AIDS than those in the RI group (21.6% vs 40.6%, $p$ = 0.01). The number of patients in the CI group who received amphotericin B due to neutropenia with refractory fever was significantly greater than that in the RI group, 64.7 % vs 42.2% ($p$ = 0.007) as shown in Table 2. Cryptococcal infections were more common in the patients in the RI group when compared with those in the CI group (34.4% vs 17.7%, $p$ = 0.02). The baseline serum BUN was higher in the CI group than in the RI group (16.4 $\pm$ 14.5 mg/dl vs 13.9 $\pm$ 8.8, $p$ = 0.03), but the baseline values of serum creatinine and calculated creatinine clearance were not significantly different between both groups. The use of medications to prevent infusion related reactions did not differ between the CI group and the RI group.

### *Outcomes*

Nephrotoxicity, infusion-related reactions, and

**Table 1.** Demographic data of the patients

| | Infusion rate | | |
|---|---|---|---|
| | CI group (n = 91) | RI group (n = 57) | p-value |
| Median age, years (range) | 40 (15-74) | 36 (16-68) | 0.03 |
| Female, No. (%) of the patients | 42 (41.2) | 28 (43.8) | 0.43 |
| Median (range) days of treatment | 11 (1-147) | 14 (5-121) | 0.11 |
| Median (range) mg accumulative dose | 400 (60-1880) | 645 (180-5820) | 0.17 |
| Diagnosis, no.(%) of the patients | | | |
| - HIV/AIDS | 22 (21.6) | 26 (40.6) | 0.01 |
| - Acute myeloid leukemia | 40 (39.2) | 24 (37.5) | |
| - Non-Hodgkin's lymphoma | 12 (11.8) | 2 (3.1) | |
| - Acute lymphocytic leukemia | 8 (7.8) | 4 (6.3) | |
| - Severe aplastic anemia | 6 (5.9) | 1 (1.6) | |
| - Chronic myeloid leukemia | 5 (4.9) | 3 (4.7) | |
| - Others | 9 (8.8) | 4 (6.3) | |
| Concurrent treatment of nephrotoxic drugs | 56 (54.9) | 30 (46.9) | 0.40 |
| - Aminoglycosides | 30 (29.4) | 20 (31.3) | |
| - Vancomycin | 14 (13.7) | 4 (6.3) | |
| - Both | 12 (11.8) | 6 (9.4) | |
| - Others | 1 (1) | 0 (0) | |

**Table 2.** Indications for amphotericin B treatment

| | CI group (102 courses in 91 patients) | RI group (64 courses in 57 patients) | p-value |
|---|---|---|---|
| Refractory fever in neutropenia (ANC < 500/cumm) * | 66 (64.7%) | 27 (42.2%) | 0.005 |
| Cryptococcal infection | 18 (17.7%) | 22 (34.4%) | 0.02 |
| Aspergillus infection | 8 (7.9%) | 9 (14.1%) | |
| Penicillium infection | 4 (3.9%) | 0 | |
| Histoplasma infection | 2 (2%) | 2 (3.1%) | |
| Mucormycoses | 2 (2%) | 1 (1.6%) | |
| Candidemia | 2 (2%) | 2 (3.1%) | |
| *Cladophialophora bantiana* brain abscess | 0 | 1 (1.6%) | |

* ANC means absolute neutrophil count

clinical outcomes of the patients are shown in Table 3. The nephrotoxicity was observed in 27.5% in the CI group and 39.1% in the RI group ($p = 0.2$), the relative risk of nephrotoxicity of the CI group when compared with that in the RI group was 0.70 (95% CI 0.45 to 1.09) and the relative risk reduction was 30% (95% CI -12% to 56%). The incidence of chills was 6.9% in the CI group and 26.6% in the RI group ($p = 0.001$), the relative risk was 0.26 (95% CI-0.11 to 0.59) and the relative risk reduction was 74.1%. There was no significant difference between nausea of 6.9% in the CI group and 12.5% in the RI group ($p = 0.169$) and phlebitis 22.5% in the CI group and 18.8% in the RI group ($p = 0.352$). Treatment failure was found in three patients with invasive aspergillosis who received continuous infusion of amphotericin B. Overall mortality at the end of therapy was significantly higher in the CI group (34.1%) than in the RI group (17.5%) ($p=0.05$), the relative risk was 1.35 (95% CI 1.06 to1.72). However most of the deaths in the CI group were unrelated to fungal infections. Chances of survival were significantly associated with age, febrile neutropenia, cryptococcal meningitis and AIDS from univariate analysis as shown in Table 4. However, a multivariate analysis

**Table 3.** Nephrotoxicity, infusion-related reactions and clinical outcomes of the patients

| | CI group (102 courses in 91 patients) | RI group (64 courses in 57 patients) | p-value | Relative risk (95% CI) |
|---|---|---|---|---|
| Nephrotoxicity | 28 (27.5%) | 25 (39.1%) | 0.16 | 0.70 (0.45-1.09) |
| Infusion related reactions | | | | |
| - chills | 7 (6.9%) | 17 (26.6%) | 0.001 | 0.26 (0.11-0.59) |
| - nausea | 7 (6.9%) | 8 (12.5%) | 0.34 | 0.55 (0.21-1.44) |
| - phlebitis | 23 (22.5) | 2 (18.8) | 0.352 | 1.20 (0.64-2.24) |
| Treatment failure | 3 (2.9%) | 0 | 0.3 | not available |
| Overall mortality | 31 (34.1%) | 10 (17.5%) | 0.05 | 1.35 (1.06-1.72) |
| Death due to fungal infections | 2 (2.2%) | 2 (3.5%) | 0.6 | 0.6 (0.1-6.4) |
| Death due to other causes | 29 (31.9%) | 8 (14%) | 0.02 | 2.8 (1.1-7.5) |

**Table 4.** Univariate and multivariate analyses of overall mortality

| | Outcome | | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|---|
| | Survival | Death | p-value | OR (95%CI) | p-value | OR (95%CI) |
| Age > 36 year | 54 (64.3%) | 30 (35.7%) | 0.021 | 0.78 (0.64-0.94) | 0.057 | |
| Febrile neutropenia | 54 (65.1%) | 29 (34.9%) | 0.042 | 0.80 (0.66-0.97) | 0.706 | |
| AIDS | 38 (88.4%) | 5 (11.6%) | 0.009 | 1.34 (1.13-1.60) | 0.008 | 0.252 (0.091-0.696) |
| Cryptococcal meningitis | 30 (90.9%) | 3 (9.1%) | 0.013 | 1.36 (1.15-1.61) | 0.346 | |
| Continuous infusion of amphotericin B | 60 (65.9%) | 31 (34.1%) | 0.046 | 0.80 (0.66-0.97) | 0.099 | |

revealed only AIDS was significantly associated with mortality, and continuous infusion of amphotericin B had not contributed to mortality.

## Discussion

The clinical practice policy on continuous intravenous infusion of amphotericin B deoxycholate used in our study was based on the evidence from a randomized controlled study comparing continuous infusion of amphotericin B with 4-hour infusion regarding the incidence of the nephrotoxicity and infusion-related reactions [22]. The nephrotoxicity was decreased from 38% to 15% and infusion-related reactions from 63% to 20%. Subsequent studies also confirmed the safety and efficacy of continuous infusion of amphotericin B [23-26]. Therefore, our study was not intended to repeat any randomized controlled study, but rather to gain further knowledge. The implementation of the clinical practice policy in our study was only meant to raise awareness of the prescribers by disseminating such a clinical practice policy and the decision to use continuous infusion or 4-hour infusion of amphotericin B was made by the responsible attending physicians. As a result, only 61.4% of amphotericin B treatments followed the recommendation in the clinical practice policy. This observation confirmed the previous findings that dissemination of the guidelines was less effective than multifaceted interventions [30-31]. Since our study was not a randomized controlled trial, many important factors relevant to the severity of infection and prognosis of the treatment were not balanced between the group receiving continuous infusion of amphotericin B and that receiving 4-hour infusion. The patients in the CI group were older and had neutropenia with refractory fever significantly more often than those in the RI group. On the other hand, HIV/AIDS and cryptococcal meningitis were greater in the RI group. All these different factors seemed to be unfavorable for the patients in the continuous infusion group.

The incidence of nephrotoxicity in the RI group was 39%, comparable to 38% observed in the randomized controlled study. However, it was 27.5% in the CI group, higher than 15% observed in the randomized controlled study. As a result, the incidence of the nephrotoxicity of the patients in the CI group was not significantly different from that in the RI group. This could be explained by the small sample size since the relative risk reduction of nephrotoxicity was 30%.

We did not include fever as an infusion-related reaction because most of the patients who were receiving amphotericin B had fever at the beginning of amphotericin B infusion. Superficial thrombophlebitis from chemical irritation in the continuous infusion regimen was not significantly greater than that in the RI group.

Treatment failure was found in three patients in the CI group. All of them had invasive aspergillosis and two of them were switched to voriconazole therapy. These failures might not be related to continuous infusion of amphotericin B since it is well recognized that many patients of invasive aspergillosis do not respond well to amphotericin B deoxycholate. If these three patients had received 4-hour infusion of amphotericin B, they would not have responded to the treatment either. The overall mortality in the CI group was found to be significantly higher than that in the RI group. However, most of the deaths in the CI group were unrelated to fungal infections or continuous infusion of amphotericin B. The subgroup analyses of the mortality group revealed that the significant difference was confined to deaths from other causes. These observations might be due to the differences in many important factors of the patients between the CI group and the RI group mentioned earlier. Multivariate analysis also confirmed that continuous infusion of amphotericin B was not associated with an increase in mortality.

**Conclusion**

Continuous infusion of amphotericin B was associated with a decrease in infusion-related reactions and tended to have less nephrotoxicity than 4-to 6-hour infusion.

**Acknowledgements**

The authors wish to thank Mr. Sutthipol Udompanthurak for statistical analyses and The Thailand Research Fund for supporting the study.

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## การใช้ยาแอมโฟเทอริซินบีหยดเข้าหลอดเลือดดำอย่างต่อเนื่องใน 24 ชั่วโมงตามนโยบายเวชปฏิบัติ

*ภาศรี มหารมณ์, วิษณุ ธรรมลิขิตกุล*

***วัตถุประสงค์:*** *เพื่อทราบผลการใช้ยาแอมโฟเทอริซินบีหยดเข้าหลอดเลือดดำอย่างต่อเนื่องใน 24 ชั่วโมงตามนโยบายเวชปฏิบัติในผู้ป่วยสามัญ ภาควิชาอายุรศาสตร์ โรงพยาบาลศิริราช เนื่องจากพบมีหลักฐานว่าการใช้ยาดังกล่าวลดพิษต่อไตได้*

***วัสดุและวิธีการ:*** *เตรียมนโยบายเวชปฏิบัติเรื่องการใช้ยาแอมโฟเทอริซินบีหยดเข้าหลอดเลือดดำอย่าง ต่อเนื่องใน 24 ชั่วโมงแทนการใช้ยา 4-6 ชั่วโมง และเผยแพร่นโยบายเวชปฏิบัตินี้แก่แพทย์ที่หอผู้ป่วยสามัญ ภาควิชาอายุรศาสตร์ ตั้งแต่เดือนมีนาคม พ.ศ. 2547 ถึงมีนาคม พ.ศ. 2549 นำข้อมูลมาวิเคราะห์ด้วยสถิติเชิงพรรณนา, การวิเคราะห์ univariate และ multivariate*

***ผลการศึกษา:*** *มีการใช้ยาแอมโฟเทอริซินบีทั้งหมด 166 ครั้งในผู้ป่วย 148 ราย การใช้ยาในผู้ป่วย 102 ครั้ง (64%) เป็นการใช้ยาอย่างต่อเนื่อง 24 ชั่วโมง (CI) ส่วนอีก 64 ครั้ง (38.6%) ใช้ยา 4-6 ชั่วโมง (RI) อายุเฉลี่ยและภาวะไข้ในขณะที่มีเม็ดเลือดขาวต่ำในกลุ่ม CI มากกว่ากลุ่ม RI ส่วนกลุ่ม RI มีผู้ป่วยเอดส์ และเยื่อหุ้มสมองอักเสบจากเชื้อคริบโตคอคคัสมากกว่ากลุ่ม CI พบอัตราการเกิดพิษต่อไต 27.5 % ในกลุ่ม CI เทียบกับ 39.1% ในกลุ่ม RI (p = 0.164) ผลข้างเคียงโดยเฉพาะอาการสั่นขณะให้ยา 6.9% ในกลุ่ม CI เทียบกับ 26.6% ในกลุ่ม RI (p = 0.001) และพบอัตราตายรวมในกลุ่ม CI มากกว่ากลุ่ม RI อย่างมีนัยสำคัญ แต่เป็นอัตราตายจากสาเหตุอื่นที่ไม่ใช่จากการได้รับยาแอมโฟเทอริซินบีหยดเข้าหลอดเลือดดำอย่างต่อเนื่อง*

***สรุป:*** *การนำแนวทางเวชปฏิบัติใช้ยาแอมโฟเทอริซินบีหยดเข้าหลอดเลือดดำอย่างต่อเนื่องใน 24 ชั่วโมง มาใช้ในภาควิชาอายุรศาสตร์สามารถลดปฏิกิริยาของยาได้และมีแนวโน้มที่จะลดพิษต่อไตได้มากกว่าการใช้ยาหยดเข้าหลอดเลือดดำใน 4-6 ชั่วโมง*

# Vancomycin Overuse in Siriraj Hospital

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***Objective:*** *An emergence of vancomycin resistant organisms particularly vancomycin-resistant enterococci (VRE) has become a serious public health concern. To prevent and control the spread of vancomycin resistant organisms, the prudent use of vancomycin is strongly recommended by the Hospital Infection Control Practices Advisory Committee (HICPAC).*

***Material and Method:*** *A 6-week prospective observational study of vancomycin use was conducted in hospitalized patients at Siriraj Hospital from February to March 2005. Indications of initiating and continuing vancomycin were categorized according to HICPAC recommendations. Factors related to the appropriateness of vancomycin use were also evaluated.*

***Results:*** *At initiation, vancomycin was inappropriately and empirically prescribed 19/222 times (8.6%) and 166/222 times (74.8%), respectively. After microbiological results were obtained, the rate of inappropriate prescription continued 132/222 times (59.5%). Furthermore, inappropriate use was significantly correlated with the type of department. There was a higher rate in the Department of Pediatrics, Surgery and Ophthalmology when compared with that of the Department of Medicine ($p = 0.001$). The inappropriate use also correlated with topical use ($p < 0.001$), intravenous administration ($p = 0.012$) and no consultation with an infectious disease specialist ($p = 0.001$). The overuse did not improve the clinical outcome.*

***Conclusion:*** *A substantial rate of inappropriate use of vancomycin was found in Siriraj Hospital. Intervention to improve appropriateness of vancomycin use should be urgently implemented to prevent and control the emergence of vancomycin resistant organisms.*

***Keywords:*** *Anti-bacterial agents, Therapeutic use, HICPAC recommendation, Prospective observational studies, Vancomycin*

***J Med Assoc Thai 2006; 89 (Suppl 5): S125-32***
***Full text. e-Journal:*** *http://www.medassocthai.org/journal*

Since 1989, a rapid increase in the incidence of infection and colonization with vancomycin-resistant enterococci (VRE) has been reported by US hospitals[1]. Currently, VRE has spread worldwide including Thailand. Hospitals in Thailand have reported the occurrence of VRE since 1995[2,3]. Furthermore, VRE have become a major global health concern. The problem has been addressed from the aspect of the clinical outcomes and in respect of the economic burden of health care facilities. VRE cause a widespread pragmatic problem on treatment because most VRE are also resistant to antibiotics recommended for treatment, such as a combination of ampicillin and aminoglycoside. The number of effective antibiotics against VRE infections is limited. An emergence of vancomycin resistance in clinical isolates of *Staphylococcus aureus* or *Staphylococcus epidermidis* is also a serious public

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health concern. In 1992, Noble and colleagues showed that the vanA gene could be transferred by cell to cell mating between enterococci and staphylococci[4]. Recently, Weigel and colleagues reported an in-vivo transfer of vancomycin resistant gene (vanA) from *Enterococcus fecalis* to a methicillin-resistant *S. aureus* (MRSA) capable of producing *S. aureus* resistant to vancomycin (VRSA)[5]. However, clinical isolates of staphylococci containing the vanB, vanC, or vanD genes have not been reported. This process may simultaneously originate heterogeneous Vancomycin intermediate resistant *S. aureus* (Hetero-VISA)[6,7] and Vancomycin Resistant *S. epidermidis* (VRSE)[8].

An increased use of vancomycin has led to selective pressure, and the subsequent appearance of VRE, Hetero-VISA, and VISA followed by VRSA has alarmed physicians and microbiologists[9]. Previous studies have shown that a sustained increase of vancomycin overuse in recent years was associated with the emergence of VRE and other resistant gram positive organisms[10,11], and a substantial reduction inpatient vancomycin use was associated with declining VRE isolation rates[12].

The Hospital Infection Control Practices Advisory Committee (HICPAC) recommended the following elements for prevention and control of the spread of vancomycin resistance, with a special focus on VRE[13].

a) Prudent vancomycin use by clinicians as shown in the appendix attached,

b) Education of hospital staff regarding the problem of vancomycin resistance,

c) Early detection and prompt reporting of vancomycin resistance in enterococci and other gram-positive microorganisms by the hospital microbiology laboratory,

d) Immediate implementation of appropriate infection-control measures to prevent person-to-person transmission of VRE.

According to the HICPAC recommendations, the inappropriateness of vancomycin use in tertiary care hospitals ranged from 17-83%[12,14-18]. In Thailand, the information on overuse of vancomycin is limited. Therefore, we conducted this study to explore the magnitude and associated factors of vancomycin overuse in Siriraj Hospital, a 2000-bed university hospital.

## Material and Method

### *Subjects and Study Design*

The study was approved by The Ethics Committee on Human Research of the Faculty of Medicine Siriraj Hospital. This prospective observational study was conducted at Siriraj Hospital, a 2,000-bed academic tertiary-care hospital in Bangkok, from February 1st to March 14th, 2005. All new vancomycin prescriptions for hospitalized patients were collected. The patients who received at least one dose of vancomycin were enrolled into the study. Demographics, clinical information, and microbiological study results were recorded. Indications for initiating and continuing vancomycin use after receiving microbiological information were evaluated. Factors that may have related to the appropriateness of vancomycin prescription, which included department patient care, suspected site of infection, route of vancomycin use, and infectious disease (ID) consultation, were also evaluated.

### *Outcome Measurement*

The appropriateness of vancomycin use at initiation and continuation was determined by using explicit criteria developed by the HICPAC[13] as summarized in the appendix. Dosing, route and duration of vancomycin administration were also evaluated. Infectious disease (ID) specialist consultation was classified as i) absence of ID specialist consultation, ii) presence and implementation of ID specialist suggestion and iii) presence but non-implementation of ID specialist suggestion. Clinical outcome was finally evaluated at the end of vancomycin use and divided into 6 categories as shown in Table 1

### *Statistical analysis*

Data were expressed as percentage and mean $\pm$ SD for nominal and continuous variables, respectively. Analyses were performed using SPSS 11.5 (SPSS Inc, Chicago, Illinois). Nominal variables were compared by a Chi-square test or Fisher's exact test and continuous variables were compared by a two-tailed unpaired t-test or Mann-Whitney U test as appropriate. The statistically significant factors were confirmed by multivariate analysis using a logistic regression model. A p value $< 0.05$ was considered significant.

## Results

### *Patient characteristics*

Two hundred and twenty two courses of vancomycin on 221 patients were included. One patient was treated twice. Patients' characteristics, site of infection and administration route are summarized in Table 2. The total amount of vancomycin used was 1,713 grams, averaging 7.72 grams per course. The cost of the vancomycin was 1,161,414 baht, based on the

**Table 1.** Therapeutic outcome

| Definition of therapeutic outcomes |
|---|
| 1. Cure: a complete resolution of symptoms and signs of infection |
| 2. Partial response: an incomplete resolution of symptoms and signs of infection |
| 3. No response: no resolution and progression of symptoms and signs of infection |
| 4. Infectious death: a death with suspected infectious cause |
| 5. Non-infectious death: a death with no suspected infectious cause |
| 6. Indeterminate outcome: no evaluation possible |

**Table 2.** Demographic data of 222 courses of prescription for 221 patients

| | Number | Percentage (%) |
|---|---|---|
| Patient characteristics (N = 222) | | |
| Gender (Male : Female) | 119:103 | |
| Mean Age (yr) | 46.65 | |
| Department (N = 222) | | |
| Medicine | 99 | 44.6 |
| Surgery | 39 | 17.6 |
| Ophthalmology | 39 | 17.6 |
| Pediatrics | 36 | 16.2 |
| Orthopedics | 5 | 2.3 |
| Obstetrics and Gynecology | 4 | 1.8 |
| Site of suspected infection* (N = 222) | | |
| Primary bacteremia | 45 | 20.3 |
| Catheter associated infection | 33 | 14.9 |
| Major organs infection | 87 | 39.2 |
| Eye-ENT infection | 42 | 18.9 |
| Antibiotic associated colitis (AAC) | 7 | 3.2 |
| No Evidence of infection | 8 | 3.6 |
| Administration route* (may be more than 1 route) | | |
| Intravenous injection (IV) | 181 | 81.5 |
| Oral administration (PO) | 8 | 3.6 |
| Topical administration (Tp) | 27 | 12.2 |
| Ophthalmic injection (Op) | 12 | 5.4 |
| Intra-cavitary injection (IC) | 2 | 0.9 |
| Antibiotic Lock Therapy (ALT) | 2 | 0.9 |

* see appendix

**Table 3.** Appropriateness of vancomycin use

| | Number | Percentage (%) |
|---|---|---|
| At initiation of treatment | | |
| Appropriate | 37 | 16.7 |
| Inappropriate | 19 | 8.6 |
| Empirical | 166 | 74.8 |
| For continuation of treatment | | |
| Appropriate | 90 | 40.5 |
| Inappropriate | 132 | 59.5 |

current price of Edicin® 339 baht/ 500 mg.

***Vancomycin-use data***

The distribution of the appropriateness of vancomycin used is presented in Table 3. According to the HICPAC recommendation, 19 (8.6%), 37 (16.7%) and 166 episodes (74.8%) of vancomycin use were appropriate, inappropriate and empirical respectively at initiation of vancomycin. At continuation, we found that 132 of 222 episodes (59.5%) were inappropriately continued.

***Associated factors for inappropriateness of use of vancomycin***

We did not find any correlation between the proportion of inappropriateness at the initiation phase and all of our influencing factors. On the contrary, inappropriateness of vancomycin use was significantly associated with the department that cared for the patient, ID-consultation pattern, site of infection and administration route of vancomycin during the continuation phase as shown in Table 4. Our data showed that inappropriate use of vancomycin was significantly lower in the Department of Medicine compared to other departments. Furthermore, the group that followed the ID suggestion was lower compared to either the non-implementation group or absence of ID suggestion group. On the other hand, we found that treating EYE-ENT infection was the most common site of vancomycin overuse. Moreover, inappropriateness of vancomycin use was significantly higher in topical and intravenous routes and it was significantly lower in oral routes.

**Table 4.** Inappropriateness of vancomycin use at continuation according to services, ID consultation pattern, site of infection and route of vancomycin use

| Factors | Total | Inappropriateness of vancomycin use | | p-value |
|---|---|---|---|---|
| | | Number | Percentage (%) | |
| Total number | 222 | 132 | 59.5 | |
| Services | | | | |
| Medicine | 99 | 40 | 40.4 | 0.001[a] |
| Surgery | 39 | 28 | 71.8 | |
| Pediatrics | 36 | 25 | 69.4 | |
| Ophthalmology | 39 | 37 | 94.9 | |
| ID-consultation | | | | |
| Implementation of suggestion | 35 | 10 | 28.6 | 0.001[b] |
| Non-implementation | 14 | 12 | 85.7 | |
| No consultation | 174 | 110 | 63.6 | |
| Suspected site of infection | | | | |
| Primary bacteremia | 45 | 31 | 68.9 | 0.001[c] |
| Catheter associated infection | 33 | 13 | 39.4 | |
| Major organs infection | 87 | 42 | 48.3 | |
| Eye-ENT infection | 42 | 39 | 92.9 | |
| AAC | 7 | 0 | 0.0 | |
| No evidence of infection | 8 | 7 | 87.5 | |
| Route(s) of vancomycin use | | | | |
| IV | | 100 | 55.2 | 0.012[d] |
| Tp | | 26 | 96.3 | <0.001[e] |
| PO | | 0 | 0.0 | 0.002[f] |

**Note:** The rates of inappropriate use of vancomycin were significantly lower in (a) the Medicine Department compared to other departments, (b) in the ID implementation group compared to others by pair wise comparisons using the Bonferroni correction. The rate of inappropriate use of vancomycin was significantly higher (c) in the treating EYE-ENT infection group compared to the other sites by pair wise comparisons using the Bonferroni correction. The rates of inappropriate use of vancomycin were significantly higher in (d) the intravenous route and (e) the topical route and it was significantly lower in (f) the oral route by using Fisher's exact test

**Table 5.** Therapeutic outcome

| Therapeutic outcome | Appropriateness of vancomycin use | | p-value |
|---|---|---|---|
| | Appropriate (%) | Inappropriate (%) | |
| Total number | 90 (40.5) | 132 (59.5) | |
| Cure or partial response | 66 (73.3) | 80 (60.6) | 0.031* |
| No response or infectious death | 21 (23.3) | 35 (26.5) | |
| Non-infectious death orindeterminate outcome | 3 (3.3) | 17 (12.9) | |

*The rate of cure and partial response was significantly higher in the appropriate use group compared to the inappropriate use group by pair wise comparisons using the Bonferroni correction

***Therapeutic outcome***

Appropriate use of vancomycin resulted in a significantly higher percentage in the cure and partial response rate (73.3%) than in the inappropriate use group (60.6%; p = 0.031) as shown in Table 5. This observation indicated that an overuse of vancomycin did not significantly improve the clinical outcome.

## Discussion

From our study, a very high rate of inappropriate use of vancomycin (59.5%) was observed particularly in the Department of Ophthalmology compared with previous reports that found inappropriate use in the Intensive care unit[19], Transplant Unit[19] and the Department of Pediatrics[20].The inappropriateness of vancomycin use was significantly higher in non-medical wards. The most common reasons for inappropriate use of vancomycin were (1) treating infected corneal ulcers with topical vancomycin eye drops, (2) treating infections caused by beta-lactam susceptible organisms (3) treating contaminated organisms in blood culture taken from asymptomatic patients.

Regarding the increasing incidence of bacterial keratitis caused by MRSA and Methicillin resistant *S. epidermidis* (MRSE)[21,22], the recommendation of the Endophthalmitis Vitrectomy Study suggested using topical vancomycin eye drops to treat postoperative endophthalmitis[23]. Therefore, vancomycin has become one of the most extensively used topical antibiotics in ophthalmology[24]. The Department of Ophthalmology in our hospital has adopted a practice policy for treating severe corneal ulcer with vancomycin eye drop. This policy is inconsistent with the HICPAC recommendation that discourage the use of topical vancomycin for reasons stared. In our study, topical vancomycin eye drops were used in 38 patients having infected corneal ulcers. Of these, one patient was documented as having infection caused by beta-lactam resistant organisms.

Moreover, we found that most vancomycin uses were not discontinued even though the microbiological test results revealed beta-lactam sensitive organisms. This might be a misconception of physicians that vancomycin is a superior antibiotic to beta-lactam for treatment of staphylococcal infections.

The burden of inappropriateness of vancomycin use in this study alarms us and an effective strategy is urgently needed to correct it. Vancomycin restriction policy seems to be risky in a hospital where MRSA is prevalent, such as our hospital (41.5% of *S. aureus* isolates were methicillin resistant)[25]. However, most of MRSA bacteremia or infection is gradually progressed. The delayed vancomycin treatment did not compromise patients' survival rates[26,27] and was safe even in the worst-case scenario such as clinically significant MRSA bacteremia[18,28].

## Conclusion

Sixty percent of vancomycin prescriptions for hospitalized patients in Siriraj Hospital demonstrated inappropriate overuse. This practice not only worsened the clinical outcome, but also consumed unnecessary expenditure of 5 million baht per year. Moreover, the potential emergence of vancomycin resistant gram positive organisms may have been increased. This should be considered as one of the major problems of antibiotic use and an effective strategy to reduce this problem must be considered.

## Acknowledgements

The authors wish to thank Mr. Suthipol Udompunturak and Miss Yadawadee Wongthanasuporn for coordinating the study, and the Thailand Research Fund for supporting the study.

## Appendix

***Recommendations for prudent vancomycin use***[13]
(Adapted from the HICPAC recommendations)

1. Situations in which the use of vancomycin is considered appropriate:

- Treatment of infections caused by beta-lactam resistant gram-positive microorganisms.
- Treatment of infections caused by gram-positive microorganisms in patients who have serious allergies to beta-lactam antimicrobials.
- When antibiotic-associated colitis fails to respond to metronidazole therapy or is severe and potentially life-threatening.
- Endocarditis prophylaxis in high risk patients following certain procedures (following the American Heart Association recommendation)
- Prophylaxis for major surgical procedures involving implantation of prosthetic materials or devices at institutions that have a high rate of infections caused by beta-lactam resistant gram positive microorganisms.

2. Situations in which the use of vancomycin is considered inappropriate:

- Routine surgical prophylaxis other than in a non life-threatening beta-lactam allergic patient.
- Empiric antimicrobial therapy for a febrile neutropenic patient, unless there is initial evidence of an infection caused by gram-positive microorganisms at institutions that have a high rate of beta-lactam resistance.
- Treatment in response to a single blood culture positive for coagulase-negative staphylococcus, if other blood cultures taken during the same time frame are negative.
- Continued empiric use for presumed infections in patients whose cultures are negative for beta-lactam-resistant gram-positive microorganisms.
- Systemic or local (e.g., antibiotic lock) prophylaxis for infection or colonization of indwelling central or peripheral intravascular catheters.
- Selective decontamination of the digestive tract.
- Eradication of MRSA colonization.
- Primary treatment of antibiotic-associated colitis.
- Routine prophylaxis for very low-birth weight infant, patients on continuous ambulatory peritoneal dialysis or hemodialysis.
- Treatment (chosen for dosing convenience) of infections caused by beta-lactam-sensitive gram-positive microorganisms in patients who have renal failure.
- Use of vancomycin solution for topical application or irrigation.

***Definition and terms***

***Suspected sites of infection***

**1. Primary bacteremia** was defined as the positive blood culture (at least one specimen) of likely uncontaminated organisms with clinical signs of systemic infection where the focal site of infection couldn't be identified.

**2. Catheter-associated infection** was defined as the clinical evidence of insertion site or tunnel infection with or without positive blood culture.

**3. Major organ(s) infection** was defined as the infection of major organs; lung, heart, urinary tract, brain, peritoneal cavity, soft tissue, musculoskeletal system.

**4. EYE-ENT infection** was defined as the infection of the eye-ear-nose-throat system

**5. Antibiotic associated colitis (AAC)** was defined as the diarrhea that appeared after antibiotic administration and was confirmed by colonoscopic gross finding or *C. difficile* was isolated.

**6. No evidence of infection** was defined as those patients who have no clinical sign of systemic inflammatory response syndrome (SIRS) nor clinical signs and symptoms of focal site of infection. (Perioperative antibiotic prophylaxis was included in this category.)

***Route(s) of vancomycin use*** were classified as

**1. Intravenous injection (IV)**

**2. Oral administration (PO)**

**3. Topical form (Tp);** ophthalmic and otic solution administration (topical solution was prepared by dissolving 500 mg of commercial vancomycin powder for injection with 10 ml. of balanced salt solution )

**4. Ophthalmic injection (Op);** subconjunctival, intra-vitreous and intra-aqueous injection

**5. Intra-cavitary injection(IC);** intra-peritoneal, intra-articular, intra-ventricular and intra-thecal injection, etc.

**6. Antibiotic Lock therapy (ALT);** the method involves instilling a highly concentrated antibiotic solution into a catheter lumen and allowing the solution to dwell for a specified time period for the purpose of sterilizing the lumen[29].

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## *การใช้ยาแวนโคมัยซินเกินความจำเป็นในโรงพยาบาลศิริราช*

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***วัตถุประสงค์:*** *เพื่อทราบการใช้ยาแวนโคมัยซินอย่างไม่เหมาะสมในโรงพยาบาลศิริราช*
***วัสดุและวิธีการ:*** *ศึกษาการใช้ยาแวนโคมัยซินแก่ผู้ป่วยในทุกรายในโรงพยาบาลศิริราชในช่วงเดือนกุมภาพันธ์ ถึงมีนาคม พ.ศ.2548 เป็นระยะเวลา 6 สัปดาห์ โดยเก็บข้อมูลการเริ่มใช้ยาตามข้อบ่งชี้ และการใช้ยาต่อเนื่อง ภายหลังทราบผลการเพาะเชื้อและความไวต่อยาปฏิชีวนะ เมื่อเปรียบเทียบกับคำแนะนำการใช้ยาของคณะกรรมการควบคุมการติดเชื้อของCDC (Centers for Disease Control) รวมถึงศึกษาปัจจัยอื่น ๆ ซึ่งอาจมีผลกระทบ*
***ผลการศึกษา:*** *ช่วงเริ่มต้นมีการสั่งยาแวนโคมัยซินอย่างไม่เหมาะสม 19 ราย (ร้อยละ 8.6) และสั่งยาไปก่อนระหว่างรอผลการตรวจหาเชื้อ 166 ราย (ร้อยละ 74.8) หลังจากทราบผลการตรวจหาเชื้อทั้งหมดแล้ว แพทย์ยังคงใช้ยาต่ออย่างไม่เหมาะสม 132 ราย (ร้อยละ 59.5) กลุ่มผู้ป่วยที่มีอัตราการใช้ยาอย่างไม่เหมาะสมต่ำกว่ากลุ่มอื่น ๆ ได้แก่ ผู้ป่วยภาควิชาอายุรศาสตร์ ($p < 0.001$) และการใช้ยาตามคำแนะนำของสาขาวิชาโรคติดเชื้อ ($p = 0.001$) ส่วนรูปแบบการบริหารยาที่มักมีการใช้อย่างไม่เหมาะสมคือ ยาในรูปหยอดตา ($p < 0.001$) หรือฉีดเข้าหลอดเลือดดำ ($p = 0.012$) นอกจากนี้ผู้ป่วยกลุ่มที่มีการใช้ยาเกินความจำเป็นไม่ได้ทำให้ผลการรักษาดีขึ้น*
***สรุป:*** *โรงพยาบาลศิริราชมีการใช้ยาแวนโคมัยซินอย่างไม่เหมาะสมสูง ดังนั้นจึงควรหาแนวทางแก้ไขอย่างเร่งด่วนเพื่อป้องกันการเพิ่มขึ้นของเชื้อดื้อยาในอนาคต*

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# Utilization of Calculated Low Density Lipoprotein Cholesterol and Measured Low Density Lipoprotein Cholesterol in Siriraj Hospital

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*A study to determine the utilization of calculated low density lipoprotein (c-LDL) cholesterol and measured low density lipoprotein (m-LDL) cholesterol was conducted. The test results of total cholesterol, triglyceride, HDL-cholesterol and m-LDL-cholesterol from the same individuals aged ≥ 18 years who had the tests done at the Department of Clinical Pathology, Faculty of Medicine Siriraj Hospital during January to December 2004 were retrieved. The c-LDL-cholesterol level was computed using Friedewald formula. There were two data sets i.e. the m-LDL-cholesterol cut-off level derivation data set (784 subjects) and the m-LDL-cholesterol cut-off level validation data set (800 subjects). The study results revealed: 1) 2.6% of the subjects had blood triglyceride > 400 mg/dl hence c-LDL-cholesterol could not be computed, 2) the correlation between c-LDL-cholesterol levels and m-LDL-cholesterol levels from both data sets was very good (r > 0.95, p < 0.001), 3) the m-LDL-cholesterol levels were usually higher than c-LDL-cholesterol levels, 4) the m-LDL-cholesterol cut-off level derivation data set showed that m-LDL-cholesterol < 87, > 143, > 188, > 233 and > 254 mg/dl were highly correlated with c-LDL-cholesterol < 100, ≥ 100, ≥ 130, ≥ 160 and ≥ 190 mg/dl respectively, 5) an application of m-LDL-cholesterol cut-off levels derived from the m-LDL-cholesterol cut-off level derivation data set to the m-LDL-cholesterol cut-off level validation data set showed that m-LDL-cholesterol < 87, > 143, > 188, > 233 and > 254 mg/dl had accuracy in predicting c-LDL-cholesterol < 100, ≥ 100, ≥ 130, ≥ 160 and ≥ 190 mg/dl of 100%, 99.7%, 100%, 100% and 100% respectively, 6) the use of m-LDL-cholesterol levels as a guide for initiating lipid-lowering agents based on cut-off values of c-LDL-cholesterol levels led to an overuse of lipid-lowering agents in 3.6% to 42.9% of the patients and 7) Nomogram for transforming m-LDL-cholesterol to c-LDL-cholesterol was developed as well as a formula for transforming m-LDL-cholesterol to c-LDL-cholesterol (c-LDL-cholesterol = 0.89 ◊ m-LDL-cholesterol). Therefore, m-LDL-cholesterol assay has a very limited use in managing individuals with suspected or known dyslipidemia. The use of m-LDL-cholesterol level as a guide for management of abnormal LDL-cholesterol conditions leads to an overuse of lipid lowering medications and an enormous expense of m-LDL-cholesterol assay.*

**Keywords:** *Low density lipoprotein cholesterol, LDL*

***J Med Assoc Thai 2006; 89 (Suppl 5): S156-63***
***Full text. e-Journal:*** *http://www.medassocthai.org/journal*

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Low density lipoprotein (LDL) is a lipoprotein consisting of cholesterol (40%-50%), phospholipids (20%-25%) and triglyceride (5%-15%). Elevation of blood LDL-cholesterol is recognized as one of the major risk factors for atherosclerosis and ischemic heart disease and a lowering of blood LDL-cholesterol could diminish the risk of ischemic heart disease[1-3]. The third report of the national cholesterol education program (NCEP III) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) classifies blood LDL-cholesterol levels as normal (blood LDL-cholesterol < 100 mg/dl), nearly-normal (blood LDL-cholesterol 100-129 mg/dl), nearly-high (blood LDL-cholesterol 130-159 mg/dl), high (blood LDL-cholesterol 160-189 mg/dl) and very high (blood LDL-cholesterol >190 mg/dl)[4]. Management of individuals with elevated blood LDL-cholesterol includes diet control, exercise, and drugs. It is suggested that 1) individuals with ≤ 1 cardiovascular risk factor who have a chance of developing ischemic heart disease of less than 10% within 10 years should receive treatment if their blood LDL-cholesterol is ≥ 190 mg/dl 2) individuals with ≥ 2 cardiovascular risk factor who have a chance of developing ischemic heart disease of less than 10% within 10 years should receive treatment if their blood LDL-cholesterol is ≥ 160 mg/dl 3) people with ≥ 2 cardiovascular risk factors who have a chance of developing ischemic heart disease of 10% to 20% within 10 years, or patients with diabetes mellitus or ischemic heart disease who have a chance of developing ischemic heart disease of more than 20% within 10 years should receive treatment if their blood LDL-cholesterol is ≥ 130 mg/dl and they should have behavior modification if their blood LDL-cholesterol is ≥ 100 mg./dl. The aforementioned blood LDL-cholesterol thresholds are based on LDL-cholesterol calculated from total cholesterol, triglyceride and high density lipoprotein (HDL) cholesterol using Friedewald's formula[5]. Calculated LDL-cholesterol (c-LDL) is equivalent to total cholesterol – HDL-cholesterol – triglyceride/5. A direct measurement for blood LDL-cholesterol (m-LDL) has been available over the past decade and this assay has become popular. The cost of an m-LDL-cholesterol assay in Siriraj Hospital is 150 baht, whereas c-LDL-cholesterol is provided without any additional cost if total cholesterol, triglyceride and HDL-cholesterol are ordered.

The objectives of the study were to determine the pattern of utilization of m-LDL-cholesterol and to determine cut-off thresholds of m-LDL-cholesterol that predict c-LDL-cholesterol cut-off levels for initiating appropriate management as recommended in NCEP III.

## Material and Method

The test results of total cholesterol, triglyceride, HDL-cholesterol and m-LDL-cholesterol from the same individuals aged ≥ 18 years during January to December 2004 were retrieved from the database of the Department of Clinical Pathology, Faculty of Medicine Siriraj Hospital. Calculated LDL-cholesterol was computed using Freidewald formula. There were two data sets. The first data set was the m-LDL-cholesterol cut-off level derivation data set. It was the test results of 784 individuals randomly selected from those who had the tests during January to June 2004. The medical records of these individuals were analyzed for demographics, cardiovascular risk factors and managements they received. The second data set was the m-LDL-cholesterol cut-off level validation data set. It was the test results of 800 individuals randomly selected from those who had the tests during July to December 2004. The data were analyzed by descriptive statistics and inferential statistics where appropriate. The correlation between c-LDL-cholesterol and m-LDL-cholesterol levels was determined by Pearson's Product Moment Correlation Coefficient. The formula for transforming m-LDL-cholesterol level to c-LDL-cholesterol level was generated from linear regression analysis. A p-value ≤ 0.05 was considered statistically significant.

## Results

1. Analyses of the test results of the m-LDL-cholesterol cut-off level derivation data set (784 individuals) revealed the following:

Twenty individuals (2.6%) had blood triglyceride > 400 mg/dl hence c-LDL-cholesterol could not be computed.

Seven hundred and sixty four individuals with blood triglyceride < 400 mg/dl had demographics and clinical features as shown in Table 1. 63.4% of them were females. A mean age was 59.4 years, mean body weight was 61.5 Kg, mean height was 159.4 cm, and mean body mass index (BMI) was 24.75 Kg/m$^2$ 22.3% of them had ischemic heart diseases, 1.6% had ≤ 1 cardiovascular risk factor, 23.6% had ≥ 2 cardiovascular risk factors; and the status of cardiovascular risk factors was not available in 52.6%.

The lipid profiles of 764 individuals with blood triglyceride < 400 mg./dl. are shown in Table 2. The m-LDL-cholesterol levels were higher than c-LDL-cholesterol levels.

**Table 1.** Demographics and cardiovascular risk factors of 764 individuals who had blood triglyceride < 400 mg/dl

| Characteristic | |
|---|---|
| Females | 484 (63.4%) |
| Mean age (SD) | 59.4 yr (13.07 yr) |
| Median age (Range) | 60.3 yr (18-89 yr) |
| Mean body weight (SD) | 59.4 Kg (13.07 Kg) |
| Median body weight (Range) | 60.0 Kg (33-102 Kg) |
| Mean height (SD) | 159.4 cm (8.09 cm) |
| Median height (Range) | 158.0 cm (140-181 cm) |
| Mean BMI (SD) | 24.75 $Kg/m^2$ (3.94 $Kg/m^2$) |
| Median BMI (Range) | 24.51 $Kg/m^2$ (17.19-37.25 $Kg/m^2$) |
| Cardiovascular Risk Factors Ischemic Heart Disease | 170 (22.3%) |
| ≥ 2 factors | 180 (23.6%) |
| 0-1 factor | 12 (1.6%) |
| not available | 402 (52.6%) |

**Table 2.** Lipid profiles of 764 individuals who had blood triglyceride < 400 mg/dl

| | Range | Mean (SD) | Median |
|---|---|---|---|
| Cholesterol (mg/dl) | 72-383 | 204.6 (46.77) | 201.0 |
| HDL-cholesterol (mg/dl) | 9-122 | 53.2 (16.51) | 51.6 |
| Triglyceride (mg/dl) | 18-398 | 131.9 (67.79) | 115.0 |
| m-LDL-cholesterol (mg/dl) | 33-295 | 145.6 (44.98) | 142.0 |
| c-LDL-cholesterol (mg/dl) | 9-267 | 124.9 (41.08) | 122.3 |

The distribution of the difference between m-LDL-cholesterol and c-LDL-cholesterol levels from 764 individuals with blood triglyceride < 400 mg/dl is shown in Table 3. 91% of them had a difference ≤ 25%.

The correlation between c-LDL-cholesterol levels and m-LDL-cholesterol levels is shown in Fig. 1. The correlation was statistically significant ($p < 0.001$) and the magnitude of the correlation was very high.

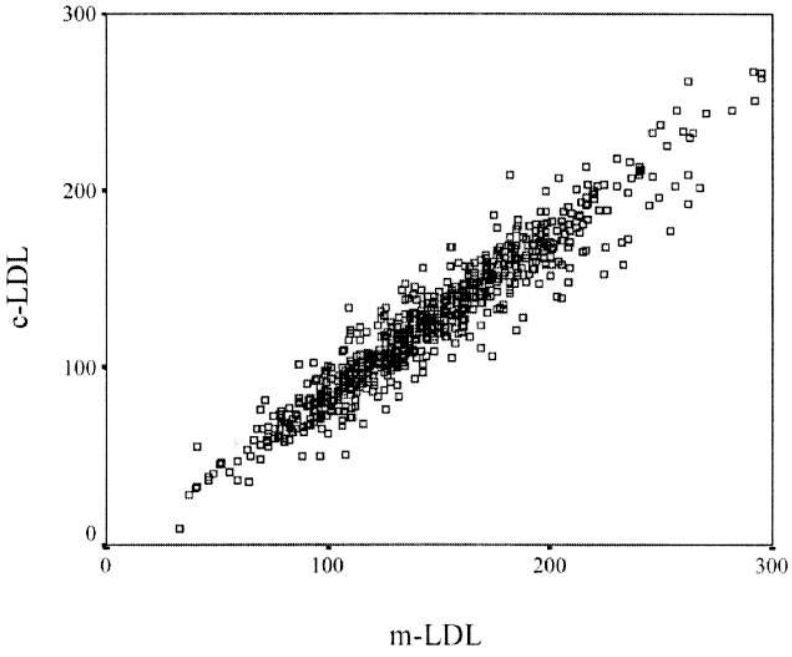
The predictive levels of m-LDL-cholesterol to determine c-LDL-cholesterol levels of < 100, ≥ 100, ≥ 130, ≥ 160 and ≥ 190 mg/dl were < 87, > 143, > 188, > 233 and > 254 mg/dl respectively (Table 4).

2. Analyses of the test results of the m-LDL-cholesterol cut-off level validation data set (800 individuals) revealed the following:

The individuals with blood triglyceride < 400 mg/dl had a mean age of 57.9 years and 61.8% of them were females. There was no statistically significant difference in demographics between the individuals in

**Table 3.** The distribution of the differences between m-LDL-cholesterol levels and c-LDL-cholesterol levels from 764 individuals with blood triglyceride < 400 mg/dl

| Difference between c-LDL- cholesterol and m-LDL- cholesterol | N (%) |
|---|---|
| ± 5% | 53 (6.9) |
| ± 10% | 139 (18.2) |
| ± 15% | 221 (28.9) |
| ± 20% | 183 (24.0) |
| ± 25% | 98 (12.8) |
| ± 30% | 36 (12.8) |
| ± 35% | 21 (2.7) |
| ± 40% | 7 (0.9) |
| ± 45% | 3 (0.4) |
| ± 50% | 1 (0.1) |
| ± 55% | 1 (0.1) |
| ± 60% | 1 (0.1) |




Pearson Correlation Coefficient (r) = 0.956, $p < 0.001$

**Fig. 1** The correlation between c-LDL-cholesterol levels and m-LDL-cholesterol levels from 764 individuals with blood triglyceride < 400 mg/dl

**Table 4.** The predictive values of m-LDL-cholesterol level to determine c-LDL-cholesterol level

| m-LDL-cholesterol (mg/dl) | c-LDL-cholesterol (mg/dl) |
|---|---|
| <87 | <100 |
| >143 | ≥100 |
| >188 | ≥130 |
| >233 | ≥160 |
| >254 | ≥190 |

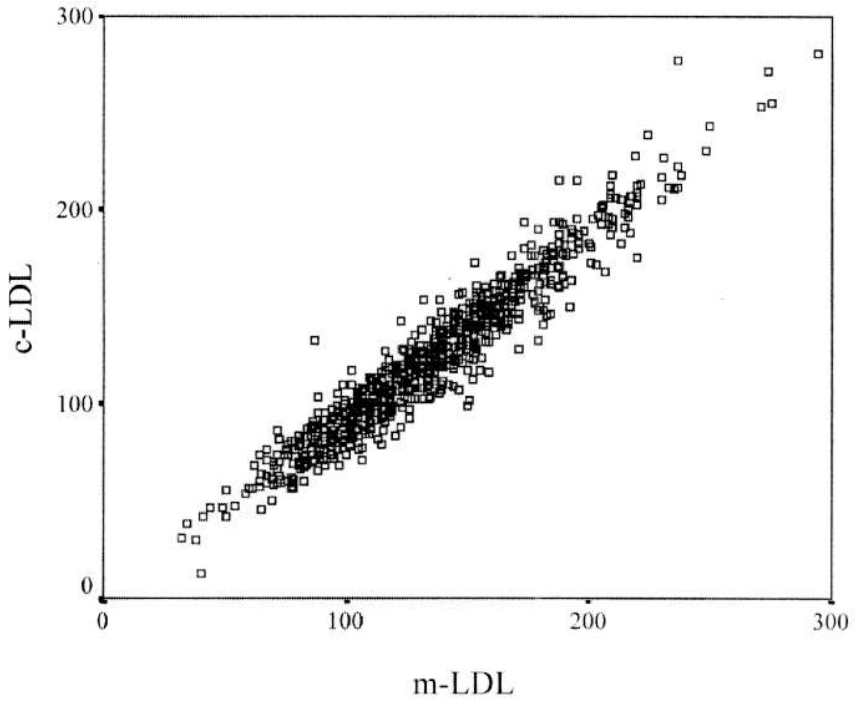
the m-LDL-cholesterol cut-off value derivation data set and the m-LDL-cholesterol cut-off value validation data set.

The lipid profiles of 800 individuals with blood triglyceride < 400 mg/dl are shown in Table 5. The m-LDL-cholesterol values were higher than c-LDL cholesterol values similar to those observed in 764 individuals in the m-LDL-cholesterol cut-off value derivation data set.

The correlation between c-LDL-cholesterol and m-LDL-cholesterol levels is shown in Fig. 2. The correlation was statistically significant ($p < 0.001$) and the magnitude of the correlation was very high.

**Table 5.** Lipid profiles of 800 individuals who had blood triglyceride < 400 mg/dl

| | Range | Mean (SD) | Median |
|---|---|---|---|
| Cholesterol (mg/dl) | 45-366 | 201.8 (45.78) | 200 |
| HDL-cholesterol (mg/dl) | 6-116 | 51.5 (14.31) | 50 |
| Triglyceride (mg/dl) | 32-398 | 131.8 (66.68) | 117 |
| m-LDL-cholesterol (mg/dl) | 32-294 | 134.9 (40.66) | 133 |
| c-LDL-cholesterol (mg/dl) | 13-281 | 124 (40.21) | 120 |




Pearson Correlation Coefficient (r) = 0.963, p < 0.001

**Fig. 2** The correlation between c-LDL-cholesterol levels and m-LDL-cholesterol levels from 800 individuals with blood triglyceride < 400 mg/dl

An application of m-LDL-cholesterol cut-off values derived from the m-LDL-cholesterol cut-off value derivation data set to the m-LDL-cholesterol cut-off value validation data set showed that m-LDL-cholesterol < 87, > 143, > 188, > 233 and > 254 mg/dl had accuracy in predicting c-LDL-cholesterol < 100, ≥ 100, ≥ 130, ≥ 160 and ≥ 190 mg/dl of 100%, 99.7%, 100%, 100% and 100% respectively.

3. The nomogram to be used for transforming m-LDL-cholesterol level to c-LDL-cholesterol level was made from the test results of 1,564 individuals who had blood triglyceride < 400 mg/dl and is shown in Fig. 3.

4. A formula for transforming m-LDL-cholesterol level to c-LDL-cholesterol level was generated from the test results of 1,564 individuals who had blood triglyceride < 400 mg./dl. using a linear regression analysis. The c-LDL-cholesterol was approximately 0.89 x m-LDL-cholesterol.

5. Analyses of a sample of individuals whose baseline m-LDL-cholesterol levels were available and who had received lipid lowering drugs based on m-LDL-cholesterol levels revealed the following observations:

Out of 28 individuals with baseline m-LDL-cholesterol level > 100 mg/dl, 27 had c-LDL-cholesterol level ≥ 100 mg/dl. Hence the treatment was inappropriately given in 1/28 (3.6%) of cases.

Out of 26 individuals with baseline m-LDL-cholesterol level > 130 mg/dl, 25 had c-LDL-cholesterol level ≥ 130 mg/dl. Hence the treatment was inappropriately given in 1/26 (3.8%) of cases.

Out of 20 individuals with baseline m-LDL-cholesterol level > 160 mg/dl, 16 had c-LDL-cholesterol level ≥ 160 mg/dl. Hence the treatment was inappropriately given in 4/20 (20%) of cases.

Out of seven individuals with baseline m-LDL-cholesterol level >190 mg./dl, four had c-LDL-cholesterol level ≥ 190 mg/dl. Hence the treatment was inappropriately given in 3/7 (42.9%) of cases.

## Discussion

Our study confirmed the findings from other reports that c-LDL-cholesterol levels are strongly

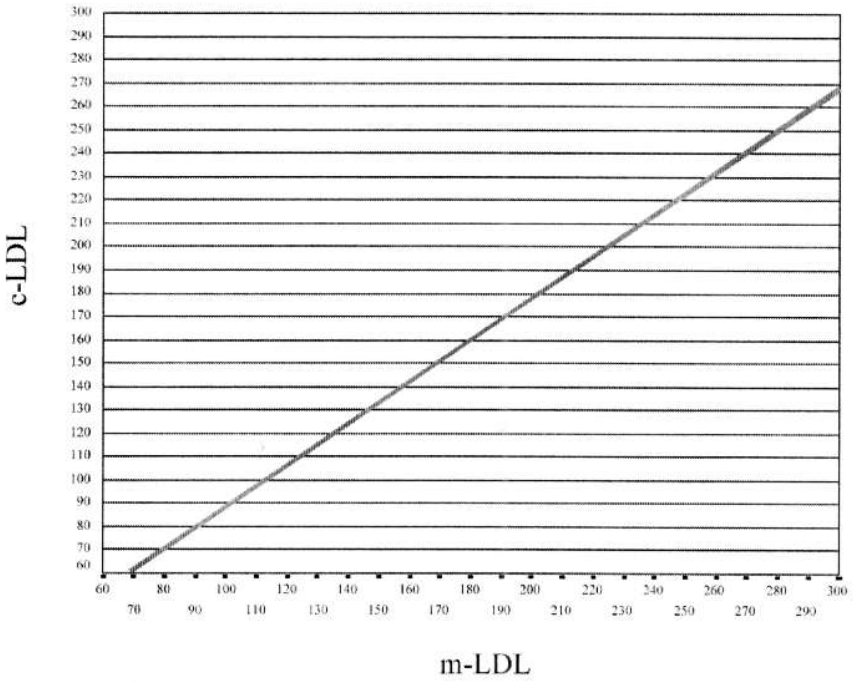



**Fig. 3** Nomogram for transforming m-LDL-cholesterol level to c-LDL-cholesterol level

correlated with m-LDL-cholesterol levels[6-9]. However, the correlation between c-LDL-cholesterol levels and m-LDL-cholesterol levels is not perfect. As a result, the values of m-LDL-cholesterol levels are not exactly the same as c-LDL-cholesterol levels and m-LDL-cholesterol levels are usually higher than c-LDL-cholesterol levels. The LDL-cholesterol cut-off values for initiating appropriate management recommended in NCEPIII are based on c-LDL-cholesterol levels. Therefore, m-LDL-cholesterol levels could not replace c-LDL-cholesterol levels if one wants to use the LDL-cholesterol cut-off values recommended in NCEPIII as a guide for management of patients with dyslipidemia. Our study demonstrated that 3.6% to 42.9% of the patients with an elevated LDL-cholesterol level received unnecessary lipid-lowering agents if the LDL-cholesterol cut-off values recommended in NCEIII were used for m-LDL-cholesterol levels. The m-LDL-cholesterol cut-off values of $<87$, $>143$, $>188$, $>233$ and $>254$ mg/dl were found to be accurate to predict the c-LDL-cholesterol levels of $<100$, $\geq 100$, $\geq 130$, $\geq 160$ and $\geq 190$ mg/dl respectively. Moreover, we observed that only 2.6% of the individuals who received lipid profile testing had blood triglyceride $>400$ mg/dl and c-LDL-cholesterol could not be computed. Hence the m-LDL-cholesterol assay is needed for this group and the cut-off thresholds for initiating lipid-lowering agents should be $>143$, $>188$, $>233$ and $>254$ mg/dl instead of $<100$, $\geq 100$, $\geq 130$, $\geq 160$ and $\geq 190$ mg/dl respectively. Until more solid evidence on the clinical benefit to patients receiving management according to the cut-off values of m-LDL-cholesterol is available, the cut-off values of c-LDL-cholesterol should not be applied to m-LDL-cholesterol test results to guide the treatment on patients. If the m-LDL-cholesterol assay becomes necessary such as in those with blood triglyceride $>400$ mg/dl, the cut-off values of $>143$, $>188$, $>233$ and $>254$ mg/dl should be considered or the m-LDL-cholesterol level should be transformed to c-LDL-cholesterol level using the nomogram in figure 3 or the m-LDL-cholesterol level should be transformed to the c-LDL-cholesterol level using the formula of c-LDL-cholesterol ~ 0.89 x m-LDL-cholesterol prior to initiating appropriate management. The aforementioned nomogram or formula for transforming m-LDL-cholesterol level to c-LDL-cholesterol level is also useful for health care providers who use m-LDL-cholesterol for monitoring the response to treatment, since the cost of a

m-LDL-cholesterol assay (150 baht) is less than the cost of a combination of total cholesterol, HDL-cholesterol and triglyceride (170 baht). In conclusion, m-LDL-cholesterol assay has a very limited use in managing individuals with suspected or known dyslipidemia. The use of m-LDL-cholesterol level as a guide for the management of abnormal LDL-cholesterol conditions leads to an overuse of lipid lowering medications and an enormous expense in m-LDL-cholesterol assay costs.

**Acknowledgement**

The authors would like to thank the Thailand Research Fund for supporting the study.

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## การใช้การตรวจ low density lipoprotein cholesterol ที่ได้จากการคำนวณและ low density lipoprotein cholesterol ที่ได้จากการวัดโดยตรงในโรงพยาบาลศิริราช

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*คณะผู้วิจัยได้ศึกษาการใช้การตรวจ low density lipoprotein (c-LDL) cholesterol ที่ได้จากการคำนวณและ low density lipoprotein (m-LDL) cholesterol ที่ได้จากการวัดโดยตรง ในโรงพยาบาลศิริราชโดยนำผลการตรวจระดับของ total cholesterol, triglyceride, high density lipoprotein (HDL) cholesterol และ m-LDL-cholesterol จากคนเดียวกันที่อายุ 18 ปีหรือมากกว่าและได้รับการตรวจระดับไขมันในเลือดที่ภาควิชาพยาธิวิทยาคลินิกระหว่างเดือนมกราคมถึงธันวาคม พ.ศ. 2547 ส่วนหนึ่งมาคำนวณค่า c-LDL-cholesterol ด้วยสูตรของ Friedewald แล้วนำผลดังกล่าวมาวิเคราะห์ความสัมพันธ์กับระดับ m-LDL-cholesterol ข้อมูลที่นำมาศึกษามี 2 ชุด ได้แก่ ข้อมูลชุดแรกที่นำมาวิเคราะห์หาเกณฑ์ของค่า m-LDL-cholesterol (derivation data set) จำนวน 784 คนและข้อมูลชุดที่สองที่นำมาทดสอบความแม่นยำของเกณฑ์ของค่า m-LDL-cholesterol ที่ได้จากข้อมูลชุดแรก (validation data set) จำนวน 800 คน พบว่า 1) ผู้มารับการตรวจร้อยละ 2.6 มีค่า triglyceride มากกว่า 400 มก./ดล. ซึ่งไม่สามารถคำนวณค่า c-LDL-cholesterol ได้ 2) ค่า c-LDL-cholesterol และ m-LDL-cholesterol ของข้อมูลทั้ง 2 ชุดมีความสัมพันธ์กันอย่างมีนัยสำคัญทางสถิติ ($p < 0.001$) และความสัมพันธ์มีขนาดมากกว่า 0.95, 3) ระดับของ m-LDL-cholesterol มักสูงกว่า c-LDL cholesterol 4) ค่า m-LDL-cholesterol cut-off < 87, > 143, > 188, > 233 and > 254 มก./ดล. จะสัมพันธ์กับค่า c-LDL-cholesterol < 100, ≥ 100, ≥ 130, ≥ 160 และ ≥ 190 มก./ดล. ตามลำดับ 5) เมื่อนำเกณฑ์ดังกล่าวจากข้อมูลชุดแรกไปประยุกต์ใช้กับข้อมูลชุดที่สองพบว่าค่า m-LDL-cholesterol < 87, > 143, > 188, > 233 and > 254 มก./ดล. มีความแม่นยำในการทำนายค่า c-LDL-cholesterol < 100, ≥ 100, ≥ 130, ≥ 160 และ ≥ 190 มก./ดล. ร้อยละ 100, 99.7, 100, 100 และ 100 ตามลำดับ 6) เมื่อวิเคราะห์ผู้ป่วยที่มีค่า m-LDL-cholesterol ก่อนการรักษาและได้รับการรักษาด้วยยาลดไขมันในเลือดโดยอาศัยระดับของ m-LDL-cholesterol เป็นแนวทางในการรักษาพบว่าผู้ป่วยร้อยละ 3.6 ถึง 42.9 ได้รับยาลดไขมันโดยไม่จำเป็น 7) ได้สร้าง nomogram สำหรับแปลงค่า m-LDL-cholesterol ให้เป็น c-LDL-cholesterol และสูตรการแปลง m-LDL-cholesterol ให้เป็น c-LDL-cholesterol โดย c-LDL-cholesterol จะมีค่า 0.89 x m-LDL-cholesterol ผลการศึกษานี้แสดงว่า m-LDL-cholesterol มีที่ใช้น้อยมาก การใช้การตรวจ m-LDL-cholesterol โดยอาศัยเกณฑ์ระดับ c-LDL-cholesterol เป็นแนวทางในการรักษาผู้ป่วยทำให้ผู้ป่วยส่วนหนึ่งได้รับยาลดไขมันในเลือดโดยไม่จำเป็นและยังสิ้นเปลืองค่าใช้จ่ายในการตรวจ m-LDL-cholesterol ด้วย*

# Epidemiology of *Acinetobacter baumannii* Infections in Siriraj Hospital 2002

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## ABSTRACT

**Objective:** To determine the epidemiology of *A.baumannii* infections in Siriraj Hospital in 2002.

**Methods:** From January to December 2002, we prospectively studied hospitalized patients in Siriraj Hospital who had *A.baumannii* isolated from their clinical specimens.

**Results:** During the study period, *A.baumannii* was isolated from clinical specimens of 208 cases. Eighty-six patients (41.3%) had *A.baumannii* infections whereas 122 patients (58.7%) had *A.baumannii* colonization. Of the 86 patients with *A.baumannii* infections, 54.7% were males and 45.3% were females. The mean age of patients was 56.1 years. Ninety-eight percent of the infections were hospital-acquired. The patients developed infection after an average of 26 days of hospitalization. Fifty-two percent of the patients were in the general wards, whereas 48% of them were in ICU. The common sites of infection were respiratory tract and skin and soft tissues. Factors associated with *A.baumannii* infection were identified in 98.8% of the patients. The most common factors were prior use of antibiotics especially ceftazidime and indwelling medical devices. The susceptibility of *A.baumannii* to carbapenems, aminoglycosides, beta-lactam/ beta-lactamase inhibitors, co-trimoxazole, fluoroquinolone, 4$^{th}$ generation cephalosporins and 3$^{rd}$ generation cephalosporins was 32%, 16%, 12 %, 9%, 7%, 4% and 3%, respectively. Fifty-seven percent of *A.baumannii* isolates were resistant to all antimicrobials currently available in Thailand. The overall mortality rate of the patients infected with *A.baumannii* was 54.7%.

**Conclusion:** Most *A.baumannii* infections in Siriraj were hospital-acquired. The most common site of infection was the respiratory tract. The majority of *A.baumannii* isolates was multi-drug resistant. The mortality rate of *A.baumannii* infections was high.

**Keywords:** *Acinetobacter baumannii* infections; Epidemiology

**Siriraj Med J 2006; 58: 951-954**
***E-journal: http://www.sirirajmedj.com***

*Acinetobacter* spp. is aerobic gram negative bacilli. Healthy individuals can harbor this organism on their skin especially over the moist areas. Skin colonization rate of in hospitalized patients was significantly more than that in healthy individuals.[1,2] This observation implies that the patients should acquire the organism while hospitalization. *Acinetobacter* spp. is also commonly found in hospital environments and it can be transmitted to the patients via hospital personnel and contaminated instruments or devices.[1,2] *Acinetobacter baumannii* is the most common species of Acinetobacter causing infections in human. Over the past decade, there have been many reports on *Acinetobacter* spp. as a common causative pathogen in intensive care unit patients and the infection was associated with indwelling medical devices, e.g., ventilator-associated pneumonia, catheter-associated urinary tract infection, blood stream infection associated with intravascular devices.[1,2] *Acinetobacter* spp. is usually resistant to many antibiotics including cephalosporins, aminoglycosides and fluoroquinolones due to various resistance mechanisms.[3] *Acinetobacter* spp. is one of the most common causes of hospital acquired infections in Thailand.[4] To our knowledge there has been no report on epidemiology of *Acinetobacter baumannii* infections in Thailand. Therefore, this study attempted to determine the clinical features, risk factors, clinical course and outcomes of patients infected with *A.baumannii* in Siriraj Hospital in 2002.

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## MATERIALS AND METHODS

This is a prospective study conducted in Siriraj Hospital, a tertiary care university hospital, from January to December 2002. The hospitalized patients who had *A. baumannii* isolated from their clinical specimens submit-

TABLE 1. Underlying diseases of 86 patients with *A.baumannii* infections.

| Diseases | N (%)* |
|---|---|
| Cerebrovascular disease | 27 (31.4) |
| Hypertension | 24 (27.9) |
| Diabetes mellitus | 23 (26.7) |
| Cancer | 14 (16.3) |
| Chronic renal failure | 14 (16.3) |
| Ischemic heart disease | 10 (11.6) |
| Chronic obstructive pulmonary disease | 9 (10.5) |
| Neutropenia | 4 (4.7) |
| Cirrhosis | 1 (1.2) |
| Others | 23 (26.7) |

* The patient could have more than one disease.

ted to Microbiology Laboratory were notified to the investigators. Then clinical information and microbiological information of the patients were collected, and the patients were followed until they left the hospital or died. The collected information was analyzed by descriptive statistics.

## RESULTS

*A. baumannii* was isolated from clinical specimens of 208 patients during the study period. Eighty-six patients (41.3%) were infected, i.e. the patients who had clinical features of infection at the site where *A. baumannii* was isolated, whereas 122 (58.7%) were colonization, i.e., the patients who did not have clinical features of infection at the site where *A. baumannii* was isolated or the patients who had clinical features of infection at the site where the organism was isolated but the infection was caused by other organisms. Patients with *A. baumannii* infections were males in 54.7% and the mean age was 56.1 years with a range from 6 days to 91 years. Ninety percent of *A. baumannii* infected patients had underlying diseases as shown in Table 1. The common underlying diseases were cerebrovascular diseases, hypertension and diabetes mellitus. Forty-eight percent of the patients were hospitalized in general wards whereas 52% were in intensive care units. The patients were admitted to medical, surgical and pediatrics department in 61%, 23% and 9%, respectively. Almost all infections (97.7%) were hospital-acquired: which were those occurred in patients after hospitalization for longer than 48 hours. Almost all patients (98.8%) had factors that might be associated with A. baumannii infections as shown in Table 2. The most common factors

TABLE 2. The factors associated with *A.baumannii* infections in 86 patients.

| Factors | N (%)* |
|---|---|
| Antibiotics | 85 (98.8) |
| Peripheral intravascular devices | 82 (95.3) |
| Urinary catheter | 73 (84.9) |
| Nasogastric tube | 69 (80.2) |
| Endotracheal tube | 62 (72.1) |
| Ventilator | 62 (72.1) |
| Surgery | 39 (45.3) |
| Central intravascular devices | 38 (44.2) |
| Immunosuppressives | 9 (10.5) |
| Chemotherapy | 5 (5.8) |
| Parenteral nutritution | 5 (5.8) |
| Others | 27 (31.4) |

* The patient could have more than one factor.

TABLE 3. The sites of *A.baumannii* infections in 86 patients.

| Sites of infection | N (%)* |
|---|---|
| Respiratory tract | 59 (68.6) |
| Skin and soft tissues | 17 (19.8) |
| Bacteremia | 6 (7.0) |
| Urinary tract | 4 (4.7) |
| Nervous system | 3 (3.5) |
| Gastrointestinal tract | 3 (3.5) |
| Others | 1 (1.2) |

* The patient could have more than one site of infection.

were prior use of antibiotics especially ceftazidime and indwelling medical devices. The patients developed infections after an average of 26 days of hospitalization. The sites of A. baumannii infections are shown in Table 3. The common sites were respiratory tract and skin and soft tissues. Seventy-one percent of the patients had *A. baumannii* as a single pathogen, whereas 29% had mixed infections with others such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Patients with respiratory tract infections tended to have mixed infections more often than infections in other sites. Almost all patients (98.8%) received various antibiotics prior to having *A. baumannii* infections as shown in Table 4. Ceftazidime was an antibiotic commonly given to the patients. The susceptibility of *A. baumannii* to carbapenems, aminoglycosides, beta-lactam/ beta-lactamase inhibitors, co-trimoxazole, fluoroquinolone, 4$^{th}$ generation cephalosporins and 3$^{rd}$ generation cephalosporins was 32%, 16%, 12 %, 9%, 7%, 4% and 3%, respectively. *A. baumannii* was resistant to all antimicrobials currently available in Thailand in 57% of the isolates. The patients with *A. baumannii* infections were usually treated with meropenem, imipenem and cefoperazone/sulbactam as shown in Table 5. The overall mortality rate of patients infected with *A. baumannii* was 54.7% and most of them died of multi-drug resistant *A. baumannii* infections. The mortality rate in those patients infected with pan-drug resistant *A. baumannii* was higher than those infected with sensitive strains.

## DISCUSSION

Our study found that less than 50% of the patients whose *A. baumannii* was present in their clinical speci-

TABLE 4. Antibiotics given to the patients prior to developing *A.baumannii* infections in 86 patients.

| Antibiotics | N (%)* |
|---|---|
| Ceftazidime | 28 (32.6) |
| Meropenem | 21 (24.4) |
| Ceftriaxone | 18 (20.9) |
| Amikacin | 14 (16.3) |
| Vancomycin | 14 (16.3) |
| Imipenem | 11 (12.8) |
| Metronidazole | 11 (12.8) |
| Cefoperazone/sulbactam | 10 (11.6) |
| Ciprofloxacin | 9 (10.5) |
| Cefotaxime | 7 (8.1) |
| Netilmicin | 7 (8.1) |
| Clindamycin | 6 (7.0) |
| Cefepime | 5 (5.8) |
| Amphotericin B | 5 (5.8) |
| Fluconazole | 1 (1.2) |
| Others | 23 (26.7) |

* The patient could have more than one antibiotic.

TABLE 5. Antibiotics for treating *A.baumannii* infections in 86 patients.

| Antibiotics | N (%)* |
|---|---|
| Meropenem | 23 (26.7) |
| Imipenem | 14 (16.3) |
| Cefoperazone/sulbactam | 9 (10.5) |
| Amikacin | 8 (9.3) |
| Netilmicin | 5 (5.8) |
| Ciprofloxacin | 4 (4.7) |
| Ceftazidime | 3 (3.5) |
| Others | 29 (33.7) |

* The patient could have more than one antibiotic.

mens were infections, whereas the majority were colonization. Therefore, healthcare providers should be aware of this observation and should avoid antibiotic treatment of patients with *A. baumannii* colonization. *Acinetobacter* spp. has been recognized as an important nosocomial pathogen over the past decade. It is usually resistant to many antibiotics empirically used for infections caused by other aerobic gram negative bacilli such as cephalosporins. As a result, the mortality of patient infected with *Acinetobacter* spp. is rather high. A report in Thailand revealed that *Acinetobacter* spp. was the most common cause of ventilatory associated pneumonia in a university hospital.[5] Our study observed that *A. baumannii* infections are more common in middle-age males. However, the patients could be babies and the elderly as seen in other studies.[6-10] This study also confirmed the observations made by others that almost all patients infected with *A. baumannii* were hospitalized longer than 48 hours. The other two patients who developed *A. baumannii* infections within 48 hours of hospitalization were those who were transferred to Siriraj Hospital from other hospitals. However, our study revealed that *A. baumannii* infections were similarly distributed in general wards and intensive care units (ICU) that was different from other studies.[11] This discrepancy could be explained by the fact that many patients in general wards in Siriraj Hospital were seriously ill but they were unable to be transferred to ICU due to a limited number of ICU beds. The average duration of hospitalization until developing *A. baumannii* infections in our study was 26 days that was longer than 10 to 14 days found in other studies.[8,12,14] However, is has been found that a long duration of hospitalization was associated with *A. baumannii* infections.[6,14] Although *A. baumannii* can cause infections in any organs, the common sites of infections seen in our study were respiratory tract and skin and soft tissues similar to other studies.[14,15] Factors found to be associated with *A. baumannii* infections were, namely: cancer, indwelling medical devices, antibiotics, parenteral nutrition, surgery, severe underlying diseases and duration of hospitalization.[12-15] Our study also observed that antibiotics, especially ceftazidime, and indwelling medical devices were common in patients infected with *A. baumannii*. In vitro susceptibility of *A. baumannii* revealed that the pathogen was usually resistant to antibiotics active for other aerobic gram negative bacilli and more than 50% of the isolates were resistant to all antibiotics currently available in Thailand. Therefore, antibiotics to be used for treating *A. baumannii* infections were limited. These included carbapenems, aminoglycosides and beta-lactam/ beta-lactamase inhibitors. An overall mortality of patients with *A. baumannii* infections was 54.7% and most of them died of multi-drug resistant *A. baumannii* infections. Polymyxins were found to be safe and effective for treatment of multi-drug resistant *A. baumannii* infections.[16] *In vitro* studies of polymyxins against *A.baumannii* resistant to all antibiotics currently available in Thailand revealed that all isolates were susceptible to polymyxins.[17] Polymyxin E has just been available in Thailand since January 2005 and the clinical trial on safety and efficacy of polymyxin E for treatment of A.baumannii infections is being conducted in Siriraj Hospital. New antibiotics such as glycylcycline were found to be active against multi-drug resistant *A.baumannii* and these antibiotics should have a role in treatment of *A.baumannii* infections in the near future.

## ACKNOWLEDGEMENTS

The authors would like to thank Infectious Disease Association of Thailand and Thailand Research Fund for supporting this study.

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## บทคัดย่อ

# ระบาดวิทยาของการติดเชื้อ *Acinetobacter baumannii* ในโรงพยาบาลศิริราช พ.ศ. 2545

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**วัตถุประสงค์:** เพื่อทราบระบาดวิทยาการติดเชื้อ *A.baumannii* ในผู้ป่วยที่รับไว้รักษาในโรงพยาบาลศิริราชในปี พ.ศ. 2545

**วิธีการ:** เฝ้าระวังการตรวจพบเชื้อ *A.baumannii* ที่ห้องปฏิบัติการจุลชีววิทยาจากตัวอย่างตรวจที่เก็บจากผู้ป่วยที่รับไว้รักษาโรงพยาบาลศิริราชตั้งแต่วันที่ 1 มกราคม ถึง 31 ธันวาคม 2545 แล้วติดตามผู้ป่วยที่มีการติดเชื้อดังกล่าวโดยเก็บข้อมูลต่าง ๆ ที่เกี่ยวข้องเพื่อนำมาวิเคราะห์

**ผลการศึกษา:** มีผู้ป่วยที่แยกได้เชื้อ *A.baumannii* จากสิ่งส่งตรวจจำนวน 208 ราย ในจำนวนนี้เป็นการติดเชื้อจำนวน 86 ราย (ร้อยละ 41.3) ส่วนอีก 122 ราย (ร้อยละ 58.7) เป็น colonization, ผู้ป่วยที่ติดเชื้อ 86 รายเป็นชายร้อยละ 54.7 และหญิงร้อยละ 45.3, ผู้ป่วยมีอายุเฉลี่ย 56.1 ปี, การติดเชื้อร้อยละ 98 เป็นการติดเชื้อในโรงพยาบาล, ระยะเวลาเฉลี่ยของการอยู่ในโรงพยาบาลก่อนมีการติดเชื้อ 26 วัน, ผู้ป่วยร้อยละ 52 อยู่ที่หอผู้ป่วยสามัญและผู้ป่วยร้อยละ 48 อยู่ที่หออภิบาล, ตำแหน่งที่มีการติดเชื้อบ่อยคือระบบการหายใจและบาดแผล, ผู้ป่วยร้อยละ 98.8 มีปัจจัยที่สัมพันธ์กับการติดเชื้อโดยปัจจัยที่พบบ่อยคือการได้รับยาต้านจุลชีพโดยเฉพาะอย่างยิ่ง ceftazidime และการมีสายเข้าสู่ร่างกาย, อัตราการดื้อยาของเชื้อ *A.baumannii* ต่อ carbapenems, aminoglycosides, beta-lactam/beta-lactamase inhibitors, co-trimoxazole, fluoroquinolone, 4th generation cephalosporins และ 3rd generation cephalosporins เป็นร้อยละ 32, 16, 12, 9, 7, 4 และ 3 ตามลำดับ เชื้อ *A.baumannii* ร้อยละ 57 ดื้อต่อยาต้านจุลชีพทุกขนานที่มีในประเทศไทย และผู้ป่วยที่ติดเชื้อ *A.baumannii* เสียชีวิตร้อยละ 54.7

**สรุป:** การติดเชื้อ *A.baumannii* ในผู้ป่วยที่รับไว้รักษาในโรงพยาบาลศิริราชเกือบทั้งหมดเป็นการติดเชื้อในโรงพยาบาล การติดเชื้อส่วนมากเป็นที่ระบบการหายใจ เชื้อก่อโรคส่วนมากดื้อต่อยาต้านจุลชีพทุกขนานที่มีในประเทศไทย และผู้ป่วยที่ติดเชื้อนี้มีอัตราตายสูง

# *Stenotrophomonas maltophilia* Infections in Hospitalized Patients at Siriraj Hospital

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## ABSTRACT

Ninety-seven strains of *Stenotrophomonas maltophilia* isolated from 62 patients hospitalized at Siriraj Hospital from September 2005 to February 2006 were studied. Ninety-two strains (94.8%) were isolated from respiratory secretions and five strains (5.2%) were from blood. Only 39.3% of the patients who had *S. maltophilia* isolated from their clinical specimens had infections. All *S. maltophilia* infections were hospital acquired and the infected patients had underlying diseases, multiple medical devices and received multiple antibiotics prior to *S. maltophilia* infections. Pneumonia was the most common site of infections. *S. maltophilia* was susceptible to co-trimoxazole in 68.8% of the isolates. The overall mortality of the patients with *S. maltophilia* infections was 45.5%.

**Keywords:** Hospitalized patients; infections; *Stenotrophomonas maltophilia*

**Siriraj Med J 2006; 58: 1110-1111**
***E-journal: http://www.sirirajmedj.com***

*Stenotrophomonas maltophilia* is a non-fermentative aerobic gram-negative bacillus formerly classified as *Pseudomonas.*[1] *S. maltophilia* is usually found in a variety of aquatic environments. *S. maltophilia* is a frequent colonizer of fluids used in the hospital setting i.e. irrigation solutions and intravenous fluids, and of patient secretions e.g., respiratory secretions, urine, wound exudates. *S. maltophilia* is an organism of low virulence and is an infrequent pathogen in humans. *S. maltophilia* must bypass normal host defenses to cause human infection. For example, if an intravenous infusion fluid contains a large amount of *S. maltophilia*, then direct injection into the bloodstream may result in blood stream infection. *S. maltophilia* has been recognized as an increasingly important nosocomial pathogen causing pneumonia, bacteremia and other infections especially in debilitated and immunocompromised cancer or hematologic malignancy patients.[1-4] Infection with *S. maltophilia* is difficult to treat since effective antibiotics against *S. maltophilia* are limited and co-trimoxazole is an antibiotic of choice.[1-5]

The objective of the study was to describe the demographics, clinical features and outcomes of hospitalized patients at Siriraj Hospital who had *S. maltophilia* isolated from their clinical specimens.

## MATERIALS AND METHODS

*S. maltophilia* isolated from the clinical specimens collected from the patients hospitalized at Siriraj Hospital during a six-month period from September 2005 to February 2006 were included. The medical records of the patients with a presence of *S. maltophilia* in their clinical specimens were reviewed.

## RESULTS

There were 97 isolates of *S. maltophilia* from 62 patients hospitalized at Siriraj Hospital during the study period. Ninety-two strains (94.8%) were isolated from respiratory secretions and five strains (5.2%) were from blood. Forty patients (64.5%) were males and 22 (35.5%) were females. The mean age of the patients was 53.1 years (median age 62 years) with an age ranged from 1 month to 90 years. Thirty patients (48.4%) were hospitalized at intensive care units (ICU). The medical records of 56 patients were available for review. Twenty-nine patients (51.8%) were medical patients and 19 (33.9%) and 6 (10.7%) were surgical and pediatrics patients respectively. Forty-nine patients (87.5%) had underlying severe or chronic diseases such as cancer, diabetes mellitus, hypertension, cerebrovascular diseases, ischemic heart diseases. *S. maltophilia* isolated from the respiratory secretions of 34 patients (60.7%) were considered colonization since the patients did not have clinical features of *S. maltophilia* pneumonia. Of 22 patients with *S. maltophilia* infections, 17 patients (77.3%) had pneumonia, 4 patients (18.2%) had bacteremia and 1 patient (4.5%) had pneumonia and bacteremia. All episodes of *S. maltophilia* infections were hospital-acquired. All patients with *S. maltophilia* infections had underlying diseases, multiple medical devices including central venous catheter, endotracheal tubes, urethral catheters, nasogastric tubes, and had received multiple antibiotics prior to developing *S. maltophilia* infections. Eighteen patients (81.8%) were hospitalized in the ICU. In vitro susceptibility of co-

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trimoxazole against 77 isolates of *S. maltophilia* revealed that 53 isolates (68.8%) were susceptible. Fifteen patients with *S. maltophilia* infections received co-trimoxazole and 10 patients survived whereas 7 patients received other antibiotics and only 2 patients survived. The overall mortality of the patients with *S. maltophilia* infections was 45.5%.

## DISCUSSION

We found that most isolates of *S. maltophilia* from respiratory secretions were colonizations, all patients with *S. maltophilia* infections had underlying diseases, multiple medical devices and had received multiple antibiotics prior to developing the infections; and a high mortality of patients with *S. maltophilia* infections confirmed the observations made earlier by others.[1-6] The responsible healthcare personnel should be aware that most of the *S. maltophilia* strains isolated from respiratory secretions were not infections and these patients did not need antibiotics specific for *S. maltophilia*. The recovery of *S. maltophilia* from respiratory secretions should be regarded as colonization until proven otherwise and a potential pathogenic role should be evaluated by an infectious disease consultant. Although *S. maltophilia* usually is resistant to aminoglycosides, antipseudomonal penicillins, and antipseudomonal third-generation cephalosporins, it usually is susceptible to co-trimoxazole. *S. maltophilia* isolated from hospitalized patients at Siriraj Hospital was less susceptible to co-trimoxazole than that in other studies.[5, 7-10] Therefore new antibiotics are needed for therapy of *S. maltophilia* infections. Tigecycline was found to be active against most isolates of *S. maltophilia*[11, 12] and this antibiotic might be beneficial for therapy of *S. maltophilia* infections. Polymyxin B was found to be active against *S. maltophilia*[13] whereas colistin (polymyxin E) was inactive against *S. maltophilia* in another study.[10] In vitro synergy of colistin with rifampin and trimethoprim/sulfamethoxazole on multidrug-resistant *S. maltophilia* was observed[14] and antibiotic combination could be another measure for therapy of *S. maltophilia* infections. Since all *S. maltophilia* infections in our study were hospital-acquired, the choice of antibiotic therapy was limited and the mortality rate was high. Effective infection control measures should be employed in order to prevent *S. maltophilia* colonizations and infections in hospitalized patients. Sources of *S. maltophilia* colonization include personnel (hands, antiseptic soaps, hand lotion), respiratory equipment and/or fluids (ultrasonic nebulizers, inhalation medications, respirator tubing condensate), IV lines and/or fluids (IV solutions, central venous catheters, pressure monitoring devices - pressure transducer fluids), urine and/or fluids (indwelling urinary catheters, urometers, irrigation solutions). Effective measures for decontamination of *S. maltophilia* in these sources and a control of patient-to-patient spread of the organism should be attempted and is of concern.

## ACKNOWLEDGEMENTS

The authors thank Mr Siripan Chaiya and Ms Lucksamee Wattanamongkolsilp for co-ordinating the study, and the Thailand Research Fund for supporting the study.

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**บทคัดย่อ**

## การติดเชื้อ *Stenotrophomonas maltophilia* ในผู้ป่วยที่รับไว้รักษาในโรงพยาบาลศิริราช

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คณะผู้วิจัยได้ศึกษาเชื้อ *Stenotrophomonas maltophilia* จำนวน 97 สายพันธุ์จากเสมหะและเลือดที่แยกได้จากผู้ป่วย 62 คนที่รับไว้รักษาในโรงพยาบาลศิริราช ระหว่างเดือนกันยายน พ.ศ. 2548 ถึงเดือนกุมภาพันธ์ พ.ศ. 2549 พบว่าเชื้อร้อยละ 94.8 แยกได้จากเสมหะ และร้อยละ 5.2 แยกได้จากเลือด ผู้ป่วยเพียงร้อยละ 39.3 เท่านั้นที่มีการติดเชื้อ *S. maltophilia* การติดเชื้อทั้งหมดเกิดในผู้ป่วยที่รับไว้รักษาโรงพยาบาลที่มีโรคประจำตัว ได้รับสายหรือท่อสอดใส่เข้าสู่ร่างกาย และได้รับยาต้านจุลชีพหลายขนานก่อนมีการติดเชื้อดังกล่าว การติดเชื้อส่วนมากคือปอดอักเสบ เชื้อ *S. maltophilia* ร้อยละ 68.8 ไวต่อยา co-trimoxazole ผู้ป่วยติดเชื้อ *S. maltophilia* มีอัตราตายร้อยละ 45.5

# Clinical Study of *Morus Alba* Linn. on Glycemic Control and Blood Lipids in Patients with Type 2 Diabetes: A Preliminary Study

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## ABSTRACT

Effects of *Morus alba*-leaf extracts on glycemic control and blood lipids were carried out in 27 patients with newly diagnosed type 2 diabetes. Water extracts of *Morus alba* leaves at a dosage of 700 mg were given to the patients thrice daily for 8 weeks. The patients did not receive any concomitant medications for diabetes or hyperlipidemia. The mean fasting plasma glucose levels at baseline, week 2, week 4, week 6 and week 8 were 155.1, 179, 173.6, 183.9 and 185.8 mg/dl, respectively (p=0.04). The mean glycosylated hemoglobin levels at baseline and week 8 were 7.6% and 8.4%, respectively (p=0.002). The mean blood total cholesterol levels at baseline, week 2, week 4, week 6 and week 8 were 229.6, 211.2, 210.2, 204.5 and 199.4 mg/dl, respectively (p<0.001). The mean blood triglyceride levels at baseline, week 2, week 4, week 6 and week 8 were 235.4, 191.3, 174.5, 183.5 and 168.2 mg/dl, respectively (p=0.001). No patients experienced side effects of the treatment. Laboratory results on CBC, urine, blood electrolytes, renal function and liver function at baseline, week 2, week 4, week 6 and week 8 were not significantly different. *Morus alba*-leaf extracts have no hypoglycemic effect but they may exert lipid lowering effects.

**Keywords:** Hyperglycemia; hyperlipidemia; *Morus alba*; type 2 diabetes

**Siriraj Med J 2006; 58: 1039-1041**
***E-journal: http://www.sirirajmedj.com***

The risk of cardiovascular diseases is increased in patients with poorly controlled diabetes mellitus and hyperlipidemia.[1,2] A number of medicinal herbs were reported to yield hypoglycemic effect.[3-5] *Morus alba* was found to contain hypoglycemic and lipid lowering effects in animals.[6-9] A toxicity study of *Morus alba* leaves revealed no remarkable acute and sub-chronic toxicities.[10] Water infusion of *Morus alba* leaves has been widely used in Thailand over the past decades. The claims for promoting consumption of *Morus alba* leaves infusion are its beneficial effects on glycemic control and hyperlipidemia in patients with diabetes.

The objective of this study was to determine whether *Morus alba*-leaf extracts improved blood glucose, glycosylated hemoglobin, total cholesterol and triglyceride levels in patients with type 2 diabetes mellitus.

## MATERIALS AND METHODS

The study protocol was approved by the Ethics Committee of the Department for Development of Thai Traditional and Alternative Medicine, Ministry of Public Health, Thailand. The study site was Pathumthani Hospital, Pathumthani, Thailand. The study was conducted from October 2004 to May 2005.

*Patients*

The eligible patients were newly diagnosed type 2 diabetes mellitus (fasting plasma glucose between 127 to 200 mg/dl) aged 40 to 70 years. The patient was excluded if he/she had acute complications of diabetes or received anti-diabetics or lipid lowering agents or was allergic to *Morus alba*.

*Plant extractions, preparations and administration*

Mulberry leaves (*Morus alba*, Nakornratchasima 50) were obtained from the Department of Agriculture, Ministry of Agriculture and Co-Operatives in Plant Genetics Conservation Project. The sample was prepared by boiling 60 kg of *Morus alba* leaves in powder form with water at the ratio of 1:5, and evaporated to dryness using spray-dried apparatus. The percentage yield of the water extract was 18% w/w. The *Morus alba*-leaf extracts used in the

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TABLE 1. Effects of Morus alba-leaf extracts on glucose, glycosylated hemoglobin (HbA1c), total cholesterol and triglyceride levels in blood of 27 diabetic patients.

| | Mean ± S.E.M. | | | |
|---|---|---|---|---|
| | Glucose (mg/dl) | Total Cholesterol (mg/dl) | Triglyceride (mg/dl) | HbA1c (%) |
| Baseline | 155.11 ± 4.15 | 229.58 ± 11.24 | 235.38 ± 20.63 | 7.57 ± 0.22 |
| Week 2 | 179.04 ± 9.26 | 211.24 ± 9.37 | 191.28 ± 15.96 | |
| Week 4 | 173.62 ± 8.76 | 210.16 ± 9.92 | 174.52 ± 18.39 | |
| Week 6 | 183.88 ± 9.50 | 204.48 ± 9.88 | 183.52 ± 21.58 | |
| Week 8 | 185.84 ± 10.23 | 199.36 ± 10.10 | 168.24 ± 18.52 | 8.43 ± 0.23 |
| P-value | 0.004 | <0.001 | 0.001 | 0.002 |

study were composed of 90% herb extracts and 10% maltodextrin. Each capsule of the study medication contained 350 mg of *Morus alba*-leaf extracts. The patient was instructed to take Morus alba-leaf extracts two capsules (700 mg) orally thrice daily before meals for eight weeks. Concomitant medications for diabetes or hyperlipidemia were not allowed during the study period.

*Outcome measures*

The patients were followed every two weeks for four visits. For each visit, the patient was asked for symptoms, examined by the investigators and had blood tests for complete blood count (CBC), fasting plasma glucose, total cholesterol, triglyceride, electrolytes, renal function, liver function as well as urine examination. Glycosylated hemoglobin assay was done at baseline and at the end of the study.

*Statistical analysis*

Data were expressed as mean ± standard error of mean (SEM). Statistical comparisons between different values were done using paired student-t-test or repeated measured one-way analysis of variance (ANOVA). Significance was accepted at $P < 0.05$.

## RESULTS

Twenty-seven patients with newly diagnosed type 2 diabete were included. Twenty-two patients were females. The mean age of the patients was 53.4 years. The patients' compliance to the study medication was satisfactory. The changes in fasting plasma glucose, glycosylated hemoglobin, blood total cholesterol and triglyceride are shown in Table 1. The mean fasting plasma glucose levels at baseline, week 2, week 4, week 6 and week 8 were 155.1, 179, 173.6, 183.9 and 185.8 mg/dl, respectively (p=0.04). The mean glycosylated hemoglobin levels at baseline and week 8 were 7.6% and 8.4%, respectively (p=0.002). The mean blood total cholesterol levels at baseline, week 2, week 4, week 6 and week 8 were 229.6, 211.2, 210.2, 204.5 and 199.4 mg/dl, respectively (p<0.001). The mean blood triglyceride levels at baseline, week 2, week 4, week 6 and week 8 were 235.4, 191.3, 174.5, 183.5 and 168.2 mg/dl, respectively (p=0.001). No patients experienced side effects of the treatment. Laboratory results on CBC, urine, blood electrolytes, renal function and liver function at baseline, week 2, week 4, week 6 and week 8 were not significantly different.

## DISCUSSION

Our study was unable to detect hypoglycemic effect of *Morus alba*-leaf extracts at a dosage of 2.1 g per day for 8 weeks. Although *Morus alba* was found to have hypoglycemic effect in several animal studies,[6-8] one of these studies used *Morus alba* root bark extract.[8] Another animal study did not observe any hypoglycemic effect of *Morus alba*.[11] The hypoglycemic effect of higher dose of Morus alba-leaf extracts or the extracts from its root bark in patients with diabetes was unknown and needed further clinical study. It should be mentioned that the levels of fasting plasma glucose and glycosylated hemoglobin at the end of treatment were significantly higher than those at baseline. The reason for this observation was unclear. The study medication was composed of maltodextrin but this substance was not related to glucose. The amount of glucose in *Morus alba*-leaf extracts was minimal and this should not explain the increase in fasting plasma glucose at the end of treatment.

However our study showed that blood total cholesterol and triglyceride levels at the end of therapy were significantly reduced from those at baseline. The magnitude of the reductions was meaningful, i.e., blood total cholesterol level was reduced by 13% whereas blood triglyceride was reduced by 28.5%, and the mean blood levels of both total cholesterol and triglyceride at the end of therapy were less than 200 mg/dl. Our observation on lipid lowering effect of *Morus alba*-leaf extracts in the patients supported the findings from animal experiments.[9] Enkhmaa, et al. studied the effects of dietary consumption of *Morus alba* leaves and their major flavonol glycoside on the development of atherosclerotic lesions in LDL receptor-deficient mice. The mice fed with dried *Morus alba*-leaf powder or *Morus alba* leaves' major flavonol glycoside in addition to an atherogenic-diet for 8 weeks had significantly lower total cholesterol and triglyceride levels in the sera when compared with the control mice. Atherosclerotic lesion areas in *Morus alba*-treated mice were significantly reduced by 52% compared with that of the controls. Although a lipid lowering effect of *Morus alba*-leaf extracts in patients with type 2 diabetes observed in our study was very promising, the study was open-labeled without concurrent controls hence the effect could partly due to co-interventions. Although diet control instructions were not officially provided to the patients by the investigators during the study period, the patients might modify their eating habits due to a concern of having diabetes and this could lead to a reduction in blood lipids. Therefore, further clinical trials on treatment of patients with hyperlipidemia comparing *Morus alba*-leaf extracts to placebo or conventional lipid lowering agents are warranted.

## CONCLUSION

The present study suggested that *Morus alba*-leaf extracts taken orally at a dosage of 700 mg thrice daily had no hypoglycemic effect but they exerted lipid lowering effect. Further clinical trials on treatment of patients with hyperlipidemia comparing *Morus alba*-leaf extracts to placebo or conventional lipid lowering agents are warranted.

## ACKNOWLEDGEMENTS

We thank the Department of Medical Sciences, Ministry of Public Health, Thailand and The Thailand Research Fund for supporting the study.

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## บทคัดย่อ

# ประสิทธิผลและความปลอดภัยของใบหม่อน (Morus alba) ในการลดระดับน้ำตาลและไขมันในเลือดในผู้ป่วยเบาหวานชนิดไม่พึ่งอินสุลิน : การศึกษาเบื้องต้น


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คณะผู้วิจัยได้ศึกษาประสิทธิผลเบื้องต้นของสารสกัดใบหม่อนในการลดระดับน้ำตาลและไขมันในเลือดในผู้ป่วยเบาหวานชนิดไม่พึ่งอินสุลินรายใหม่จำนวน 27 คนที่ได้รับสารสกัดใบหม่อนด้วยน้ำขนาด 350 มิลลิกรัมบรรจุในแคปซูล รับประทานครั้งละ 2 แคปซูล วันละ 3 ครั้งก่อนอาหาร ติดต่อกันนาน 8 สัปดาห์ ผู้ป่วยทุกรายไม่ได้รับยารักษาเบาหวานหรือยาลดไขมันร่วมด้วย ระดับน้ำตาลในเลือดเฉลี่ยก่อนการรักษาและสัปดาห์ที่ 2, 4, 6 และ 8 ภายหลังการรักษามีค่า 155.1, 179, 173.6, 183.9 and 185.8 มก/ดล. ตามลำดับ (p=0.004) ระดับ glycosylated hemoglobin เฉลี่ยก่อนการรักษาและสัปดาห์ที่ 8 ภายหลังการรักษามีค่า 7.6% และ 8.4% ตามลำดับ (p=0.002) ระดับ total cholesterol เฉลี่ยก่อนการรักษาและสัปดาห์ที่ 2, 4, 6 และ 8 ภายหลังการรักษามีค่า 229.6, 211.2, 210.2, 204.5 และ 199.4 มก/ดล. ตามลำดับ (p<0.001) ระดับ triglyceride เฉลี่ยก่อนการรักษาและสัปดาห์ที่ 2, 4, 6 และ 8 ภายหลังการรักษามีค่า 235.4, 191.3, 174.5, 183.5 และ 168.2 มก/ดล. ตามลำดับ (p=0.001) ผู้ป่วยทุกรายไม่มีอาการข้างเคียงจากการรักษา สารสกัดใบหม่อน 2.1 กรัมต่อวันไม่สามารถลดระดับน้ำตาลในเลือดของผู้ป่วยเบาหวานได้ แต่อาจลดระดับไขมันในเลือดได้

# Efficacy and Safety of Cinnamon Stomachic Mixture for Patients with Functional Dyspepsia

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## ABSTRACT

Health care personnel at a community hospital have used cinnamon stomachic mixture for treatment of patients with functional dyspepsia for many years and they claimed that cinnamon stomachic mixture was effective without any supportive evidence.

**Objective:** To determine the efficacy, safety, patients' compliance and satisfaction with the treatment of cinnamon stomachic mixture.

**Methods:** This was a randomized controlled study in 318 adults with functional dyspepsia presenting to 6 community hospitals. The patients were randomized to receive 105 mg of simethicone three times a day or 30 ml of cinnamon stomachic mixture three times a day for 7 to 14 days. The patients were evaluated for improvement of symptoms, compliance to medication and patients' satisfaction with the treatment. The data were analysed by descriptive statistics, chi-square statistics, student t test, analysis of variance and non-parametric tests where appropriate.

**Results:** One hundred and fifty patients received simethicone and 168 patients received cinnamon stomachic mixture. The baseline characteristics of the patients in both groups were not significantly different. The patients' compliance to simethicone and cinnamon stomachic mixture was 82% and 89.3% respectively (p=0.09). The severity of the symptoms after treatment and the response rates were not significantly different between both groups. Side effects were observed in 9.3% and 9.5% in the simethicone group and the cinnamon stomachic mixture group respectively. Most of the patients in both groups were satisfied with the treatments they received. The cost of a 14-day course of cinnamon stomachic mixture was 36 baht compared with 84 baht for that of simethicone.

**Conclusion:** Cinnamon stomachic mixture is effective and safe for the treatment of the patients with functional dyspepsia similar to simethicone.

**Keywords:** Cinnamon stomachic mixture; functional dyspepsia; simethicone

**Siriraj Med J 2006; 58: 1103-1106**
***E-journal: http://www.sirirajmedj.com***

Dyspepsia refers to a group of upper gastrointestinal symptoms that occur commonly in adults. Dyspepsia is known to result from organic causes, but the majority of patients suffer from non-ulcer or functional dyspepsia.[1] The generally accepted definition by most clinicians includes the presence of upper abdominal pain or discomfort with or without other upper gastrointestinal symptoms, such as nausea, belching and vomiting. In studies using "upper abdominal pain" as the definition, the prevalence of uninvestigated dyspepsia has varied between 7%-34.2%.[1] Two recent randomized controlled trials revealed that simethicone was more effective than a placebo for the treatment of patients with functional dyspepsia and the response observed in the simethicone group was not significantly different from that in the cisapride

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**TABLE 1.** Baseline characteristics of the study patients.

| Characteristic | Simethicone gr. (N=150) | Cinnamon stomachic mixture gr. (N=168) | P |
|---|---|---|---|
| Male : Female | 45 : 105 | 44 : 124 | 0.53 |
| Mean age, yr ± SD (Range) | 48.6 ± 12.8 (19-80) | 48.6 ± 13.3 (20-91) | 0.99 |
| Body weight, kg ± SD (Range) | 57.8 ± 10.9 (35-97) | 56.7 ± 13.3 (36-79) | 0.2 |
| Mean symptom score ± SD | 53.7 ± 21.9 | 51.9 ± 19.5 | 0.36 |
| Median symptom score | 50 | 50 | |
| Range of symptom score | 20 - 100 | 15 - 100 | |

group.[2,3] The cinnamon stomachic mixture has been produced and used for the treatment of patients with functional dyspepsia at a community hospital (Uthong Hospital) in Thailand for many years. The health care providers at this community hospital claimed that most of the patients responded to cinnamon stomachic mixture and they were also satisfied with the treatment they received.

The objective of this study was to determine the efficacy and safety of cinnamon stomachic mixture for treatment of patients with functional dyspepsia.

## MATERIALS AND METHODS

The study was approved by the Ethics Committee of the Department of Development of Thai Traditional Medicine and Alternative Medicine, Ministry of Public Health. This was a randomized controlled study conducted in 6 community hospitals namely Uthong Hospital, Kudchum Hospital, Bangrathum Hospital, Wangchan Hospital, Soongnern hospital and Somdej-Prayuparap-Lerng-Nok-Ta Hospitals in Thailand. The eligibility criteria for the study subjects were 1) age 20 years, 2) symptoms of dyspepsia, 3) duration of symptoms between 3 days to 30 days and 4) agreed to participate in the study and signed the written informed consent form. The exclusion criteria were 1) pregnancy, 2) had symptoms suggestive of organic diseases i.e. fever, vomiting, hematemesis, melena, diarrhea, weight loss > 3 kilograms within a month and symptoms of other organic diseases, 3) had signs suggestive of organic diseases i.e. anemia, jaundice, hepatomegaly, splenomegaly, abdominal mass, signs of chronic liver diseases, ascites, abdominal tenderness or guarding, absence of bowel sounds, signs of intestinal obstruction and signs of other organic diseases, 4) had been taking ulcerogenic drugs e.g. aspirin, NSAIDS, and 5) allergic to simethicone or any components of cinnamon stomachic mixture.

The subjects were randomized to the simethicone group or the cinnamon stomachic mixture group by block randomization. The subjects in the simethicone group received simethicone tablet of 105 mg. 3 times daily for 7 to 14 days. The subject in the cinnamon stomachic mixture group received 30 ml of cinnamon stomachic mixture 3 times daily for 7 to 14 days. Each milliliter of cinnamon stomachic contained cinnamon bark *(Cinnamomum verum)*, "samunlawaeng" bark *(Cinnamomum bejolghota)*, licorice *(Glycyrrhiza glabra)* and clove *(Syzygium aromaticum)* at the amount equivalent to 7.14 mg of each crude drug.

The cinnamon stomachic mixture was produced by boiling 50 grams of dried cinnamon, samunlawaeng, licorice and dried clove in 7,000 ml of water for 15 minutes. Then a teaspoon of camphor and 70 ml of paraben were added after leaving such a solution at room temperature for 5 minutes. The preparation was left overnight and was distilled through a clean cloth before bottling the distilled solution in 300 ml glass bottles.

A sample size of 200 per group was estimated from the following information 1) the mean difference of the symptom score at baseline and at the end of treatment was 30 (from 60 to 30) in the simethicone group and 25 (from 60 to 35) in the cinnamon stomachic mixture group, 2) the standard deviation of the mean difference in the symptom score was 20, 3) type I error was 5%, and 4) type II error was 20%.

All subjects received instructions on eating habits and avoidance of the substances that might precipitate the dyspeptic symptoms. The subject was evaluated for dyspeptic symptoms at entry and day 7 and day 14 after treatment using a visual analog scale of 0 (no symptoms) to 100 (unbearable symptoms). Any concomitant or additional treatment, compliance to the study medications, new symptom and satisfaction with the study medication received including the convenience of taking medication, taste and odor of the medications were also recorded at follow up visits. The data were analyzed by descriptive statistics, chi square statistics, student t test, analysis of variance and non-parametric test where appropriate. The p value of $< 0.05$ was considered statistically significant.

## RESULTS

There were 318 subjects, 150 in the simethicone group and 168 in the cinnamon stomachic mixture group. The baseline characteristics of the patients are shown in Table 1. Seventy percent of the patients were females. The mean age, mean body weight and mean symptom score of the patients in both groups were not significantly

**TABLE 2.** Treatment responses in terms of symptom score.

| | Mean symptom score ± SEM | | |
|---|---|---|---|
| | Simethicone gr. (N=150) | Cinnamon stomachic mixture gr. (N=168) | P |
| Before treatment | 53.7 ± 1.8 | 51.9 ± 1.5 | 0.36 |
| Day 7 after treatment | 32.5 ± 1.6 | 29.3 ± 1.6 | 0.17 |
| Day 14 after treatment | 16.1 ± 1.5 | 15.5 ± 1.2 | 0.76 |
| | p<0.001 | p<0.001 | |

**TABLE 3.** Treatment responses in terms of disappearance of symptoms.

| | Number of patients (%) with symptom score 10 | | |
|---|---|---|---|
| | Simethicone gr. (N=150) | Cinnamon Stomachic Mixture gr. (N=168) | P |
| Before treatment | 0 | 0 | |
| Day 7 after treatment | 22 (14.7%) | 36 (21.4%) | 0.15 |
| Day 14 after treatment | 99 (66%) (95% CI 58.1% - 73.1%) p<0.001 | 106 (63.1%) (95% CI 55.6% - 70%) p<0.001 | 0.67 |

different. Concomitant treatments such as antacid were given to 20% and 11.9% of the patients in the simethicone group and the cinnamon stomachic mixture group respectively (p=0.07). A full compliance to the medications was reported in 82% and 89.3% of the patients in the simethicone group and the cinnamon stomachic mixture group respectively (p=0.09). The mean symptom scores at the baseline and those during and at the end of treatment are shown in Table 2. The mean symptom scores at the baseline in both groups were not significantly different (p=0.14). The mean symptom score on day 7 and day 14 was significantly less than that at the baseline in both groups (p<0.001). The mean symptom scores on day 7 and day 14 in both groups were not significantly different. The treatment responses in terms of disappearance of symptoms (symptom score 10) are shown in Table 3. The response rates on day 7 and day 14 were significantly greater than those at the baseline in both groups (p<0.001). The response rates on day 7 and day 14 in both groups were not significantly different. Side effects were observed in 9.3% and 9.5% in the simethicone group and the cinnamon stomachic mixture group respectively. The common side effects were nausea, eructation, air discharge from the anus, dizziness and constipation. All side effects were mild and no medication-related serious adverse events were observed. Most of the patients in both groups were satisfied with the treatments they received i.e. 80% and 83.3% of the patients in the simethicone group and the cinnamon stomachic mixture group indicated that they would like to receive the same treatments if they had the same symptoms.

## DISCUSSION

The Gastroenterological Association of Thailand reported that the prevalence of dyspepsia in Thais was 20% to 25% and the incidence of dyspepsia in Thais was 1% to 2%. A significant proportion of dyspeptic patients were functional dyspepsia cases. Therefore functional dyspepsia is one of the very common health problems in Thailand and it consumes a large amount of health care resources. A meta-analysis on psychological interventions for non-ulcer dyspepsia concluded that there was insufficient evidence to confirm the efficacy of psychological intervention in non-ulcer dyspepsia.[4] Another meta-analysis on pharmacological interventions for non-ulcer dyspepsia revealed that prokinetics, H2 receptor antagonists and proton pump inhibitors were effective in therapy of non-ulcer dyspepsia.[5] These effective medications are expensive and have side effects. Many herbal medicines were found to be effective for treatment of functional dyspepsia. They were ganaton, extracts from bitter candy tuft, matricaria flower, peppermint leaves, caraway, licorice root & lemon balm, artichoke leaf extract, iberogast, peppermint oil & caraway oil and red pepper.[6-12] However there has been no study on the efficacy and safety of cinnamon stomachic mixture for treatment of functional dyspepsia.

We conducted this randomized controlled study in 6 community hospitals where sophisticated investigations such as gastroscopic examination and urea breath test were unavailable and we needed to enroll the subjects diagnosed as having functional dyspepsia based on their clinical features. Simethicone was chosen as a comparator drug instead of placebo because there was evidence that simethicone was more effective than a placebo in treating functional dyspepsia[2,3]. Simethicone was also the medication most commonly used by health care personnel at these community hospitals for treating the patients with functional dyspepsia. We did not use cisapride in our study although it was a prokinetic drug because cisapride has many drug interactions leading to serious side effects and it is no longer a treatment option in functional dyspepsia.[13,14]

Our study found that cinnamon stomachic mixture was effective in alleviating the symptoms by 70% and had a favorable response of 63% at the end of 2 weeks, similar to that of simethicone. The use of cinnamon stomachic mixture for longer duration might increase the response rate since many clinical studies on the treatment of functional dyspepsia used the study medications for longer than 4 weeks[2, 3, 9, 12, 15-17] and they found a favorable response of up to 80%. However, we did not use a longer duration of treatment since we thought that the patients who did not respond to a 2-week course of medication should have further appropriate investigations performed to detect organic causes of their persistent dyspeptic symptoms. The side effects of cinnamon stomachic mixture were uncommon and all of them had mild severity. The patients who received cinnamon stomachic mixture showed a very good compliance to treatment and were satisfied with this treatment. Moreover the cost of a 14-day course of cinnamon stomachic mixture was 36 baht compared with 84 baht for that of simethicone.

In summary cinnamon stomachic mixture for 2 weeks is effective, safe and cheap in relieving the symptoms of 60% of the patients with a clinical diagnosis of functional dyspepsia and it should be included as a treatment option for functional dyspepsia, especially in community hospitals.

## ACKNOWLEDGEMENTS

The authors thank the Department of Development of Thai Traditional Medicine and Alternative Medicine, Ministry of Public Health and the Thailand Research Fund for supporting the study. We also thank Ms Luksamee wattanamongkolsilp and Mr. Suthiphol Udompunturuk for statistical analyses.

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## บทคัดย่อ

# ประสิทธิผลและความปลอดภัยของยาธาตุอบเชยในการรักษาผู้ป่วย Functional Dyspepsia


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บุคลากรการแพทย์ที่ปฏิบัติงานที่โรงพยาบาลชุมชนรักษาผู้ป่วย functional dyspepsia ด้วยยาธาตุอบเชยพบว่าผู้ป่วยส่วนมากมีอาการทุเลาหรืออาการหายไป แต่ยังไม่มีการวิจัยทางคลินิกเพื่อประเมินประสิทธิผลและความปลอดภัยของยาธาตุอบเชยตำรับนี้

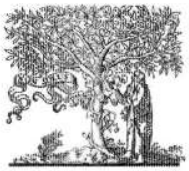
**วัตถุประสงค์:** เพื่อทราบประสิทธิผล ความปลอดภัยของการรักษาผู้ป่วย functional dyspepsia ด้วยยาธาตุอบเชย

**วิธีการ:** การวิจัยนี้ใช้รูปแบบ Randomized controlled study ดำเนินการที่โรงพยาบาลชุมชน 6 แห่งในผู้ใหญ่ที่ได้รับการวินิจฉัยโดยอาศัยลักษณะทางคลินิกว่าเป็น functional dyspepsia จำนวน 318 คน ผู้ป่วยถูกสุ่มให้ได้รับ simethicone ขนาด 105 มก รับประทานวันละ 3 ครั้งหลังอาหาร หรือยาธาตุอบเชยรับประทานครั้งละ 30 มล วันละ 3 ครั้งหลังอาหารติดต่อกันนาน 7-14 วัน ผู้ป่วยได้รับการประเมินผลการรักษาภายหลังการรักษานาน 7 วัน และ 14 วัน โดยประเมินอาการทั้งหมดของผู้ป่วย ความสม่ำเสมอของการรับประทานยาที่ได้รับ ผลข้างเคียงของการรักษา และความพึงพอใจของผู้ป่วยต่อการรักษาที่ได้รับ นำข้อมูลมาวิเคราะห์ด้วยสถิติเชิงพรรณนา, chi-square statistics, student t test หรือ analysis of variance หรือ non-parametric test

**ผลการศึกษา:** ผู้ป่วย 150 คนได้รับ simethicone และผู้ป่วย 168 คนได้รับยาธาตุอบเชย ลักษณะทั่วไปของผู้ป่วยทั้ง 2 กลุ่มไม่แตกต่างกันอย่างมีนัยสำคัญ ผู้ป่วยร้อยละ 82 ในกลุ่ม simethicone และร้อยละ 89.3 ในกลุ่มยาธาตุอบเชย (p=0.09) รับประทานยาครบทุกมื้อ อาการของผู้ป่วยและความรุนแรงเฉลี่ยอาการของผู้ป่วยภายหลังการรักษาด้วย simethicone หรือยาธาตุอบเชยไม่แตกต่างกันอย่างมีนัยสำคัญ จำนวนผู้ป่วยที่อาการดีขึ้นมากหรืออาการหายไปภายหลังการรักษาด้วย simethicone หรือยาธาตุอบเชยเพิ่มขึ้นจากก่อนการรักษาอย่างมีนัยสำคัญ และจำนวนผู้ป่วยที่อาการดีขึ้นมากหรืออาการหายไปภายหลังการรักษาด้วย simethicone หรือยาธาตุอบเชยไม่แตกต่างกันอย่างมีนัยสำคัญ ผลข้างเคียงของการรักษาพบร้อยละ 9.3 ในกลุ่ม simethicone และร้อยละ 9.5 ในกลุ่มยาธาตุอบเชย และผู้ป่วยส่วนมากที่ได้รับ simethicone หรือได้รับยาธาตุอบเชยพึงพอใจต่อการรักษาที่ได้รับไม่แตกต่างกัน ค่าใช้จ่ายของยาธาตุอบเชยประมาณ 36 บาท ส่วนค่าใช้จ่ายของ simethicone ประมาณ 84 บาท

**สรุป:** ยาธาตุอบเชยรับประทานติดต่อกัน 14 วันมีประสิทธิผลและปลอดภัยในการรักษาผู้ป่วย functional dyspepsia ไม่แตกต่างจากการรักษาด้วย simethicone

International Journal of Infectious Diseases (2007) 11, 402–406



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# Efficacy and safety of colistin (colistimethate sodium) for therapy of infections caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in Siriraj Hospital, Bangkok, Thailand

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Received 22 June 2006; received in revised form 31 August 2006; accepted 18 September 2006
**Corresponding Editor:** Andy I.M. Hoepelman, Utrecht, The Netherlands

**KEYWORDS**
Colistin;
*Pseudomonas aeruginosa*;
*Acinetobacter baumannii*

**Summary**
*Objective:* To determine the efficacy and safety of colistin (colistimethate sodium) produced by a local pharmaceutical company in Thailand for the treatment of infections caused by multidrug-resistant (MDR) *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.
*Methods:* Patients hospitalized at Siriraj Hospital between January 2005 and April 2006, who had infections caused by MDR *P. aeruginosa* or *A. baumannii*, were enrolled in the study. Colistin (colistimethate sodium) at a dosage of 5 mg/kg/day was given intravenously in two divided doses. Primary outcomes were the clinical response and 30-day mortality; secondary outcomes were microbiological response and adverse events.
*Results:* Ninety-three patients infected with MDR *P. aeruginosa* and *A. baumannii* were enrolled. Seventy-eight patients (71 with *A. baumannii* and seven with *P. aeruginosa*) received colistin, whereas 15 patients (12 with *A. baumannii* and three with *P. aeruginosa*) received other antibiotics. The mean age, gender, underlying conditions and severity of illness of the patients in both groups were not significantly different. In the colistin group, 63 patients (80.8%) had a favorable clinical response and 94.9% had a microbiological response. The overall mortality of the patients in the colistin group was 46.2% and that in the non-colistin group was 80%. Nephrotoxicity was found in 24 patients (30.8%) in the colistin group and 17 of them had predisposing factors contributing to their renal dysfunction. No neurotoxicity was observed among the 78 patients.

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doi:10.1016/j.ijid.2006.09.011

*Conclusion:* Locally produced colistin appears to be safe and effective for the treatment of infections caused by MDR *P. aeruginosa* and *A. baumannii* in Thai adult patients.


## Introduction

Nosocomial infections caused by multidrug-resistant (MDR) organisms are emerging worldwide.[1–3] The incidence of MDR pathogens, particularly *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, in Thailand has dramatically increased.[4] A prospective cohort study of 208 clinical isolates of *A. baumannii* recovered from the patients in Siriraj Hospital from January to December 2002, revealed that 86 strains (41.3%) were isolated from the infected patients and the remaining 58.7% were colonizers.[5] In this study, 57% of *A. baumannii* isolates were resistant to all antimicrobial agents available in Thailand including beta-lactams, aminoglycosides and fluoroquinolones, and the overall mortality rate of the patients infected with pandrug-resistant *A. baumannii* was 79%.[5] The study of 104 clinical isolates of *A. baumannii* from 100 hospitalized patients at Maharaj Nakorn Chiang Mai hospital, Thailand also observed that 46% of the isolates were pandrug-resistant and the overall mortality was 52%.[6]

Over the past few years there have been reports on treating patients infected with MDR *A. baumannii* and *P. aeruginosa* with polymyxin B and colistin.[7–9] They found that polymyxin B and colistin had modest efficacy and were safe. In vitro activity of polymyxin B and colistin against 100 clinical isolates of MDR *A. baumannii* and 100 isolates of *P. aeruginosa* collected from the patients hospitalized at Siriraj Hospital from 2002 and 2003, revealed that all isolates were susceptible to polymyxin B and colistin.[10] However polymyxins are not available in Thailand and international pharmaceutical companies do not have a policy to import polymyxins to Thailand. Therefore we asked a local pharmaceutical company to produce colistin and this product has been approved by the Thai Food and Drug Administration since 2004.

The objective of this study was to determine the efficacy and safety of colistin produced by a local pharmaceutical company in Thailand for the treatment of infections caused by MDR *P. aeruginosa* and *A. baumannii*.

## Methods

The study was approved by the ethics committee on human research of the Faculty of Medicine Siriraj Hospital, and all participating subjects signed the informed consent form. This was a pragmatic clinical trial conducted at Siriraj Hospital, Bangkok, Thailand, between January 2005 and April 2006. The eligible subjects were hospitalized patients over the age of 18 years who were infected with *A. baumannii* or *P. aeruginosa* resistant to beta-lactams, fluoroquinolones and aminoglycosides. We excluded patients with infections caused by *A. baumannii* or *P. aeruginosa* with other bacteria from our study because we felt that it was difficult to determine the efficacy of colistin for treatment of infections caused by MDR *A. baumannii* or *P. aeruginosa*. Colistin was offered to all such patients and if the patients and their responsible physicians agreed to have colistin treatment, the patients received intravenous colistin (colistimethate sodium) of 5 mg/kg/day in two divided doses. The dosage of colistin was adjusted according to the patients' renal function.[11] If the patients or their responsible physicians did not wish to join the study, they received other antibiotics according to their physicians' decisions and these patients were defined as the 'non-colistin group'.

All isolates of *A. baumannii* and *P. aeruginosa* from the eligible patients were tested for colistin susceptibility by E-test according to the manufacturer's guidelines (AB Biodisk, Sweden). A suspension of each isolate in Mueller–Hinton broth (BBL-Becton Dickinson, USA), adjusted to the density of a 0.5 McFarland standard, was swabbed in three directions to ensure uniform growth onto Mueller–Hinton agar (BBL-Becton Dickinson, USA) plates. Once the agar surface was completely dry, an E-test colistin strip (ranging from 0.06 to 1024 μg/ml) was applied to each plate and the plates were incubated at 35 °C for 16–20 hours. The minimum inhibitory concentration (MIC) was read where inhibition of growth intersected the E-test strip. Quality control strains of *Escherichia coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were used with the reference MIC range of 0.125–0.5 and 0.5–2 mg/l, respectively. The susceptible isolate was defined as having a MIC of $\leq$2 mg/l. Quantitative colistin serum level was determined by microbiological assay.[12]

The primary outcomes were the clinical response and 30-day mortality. A good clinical response referred to a combination of clinical cure and clinical improvement. Clinical cure was defined as a disappearance of symptoms and signs of infection and clinical improvement was defined as a partial resolution of the symptoms and signs of infection. The secondary outcomes were microbiological response and adverse effects. Successful microbiological response was defined as an eradication of the causative organisms at the end of treatment. Nephrotoxicity was defined as an increase in serum creatinine of at least two-fold of the baseline value or a 30% decrease of creatinine clearance from the baseline value.

## Results

Between January 2005 and April 2006, 93 patients met the inclusion criteria. Seventy-eight patients were in the colistin group and 15 patients in the non-colistin group. The baseline characteristics of the patients are shown in Table 1. The mean age, gender, underlying conditions, and severity of illness of the patients in both groups were not significantly different.

Presenting infections in the colistin group were: pneumonia (54), bacteremia and/or catheter related infection (9), intra-abdominal infection (5), urinary tract infection (4), skin and soft tissue infection (5), and sinusitis (1). In the colistin group, 71 patients (91%) were infected with *A. baumannii* and

Table 1 Baseline characteristics of the patients

| Characteristic | Colistin group ($N = 78$) | Non-colistin group ($N = 15$) |
|---|---|---|
| Male | 45 (57.7%) | 11 (73.3%) |
| Mean age, years (range) | 63.5 (18–103) | 58.9 (27–90) |
| ICU admission | 45 (57.7%) | 5 (33.3%) |
| Mechanical ventilation | 62 (79.5%) | 14 (93.3%) |
| Mean APACHE II score | 21.9 | 22.3 |
| Pre-existing renal impairment (serum creatinine ≥1.5 mg/dl) | 37.2% | 40% |
| Pathogenic organism | | |
| *Acinetobacter baumannii* | 71 (91.0%) | 12 (80%) |
| *Pseudomonas aeruginosa* | 7 (9.0%) | 3 (20%) |
| Underlying condition | | |
| Diabetes mellitus with or without other medical conditions | 16 (20.5%) | 1 (6.7%) |
| Cardiovascular diseases | 3 (3.9%) | 3 (20%) |
| Cancers | 6 (7.7%) | 1 (6.7%) |
| Immunosuppressive treatment | 4 (5.1%) | – |
| Cerebrovascular diseases | 7 (9.0%) | – |
| Chronic obstructive pulmonary disease | 7 (9.0%) | – |
| Other chronic medical conditions | 12 (15.4%) | 4 (26.7%) |
| Traumatic surgical patients | 10 (12.8%) | 4 (26.7%) |
| Recent cardiovascular surgery | 8 (10.3%) | 2 (13.3%) |
| Recent brain surgery | 4 (5.1%) | – |
| Recent abdominal surgery | 1 (1.3%) | – |

seven (9%) were infected with *P. aeruginosa*, whereas 12 patients (80%) were infected with *A. baumannii* and three (20%) were infected with *P. aeruginosa* in the non-colistin group. In vitro susceptibility tests determined by E-test revealed that all *A. baumannii* and *P. aeruginosa* isolates had a MIC of colistin less than 2 mg/l and were considered susceptible to colistin. In the colistin group, 33 patients (42.3%) received colistin alone, whereas 45 patients (57.7%) received colistin with other antibiotics including vancomycin, aminoglycosides, metronidazole or carbapenems. In the non-colistin group, the patients received carbapenems (6), cefoperazone/sulbactam (3), cefoperazone/sulbactam combined with netilmicin (4), and cefoperazone/sulbactam combined with carbapenem (2).

The treatment outcomes are shown in Table 2. Sixty-four patients (82.1%) in the colistin group had a good clinical response. The clinical response in the patients who received colistin alone was 84.8% and in those who received colistin with other antibiotics was 77.8%; only four patients (26.7%) in the non-colistin group responded.

All cause mortality within 30 days was 46.2% in the colistin group and 80% in the non-colistin group ($p = 0.03$). The relative risk of death in the colistin group was 0.58 of the non-colistin group with a 95% confidence interval (CI) of 0.41 to 0.82. The difference in mortality was statistically significant and the number needed to treat (NNT) was approximately three, which implies that only three patients infected with MDR *A. baumannii* or *P. aeruginosa* needed to be treated with colistin in order to prevent one additional death. The overall mortality rates of the patients infected with *A. baumannii* and *P. aeruginosa* in the colistin group were 46.5% and 42.9%, respectively.

A microbiological response was found in 94.9% of the patients in the colistin group and none in the non-colistin group. Nephrotoxicity was observed in 24 patients (30.8%) in the colistin group. The incidence of nephrotoxicity of the patients in the colistin group was significantly less than that in the non-colistin group. Seventeen (70.8%) of 24 patients in the colistin group who developed nephrotoxicity had other predisposing factors contributing to a decline in renal function including nephrotoxic drugs, chronic kidney diseases, and hypovolemia. Nephrotoxic effects were mild and reversible without requiring renal replacement therapy. No neurotoxicity or drug reaction was observed in the patients who received colistin. The average dose of colistin was 179.6 mg/day, the average duration of colistin treatment was 11.9 days, and the average total dose of colistin was 2.1 g/patient/course.

Table 2 Treatment outcomes of the patients

| Outcome | Colistin group ($N = 78$) | Non-colistin group ($N = 15$) | $p$ Value |
|---|---|---|---|
| Good clinical response | 63 (80.8%) | 4 (26.7%) | <0.001 |
| All cause mortality within 30 days | 36 (46.2%) | 12 (80%) | 0.03 |
| Microbiological response | 74 (94.9%) | 0 | <0.001 |
| Nephrotoxicity | 24 (30.8%) | 10 (66.7%) | 0.02 |
| Neurotoxicity | 0 | 0 | |

## Discussion

This study used colistimethate sodium (also called colistin methanesulfate, pentasodium colistimethane sulfate, or colistin sulfonyl methate), which is less potent and less toxic than colistin sulfate.[13,14] Colistin has a narrow spectrum of antimicrobial activity and is active against most aerobic Gram-negative bacilli including *P. aeruginosa* and *Acinetobacter spp*, even the organisms that are multidrug-resistant.[13] Several reports published during the period 1999 to 2003 revealed that polymyxins were effective and safe for treatment of patients infected with MDR Gram-negative bacteria including *A. baumannii* and *P. aeruginosa*.[7–9] We therefore attempted to study the efficacy and safety of locally produced colistin.

We were unable to do a randomized controlled study to compare colistin with other antibiotics since it would be unethical to provide antibiotics likely to be ineffective to patients, while the antibiotic active against the causative pathogens, colistin, was available. Therefore we had to offer colistin to all patients who had infections caused by *A. baumannii* or *P. aeruginosa* resistant to beta-lactams, fluoroquinolones and aminoglycosides. However, the baseline characteristics of the patients including mean age, gender, underlying conditions, severity of illness and the sites of infections of the patients in both groups were comparable.

The results from our study also showed a good clinical outcome and less overall mortality in patients who received colistin for treatment of MDR *A. baumannii* and *P. aeruginosa*. A good clinical outcome was found in 82.1% of patients treated with colistin no matter how the patients received it, alone or with other antibiotics. Overall mortality decreased from 79% in a previous study of *A. baumannii* infections in the same hospital to 46.5% of the patients infected with *A. baumannii* treated with colistin in this study.[5] The overall mortality in the non-colistin group in this study was still up to 80%. Furthermore, NNT for mortality from our study was only three, indicating that only three patients infected with MDR *A. baumannii* or *P. aeruginosa* needed to be treated with colistin in order to prevent one additional death. Moreover the cost of colistin was approximately 10 to 20 times lower than that of other antibiotics used to treat MDR *A. baumannii* and *P. aeruginosa* such as carbapenems, cefoperazone/sulbactam, and cephalosporins with or without aminoglycosides.

A microbiological response was observed in 74 patients (94.9%) in the colistin group. Three patients who did not have a microbiological response also had a good clinical outcome. However, antibiotic susceptibility profiles of these persistent isolates were different from those of the original isolates and these isolates could be new colonizers. In four patients who had no microbiological response after 72 hours of colistin treatment, the serum levels of colistin were measured by bioassay and the results showed that colistin levels were adequate at 4–8 times above the MIC of the organism. Therefore the same dose of colistin was continued for 7 days and all patients eventually had a microbiological response. We excluded patients with infections caused by *A. baumannii* or *P. aeruginosa* with other bacteria from our study, therefore the efficacy of colistin for treatment of mixed infections is unknown.

Nephrotoxicity is an important side effect of colistin. In our study, nephrotoxicity was found in 30.8% of the patients receiving colistin; this is comparable to the results found in a previous report.[15] Some patients in the colistin group who developed nephrotoxicity also had other contributing factors. Nephrotoxicity in these patients was mild and reversible without requiring renal replacement therapy. Some patients had improvement in their renal function after colistin treatment, which implies that the worsening of renal function was probably due to a severe infection or other conditions. The incidence of nephrotoxicity of the patients in the non-colistin group was significantly more than that in the colistin group. This observation might be due to uncontrolled infections and the side effects of medications including antibiotics given to the patients. No neurotoxicity or drug reaction was observed in the patients in our series.

Although the ability of Gram-negative bacteria to develop resistance to colistin is rare, such Gram-negative bacteria can develop resistance to colistin through mutation or adaptation mechanisms.[13,16] We therefore recommend that colistin, as the only currently available drug for the treatment of MDR Gram-negative bacteria in Thailand, should be reserved for treatment of infections caused by multidrug-resistant Gram-negative bacteria that are only susceptible to colistin.

In summary, we found that colistin appears to be safe and effective for treatment of infections caused by multidrug-resistant *P. aeruginosa* and *A. baumannii* in Thai adult patients. Treatment with colistin decreases patient mortality and is cost-effective.

## Acknowledgements

The authors thank the Thailand Research Fund for supporting the study, Atlantic Pharmaceutical Co. Ltd for supplying colistin and colistin E-test strips, Ms Pornsiri Chinsawangwatanakul and Ms Sunee Thanakhumtorn for coordinating the study, and Dr Methee Chayakulkeeree for reviewing the manuscript.

*Conflict of interest:* No conflict of interest to declare.

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# Implementation of chlorhexidine gluconate for central venous catheter site care at Siriraj Hospital, Bangkok, Thailand

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***Background:*** A meta-analysis and cost-effectiveness analysis of randomized controlled trials comparing chlorhexidine gluconate with povidone-iodine solutions for venous catheter site care found that the use of chlorhexidine gluconate significantly reduced the risk for catheter-related bloodstream infections and that it was cost-effective. The objective of the study was to implement locally formulated chlorhexidine gluconate for central venous catheter (CVC) site care in intensive care units (ICUs) at Siriraj Hospital.
***Methods:*** The study was conducted in 312 subjects who needed CVC insertions in 3 ICUs from January to July 2006. One hundred twenty subjects received 2% chlorhexidine gluconate in 70% alcohol, whereas 192 subjects received 10% povidone-iodine as the antiseptic solution for CVC site care. The patients were assessed for CVC-related infections and for any adverse effects of 2% chlorhexidine gluconate in 70% alcohol.
***Results:*** The incidence of CRBSIs in the indwelling CVC subjects who received 2% chlorhexidine gluconate in 70% alcohol was less than those who received 10% povidone-iodine during the same period, 3.2 versus 5.6 episodes per 1000 CVC days, respectively ($P$ = .06; OR, 3.26; 95% CI: 0.97-10.92). No adverse effects related to using 2% chlorhexidine gluconate in 70% alcohol were observed.
***Conclusion:*** The locally formulated 2% chlorhexidine gluconate in 70% alcohol was safe, effective, and efficient for CVC site care in ICUs at Siriraj Hospital. (Am J Infect Control 2007;35:585-8.)

Insertions of central venous catheters (CVC) are indispensable in modern-day medical practice, particularly in intensive care units (ICUs). Although such catheters provide necessary vascular access, their use puts patients at risk for local and systemic infectious complications, including local site infection, catheter-related bloodstream infections (CRBSIs), septic thrombophlebitis, endocarditis, and other metastatic infections. The majority of hospital-acquired BSIs are associated with the use of a CVC. Rates of CVC-associated BSI vary considerably by hospital size, hospital service/unit, and type of CVC. During 1992-2001, National Nosocomial Infections Surveillance (NNIS) hospitals in the United States reported ICU rates of CVC-associated BSI ranging from 2.9 to 11.3 episodes per 1000 CVC days.[1] Bloodstream infections related to the use of CVCs are an important cause of patient morbidity and mortality and increased health care costs.[2] One of the major areas of emphasis in the evidence-based guidelines for preventing CABSIs is using a 2% chlorhexidine preparation for skin antisepsis.[3] The aforementioned recommendation is based on evidence from a meta-analysis of randomized controlled trials comparing chlorhexidine gluconate with povidone-iodine solutions for catheter site care.[4] Among patients with a CVC, chlorhexidine gluconate reduced the risk for CRBSIs by 49%. The cost-effectiveness analysis of chlorhexidine gluconate compared with povidone-iodine solution for vascular catheter insertion site care revealed that the use of chlorhexidine gluconate in place of povidone-iodine was a simple and cost-effective method of improving patient safety in the hospital setting.[5]

Siriraj Hospital is a tertiary care university hospital in Bangkok, Thailand. The capacity of the hospital is 2335 beds: 2200 beds in 111 general wards and 135 beds in 10 ICUs. The incidence of CRBSIs was 5 episodes per 1000 CVC days in 2005. The recommended antiseptic for CVC site care in the hospital's work instructions is 10% povidone-iodine. We attempted to change the policy on using antiseptic solution for CVC site care in Siriraj Hospital to improve the quality

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Supported by the Thailand Research Fund and Faculty of Medicine of Siriraj Hospital.

0196-6553/$32.00



doi:10.1016/j.ajic.2006.12.002

in health care and patient safety. We conducted the cost-effectiveness analysis of chlorhexidine gluconate compared with povidone-iodine solution for CVC site care using the local data of Siriraj Hospital in 2005. We also found that the use of chlorhexidine, rather than povidone-iodine, for CVC site care resulted in savings of US $8 per catheter used, despite the fact that the cost of the chlorhexidine gluconate formulation was 10% more than povidone-iodine.[6] Hence, chlorhexidine gluconate should replace 10% povidone-iodine as a skin antisepsis for CVC site care in Siriraj Hospital. However, chlorhexidine solution for use as skin antisepsis for CVC site care is not available in Thailand. Therefore, we asked the Pharmacy Department of our hospital to formulate 2% chlorhexidine gluconate in 70% alcohol for CVC site care. The formulation was made by diluting 20% chlorhexidine gluconate and 95% ethyl alcohol in purified water to achieve 2% chlorhexidine gluconate in 70% alcohol. The solution was found to contain good antimicrobial activity up to 6 months after production. This study described an implementation of locally produced 2% chlorhexidine gluconate in 70% alcohol for CVC site care in ICUs at Siriraj Hospital.

## METHODS

The study was approved by the Ethics Committee on Human Research, Faculty of Medicine Siriraj Hospital. The written consent form to join the study was signed by the participating subjects or their legal guardians. The study sites were a medical ICU and 2 surgical ICUs. The study was conducted during January to July 2006. The study subjects were adult patients hospitalized at 3 study ICUs who needed CVC insertion. The CVC insertion was performed in ICUs under a maximal sterile barrier. The responsible health care personnel were encouraged to use 2% chlorhexidine gluconate in 70% alcohol as the antiseptic solution for CVC site care. The 2% chlorhexidine gluconate in 70% alcohol was to be used for painting the skin over the CVC insertion area and for cleaning the skin at the CVC insertion site thereafter every 24 to 48 hours and as needed. The participating subjects were assessed daily for CVC-related infections until 48 hours after the CVC had been removed. A blood sample was drawn from the CVC for culture on days 3 and 7 and every 7 days thereafter until the CVC was removed. A CRBSI is defined as bacteremia/fungemia in a patient with a CVC with at least 1 positive blood culture obtained from a peripheral vein, clinical manifestations of infections (ie, fever, chills, and/or hypotension), and no apparent source for the BSI except the CVC. The subjects were also observed for any adverse effects of 2% chlorhexidine gluconate in 70% alcohol. We aimed to recruit 110 subjects to determine whether the incidence of CRBSIs was decreased to 2.5 episodes per 1000 CVC days. The data analyses were performed by descriptive statistics and multiple logistic regression. Multiple logistic regression was employed to test whether there was a difference in the occurrence of CRBSIs between the 2 methods, adjusting for the natural logarithm of number of insertion days. Goodness of fit of the model was assessed using the Hosmer-Lemeshow test.

## RESULTS

There were 312 patients in 3 ICUs who received CVC insertions during the study period. The total CVC insertion days were 2190. One hundred twenty subjects (933 CVC days) received 2% chlorhexidine gluconate in 70% alcohol, whereas 192 subjects (1257 CVC days) received 10% povidone-iodine as the sole agent for CVC site care. The characteristics of the patients in the chlorhexidine group were as follows: (1) 59.2% were males; (2) 55.8% were surgical ICU patients; (3) sites of CVC insertion were internal jugular vein (58.3%), subclavian vein (23.3%), and femoral vein (15.8%); (4) types of CVC were pulmonary artery catheter (36.7%) and multilumen catheter (40%); (5) mean APACHE II score was 27; and (6) average duration of indwelling CVC was 7.8 days. The aforementioned characteristics were not significantly different from those in the povidone-iodine group. The incidence of CRBSIs of the patients in the study ICUs and other ICUs during the study period and in 2005 are shown in Table 1. The overall incidence of CRBSIs in the indwelling CVC patients in all ICUs during January to July 2006 was slightly higher than that during January to December 2005, 6.4 vs 4.8 episodes per 1000 CVC days, respectively. The incidence of CRBSIs in the indwelling CVC patients in the study ICUs who received 2% chlorhexidine gluconate in 70% alcohol was less than those who received 10% povidone-iodine during the same period, 3.2 vs 5.6 episodes per 1000 CVC days, respectively ($P = .06$; OR, 3.26; 95% CI: 0.97-10.92). All patients who had CRBSIs were symptomatic and received antimicrobial agents. The mortality rate of the patients with CRBSI was 40%. No adverse effects related to using 2% chlorhexidine gluconate in 70% alcohol were observed in the participating subjects.

## DISCUSSION

Health research findings should be appropriately utilized and ultimately have impact on policy, practice, and patients' outcomes. The key messages from the 2004 *World Report on Knowledge for Better Health* are that biomedical discoveries cannot improve people's health without studies to find out how to apply them specifically within different health systems, population

**Table 1.** The incidence of CRBSIs of the patients with indwelling CVC in Siriraj Hospital ICUs during January to July 2006 and January to December 2005

| Period | Type of ICU | Type of antiseptic solution | Incidence of CRBSIs per 1000 CVC days |
|---|---|---|---|
| January to July 2006 | 3 Study ICUs | 2% Chlorhexidine gluconate in 70% alcohol | 3.2 |
| January to July 2006 | 3 Study ICUs | 10% Povidone-iodine | 5.6 |
| January to July 2006 | Other ICUs | 10% Povidone-iodine | 6.6 |
| January to July 2006 | All ICUs | 10% Povidone-iodine | 6.4 |
| January to December 2005 | 3 Study ICUs | 10% Povidone-iodine | 5.0 |
| January to December 2005 | Other ICUs | 10% Povidone-iodine | 4.6 |
| January to December 2005 | All ICUs | 10% Povidone-iodine | 4.8 |

groups, and diverse political and social contexts and that stronger emphasis should be placed on translating knowledge into actions to improve health, thereby bridging the gap between what is known and what is actually being done.[7] The framework for bridging the gap between knowledge and action for health was proposed.[8]

The current situation on the use of antiseptic solution for CVC site care at Siriraj Hospital was a "know-do" gap. Our study was not intended to be a randomized controlled study to determine the efficacy and safety of 2% chlorhexidine gluconate in 70% alcohol compared with 10% povidone-iodine because it has already been demonstrated that chlorhexidine gluconate is more effective and efficient.[4,5] Moreover, the Ethics Committee on Human Research would not allow us to conduct such a study design knowing that one intervention is more effective than another. Therefore, our study was an operational research to implement a new intervention that has been proven for effectiveness and efficiency in health care services and to convince health care personnel that a locally formulated 2% chlorhexidine gluconate in 70% alcohol was effective and safe. Because this was an operational research, we encouraged health care personnel to use the new intervention and we also asked the patients or their legal representatives for their willingness to join the study. Many patients in the study ICUs still received povidone-iodine because (1) they were unable to give consent and their legal representatives were not present at the time we inserted the CVC, and (2) some health care personnel preferred povidone-iodine because of its dark brown color on the painted skin, whereas the skin painted with chlorhexidine did not contain any color.

The results of the implementation of the locally produced 2% chlorhexidine gluconate in 70% alcohol as skin antisepsis for CVC site care revealed that the incidence of CRBSIs in the indwelling CVC patients who received 2% chlorhexidine gluconate in 70% alcohol was less than that of 10% povidone-iodine. A reduction of the incidence of CRBSIs in the indwelling CVC patients who received 2% chlorhexidine gluconate in 70% alcohol likely resulted from the implementation of 2% chlorhexidine gluconate in 70% alcohol to replace 10% povidone-iodine. The reduction of CRBSIs in the patients who received chlorhexidine gluconate from 36% to 43% observed in our study was less than the average value of 49% from the meta-analysis.[4] This might be due to a difference in the patient population and the ICU settings in Siriraj Hospital. However, the sensitivity analysis of the cost-effectiveness study using the local data revealed that the use of 2% chlorhexidine gluconate in 70% alcohol still saved cost, even if the incidence of CRBSIs in the indwelling CVC patients who received 2% chlorhexidine gluconate in 70% alcohol was reduced by 10% or the cost of 2% chlorhexidine gluconate in 70% alcohol exceeded US $6 per 100 mL. Our implementation of chlorhexidine gluconate in place of the current standard solution for CVC site care in ICUs at Siriraj Hospital confirms that the new intervention is a cost-effective method, it improves the safety of patients hospitalized in ICUs, and it enhances the quality of health care service at Siriraj Hospital.

The study results were presented to the dean and the hospital administrator in September 2006, and the policy on replacing 10% povidone-iodine with 2% chlorhexidine gluconate in 70% alcohol as a skin antisepsis for CVC site care was adopted. A revision of the practice guidelines on using antiseptic solution for CVC site care was made. The Pharmacy Department of Siriraj Hospital has produced 2% chlorhexidine gluconate in 70% alcohol with a dark blue color to be used as antiseptic solution for CVC site care for all ICUs since November 2006. The study results were presented at the infection control meeting, and several regional hospitals in Thailand switched skin antisepsis from povidone-iodine to chlorhexidine gluconate.

It is hoped that the study we have described will encourage responsible health care institutions to pay more attention to narrowing the gap between what

we have the knowledge to do and what is actually done as well as on developing a culture in which decisions taken by the policy makers, the health professionals, and the public are based on evidence.

The authors thank Montree Suwanich, Tanita Thaweethamcharoen, and Bordeesuda Suiwongsa for formulating and producing 2% chlorhexidine gluconate in 70% alcohol; Suwanna Trakulsomboon for testing antibacterial activities of chlorhexidine gluconate; Chulaluk Komoltri for analyzing the data; Sunee Tanakumtorn and Laksamee Wattanamongkolsil for coordinating the study; Thepnimitr Judaeng for providing the data on CRBSIs in ICU patients; and Dr. Surat Tongyoo, Dr. Chiarat Permpikul, and Dr. Puttipannee Vorrakitpokatorn for their supervision.

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# Prevalence of Antibiotic-Resistant Bacteria Colonized in Neutropenic Patients at Siriraj Hospital

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## ABSTRACT

**Objective:** To determine prevalence of antibiotic-resistant bacteria colonized in throat and gastrointestinal tract of neutropenic patients at Siriraj Hospital.

**Methods:** Adult patients who had recent neutropenia (absolute neutrophils <500) without any evidence of infections were recruited from January 2006 to March 2007 at Hematology Clinic and Department of Medicine Siriraj Hospital. The throat swabs and stool samples or peri-anal swabs collected from the patients were sent for bacterial culture and antibiotic susceptibility testing.

**Results:** There were 140 patients. 75 (53.6%) were females. The mean age was 49.3 years. The major underlying diseases were leukemia (53.6%) and lymphoma (33.3%). The main causes of neutropenia were chemotherapy-induced (84.3%) and the underlying diseases (15.7%). The bacteria commonly recovered from the stools or throat swabs of the patients were *E.coli* (77.9%), *Klebsiella pneumoniae* (46.4%), *Enterobacter* sp (20%) and *Enterococcus* sp. (45.7%). ESBL-producing gram negatives, *Pseudomonas aeruginosa*, *Acinetobacter* sp. and MRSA were found in 13.6%, 8.6%, 5% and 1.4% respectively. The susceptibility rate of *E.coli*, *Klebsiella pneumoniae* and *Enterobacter* sp. to co-trimoxazole, co-amoxiclav and ciprofloxacin was 51.5%, 73.2% and 74.8% respectively. Less than 50% of ESBL-producing gram negatives, *Pseudomonas aeruginosa* and *Acinetobacter* sp. were susceptible to the aforementioned oral antibiotics.

**Conclusion:** Ciprofloxacin or co-amoxiclav seems to be a suitable oral antibiotic for preventing gram negative bacterial infection in ambulatory neutropenic patients in Thailand. However, the patients receiving such antibiotics still have more than 25% risk of carrying gram negatives resistant to both antibiotics.

**Keywords:** Antibiotic prophylaxis; neutropenia

**Siriraj Med J 2007; 59: 344-347**
***E-journal: http://www.sirirajmedj.com***

Neutropenia is defined as an absolute neutrophil count in a peripheral blood sample less than 500 cells/cubic mm. The common causes of neutropenia are hematologic malignancy and chemotherapy-induced. Neutropenia is a major risk factor for acquiring infections. The common causative agents causing infections in neutropenic patients are gram-negative bacteria that are endogenous florae or acquiring from the environments especially during hospitalization.[1-4] The causative agents are usually colonized in the throat and gastrointestinal tract of the neutropenic patients. Therefore an administration of antibiotic in order to prevent infections in neutropenic patients has been attempted. Two recent meta-analyses on efficacy of oral prophylactic antibiotics in afebrile neutropenic patients revealed that oral prophylactic antibiotics decreased Gram-negative bacteraemia and infection related mortality due to bacterial causes during neutropenic episodes.[5,6] The recommended oral antibiotics for prevention of infections in neutropenic patients in many studies included in the meta-analyses were co-trimoxazole or fluoroquinolones. Most of the studies on antibiotic prophylaxis in neutropenic patients were conducted in developed countries where antibiotics were only prescribed by physicians. Oral antibiotics including co-trimoxazole and fluoroquinolones are available in drug stores in Thailand without any prescription and they are also used in animal industry.[7] Therefore the endogenous florae of the neutropenic patients in Thailand may be resistant to the commonly used oral antibiotics and such oral antibiotics are ineffective

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in preventing infections in Thai neutropenic patients.

The objective of the study was to determine prevalence of antibiotic-resistant bacteria colonized in throat and gastrointestinal tract of neutropenic patients at Siriraj Hospital.

## MATERIALS AND METHODS

The study was approved by the Ethics Committee on Human Research of Faculty of Medicine Siriraj Hospital. The study was conducted at Hematology Clinic and Department of Medicine, Siriraj Hospital from January 2006 to March 2007. The eligible subjects were adult aged 18 years or older who had neutropenia without any symptoms and signs of infections. A throat swab and stool sample or peri-anal swab were taken from each subject and were sent to laboratory of Division of Infectious Diseases and Tropical Medicine, Faculty of Medicine Siriraj Hospital. The specimens were inoculated onto blood agar plate and McConkey agar plate, and were kept at 35°C for 18 hours. The colonies grown on the plates were identified by conventional methods.[8] In vitro antibiotic susceptibility of aerobic Gram negative bacilli were performed by disc diffusion method.[9] The tested antibiotics were co-trimoxazole, co-amoxiclav, ciprofloxacin, ceftriaxone, ceftazidime, amikacin and imipenem. The data were analysed by descriptive statistics. The sample size of 140 subjects was calculated according to an estimated prevalence of gram negative bacilli resistant to fluoroquinolones was 10% ± 5% and type I error was 5%.

## RESULTS

Of 140 enrolled subjects, 75 (53.6%) were females. The mean age of the subject was 43.9 years. Most of the subjects had acute leukemia (53.6%) and lymphoma (33.3%). The causes of neutropenia were chemotherapy-induced (84.3%) and their diseases (15.7%). The characteristics of the subjects are shown in Table 1. There were 275 samples collected from the patients; 140 samples were throat swabs and 135 samples were stool samples or peri-anal swabs. The bacteria isolation rates are shown in Table 2. The presence of pathogenic bacteria was found in 33.6% of the throat swabs and 82.2% of the stool samples or peri-anal swabs.

The types of bacteria isolated from throat swabs, stool samples and peri-anal swabs are shown in Table 3. *Klebsiella* sp. was the most common pathogen isolated from throat swabs of 15% of the patients whereas *Pseudomonas aeruginosa* was recovered from 7.1% of the patients. *E.coli, Klebsiella* sp. and *Entrococcus* sp. were isolated from stools and peri-anal swabs in 76.3%, 32.6% and 45.9% respectively. Multidrug resistant gram negative bacilli i.e. ESBL-producing *E.coli, P.aeruginosa* and *Acinetobacter* sp. were observed in 12.6%, 1.5% and 0.9% of the stool samples or peri-anal swabs respectively. MRSA was found in stools of 2 patients (1.4%). The bacteria commonly recovered from the stools or throat swabs of the patients were *E.coli* (77.9%), *Klebsiella pneumoniae* (46.4%), *Enterobacter* sp (20%) and *Enterococcus* sp. (45.7%). ESBL-producing gram negatives, *Pseudomonas aeruginosa, Acinetobacter* sp. and MRSA were found in 13.6%, 8.6%, 5% and 1.4% respectively.

In vitro susceptibility of colonized gram negative bacteria in throat and gastrointestinal tract of the patients to potentially used antibiotic are shown in Table 4. Approximately 50% of colonized gram negative bacilli were resistant to co-trimoxazole. Co-amoxiclav and ciprofloxacin were active against 73.2% to 74.8% of colonized gram negative bacilli. However they were much less active against multidrug resistant gram negative bacilli i.e. ESBL-producing strains, *P. aeruginosa.* and *Acinetobacter* sp. Ceftriaxone was active against most strains of colonized gram negative bacilli excluding ESBL-producing strains and *P.aeruginosa* and *Acinetobacter* sp. Ceftazidime was active against most strains of colonized gram negative bacilli and *P.aeruginosa* excluding ESBL-producing strains. Amikacin and Imipenem were active against most strains of colonized gram negative bacilli including ESBL-producing strains and *P.aeruginosa.*

TABLE 1. Characteristics of the subjects.

| Characteristic | Number (%) |
|---|---|
| Gender (N=140) | |
| Male | 65 (46.4%) |
| Female | 75 (53.6%) |
| Type of cancer (N=122) | |
| Leukemia | 75 (53.6%) |
| Lymphoma | 46 (33.3%) |
| Breast cancer | 1 (0.7%) |
| Others | |
| Aplastic anemia (6) | |
| Myelodysplastic syndrome (3) | |
| SLE (2) | |
| Rheumatoid arthritis (1) | |
| Chronic neutropenia (1) | |
| Waldenstorm macroglobulinemia (1) | |
| Multiple myeloma (2) | |
| Malignant thymoma (1) | |
| Polycythemia vera (1) | |
| Cause of neutropenia (N=140) | |
| Chemotherapy-induced | 118 (84.3%) |
| Disease | 22 (15.7%) |

## DISCUSSION

Although many reports demonstrated that antibiotic prophylaxis for the patients with neutropenia decreased bacterial infection episodes and mortality, the guidelines on management of the patients with neutropenia did not recommend routine antibacterial prophylaxis for all patients with neutropenia.[10] The main concern is that administration of antibiotics may be associated with increased carriage of antibiotic-resistant bacteria and antibiotic resistant bacterial infections. A systematic review on the effect of fluoroquinolone prophylaxis in afebrile neutropenic patients on microbial resistance revealed that the relative risk of an increase in colonization with organisms resistant to fluoroquinolones in the neutropenic patients who received fluoroquinolone prophylaxis was 1.68.[11] However, the risk was not statistically significant; that might be due to a small sample size. There was no difference in the number of patients developing infections caused by resistant

TABLE 2. Rate of recovery of bacteria from throat swabs, stools and peri-anal swabs.

| | Number of samples (%) |
|---|---|
| No bacteria found | 117 (42.5%) |
| Bacteria | 158 (57.5%) |
| Throat | 47 (33.6%) |
| Stool or peri-anal swab | 111 (82.2%) |
| Total | 275 (100%) |

TABLE 3. Types of bacteria recovered from throat swabs, stools and peri-anal swabs.

| Bacteria | Total samples (N=275) | Stool/ peri-anal swab samples (N=135) | Throat swab samples (N=140) | Total subjects (N=140) |
|---|---|---|---|---|
| *E.coli* (ESBL-) | 91 (33.1%) | 86 (63.7%) | 5 (3.6%) | 91 (65%) |
| *E.coli* (ESBL+) | 18 (6.6%) | 17 (12.6%) | 1 (0.7%) | 18 (12.9%) |
| *Klebsiella* (ESBL-) | 64 (23.3%) | 44 (32.6%) | 20 (14.3%) | 64 (45.7%) |
| *Klebsiella* (ESBL+) | 1 (0.4%) | 0 | 1 (0.7%) | 1 (0.7%) |
| *Enterobacter* sp. | 28 (10.2%) | 17 (12.6%) | 14 (10%) | 28 (20%) |
| *Proteus* sp. | 11 (4%) | 11 (8.2%) | 0 | 11 (7.9%) |
| *P.aeruginosa* | 12 (4.4%) | 2 (1.5%) | 10 (7.1%) | 12 (8.6%) |
| *Acinetobacter* sp. | 7 (2.6%) | 1 (0.9%) | 6 (4.3%) | 7 (5.0%) |
| Non-fermenters | 5 (2.1%) | 1 (0.9%) | 4 (3.3%) | 5 (3.6%) |
| *Enterococcus* sp. | 64 (23.3%) | 62 (45.9%) | 2 (1.4%) | 64 (45.7%) |
| MSSA | 6 (2.2%) | 4 (3%) | 2 (1.4%) | 6 (4.3%) |
| MRSA | 2 (0.4%) | 2 (1.5%) | 0 | 2 (1.4%) |
| Yeast | 7 (2.5%) | 1 (0.7%) | 6 (4.3%) | 7 (5%) |
| Other GNR | 9 (3.3%) | 9 (6.7%) | 0 | 9 (6.4%) |

ESBL = Extended-Spectrum-Beta-Lactamase enzyme
MSSA = Methicillin-Sensitive *S.aureus*
MRSA = Methicillin-Resistant *S.aureus*

pathogens. In trials comparing fluoroquinolone with co-trimoxazole prophylaxis, there were fewer incidents of colonization by bacteria resistant to the prophylactic agent in the fluoroquinolone arm than in the co-trimoxazole arm. The aforementioned finding of a statistically non-significant increase in colonization with organisms resistant to fluoroquinolones in the neutropenic patients who received fluoroquinolone prophylaxis along with a clear benefit of antibiotic prophylaxis in afebrile neutropenic patients from the recent meta-analyses will lead to a widespread use of antibiotic prophylaxis in the neutropenic patients in Thailand. Therefore the data on antibiotic susceptibility of colonized bacteria in neutropenic patients should be made available at each institution in order to determine a suitable antibiotic. Gram negative bacilli are still the most common causative agents of infections in Thai neutropenic patients.[1,2] The recovery rate of gram negative bacilli from gastrointestinal tract of the neutropenic patients in this study was only 82.2%. This observation might be due to the fact that 60% of the samples were peri-anal swabs and all samples with negative cultures were derived from the peri-anal swabs. We had to take the peri-anal swabs instead of collecting stool samples from such patients because they were ambulatory patients and we avoided doing rectal swabs since there was a risk of bacteremia from such procedure. Therefore the observations from this study should be considered as the best-case scenario.

Although co-trimoxazole is a recommended antibiotic for prevention of infection in afebrile neutropenic patients, it should not be used in Thai neutropenic patients since only 50% of colonized gram negative bacteria were susceptible to co-trimoxazole. If the responsible physicians would like to prescribe oral antibiotic for afebrile Thai neutropenic patients, fluoroquinolones or co-amoxiclav should be more suitable. However the physicians who want to prescribe fluoroquinolone or co-amoxiclav prophylaxis to Thai neutropenic patients should be aware of the following considerations: 1) More than 25% of colonized bacteria are not susceptible to fluoroquinolone or co-amoxiclav, 2) An increased risk of colonization with organisms resistant to fluoroquinolone occurs in the neutropenic patients who received fluoroquinolone prophylaxis, 3) The patients given fluoroquinolone prophylaxis should not be treated empirically with fluoroquinolones for suspected infections, 4) Cross resistance between fluoroquinolones and beta-lactams is possible, 5) Development of beta-lactam resistant colonized bacteria and beta-lactam resistant bacterial infections following beta-lactams prophylaxis is unknown, and 6) Prior exposure to beta-lactams is shown to be associated with infections with ESBL-producing gram negative bacilli.[12]

Since infections do not occur in all afebrile neutropenic patients, antibiotic prophylaxis should be considered in only afebrile neutropenic patients who had a higher risk of developing infections. Therefore, a study on identification of risk factors associated with infections in afebrile neutropenic patients should be conducted. Moreover, a cost effectiveness analysis of the administration of antibiotic prophylaxis in afebrile neutropenic patients should also be performed in order to determine if antibiotic prophylaxis should be given to all Thai afebrile neutropenic patients.

## ACKNOWLEDGEMENTS

The authors thank the personnel in the laboratory of Division of Infectious Diseases and Tropical Medicine for performing the cultures and antibiotic susceptibility testing, Ms. Laksamee Watanamongkolsilp for data management and Faculty of Medicine Siriraj Hospital and Thailand Research Fund for supporting the study.

TABLE 4. In vitro antibiotic susceptibility of gram negative bacilli.

| Bacteria | Co-trimoxazole | Co-amoxiclav | Ciprofloxacin | Ceftriaxone | Ceftazidime | Amikacin | Imipenem |
|---|---|---|---|---|---|---|---|
| Gram negative bacilli (GNBs)* | 51.5% | 73.2% | 74.8% | 83.9% | 91.9% | 92.4% | 96.3% |
| ESBL-producing GNBs** | 11.4% | 47.3% | 23.1% | 35.1% | 41% | 100% | 100% |
| *P.aeruginosa* | 0 | 8.7% | 54.9% | 8.6% | 82.1% | 82.5% | 91.2% |

* *E.coli* and *Klebsiella* sp., *Enterobacter* sp., *Proteus* sp., non-fermenters
** *E.coli* and *Klebsiella* sp.

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# Pyridoxine (Vitamin B6) Usage in Tuberculosis Patients at Siriraj Hospital

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## ABSTRACT

**Objective:** To determine the prevalence and factors associated with pyridoxine usage in tuberculosis patients who received isoniazid at Siriraj Hospital.

**Methods:** The medical records of 254 patients with tuberculosis who received isoniazid at Siriraj Hospital during January 2006 to February 2007 were analyzed.

**Results:** Of 254 patients, 132 (52%) were males and the mean age was 44.5 years. The common underlying diseases were HIV infections, diabetes mellitus and cancers. Pulmonary tuberculosis was the most common type of tuberculosis (67.7%). Pyridoxine was given to 213 patients (83.9%) who received isoniazid. Pyridoxine was usually prescribed to the patients with HIV infections or diabetes mellitus. Peripheral neuropathy was observed in a patient who received antituberculous drugs along with pyridoxine, stavudine, lamivudine and nevirapine. His peripheral neuropathy improved after stavudine was switched to zidovudine.

**Conclusion:** Pyridoxine is usually given to tuberculosis patients who receive isoniazid despite of lacking any solid evidence on effectiveness of pyridoxine in preventing peripheral neuropathy.

**Keywords:** Isoniazid; peripheral neuropathy; pyridoxine; vitamin B6

**Siriraj Med J 2007; 59: 348-349**
***E-journal: http://www.sirirajmedj.com***

Isoniazid is still considered as the first line drug for treatment and prevention of tuberculosis.[1] A side effect of isoniazid therapy is peripheral neuropathy. Peripheral neurotoxicity is dose-related and is uncommon (<0.2%) at conventional doses.[2-6] Plasma levels of pyridoxal phosphate were determined in 20 patients with pulmonary tuberculosis before and after one week of drug therapy including isoniazid revealed that pyridoxal phosphate levels decreased in all but one subject who inadvertently received pyridoxine supplementation.[7] Isoniazid was also found to induce pyridoxine deficiency.[8] Therefore it is suggested that pyridoxine or vitamin B6 supplementation should be given to patients with newly diagnosed tuberculosis especially those with an increased risk of neuropathy such as nutritional deficiency, diabetes, HIV infection, renal failure, and alcoholism, as well as for pregnant and breast-feeding women in order to prevent neuropathy.[7,9] To the best of our knowledge, there was only a prospective single blind placebo controlled study to establish whether pyridoxine supplementation of isoniazid therapy was useful in 85 children with tuberculosis.[10] The study results revealed no case of neurological or neuropsychiatric disorder either in the group which received pyridoxine or in the placebo group during the six months of the treatment and three months after the treatment. Therefore pyridoxine supplementation of isoniazid therapy might be unnecessary.

The objective of the study was to determine the prevalence and the factors associated with pyridoxine usage in tuberculosis patients who received isoniazid at Siriraj Hospital.

## MATERIALS AND METHODS

The list of the patients who attended the out-patient department of Siriraj Hospital and who received isoniazid from January 2006 to February 2007 was provided by Siriraj Computer Center. The medical records of 254 patients were retrieved and reviewed for demographics, the underlying diseases, the sites of tuberculosis, anti-tuberculosis regimens and other concomitant medications including pyridoxine, and peripheral neuropathy. The information was extracted from the medical records and filled in the case record forms. The data were analyzed by descriptive statistics, student-t-test and chi-square statistics.

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TABLE 1. Comparison of the patients who received pyridoxine with those who did not receive pyridoxine.

| Character | Patients with pyridoxine (N=213) | Patients without pyridoxine (N=41) | p |
|---|---|---|---|
| Male | 105 (49.3%) | 27 (65.9%) | 0.05 |
| Mean age (SD), years | 44.6 (16.8) | 44.1 (16.8) | 0.87 |
| Age >70 years | 20 (9.4%) | 4 (9.8%) | 1.00 |
| Pulmonary tuberculosis | 140 (65.7%) | 32 (78.1%) | 0.12 |
| Tuberculous lymphadenopathy | 35 (30.5%) | 5 (12.2%) | 0.49 |
| Tuberculous osteomyelitis | 8 (3.8%) | 1 (2.4%) | 1.00 |
| Disseminated tuberculosis | 5 (2.4%) | 0 | 1.00 |
| HIV infections | 49 (23.0%) | 0 | <0.01 |
| Diabetes mellitus | 19 (8.9%) | 0 | 0.05 |
| Alcoholics | 7 (30.3%) | 0 | 0.6 |
| Chronic renal failure | 3 (1.4%) | 0 | 1.0 |
| Concomitant stavudine | 21 (9.9%) | 0 | 0.03 |
| Concomitant prednisolone | 2 (0.9%) | 1 (2.4%) | 0.41 |

## RESULTS

Of 254 patients, 132 (52%) were males. The mean age, SD and age range of the patients was 44.5 years, 16.7 years and 17 to 84 years respectively. One hundred and fifty patients (59.1%) had known underlying conditions including HIV infections (19.3%), diabetes mellitus (7.5%), cancer (5.1%), chronic hepatitis (2%), and chronic renal failure (1.2%). The sites of tuberculosis were lungs (67.7%), lymph nodes (15.7%), bones (3.5%), meninges (1.6%) and others (9.5%). Two hundred and six patients (81.1%) received isoniazid plus rifampicin, ethambutol and pyrazinamide whereas other regimens including isoniazid were given to 17.3% of the patients. Four patients (1.6%) received isoniazid as tuberculosis prophylaxis. The common concomitant medications were antiretroviral agents in 22 patients (8.7%) and antidiabetics in 19 patients (7.5%). Antiretroviral agents were stavudine (19 patients), lamivudine (21 patients), nevirapine (9 patients), efavirenz (16 patients), zidovudine (4 patients). Pyridoxine was given to 213 patients (83.9%) who received isoniazid of which 167 patients (83.9%) received pyridoxine, 50 mg or less, per day and the rest received pyridoxine, more than 50 mg per day. One hundred and ninety five patients (91.5%) received pyridoxine along with isoniazid at the commencement of tuberculosis treatment. A comparison of the patients who received pyridoxine (213 patients) with those who did not receive pyridoxine (41 patients) is shown in Table 1. Pyridoxine was usually prescribed to male patients, patients with HIV infections, diabetes mellitus and the patients who required stavudine. Peripheral neuropathy was observed in a patient with HIV infection who received anti-tuberculous drugs including isoniazid along with pyridoxine at the commencement of antituberculosis drugs. He also received stavudine, lamivudine and nevirapine. His peripheral neuropathy improved after stavudine was switched to zidovudine.

## DISCUSSION

Our findings revealed that 83.9% of tuberculosis patients at Siriraj Hospital received pyridoxine supplementation of isoniazid therapy, with male patients, patients with HIV infection, diabetes mellitus and the patients who required stavudine being more likely to received pyridoxine. These observations indicated that the physicians providing medical care for tuberculosis patients followed the opinion-based recommendations. We found only one case of peripheral neuropathy in a tuberculosis patient, despite the patient received pyridoxine supplementation. The peripheral neuropathy in this patient could be associated with stavudine since the peripheral neuropathy disappeared after stavudine was discontinued. Since the incidence of peripheral neuropathy in isoniazid recipients was extremely low and a high dose of pyridoxine was found to be an effective treatment of isoniazid induced peripheral neuropathy,[11] a routine use of pyridoxine in tuberculosis patients who receive isoniazid may be unnecessary and this common practice should be considered. Disadvantages of pyridoxine usage include a risk of side effects[12] and cost. The cost of pyridoxine supplementation for nine months is 800 Baht. Therefore a large randomized controlled trial of pyridoxine for prevention of peripheral neuropathy in the patients receiving isoniazid should be conducted in order to determine if pyridoxine is really effective for preventing peripheral neuropathy in isoniazid receivers. Moreover, if pyridoxine is found to be effective, a cost effectiveness analysis of pyridoxine for preventing isoniazid-induced peripheral neuropathy should be performed. In the meantime, a routine use of pyridoxine supplementation of isoniazid therapy should be discouraged due to a lack of solid evidence on the effectiveness of pyridoxine for preventing peripheral neuropathy in isoniazid recipients.

## ACKNOWLEDGEMENTS

The authors thank the Thailand Research Fund for supporting the study.

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# In Vitro Activity of Ceftobiprole Against Hospital-Acquired Bacteria Commonly Causing Infections in Hospitalized Patients at Siriraj Hospital

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## ABSTRACT

**Background:** Ceftobiprole is a novel parenteral cephalosporin whose broad spectrum of activity includes most clinically important gram-positive and gram-negative bacteria.
**Objective:** To determine the in vitro activity of ceftobiprole against resistant bacteria commonly causing infections in hospitalized patients at Siriraj Hospital.
**Methods:** The studied organisms were MRSA (32 isolates), *Enterococcus* sp. (30 isolates), ESBL-producing *E.coli* (20 isolates), ESBL-producing *K.pneumoniae* (20 isolates), MDR *P.aeruginosa* (30 isolates) and MDR *A.baumannii* (30 isolates). The susceptibility of ceftobiprole was determined by the disk diffusion test for all 162 isolates and the MIC was determined by the E-test method for 5 isolates of each organism.
**Results:** All isolates of MRSA and 77% of *Enterococcus* sp. isolates were susceptible to ceftobiprole. All isolates of ESBL-producing *E.coli* and MDR *A.baumannii* were not susceptible to ceftobiprole. Only 10% to 20% of ESBL-producing *K.pneumoniae* and *P.aeruginosa* were susceptible to ceftobiprole. The MICs of ceftobiprole against all tested organisms were correlated with the inhibition zone diameters.
**Conclusion:** Ceftobiprole is very active against MRSA and is moderately active against *Enterococcus* sp. Ceftobiprole is considered inactive or less active against ESBL-producing gram negatives, MDR *P.aeruginosa* and MDR *A.baumannii*.

**Keywords:** *Acinetobacter baumannii;* Ceftobiprole; *Enterococcus* sp; ESBL-producing *E.coli;* ESBL-producing *K.pneumoniae;* In vitro activity; methicillin-resistant *Staphylococcus aureus; Pseudomonas aeruginosa*

**Siriraj Med J 2007; 59: 350-352**
***E-journal: http://www.sirirajmedj.com***

The bacteria commonly causing infections in hospitalized patients at Siriraj Hospital were *Pseudomonas aeruginosa*, ESBL-producing gram negative bacilli, *Acinetobacter baumannii* and methicillin-resistant *Staphylococcus aureus* (MRSA).[1-4] Most of these organisms were multidrug-resistant (MDR) to currently available antibiotics including beta-lactams, aminoglycosides and fluoroquinolones.[2-5] Therefore, a search for new agents effective against the aforementioned pathogens is needed. Ceftobiprole is a novel parenteral cephalosporin whose broad spectrum of activity includes most clinically important gram-positive and gram-negative bacteria.[6,7] The objective of the study was to determine the in vitro activity of ceftobiprole against MRSA, *Enterococcus* sp., ESBL-producing *E.coli* and *K.pneumoniae*, MDR *P.aeruginosa* and MDR *A.baumannii* isolated from the patients hospitalized at Siriraj Hospital.

## MATERIALS AND METHODS

### *Bacterial Isolates*

The studied organisms were isolated from different patients hospitalized at Siriraj Hospital. They were MRSA (32 isolates), *Enterococcus sp.* (30 isolates), ESBL-producing *E.coli* (20 isolates), ESBL-producing *K.pneumoniae* (20 isolates), MDR *P.aeruginosa* (30 isolates) and MDR *A.baumannii* (30 isolates). MDR *P.aeruginosa* and MDR *A.baumannii* were resistant to all beta-lactams, aminoglycosides and fluoroquinolones currently available in Thailand in 2007.

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TABLE 1. Susceptibility profiles of the quality control strains.

| QC Organism | Inhibition zone (mm) | | MIC : E-test (ug/ml) | |
|---|---|---|---|---|
| | QC Range | Test | QC Range | Test |
| *E.coli* ATCC 25922 | 30 - 36 | 33 | 0.032 - 0.125 | 0.047 |
| *P. aeruginosa* ATCC 27853 | 23 - 31 | 26 | 1 - 4 | 2 |
| *S. aureus* ATCC 25923 | 26 - 34 | 30 | - | - |
| *S. aureus* ATCC 29213 | - | - | 0.25 - 1 | 0.5 |

TABLE 2. The breakpoints of susceptibility to ceftobiprole.

| Interpretation | Inhibition zone diameter (mm) | MIC (mg/L) |
|---|---|---|
| Susceptible | ≥ 20 | ≤ 4 |
| Intermediate | 17 - 19 | 8 |
| Resistant | ≤ 16 | ≥ 16 |

TABLE 3. The inhibition zone diameters of ceftobiprole for the tested organisms.

| | ≥ 20 mm. | 17 - 19 mm. | ≤ 16 mm. |
|---|---|---|---|
| MRSA (N=32) | 32 (100%) | - | - |
| *Enterococcus* sp. (N=30) | 23 (77%) | 2 (7%) | 5 (17%) |
| ESBL-producing *E.coli* (N=20) | - | - | 20 (100%) |
| ESBL-producing *K.pneumoniae* (N=20) | 2 (10%) | 2 (10%) | 16 (80%) |
| MDR *P.aeruginosa* (N=30) | 6 (20%) | 1 (3%) | 23 (77%) |
| MDR *A.baumannii* (N=30) | - | 1 (3%) | 29 (97%) |

TABLE 4. The correlations between inhibition zone diameters and MICs of ceftobiprole.

| **Organism : MRSA** | | |
|---|---|---|
| Zone Diameter (mm) | Interpretation | MIC (mg/L) |
| 22 | susceptible | 1.5 |
| 23 | susceptible | 1.5 |
| 27 | susceptible | 0.75 |
| 21 | susceptible | 1.5 |
| 26 | susceptible | 0.5 |
| **Organism : *Enterococcus* sp.** | | |
| Zone Diameter (mm) | Interpretation | MIC (mg/L) |
| 6 | resistant | >256 |
| 6 | resistant | >256 |
| 21 | susceptible | 0.25 |
| 6 | resistant | >256 |
| 6 | resistant | >256 |
| **Organism : ESBL-producing *E.coli*** | | |
| Zone Diameter (mm) | Interpretation | MIC (mg/L) |
| 6 | resistant | >256 |
| 13 | resistant | 16 |
| 6 | resistant | 128 |
| 10 | resistant | 32 |
| 6 | resistant | >256 |
| **Organism : ESBL-producing *K.pneumoniae*** | | |
| Zone Diameter (mm) | Interpretation | MIC (mg/L) |
| 6 | resistant | >256 |
| 6 | resistant | >256 |
| 14 | resistant | 12 |
| 9 | resistant | >256 |
| 12 | resistant | 16 |
| **Organism : MDR *P.aeruginosa*** | | |
| Zone Diameter (mm) | Interpretation | MIC (mg/L) |
| 6 | resistant | >256 |
| 6 | resistant | >256 |
| 6 | resistant | >256 |
| 15 | resistant | 8 |
| 6 | resistant | >256 |
| **Organism : MDR *A.baumannii*** | | |
| Zone Diameter (mm) | Interpretation | MIC (mg/L) |
| 6 | resistant | >256 |
| 9 | resistant | 256 |
| 13 | resistant | 16 |
| 17 | intermediate | 3 |
| 6 | resistant | >256 |

### *Susceptibility Test*

The susceptibility of ceftobiprole was determined by the disk diffusion test for all 162 isolates and the minimum inhibitory concentration (MIC) was determined by the E-test method for 5 isolates of each organism. A 30 ug dise of ceftobiprole (MASTDISC) and the E-test strips with ceftobiprole concentration of 0.016 to 256 mg/L were used. The quality control strains were *E.coli* ATCC 25922, *P.aeruginosa* ATCC 27853, *S.aureus* ATCC 25923 and *S.aureus* ATCC 29213. The methodology for the susceptibility testing was done by direct colony suspension as recommended by the CLSI.[8] The test isolate was grown overnight on blood agar at 35 C, and colonies were picked to suspend in sterile normal saline equivalent to a 0.5 McFarland standard. The suspension was inoculated onto Mueller-Hinton agar. The ceftobiprole discs and the E-test strips were then placed on the agar according to the manufacturer's recommendation. The agar plates were incubated at 35 C for 16-18 hours before the inhibition zone and the MIC results were read.

## RESULTS

The inhibition zone diameters and/or MICs of ceftobiprole against *E.coli* ATCC 25922, *P.aeruginosa* ATCC 27853, *S.aureus* ATCC 29213 and *S.aureus* ATCC 25923 were within the reference limits as shown in Table 1. The breakpoints of susceptibility to ceftobiprole are shown in Table 2. The inhibition zone diameters of ceftobiprole for the studied organisms are shown in Table 3. All isolates of MRSA and 77% of *Enterococcus* sp. isolates were susceptible to ceftobiprole. All isolates of ESBL-producing *E.coli* and MDR *A.baumannii* were not susceptible to ceftobiprole. Only 10% to 20% of ESBL-producing *K.pneumoniae* and MDR *P.aeruginosa* were susceptible to ceftobiprole. The correlations between the inhibition zone diameters and the MIC results of ceftobiprole against 5 isolates of each test organism are shown in Table 4. The MIC results of ceftobiprole against all studied organisms were correlated with the inhibition zone diameters.

## DISCUSSION

Ceftobiprole (BAL 9141) is a new member of the pyrrolidinone-3-ylidenemethyl cephems that has documented activity against MRSA ($MIC_{90}$ 2-4 mg/L), *Enterococcus faecalis* ($MIC_{90}$ 4 mg/L) and penicillin-resistant pneumococci ($MIC_{90}$ 2 mg/L), while preserving the anti-gram-negative activity of third- or fourth-generation cephalosporins.[6,9] The

mode of action of ceftobiprole against staphylococci with altered Penicillin Binding Protein - PBP2a is a very high PBP enzyme affinity coupled with resistance to β-lactamases and a more stable acyl-enzyme complex.[9] Our study revealed that all MRSA isolates and 77% of *Enterococcus* sp. isolates were also susceptible to ceftobiprole similar to earlier reports from other countries.[6,9] However *Enterococcus faecium* was less susceptible to *Entercoccus faecalis*, 90% vs. 22%.[6] We found that all isolates of ESBL-producing *E.coli* and MDR *A.baumannii* were not susceptible to ceftobiprole whereas only 10% to 20% of ESBL-producing *K.pneumoniae* and *P.aeruginosa* were susceptible to ceftobiprole. ESBL-producing *E.coli* and *K.pneumoniae* were found to be less susceptible to ceftobiprole when compared with non-ESBL-producing *E.coli* and *K.pneumoniae*, 12%-26% vs. 97%-100%.[6] The activity of ceftobiprole against MDR *P.aeruginosa* and MDR *A.baumannii* observed in our study was less than that from another study, 0%-20% vs. 46%-70%.[6] These discrepancies might be explained by the fact that the gram negative bacilli chosen for our in vitro study were all multidrug-resistant because we intended to search for antibiotics that might be active against prevalent MDR organisms in our institution. Our study results suggested that ceftobiprole could be used as an alternative to vancomycin for treatment of MRSA infections. Ceftobiprole's activity against MDR gram negatives is similar to ceftriaxone.

## ACKNOWLEDGEMENTS

The authors thank Janssen-Cilag Ltd. (Thailand) for providing ceftobiprole discs and E-test strips, and The Thailand Research Fund for supporting the study.

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# Development of Appropriate Procedures for Inflation of Endotracheal Tube Cuff in Intubated Patients

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***Background:*** *Hyperinflation of endotracheal tube cuff causes tracheal mucosal damage and underinflation increases the risk of pneumonia. The current practice on inflation of endotracheal tube cuff in the intubated patients hospitalized at Siriraj Hospital uses the estimation method. The authors determined appropriateness of such current practice and developed an appropriate procedure for inflation of endotracheal tube cuff in intubated patients.*

***Material and Method:*** *The endotracheal tube cuff pressures of 34 intubated patients in Siriraj Hospital were measured by manometer once daily. Inflation of the endotracheal tube cuffs of 20 patients was done and the volume of air required to optimize the intracuff pressure of 25 $cmH_2O$ was recorded. The intracuff pressure was measured every one hour for eight consecutive hours in the patients who had initial intracuff pressure of 25 $cmH_2O$ and 30 $cmH_2O$. The nurses in the experimental wards used a manometer as a guide to inflate endotracheal tube cuff until the intracuff pressure was 30 $cmH_2O$ every eight hours, whereas the control wards used conventional procedures to inflate the endotracheal tube cuff. The endotracheal tube cuff pressures of the patients in both groups were measured twice daily.*

***Results:*** *Only 34% of intracuff pressure measurements were 20-30 $cmH_2O$. The mean volume of inflated air required to achieve an intracuff pressure of 25 $cmH_2O$ was 7.1 ml. An initial intracuff pressure of 30 $cmH_2O$ decreased to 20 $cmH_2O$ at 7 to 9 hours after inflation. The rate of optimum endotracheal tube cuff pressure was 90.5% in the group guided by manometer and 31.8% in the conventional procedure group ($p < 0.001$, RR 2.85, 95% CI 2.44-3.32).*

***Conclusion:*** *Inflation of endotracheal tube cuff should be guided by manometer to achieve a pressure of 30 $cmH_2O$ every eight hours.*

***Keywords:*** *Endotracheal tube cuff pressure, Intubated patients*

***J Med Assoc Thai 2007; 90 (Suppl 2): 74-8***
***Full text. e-Journal:*** *http://www.medassocthai.org/journal*

Many hospitalized patients need endotracheal intubation. An inflation of the endotracheal tube cuff is important to secure the tube in position in the trachea to prevent self-extubation. The effects of endotracheal tube cuff pressure are well documented. Hyperinflation of endotracheal tube cuff causes tracheal mucosal damage subsequent to restricted capillary blood flow[1-3] and underinflation of the cuff increases pulmonary aspiration risk leading to pneumonia[4]. Therefore, it is recommended that endotracheal tube cuff pressure should be within 20 to 30 cm $H_2O$[1,5,6]. Estimation of endotracheal tube cuff pressure by finger palpation of the external balloon is one of the methods currently used in the clinical setting. It was shown that an inflation of endotracheal tube cuff to achieve optimum pressure by experienced healthcare personnel or using finger palpation of the external balloon or inflating a particular air volume was not accurate, and the use of direct measurement of cuff pressure by manometer is recommended[1,7-11]. A survey of 64 acute care hospitals in the northeastern United States revealed that intracuff pressures were measured every

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8 to 12 hours or daily with a recommended maximum range of 20 to 30 cm $H_2O$[1,2]. The current practice on inflation of endotracheal tube cuff in the intubated patients hospitalized in general wards of Department of Medicine, Siriraj Hospital is estimating endotracheal tube cuff pressure by finger palpation of the external balloon or inflating 5 ml of air. The frequency of inflating endotracheal tube cuff varies from once daily to every other day or when the external balloon of the endotracheal tube cuff is soft. The objectives of the present study were to determine an appropriateness of such current practice and to develop appropriate procedure for inflation of endotracheal tube cuff in the intubated patients.

## Material and Method

### *Determination of frequency of optimum endotracheal tube cuff pressure*

Thirty-four hospitalized patients with indwelling endotracheal tubes in 10 general medical wards in Siriraj Hospital between August and October 2006 were included. The endotracheal tube cuff pressure of each patient was measured by manometer (VBM Medizintecnik GmbH) once daily until the endotracheal tube was removed. The data were analyzed by descriptive statistics.

### *Determination of the volume of air required to optimize the endotracheal tube cuff pressure*

Inflation of the endotracheal cuff of 20 patients was done and the volume of air required to optimize the endotracheal tube cuff pressure to 25 $cmH_2O$ was recorded and analyzed by descriptive statistics.

### *Determination of the kinetics of endotracheal tube cuff pressure*

The cuffs of endotracheal tubes of three patients were inflated until the cuff pressure achieved 25 $cmH_2O$ and the cuff pressure was measured every one hour for eight consecutive hours. The cuffs of the endotracheal tubes of another three patients were inflated until the cuff pressure achieved 30 $cmH_2O$ and the cuff pressure was measured every one hour for eight consecutive hours.

### *Assessment of frequency of optimum endotracheal tube cuff pressure between the two procedures*

This experiment was conducted in December 2006. The nurses in three general wards were instructed to use the manometer as a guide to inflate the endotracheal tube cuff until the intracuff pressure was 30 $cmH_2O$ every eight hours (experimental wards). Another seven general wards used the conventional procedures to inflate the endotracheal tube cuff (control wards). The investigators measured the endotracheal tube cuff pressure of the intubated patients in all general medical wards twice daily until the endotracheal tubes were removed. The rates of optimum intracuff pressure between both groups of the general medical wards were compared by chi-square statistics.

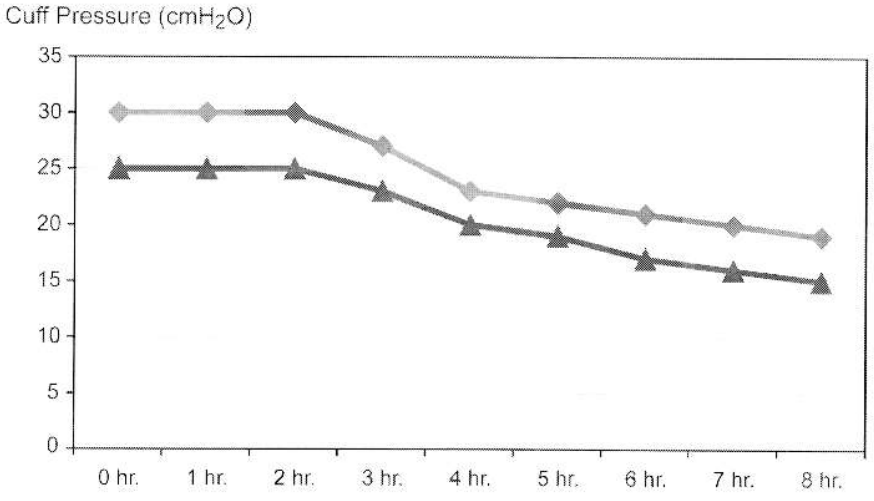


Fig. 1 Kinetics of endotracheal tube cuff pressure ($cmH_2O$) for 8 consecutive hours

**Table 1.** Comparison of frequency of optimum endotracheal tube cuff pressure between the two procedures

| | 3 Experimental Wards | 7 Control Wards | |
|---|---|---|---|
| Number of Patients | 20 | 39 | |
| Number of Intracuff Pressure Measurements | 200 | 387 | |
| Number of Measurements with Intracuff Pressure 20-30 $cmH_2O$ | 181 (90.5%) | 123 (31.8%) | $p < 0.001$ RR 2.85 (95%CI 2.44-3.32) |
| Number of Measurements with Intracuff Pressure > 30 $cmH_2O$ | 7 (3.5%) | 83 (21.4%) | |
| Number of Measurements with Intracuff Pressure < 20 $cmH_2O$ | 12 (6%) | 181 (46.8%) | |
| Range of Intracuff Pressure | 10-34 $cmH_2O$ | 4-120 $cmH_2O$ | |

## Results

### *Frequency of optimum endotracheal tube cuff pressure*

The endotracheal tube cuff pressures of 34 patients (188 measurements) revealed that 33% of the measurements were between 20 and 30 cmH2O, 51.6% of the measurements were lower than 20 $cmH_2O$ and 15.4% of the measurements were higher than 30 $cmH_2O$. The lowest intracuff pressure was 5 $cmH_2O$ and the highest intracuff pressure was 55 $cmH_2O$.

### *The volume of air required to optimize the endotracheal tube cuff pressure*

The mean volume of inflated air required to achieve an intracuff pressure of 25 $cmH_2O$ was 7.1 ml, a standard deviation was 1.8 ml, the smallest air volume of 4.5 ml and the largest air volume was 12 ml. No association between the air volume required to achieve an intracuff pressure of 25 $cmH_2O$ and the type of endotracheal tube, gender & age & body weight of the patients was observed.

### *Kinetics of endotracheal tube cuff pressure*

The decrements of endotracheal tube cuff pressure over eight hours are shown in Fig. 1. An initial endotracheal tube cuff pressure of 25 $cmH_2O$ decreased to 20 $cmH_2O$ at 4 to 5 hours after inflation whereas an initial endotracheal tube cuff pressure of 30 $cmH_2O$ decreased to 20 $cmH_2O$ at 7 to 9 hours after inflation.

### *Frequency of optimum endotracheal tube cuff pressure between the two procedures*

The endotracheal tube cuff pressures of the patients in the experimental wards and those in the control wards are shown in Table 1. The rate of optimum endotracheal tube cuff pressure was 90.5% in the group guided by the manometer and 31.8% in the conventional procedure group ($p < 0.001$, RR 2.85, 95% CI 2.44-3.32). The rates of low endotracheal tube cuff pressure and high endotracheal tube cuff pressure were also significantly higher in the conventional procedure group. The lowest endotracheal tube cuff pressure was 4 $cmH_2O$ and the highest endotracheal tube cuff pressure was 120 $cmH_2O$ in the conventional procedure group. Healthcare personnel who used the manometer as a guide for inflating the endotracheal tube cuff indicated that the procedure was quite simple and convenient, and it took only one minute to do so.

## Discussion

The authors' observations confirmed the findings of the previous reports that an inflation of endotracheal tube cuff by experienced healthcare personnel or using finger palpation of the external balloon or inflating a particular air volume was insufficient to achieve optimum cuff pressure[1,7-11]. Most of the intubated patients whose endotracheal cuffs were inflated by the current procedures were at risk of tracheal mucosal ischemia due to hyperinflation and pneumonia due to underinflation of the endotracheal tube cuff. The authors also observed that it was not possible to recommend an inflation of endotracheal tube cuff with a particular air volume since there was no association between the air volume required to achieve an intracuff pressure of 25 $cmH_2O$ and the type of endotracheal tube, gender & age & body weight of the patients. The mean volume of air required to optimize the endotracheal tube cuff pressure of 25 $cmH_2O$ in the present study was 7.1 ml. The observed value was more than 4 ml in the previous report[5]. This might be due to a

difference in the type of endotracheal tube. The present study on kinetics of endotracheal tube cuff pressure revealed that endotracheal tube cuff pressure needed to be measured and refilled every eight hours and the recommendation on checking the endotracheal cuff pressure once daily[13] was not valid in the present settings. The authors also showed that using the manometer as a guide to inflate the endotracheal tube cuff until the intracuff pressure was 30 $cmH_2O$ every eight hours led to a significantly higher rate of endotracheal tube cuff pressure within the recommended range of 20-30 $cmH_2O$. Healthcare personnel who used the manometer as a guide for injecting air into the cuff were satisfied with the procedure and it took only one minute to do this. Many patients who received conventional procedures for inflating endotracheal tube cuff were at an increased risk of tracheal mucosal ischemia and pneumonia due to hyperinflation or underinflation of the endotracheal cuff similar to the observations made earlier. Therefore, the current procedures for inflating the endotracheal tube cuff should be abandoned since some patients had very low intracuff pressure and some patients had extremely high intracuff pressure up to 120 $cmH_2O$. A limitation of the present study was the authors did not compare the ultimate outcomes of the patients who had optimum endotracheal tube cuff pressure with those who had intracuff pressures outside the recommended range.

Based on the aforementioned observations, the authors recommend that inflation of endotracheal tube cuff should be guided by the manometer to achieve an intracuff pressure of 30 $cmH_2O$ every eight hours.

The aforementioned observations and recommendation were presented to Siriraj Hospital administrators in January 2007. The recommendation was adopted as a clinical practice policy for all medical wards and the hospital has provided a manometer for each medical ward since February 2007.

**Acknowledgements**

The authors wish to thank the Faculty of Medicine Siriraj Hospital and The Thailand Research Fund for supporting the present study.

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## การพัฒนาแนวทางการเติมลมใน cuff ของท่อช่วยหายใจในผู้ป่วยที่มีท่อช่วยหายใจ

ศิรินทร์ทิพย์ ศรีเดิมมา, สราวุธ ลิ้มตั้งตุระกูล, พูนทรัพย์ วงศ์สุรเกียรติ์, วิษณุ ธรรมลิขิตกุล

*การเติมลมใน cuff ของท่อช่วยหายใจในผู้ป่วยที่มีท่อช่วยหายใจที่มากเกินไปจะกดเยื่อบุท่อลมจนขาดเลือด ส่วนการเติมลมที่น้อยเกินไปจะเกิดปอดอักเสบ วิธีปฏิบัติการเติมลมใน cuff ของท่อช่วยหายใจที่บุคลากรของโรงพยาบาลศิริราชปฏิบัติใช้วิธีคาดประมาณ วัตถุประสงค์ของการศึกษานี้เพื่อสร้างแนวทางการเติมลมใน cuff ของท่อช่วยหายใจในผู้ป่วยที่มีท่อช่วยหายใจ*

***วัสดุและวิธีการ** : สำรวจความดันใน cuff ของท่อช่วยหายใจในผู้ป่วย 34 คนที่รับไว้รักษาที่หอผู้ป่วยสามัญโดยวัดความดันใน cuff ของผู้ป่วยวันละครั้งด้วยเครื่องวัดความดัน, เติมลมใน cuff ของท่อช่วยหายใจในผู้ป่วย 20 คน จนได้ความดันใน cuff เป็น 25 ซม.น้ำแล้วบันทึกปริมาณลมที่ใช้, สังเกตการลดลงของความดันใน cuff ภายหลังเติมลมจนได้ความดัน 25 ซม.น้ำ และ 30 ซม.น้ำ, ฝึกพยาบาลใน 3 หอผู้ป่วยให้ใช้เครื่องวัดความดันเป็นแนวทางในการเติมลมใน cuff ให้เป็น 30 ซม.น้ำ ทุก 8 ชั่วโมง ส่วนอีก 7 หอผู้ป่วยใช้วิธีการเติมลมตามแนวทางที่เคยปฏิบัติอยู่เดิม แล้ววัดความดันใน cuff ด้วยเครื่องวัดความดันวันละ 2 ครั้ง*

***ผลการศึกษา** : ร้อยละ 34 ของการวัดความดันใน cuff อยู่ในช่วง 20 ถึง 30 ซม.น้ำ, ค่าเฉลี่ยของปริมาณลมที่ทำให้ความดันใน cuff เป็น 25 ซม.น้ำ คือ 7.1 มล., การเติมลมให้ได้ความดันตั้งต้น 30 ซม.น้ำ สามารถคงความดัน ≥ 20 ซม.น้ำ ได้นาน 7-8 ชั่วโมง, ร้อยละ 90.5 ของการวัดความดันใน cuff ของผู้ป่วยในหอผู้ป่วยที่ใช้เครื่องวัดความดันมีความดันอยู่ในช่วง 20 ถึง 30 ซม.น้ำ ซึ่งมากกว่ากลุ่มที่เติมลมโดยการคาดประมาณ (ร้อยละ 31.8) อย่างมีนัยสำคัญ ($p<0.001$, RR 2.85, 95%CI 2.44-3.32)*

***สรุป** : การเติมลมใน cuff ของท่อช่วยหายใจในผู้ป่วยที่มีท่อช่วยหายใจควรใช้เครื่องวัดความดันเป็นแนวทางโดยเติมลมจนได้ความดัน 30 ซม.น้ำ ทุก 8 ชั่วโมง*

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY FEBRUARY 2008, VOL. 29, NO. 2

ORIGINAL ARTICLE

# Randomized Controlled Trial and Meta-analysis of Oral Decontamination with 2% Chlorhexidine Solution for the Prevention of Ventilator-Associated Pneumonia

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OBJECTIVE. To determine the effectiveness of oral decontamination with 2% chlorhexidine solution for the prevention of ventilator-associated pneumonia (VAP).

DESIGN. Randomized controlled trial and meta-analysis.

SETTING. A tertiary care university hospital in Bangkok, Thailand.

PARTICIPANTS. Adult patients who received mechanical ventilation and who were hospitalized in intensive care units and general medical wards.

METHODS. The patients were randomized to receive oral decontamination with 2% chlorhexidine solution or normal saline solution 4 times per day until their endotracheal tubes were removed. The outcome measures were the development of VAP and oropharyngeal colonization with gram-negative bacilli. Meta-analysis was performed by combining the results of the present study with those from another randomized controlled trial that also used a 2% chlorhexidine formulation for oral decontamination.

RESULTS. The characteristics of the patients in the chlorhexidine group ($n = 102$) and the normal saline group ($n = 105$) were not significantly different. The incidence of VAP in the chlorhexidine group was 4.9% (5 of 102), and the incidence in the normal saline group was 11.4% (12 of 105) ($P = .08$). The rate of VAP in the chlorhexidine group was 7 episodes per 1,000 ventilator-days, and the rate in the normal saline group was 21 episodes per 1,000 ventilator-days ($P = .04$). Irritation of the oral mucosa was observed in 10 (9.8%) of the patients in the chlorhexidine group and in 1 (0.9%) of the patients in the normal saline group ($P = .001$). Oropharyngeal colonization with gram-negative bacilli was either reduced or delayed in the chlorhexidine group. Overall mortality of the patients did not differ significantly between the groups. Meta-analysis of 2 randomized controlled trials revealed an overall relative risk of VAP for patients in the chlorhexidine group of 0.53 (95% confidence interval, 0.31-0.90; $P = .02$).

CONCLUSION. Oral decontamination with 2% chlorhexidine solution is an effective and safe method for preventing VAP in patients who receive mechanical ventilation.

*Infect Control Hosp Epidemiol* 2008; 29:131-136

Nosocomial pneumonia among patients receiving mechanical ventilation, also called ventilator-associated pneumonia (VAP), is an important nosocomial infection worldwide, which leads to increases in length of hospital stay, healthcare costs, and mortality.[1-5] The rate of VAP in Siriraj Hospital (Bangkok, Thailand) was 14 episodes per 1,000 ventilator-days, and 90% of the causative agents were gram-negative bacilli.[5] An episode of VAP in Siriraj Hospital increased the length of a patient's hospital stay by a mean of 13.2 days, increased the cost of antimicrobial therapy by a mean of $400, and contributed to a 20% increase in mortality.[5] Oral and dental colonization with pathogens in patients who received mechanical ventilation is associated with the development of VAP.[6,7] Therefore, oral decontamination with antibiotics and/or antiseptics has been attempted for the prevention of pneumonia in these patients.

A meta-analysis of good-quality randomized controlled trials[8-11] of oral decontamination with antibiotics for the prevention of pneumonia in patients who received mechanical ventilation revealed that topical antibiotic therapy was not an effective method of preventing VAP. Randomized controlled trials of oral decontamination showed that topical use of 0.12% or 0.2% chlorhexidine solution was effective for preventing pneumonia in patients who underwent cardiothoracic surgery.[8-17] The Centers for Disease Control and Prevention guideline for the prevention of healthcare-associated pneumonia published in 2004 made no recommendation on routine oral decontamination with chlorhexidine solution for

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Received July 30, 2007; accepted October 12, 2007; electronically published December 31, 2007.
 0899-823X/2008/2902-0006$15.00. DOI: 10.1086/526438

the prevention of healthcare-associated pneumonia in critically ill patients and other patients who received mechanical ventilation and were at high risk for pneumonia.[18]

In 2006, we initiated a randomized controlled trial to determine the effectiveness and safety of using a higher concentration of chlorhexidine in solutions used for oral decontamination to prevent VAP. However, 3 meta-analyses published in 2007 revealed that oral decontamination with chlorhexidine solution reduced pneumonia in patients who received mechanical ventilation.[19-21] These meta-analyses included a randomized controlled trial published in 2006 that used 2% chlorhexidine solution for oral decontamination.[22] They found that 2% chlorhexidine oral decontamination was marginally effective for the prevention of pneumonia in patient who received mechanical ventilation, with a relative risk (RR) of 0.58 (95% confidence interval [CI], 0.31-1.09). Hence, we also performed a meta-analysis that included only the randomized controlled trials that evaluated oral decontamination with 2% chlorhexidine to prevent pneumonia in patients who received mechanical ventilation.

## METHODS

### Randomized Controlled Trial

The study was approved by the Ethics Committee on Human Research, Faculty of Medicine Siriraj Hospital. The study was conducted from January 2006 through March 2007 at Siriraj Hospital, which is a 2,300-bed, tertiary care university hospital.

Eligible patients were adults aged 18 years or older who were hospitalized in intensive care units (a total of 36 beds) or general medical wards (a total of 240 beds) at Siriraj Hospital and who received mechanical ventilation. Patients who had pneumonia at enrollment or who had a chlorhexidine allergy were excluded. Each eligible patient was randomized to the chlorhexidine group or the normal saline group by

TABLE 1. Demographic and Clinical Characteristics of 207 Study Patients Who Received Mechanical Ventilation and Oral Decontamination

| Characteristic | Chlorhexidine group ($n$ = 102) | Normal saline group ($n$ = 105) | $P$ |
|---|---|---|---|
| Age, mean ± SD, years | 56.5 ± 20.1 | 60.3 ± 19.1 | .15 |
| Sex | | | |
| Male | 50 (49.1) | 51 (48.6) | .78 |
| Female | 52 (50.9) | 54 (51.4) | |
| Ward | | | |
| Surgical ICU | 50 (49.0) | 51 (48.6) | .99 |
| General medical ward | 40 (39.2) | 42 (40.0) | |
| Medical ICU | 12 (11.8) | 12 (11.4) | |
| Underlying disease | | | |
| Yes | 75 (73.5) | 75 (71.4) | .75 |
| No | 27 (26.5) | 30 (28.6) | |
| Reason for endotracheal intubation | | | |
| Upper airway obstruction | 15 (14.7) | 23 (21.9) | .21 |
| Oxygenation failure | 66 (64.7) | 61 (58.0) | .39 |
| Airway protection | 31 (30.4) | 40 (38.0) | .30 |
| Secretion obstruction | 32 (31.4 ) | 33 (31.4) | .99 |
| Ventilatory failure | 45 (44.1) | 42 (40.0) | .57 |
| Duration of mechanical ventilation, mean, days | 4.5 | 5.2 | .38 |
| Risk factor for VAP | | | |
| Prior infection | 23 (22.5) | 30 (28.6) | .33 |
| Prior antibiotic use | 48 (47.0) | 60 (57.1) | .16 |
| Bronchodilator use | 11 (10.8) | 10 (9.5) | .82 |
| Corticosteroid use | 9 (8.8) | 16 (15.2) | .2 |
| Acid reduction agent use | 75 (73.5) | 69 (65.7) | .28 |
| Reintubation | 5 (4.9) | 5 (4.8) | .99 |
| Invasive device(s) present | 59 (57.8) | 65 (61.9) | .56 |
| Nasogastric tube present | 85 (83.3) | 86 (81.9) | .99 |
| Thoracoabdominal surgery | 29 (28.4) | 28 (26.7) | .87 |
| APACHE II score, mean ± SD | 16.7 ± 7.9 | 18.2 ± 8.1 | .16 |

NOTE. Data are no. (%) of patients, unless otherwise indicated. APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; VAP, ventilator associated pneumonia.

TABLE 2. Outcomes for 207 Study Patients Who Received Mechanical Ventilation and Oral Decontamination

| Variable | Chlorhexidine group ($n$ = 102) | Normal saline group ($n$ = 105) | $P$ |
|---|---|---|---|
| No. (%) of patients who developed VAP | 5 (4.9) | 12 (11.4) | .08[a] |
| No. of cases of VAP per 1,000 ventilator-days, mean | 7 | 21 | .04 |
| No. (%) of patients with irritation of oral mucosa | 10 (9.8) | 1 (0.9) | .001 |

NOTE. VAP, ventilator-associated pneumonia.
[a] Relative risk, 0.43 (95% confidence interval, 0.16-1.17).

stratified randomization according to the sex and hospital location of the eligible patient. Patients in the chlorhexidine group received oral care 4 times per day that involved brushing the teeth, suctioning any oral secretions, and rubbing the oropharyngeal mucosa with 15 mL of a 2% chlorhexidine solution formulated and produced by the hospital's pharmacy department. The patients in the normal saline group underwent the same oral care procedure, except that their procedures used normal saline solution instead of chlorhexidine solution. The oropharyngeal cleaning with 2% chlorhexidine solution or normal saline solution was continued until the endotracheal tube was removed. All participating wards employed their usual care protocols, according to which a semirecumbent body position was maintained, if possible. Neither selective decontamination of the digestive tract nor continuous aspiration of subglottic secretions were performed for any patient.

Each patient was examined daily for the presence of pneumonia. A diagnosis of VAP was made if the patient had a new, persistent, or progressive infiltrate visible on a chest radiograph in combination with at least 3 of the following 4 criteria: (1) body temperature greater than 38°C or less than 35.5°C, (2) leukocytosis (defined as more than $10 \times 10^3$ leukocytes/mm$^3$) or leukopenia (defined as less than $3 \times 10^3$ leukocytes/mm$^3$), (3) purulent tracheal aspirate, and/or (4) a semiquantitative culture of tracheal aspirate samples that was positive for pathogenic bacteria. An oropharyngeal swab sample was taken from each patient immediately after endotracheal intubation, on day 3 after intubation, on day 7 after intubation, and every 7 days thereafter until the endotracheal tube was removed or the patient developed pneumonia. The oropharyngeal swab sample was placed on blood agar and McConkey agar for semiquantitative culture. The bacterial colonies on agar plates were graded as 1+, 2+, 3+, or 4+ to indicate growth seen in quadrants 1, 2, 3, or 4 of the plates; the plates without growth were graded "no growth."

A sample size of 108 patients per group was estimated to be necessary in order to determine whether oral decontamination with 2% chlorhexidine solution could reduce the rate of VAP from 14 to 7 episodes per 1,000 ventilator-days with 5% type I error (1-sided) and 80% power. The data were analyzed by descriptive statistics, the unpaired Student $t$ test, $\chi^2$ square statistics, and the Mann-Whitney $U$ test, as appropriate. A $P$ value of .05 or less was considered statistically significant.

### Meta-analysis

Randomized controlled trials that used a 2% chlorhexidine formulation for oral decontamination as the sole intervention for patients receiving mechanical ventilation and reported the incidence of pneumonia as a study outcome were selected from the studies included in 3 recent meta-analyses.[19-21] The details of the selected studies were reviewed, and the data were combined with the data from the present randomized controlled trial by use of RevMan software, version 4.2 (Cochrane Collaboration). The pooled effect sizes of relative risk were estimated with the Mantel-Haenszel fixed effect model.

## RESULTS

### Randomized Controlled Trial

Of 207 patients enrolled to the study, 102 were randomized to the chlorhexidine group and 105 to the normal saline group. Patients' demographic characteristics, location, disease severity, and duration of mechanical ventilation did not differ significantly (Table 1). The effectiveness and safety of using a 2% chlorhexidine solution for oral decontamination to prevent VAP are shown in Table 2. The incidence of VAP was 4.9% (5 of 102) in the chlorhexidine group and 11.4% (12 of 105) in the normal saline group (RR, 0.43 [95% CI 0.16-1.17]; $P$ = .08). The mean number of cases of VAP was 7 episodes per 1,000 ventilator-days in the chlorhexidine group and 21 episodes per 1,000 ventilator-days in the normal saline group ($P$ = .04). In all patients, VAP was caused by gram-negative bacilli. Mild and reversible irritation of the oral mucosa was observed in 10 (9.8%) of the chlorhexidine group, compared with 1 (0.9%) of the normal saline group ($P$ = .001). The outcomes for 110 patients who received mechanical ventilation for longer than 2 days are shown in Table 3. The patients in the chlorhexidine group also had less risk of developing VAP, compared with the normal saline group.

TABLE 3. Outcomes for 110 Patients Who Received Mechanical Ventilation for More Than 2 Days

| Variable | Chlorhexidine group ($n$ = 58) | Normal saline group ($n$ = 52) | $P$ |
|---|---|---|---|
| No. (%) of patients who developed VAP | 5 (8.6) | 10 (19.2) | .11[a] |
| No. of cases of VAP per 1,000 ventilator-days, mean | 13 | 23 | .06 |

NOTE. VAP, ventilator-associated pneumonia.
[a] Relative risk, 0.45 (95% confidence interval, 0.16-1.23).

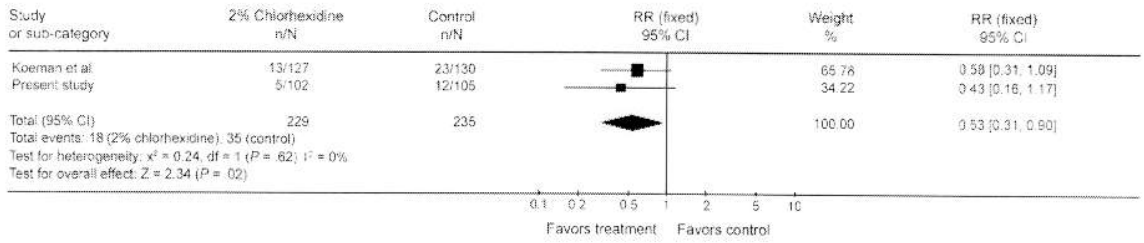


FIGURE. Forest plot of the meta-analysis (fixed effect model) of data from the Koeman et al.[22] study and data from the present study on all patients who received mechanical ventilation. CI, confidence interval.

Observations regarding oropharyngeal colonization with gram-negative bacilli revealed the following findings: (1) gram-negative bacilli were present on the day of enrollment in 63 (61.8%) of the chlorhexidine group and in 71 (67.6%) of the normal saline group, (2) a total of 15 (38.5%) of 39 patients in the chlorhexidine group and 28 (82.4%) of 34 in the normal saline group were newly colonized with gram-negative bacilli, (3) at total of 12 (19.1%) of 63 patients in the chlorhexidine group and 0% of the normal saline group converted from being colonized with gram-negative bacilli to not being colonized, (4) a total of 21 (53.8%) of 39 patients in the chlorhexidine group and 3 (8.8%) of 34 in the normal saline group had no gram-negative bacilli recovered from oropharyngeal swab samples over the whole study period, (5) the amount of gram-negative bacilli recovered on culture increased in 9 (14.3%) of 63 patients in the chlorhexidine group and 36 (50.7%) of 71 in the normal saline group; and (6) the amount of gram-negative bacilli recovered was reduced in 27 (42.8%) of 63 patients in the chlorhexidine group and in 10 (14.1%) of 71 in the normal saline group. The overall mortality rate for the patients in the chlorhexidine group was 32.3% (36 of 102), compared with 35.2% (37 of 105) in the normal saline group ($P = .7$).

### Meta-analysis

We found that there was only 1 randomized controlled trial that evaluated oral decontamination with a 2% chlorhexidine formulation as the sole intervention for patients who received mechanical ventilation that also reported the incidence of pneumonia as a study outcome.[22] We performed a pooled analysis of data from that trial and data from all patients in the present trial, as well as a pooled analysis of data from that trial and data from the patients in the present trial who received mechanical ventilation for more than 48 hours. The results of the first pooled analysis are shown in the Figure. Heterogeneity was not detected in either analysis ($P > .5$). There was a significant reduction in the rate of VAP among patients in the chlorhexidine group, with a relative risk of 0.53 (95% CI, 0.31-0.90; $P = .02$) for all patients and a relative risk of 0.54 (95% CI, 0.31-0.92; $P = .02$) for patients who received mechanical ventilation for more than 48 hours. A total of 14 patients would need to receive oral decontamination with 2% chlorhexidine solution to prevent 1 additional case of VAP.

## DISCUSSION

Chlorhexidine is a broad spectrum antiseptic agent. Its spectrum of antimicrobial activity includes gram-negative and gram-positive bacteria.[23] Among its most important attributes is its persistence: it remains chemically active on tissue for up to 6 hours. Chlorhexidine solution has been used as an anti-infective oral rinse in dental medicine. Although oral decontamination with low concentrations of chlorhexidine (0.12%-0.2%) has been found to be effective in preventing pneumonia in patients undergoing cardiothoracic surgery, its role in preventing pneumonia in critically ill patients who received mechanical ventilation had not been established prior to 2006.[19-21] Therefore, we hypothesized that oral decontamination with a higher concentration of chlorhexidine might be more effective at preventing pneumonia in critically ill patients than is decontamination with a low-concentration solution. We asked the hospital's pharmacy department to formulate and produce a 2% chlorhexidine oral solution. An in vitro study of locally produced 2% chlorhexidine solution in our laboratory revealed that it was active against multidrug-resistant bacteria, including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and methicillin-resistant *Staphylococcus aureus*.

We were unable to do a blind study because the odor and taste of the chlorhexidine solution were quite different from those of the normal saline solution. However, the assessors who determined whether a patient developed pneumonia were unaware of the patient's study group assignment. The results of our randomized controlled trial demonstrated that oral decontamination with 2% chlorhexidine solution was effective at preventing pneumonia in patients who received mechanical ventilation, similar to the results of a recent study published in 2006.[22] Our study paid more attention to oropharyngeal colonization with gram-negative bacilli, because more than 90% of cases of VAP in our hospital were caused by gram-negative bacilli.[5] More than 60% of the patients in our study had oropharyngeal colonization with gram-negative bacilli, because a large proportion of them had chronic un-

derlying diseases or had been hospitalized prior to endotracheal intubation. Among the patients who received 2% chlorhexidine oral rinse, the rate of oropharyngeal colonization with gram-negative bacilli was reduced or the onset of colonization was delayed.

Although a combination of chlorhexidine and colistin resulted in better oropharyngeal decontamination for gram-negative bacteria than did chlorhexidine alone, both regimens appeared equally effective at preventing VAP.[22] Therefore, use of 2% chlorhexidine solution alone should be sufficient for prevention of VAP in patients who receive mechanical ventilation. It should be noted that 9.8% of the patients who received 2% chlorhexidine oral solution developed irritation of the oral mucosa. We observed that many patients who developed irritation were hospitalized in wards in which the personnel responsible for oral care usually vigorously rubbed the oropharyngeal mucosa with gauze soaked with 2% chlorhexidine solution. The incidence of irritation was reduced after personnel were instructed to clean the oropharyngeal mucosa gently. Healthcare workers should be aware of this side effect and should discontinue the use of 2% chlorhexidine oral solution if a patient experiences severe irritation of the oral mucosa.

We analyzed combined data from our study and another study because both studies were randomized controlled trials and both used the same concentration of chlorhexidine. Although there were several differences between the studies with respect to the formulation of 2% chlorhexidine solution and the eligibility criteria of the patients enrolled, the test of heterogeneity revealed a $P$ value of greater than 0.1, indicating that there was no significant heterogeneity between the studies and that the results from both studies could be combined. Similar to the results from other meta-analyses, the pooled analysis of data from the other trial and data from all patients from our study revealed a significant reduction in the rate of VAP in the chlorhexidine group, as did a pooled analysis of data from the other study and data for patients in this study who received more than 48 hours of mechanical ventilation.[20]

Although oral decontamination with chlorhexidine reduced the risk of VAP in patients who received mechanical ventilation, no differences in duration of mechanical ventilation, length of intensive care unit stay, or mortality could be demonstrated.[20,22] Our study also failed to demonstrate a reduction in the mortality rate among patients who received oral decontamination with chlorhexidine. Nevertheless, oral decontamination with 2% chlorhexidine solution for the prevention of VAP is still considered a cost-effective strategy, because the cost of the solution in Siriraj Hospital was only 40 cents per day and the number needed to treat is 14. At our institution, the mean total cost of 2% chlorhexidine solution for 14 patients was $34, which is much less than the mean cost of antibiotic therapy to treat an episode of VAP ($400). Therefore, beginning in August 2007, Siriraj Hospital adopted a policy that recommended oral decontamination with 2% chlorhexidine solution for prevention of VAP for adult patients who receive mechanical ventilation.

## ACKNOWLEDGMENTS

We thank Ms. Tanita Thaweethamcharoen for formulating and producing the 2% chlorhexidine oral solution, Ms. Suwanna Trakulsomboon for testing the antibacterial activity of the 2% chlorhexidine solution, the personnel in the laboratory of Division of Infectious Diseases and Tropical Medicine for performing cultures of oropharyngeal samples, Ms. Laksamee Watanamongkolsilp for data management, Ms. Chulaluk Komoltri for analyzing the data, Ms. Sunee Tanakumtorn for coordinating the study, Dr. Akarin Nimmannit for performing the meta-analysis, and Dr. Chairat Permpikul and Dr. Puttipannee Vorrakitpokatorn for their supervision.

*Financial support.* The Thailand Research Fund and Faculty of Medicine Siriraj Hospital.

*Potential conflicts of interest.* All authors report no conflicts of interest relevant to this article.

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# Funding agencies in low- and middle-income countries: support for knowledge translation

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**Objective** The aim was to describe how selected health research funding agencies active in low- and middle-income countries promote the translation of their funded research into policy and practice.

**Methods** We conducted inductive analysis of semi-structured interviews with key informants from a purposive sample of 23 national and international funding agencies that fund health research in Brazil, Colombia, India, the Philippines, South Africa and Thailand. We also surveyed web sites.

**Findings** We found a commitment to knowledge translation in the mandate of 18 of 23 agencies. However, there was a lack of common terminology. Most of the activities were traditional efforts to disseminate to a broad audience, for example using web sites and publications. In addition, more than half (13 of 23) of the agencies encouraged linkage/exchange between researchers and potential users, and 6 of 23 agencies described "pull" activities to generate interest in research from decision-makers. One-third (9 of 23) of funding agencies described a mandate to enhance health equity through improving knowledge translation. Only 3 of 23 agencies were able to describe evaluation of knowledge translation activities. Furthermore, we found national funding agencies made greater knowledge translation efforts when compared to international agencies.

**Conclusion** Funding agencies are engaged in a wide range of creative knowledge translation activities. They might consider their role as knowledge brokers, with an ability to promote research syntheses and a focus on health equity. There is an urgent need to evaluate the knowledge translation activities of funding agencies.

Bulletin of the World Health Organization 2008;86:524–534.

*Une traduction en français de ce résumé figure à la fin de l'article. Al final del artículo se facilita una traducción al español.* الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

## Introduction

For knowledge to benefit society, it needs to be shared, communicated and translated into policy, practice or community action.[1] Increased commitment to knowledge translation is reflected by the 58th World Health Assembly's declaration in 2005, which encouraged enhanced knowledge transfer.[2] Several international initiatives focus on knowledge translation in low- and middle-income countries (LMICs) such as the Overseas Development Institute's RAPID programme (Research and Policy in Development), the WHO/PAHO EVIPNet initiative (Evidence-Informed Policy Networks) and the WHO Knowledge Management and Sharing initiative.

The WHO Department of Knowledge Management and Sharing defines knowledge translation as: "The synthesis, exchange and application of knowledge by relevant stakeholders to accelerate the benefits of global and local innovation in strengthening health systems and improving people's health."[3] Because of the dearth of primary research performed in their own countries and the disproportionately low research resources available, LMICs need to engage in the translation of knowledge that is cost-effective and applicable to their local settings.[4]

Knowledge translation is a complex and nonlinear process, and is generally slow, particularly in LMICs.[5,6] Slow knowledge transfer can result in inappropriate care. Many examples in LMICs have shown variations in practice despite established guidelines; for

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doi:10.2471/BLT.07.040386
(*Submitted: 17 January 2007 – Revised version received: 21 December 2007 – Accepted: 2 January 2008 – Published online: 1 April 2008*)

example, antibiotic prophylaxis with caesarean section,[7] management of acute myocardial infarction[8] and management of pneumonia.[9] In one example, a study of Shanghai hospitals found that more than 70% of births involved clinical practices that are ineffective and should be avoided based on the best available evidence from the Cochrane Library.[10]

Knowledge translation may help bridge the know–do gap, particularly in disadvantaged populations.[3] Utilization of treatments with demonstrated effectiveness, such as immunization, oral rehydration for diarrhoea and treatment for acute respiratory infection, is up to 50% lower for the poorest.[11–13] Knowledge translation interventions that enhance access, diagnostic accuracy, provider compliance or consumer adherence could enhance community effectiveness of interventions in disadvantaged populations.[14]

Because research funding agencies are the gatekeepers to funds for conducting research, they may be able to encourage knowledge translation and exchange by their funding recipients. They can also actively disseminate information, involve end users in prioritizing research topics and fund implementation research. However, little is known about funding agency policies to promote knowledge translation.

This project was designed as an exploratory, descriptive study to increase understanding of the knowledge translation policies and activities of applied health research funders within LMICs and international funding agencies.

## Methods

We conducted inductive analysis of semi-structured interviews with key informants from a judgement sample of funding agencies supplemented by document analysis from the agency web sites, including strategic plans, mandate and application procedures. This method provides a richness of data that cannot be assessed using questionnaire surveys since participants could respond freely as well as illustrate concepts with examples and the interviewer could probe for more details.[15] Document analysis and findings from interviews were triangulated to present a complete picture of knowledge translation activities. We used the Lavis framework of push, pull, linkage/exchange and integrated efforts to classify knowledge translation activities.[16]

### Sampling

We selected six LMICs, based on the presence of substantial within-country health research funding: Brazil, Colombia, India, the Philippines, South Africa and Thailand. None of these countries were among the least developed countries, where external funding agencies would be responsible for a larger proportion of health research funding (e.g. Bangladesh or Mozambique).[17] Because this is an exploratory study of knowledge translation, we chose to use criterion-based purposive sampling, a non-probability sampling method that selects informants based on predefined criteria.[18] As with other non-probability sampling methods, purposive sampling does not produce a sample that is representative of a larger population, but it is useful to study a clearly defined group. Our criterion for selecting funding agencies was the extent to which they funded applied health research. We selected a total of 14 national funding agencies from these six LMICs and nine international funding agencies, based on these criteria. Some country investigators applied additional criteria that are listed in Table 1. For each agency, we aimed to interview three key informants: someone from senior management with strategic responsibility, a research manager with responsibility for applied research programmes and a knowledge transfer officer. We interviewed key informants from 23 agencies between September 2003 and September 2004 (Table 1).

### Interviews

The interviews were conducted face-to-face or via telephone by one of the authors, using a semi-structured interview framework (Table 2). Participants were asked to provide relevant documents or web sites that contained policy statements on knowledge translation as well as copies of grant application forms. Data was extracted using the same framework as the interview guide.

The interview guide was translated into Portuguese, Spanish and Thai. Each translation was back-translated into English by a second translator who had not seen the original English version. The English back-translation and the original were then compared. If the back-translated items and the original did not agree, the first translator conducted a second translation. A second back-translation was repeated. This process continued until the translation was judged satisfactory.

The audio-tapes were transcribed verbatim and verified by the interviewer before analysis. Transcripts were coded in their original language, and then translated to English to permit comparison of the findings from all the countries using the same approach used to translate the interview guide.

Two types of bias threaten this type of semi-structured interview and inductive analysis: description bias and interpretation bias. To minimize description bias, we transcribed interviews verbatim and used back-translation methods to ensure accurate translations. To minimize interpretation bias, we asked agency interviewees to verify data and we verified the coding with all co-investigators.

## Analysis

We used inductive analysis to code and categorize data.[19,20] We identified eight main themes: role of agency, background, researcher requirements, application process, dissemination activities, agency initiatives, evaluation and target audience. We further identified subcategories within each of these codes. Each of the LMIC investigators used these codes and subcategories to classify their data. The initial coding of all the data was performed by the interviewers in the LMIC and the co-investigator in that country.

To ensure that analysis was consistent between countries, we checked the classification of the verbatim transcripts at the central coordinating office in Ottawa, Canada, and finalized the coding by consensus through conference calls and e-mails with the investigators to ensure common understanding. We verified the final coding with the interviewees, allowing them to add or update information.

The analysis of this hypothesis-generating study focused on the nature of the knowledge translation activities of funding agencies and their perception about needs for improvement. We did not aim to compare funding

Table 1. **Funding agencies interviewed**

| Country | Abbreviation | Organization | Additional selection criteria |
|---|---|---|---|
| International | CIDA | Canadian International Development Agency | – |
| | DFID | Department for International Development (United Kingdom) | – |
| | IDRC | International Development Research Centre | – |
| | USAID | United States Agency for International Development | – |
| | WHO/TDR | WHO – Special Programme for Research and Training in Tropical Diseases | – |
| International agencies interviewed at country offices | CIDAb | CIDA – Brazil office | Continued support of regional development |
| | PAHO | Pan American Health Organization – Brazil office | – |
| | WBp | World Bank – Philippines office | Chosen because of its extensive and innovative knowledge translation activities |
| Brazil | FAPESP | State of São Paulo Research Foundation | Most stable research granting institution |
| | CNPq | National Council for Scientific and Technological Development | Responsible for establishing national policies for research |
| Colombia | Colciencias | Instituto Colombiano para el Desarrollo de la Ciencia y la Tecnología | External recognition as research funders; number of projects supported; availability of key informants |
| | MSP | Ministry for Social Protection (equivalent to Ministry of Health) | |
| India | ICSSR | Indian Council for Social Science Research | – |
| | DFIDi | Department for International Development – India office | – |
| | ICMR | Indian Council of Medical Research | Largest national funding agency for medical research |
| Philippines | PCHRD | Philippine Council for Health Research and Development | Mandated by law to perform and promote basic and applied research |
| | DOH | Department of Health | Focused on systems and health-care delivery research |
| South Africa | MRC | Medical Research Council of South Africa | – |
| | HST | Health Systems Trust | – |
| Thailand | TRF | Thailand Research Fund | Major national funding agencies and the extent to which they were likely to perform knowledge translation |
| | HSRI | Health Systems Research Institute | |
| | NRCT | National Research Council of Thailand | |
| | NSTDA | National Science and Technology Development Agency | |

agencies, hence individual results for each funding agency are not presented. Furthermore, because we did not interview all departments within each agency, we could not be certain that we had captured all knowledge translation activities.

## Results

### Coding

We developed the final coding of each interview by consensus discussion with the country teams and the Ottawa team. We kept records of the changes to the coding based on consensus discussion. We found that 89% of the coded text was identical between the original country team coding and the final coding. Most of the differences in coding were due to country teams placing descriptions of specific activities into the five general activities of the funding agency, which were intended to contain broad approaches rather than specific activities.

### Analytical framework

Based on analysis of the interviews, we defined five broad categories of funding agency activities related to knowledge translation as follows: (1) "pull" was defined as: activities where the research agenda was set by policy-makers, activities that aimed to increase skills and capacity of policy-makers to use research evidence; (2) "push" was defined as: activities that encouraged researchers to communicate effectively with decision-makers; (3) "linkage/exchange" was defined as: creating linkages between researchers and policy-makers (e.g. workshops, conferences or knowledge brokers); (4) "communication" was defined as: the funding agency itself translating or communicating research results to research users and policy-makers; and (5) "funding opportunities" were defined as: specific funding opportunities that encouraged researchers to engage in knowledge translation strategies themselves.

We added the last two categories based on inductive analysis since

Table 2. **Semi-structured interview framework on knowledge translation activities**

| General | Specific |
|---|---|
| Research governance | • Overarching impact of legislative climate<br>• Mandate for knowledge translation<br>• Focus on disadvantaged |
| Mission statement mentions knowledge translation | • Overall strategy for knowledge translation<br>• Future plans for knowledge translation<br>• Definition of knowledge translation<br>• Focus on disadvantaged |
| Resources allocated to knowledge translation activities | • Funding and research training grants in knowledge translation, including special calls<br>• Policy on knowledge translation activities funded at the organization level<br>• Budget for knowledge translation activities<br>• Monitoring of knowledge translation activities<br>• Impact of budget cuts on knowledge translation, if a priority |
| Documents dealing with knowledge translation | • Types and volume of materials produced<br>• Means of dissemination of documents<br>• Funder publishes monographs, executive summaries/fact sheets regarding research<br>• Web pages devoted to research results<br>• Focus on disadvantaged |
| Target audiences for knowledge translation activities | • Means of communication in knowledge translation activities |
| Evaluation | • Evaluation of impact of activities – efforts to monitor dissemination/impact<br>• Examples of impact of activities<br>• Examples affecting disadvantaged populations |
| Application form/procedure | • Statements about knowledge translation in application form – requirement for activities as a condition of funding<br>• Partnership requirement between researcher and stakeholders<br>• Requirement to address relevance of study at application stage<br>• Lay summary requirements<br>• Dedicated budget items<br>• Policy for eligible expenditures<br>• Contractual requirements for knowledge translation |
| Funders' expectations of researcher's responsibility for dissemination and implementation | Requirements for the researchers to engage in the following knowledge translation activities:<br>• final reports to funding agency – format and level of detail<br>• participation in workshops<br>• intellectual property rights, acknowledgement and attribution of funding sources, etc. |
| Knowledge translation facilitation by funders working with researchers | • Funder has communication department to assist researchers (example of activities)<br>• Funder issues press releases regarding funded researchers<br>• Requirement to report back study outcomes<br>• Target audience for activities – who are they and how do they identify them |

communication efforts and funding opportunities were described as two important ways that funding agencies support knowledge translation. These categories did not fit into the Lavis framework of push, pull and linkage/exchange.

We found that these five codes for general knowledge translation activities were mutually exclusive, i.e. despite allowing double-coding of text where relevant, no text was placed in more than one of the five general activities. We found two cases from the 23 agencies where negotiation of meaning with the Ottawa team resulted in reclassifying push activities as pull activities.

## Mandate

Thirteen of 23 agencies described a favourable political climate to knowledge translation, mainly due to increasing realization that research needs to infiltrate policy and action to benefit health. Respondents described the following barriers to knowledge translation: lack of tools, lack of funding for knowledge translation, little involvement of key stakeholders in the research process and competition between stakeholders.

"Do we have all the skills necessary, or the time even, ... to perhaps advise our partners how that's to have a policy impact ..."

"... needs to do a lot more consultation with stakeholders from the start,

so that consensus and coalitions supporting reform are established and gain momentum"

None of the respondents mentioned criteria regarding the type of knowledge or evidence needs to be translated into policy and practice, or when knowledge translation needs to be done.

Eighteen of 23 funding agencies describe some aspect of knowledge translation in their mandate (Table 3). However, the activities and definition of knowledge translation varied dramatically across different funding agencies, ranging from dissemination to brokering between researchers and decision-makers (Table 3).

"We're not an activist funding organization, per se. That's where the broker versus advocate role comes in."

Nine of 23 agencies described the focus of the knowledge translation activities as ensuring that funded research contributed to improving the health of their communities.

## Budget and priority

Eight of 23 agencies ranked knowledge translation as a high priority. Seven of 23 agencies were able to report the percentage of their total budget spent on knowledge translation; all reported less than 20%. Three agencies reported that the knowledge translation budget would withstand cutbacks to the total budget.

## Dissemination

One-third of agencies viewed dissemination as a shared responsibility between researcher and the funding agency. Others defined the main responsibility for dissemination as the role of researchers, funding agencies or partners. Dissemination activities were described as highly variable.

Most of the activities that agencies required, expected or encouraged by researchers were traditional within science communication such as producing a final report or journal publication. Thirteen of 23 agencies also required or encouraged researchers to partner with decision-makers and research users. Six agencies stated that researchers were encouraged to engage in pull activities that aim to increase the appetite for research by decision-makers. For example, Pan American Health Organization (PAHO)

Table 3. **Funding agencies and knowledge translation definition**

| Country | Abbreviation | Mandate | Selected quotes defining knowledge translation |
|---|---|---|---|
| International | IDRC | yes | "Do you want to be a broker, or do you want to be an advocate?" |
| | CIDA | no | "Knowledge is demand driven, based on political will" |
| | USAID | yes | "Whole series of advocacy, engagement" |
| | DFID | yes | "Research communication" |
| | WHO/TDR | yes | "Making that leap between the science and its application" |
| Brazil | FAPESP | no | "Research to be placed on a production scale" |
| | CNPq | no | "Transformation of more basic knowledge to an application in society" |
| | CIDAb | no | "Translation of knowledge into action" |
| Colombia | Colciencias | yes | "Social appropriation of knowledge" |
| | PAHO | yes | "If there is access to information about health, the gap between haves and have-nots will be closed" |
| | MSP | no | "Intent to make the findings public" |
| India | ICSSR | yes | "Building greater awareness about research and other activities with a view to promoting the social sciences" |
| | DFIDi | yes | "Knowledge exchange wherein the research findings are discussed and shared among partners" |
| | ICMR | yes | "Applied and operational research ... translation of research findings into policy and action" |
| Philippines | WBp | yes | "Creating, sharing, and applying knowledge and managing that knowledge" |
| | PCHRD | yes | "[It] is really evidence-based policy making ... It suggests that whenever you do research, you'll have to involve the stakeholders, the users (potential users) even in the conception and in every step of the research process" |
| | DOH | yes | "Ensure access to knowledge for evidence-based decision making" |
| South Africa | MRC | yes | "Knowledge translation is also taking possession of (transferred) knowledge" |
| | HST | yes | "Implementation on the ground, as well as the communication on advocacy component" |
| Thailand | TRF | yes | "Use of research findings for national development" |
| | HSRI | yes | "Implement the essential knowledge and information obtained from research for the formulation of a national health policy" |
| | NRCT | yes | "Dissemination of research findings" |
| | NSTDA | yes | "Transfer the research findings to the public and commercial sectors" |

CIDA, Canadian International Development Agency; CIDAb, CIDA – Brazil Office; Colciencias, Instituto Colombiano para el Desarrollo de la Ciencia y la Tecnología; CNPq, National Council for Scientific and Technological Development; DFID, Department for International Development (the United Kingdom); DFIDi, DFID – India office; DOH, Department of Health; FAPESP, State of São Paulo Research Foundation; HSRI, Health Systems Research Institute; HST, Health Systems Trust; ICMR, Indian Council of Medical Research; ICSSR, Indian Council for Social Science Research; IDRC, International Development Research Centre; MRC, Medical Research Council of South Africa; MSP, Ministry for Social Protection (equivalent to Ministry of Health); NRCT, National Research Council of Thailand; NSTDA, National Science and Technology Development Agency; PCHRD, Philippine Council for Health Research and Development; PAHO, Pan American Health Organization; TRF, Thailand Research Fund; USAID, United States Agency for International Development; WBp, World Bank – Philippines office; WHO/TDR, WHO – Special Programme for Research and Training in Tropical Diseases.

supported national research councils, including ministries of health.

## Application process

At the time of application, 15 of 23 agencies described a requirement to partner with decision-makers, 12 of 23 agencies required researchers to state the policy relevance and significance of their research, and 11 of 23 agencies required researchers to define a knowledge translation audience (Table 4). Other activities described at the application stage were provision of a lay summary proposal, and a knowledge translation plan including dissemination, web development, publication and conferences (Table 5).

Table 4. **Requirements from the researcher at the time of application**

| Requirements | No. of international agencies | No. of national agencies |
|---|---|---|
| Partner with decision-makers | 7/9 | 8/14 |
| Provide knowledge translation plan | 3/9 | 10/14 |
| State policy relevance | 4/9 | 8/14 |
| Define knowledge translation target audience | 3/9 | 8/14 |
| Provide lay summary proposal | 3/9 | 3/14 |

## Agency initiatives

The agencies used five general strategies to support knowledge translation. These were classified as push, pull, linkage/exchange, communication and funding opportunities.

Funding mechanisms to promote knowledge translation included funding teams (including research users); funding conferences of researchers and research users; knowledge translation requests for applications; funding special centres and chairs for knowledge translation; and seeking commercialization opportunities (Table 6).

Twenty-two of 23 agencies described active involvement in communication activities such as communication to different audiences through web sites and paper journals (Table 6). These included development of audience-tailored web pages such as the South Africa Medical Research Council's AfroAIDS web site (available at: http://www.AfroAIDSinfo.org), lay summaries and use of media.

Linkage/exchange activities were described by 22 of 23 agencies, and included activities such as consulting stakeholders to set the research agenda, creating networks and programmes for decision-makers (Table 6). For example, the Indian Council of Medical Research funded partnerships with the private sector to improve access and availability of drugs for diseases of poverty, such as typhoid and measles vaccines.[21]

Half the agencies described some type of pull activity to increase skills of policy-makers to use research or increase their involvement in setting the research agenda, and fewer of these activities were described by each agency than the push and linkage/exchange types. These activities included tools development, programmes for decision-makers and workshops for decision-makers. For example, the Philippines Council for Health Research and Development described hosting research forums to expose decision-makers to research evaluation and critical appraisal.

The research team selected seven examples of innovative techniques ("gems") based on how they illustrate the diversity of ways in which funding agencies are engaging in knowledge translation (Table 7).

## Equity

Nine agencies described poverty reduction or improved health equity as part of their main focus. Examples of equity-focused knowledge translation activities by funding agencies included: the WHO/TDR (Department of Research and Training in Tropical Diseases) programme to eliminate leprosy, the investment in schistosomiasis research in Brazil by FAPESP (Foundation for Research Support of the State of São Paulo), support of higher education for women and girls by USAID (United States Agency for International Development), and the destigmatization of groups at high-risk for HIV/AIDS sponsored by CIDA (Canadian International Development Agency).

## Evaluation of agency activities

Thirteen agencies described evaluation tools to assess whether projects met their expectations. Eight agencies reported that they had an evaluation framework for knowledge translation activities. Tools used to evaluate the impact of knowledge translation activities were: (1) client/user surveys to assess how knowledge was used in practice and policy, and which products were most effective and useful; (2) visits to web sites; (3) number of telephone or e-mail queries on an information system; (4) requests for information from research users; and (5) outcome mapping.[22]

"There was a study..., [which showed that] only about 15% [of research funded by our agency] has been translated, meaning actually utilized into something – commercialized, adopted ... really utilized."

## Target audience

All funding agencies described several target audiences. The most commonly described target audience was decision-makers (16 agencies) and academics (12 agencies), followed by hospital managers (10 agencies), practitioners (10 agencies), other researchers (9 agencies), industry (9 agencies), researcher funders (8 agencies), general public (7 agencies), health-care professional organizations (7 agencies), media (6 agencies) and consumer organizations (3 agencies).

Table 5. **Budget allowances related to knowledge translation**

| Budget allowances | No. of international agencies | No. of national agencies |
|---|---|---|
| Dissemination | 3/9 | 7/14 |
| Workshops | 1/9 | 8/14 |
| Publication | 1/9 | 7/14 |
| Translation | 2/9 | 4/14 |
| Web development | 1/9 | 1/14 |

### National versus international funding agencies

In this sample, the national agencies engaged in more knowledge translation activities than their international counterparts across all categories. For example, more national agencies required researchers to provide a knowledge translation plan (10/14 versus 3/9), identify a target audience (8/14 versus 3/9) and provided a budget for workshops (8/14 versus 1/9). More national agencies reported issuing requests for applications on knowledge translation using the media (13/14 versus 4/9) and stakeholder consultation (13/14 versus 6/9). The World Bank in the Philippines was a notable exception to other international funding agencies, as it had strong knowledge translation activities globally.

Table 6. **Agency initiatives**

| Initiatives | No. of international agencies | No. of national agencies |
|---|---|---|
| **Push** | | |
| Use of media | 4/9 | 13/14 |
| Lay summaries on web site | 6/9 | 5/14 |
| Use of drama | 0/9 | 3/14 |
| **Pull** | | |
| Development of tools | 3/9 | 5/14 |
| Programmes for decision-makers | 3/9 | 5/14 |
| **Linkage/exchange** | | |
| Linkage/exchange | 9/9 | 13/14 |
| Consult stakeholders to set research agenda | 6/9 | 13/14 |
| Create/fund networks | 7/9 | 8/14 |
| Meta-linkage | 3/9 | 5/14 |
| Organize video conferences | 1/9 | 2/14 |
| **Communication** | | |
| Audience-tailored publications | 9/9 | 13/14 |
| Audience-tailored web pages | 8/9 | 7/14 |
| Produce/fund journals | 3/9 | 9/14 |
| **Funding opportunities** | | |
| Fund targeted workshops | 7/9 | 11/14 |
| Fund conference grants | 4/9 | 10/14 |
| Fund teams of investigators | 6/9 | 7/14 |
| Fund knowledge translation requests for applications | 2/9 | 7/14 |
| Fund knowledge translation centres | 3/9 | 6/14 |
| Fund chairs | 2/9 | 1/14 |
| Other funding opportunities | 2/9 | 1/14 |

## Discussion

This was a descriptive, exploratory study which identified substantial interest in knowledge translation of research results by both national and international funding agencies that support research in LMICs. We generated four hypotheses useful to studying the role of funding agencies in knowledge translation. First, national funding agencies in this sample demonstrated a greater commitment to knowledge translation activities than international funding agencies. Second, adoption of a systematic framework to knowledge translation might contribute to conceptual clarity in this field. Third, knowledge translation frameworks need to be modified to capture activities by funding agencies. Fourth, funding agencies are moving away from traditional methods of disseminating results and are being creative about reaching relevant audiences.

These findings suggest that national agencies may be more motivated to engage in knowledge translation activities than international funding agencies (with the exception of the World Bank in the Philippines). These findings lend credence to the perception that international funding agencies may not be well connected to realities on the ground at country-level. Furthermore, these findings support the focus on increasing funding for national health research within countries, as recommended by the Commission on Health Research for Development in 1990 (Karolinska Institute, Sweden). However, since international funding agencies still support over 90% of research in some low-income countries,[16] their lack of focus on knowledge translation is worrisome. Encouragingly, there was interest in all international funding agencies to increase their knowledge translation activities in the next five years.

A common terminology for knowledge translation could be useful in better defining both existing and planned funding agency activities. We found different definitions and understanding of knowledge translation both within and between agencies (Table 3). The different terminologies reflect differences in the mandates of these organizations but also suggest a lack of conceptual clarity around knowledge translation.

We found a lack of consideration in determining which evidence required translation and the need for tailored approaches for different audiences. Despite the relatively incomplete evidence-base on the effectiveness of different knowledge translation strategies, there is evidence to support the use of audience-specific strategies (e.g. consumers, practitioners, policy-makers) to address audience-specific barriers and facilitators.[23–25] Furthermore, there are convincing arguments that knowledge transfer should be based on rigorous meta-analysis of systematic reviews based on all available studies rather than single studies, because systematic reviews increase confidence in results, reduce the chances of being misled and efficiently summarize all published literature.[26] Adoption of a systematic framework to knowledge translation would contribute to conceptual clarity in this field. For example, the five step approach to knowledge transfer, described by Lavis, provides a framework to assess what should be transferred, to whom, by whom, how and with what effect.[24]

Table 7. **Examples of innovative and promising knowledge translation activities ("gems")**

| Agency | "Gem" activity | Category | Description |
|---|---|---|---|
| DFID | Increase incentives for researchers to engage in knowledge translation by addressing rules for university rankings that are based on publications | Push | Working with the Offices of Science and Technology in the United Kingdom to change the higher education funding system to increase recognition for knowledge translation by modifying the research assessment exercise (which rates universities according to what they publish in high-tech and high level journals) |
| Colciencias | Cartoons for children on television with important research findings | Communication | Five-minute cartoons describing research results to children are produced by the agency along with the researchers involved; these cartoons are broadcast through a large private national television network twice a week (Saturday and Sunday) in schedules appropriate for children; 25 programmes were produced during the first season |
| IDRC | Small grants available to move research into practice | Funding opportunities | "Windows of Opportunity" small grants available for teams to move research further into practice in specific environment |
| FAPESP | Private sector and public partnerships for technology transfer | Linkage/exchange | In Brazil, partnerships between private enterprises and public agencies for funding basic research and developing technology based on that locally-conducted basic science |
| Department of Health, Philippines | Creation of a knowledge translation bureau | Linkage/exchange | The Health Policy Development and Planning Bureau was created with a mandate to link research and policy |
| World Bank-Philippines | Call for proposals addressed to the general public in the Filipino language | Funding opportunities | In the Philippines, requests for proposals are usually written in English and addressed to researchers |
| ICMR-India | Establishing partnerships for improving the availability and access and decreasing cost of drugs needed for diseases of poverty | Linkage/exchange | E.g. TDR and Asta Medical (Germany) for a microbicide; WHO and Smith Kline Beecham for filariasis elimination strategy |

Colciencias, Instituto Colombiano para el Desarrollo de la Ciencia y la Tecnología; DFID, Department for International Development (the United Kingdom); FAPESP, State of São Paulo Research Foundation; ICMR, Indian Council of Medical Research; IDRC, International Development Research Centre.

We found that the Lavis framework of push, pull and linkage/exchange was a useful tool to categorize knowledge translation activities. However, we found that these three categories alone did not capture all of the activities of funding agencies, therefore we added two codes for general activities by funding agencies: communication and funding opportunities. These five categories represented mutually exclusive codes that provided a useful basis for classifying activities. In our analysis of the discrepancies in coding between country teams and the Ottawa team, we found the greatest differences in interpretation between the push and communication categories. Our category of push was intended to capture activities that focused on researchers summarizing the actionable messages based on their research, going beyond traditional publications or reports to stating the policy relevance of their research findings.

We found several creative and innovative strategies such as the "gems" in Table 7. These creative strategies show that funding agencies are moving away from traditional methods of disseminating results.

Ability to evaluate the impact of knowledge translation strategies was lacking in all agencies. Lack of evaluation frameworks limit the ability to show whether knowledge translation efforts indeed enhance research-related policy, services (health and intersectoral) and societal impacts.[27]

Knowledge translation is a complex process which can enhance the health of disadvantaged populations, by improving access, diagnostic accuracy, compliance and adherence of effective services.[3,13] We found a commitment to enhancing health of disadvantaged populations by one-third of funding agencies. We also found examples of knowledge translation activities that were focused on enhancing the health of the disadvantaged, such as the WHO/TDR programme to eliminate leprosy. Increased focus is needed to ensure that knowledge translation activities benefit the most disadvantaged populations.

An increasing number of organizations internationally are dedicated to knowledge translation. The activities of these organizations were not captured by our study, such as the WHO/PAHO EVIPNet), the Overseas Development Institute's RAPID programme and the Getting Research into Policy and Practice (GRIPP) initiative. These international initiatives represent an exciting opportunity to explore the effectiveness of different knowledge translation strategies.

Our results may overestimate the amount of knowledge translation activities since any activity (no matter how small) was scored as a "yes". We only interviewed three people from each agency so we may not have cap-

tured all knowledge translation activities. However, we tried to ensure interviewees represented a senior policymaker, someone responsible for knowledge translation and a project officer. Three funding agencies interviewed for this study did not consider knowledge translation a main part of their mandate. This data was collected between September 2003 and September 2004, before the Ministerial Summit on Health Research convened by WHO in Mexico. Advocacy for knowledge translation has increased since the Summit, but it remains to be seen if funding agencies have actually shifted significant resources to this important area. This study provides a useful scan of the activities of these 23 agencies and the types of activities in which they are engaging.

Because this is a qualitative research study that used a judgement sample, we focused less on external validity and more on maximizing internal validity. Therefore, these results apply to the sample of funding agencies selected and included in this study and are not intended to be generalized to other funding agencies.

## Conclusion

Previous research on knowledge translation has mostly ignored the role of funding agencies. This descriptive study shows an encouraging support for knowledge translation by national funding agencies, with a lag in support from international funding agencies. Funding agencies need to agree on a common terminology, consider the need for approaches tailored to specific audiences and identify their niche roles in knowledge translation, which may differ according to their defined mandates. Funding agencies might consider their role as knowledge brokers, by fostering and encouraging interactions between researchers and relevant stakeholders. As knowledge brokers, funding agencies could promote research syntheses and a focus on health equity. There is an urgent need to evaluate these funding agency knowledge translation activities to learn what works, why and in what context, in order to better justify spending on knowledge translation and to improve performance. ■

**Funding:** Peter Tugwell is supported by a Canada Research Chair in Health Equity. Jeremy Grimshaw is supported by a Canada Research Chair in Knowledge Translation. Visanu Thamlikitkul is supported by The Thailand Research Fund. Vivian Welch is supported by a Canadian Institutes of Health Research doctoral scholarship.

**Competing interests:** None declared.

## Résumé

### Aide à la transposition dans la pratique des connaissances par les agences de financement des pays à revenu faible ou moyen

**Objectif** Décrire comment certaines agences, qui financent la recherche en santé dans des pays à revenu faible ou moyen, favorisent la transposition sous forme politique et pratique des recherches financées.

**Méthodes** Nous avons réalisé une analyse inductive d'entretiens semi-structurés menés avec des informateurs clés d'un échantillon choisi à dessein de 23 agences nationales et internationales, qui financent des recherches en Afrique du Sud, au Brésil, en Colombie, en Inde, aux Philippines, et en Thaïlande. Nous avons également effectué une enquête sur des sites Internet.

**Résultats** Nous avons relevé un engament à transposer les connaissances en pratique dans le mandat de 18 des 23 agences de l'échantillon. Cependant, la terminologie utilisée était peu homogène. La plupart des activités mentionnées sont des efforts classiques de diffusion auprès d'une large audience, par le biais par exemple de sites Internet ou de publications. En outre, plus de la moitié des agences (13 sur 23) encouragent les liens et les échanges entre chercheurs et utilisateurs potentiels et 6 agences sur 23 décrivent des activités de type « pull » pour intéresser les décideurs aux travaux de recherche. Un tiers des agences (9 sur 23) indiquent dans leur mandat vouloir améliorer l'équité en matière de santé par une meilleure transposition dans la pratique des connaissances. Seules 3 des 23 agences sont en mesure de mentionner une évaluation des activités de transposition en pratique des connaissances. Nous avons en outre constaté que les agences de financement nationales faisaient de plus grands efforts pour assurer cette transposition que les agences internationales.

**Conclusion** Les agences de financement ont entrepris des activités très diverses de transposition en pratique des connaissances. Elles peuvent se considérer comme ayant un rôle de courtier en connaissances et comme ayant la capacité de promouvoir une synthèse des recherches et une convergence de l'attention sur l'équité en termes de santé. Il est urgent d'évaluer les activités de transposition en pratique des connaissances menées par les agences de financement.

## Resumen

### Organismos de financiación en países de ingresos bajos y medios: apoyo a la traslación de conocimientos

**Objetivo** Describir cómo algunos organismos de financiación de investigaciones sanitarias que operan en países de ingresos bajos y medios promueven la traslación de las investigaciones que financian en políticas y prácticas.

**Métodos** Realizamos análisis inductivos de entrevistas semiestructuradas con informantes clave a partir de una muestra intencionada de 23 organismos nacionales e internacionales que financian investigaciones sanitarias en el Brasil, Colombia, la India, Filipinas, Sudáfrica y Tailandia. También sondeamos diversos sitios web.

**Resultados** Detectamos muestras de compromiso en favor de la traslación de conocimientos en el mandato de 18 de 23

organismos. Sin embargo, no había una terminología común. La mayoría de las actividades consistían en las iniciativas tradicionales de difusión de información entre un público amplio, por ejemplo a través de sitios web y publicaciones. Además, más de la mitad (13 de 23) de los organismos fomentaban el establecimiento de vínculos y el intercambio entre los investigadores y los usuarios potenciales, y 6 de los 23 organismos describieron actividades de «atracción» para generar interés por las investigaciones entre los decisores. La tercera parte (9 de 23) de los organismos de financiación tenían encomendado el fomento de la equidad sanitaria mediante la mejora de la traslación de conocimientos. Sólo 3 de los 23 organismos podían hacer una evaluación posterior de sus actividades de traslación de conocimientos. Además, observamos que los organismos de financiación nacionales hacían un mayor esfuerzo de traslación de conocimientos que los organismos internacionales.

**Conclusión** Los organismos de financiación participan en una amplia gama de actividades creativas de traslación de conocimientos y podrían tal vez estudiar su papel como intermediarios en ese ámbito, facultados para promover síntesis de investigaciones y un mayor énfasis en la equidad sanitaria. Es necesario evaluar urgentemente las actividades de traslación de conocimientos de los organismos de financiación.

## ملخص

### وكالات تمويل البحوث الصحية في البلدان المنخفضة والمتوسطة الدخل، ودورها في دعم ترجمة المعارف إلى سياسات وممارسات

**الغرض:** استهدفت هذه الدراسة بيان إلى أي مدى تقوم بعض الوكالات الممولة للبحوث الصحية، العاملة في البلدان ذات الدخل المنخفض والدخل المتوسط، بتعزيز ترجمة نتائج البحوث التي تمولها إلى سياسات وممارسات.

**الطريقة:** أجرى الباحثون تحليلاً استقرائياً لنتائج مقابلات شبه منظمة مع مقدمي المعلومات الرئيسيين في عينة قوامها 23 وكالة اختيرت عن قصد من بين الوكالات الوطنية والدولية الممولة للبحوث الصحية في البرازيل، وكولومبيا، والهند، والفلبين، وجنوب أفريقيا، وتايلاند. كما أجرى الباحثون مسحاً لمواقع الإنترنت.

**الموجودات:** لاحظ الباحثون التزاماً بترجمة المعارف إلى سياسات وممارسات في اختصاصات 18 وكالة من الـ 23 وكالة. ولكن لوحظت قلة في المصطلحات المشتركة في اختصاصات هذه الوكالات. وكانت معظم الأنشطة مجرد جهود تقليدية لبث المعارف إلى الجمهور العام، باستخدام المنشورات ومواقع الإنترنت، على سبيل المثال. كما لوحظ أن أكثر من نصف الوكالات (13 من 23 وكالة) تشجع التواصل أو تبادل المعلومات بين الباحثين والمستخدمين المحتملين للمعارف، وأن 6 من 23 وكالة قدّمت تصوراً لبعض الأنشطة التي تولد الاهتمام بالبحوث لدى متخذي القرار. ولوحظ أن ثلث العينة (9 من 23 وكالة) قدمت تصوراً للاختصاصات التي تكفل تحسين مظاهر المساواة في الصحة، من خلال تحسين ترجمة المعارف إلى سياسات وممارسات. وقد نجحت 3 وكالات فقط من 23 وكالة في وضع تصور لعملية تقييم أنشطة ترجمة المعارف. كما لاحظ الباحثون أن وكالات التمويل الوطنية تبذل جهوداً أكبر في ترجمة المعارف، بالمقارنة مع الوكالات الدولية.

**الاستنتاج:** تشارك وكالات التمويل في طيف عريض من الأنشطة المبتكرة لترجمة المعارف. وترى هذه الوكالات أن دورها هو دور وسيط للمعارف، لديه القدرة على تعزيز عملية تجميع البحوث، ويركز على تحقيق المساواة في الصحة. وخلُصَت الدراسة إلى وجود حاجة عاجلة إلى تقييم أنشطة وكالات التمويل في ترجمة المعارف إلى سياسات وممارسات.

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*Journal of Antimicrobial Chemotherapy*
doi:10.1093/jac/dkm488
Advance Access publication 19 December 2007

## *In vitro* activity of ceftobiprole against *Burkholderia pseudomallei*

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Keywords: *B. pseudomallei*, melioidosis, cephalosporins

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Sir,

*Burkholderia pseudomallei*, a Gram-negative bacterium, causes a disease called melioidosis in humans and animals.[1] The bacterium is a soil organism found mainly in Southeast Asia and Northern Australia. Antibiotics currently recommended for therapy of melioidosis are ceftazidime, imipenem, meropenem, amoxicillin/clavulanate, trimethoprim/sulfamethoxazole, doxycycline and chloramphenicol.[1] A development of resistance of *B. pseudomallei* to the aforementioned antibiotics has been recognized;[2,3] hence, a search for new agents effective against *B. pseudomallei* is needed.

Ceftobiprole is a novel parenteral cephalosporin whose broad spectrum of activity includes most clinically important Gram-positive and Gram-negative bacteria.[4]

One hundred and fifteen strains of ceftazidime-susceptible *B. pseudomallei* from different infected patients were selected from our collection. All strains were identified as *B. pseudomallei* by API 20NE (bioMérieux, France). *In vitro* susceptibility was determined by Kirby-Bauer disc diffusion for all 115 strains and Etest for 5 randomly chosen strains. Paper discs containing 30 μg ceftobiprole per disc (MASTDISC) and Etest strips of ceftobiprole at concentrations of 0.016–256 mg/L were provided by Janssen-Cilag (Thailand). The disc diffusion test was repeated for six strains of *B. pseudomallei* in order to determine the reproducibility of the test. The methodology for susceptibility testing was performed by direct colony suspension according to guidelines suggested by the CLSI.[5] Quality control was performed by testing susceptibility of *Pseudomonas aeruginosa* ATCC 27853. The proposed breakpoints for inhibition zone diameters of ceftobiprole are $\geq$20 mm for susceptible, 17–19 mm for intermediate and $\leq$16 mm for resistant. The proposed breakpoints for MICs of ceftobiprole are $\leq$4 mg/L for susceptible, 8 mg/L for intermediate and $\geq$16 mg/L for resistant.

The inhibition zone diameter of ceftobiprole against *P. aeruginosa* ATCC 27853 was within the reference limits. The distribution of inhibition zone diameters of ceftobiprole against *B. pseudomallei* is shown in Table 1. Inhibition zone diameters of $\geq$20, 17–19 and $\leq$16 mm were observed in 46 (40%), 55 (47.8%) and 14 (12.2%) strains, respectively. Four strains of *B. pseudomallei* with inhibition zone diameters of 15–19 mm on the initial disc diffusion test had identical inhibition zone diameters on the second test. Another two strains with an inhibition zone diameter of >20 mm had 1 mm difference in inhibition zone diameter on the second test, but the inhibition zone diameters from both tests were still within susceptible values. Four *B. pseudomallei* strains with an inhibition zone diameter of 17–19 mm had MICs of ceftobiprole of 6–8 mg/L, whereas a strain with an inhibition zone diameter of 16 mm had an MIC of 16 mg/L.

Our findings indicate that the *in vitro* activity of ceftobiprole against *B. pseudomallei* determined by Kirby-Bauer disc diffusion is reproducible and correlates with that determined by Etest. Ceftobiprole has less *in vitro* activity than ceftazidime against *B. pseudomallei*, and only 40% of *B. pseudomallei* strains are susceptible to ceftobiprole.

## Acknowledgements

We thank Janssen-Cilag (Thailand) and The Thailand Research Fund for supporting the study.

## Funding

V. T. is a recipient of Senior Researcher Scholar of the Thailand Research Fund. Janssen-Cilag (Thailand) provided ceftobiprole susceptibility discs and Etest strips for this study.

## Transparency declarations

None to declare.

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**Table 1.** Distribution of ceftobiprole inhibition zone diameter for 115 strains of *B. pseudomallei*

| No. of strains (%) for which the inhibition zone diameter was | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 13 mm | 15 mm | 16 mm | 17 mm | 18 mm | 19 mm | 20 mm | 21 mm | 22 mm | 23 mm | 25 mm |
| 1 (0.9) | 5 (4.3) | 8 (7.0) | 25 (21.7) | 19 (16.5) | 11 (9.6) | 30 (26.1) | 7 (6.1) | 3 (2.6) | 4 (3.5) | 2 (1.7) |

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*Journal of Antimicrobial Chemotherapy*
doi:10.1093/jac/dkm501
Advance Access publication 21 December 2007

## Treatment of external ventricular drain-associated ventriculitis caused by *Enterococcus faecalis* with intraventricular daptomycin

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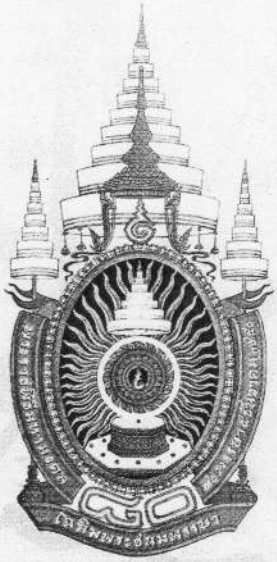
Sir,

External ventricular drains (EVDs) are essential monitoring devices in neurosurgery, and direct portals for the removal of cerebrospinal fluid (CSF), including the temporary control of raised intracranial pressure, and for the instillation of therapeutic agents. Their benefits must be balanced against the complications associated with their use, the most important of which is infection (ventriculitis). Most patients with EVD-associated ventriculitis can be cured by instilling antibiotics directly into the ventricles.[1] We describe here a patient with such an infection treated by administering daptomycin using this route.

A 62-year-old man was admitted to this hospital with a subarachnoid haemorrhage and underwent coil occlusion of an anterior communicating artery aneurysm. Four days later, he became confused and was noted to have raised intracranial pressure; a lumbar drain was inserted. He subsequently became pyrexial and culture of CSF obtained via the lumbar drain yielded *Klebsiella pneumoniae*. An EVD was inserted and the ventriculitis was successfully treated with a 14 day course of intravenous ceftazidime and intraventricular gentamicin. The intention was to remove the EVD on day 30. However, Gram's stain examination of a sample of CSF showed Gram-positive cocci, and *Enterococcus faecalis*, which was susceptible to ampicillin and vancomycin, but exhibited high-level resistance to gentamicin (MIC > 200 mg/L), was isolated. Vancomycin (10 mg) was instilled into the ventricles, but, after 8 days of therapy, *E. faecalis* was still recovered from the CSF. The MIC of daptomycin for this strain was 2.0 mg/L, as determined by an Etest on Mueller–Hinton agar, and this drug was administered intravenously at a dosage of 1 g (12 mg/kg) once daily. In addition, the EVD was removed and an Ommaya reservoir was implanted. Following a further 4 days of therapy with intraventricular vancomycin, *E. faecalis* was again recovered from the CSF. It was therefore decided to instil daptomycin into the ventricles at a dosage of 10 mg every third day; consent was obtained from the patient. Trough and peak daptomycin CSF concentrations (determined just before and 30 min after a dose, respectively, by high-performance liquid chromatography at the Department of Medical Microbiology, Southmead Hospital, Bristol, UK) were 23 and 483 mg/L, respectively. The dosage of daptomycin was reduced to 5 mg every third day, and trough and peak daptomycin CSF concentrations at the lower dosage were 9.9 and 139 mg/L, respectively. The CSF became sterile within 3 days of commencing intraventricular daptomycin and remained so throughout the 2 week treatment period. The patient remained well and he was eventually discharged from hospital. However, he was re-admitted 28 days later with symptoms and signs of meningitis. Culture of a sample of CSF yielded *E. faecalis* with the same antibiogram as the original isolate and treatment with intraventricular daptomycin at a dosage of 5 mg every third day was restarted. In addition, the Ommaya reservoir was replaced with an EVD. Daptomycin was administered for 4 weeks during which time he experienced transient pyrexias after each instillation of daptomycin; this side effect was resolved when the treatment was discontinued. The CSF became sterile, the EVD was removed and he was discharged from hospital 39 days after he had been re-admitted. Clinical and bacteriological cures were sustained after follow-up for more than 1 year.

EVD-associated ventriculitis is one of the most common infections in neurosurgical practice. Until recently, only three antibiotics have been available in formulations suitable for intraventricular use: vancomycin, gentamicin and colomycin. Enterococci are increasingly being recognized as causes of ventriculitis in neurosurgical patients, and some strains exhibit resistance to vancomycin or high-level resistance to the aminoglycosides, thereby limiting treatment options. Linezolid has been used successfully as systemic therapy in such cases.[2,3] However, this antibiotic is not bactericidal and prolonged courses increase the risks of adverse effects. Daptomycin is the first of a new class of antibiotics, the cyclic lipopeptides. It has been shown to be rapidly bactericidal against enterococci, including vancomycin-resistant strains.[4] Daptomycin penetrates poorly into the CSF compartment when given by the systemic route. In a rabbit model of meningitis caused by *Streptococcus pneumoniae*, only 5% of the corresponding serum concentration was achieved in the CSF, and the drug failed to sterilize the CSF after 4 days, despite the administration of a high dosage.[5] On the other hand, a study involving a rabbit model of *Staphylococcus aureus* ventriculitis demonstrated that intraventricular daptomycin achieved greater bactericidal activity, more rapid killing kinetics and a longer half-life in the ventricles than intraventricular vancomycin.[6] Many years' experience of managing patients with EVD-associated ventriculitis by instilling antibiotics into the ventricles encouraged us to treat the patient described in this report with intraventricular daptomycin. This present experience suggests that intraventricular daptomycin is an effective therapy of patients with EVD-associated ventriculitis caused by enterococci; it may be equally appropriate as treatment



# งานวิจัยพื้นฐาน
## ฐานรากของการพัฒนาประเทศ ตามปรัชญาเศรษฐกิจพอเพียง

## การวิจัยพื้นฐานเพื่อพัฒนาสุขภาพ

หนังสือเฉลิมพระเกียรติ
เนื่องในโอกาสมหามงคลเฉลิมพระชนมพรรษา ๘๐ พรรษา
๕ ธันวาคม ๒๕๕๐


สำนักงานกองทุนสนับสนุนการวิจัย (สกว.)

# 20

# การจัดการความรู้เพื่อพัฒนาบริการสุขภาพ

ศ.นพ. วิษณุ ธรรมลิขิตกุล

ผู้เขียนได้รับทุนเมธีวิจัยอาวุโสจากสำนักงานกองทุนสนับสนุนการวิจัยตั้งแต่ พ.ศ. 2544 - 2550 ในโครงการ 'Knowledge Management to Promote Evidence-Informed Healthcare Policy and Practice' บทความนี้นำเสนอแนวคิดและแนวทางสำคัญของการจัดการความรู้เพื่อพัฒนาบริการสุขภาพ และประสบการณ์การจัดการความรู้ด้านการรักษาและป้องกันโรคติดเชื้อ และด้านการรักษาโรคด้วยการแพทย์แผนไทย

## 20.1 แนวคิดและแนวทางสำคัญของการจัดการความรู้เพื่อพัฒนาบริการสุขภาพ

พันธกิจหลักของบุคลากรสาธารณสุขมี 3 ด้าน คือ การบริการ การสอน และการวิจัย พันธกิจทั้ง 3 ด้านนี้เชื่อมโยงกันด้วย 'ความรู้' กล่าวคือ การวิจัยเป็นการสร้างความรู้ การสอนเป็นการถ่ายทอดความรู้ และการบริการเป็นการใช้ความรู้ ดังนั้นบุคลากรสาธารณสุขผู้ทำวิจัยต้องตระหนักว่า เรื่องวิจัยต้องเกี่ยวข้องกับปัญหาสุขภาพของประเทศไทย และผลการวิจัยต้องเป็นความรู้ที่ถูกต้องซึ่งนำไปประยุกต์ใช้ในการกำหนดนโยบายสุขภาพและบริการสุขภาพ ซึ่งเป็นเป้าหมายสำคัญของการวิจัยได้ ส่วนบุคลากรสาธารณสุขผู้ให้บริการและสอน ต้องนำความรู้ที่ได้จากการวิจัยไปประยุกต์ใช้ เพื่อให้การบริการสุขภาพและการสอนเป็นการบริการสุขภาพและการสอนที่มีความรู้เป็นฐาน (Evidence-Based หรือ Knowledge-Based Healthcare Practice and Education)

ความรู้ด้านสุขภาพมี 3 ประเภท ได้แก่

1) ความรู้แจ้งชัด หรือความรู้ที่เป็นรูปธรรม (Explicit Knowledge) คือ ผลการวิจัยที่มีการวางแผนและการดำเนินการอย่างเหมาะสมที่เผยแพร่ทางสื่อต่างๆ โดยเฉพาะอย่างยิ่งวารสารการแพทย์ ความรู้ประเภทนี้เปรียบได้กับภูเขาน้ำแข็งส่วนที่โผล่พ้นน้ำ
2) ความรู้ฝังลึก หรือความรู้ซ่อนเร้น หรือความรู้ที่เป็นนามธรรม (Tacit Knowledge) คือ ความรู้ ทักษะ ความเชี่ยวชาญที่แฝงอยู่ในบุคคล มักไม่มีการถ่ายทอดเป็นเอกสาร เป็นความรู้ที่อยู่กับตัวบุคคล เป็นประสบการณ์ที่สะสมมานาน เป็นภูมิปัญญาเฉพาะถิ่น ความรู้ประเภทนี้เปรียบได้กับภูเขาน้ำแข็งส่วนที่อยู่ใต้น้ำใกล้กับผิวน้ำ
3) ความรู้ที่ยังค้นไม่พบ คือ ความจริงตามธรรมชาติที่รอให้มนุษย์ค้นให้พบ ความรู้ประเภทนี้เปรียบได้กับภูเขาน้ำแข็งที่อยู่ใต้น้ำเช่นกัน



การวิจัยไม่ใช่มาตรการสำคัญเพียงมาตรการเดียวในการแก้ไขปัญหาสุขภาพ เพราะปัญหาสุขภาพจำนวนมากมีความรู้สำหรับแก้ปัญหาสุขภาพเหล่านั้นอยู่แล้ว แต่การที่ปัญหาสุขภาพเหล่านั้นยังคงมีอยู่เนื่องจากยังไม่มีผู้นำความรู้ที่มีอยู่แล้วไปประยุกต์ใช้ ดังนั้นการนำความรู้ไปใช้ประโยชน์จึงมีความสำคัญไม่น้อยกว่าการวิจัย และการจัดสรรทรัพยากรด้านการวิจัยต้องคำนึงถึงการนำความรู้จากการวิจัยไปประยุกต์ใช้ด้วย องค์การที่สนับสนุนการวิจัยจำนวนมากได้ตระหนักถึงความสำคัญของการนำผลงานวิจัยไปใช้ประโยชน์และมีโครงการสนับสนุนการนำความรู้จากการวิจัยไปใช้ประโยชน์ด้วยนอกเหนือจากการสนับสนุนการวิจัย

ความรู้เป็นสมบัติสาธารณะที่เป็นผลจากการลงทุนวิจัยไปแล้วอย่างมากมาย หากนำความรู้เหล่านั้นมาใช้ประโยชน์ได้มาก ก็จะทำให้การวิจัยเป็นการลงทุนที่คุ้มค่ามากยิ่งขึ้น ความรู้จำนวนมากที่มีอยู่แล้วไม่ถูกนำมาใช้ในการกำหนดนโยบายสุขภาพและบริการสุขภาพ (Know-Do Gap) ในขณะที่นโยบายสุขภาพและบริการ

สุขภาพจำนวนมาก มิได้มีความรู้ที่ได้จากการวิจัยเป็นฐาน (Do-Know Gap) นอกจากนี้ การนำความรู้จากการวิจัยไปใช้ประโยชน์ต้องใช้เวลานานมาก มีรายงานว่าต้องใช้เวลาเฉลี่ย 17 ปีในการนำความรู้จากการวิจัยเพียงร้อยละ 13 ไปใช้ประโยชน์ในการกำหนดนโยบายสุขภาพและบริการสุขภาพ

การนำความรู้จากการวิจัยไปใช้ประโยชน์ ต้องมีระบบและวิธีการจัดการความรู้ (Knowledge Management) การจัดการความรู้มีกระบวนการและวิธีการแตกต่างกัน ขึ้นอยู่กับประเภทของความรู้ กล่าวคือ

การจัดการความรู้ประเภท Explicit Knowledge คือ การถ่ายทอดความรู้ หรือการนำความรู้ไปใช้กำหนดนโยบายสุขภาพและบริการสุขภาพ (Knowledge Translation หรือ Knowledge Implementation)

การจัดการความรู้ประเภท Tacit Knowledge คือ การถ่ายทอดความรู้ หากความรู้นั้นสามารถนำไปใช้ประโยชน์ได้แล้ว และการเปลี่ยนความรู้ประเภท Tacit Knowledge ให้เป็นความรู้ประเภท Explicit Knowledge (Knowledge Transformation) ก่อนการถ่ายทอดความรู้

การจัดการความรู้ประเภทที่ยังค้นไม่พบ คือ การวิจัย (Knowledge Generation) เพื่อให้ได้ความรู้ประเภท Explicit Knowledge ก่อนการถ่ายทอดความรู้

การจัดการความรู้ต้องอาศัยผู้จัดการความรู้ (Knowledge Manager หรือ Knowledge Convenor หรือ Knowledge Broker) ที่มีทักษะในการแปลงความรู้ที่ได้จากการวิจัยให้เป็นนโยบายสุขภาพ และวิธีบริการสุขภาพที่สามารถนำไปใช้ได้อย่างมีประสิทธิภาพและทั่วถึง และมีความสามารถในการประสานให้เกิดการวิจัยประเภท Practical Research หรือ Health Service Research หรือ Health Policy Research ซึ่งเป็นการวิจัยเพื่อแสวงหาความรู้ในการตอบคำถามที่เฉพาะของผู้บริหารและผู้ประกอบวิชาชีพเวชกรรม (Policy-Driven หรือ User-Driven Research) ได้ การมีผู้จัดการความรู้มีความจำเป็น เนื่องจากนักวิจัยส่วนมากไม่มีความพร้อมและไม่มีทักษะในการนำความรู้ที่ได้จากการวิจัยไปใช้ประโยชน์อย่างแท้จริง นอกเหนือจากการเผยแพร่ผลงานวิจัยทางสื่อต่างๆ นอกจากนี้ การนำความรู้ไปใช้ประโยชน์อาจต้องปรับความรู้ดังกล่าวให้เหมาะสมกับบริบทของชุมชนที่จะใช้ความรู้เหล่านั้นด้วย

กระบวนการจัดการความรู้จากประสบการณ์การจัดการความรู้ของผู้เขียน ได้แสดงไว้ในรูป 20.1 กระบวนการจัดการความรู้เริ่มต้นจากประเด็นสำคัญสองประเด็น ได้แก่

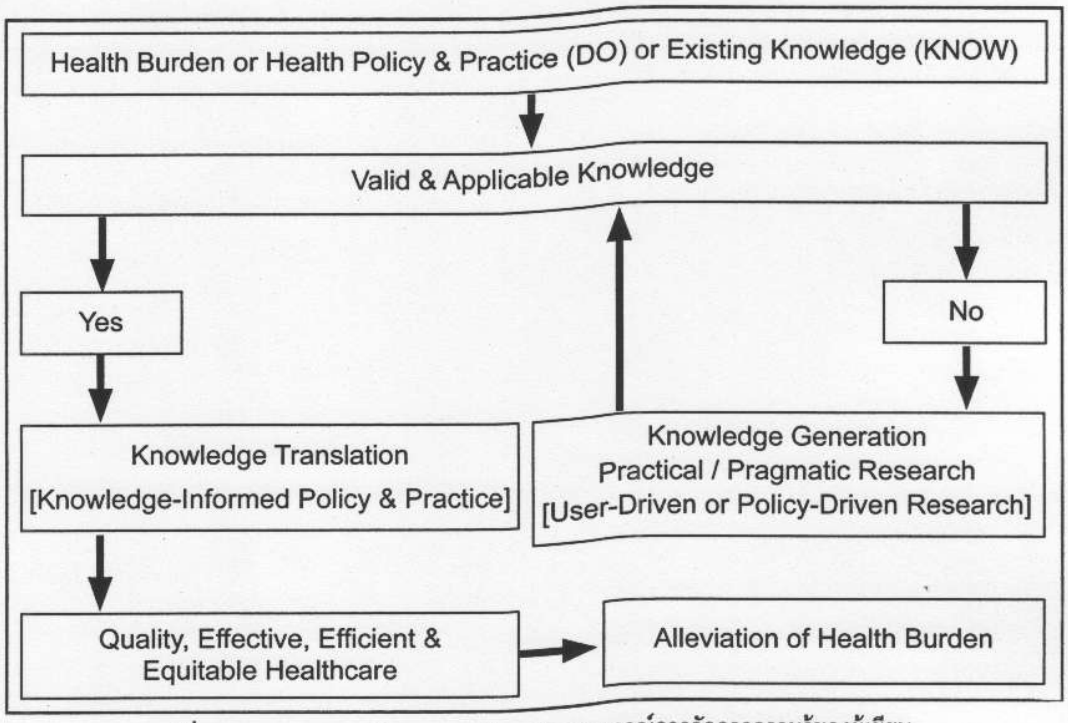
ก. หากเริ่มต้นจากปัญหาสุขภาพ หรือนโยบายสุขภาพ หรือบริการสุขภาพที่ปฏิบัติอยู่ ก็สืบค้นความรู้ที่มีอยู่แล้ว หากการสืบค้นพบว่ายังไม่มีความรู้ หรือความรู้ที่มีอยู่ยังไม่ถูกต้อง หรือความรู้ที่มีอยู่ยังนำไปใช้ไม่ได้ ก็จัดให้มีการวิจัยจนได้ความรู้ที่ถูกต้องและนำไปใช้ได้ ก่อนนำความรู้นั้นไปใช้ หากการสืบค้นพบว่ามีความรู้ที่ถูกต้องและนำมาใช้ได้ ก็ดำเนินการนำความรู้นั้นมากำหนดเป็นนโยบายสุขภาพและวิธีบริการสุขภาพ เพื่อเผยแพร่ไปสู่ผู้ประกอบวิชาชีพเวชกรรมกลุ่มเป้าหมาย แล้วประเมินปัญหาสุขภาพ หรือนโยบายสุขภาพ หรือบริการสุขภาพที่ปฏิบัติอยู่ซ้ำ

ข. หากเริ่มต้นจากความรู้ที่มีอยู่แล้ว ก็ประเมินความรู้ดังกล่าว หากประเมินแล้วพบว่าความรู้ที่มีอยู่ยังไม่ถูกต้อง หรือความรู้ที่มีอยู่ยังนำไปใช้ไม่ได้ ก็จัดให้มีการวิจัยจนได้ความรู้ที่ถูกต้องและนำไปใช้ได้ ก่อนนำความรู้นั้นไปใช้ หากประเมินแล้วพบว่าความรู้ดังกล่าวถูกต้องและนำมาใช้ได้ ก็ดำเนินการนำความรู้นั้นมากำหนดเป็นนโยบายสุขภาพและวิธีบริการสุขภาพเพื่อเผยแพร่ไปสู่ผู้ประกอบวิชาชีพเวชกรรมกลุ่มเป้าหมาย แล้วประเมินปัญหาสุขภาพ หรือนโยบายสุขภาพ หรือบริการสุขภาพที่ปฏิบัติอยู่ซ้ำ

ดังนั้น กระบวนการจัดการความรู้ดังกล่าวข้างต้นล้วนเป็นการวิจัยทั้งสิ้น การวิจัยเพื่อให้ได้ความรู้ใหม่ที่ถูกต้องและนำไปใช้ได้ คือ การวิจัยในบริบททั่วไป (Knowledge Generation) ส่วนการนำความรู้ที่ถูกต้องและ

ประยุกต์ใช้ได้มากำหนดเป็นนโยบายสุขภาพและวิธีบริการสุขภาพ เพื่อเผยแพร่ไปสู่ผู้ประกอบวิชาชีพเวชกรรม กลุ่มเป้าหมาย แล้วประเมินปัญหาสุขภาพ หรือนโยบายสุขภาพ หรือบริการสุขภาพที่ปฏิบัติอยู่ซ้ำ ก็เป็นการวิจัยประเภท Knowledge Implementation หรือ Health Service Research

การจัดการความรู้ด้วยกระบวนดังกล่าวข้างต้น จะได้ผลลัพธ์คือ มีบริการสุขภาพที่ปลอดภัย มีประสิทธิผล มีคุณภาพ มีความคุ้มค่า และมีความเป็นธรรม อันเป็นการแก้ไขปัญหาสุขภาพของผู้รับบริการรายบุคคล และลดขนาดของปัญหาสุขภาพได้ในภาพรวม




**รูปที่ 20.1:** กระบวนการจัดการความรู้จากประสบการณ์การจัดการความรู้ของผู้เขียน

## 20.2 การจัดการความรู้เพื่อพัฒนาการรักษาและการป้องกันโรคติดเชื้อ

ผู้เชี่ยวชาญด้านโรคติดเชื้อส่วนหนึ่งเชื่อว่า มนุษย์จะควบคุมหรือกำจัดโรคติดเชื้อให้หมดไป และโรคติดเชื้อจะไม่เป็นปัญหาสุขภาพที่สำคัญอีกต่อไปเมื่อเริ่มมียาต้านจุลชีพและวัคซีนเมื่อ 40 ปีก่อน แต่การณ์กลับมิได้เป็นเช่นนั้น เพราะนอกจากโรคติดเชื้อไม่หมดไปแล้ว โรคติดเชื้อยังคงเป็นปัญหาสุขภาพที่สำคัญและเพิ่มมากขึ้นอย่างต่อเนื่อง โรคติดเชื้อมี Disability-Adjusted Life-Years (DALYs) ประมาณร้อยละ 30 ทั่วโลก และโรคติดเชื้อมี DALYs ประมาณร้อยละ 25 ในประเทศไทย ปัจจัยสำคัญที่ทำให้โรคติดเชื้อยังคงเป็นปัญหาสุขภาพที่สำคัญ และเพิ่มมากขึ้นอย่างต่อเนื่อง คือ มีโรคติดเชื้ออุบัติใหม่ (Emerging infectious diseases) และโรคติดเชื้ออุบัติซ้ำ (Re-emerging infectious diseases) อย่างต่อเนื่อง (เช่น โรคติดเชื้อ Human Immunodeficiency Virus, HIV, Severe Acute Respiratory Syndrome, SARS, Avian Influenza) โรคที่เดิมเชื่อว่าไม่ใช่โรคติดเชื้อก็กลับเป็นโรคติดเชื้อ (เช่น โรคแผลที่กระเพาะอาหาร มะเร็งปากมดลูก) โรคติดเชื้อที่เกิดจากเชื้อดื้อยาต้านจุลชีพ (เช่น Methicillin-resistant S. *aureus*, MRSA, Multidrug-resistant *M. tuberculosis*) โรคติดเชื้อที่

สัมพันธ์กับการดูแลรักษาผู้ป่วยโดยบุคลากรการแพทย์ (เช่น การติดเชื้อในโรงพยาบาล การติดเชื้อที่สัมพันธ์กับภาวะภูมิต้านทานบกพร่องจากการรักษาด้วยยากดภูมิต้านทานหรือมีของแปลกปลอมในร่างกาย)

ผู้เขียนได้ใช้กระบวนการจัดการความรู้ดังแสดงในรูป 20.1 เพื่อพัฒนาการรักษาโรคติดเชื้อที่เกิดจากแบคทีเรียดื้อยาต้านจุลชีพ และการป้องกันโรคติดเชื้อในโรงพยาบาล ดังนี้

### 20.2.1 การรักษาโรคติดเชื้อที่เกิดจากแบคทีเรียดื้อยาต้านจุลชีพ

โรคติดเชื้อจากแบคทีเรียดื้อยาต้านจุลชีพที่สำคัญในประเทศไทย ได้แก่ Drug-resistant *Streptococcus pneumoniae*, methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum beta-Lactamase (ESBL)-producing *E. coli & Klebsiella pneumoniae*, multidrug-resistant *Pseudomonas aeruginosa*, multidrug-resistant *Acinetobacter baumannii*

#### *1) การรักษาโรคติดเชื้อจากแบคทีเรียดื้อยาต้านจุลชีพด้วย Colistin*

ความชุกของ *A. baumannii* ดื้อยาต้านจุลชีพทุกขนานทั้ง Beta-Lactams, Aminoglycosides และ Fluoroquinolones ในโรงพยาบาลศิริราชเพิ่มจากร้อยละ 4 เมื่อ พ.ศ. 2541 เป็นร้อยละ 57 ใน พ.ศ. 2546 ผู้ป่วยเหล่านี้มักได้รับการรักษาด้วยยาต้านจุลชีพหลายขนานร่วมกัน (เช่น Meropenem ร่วมกับ Netilmicin ร่วมกับ Cefoperazone/ Sulbactam) โดยมีค่าใช้จ่ายเฉพาะยาต้านจุลชีพประมาณวันละ 6,000 บาท ผู้ป่วยที่ติดเชื้อดื้อยาคังกล่าวเสียชีวิตร้อยละ 80 ผู้เขียนได้ศึกษาและทราบว่าปัจจัยเสี่ยงของการติดเชื้อดื้อยา คือ การมีสายหรือท่อต่างๆ ในร่างกาย และการได้รับยาต้านจุลชีพมาก่อน ซึ่งปัจจัยเหล่านี้มักแก้ไขไม่ได้ เพราะผู้ป่วยเหล่านี้เจ็บป่วยรุนแรงและจำเป็นต้องได้รับการรักษาดังกล่าว

ผู้เขียนได้สืบค้นวิธีรักษาโรคติดเชื้อดื้อยาดังกล่าวพบว่ายากลุ่ม Polymyxins (Polymyxin B และ Colistin) ซึ่งเป็นยาต้านจุลชีพเก่าตั้งแต่ พ.ศ. 2490 แต่หยุดใช้ไปเนื่องจากมีพิษและมียาขนานอื่นทดแทนได้ ถูกนำกลับมาใช้รักษาการติดเชื้อดื้อยานี้ได้ผลปานกลาง ผู้เขียนจึงทดสอบฤทธิ์ของยา Polymyxin B และ Colistin ต่อเชื้อ *P. aeruginosa* และ *A. baumannii* ที่ดื้อยาต้านจุลชีพทุกขนานซึ่งแยกได้จากผู้ป่วยที่รับไว้รักษาที่โรงพยาบาลศิริราชเชื้อละ 100 สายพันธุ์พบว่า เชื้อทุกสายพันธุ์ไวต่อ Polymyxin B และ Colistin แต่ยาทั้งสองขนานไม่มีจำหน่ายในประเทศไทย หากมีผู้ป่วยติดเชื้อดังกล่าวและรับผิดชอบค่ายาได้ ผู้ป่วยต้องไปซื้อยาจากต่างประเทศซึ่งมีค่าใช้จ่ายสูงมาก และไม่เป็นธรรมกับผู้ป่วยที่ไม่สามารถรับผิดชอบค่าใช้จ่ายได้ ผู้เขียนได้ติดต่อกับบริษัทยาให้นำยาดังกล่าวมาจำหน่ายในประเทศไทย แต่ไม่มีบริษัทใดประสงค์จะนำยาดังกล่าวมาจำหน่ายในประเทศไทย

ผู้เขียนได้ทบทวนตำรับยาของสำนักงานคณะกรรมการอาหารและยา กระทรวงสาธารณสุขพบว่าบริษัทแอคแลนติคเคยผลิตยา Colistin ชนิดรับประทาน และชนิดฉีดซึ่งมียาชา Dibucaine เป็นส่วนผสมอยู่ด้วยเมื่อ 30 ปีก่อน แต่ได้เลิกผลิตนานแล้ว ผู้เขียนจึงติดต่อบริษัทแอคแลนติคและชี้แจงความจำเป็นของยาดังกล่าวให้ผู้เกี่ยวข้องทราบ ซึ่งบริษัทแอคแลนติคก็ได้ผลิตยา Colistin อีกครั้ง แต่ยานี้ต้องขึ้นทะเบียนใหม่กับสำนักงานคณะกรรมการอาหารและยา กระทรวงสาธารณสุข เพราะต้องเปลี่ยนสูตรตำรับเป็นยา Colistin เดี่ยว เนื่องจากยาชาที่เป็นส่วนผสมด้วยนั้นเป็นยาที่ไม่ปลอดภัย ผู้เขียนได้ประสานงานกับสำนักงานคณะกรรมการอาหารและยาในการขึ้นทะเบียนยา Colistin โดยใช้เวลาประมาณ 8 เดือน จนได้ทะเบียนยาเมื่อ พ.ศ. 2547

ผู้เขียนได้ทดสอบฤทธิ์การทำลายเชื้อด้วยยา Colistin ที่ผลิตภายในประเทศพบว่า ยาดังกล่าวมีฤทธิ์ต่อเชื้อดื้อยา และได้ประเมินประสิทธิผลและความปลอดภัยของยา Colistin ที่ผลิตภายในประเทศ ในการรักษาผู้ป่วยในโรงพยาบาลศิริราชจำนวน 93 รายที่ติดเชื้อ *P. aeruginosa* และ *A. baumannii* ที่ดื้อยาต้านจุลชีพ

ทุกขนานพบว่า กลุ่มผู้ป่วยที่ได้รับการรักษาด้วย Colistin มีอัตราหายจากการติดเชื้อและอัตราที่เชื้อหมดไปจากร่างกายมากกว่ากลุ่มผู้ป่วยที่ได้รับการรักษาด้วยยาอื่น อัตราตายของกลุ่มผู้ป่วยที่ได้รับการรักษาด้วย Colistin ก็ลดลงจากกลุ่มผู้ป่วยที่ได้รับการรักษาด้วยยาอื่นร้อยละ 50 นอกจากนี้ พิษและผลข้างเคียงของยาในกลุ่มที่ได้รับ Colistin ยังน้อยกว่ากลุ่มที่ได้รับยาอื่น แสดงว่า Colistin มีประสิทธิผลและปลอดภัยในการรักษาการติดเชื้อดื้อยา

โรงพยาบาลศิริราชได้บรรจุยา Colistin อยู่ในรายการยาของโรงพยาบาลศิริราชตั้งแต่เดือนมีนาคม พ.ศ. 2548 และบริษัทแอฑแลนติคจำหน่ายยา Colistin ทั่วประเทศตั้งแต่เดือนพฤษภาคม พ.ศ. 2548 โดยมีค่าใช้จ่ายประมาณวันละ 300 บาท ซึ่งน้อยกว่าการรักษาด้วยยาอื่นหลายขนานร่วมกันประมาณ 20 เท่า

ผลได้และผลกระทบจากการจัดการความรู้เรื่องการรักษาโรคติดเชื้อที่ดื้อยาต้านจุลชีพด้วย Colistin คือ บทความตีพิมพ์ในวารสารการแพทย์ 3 เรื่อง ผลงานวิจัยได้รับรางวัล 1 รางวัล มียา Colistin ใช้ในประเทศไทย ผู้ป่วยหายจากการติดเชื้อดื้อยามากขึ้น โอกาสที่ผู้ป่วยเสียชีวิตจากการติดเชื้อดื้อยาลดลงร้อยละ 50 ค่าใช้จ่ายในการรักษาการติดเชื้อดื้อยาลดลง 20 เท่า โดยโรงพยาบาลศิริราชประหยัดค่ายาต้านจุลชีพสำหรับรักษาการติดเชื้อดื้อยามากกว่า 20 ล้านบาทในปี พ.ศ. 2549 นอกจากนี้ การจัดการความรู้ในเรื่องนี้ยังส่งเสริมอุตสาหกรรมยาภายในประเทศ และยังเป็นการเผยแพร่การรักษาการติดเชื้อดื้อยาด้วยยา Colistin ไปสู่หน่วยงานและผู้ประกอบวิชาชีพเวชกรรมทั่วไปโดยกลไกการตลาดของภาคเอกชนด้วย

***2) การทดสอบฤทธิ์ยาต้านจุลชีพขนานใหม่กับเชื้อดื้อยาที่แยกได้จากผู้ป่วยในประเทศไทย***

ผู้เขียนได้ประสานงานกับผู้เกี่ยวข้อง ทดสอบฤทธิ์ของยาต้านจุลชีพขนานใหม่กับเชื้อดื้อยาที่แยกได้จากผู้ป่วยในประเทศไทยพบข้อมูล ดังนี้

- Drug-resistant *Streptococcus pneumoniae* ไวต่อยา Telithromycin
- Methicillin-resistant *Staphylococcus aureus* (MRSA) ไวต่อยา Linezolid
- Extended-spectrum Beta-Lactamase (ESBL)-Producing *E. coli* & *Klebsiella pneumoniae* ไวต่อยา Colistin และ Tigecycline
- Multidrug-Resistant *Pseudomonas aeruginosa* และ Multidrug-resistant *Acinetobacter baumannii* ไวต่อยา Colistin
- Multidrug-resistant *Acinetobacter baumannii* ไวต่อยา Tigecycline
- *Burkholderia pseudomallei* และ *Burkholderia thailandensis* ไวต่อยา Tigecycline
- Methicillin-resistant *Staphylococcus aureus* (MRSA) ไวต่อยา Ceftobiprole

ผลได้และผลกระทบจากการจัดการความรู้เรื่องการทดสอบฤทธิ์ยาต้านจุลชีพขนานใหม่กับเชื้อดื้อยาที่แยกได้จากผู้ป่วยในประเทศไทย คือ บทความตีพิมพ์ในวารสารการแพทย์ 7 เรื่อง และมีข้อมูลสำหรับผู้ประกอบวิชาชีพเวชกรรมใช้ประกอบการตัดสินใจเลือกใช้ยาต้านจุลชีพขนานใหม่กับเชื้อดื้อยา



### 20.2.2 การป้องกันโรคติดเชื้อในโรงพยาบาล

โรคติดเชื้อในโรงพยาบาล (Hospital-acquired infections หรือ nosocomial infections) หมายถึง โรคติดเชื้อที่เกิดขึ้นใหม่ในผู้ป่วยที่รับไว้รักษาในโรงพยาบาล โรคติดเชื้อในโรงพยาบาลพบได้ประมาณร้อยละ 10 ของผู้ป่วยที่รับไว้รักษาในโรงพยาบาล การติดเชื้อในโรงพยาบาลทำให้ผู้ป่วยอยู่โรงพยาบาลนานขึ้น มีโอกาสเสียชีวิตจากการติดเชื้อ และเสียค่าใช้จ่ายในการรักษามากขึ้น โรคติดเชื้อในโรงพยาบาลที่พบบ่อย ได้แก่ ปอดอักเสบติดเชื้อที่สัมพันธ์กับเครื่องช่วยหายใจ (Ventilator-associated pneumonia), การติดเชื้อที่ทางเดิน

ปัสสาวะที่สัมพันธ์กับการคาสายสวนปัสสาวะ (Catheter-associated urinary tract infections) และการติดเชื้อในกระแสเลือดที่สัมพันธ์กับการใส่สายสวนหลอดเลือด (Catheter-associated blood stream infections)
การป้องกันปอดอักเสบติดเชื้อที่สัมพันธ์กับเครื่องช่วยหายใจ

ผู้ป่วยจำนวนมากที่รับไว้รักษาในโรงพยาบาลต้องใช้เครื่องช่วยหายใจ ภาวะแทรกซ้อนสำคัญของการใช้เครื่องช่วยหายใจ คือ ปอดอักเสบติดเชื้อ เนื่องจากผู้ป่วยเหล่านี้มีท่อช่วยหายใจอยู่ในท่อลม (Trachea) ทำให้น้ำลายในช่องปากซึ่งมีเชื้อโรคอาศัยอยู่ไหลลงปอดได้ทางบริเวณรอบๆ ท่อช่วยหายใจ มาตรการป้องกันน้ำลายไม่ให้ไหลลงปอดทางบริเวณรอบๆ ท่อช่วยหายใจ และการลดจำนวนเชื้อโรคในช่องปากจะป้องกันปอดอักเสบติดเชื้อ ได้แก่

**1) การจัดผู้ป่วยที่ได้รับเครื่องช่วยหายใจอยู่ในท่าศีรษะสูง (Semi-Recumbent Position)**

มีหลักฐานจากการวิจัยแสดงว่า การจัดผู้ป่วยที่ได้รับเครื่องช่วยหายใจอยู่ในท่าศีรษะสูงจากแนวราบประมาณ 45 องศา ลดโอกาสที่น้ำลายไหลลงปอดได้ หลักฐานการวิจัยทางคลินิกที่รายงานเมื่อ พ.ศ. 2542 แสดงว่ากลุ่มผู้ป่วยที่ได้รับเครื่องช่วยหายใจที่อยู่ในท่าศีรษะสูงมีอุบัติการณ์ของปอดอักเสบติดเชื้อลดลงมากกว่า 4 เท่า เมื่อเปรียบเทียบกับผู้ป่วยที่อยู่ในท่านอนราบ ความรู้ดังกล่าวนี้ได้รับการประเมินแล้วว่าเป็นความรู้ที่ถูกต้องและนำมาใช้กับผู้ป่วยของโรงพยาบาลศิริราชได้

การสำรวจท่าของผู้ป่วยที่ได้รับเครื่องช่วยหายใจจำนวน 95 ราย ที่หอผู้ป่วยอายุรศาสตร์ โรงพยาบาลศิริราชระหว่างเดือนกุมภาพันธ์-มีนาคม พ.ศ. 2546 พบว่าผู้ป่วยเพียงร้อยละ 17 เท่านั้นที่อยู่ในท่าศีรษะสูง การสอบถามแพทย์ประจำบ้านอายุรศาสตร์เกี่ยวกับท่าของผู้ป่วยที่ได้รับเครื่องช่วยหายใจพบว่าแพทย์ประจำบ้านอายุรศาสตร์เพียงร้อยละ 27 เท่านั้นที่ระบุว่าผู้ป่วยที่ได้รับเครื่องช่วยหายใจควรอยู่ในท่าศีรษะสูงด้วยเหตุผลอื่นที่ไม่ใช่การป้องกันปอดอักเสบติดเชื้อ การสอบถามพยาบาลหอผู้ป่วยอายุรศาสตร์เกี่ยวกับท่าของผู้ป่วยที่ได้รับเครื่องช่วยหายใจพบว่า พยาบาลเพียงร้อยละ 27 เท่านั้นที่ระบุว่าผู้ป่วยที่ได้รับเครื่องช่วยหายใจควรอยู่ในท่าศีรษะสูง แสดงว่าบุคลากรที่หอผู้ป่วยไม่ทราบว่ามีความรู้ที่แสดงว่าการจัดให้ผู้ป่วยที่ได้รับเครื่องช่วยหายใจอยู่ในท่าศีรษะสูงป้องกันปอดอักเสบติดเชื้อได้ และการจัดท่าผู้ป่วยส่วนมากที่ได้รับเครื่องช่วยหายใจที่ปฏิบัติอยู่ (ท่านอนราบ) ไม่สอดคล้องกับความรู้ที่มีอยู่

ผู้เขียนจึงประสานงานการปรับเปลี่ยนนโยบายและวิธีปฏิบัติการจัดท่าผู้ป่วยที่ได้รับเครื่องช่วยหายใจให้อยู่ในท่าศีรษะสูง โดยการเตรียมและเผยแพร่แนวทางปฏิบัติในเรื่องนี้ ทั้งสื่อที่เป็นเอกสารและการประชุมชี้แจงพยาบาลและแพทย์ประจำบ้าน รวมทั้งทำป้ายที่ระบุว่าผู้ป่วยที่ได้รับเครื่องช่วยหายใจรายนี้ต้องอยู่ในท่าศีรษะสูงสำหรับแขวนไว้ที่ปลายเตียงผู้ป่วยเพื่อเตือนบุคลากรที่เกี่ยวข้อง ร่วมกับการย้ำเตือนบุคลากรที่เกี่ยวข้องเป็นระยะๆ พบว่าอัตราที่ผู้ป่วยที่ได้รับเครื่องช่วยหายใจอยู่ในท่าศีรษะสูงเพิ่มขึ้นจากร้อยละ 17 เป็นร้อยละ 76 และอัตราการเกิดปอดอักเสบติดเชื้อลดลงจาก 11.3 ครั้งต่อ 1,000 วันของการใช้เครื่องช่วยหายใจ เหลือ 9.4 ครั้งต่อ 1,000 วันของการใช้เครื่องช่วยหายใจ

ผลได้และผลกระทบจากการจัดการความรู้เรื่องการจัดท่าผู้ป่วยที่ได้รับเครื่องช่วยหายใจให้อยู่ในท่าศีรษะสูง ซึ่งไม่มีค่าใช้จ่ายเพิ่มขึ้นในการนำไปปฏิบัติมาใช้ประโยชน์ในโรงพยาบาลศิริราช คือผู้ป่วยที่ได้รับเครื่องช่วยหายใจมีโอกาสปอดอักเสบติดเชื้อลดลง ผู้เกี่ยวข้องตระหนักว่าการกำหนดวิธีปฏิบัติต่อผู้ป่วยต้องมีความรู้เป็นฐาน และมีบทความตีพิมพ์ในวารสารหนึ่งเรื่อง

**2) การเติมลมปริมาณที่เหมาะสมในกระเปาะของท่อช่วยหายใจ**

การคาท่อช่วยหายใจในผู้ป่วยที่ได้รับเครื่องช่วยหายใจ จำเป็นต้องเติมลมในกระเปาะของท่อช่วยหายใจเพื่อให้ท่อช่วยหายใจคาอยู่ในท่อลมโดยไม่เลื่อนหลุดจากท่อลม และป้องกันลมจากเครื่องหายใจรั่ว มีหลักฐาน

แสดงว่า การเติมลมในกระเปาะของท่อช่วยหายใจจนความดันในกระเปาะมากกว่า 30 เซนติเมตรน้ำ เยื่อบุท่อลมจะถูกกดจนขาดเลือดและท่อลมอาจทะลุได้ ส่วนการเติมลมในกระเปาะของท่อช่วยหายใจโดยความดันในกระเปาะน้อยกว่า 20 เซนติเมตรน้ำ น้ำลายจะไหลลงปอดและเกิดปอดอักเสบติดเชื้อได้ ดังนั้น ความดันในกระเปาะที่เหมาะสมคือ 20-30 เซนติเมตรน้ำ นอกจากนี้ยังมีหลักฐานแสดงว่าการเติมลมด้วยการคาดประมาณเป็นวิธีที่ไม่แม่นยำ ความรู้ดังกล่าวนี้ได้รับการประเมินแล้วว่าเป็นความรู้ที่ถูกต้องและนำมาใช้กับผู้ป่วยของโรงพยาบาลศิริราชได้

วิธีการใส่ลมในกระเปาะของท่อช่วยหายใจของผู้ป่วยในหอผู้ป่วยอายุรศาสตร์ โรงพยาบาลศิริราช ทำโดยพยาบาลด้วยการเติมลมจนไม่มีลมรั่วจากเครื่องช่วยหายใจ และคลำกระเปาะได้ความตึงพอประมาณ บางหอผู้ป่วยใส่ลมครั้งละ 5-7 มิลลิลิตร และเติมลมซ้ำทุก 1-2 วัน การสำรวจความดันในกระเปาะของท่อช่วยหายใจของผู้ป่วยที่ได้รับเครื่องช่วยหายใจที่หอผู้ป่วยอายุรศาสตร์ โรงพยาบาลศิริราช ด้วยเครื่องวัดความดันโดยตรงพบว่าผู้ป่วยเพียงร้อยละ 33 มีความดันในกระเปาะ 20-30 เซนติเมตรน้ำ ผู้ป่วยร้อยละ 52 มีความดันในกระเปาะน้อยกว่า 20 เซนติเมตรน้ำซึ่งเสี่ยงต่อปอดอักเสบติดเชื้อ และผู้ป่วยร้อยละ 15 มีความดันในกระเปาะมากกว่า 30 เซนติเมตรน้ำซึ่งเป็นอันตรายต่อผู้ป่วย แสดงว่าวิธีการเติมลมในกระเปาะของท่อช่วยหายใจที่ปฏิบัติอยู่ไม่เหมาะสมและสมควรเปลี่ยนแปลง

ผู้เขียนได้ประสานงานการกำหนดนโยบายและวิธีปฏิบัติการเติมลมในกระเปาะของท่อช่วยหายใจของผู้ป่วยที่ได้รับเครื่องช่วยหายใจโดยการวิจัย เพื่อให้ได้ความรู้ที่เกี่ยวข้อง ดังนี้

การศึกษาปริมาณลมที่เติมในกระเปาะจนได้ความดัน 20-30 เซนติเมตรน้ำ พบว่าปริมาณลมที่เติมในกระเปาะจนได้ความดัน 20-30 เซนติเมตรน้ำ ของผู้ป่วยแต่ละรายแปรผันมากจนไม่สามารถกำหนดปริมาณลมค่าเดียวที่ใช้เติมในกระเปาะจนได้ความดันในกระเปาะ 20-30 เซนติเมตรน้ำในผู้ป่วยทุกรายได้

การศึกษาอัตราการลดลงของความดันในกระเปาะภายหลังจากเติมลมจนได้ความดันที่เหมาะสมแล้ว พบว่า หากเติมลมจนได้ความดันตั้งต้นในกระเปาะ 30 เซนติเมตรน้ำ ความดันในกระเปาะยังคงมากกว่า 20 เซนติเมตรน้ำ นานประมาณ 8 ชั่วโมง

ดังนั้น ผู้เขียนจึงกำหนดนโยบายและวิธีปฏิบัติการเติมลมในกระเปาะของท่อช่วยหายใจของผู้ป่วยที่ได้รับเครื่องช่วยหายใจว่า ต้องใช้เครื่องวัดความดันโดยตรงเป็นแนวทาง โดยให้เติมลมจนได้ความดันตั้งต้นในกระเปาะ 30 เซนติเมตรน้ำ และเติมลมจนได้ความดันในกระเปาะ 30 เซนติเมตรน้ำทุก 8 ชั่วโมง

ผู้เขียนได้ประเมินการนำนโยบายและวิธีปฏิบัติดังกล่าวไปใช้จริงโดยแบ่งหอผู้ป่วยเป็น 2 กลุ่ม กลุ่มหนึ่งเติมลมด้วยวิธีเดิมที่ปฏิบัติอยู่ ส่วนอีกกลุ่มหนึ่งเติมลมโดยใช้เครื่องวัดความดันโดยตรงเป็นแนวทางโดยใส่ลมจนได้ความดันตั้งต้นในกระเปาะ 30 เซนติเมตร และเติมลมจนได้ความดันในกระเปาะ 30 เซนติเมตร ทุก 8 ชั่วโมง พบว่ากลุ่มที่เติมลมโดยใช้เครื่องวัดความดันโดยตรงเป็นแนวทางมีความดันในกระเปาะ 20-30 เซนติเมตรน้ำร้อยละ 91 ส่วนกลุ่มที่ปฏิบัติตามวิธีเดิมมีความดันในกระเปาะ 20-30 เซนติเมตรน้ำเพียงร้อยละ 32 ผู้ปฏิบัติตามวิธีที่แนะนำแจ้งว่าการเติมลมโดยใช้เครื่องวัดความดันโดยตรงทำได้สะดวกและใช้เวลาเพียง 1 นาทีเท่านั้น แสดงว่าการเติมลมในกระเปาะของท่อช่วยหายใจด้วยเครื่องวัดความดันโดยตรงจนได้ความดันตั้งต้นในกระเปาะ 30 เซนติเมตร และเติมลมจนได้ความดันในกระเปาะ 30 เซนติเมตรทุก 8 ชั่วโมง ทำให้ความดันในกระเปาะอยู่ในช่วงที่เหมาะสมมากกว่าวิธีเดิมชัดเจน

ผู้เขียนได้นำเสนอผลการศึกษาดังกล่าวต่อผู้บริหารโรงพยาบาลศิริราช ซึ่งผู้บริหารก็เห็นชอบกับนโยบายและวิธีปฏิบัติดังกล่าว โดยโรงพยาบาลได้จัดหาเครื่องวัดความดันให้ทุกหอผู้ป่วย สำหรับใช้เป็นแนวทางในการเติมลมในกระเปาะของท่อช่วยหายใจ

ผลได้และผลกระทบจากการจัดการความรู้เรื่องการเติมลมปริมาณที่เหมาะสมในกระเปาะของท่อช่วยหายใจให้ได้ความดันที่เหมาะสม คือผู้ป่วยที่ได้รับเครื่องช่วยหายใจเสี่ยงต่อปอดอักเสบติดเชื้อและภาวะแทรกซ้อนต่อท่อหายใจลดลง บทความตีพิมพ์ในวารสารการแพทย์หนึ่งเรื่อง และรางวัลผลงานวิจัยหนึ่งรางวัล

**3) การใช้น้ำยา 2% Chlorhexidine ทำความสะอาดช่องปากผู้ป่วยที่ได้รับเครื่องช่วยหายใจ**

ปอดอักเสบติดเชื้อในผู้ป่วยที่ได้รับเครื่องช่วยหายใจ มักเกิดจากน้ำลายในช่องปากซึ่งมีเชื้อโรคอาศัยอยู่ไหลลงปอด มีหลักฐานแสดงว่าการลดจำนวนเชื้อโรคในช่องปากด้วยน้ำที่มียาทำลายเชื้อผสมอยู่ป้องกันปอดอักเสบติดเชื้อได้ ความรู้ดังกล่าวนี้ได้รับการประเมินแล้วว่าอาจเป็นความรู้ที่ถูกต้องแต่อาจนำมาใช้กับผู้ป่วยของโรงพยาบาลศิริราชไม่ได้จากหลายปัจจัย เช่น ลักษณะของผู้ป่วยที่แตกต่างกัน วิธีการดูแลรักษาผู้ป่วยที่ได้รับเครื่องช่วยหายใจที่แตกต่างกัน

ผู้เขียนจึงประสานงานกับผู้เกี่ยวข้องดำเนินการวิจัยเปรียบเทียบการทำความสะอาดช่องปากผู้ป่วยที่ได้รับเครื่องช่วยหายใจระหว่างวิธีที่ปฏิบัติอยู่โดยใช้น้ำเกลือกับการใช้น้ำยา 2% Chlorhexidine พบว่ากลุ่มผู้ป่วยที่ได้รับน้ำยา 2% Chlorhexidine มีอุบัติการณ์ของปอดอักเสบติดเชื้อลดลงร้อยละ 50 และปริมาณแบคทีเรียกรัมลบในช่องปากก็ลดลงมากกว่ากลุ่มผู้ป่วยที่ได้รับน้ำเกลือ ผู้ป่วยร้อยละ 10 ที่ได้รับน้ำยา 2% Chlorhexidine มีการระคายเคืองเยื่อบุช่องปากโดยอาการไม่รุนแรง และเมื่อปรับเปลี่ยนวิธีเช็ดถูช่องปากด้วยน้ำยาทำลายเชื้อก็พบการระคายเคืองลดลง แสดงว่าการทำความสะอาดช่องปากผู้ป่วยที่ได้รับเครื่องช่วยหายใจด้วยน้ำยา 2% Chlorhexidine ป้องกันปอดอักเสบติดเชื้อในผู้ป่วยของโรงพยาบาลศิริราชได้

ผู้เขียนได้ประสานงานกับโรงพยาบาลศิริราชปรับเปลี่ยนแนวทางการทำความสะอาดช่องปากผู้ป่วยที่ได้รับเครื่องช่วยหายใจจากวิธีที่ปฏิบัติอยู่จากการใช้น้ำเกลือให้เป็นน้ำยา 2% Chlorhexidine และประสานงานกับฝ่ายเภสัชกรรมในการเตรียมน้ำยา 2% Chlorhexidine สำหรับทำความสะอาดช่องปากผู้ป่วยที่ได้รับเครื่องช่วยหายใจด้วย

ผลได้และผลกระทบจากการจัดการความรู้เรื่องการใช้น้ำยา 2% Chlorhexidine สำหรับทำความสะอาดช่องปากผู้ป่วยที่ได้รับเครื่องช่วยหายใจ คือ จำนวนผู้ป่วยและโอกาสเกิดปอดอักเสบติดเชื้อในผู้ป่วยที่ได้รับเครื่องช่วยหายใจลดลง และบทความตีพิมพ์ในวารสารการแพทย์หนึ่งเรื่อง

***การป้องกันการติดเชื้อที่ทางเดินปัสสาวะที่สัมพันธ์กับการคาสายสวนปัสสาวะ***

ผู้ป่วยจำนวนมากที่รับไว้รักษาในโรงพยาบาลจำเป็นต้องคาสายสวนปัสสาวะ ภาวะแทรกซ้อนสำคัญของการคาสายสวนปัสสาวะ คือการติดเชื้อที่ทางเดินปัสสาวะ เนื่องจากเชื้อโรคบริเวณรอบรูเปิดของท่อปัสสาวะหรือในปัสสาวะที่ค้างอยู่ในสายสวนลุกลามเข้าสู่กระเพาะปัสสาวะ การต่อสายสวนปัสสาวะกับสายต่อและถุงรองรับปัสสาวะให้อยู่ในระบบปิดตลอดเวลา น่าจะลดโอกาสติดเชื้อที่ทางเดินปัสสาวะในผู้ป่วยคาสายสวนปัสสาวะได้

แนวทางปฏิบัติของโรงพยาบาลศิริราชคือให้เปลี่ยนถุงรองรับปัสสาวะทุก 3 วัน ในขณะที่ Centers for Disease Control and Prevention ของประเทศสหรัฐอเมริกาแนะนำให้เปลี่ยนถุงรองรับปัสสาวะเมื่อจำเป็นเท่านั้น คือ เมื่อระบบการระบายปัสสาวะอุดตันหรือฉีกขาด การเปลี่ยนถุงรองรับปัสสาวะทุก 3 วันทำให้ระบบปิดเสียไปมีโอกาสติดเชื้อได้ และยังสิ้นเปลืองถุงรองรับปัสสาวะด้วย การสืบค้นข้อมูลพบว่ายังไม่มีความรู้ในเรื่องนี้ ดังนั้น แนวทางปฏิบัติของโรงพยาบาลศิริราช และคำแนะนำของ Centers for Disease Control and Prevention ประเทศสหรัฐอเมริกาจึงไม่ใช่ความรู้ แต่เป็นเพียงความเชื่อและความเห็นเท่านั้น

ผู้เขียนจึงประสานงานกับหน่วยงานที่เกี่ยวข้อง ดำเนินการวิจัยโดยแบ่งผู้ป่วยที่คาสายสวนปัสสาวะออกเป็นสองกลุ่ม กลุ่มหนึ่งเปลี่ยนถุงรองรับปัสสาวะทุก 3 วัน ส่วนอีกกลุ่มหนึ่งเปลี่ยนถุงรองรับปัสสาวะเมื่อระบบการระบายปัสสาวะอุดตันหรือฉีกขาดเท่านั้น พบว่าอุบัติการณ์ของการติดเชื้อที่ทางเดินปัสสาวะของผู้ป่วยทั้งสอง

กลุ่มไม่แตกต่างกัน โดยกลุ่มที่เปลี่ยนถุงรองรับปัสสาวะทุก 3 วันมีแนวโน้มว่าเกิดการติดเชื้อบ่อยกว่า

ผู้เขียนได้นำเสนอผลการวิจัยดังกล่าวต่อผู้บริหารโรงพยาบาลศิริราช และเสนอให้โรงพยาบาลศิริราชเปลี่ยนนโยบายและวิธีปฏิบัติจากการเปลี่ยนถุงรองรับปัสสาวะทุกสามวัน เป็นให้เปลี่ยนถุงรองรับปัสสาวะเมื่อระบบการระบายปัสสาวะอุดตันหรือฉีกขาด ซึ่งผู้บริหารก็เห็นชอบกับแนวปฏิบัติดังกล่าว โดยโรงพยาบาลได้แจ้งให้หอผู้ป่วยทุกแห่งทราบและถือเป็นแนวปฏิบัติ

ผลได้และผลกระทบจากการจัดการความรู้เรื่องการเปลี่ยนถุงรองรับปัสสาวะในผู้ป่วยที่คาสายสวนปัสสาวะ คือ โรงพยาบาลศิริราชประหยัดค่าถุงรองรับปัสสาวะปีละ 1 ล้านบาท ประหยัดเวลาของบุคลากรปีละ 4,000 ชั่วโมง ลดปริมาณขยะพลาสติกปีละ 3,600 กิโลกรัม และบทความตีพิมพ์ในวารสารการแพทย์หนึ่งเรื่อง ผลงานวิจัยได้รับรางวัลหนึ่งรางวัล นอกจากนี้ ผู้เขียนยังเผยแพร่ผลการวิจัยดังกล่าวในการประชุมวิชาการหลายครั้งและสถานพยาบาลหลายแห่งได้นำแนวปฏิบัตินี้ไปใช้ด้วย

***การป้องกันการติดเชื้อในกระแสเลือดที่สัมพันธ์กับการใส่สายสวนหลอดเลือด***

การติดเชื้อในกระแสเลือดที่สัมพันธ์กับการใส่สายสวนหลอดเลือดในผู้ป่วยที่รับไว้รักษาในโรงพยาบาลศิริราช พบประมาณ 5 ครั้งต่อการคาสายสวนหลอดเลือด 1,000 วัน การติดเชื้อในกระแสเลือดแต่ละครั้งทำให้ผู้ป่วยอยู่โรงพยาบาลนานขึ้น 15 วัน เสียค่ายาต้านจุลชีพในการรักษา 11,000 บาท และมีโอกาสเสียชีวิตร้อยละ 20

แนวทางปฏิบัติการใช้น้ำยาทำลายเชื้อที่ผิวหนังบริเวณที่จะใส่สายสวนหลอดเลือดของโรงพยาบาลศิริราชระบุว่าให้ใช้น้ำยา 10% Povidone Iodine มีหลักฐานเมื่อ พ.ศ. 2545 แสดงว่าการใช้น้ำยา 2% Chlorhexidine ใน 70% Alcohol ลดโอกาสติดเชื้อในกระแสเลือดจากการใส่สายสวนหลอดเลือดลงได้ร้อยละ 50 เมื่อเปรียบเทียบกับน้ำยา 10% Povidone Iodine แนวทางปฏิบัติการใส่สายสวนหลอดเลือดของ Centers for Disease Control and Prevention ของประเทศสหรัฐอเมริกาก็แนะนำให้ใช้น้ำยา 2% Chlorhexidine ทำลายเชื้อที่ผิวหนังบริเวณที่จะใส่สายสวนหลอดเลือด ความรู้ดังกล่าวนี้ได้รับการประเมินแล้วว่าเป็นความรู้ที่ถูกต้องแต่ยังไม่ทราบว่าจะนำมาใช้ในโรงพยาบาลศิริราชได้หรือไม่ เนื่องจากน้ำยา 2% Chlorhexidine ใน 70% Alcohol แพงกว่า 10% Povidone Iodine และบุคลากรของโรงพยาบาลศิริราชคุ้นเคยกับการใช้น้ำยา 10% Povidone Iodine

ผู้เขียนจึงประสานงานกับผู้เกี่ยวข้องวิเคราะห์ความคุ้มค่า (Cost-Effectiveness Analysis) ของการใช้น้ำยา 2% Chlorhexidine ใน 70% Alcohol เปรียบเทียบกับน้ำยา 10% Povidone Iodine โดยอาศัย Decision Analysis Tree เดียวกับรายงานจากต่างประเทศ แต่ใส่ข้อมูลของโรงพยาบาลศิริราชทั้งต้นทุนและผลลัพธ์แทนข้อมูลจากต่างประเทศ พบว่าการใช้ 2% Chlorhexidine ใน 70% Alcohol มีความคุ้มค่ากว่า 10% Povidone Iodine ดังนั้น ผู้เขียนจึงประสานงานกับฝ่ายเภสัชกรรม โรงพยาบาลศิริราชผลิตน้ำยา 2% Chlorhexidine ใน 70% Alcohol เนื่องจากน้ำยาดังกล่าวยังไม่มีจำหน่ายในประเทศไทย

ผู้เขียนได้ประสานงานกับผู้เกี่ยวข้องนำน้ำยา 2% Chlorhexidine ใน 70% Alcohol ที่ผลิตโดยฝ่ายเภสัชกรรม โรงพยาบาลศิริราชมาทดลองใช้ในหออภิบาล 3 แห่งในโรงพยาบาลศิริราช พบว่ากลุ่มผู้ป่วยที่ได้รับน้ำยา 2% Chlorhexidine ใน 70% Alcohol มีอุบัติการณ์ของการติดเชื้อในกระแสเลือดน้อยกว่ากลุ่มที่ได้รับน้ำยา 10% Povidone Iodine ประมาณร้อยละ 43 อย่างไรก็ตาม บุคลากรของหอผู้ป่วยที่ศึกษาใช้น้ำยา 2% Chlorhexidine ใน 70% Alcohol กับผู้ป่วยเพียงร้อยละ 39 ปัจจัยหนึ่งที่ทำให้บุคลากรยังนิยมใช้น้ำยา 10% Povidone Iodine คือเมื่อทาน้ำยา 10% Povidone Iodine บนผิวหนัง ผิวหนังส่วนที่ทาน้ำยานี้แล้วจะมีสีน้ำตาลชัดเจน ทำให้ทาน้ำยาที่ผิวหนังได้ทั่วถึงกว่าน้ำยา 2% Chlorhexidine ใน 70% Alcohol ซึ่งทาแล้วไม่ปรากฏสีบน

ผิวหนัง

ผู้เขียนได้นำเสนอผลการวิจัยดังกล่าว และเสนอให้โรงพยาบาลศิริราชเปลี่ยนนโยบายและวิธีปฏิบัติจากน้ำยา 10% Povidone Iodine เป็นน้ำยา 2% Chlorhexidine ใน 70% Alcohol ต่อผู้บริหารโรงพยาบาลศิริราช ซึ่งผู้บริหารก็เห็นชอบกับนโยบายและวิธีปฏิบัติดังกล่าว โดยโรงพยาบาลได้ให้ฝ่ายเภสัชกรรมผลิตน้ำยา 2% Chlorhexidine ใน 70% Alcohol โดยให้ปรับสีของน้ำยาให้เข้มขึ้นจนผิวหนังที่ทาน้ำยานี้มีสีติดที่ผิวหนังได้ และโรงพยาบาลศิริราชได้สนับสนุนให้หอผู้ป่วยทุกแห่งใช้น้ำยา 2% Chlorhexidine ใน 70% Alcohol ตั้งแต่เดือนกุมภาพันธ์ พ.ศ. 2550 ผู้เขียนกำลังประสานงานให้ภาคเอกชนผลิตน้ำยา 2% Chlorhexidine ใน 70% Alcohol ออกจำหน่ายให้สถานพยาบาลทั่วไปด้วย

ผลได้และผลกระทบจากการจัดการความรู้เรื่องการป้องกันการติดเชื้อในกระแสเลือดจากการใส่สายสวนหลอดเลือดด้วยน้ำยา 2% Chlorhexidine ใน 70% Alcohol คือ ผู้ป่วยที่ได้รับการใส่สายสวนหลอดเลือดมีการติดเชื้อในกระแสเลือดลดลง และบทความตีพิมพ์ในวารสารการแพทย์สองเรื่อง

## 20.3 การจัดการความรู้เพื่อพัฒนาการรักษาโรคด้วยการแพทย์แผนไทย

อุปสรรคสำคัญที่ทำให้บุคลากรสาธารณสุขส่วนมากไม่ยอมรับและไม่นิยมใช้การแพทย์แผนไทยในการประกอบวิชาชีพเวชกรรมเนื่องจากการแพทย์แผนไทยส่วนมากเป็นความรู้ฝังลึก (Tacit Knowledge) ดังนั้นหากต้องการให้การแพทย์แผนไทยได้รับความยอมรับจากบุคลากรสาธารณสุข ก็จำเป็นต้องเปลี่ยนความรู้ฝังลึกให้กลายเป็นความรู้ชัดแจ้ง (Explicit Knowledge) โดยการวิจัยทางคลินิก นอกจากนี้ มีรายงานผลการวิจัยพื้นฐานเกี่ยวกับฤทธิ์และกลไกการออกฤทธิ์ของสมุนไพรจำนวนมากในวารสารการแพทย์โดยไม่มีการวิจัยต่อยอด ดังนั้นการจัดการความรู้เกี่ยวกับการรักษาโรคด้วยการแพทย์แผนไทยของโครงการนี้ จึงเน้นที่การวิจัยทางคลินิกเพื่อต่อยอดจากงานวิจัยพื้นฐาน (Translational Research) และการวิจัยทางคลินิกเพื่อเปลี่ยนความรู้ฝังลึกให้กลายเป็นความรู้ชัดแจ้ง (Transformational Research)

ผู้เขียนใช้กระบวนการจัดการความรู้เพื่อพัฒนาการรักษาโรคด้วยการแพทย์แผนไทยส่วนหนึ่ง ดังนี้

### 20.3.1 การรักษาผู้ป่วยข้อเข่าเสื่อมด้วยสารสกัดขมิ้น

คนไทยอายุมากว่า 60 ปีประมาณร้อยละ 40 มีโรคข้อเข่าเสื่อม ผู้ป่วยโรคนี้มีอาการปวดเข่า และใช้เข่าในการประกอบกิจวัตรประจำวันและการทำงานอย่างลำบาก การรักษาผู้ป่วยข้อเข่าเสื่อมนอกจากการฝึกกำลังกล้ามเนื้อต้นขาให้แข็งแรงแล้ว ผู้ป่วยส่วนมากได้รับยาประเภท Non-Steroidal Anti-Inflammatory (NSAIDs) ยาดังกล่าวมีผลข้างเคียงทำให้กระเพาะอาหารอักเสบ มีแผลที่กระเพาะอาหาร และเลือดออกจากกระเพาะอาหาร

หลักฐานจากการวิจัยพื้นฐานทั้งการศึกษาในห้องปฏิบัติการและสัตว์ทดลองแสดงว่า สารสกัดขมิ้นมีฤทธิ์ต้านการอักเสบด้วยกลไกหลายชนิด รวมทั้งการยับยั้งเอนไซม์ Cyclooxygenase-2 (COX-2) ด้วย อาสาสมัครที่ได้รับสารสกัดขมิ้นขนาด 8,000 มิลลิกรัมติดต่อกัน 3 เดือนก็ไม่มีผลข้างเคียง การสืบค้นข้อมูลไม่พบข้อมูลการรักษาโรคข้อเสื่อมด้วยสารสกัดขมิ้น

ผู้เขียนจึงประสานงานการวิจัยต่อยอดจากการวิจัยพื้นฐาน (Translational Research) ด้วยการวิจัยทางคลินิกในผู้ป่วยข้อเข่าเสื่อมจำนวน 107 คน โดยแบ่งผู้ป่วยเป็น 2 กลุ่ม กลุ่มหนึ่งได้รับยา Ibuprofen ส่วนอีกกลุ่มหนึ่งได้รับสารสกัดขมิ้นนาน 6 สัปดาห์ พบว่าอาการปวดเข่าและการทำงานของเข่าในผู้ป่วยที่ได้รับสารสกัดขมิ้นดีขึ้นมากภายหลังการรักษา และผลการรักษาดังกล่าวไม่แตกต่างจากการรักษาด้วย Ibuprofen โดยผลการ

รักษาในกลุ่มสารสกัดขมิ้นมีแนวโน้มดีกว่ากลุ่ม Ibuprofen ผู้ป่วย 1 รายที่ได้รับ Ibuprofen มีเลือดออกจากกระเพาะอาหาร แสดงว่าสารสกัดขมิ้นมีประสิทธิผลและปลอดภัยในการรักษาโรคข้อเข่าเสื่อมไม่แตกต่างจากยากลุ่ม NSAIDs

ผลได้และผลกระทบจากการจัดการความรู้เรื่องการรักษาผู้ป่วยข้อเข่าเสื่อมด้วยสารสกัดขมิ้น คือ บทความตีพิมพ์ในวารสารการแพทย์หนึ่งเรื่อง มีความรู้ใหม่ซึ่งเป็นทางเลือกในการรักษาโรคข้อเข่าเสื่อม และองค์การเภสัชกรรมกำลังดำเนินการผลิตสารสกัดขมิ้นสำหรับรักษาข้อเข่าเสื่อมออกจำหน่าย

### 20.3.2 การรักษาผู้ป่วย Functional Dyspepsia ด้วยยาธาตุอบเชย

คนไทยร้อยละ 20-25 มีอาการปวดท้อง แน่นท้อง ท้องอืด (Dyspepsia) สาเหตุส่วนมากของอาการดังกล่าวไม่ทราบสาเหตุ จึงนิยมเรียกภาวะนี้ว่า Non-Ulcer Dyspepsia หรือ Functional Dyspepsia บุคลากรการแพทย์ที่โรงพยาบาลอู่ทองใช้ยาธาตุอบเชยที่เตรียมโดยโรงพยาบาลอู่ทองรักษาผู้ป่วย Functional Dyspepsia มานานแจ้งว่า ผู้ป่วย Functional Dyspepsia ส่วนมากที่ได้รับการรักษาด้วยยาธาตุอบเชยมีอาการทุเลาหรืออาการหายไป การสืบค้นข้อมูลพบว่ายังไม่มีความรู้ในเรื่องนี้ ดังนั้น การรักษาผู้ป่วย Functional Dyspepsia ด้วยยาธาตุอบเชยจึงเป็นความรู้ประเภทความรู้ฝังลึก (Tacit Knowledge)

ผู้เขียนจึงประสานงานกับผู้เกี่ยวข้องและโรงพยาบาลชุมชน 6 แห่ง ดำเนินการวิจัยทางคลินิกเพื่อทราบประสิทธิผลและความปลอดภัยของยาธาตุอบเชยตำรับดังกล่าวอย่างเป็นรูปธรรมในผู้ใหญ่ที่เป็น Functional Dyspepsia จำนวน 318 คน โดยแบ่งผู้ป่วยเป็น 2 กลุ่ม กลุ่มหนึ่งได้รับ Simethicone ส่วนอีกกลุ่มหนึ่งได้รับยาธาตุอบเชยติดต่อกันนาน 7-14 วัน พบว่าอาการของผู้ป่วยและความรุนแรงของอาการของผู้ป่วยภายหลังการรักษาด้วยยาธาตุอบเชยดีขึ้นมากเมื่อเปรียบเทียบกับก่อนการรักษา และผลการรักษาไม่แตกต่างจากกลุ่มผู้ป่วยที่ได้รับ Simethicone ผลข้างเคียงของการรักษาก็ไม่แตกต่างกัน ผู้ป่วยส่วนมากที่ได้รับ Simethicone หรือยาธาตุอบเชยพึงพอใจต่อการรักษาที่ได้รับไม่แตกต่างกัน แสดงว่ายาธาตุอบเชยมีประสิทธิผลและปลอดภัยในการรักษาผู้ป่วย Functional Dyspepsia ไม่แตกต่างจากการรักษาด้วย Simethicone

ผลได้และผลกระทบจากการจัดการความรู้เรื่องการรักษาผู้ป่วย Functional Dyspepsia ด้วยยาธาตุอบเชย คือ มีความรู้ใหม่ซึ่งเป็นทางเลือกในการรักษาผู้ป่วย Functional Dyspepsia สำหรับใช้เป็นหลักฐานสนับสนุนการใช้ยาตำรับนี้ ประหยัดค่ารักษา เพราะยาธาตุอบเชยราคา 36 บาท ส่วน Simethicone ราคา 84 บาท สนับสนุนการผลิตและจำหน่ายยาธาตุอบเชยตำรับนี้ของโรงพยาบาลอู่ทอง ยาตำรับนี้กำลังได้รับการบรรจุไว้ในบัญชียาสมุนไพรแห่งชาติ และบทความตีพิมพ์ในวารสารการแพทย์หนึ่งเรื่อง

### 20.3.3. การรักษาผู้ปวดเมื่อยกล้ามเนื้อด้วยการนวดแผนไทย

อาการปวดเมื่อยกล้ามเนื้อพบได้บ่อยมาก อาการดังกล่าวมักเกิดจากการทำงานของกล้ามเนื้อมากเกินไป และการปรับท่าทางของร่างกายที่ไม่เหมาะสม ผู้ป่วยส่วนมากที่มีอาการปวดเมื่อยกล้ามเนื้อมักได้รับยาแก้ปวดประเภท Non-Steroidal Anti-Inflammatory (NSAIDs) ยาดังกล่าวมีผลข้างเคียงทำให้กระเพาะอาหารอักเสบ มีแผลที่กระเพาะอาหาร และเลือดออกจากกระเพาะอาหาร

การนวดเพื่อรักษาอาการปวดเมื่อยกล้ามเนื้อ เป็นการรักษาประเภทการแพทย์แผนไทยชนิดหนึ่งที่ใช้กันทั่วไป การสืบค้นข้อมูลพบว่ามีหลักฐานชี้แนะว่า การนวดมีประโยชน์ในการรักษาอาการปวด แต่ความรู้ดังกล่าวไม่น่านำมาใช้ได้กับการนวดแผนไทยในการรักษาอาการปวดเมื่อยกล้ามเนื้อได้ เพราะวิธีการนวดแตกต่างกันและสาเหตุของการปวดก็แตกต่างกันด้วย

ผู้เขียนได้ประสานงานกับผู้เกี่ยวข้องดำเนินการวิจัยประสิทธิผลของการนวดแผนไทยแบบราชสำนักในผู้ที่มีอาการปวดเมื่อยกล้ามเนื้อบริเวณไหล่ หลัง และคอจำนวน 115 คน ด้วยการนวดแผนไทยแบบราชสำนัก แล้วประเมินผลโดยสอบถามความรุนแรงของอาการปวดเมื่อยก่อนและหลังการรักษาด้วยการนวด พบว่าคะแนนความรุนแรงของอาการปวดเมื่อยภายหลังการนวดลดลงจากก่อนการนวดชัดเจน โดยไม่พบผลข้างเคียงและภาวะแทรกซ้อนจากการนวด แสดงว่าการนวดแผนไทยแบบราชสำนักปลอดภัยและบรรเทาอาการปวดเมื่อยกล้ามเนื้อได้ดี

ผลได้และผลกระทบจากการจัดการความรู้เรื่องการรักษาผู้ปวดเมื่อยกล้ามเนื้อด้วยการนวดแผนไทย คือ บทความตีพิมพ์ในวารสารการแพทย์หนึ่งเรื่อง ผลงานวิจัยได้รับรางวัลหนึ่งรางวัล มีความรู้ที่ยืนยันว่า การนวดแผนไทยแบบราชสำนักปลอดภัยและบรรเทาอาการปวดเมื่อยกล้ามเนื้อได้ดี และสามารถใช้เป็นทางเลือกในการรักษาผู้ที่ปวดเมื่อยกล้ามเนื้อนอกจากการใช้ยาได้

## 20.4 บทสรุป

ตัวอย่างการจัดการความรู้ที่ได้นำเสนอข้างต้นซึ่งเน้นการนำทรัพยากร (ความรู้) ที่มีอยู่แล้วมาใช้พัฒนาบริการสุขภาพให้มีคุณภาพ มีความคุ้มค่า และพึ่งพาตนเองได้นั้น มีแนวคิดมาจากพระราชดำริของสมเด็จพระมหิตลาธิเบศร อดุลยเดชวิกรม พระบรมราชชนก ซึ่งคณะแพทยศาสตร์ศิริราชพยาบาลได้นำมาเป็นปรัชญาของคณะแพทยศาสตร์ศิริราชพยาบาล คือ True success is not in the learning, but in its application to the benefit of mankind และยังสอดคล้องกับปรัชญาเศรษฐกิจพอเพียงซึ่งเป็นพระราชดำริของพระบาทสมเด็จพระเจ้าอยู่หัวด้วย

ผู้เขียนหวังว่าแนวคิดและแนวทางการจัดการความรู้เพื่อพัฒนาบริการสุขภาพ และตัวอย่างการจัดการความรู้ที่นำเสนอนี้จะมีส่วนทำให้นักวิจัย ผู้บริหารแหล่งทุนวิจัย และผู้บริหารสถาบันการแพทย์ได้ตระหนักถึงความสำคัญของการจัดการความรู้เพื่อพัฒนาบริการสุขภาพ โดยนำความรู้ที่ได้จากการวิจัยไปใช้ประโยชน์ด้วยการวิจัยประเภท Knowledge Implementation หรือ Health Service Research รวมทั้งการปลูกฝังให้ผู้กำหนดนโยบายสุขภาพและผู้ให้บริการสุขภาพมีวัฒนธรรมในการกำหนดนโยบายสุขภาพและบริการสุขภาพที่มีความรู้เป็นฐาน


## กิตติกรรมประกาศ

ผู้เขียนขอขอบคุณนักวิจัย บุคลากร และหน่วยงานต่างๆ ที่ร่วมโครงการนี้ คณะแพทยศาสตร์ศิริราชพยาบาลและสำนักงานกองทุนสนับสนุนการวิจัยที่สนับสนุนโครงการนี้ และศาสตราจารย์นายแพทย์วิจารณ์ พานิช ที่ทบทวนบทความนี้




## เอกสารอ้างอิง

เอกสารผลงานวิจัยส่วนหนึ่งในโครงการ 'Knowledge Management to Promote Evidence-Informed Healthcare Policy and Practice' ที่ได้รับการสนับสนุนจากสำนักงานกองทุนสนับสนุนการวิจัย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THE JOURNAL OF ALTERNATIVE AND COMPLEMENTARY MEDICINE
Volume 15, Number 8, 2009, pp. 891–897

DOI: 10.1089/acm.2008.0186

**Original Article**

# Efficacy and Safety of *Curcuma domestica* Extracts in Patients with Knee Osteoarthritis

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## Abstract

***Objective:*** The objective of this study was to determine the efficacy and safety of *Curcuma domestica* extracts in pain reduction and functional improvement in patients with knee osteoarthritis.
***Study design and setting:*** The design and setting were a randomized controlled study at a university hospital in Bangkok, Thailand.
***Methods:*** One-hundred and seven (107) patients with primary knee osteoarthritis (OA) with pain score of ≥5 were randomized to receive ibuprofen 800 mg per day or *C. domestica* extracts 2 g per day for 6 weeks. The main outcomes were improvement in pain on level walking, pain on stairs, and functions of knee assessed by time spent during 100-m walk and going up and down a flight of stairs. The adverse events were also recorded.
***Results:*** Fifty-two (52) and 55 patients were randomized to *C. domestica* extracts and ibuprofen groups, respectively. Baseline characteristics of the patients in both groups were not different. The mean scores of the aforementioned outcomes at weeks 0, 2, 4, and 6 were significantly improved when compared with the baseline values in both groups. There was no difference in those parameters between the patients receiving ibuprofen and *C. domestica* extracts, except pain on stairs ($p = 0.016$). No significant difference of adverse events between both groups was found (33.3% versus 44.2%, $p = 0.36$ in *C. domestica* extracts and ibuprofen groups, respectively).
***Conclusions:*** *C. domestica* extracts seem to be similarly efficacious and safe as ibuprofen for the treatment of knee OA.

## Introduction

Osteoarthritis (OA) is the most common degenerative joint disorder and a major public health problem throughout the world.[1] The prevalence of knee OA in Thai elderly ranged from 34.5% to 45.6%.[2] Knee OA causes pain and dysfunction in 20% of elderly persons.[3] It is the fourth most important global cause of disability in women and the eighth most important in men.[4] Physical disability arising from pain and loss of functional capacity reduces the quality of life and increases the risks of morbidity and mortality.[5] Among treatment modalities, nonsteroidal anti-inflammatory drugs (NSAIDs) are the most common treatment modality to relieve pain for OA, but most of them can cause undesirable effects on the gastrointestinal tract (i.e., ulceration, bleeding, and perforation of stomach and duodenum).[6,7]

The extracts from *Curcuma domestica*, a spice used as a coloring agent (yellow) and a preservative in Thai food, have been used for a century. *In vitro* studies showed that curcumin had an inhibitory effect on substances playing an important role in the inflammatory pathway. The mechanisms by which curcumin prevents inflammation are postulated through inhibition of lipo-oxygenase,[8] cyclo-oxygenase,[9] and phospholipase.[10] Curcumin also inhibited the secretion of collagenase, elastase, and hyaluronidase.[11] Moreover, curcumin was found to inhibit the activation of free radical activated transcription factors such as AP-1 and nuclear factor kappa B[12] and reduce the proinflammatory cytokines such as tumor necrosis factor alpha, interleukin-1 beta, and interleukin-8.[13]

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Furthermore, curcumin exhibited anti-oxidant properties by the inhibition of nitric oxide synthase production.[13,14] Recently, there was evidence of curcumin in inhibiting collagenase and stromelysin expression at micromolar concentrations, which suggested its therapeutic potential for the treatment of arthritis.[15] There were six studies of curcumin in humans including a phase 1 trial with 25 subjects using up to 8,000 mg of curcumin per day for 3 months and five other trials using 1125–2500 mg of curcumin per day.[16] All studies revealed that curcumin was safe and contained anti-inflammatory activity.

The objective of the study was to determine the efficacy and safety of *C. domestica* extracts in pain reduction and functional improvement in patients with knee OA.

## Patients and Methods

The study was approved by the Ethics Committee on Human Research of the Faculty of Medicine Siriraj Hospital, Mahidol University and informed consents were obtained from all participating subjects. The study was conducted at Siriraj Hospital, a tertiary care medical center in Bangkok, Thailand, from April 2005 to May 2006. The eligible subject was an adult with primary knee OA according to the criteria proposed by the American Rheumatism Association.[17] The subject must have knee pain and radiographic osteophytes and at least one of the following features: (1) age >50 years, (2) morning stiffness <30 minutes in duration, (3) and crepitus on motion. Patients who had a pain score in the numerical rating scale of ≥5 of 10 were recruited. Any patients who had peptic ulcer, hepatobiliary tract disease, or known allergy to curcumin or ibuprofen were excluded.

The subjects were asked to discontinue their medications related to the treatment of knee OA (e.g., NSAIDs, glycosaminoglycan derivative drugs) 1 week before randomization. The computerized randomization code was kept by a research assistant who was not directly involved in the study. All subjects were randomly allocated to receive either ibuprofen (400 mg twice daily) or *C. domestica* extracts (500 mg four times daily) for 6 weeks. Ibuprofen 800 mg per day was used according to the rheumatologist's recommendation for treatment in Thai elderly patients with OA to correspond with the smaller size of Thai elderly and to minimize the risk of gastrointestinal side-effects. The patients were instructed not to use any other medications or herbs.

*C. domestica* extracts were produced by the Thai Government Pharmaceutical Organization. The preparations were made under the Good Manufacturing Procedures Standard. Dried rhizomes of *C. domestica* were grounded into powder. The turmeric powder was extracted with ethanol and then evaporated at low pressure to obtain ethanolic extracts containing oil and curcuminoids. The oil part was then removed in order to have curcuminoids extracts. Each capsule of *C. domestica* extracts contained 250 mg of curcuminoids.

Only the assistant knew which treatment was being provided to the patient. The physician who assessed the treatment outcomes was unaware of the patient's group of treatment. The patients were assessed every 2 weeks by the same assessor. The main outcomes consisted of pain on level walking and pain on stairs assessed by a numerical rating scale and knee functions assessed by the time spent on a 100-m walk and going up and down a flight of stairs (10 steps). The time was measured by using digital stopwatch. Its resolution was within 0.001 seconds. The study was conducted at the same location for all patients. For safety concern, all patients had blood tests including complete blood count, liver function, and renal function at week 0 and week 6. Adverse events were recorded from new symptoms experienced by the patients as well as a change in laboratory profiles. The medication could be discontinued when the patients rated pain of less than 3, since this pain magnitude is considered mild and the patient is willing to tolerate it. Compliance to medication was assessed by the pill count method. At week 6, the patients' satisfaction with treatment was also evalu-

TABLE 1. DEMOGRAPHIC CHARACTERISTICS AND BASELINE SCORES OF THE PATIENTS

| | C. domestica (n = 52) | *Ibuprofen* (n = 55) |
|---|---|---|
| Mean age ± SD (years) | 61.4 ± 8.7 | 60.0 ± 8.4 |
| Gender: female (%) | 41 (78.8%) | 45 (81.8%) |
| Mean BMI ± SD (kg/m$^2$) | 26.4 ± 3.7 | 26.8 ± 4.8 |
| Mean duration of symptoms ± SD (months) | 19.1 ± 19.6 | 22.3 ± 26.4 |
| Affected knee | | |
| Right | 13 (25.0%) | 15 (27.3%) |
| Left | 13 (25.0%) | 14 (25.4%) |
| Bilateral | 26 (50.0%) | 26 (47.3%) |
| Using gait aid | 4 (7.7%) | 1 (1.8%) |
| Using knee braces | 16 (30.8%) | 10 (18.2%) |
| Mean pain scores on level walking | 5.3 ± 2.3 | 5.0 ± 1.9 |
| Mean pain scores on stairs | 5.7 ± 2.1 | 6.2 ± 2.2 |
| Mean time spent on a 100-m walk ± SD (sec) | 107.9 ± 24.6 | 103.6 ± 22.2 |
| Mean time spent on going up and down a flight of stairs ± SD (sec) | 31.2 ± 12.6 | 30.3 ± 13.8 |

*C. domestica*, *Curcuma domestica*; SD, standard deviation; BMI, body-mass index.

TABLE 2. MEAN VALUE OF PAIN ON LEVEL WALKING, PAIN ON STAIRS, TIME SPENT ON 100-M WALK AND GOING UP AND DOWN A FLIGHT OF STAIRS BETWEEN TWO GROUPS AT WEEK 0, WEEK 6, CHANGE SCORE AND DIFFERENCE OF CHANGE SCORES AMONG TWO GROUPS

| | C. domestica (n = 45) | | | *Ibuprofen* (n = 46) | | | | |
|---|---|---|---|---|---|---|---|---|
| | *Week 0 score* | *Week 6 score* | *Change score* | *Week 0 score* | *Week 6 score* | *Change score* | *Difference of change score (95% CI)*[a] | *p-value*[*] |
| Pain on level walking | 5.3 ± 2.3 | 2.7 ± 2.5 | 2.7 ± 2.6 | 5.0 ± 1.9 | 3.1 ± 2.3 | 2.0 ± 2.3 | 0.67 (−0.35 to 1.68) | 0.20 |
| Pain on stairs | 5.7 ± 2.1 | 3.1 ± 1.5 | 2.5 ± 2.2 | 6.2 ± 2.2 | 3.8 ± 2.4 | 2.5 ± 2.6 | −0.06 (−1.07 to 0.96) | 0.92 |
| Time spent on 100-m walk (sec) | 107.9 ± 24.6 | 96.7 ± 17.0 | 10.1 ± 16.8 | 103.6 ± 22.2 | 97.0 ± 25.7 | 5.0 ± 16.9 | 5.07 (−2.09 to 12.23) | 0.16 |
| Time spent on going up and down a flight of stairs (sec) | 31.2 ± 12.6 | 24.8 ± 10.2 | 6.0 ± 6.9 | 30.3 ± 13.8 | 25.9 ± 12.3 | 3.3 ± 8.3 | 2.75 (−0.50 to 5.99) | 0.10 |

[a]Difference = change score of *C. domestica* − change score of ibuprofen.
[*]Independent *t*-test.

ated by a five-category scale (i.e., high, moderate, little, same, or dissatisfaction).

A sample size of 50 patients per group was calculated as a noninferiority trial, with the assumption that the significant difference in pain score after treatment with ibuprofen and *C. domestica* extracts was ±1 point with standard deviation (SD) of 2, 5% type I error, and 20% type II error. Repeated-measures analyses of variance were used to analyze the main outcomes. The differences in mean value of pain and time spent on a 100-m walk and going up and down a flight of stairs at week 6 between ibuprofen and *C. domestica* groups were analyzed by independent *t*-test. The $\chi^2$ test was used to analyze adverse events and satisfaction level. Student's *t*-test was used to analyze the compliance of drug intake. The per-protocol analysis was chosen for this noninferiority trial.[18]

## Results

Of 190 patients screened, 107 fulfilled selection criteria and were enrolled in the study. Fifty-two (52) and 55 patients were randomized to *C. domestica* extracts and ibuprofen groups, respectively. At the end of the trial, 45 patients (86.5%) in the *C. domestica* extracts and 46 patients (83.6%) in the ibuprofen group completed the study. The reasons for lost-to-follow-up in both groups were inconvenience to return for follow-up visits (6 in the *C. domestica* group and 6 in the ibuprofen group) and having adverse events (1 in the *C. domestica* group and 3 in the ibuprofen group). The baseline characteristics of the patients in each group are shown in Table 1. The majority of subjects were overweight elderly women (average body mass index [BMI] > 25). The duration of symptoms before entering the trial was approximately 20

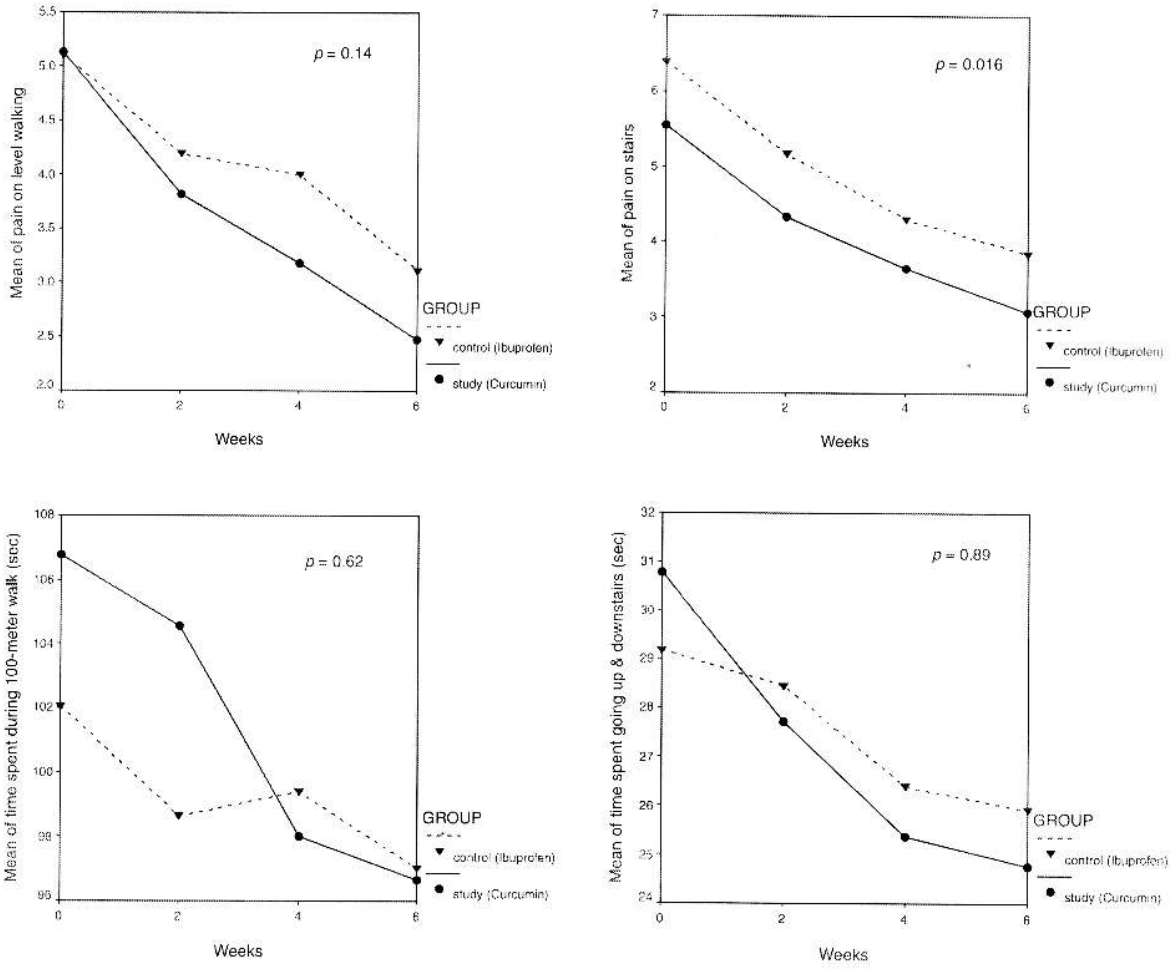


FIG. 1. Mean pain scores on level walking, pain on stairs, time spent on a 100-m walk, and going up and down a flight of stairs at week 0, 2, 4, and 6 (per protocol analysis).

TABLE 3. ADVERSE EVENTS BETWEEN TWO GROUPS

| | C. domestica (n = 48) | *Ibuprofen* (n = 52) | p-*value*[*] |
|---|---|---|---|
| Total no. of patients with an AE | 16 (33.3%) | 23 (44.2%) | 0.36 |
| Adverse events | | | |
| Dyspepsia | 10 (20.8%) | 14 (26.9%) | |
| Dizziness | 5 (10.4%) | 2 (3.8%) | |
| Nausea/vomiting | 3 (6.3%) | 3 (5.8%) | |
| Loose stool | 2 (4.2%) | 1 (1.9%) | |
| Constipation | 0 | 2 (3.8%) | |
| Dry mouth | 0 | 2 (3.8%) | |
| Rash | 0 | 1 (1.9%) | |
| Fatigue | 0 | 1 (1.9%) | |
| GI bleeding | 0 | 1 (1.9%) | |
| Feeling of drug obstructed in the throat | 1 (2.1%) | 0 | |

Some patients experienced more than one event.
[*] $\chi^2$ test.
AE, adverse event; GI, gastrointestinal.

months. Half of the subjects had bilateral knee OA. Some of them used gait aids and knee braces. The mean pain scores on level walking were 5.3 and 5.0, and mean pain scores on stairs were 5.7 and 6.2 in the *C. domestica* extracts and the ibuprofen groups, respectively. Time spent on the 100-m walk was approximately 100 seconds and on going up and down a flight of stairs was approximately 30 seconds. Only 2 patients in the *C. domestica* group discontinued medication when the pain score was less than 3.

The mean value of pain on level walking, pain on stairs, time spent on 100-m walk, and going up and down a flight of stairs between two groups at week 0, week 6, and change score and difference of change scores between the two groups are shown in Table 2. The differences of all outcomes were not statistically different. However, the *C. domestica* group seemed to have less time spent on the 100-m walk and going up and down a flight of stairs. Figure 1 demonstrates the mean scores of pain on level walking, pain on stairs, time-spent on a 100-m walk, and going up and down a flight of stairs at week 0, 2, 4, and 6 between the two groups. Those aforementioned outcomes in each group were significantly improved when compared with the baseline values. However, there were no differences in those parameters between the patients receiving ibuprofen and *C. domestica* extracts except for pain on stairs ($p = 0.016$). The pain score, time spent on level walking, and stairs showed decreasing trends in both groups.

The adverse events of the *C. domestica* and ibuprofen groups are shown in Table 3. No difference was found (33.3% versus 44.2%, $p = 0.36$). The common adverse events were dyspepsia, dizziness, nausea and vomiting, and loose stool. The blood tests between week 0 and week 6 in both groups did not reveal significant changes. For medication intake, the patients in the ibuprofen group had better compliance than those in *C. domestica* extracts group (90.1% versus 82.8%, $p = 0.001$).

The patients' satisfaction with treatment was not different ($p = 0.15$) in both groups as shown in Table 4. Most subjects rated themselves as having moderate to high satisfaction (91.1% and 80.4% in the *C. domestica* extracts and the ibuprofen groups, respectively).

## Discussion

Curcumin exhibits various pharmacologic activities including anti-inflammatory, anti-oxidant, anticarcinogenic, antiviral, and anti-infectious properties.[19] The anti-inflammatory activity of curcumin extracts was demonstrated by inhibition of many different molecules that play a major role in inflammation.[16] Patients with knee OA suffer with pain from an inflammatory process of the knee joint. Regarding the lack of studies comparing the efficacy of curcumin and NSAIDs in patients with knee OA, this study has pertinently

TABLE 4. PATIENTS' SATISFACTION AT WEEK 6

| *Satisfaction level* | C. domestica (n = 45) | *Ibuprofen* (n = 46) | p-*value*[*] |
|---|---|---|---|
| High | 20 (44.4%) | 15 (32.6%) | 0.15 |
| Moderate | 21 (46.7%) | 22 (47.8%) | |
| Little | 1 (2.2%) | 5 (10.9%) | |
| Same | 3 (6.7%) | 3 (6.5%) | |
| Dissatisfaction | 0 (0) | 1 (2.2%) | |

[*] $\chi^2$ for trend.

shown the efficacy of curcumin to relieve pain and to improve knee functions.

In our study, ibuprofen was chosen to be a comparator because scientific evidence from meta-analysis revealed that NSAIDs were superior to acetaminophen for improving knee and hip pain in people with moderate-to-severe levels of pain from OA.[20,21] Additionally, no significant difference in safety was found between acetaminophen and NSAIDs.

There were studies demonstrating the efficacy of curcumin in reducing inflammation in postoperative patients,[22] and rheumatoid arthritis.[23] Recently, an *in vivo* study revealed the efficacy of curcumin in preventing joint inflammation, but it should be started before the onset of inflammation.[24] However, no study reported the efficacy of curcumin in patients with OA.[25]

The effect of weight on drug level or volume distribution should also be considered because the majority of subjects in this study were overweight (mean BMI = 26.4–26.8 $kg/m^2$). There was a study demonstrating that peak ibuprofen concentration was significantly decreased and volume of distribution was increased in obese subjects compared to normal body weight subjects.[26] The data indicated that the ibuprofen dose may be increased in obese patients without changing the dose interval in order to achieve necessary plasma concentrations.

Concerning the safety, the prevalence of adverse events was not different between the two groups. Ten (10) patients (20.8%) in the *C. domestica* extracts group experienced dyspepsia. The meaning of dyspepsia varied from bloating, passing gas, to irritation. Many patients in the *C. domestica* extracts group who had bloating symptoms and passing gas notified us that these symptoms were beneficial effects, whereas those in the ibuprofen group reported gastrointestinal irritation symptoms. These dyspeptic symptoms observed in the *C. domestica* extracts group could be due to their digestive properties. No other serious adverse event was found, as well as meaningful changes in blood tests. We were able to provide 2,000 mg/day of *C. domestica* extracts to the patients up to 6 weeks because curcumin was found to be safe even after high dose ingestion up to 8,000 mg/day for 3 months.[27]

At the end of the study, however, we found that compliance of drug intake during 6 weeks in the ibuprofen group was better than that in the *C. domestica* group. This was due to the fact that ibuprofen was given twice a day, whereas *C. domestica* extracts had to be taken four times a day. More subjects evaluated themselves with moderate to high satisfaction in *C. domestica* than in the ibuprofen group. Some patients in the ibuprofen group rated themselves as having little satisfaction and dissatisfaction (10.9% and 2.2%, respectively). None in the *C. domestica* group felt unsatisfied. This may reflect the satisfaction of the patients with *C. domestica* even it had to be taken four times a day.

The results of this study suggested that *C. domestica* extracts might be as effective as ibuprofen in alleviating knee pain and improving knee functions even though there was a trend toward a greater effect in patients receiving *C. domestica* extracts. However, we were unable to claim that efficacy of both treatments was equivalent because the upper limit of the 95% confidence interval (CI) of mean difference of the pain score exceeds the prespecified range of equivalence. Additionally, the wide range of 95% CI meant that our study had an inadequate sample size. Based on the SD of 2.36, the proper sample size should be 70 patients per group. Therefore, an additional study with adequate sample size and using a higher dose of ibuprofen in the comparison group should be performed to demonstrate the efficacy of *C. domestica* extracts in relieving pain and improving function in patients with knee OA.

## Conclusions

*C. domestica* extracts seem to be efficacious and safe for the treatment of knee OA similarly to ibuprofen. However, more studies with an adequate sample, a higher dose of ibuprofen in the comparison group, and double-blind technique are recommended to demonstrate the efficacy of *C. domestica* extracts in alleviating knee pain and improving knee functions. The safety profiles of *C. domestica* extracts were also demonstrated.

## Acknowledgments

The authors thank the Department of Development of Thai Traditional Medicine and Alternative Medicine, Ministry of Public Health, and the Thailand Research Fund for supporting the study and Mr. Suthiphol Udompunturuk for statistical analyses. We also thank Associate Professor Sucheera Phattharayuttawat and Associate Professor Manee Rattanachaiyanon for reviewing the manuscript.

## Author Disclosure Statement

No competing financial interests exist.

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*Original Article*

# การทบทวนวรรณกรรมอย่างเป็นระบบการศึกษาประสิทธิภาพทางคลินิกของกระเจี๊ยบแดง

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[2] คณะแพทยศาสตร์ ศิริราชพยาบาล มหาวิทยาลัยมหิดล

## บทคัดย่อ

กระเจี๊ยบแดง (*Hibiscus sabdariffa*) เป็นพืชสมุนไพรซึ่งมีการใช้ประโยชน์สืบเนื่องมาเป็นเวลานาน จวบจนปัจจุบัน การศึกษาจำนวนมากก็ยังไม่สามารถระบุฤทธิ์และคุณสมบัติของกระเจี๊ยบแดงอย่างชัดเจนได้ ดังนั้นจึงควรรวบรวมผลการศึกษาที่ได้เพื่อสรุปให้ชัดเจนว่ากระเจี๊ยบแดงมีฤทธิ์รักษาโรคหรือภาวะต่าง ๆ ได้จริงหรือไม่ การวิจัยนี้มีวัตถุประสงค์เพื่อรวบรวมและทบทวนวรรณกรรมอย่างเป็นระบบเกี่ยวกับประสิทธิภาพทางคลินิกของกระเจี๊ยบแดง ผู้วิจัยได้ทำการสืบค้นข้อมูลงานวิจัย จากฐานข้อมูลอิเล็กโทรนิกส์ ได้แก่ Medline (1966-2006), Cumulative Index to Nursing, Allied Health Literature (CINAHL), International Pharmaceutical Abstracts (IPA) (1970 – 2006), Current Contents, Cochrane Library และ Thai Index Medicus นอกจากนี้ ได้สืบค้นจากบรรณานุกรมของรายงานการวิจัยต้นฉบับและติดต่อกับผู้เชี่ยวชาญในสาขาที่เกี่ยวข้อง

ผลการศึกษาพบงานวิจัยเกี่ยวกับฤทธิ์ของกระเจี๊ยบแดงทั้งหมด 66 ฉบับ แต่งานวิจัยที่ผ่านเกณฑ์คัดเลือกเข้าการศึกษา และนำมาทบทวนงานวิจัยอย่างเป็นระบบในการศึกษานี้ มีเพียง 2 ฉบับ ซึ่งทั้งหมดเป็นการวิจัยเกี่ยวกับฤทธิ์ในการลดความดันเลือดของกระเจี๊ยบแดง ฉบับแรกเป็นการศึกษาประสิทธิผล (effectiveness) ของชาชงกระเจี๊ยบแดง และความทนของผู้ป่วย (tolerability) โดยศึกษาในผู้ป่วยโรคความดันเลือดสูงในระดับอ่อนถึงปานกลาง (mild to moderate hypertension) ผลการวิจัยพบว่ายา captopril และ ชาชงกระเจี๊ยบแดงมีประสิทธิภาพในการรักษาไม่แตกต่างกัน และตัวอย่างในสองกลุ่มมีความทนต่อยาไม่ต่างกัน ส่วนฉบับที่ 2 เป็นการศึกษาเพื่อประเมินผลลดความดันเลือดของชากระเจี๊ยบแดง (sour tea) ในผู้ป่วยโรคความดันเลือดสูงที่ไม่รู้สาเหตุ (essential hypertension) ซึ่งผลการวิจัยพบว่า ณ วันที่ 12 ของการศึกษา ชากระเจี๊ยบสามารถลดทั้งความดันเลือดขณะหัวใจบีบตัว (systolic) และขณะหัวใจคลายตัว (diastolic) เมื่อเทียบกับวันแรก ได้อย่างมีนัยสำคัญ ($P < 0.01$) เมื่อประเมินคุณภาพการวิจัยโดยใช้เกณฑ์ของ Jadad และคณะ พบว่างานวิจัยทั้งสองฉบับมีคุณภาพต่ำ (Jadad score = 2/5) ผลการศึกษาแบบการทบทวนงานวิจัยอย่างเป็นระบบนี้สามารถใช้เป็นข้อมูลสนับสนุนว่า ชากระเจี๊ยบแดงอาจมีผลลดความดันเลือด โดยเฉพาะความดันเลือดสูงในระดับอ่อนถึงปานกลาง ควรมีการศึกษาทางคลินิกแบบ randomized controlled trials เพื่อทดสอบฤทธิ์ลดความดัน และผลทางคลินิกอื่น ๆ ของกระเจี๊ยบแดงให้มากขึ้น

**คำสำคัญ:** การทบทวนวรรณกรรมอย่างเป็นระบบ, ประสิทธิภาพทางคลินิก, กระเจี๊ยบแดง

***Thai Pharm Health Sci J 2006;1(3):219-225***[§]

## บทนำ

ปัจจุบัน แนวคิดเกี่ยวกับการใช้สมุนไพรได้รับการยอมรับอย่างกว้างขวาง จากการสำรวจพบว่า ร้อยละ 24.6 ของประชากรไทยยังคงใช้ยาแผนโบราณและสมุนไพรในการบำบัดรักษาความเจ็บป่วย[1] ซึ่งอาจเป็นเพราะสมุนไพรเป็นสิ่งที่คนไทยใช้สืบทอดกันมาเป็นเวลานาน ประกอบกับเทคโนโลยีทางการแพทย์สมัยใหม่ยังกระจายไปสู่ประชาชนอย่างไม่ทั่วถึงและมีราคาแพง นอกจากนี้ อาจเป็นเพราะองค์การอนามัยโลกได้ออกแถลงการณ์แห่งอัลมา-อตาว่าด้วยการสาธารณสุขมูลฐาน ในปี พ.ศ. 2521[2] เพื่อสนับสนุนให้สมาชิกส่งเสริมพัฒนาการรักษาแบบพื้นบ้าน

สำหรับประเทศไทย ในช่วงปลายแผนพัฒนาเศรษฐกิจแห่งชาติฉบับที่ 5 (พ.ศ. 2528) ได้มีการดำเนินโครงการสมุนไพรกับการสาธารณสุขมูลฐาน โดยการสนับสนุนของสหพันธรัฐเยอรมนี (โครงการสมุนไพร GTZ, German

[§] 11th year of Srinakharinwirot Journal of Pharmaceutical Sciences

Agency for Technical Cooperation)[3] และปัจจุบันมีนโยบายส่งเสริมการใช้ประโยชน์จากสมุนไพร เพื่อให้เกิดการพึ่งพาตนเองด้านสุขภาพอนามัยของประชาชนไทย โดยพัฒนาความรู้เรื่องสมุนไพรแก่ประชาชน ร่วมกับการพัฒนาเทคโนโลยีของการแพทย์แผนโบราณและการสนับสนุนข่าวสารทางวิชาการ[4]

กระเจี๊ยบแดง (*Hibiscus sabdariffa*) เป็นพืชสมุนไพรซึ่งมีการใช้ประโยชน์ในหลายประเทศสืบเนื่องมาเป็นเวลานาน กระเจี๊ยบแดงสามารถนำมาใช้ทำอาหาร และใช้เพื่อการรักษาโรค ซึ่งการรักษาสมัยดั้งเดิมใช้กระเจี๊ยบแดงเป็นยาขับปัสสาวะ (diuretic), รักษาภาวะผิดปกติของระบบทางเดินอาหารและไขมันในเลือดสูง ใช้ขับเหงื่อและลดความดันเลือด[5] ปัจจุบันมีการศึกษาทดลองเกี่ยวกับฤทธิ์ของกระเจี๊ยบแดงจำนวนมาก ทั้ง ฤทธิ์ป้องกันและรักษาภาวะติดเชื้อทางเดินปัสสาวะส่วนล่าง[6] ฤทธิ์การเป็นสารต้านออกซิเดชัน (antioxidant)[7,8] ฤทธิ์ต้านการเกิดโรคหลอดเลือดแข็งตัว (antiatherosclerosis)[9] และฤทธิ์ลดความดันเลือด[10,11] อย่างไรก็ตาม การศึกษาจำนวนมากยังไม่สามารถระบุฤทธิ์และคุณสมบัติของกระเจี๊ยบแดงอย่างชัดเจนได้ ดังนั้นจึงจำเป็นที่จะต้องรวบรวมผลการศึกษาที่ได้เพื่อสรุปให้ชัดเจนว่ากระเจี๊ยบแดงมีประสิทธิภาพทางคลินิกในการรักษาโรคหรือภาวะต่าง ๆ ที่ได้กล่าวมาข้างต้นจริงหรือไม่

การทบทวนวรรณกรรมอย่างเป็นระบบ เป็นรูปแบบการวิจัยประเภทหนึ่งที่ใช้วิธีการที่เป็นระบบ (systematic) และมีความชัดเจน (explicit) ในการสืบค้น คัดเลือก และประเมินคุณภาพงานวิจัยที่เกี่ยวข้อง เพื่อนำมาสังเคราะห์และสรุปเป็นผลการศึกษา ปัจจุบันการวิจัยประเภทนี้ได้รับการยอมรับว่าเป็นงานวิจัยที่ให้ข้อมูลที่น่าเชื่อถือในลำดับแรกเมื่อเทียบกับงานวิจัยประเภทอื่น ๆ[12] ด้วยเหตุนี้ผู้วิจัยจึงใช้รูปแบบการวิจัยนี้ในการรวบรวมข้อมูลประสิทธิภาพทางคลินิกของกระเจี๊ยบแดง

## วิธีการศึกษา

ผู้วิจัยทำการสืบค้นข้อมูลจากฐานข้อมูลคอมพิวเตอร์ ได้แก่ Medline (1966-2006), Cumulative Index to Nursing, Allied Health Literature (CINAHL), International Pharmaceutical Abstracts (IPA) (1970 – 2006), Current Contents, Cochrane Library, และ Thai Index Medicus และจากบรรณานุกรมของรายงานการวิจัยต้นฉบับ ตั้งแต่เดือนมิถุนายน พ.ศ. 2548 ถึง เดือนกุมภาพันธ์ พ.ศ. 2549 นอกจากนี้ ผู้วิจัยได้ติดต่อเพื่อสอบถามข้อมูลจากผู้เชี่ยวชาญด้านสมุนไพรจำนวน 2 ท่าน และติดต่อขอข้อมูลจากสำนักงานข้อมูลสมุนไพร คณะเภสัชศาสตร์ มหาวิทยาลัยมหิดล และกรมพัฒนาการแพทย์แผนไทยและแพทย์ทางเลือก กระทรวงสาธารณสุข สำหรับคำที่ใช้ในการสืบค้น คือ Hibiscus, *Hibiscus sabdariffa*, Roselle, red sorrel, karkade, กระเจี๊ยบ และกระเจี๊ยบแดง

### เกณฑ์ในการคัดเลือกงานวิจัยเข้าการศึกษา

การสืบค้นงานวิจัยของกระเจี๊ยบแดง เพื่อรวบรวมและนำมาทบทวนวรรณกรรมอย่างเป็นระบบ (systematic review) นั้น มีเกณฑ์คัดเลือกงานวิจัยดังนี้ คือ เป็นการศึกษาวิจัยฤทธิ์ของกระเจี๊ยบแดงในมนุษย์ และเป็นงานวิจัยในรูปแบบการศึกษาทดลองเชิงสุ่มที่มีกลุ่มเปรียบเทียบ (randomized controlled trial)

### การคัดย่อและสรุปผลการวิจัย

ผู้วิจัยใช้แบบคัดย่อข้อมูล (data abstraction form) เพื่อคัดย่อข้อมูลจากงานวิจัย ได้แก่ ฤทธิ์ของกระเจี๊ยบแดง จำนวนและลักษณะของกลุ่มตัวอย่าง ขนาดและวิธีใช้ รูปแบบของผลิตภัณฑ์ ระยะเวลาที่ใช้ การวัดผลการวิจัย โดยการศึกษาที่ผ่านการคัดเลือกทั้งหมดจะถูกนำมาประเมินคุณภาพงานวิจัยโดยใช้แบบประเมินซึ่งสร้างขึ้นโดย Jadad และคณะ[13] สำหรับประเด็นที่ใช้ประเมินงานวิจัยประกอบด้วย กระบวนการสุ่ม (randomization) การปกปิดการแบ่งกลุ่ม (allocation concealment) วิธีการปกปิดสิ่งทดลอง (blinding) และการให้คำอธิบายเกี่ยวกับการออกจากการศึกษาของกลุ่มตัวอย่าง

## ผลการศึกษา

### ผลการสืบค้นงานวิจัย

ผลการสืบค้นงานวิจัยของสมุนไพรกระเจี๊ยบแดงจากฐานข้อมูลคอมพิวเตอร์ การติดต่อผู้เชี่ยวชาญด้านสมุนไพร และจากบรรณานุกรมของรายงานการวิจัยต้นฉบับ พบว่ามีงานวิจัยเกี่ยวกับฤทธิ์ของกระเจี๊ยบแดงทั้งหมด 66 ฉบับ แต่ในจำนวนนี้มีงานวิจัยที่ศึกษาฤทธิ์ของกระเจี๊ยบแดงในมนุษย์เพียง 5 ฉบับ อย่างไรก็ตาม มีงานวิจัยเพียง 2 ฉบับเท่านั้น[10,11] ที่ผ่านเกณฑ์การคัดเลือกเข้าสู่การศึกษานี้ (ตารางที่ 1) สำหรับงานวิจัยอีก 3 ฉบับ[6,14,15] ถูกคัดออกเนื่องจากไม่ใช่การศึกษาทดลองเชิงสุ่มที่มีกลุ่มเปรียบเทียบ

## ประสิทธิภาพทางคลินิกของกระเจี๊ยบแดง

ผลจากการสืบค้นข้อมูลพบงานวิจัยที่ศึกษาเกี่ยวกับฤทธิ์ในการลดความดันเลือดของกระเจี๊ยบแดงในมนุษย์ และรูปแบบการศึกษาเป็นการศึกษาทดลองเชิงสุ่มที่มีกลุ่มเปรียบเทียบ จำนวน 2 ฉบับ งานวิจัยฉบับแรกเป็นของ Herrera-Arellano และคณะ[10] เป็นการศึกษาประสิทธิผล (effectiveness) และ ความทน (tolerability) ต่อชาชงกระเจี๊ยบแดง (*Hibiscus sabdariffa*) ในผู้ป่วยโรคความดันเลือดสูงระดับอ่อนถึงปานกลาง งานวิจัยนี้ได้เปรียบเทียบประสิทธิผลของชาชงที่เตรียมจากกลีบเลี้ยง (calyx) ของกระเจี๊ยบแดง โดยกลุ่มตัวอย่างที่เข้าร่วมงานวิจัยต้องมี

**ตารางที่ 1** ลักษณะงานวิจัยและผลลัพธ์งานวิจัย

| ผู้แต่ง | รูปแบบงานวิจัย | Jadad Score | กลุ่มตัวอย่าง | โรคที่ทำการศึกษา | การให้สิ่งทดลอง | | การวัดผลลัพธ์ | ผลการวิจัยหลัก |
|---|---|---|---|---|---|---|---|---|
| | | | | | กลุ่มควบคุม | กลุ่มทดลอง | | |
| Herrera-Arellano et al[10] | การศึกษาทดลองเชิงสุ่มที่มีกลุ่มเปรียบเทียบ | 2/5 | ผู้ป่วยโรคความดันเลือดสูงระดับอ่อนถึงปานกลาง จำนวน 90 คน (เหลือ 70 คน ณ วันสุดท้ายของการศึกษา) | โรคความดันเลือดสูงในระดับอ่อนถึงปานกลาง | captopril 25 มก. 1 เม็ดทุก 12 ชม. เป็นเวลา 4 สัปดาห์ | ชากระเจี๊ยบแดง 10 กรัม ต้มวันละครั้ง ก่อนอาหารเช้า เป็นเวลา 4 สัปดาห์ | - ความแตกต่างของความดันเลือดที่วัดได้วันที่ 12 เทียบกับวันแรก<br>- ความแตกต่างของการเกิดผลข้างเคียง | ผลในการลดความดันเลือดและความทนต่อชาชงกระเจี๊ยบแดงซึ่งมีสารแอนโทไซยานิน 9.6 มก. และ captopril 50 มก./วัน ไม่แตกต่างกัน |
| Haji Faraji et al[11] | การศึกษาทดลองเชิงสุ่มที่มีกลุ่มเปรียบเทียบ | 2/5 | ผู้ป่วยโรคความดันเลือดสูงจำนวน 80 คน (เหลือ 54 คน ณ วันสุดท้ายของการศึกษา) | โรคความดันเลือดสูงไม่รู้สาเหตุ | ชาธรรมดา 1 แก้ว อย่างน้อย 1 ชม. ก่อนวัดความดันเลือด เป็นเวลา 12 วัน | ชากระเจี๊ยบแดง 1 แก้ว อย่างน้อย 1 ชม. ก่อนวัดความดันเลือด เป็นเวลา 12 วัน | ความแตกต่างของความดันเลือด ณ วันที่ 4, 8, 12 และ 3 วันหลังจากเลิกใช้ | SBP* และ DBP** ของกลุ่มทดลองลดลงมากกว่ากลุ่มควบคุมอย่างมีนัยสำคัญ ณ วันที่ 12 |

* SBP = ความดันเลือดขณะหัวใจบีบตัว
** DBP = ความดันเลือดขณะหัวใจคลายตัว

คุณสมบัติต่อไปนี้ ต้องได้รับการวินิจฉัยว่าเป็นโรคความดันเลือดสูงระดับอ่อนถึงปานกลาง ไม่ได้รับยาลดความดันเลือดมาอย่างน้อย 1 เดือนก่อนเข้าร่วมการวิจัย และยินยอมที่จะเข้าร่วมการวิจัย ตัวอย่างถูกแบ่งเป็น 2 กลุ่มโดยใช้ตารางเลขสุ่ม กลุ่มทดลองได้รับผงกระเจี๊ยบแดง (ประมาณ 10 กรัม มี สาร anthocyanins 9.62 มิลลิกรัม) ซึ่งบรรจุอยู่ในซองกระดาษ วิธีการใช้ยา คือ เติมน้ำเดือดลงในชาและตั้งทิ้งไว้ประมาณ 10 นาที รับประทานวันละครั้งก่อนอาหารเช้าเป็นเวลา 4 สัปดาห์ ส่วนกลุ่มควบคุมได้รับยา captopril 25 mg รับประทานทุก 12 ชั่วโมงเป็นเวลา 4 สัปดาห์เช่นกัน

ผลลัพธ์หลักของการวิจัยนี้ คือ ประสิทธิผลของการรักษา (therapeutic effectiveness) ความทนต่อการรักษา (therapeutic tolerability) และความสำเร็จจากการรักษา (therapeutic success) โดยผู้วิจัยพิจารณาว่าชาชงกระเจี๊ยบแดงมีประสิทธิผลในการรักษาโรคความดันเลือดสูง เมื่อความดันขณะหัวใจคลายตัวของกลุ่มตัวอย่างที่ได้รับชาดังกล่าวลดลงอย่างน้อย 10 มิลลิเมตรปรอท ณ วันสุดท้ายของการศึกษา สำหรับความทนต่อการรักษาได้ประเมินจากการเกิดผลข้างเคียงและความรุนแรงของอาการที่เกิดขึ้น ซึ่งผลการวิจัยพบว่ากลุ่มตัวอย่างทั้งสองกลุ่มมีความทนต่อยาไม่แตกต่างกันและประสิทธิภาพของการรักษาของชากระเจี๊ยบแดงและยา captopril ไม่มีความแตกต่างกัน (ไคสแควร์, $P > 0.56$) ส่งผลให้ผลสำเร็จของการรักษา (therapeutic effectiveness) ของทั้งสองกลุ่มซึ่งพิจารณาร่วมกันระหว่างประสิทธิผลของการรักษาและความทนต่อยาไม่แตกต่างกันด้วย นอกจากนี้ จากการวิจัยพบปริมาณของโซเดียมในปัสสาวะของผู้ป่วยในกลุ่มที่ได้รับชาชงกระเจี๊ยบแดงก่อนและหลังการวิจัยเพิ่มขึ้นอย่างมีนัยสำคัญ (ANOVA, $P < 0.001$)

สิ่งทดลองในการวิจัยนี้มีความแตกต่างกันอย่างชัดเจนทั้งลักษณะทั่วไป รูปแบบผลิตภัณฑ์ และวิธีการใช้ยา ดังนั้นจึงยากที่จะทำการปกปิด (blinding) ไม่ให้ผู้ป่วยทราบ อย่างไรก็ตาม การวิจัยนี้ได้ปกปิดแพทย์ผู้วัดความดัน ดังนั้นจึงเป็นการวิจัยที่ปกปิดแบบทางเดียว (single blind) การวิจัยนี้ไม่ได้ปกปิดการแบ่งกลุ่ม อีกทั้งการวิเคราะห์ความสำเร็จของการรักษา ซึ่งหมายรวมถึงประสิทธิผลของการรักษาและความทนต่อการรักษานั้น ไม่ได้ใช้การวิเคราะห์ผลการศึกษาโดยคำนวณจากผู้ป่วยทั้งหมดที่เข้าร่วมการศึกษา (intention-to-treat analysis) ดังนั้น เมื่อประเมินคุณภาพการวิจัยโดยใช้

เกณฑ์ของ Jadad และคณะ[13] พบว่างานวิจัยนี้มีคุณภาพต่ำ (Jadad score =2/5: ตารางที่ 2)

**ตารางที่ 2** การประเมินคุณภาพงานวิจัยตามเกณฑ์ของ Jadad และคณะ

| เกณฑ์ของ Jadad และคณะ[13] | Herrera-Arellano และคณะ[10] | Haji Faraji และคณะ[11] |
|---|---|---|
| 1. การวิจัยใช้กระบวนการสุ่ม (randomization) | ใช่ | ใช่ |
| 2. การวิจัยมีรูปแบบปกปิดแบบสองทาง (double blind) | ไม่ใช่ | ไม่ใช่ |
| 3. มีการบันทึกและอธิบายเหตุผลของการออกจากการศึกษาของตัวอย่าง | ใช่ | ใช่ |
| 4. มีการอธิบายถึงวิธีการสุ่ม | ใช่ | ใช่ |
| 5. มีการอธิบายถึงการปกปิดแบบสองทาง | ไม่ใช่ | ไม่ใช่ |
| **Jadad Score** | **2** | **2** |

งานวิจัยฉบับที่ 2 เป็นงานของ Haji Faraji และคณะ[11] เป็นการศึกษาเพื่อประเมินผลของชากระเจี๊ยบแดง (sour tea) ในผู้ป่วยโรคความดันเลือดสูงที่ไม่รู้สาเหตุ (essential hypertension) กลุ่มตัวอย่างของการวิจัย คือ ผู้ป่วยที่ลงทะเบียนหรือรับบริการที่คลินิกความดันเลือดสูง เกณฑ์ในการเลือกผู้ป่วยเข้าร่วมการวิจัยประกอบด้วย ความดันขณะหัวใจบีบตัว (systolic) ในระดับ 160 - 180 มิลลิเมตรปรอท และ/หรือความดันขณะหัวใจคลายตัว (diastolic) ในระดับ 100 - 114 มิลลิเมตรปรอท ใช้ยาลดความดันเลือดไม่เกิน 2 ชนิด และไม่เป็นโรคอันเนื่องจากโรคความดันเลือดสูง (secondary hypertension) เช่น ความผิดปกติเกี่ยวกับระบบหัวใจและหลอดเลือด โรคไทรอยด์หรือโรคเบาหวาน ผู้ป่วยที่ผ่านเกณฑ์คัดเลือกจำนวน 80 คน ถูกแบ่งเป็น 2 กลุ่ม โดยใช้ตารางเลขสุ่ม ผู้ป่วยในกลุ่มทดลองได้รับชากระเจี๊ยบแดง (เตรียมโดยใช้ผงกระเจี๊ยบ 2 ช้อนชา ละลายในน้ำเดือด 1 แก้วทิ้งไว้ 20 - 30 นาที) ดื่มก่อนวัดความดันเลือดอย่างน้อย 1 ชั่วโมง ส่วนกลุ่มควบคุมได้รับชาธรรมดา (ordinary tea) มีวิธีการใช้ยาเช่นเดียวกับชากระเจี๊ยบแดง

ผู้วิจัยวัดความดันเลือดวันที่ 4, 8, 12 (วันสุดท้ายของการใช้ชาชง) และ วันที่ 15 (หลังจากที่หยุดใช้ชาแล้ว 3 วัน) ผลการวิจัยพบว่า ณ วันที่ 12 ความดันเลือดในผู้ป่วยกลุ่มทดลองมีค่าความดันเลือดต่ำสุดเมื่อเทียบกับวันแรก (ความดันขณะหัวใจบีบตัวลดลง 12% และความดันขณะหัวใจคลายตัวลดลง 10.8%) และเมื่อเปรียบเทียบทั้งสองกลุ่มพบว่าความดันขณะหัวใจบีบตัวและความดันขณะหัวใจคลายตัวของผู้ป่วยในกลุ่มทดลองลดลง 1.8 เท่า และ 2.1 เท่า ตามลำดับ และหลังจากหยุดใช้ชา (วันที่ 15) ความดันขณะหัวใจบีบตัวและความดันขณะหัวใจคลายตัวของผู้ป่วยในกลุ่มทดลองเพิ่มขึ้น 8.7 เท่า และ 11.7 เท่า ตามลำดับ เมื่อเทียบกับกลุ่มควบคุม การวิจัยนี้สรุปว่าชากระเจี๊ยบมีผลลดความดันเลือดทั้งความดันขณะหัวใจบีบตัวและความดันขณะหัวใจคลายตัว โดยผลลดความดันจะมากขึ้นเมื่อใช้อย่างต่อเนื่อง

ประเด็นที่น่าพิจารณาสำหรับงานวิจัยฉบับที่ 2 คือ ผู้วิจัยกล่าวถึงการปกปิด แต่ไม่ให้รายละเอียดของวิธีการปกปิดนั้น จึงไม่สามารถยืนยันได้ว่าจะสามารถปกปิดผู้เข้าร่วมการวิจัยไม่ให้ทราบชนิดชาที่ตนเองได้รับได้จริงหรือไม่ นอกจากนี้ การให้สิ่งทดลอง (ชากระเจี๊ยบแดงและชาธรรมดา) ผู้วิจัยระบุว่าให้ผู้ป่วยดื่มชาชง 1 แก้วก่อนวัดความดันเลือดอย่างน้อย 1 ชั่วโมง โดยไม่ได้ระบุถึงความถี่ของการใช้ชาใน 1 วัน และไม่ได้นำเสนอข้อมูลระยะเวลาโดยเฉลี่ยของการดื่มชาชงของผู้ป่วยก่อนวัดความดันเลือด

นอกจากนี้ จากคำแนะนำการใช้ชาที่ระบุว่าชงผงกระเจี๊ยบแดง 2 ช้อนชาต่อน้ำเดือด 1 แก้ว ทิ้งไว้ 20 - 30 นาที พบว่าเป็นคำแนะนำที่ไม่ชัดเจน เพราะหากมีการใช้ปริมาณน้ำที่ต่างกันหรือชงในน้ำเดือดโดยใช้เวลาต่างกันอาจส่งผลให้ได้รับปริมาณสารสำคัญที่มีผลต่อความดันเลือดต่างกัน และประเด็นที่สาม การวิจัยนี้วิเคราะห์ผลการทดลองจากผู้เข้าร่วมการศึกษาที่เป็นไปตามเงื่อนไขของการศึกษาเท่านั้น (per protocol analysis) กล่าวคือ ทำการวิเคราะห์ผลจากผู้เข้าร่วมการวิจัยที่อยู่ร่วมการวิจัยจนการวิจัยสิ้นสุด จากการประเมินคุณภาพงานวิจัยตามเกณฑ์ของ Jadad และคณะ[13] พบว่างานวิจัยฉบับนี้มีคุณภาพต่ำเช่นกัน (Jadad score = 2/5) (ตารางที่ 2)

## อภิปรายผลการศึกษา

จากการทบทวนงานวิจัยที่เกี่ยวกับประสิทธิภาพทางคลินิกของกระเจี๊ยบแดง พบงานวิจัยเกี่ยวกับฤทธิ์ของกระเจี๊ยบแดงในมนุษย์ และรูปแบบการศึกษาเป็นการศึกษาทดลองที่มีกลุ่มเปรียบเทียบ จำนวน 5 ฉบับ[6,10,11,14,15] แต่เนื่องจากงานวิจัย 3 ฉบับ[6,14,15] มีรูปแบบการศึกษาที่เป็นการศึกษาเชิงทดลองที่ไม่มีกลุ่มเปรียบเทียบ (non-randomized controlled trial) จึงไม่ผ่านเกณฑ์ในการคัดเลือกงานวิจัยครั้งนี้ ทำให้มีงานวิจัยจำนวน 2 ฉบับ[10,11] ที่ผ่านเกณฑ์ ซึ่งเป็นการศึกษาผลของกระเจี๊ยบแดงต่อความดันเลือด

งานวิจัยทั้งสองฉบับมีความแตกต่างกันในหลายประเด็น ทั้งในเรื่องกลุ่มตัวอย่าง วิธีการดำเนินการวิจัย สิ่งเปรียบเทียบ ปริมาณสารสำคัญและความเข้มข้นของกระเจี๊ยบแดงที่ใช้ เมื่อ

ทำการประเมินคุณภาพโดยใช้เกณฑ์ของ Jadad และคณะ[13] พบว่างานวิจัยทั้งสองฉบับมีคุณภาพต่ำ ดังนั้นการวิจัยทั้งสองฉบับที่ระบุว่าชาชงจากกระเจี๊ยบแดงมีผลลดความดันเลือดนั้นยังคงต้องการข้อมูลยืนยันจากการวิจัยอื่น ๆ เพิ่มเติม

การวิจัยของ Herrera-Arellano และคณะ[10] ไม่มีการปกปิดผู้เข้าร่วมการวิจัย ซึ่งอาจทำให้เกิดปัญหาการปนเปื้อน (contamination) จากสิ่งอื่นนอกเหนือจากสิ่งที่ศึกษา และอาจทำให้การถอนตัวของผู้เข้าร่วมการวิจัย (drop out) เพิ่มมากขึ้น ส่วนงานวิจัยของ Haji Faraji และคณะ[11] ไม่ได้แสดงความดันเลือดก่อนเข้าร่วมงานวิจัยของกลุ่มตัวอย่าง แต่ได้ระบุเกณฑ์ในการคัดคนเข้าร่วมการศึกษาว่าต้องมีความดันขณะหัวใจบีบตัวอยู่ในช่วง 160 - 180 มิลลิเมตรปรอท และความดันขณะหัวใจคลายตัว อยู่ในช่วง 100 - 114 มิลลิเมตรปรอท งานวิจัยนี้จะมีความน่าเชื่อถือมากขึ้น หากได้ระบุส่วนของกระเจี๊ยบแดงที่ใช้ทำชา มีการวิเคราะห์หาปริมาณสารสำคัญของชากระเจี๊ยบแดงที่ใช้ รวมทั้งหากได้ระบุข้อบ่งใช้ที่ชัดเจน นอกจากนี้ เพื่อลดอคติ (bias) ที่อาจเกิดขึ้น การวิเคราะห์ผลการวิจัยควรใช้การวิเคราะห์ผลการศึกษาโดยคำนวณจากผู้ป่วยทั้งหมดที่เข้าร่วมการศึกษา อย่างไรก็ตาม จากผลการวิจัยดังกล่าวสามารถนำมาเป็นข้อมูลที่ช่วยสนับสนุนว่าชากระเจี๊ยบแดงมีผลในการช่วยลดลดความดันเลือด โดยเฉพาะความดันเลือดสูงในระดับอ่อนถึงปานกลาง โดยผลลดความดันเลือดของชากระเจี๊ยบแดงซึ่งเตรียมจากผงกระเจี๊ยบแดง (ประมาณ 10 กรัม มี สาร anthocyanins 9.62 มิลลิกรัม) ไม่แตกต่างจากการใช้ยา captopril 25 มิลลิกรัม ทุก 12 ชั่วโมง เป็นเวลา 4 สัปดาห์

ในส่วนของความทนต่อชาชงกระเจี๊ยบแดง Herrera-Arellano และคณะ[10] พบว่าผู้ป่วยทนต่อชากระเจี๊ยบแดงและยา captopril ไม่แตกต่างกัน แต่งานวิจัยฉบับนี้ไม่ได้ระบุถึงผลข้างเคียง (side effects) ที่เกิดขึ้น อย่างไรก็ตาม มีการวิจัยเกี่ยวกับความเป็นพิษ (toxicity) ของสารสกัดจากกลีบเลี้ยงของกระเจี๊ยบแดงในสัตว์ทดลอง ซึ่งผลจากการศึกษาพบว่าการได้รับสารสกัดจากกลีบเลี้ยงของกระเจี๊ยบแดง (calyx infusion) ของกระเจี๊ยบแดงมากกว่า 5,000 มิลลิกรัม/กิโลกรัม ทำให้หนูทดลองตายครึ่งหนึ่ง และการให้สารสกัดจากกระเจี๊ยบแดงในขนาดสูง (4.6 กรัม/กิโลกรัม) แก่หนูเป็นเวลา 12 สัปดาห์ ทำให้เกิดพิษต่อไตได้[16] จากการทบทวนงานวิจัยยังไม่พบการศึกษาความพิษของกระเจี๊ยบแดงในมนุษย์ ทั้งนี้มีข้อมูลทางวิทยาศาสตร์ที่ยืนยันว่าพืชในสกุล Hibiscus ทั้งหมดไม่มีพิษต่อมนุษย์[17]

กลไกที่เป็นไปได้ที่ทำให้กระเจี๊ยบแดงมีประสิทธิภาพในการลดความดันเลือด คือ ฤทธิ์ขับปัสสาวะ (diuretic)[18,19] ฤทธิ์ขยายหลอดเลือด (vasodilator)[18,19] การเปลี่ยนแปลง $Ca^{2+}$ channel[18] ฤทธิ์ยับยั้ง Angiotensin Converting Enzyme (ACE Inhibitor)[19-21] การขัดขวางการจับของ Angiotensin II และ Angiotensin$_1$ receptor[22] ซึ่งกลไกเหล่านี้ อาจเป็นผลจากสารสำคัญกลุ่ม anthocyanin ที่พบได้ในสารสกัดของกระเจี๊ยบแดง[18] อย่างไรก็ตาม สารสำคัญและกลไกที่แท้จริงของการลดความดันเลือดของกระเจี๊ยบแดงยังต้องการข้อมูลจากงานวิจัยเพิ่มเติม

จากข้อมูลที่ได้จากการทบทวนงานวิจัยครั้งนี้ ถึงแม้ว่าผู้วิจัยได้สืบค้นข้อมูลจากแหล่งข้อมูลที่หลากหลาย แต่ก็ยังไม่สามารถยืนยันได้ว่าข้อมูลงานวิจัยที่สืบค้นได้เป็นงานวิจัยรูปแบบการศึกษาทดลองเชิงสุ่มที่มีกลุ่มเปรียบเทียบทั้งหมดที่ศึกษาเกี่ยวกับประสิทธิภาพทางคลินิกของกระเจี๊ยบแดง และชาชงกระเจี๊ยบแดงมีสามารถใช้ลดความดันเลือดได้อย่างมีประสิทธิภาพ เนื่องจากบางครั้งการวิจัยเกี่ยวกับสมุนไพรมีการตีพิมพ์ในวารสารซึ่งไม่สามารถเข้าถึงได้โดยใช้ฐานข้อมูลอิเล็กโทนิกส์ และการวิจัยที่ให้ผลในทางลบมักจะไม่ได้รับการตีพิมพ์[23]

กระเจี๊ยบแดงเป็นพืชสมุนไพรที่สามารถนำมาใช้ประโยชน์ได้หลายส่วน ในประเทศอินเดีย แอฟริกาและเม็กซิโก ใช้ทุกส่วนที่อยู่เหนือดินของพืชชนิดนี้ทางการแพทย์ โดยใช้สารสกัดของใบหรือกลีบเลี้ยง เป็นยาขับปัสสาวะ กระตุ้นการหลั่งน้ำดี เป็นยาแก้ไข้ ลดความหนืดของเลือดและกระตุ้นให้ลำไส้มีการบีบตัว ในแอฟริกาตะวันออก มีการใช้สารสกัดจากกลีบเลี้ยง ซึ่งเรียกว่า "Sudan tea" บรรเทาอาการไอ และใช้น้ำกระเจี๊ยบแดง ร่วมกับเกลือ พริกไทย มหาหิงคุ์และน้ำเชื่อมในการรักษาภาวะเบื่ออาหาร[24] สำหรับประเทศไทย ข้อมูลจากสถาบันการแพทย์แผนไทยระบุว่า ยอดและใบของกระเจี๊ยบแดงช่วยย่อยอาหาร ละลายเสมหะ ขับปัสสาวะ เป็นยาบำรุงธาตุ และยาระบาย ใช้ตำพอกฝี ต้มน้ำชะล้างแผล กลีบเลี้ยงช่วยทำให้สดชื่น ขับน้ำดี ลดไข้ แก้ไอ แก้นิ่ว แก้กระหายน้ำ ส่วนเมล็ดมีสรรพคุณลดไขมันในเลือด บำรุงเลือด บำรุงธาตุ ขับน้ำดี แก้ปัสสาวะขัดและเจ็บ[25] จากที่กล่าวมาข้างต้นจะเห็นว่ากระเจี๊ยบแดงเป็นพืชสมุนไพรอีกชนิดหนึ่งที่มีความเป็นไปได้สูงในการนำมาใช้ในเป็นสมุนไพรพื้นบ้านตลอดจนเพื่อศึกษาทดลองและพัฒนาเป็นยาแผนปัจจุบัน

การวิจัยเพื่อศึกษาถึงประสิทธิภาพทางคลินิกของกระเจี๊ยบแดงในอนาคต ควรมีการออกแบบงานวิจัยโดยใช้รูปแบบการวิจัยแบบสุ่มและมีการปกปิดแบบสองทาง (double blinding) มีการเปรียบเทียบกับยาหลอกหรือยาที่เป็นมาตรฐานของการรักษาในปัจจุบัน ระยะเวลาศึกษาต้องเอื้อให้สามารถเห็นผลของยาต่อการเปลี่ยนแปลงของภาวะโรคได้

นอกจากนี้ ควรคำนวณขนาดกลุ่มตัวอย่างที่เหมาะสม และสำหรับผลิตภัณฑ์จากกระเจี๊ยบแดงที่จะนำมาศึกษา ควรผ่านการระบุและตรวจวิเคราะห์ปริมาณสารสำคัญ โดยหน่วยงานที่มีมาตรฐานและไม่เกี่ยวข้องกับการวิจัย


## กิตติกรรมประกาศ

งานวิจัยนี้ได้รับทุนสนับสนุนจากสำนักงานกองทุนสนับสนุนการวิจัย (สกว.)


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*Original Article*

# A Systematic Review of Clinical Efficacy of *Hibiscus sabdariffa*

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## ABSTRACT

*Hibiscus sabdariffa* is a medicinal plant widely used in several countries for a long time. Nowadays, a number of effects including antihypertensive effect, prevention and treatment of urinary tract infection, anti-oxidation, and anti-atherosclerotic effect have been reported. However, since the results from studies were inconclusive, a conclusion on whether *Hibiscus sabdariffa* possesses such beneficial effects is highly needed. This study aimed to examine the efficacy and tolerability of *Hibiscus sabdariffa* compared to other interventions in randomized controlled trials by means of a systematic review. We searched studies and relevant information from Medline (1966-2006), Cumulative Index to Nursing Allied Health Literature (CINAHL) (1982-2006), International Pharmaceutical Abstracts (IPA) (1970 – 2006), Current Content, Cochrane Library, and Thai Index Medicus, bibliographies of retrieved articles and experts in the field.

There were 66 clinical trials examining effects of *Hibiscus sabdariffa*. We found five trials studying the efficacy of Roselle on human; however, only two were randomized controlled trials. These two studies were included in our present study. The first trial tested antihypertensive effect of the tea of dried calyx of *Hibiscus sabdariffa* compared with captopril (25 mg every 12 hours) in patients with mild to moderate hypertension. The study found no difference regarding efficacy and tolerability between *Hibiscus sabdariffa* tea and captopril. The second study reported that at day 12 of the treatment, sour tea (the tea made from *Hibiscus sabdariffa*) significantly reduced both systolic and diastolic blood when compared with baseline ($P < 0.01$). The two studies included in this systematic review had a relatively low quality (Jadad's score of 2 for both). In conclusion, the antihypertensive effect of *Hibiscus sabdariffa* is somewhat evident but well conducted randomized controlled trials are highly needed to confirm such antihypertensive effect, and to examine also its other clinical benefits.

**Key words:** systematic review, clinical efficacy, *Hibiscus sabdariffa*

***Thai Pharm Health Sci J 2006;1(3):219-225***[§]

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[§] 11th year of Srinakharinwirot Journal of Pharmaceutical Sciences

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2007; **16**: 1031–1037
Published online 6 June 2007 in Wiley InterScience (www.interscience.wiley.com) **DOI**: 10.1002/pds.1429

ORIGINAL REPORT

# Utilisation review of clopidogrel: are they used under the FDA-approved indications?†

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## SUMMARY

**Background** Clopidogrel has shown benefit in patients with increased risk of cardiovascular diseases. Due to its high acquisition cost and its increased use, this study was conducted to review the use of clopidogrel based on the Food and Drug Administration (FDA)-approved indications and the ST-segment elevation myocardial infarction (STEMI).

**Method** This was a cross-sectional study conducted at a tertiary-care, university-affiliated hospital in the Northern part of Thailand. Medical records of patients receiving clopidogrel during January 2005 to February 2006 were reviewed. Baseline characteristics of patients along with specific information regarding the use of clopidogrel were collected. Data were analysed using descriptive statistics.

**Result** A total of 191 patients were included in this utilisation review (95 and 96 were inpatient and outpatient, respectively). The use of clopidogrel was deemed appropriate in 82.7% of cases including 72.2% for FDA-approved indications and 10.5% for STEMI. Clopidogrel/aspirin combination was indicated in 93 patients; however, 22 patients received clopidogrel monotherapy. On the contrary, 10 patients received clopidogrel/aspirin combination when only clopidogrel monotherapy was indicated. Moreover, 60% of patients who received clopidogrel monotherapy had no history of aspirin intolerance or recurrent events while on aspirin therapy.

**Conclusion** The results showed that the majority of clopidogrel use was deemed appropriate based on FDA-approved indications and for medically justified indication. However, a significant number of patients received clopidogrel instead of aspirin while no aspirin intolerance was documented. Therefore, efforts should be made to promote the appropriate use of this agent to improve patient outcomes. Copyright © 2007 John Wiley & Sons, Ltd.

KEY WORDS — clopidogrel; drug use evaluation; utilisation review

*Received 24 December 2006; Revised 11 April 2007; Accepted 30 April 2007*

## INTRODUCTION

Antiplatelet is unquestionably one of the standard therapies for the prevention and treatment of atherothrombotic diseases including myocardial infarction (MI), ischemic stroke/transient ischemic attack (TIA) and peripheral arterial disease (PAD).[1–8] Among the available antiplatelet agents, aspirin has been considered to be the gold standard due to its proven effectiveness in both primary and secondary prevention of atherothrombotic diseases. However, due to its adverse drug reaction profiles, attempts have been made to search for novel antiplatelets with improved safety profile.[9–11] Among the newer antiplatelets introduced into clinical use since 1990s, clopidogrel, a member of adenosine diphosphate receptor antago-

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† No conflict of interest was declared.

nists, is perhaps the most well-studied antiplatelet in the modern era of antiplatelet research. Clopidogrel has been shown to be slightly more effective than aspirin in the reduction of MI, ischemic stroke and vascular death among patients with history of MI, ischemic stroke/TIA and PAD.[12,13] However, the role of clopidogrel is clearly expanded in clinical use based on the dual antiplatelet therapy concept which is supported by several large randomised controlled trials in the prevention of cardiovascular diseases.[14–19] A combination of aspirin with clopidogrel has been shown to be superior to aspirin alone in the reduction of cardiovascular morbidity and mortality among patients with acute coronary syndrome,[14,15] patients undergoing percutaneous coronary intervention (PCI)[16,17] and ST-segment elevation (STEMI) with or without fibrinolytic therapy.[18,19] Results of these trials also show clear advantage of clopidogrel over aspirin in terms of safety profile, most notably, and gastrointestinal side effects.

Despite its clear evidence of benefit and improved safety profile,[12–21] clopidogrel is associated with high acquisition cost. In the era of healthcare budget reform, promoting rational use of clopidogrel based on proven clinical evidence is the key step to maximise the cost-effectiveness of such treatment. Previous studies aiming to evaluate the use of clopidogrel suggested that inappropriate use of this agent is not uncommon.[22,23] In Thailand, data on this issue are currently lacking. Therefore, we conducted this study in order to evaluate the use of clopidogrel in the hospital which may be of benefit in finding measures to promote the cost-effective use of clopidogrel.

## METHOD

This study was a retrospective medical record review conducted at a tertiary-care, university-affiliated hospital located in the Northern part of Thailand. The study protocol was approved by the Ethics Committee of the hospital. To ensure that our data reflected the most current practice based on current evidence, all patients receiving clopidogrel during January 2005 to February 2006 were identified using pharmacy database and served as our pool population. There were a total of 847 medical records which included 353 inpatient records and 423 outpatient records. Random sampling was performed to select 110 records from each group. To avoid duplication since one patient may have medical record both as inpatient and outpatient, once a patient has been sampled out of the pool population from the inpatient records, the outpatient record of the same patient will not be chosen again. During the record retrieval, 15 and 14 inpatient and outpatient records were missing, respectively. Therefore, only 95 inpatient records and 96 outpatient records were included in the final data analysis.

### *Data collection*

We reviewed medical records of the samples and collected patient data using a standardised data collection form. The form included demographic information, past medical history, dosage regimen of clopidogrel and indication information. We determined specifically whether clopidogrel was used in accordance to the Food and Drug Administration (FDA)-approved indications. The FDA-approved indications for the combination therapy of clopidogrel and aspirin include unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI) and PCI.[12] The FDA-approved indications for clopidogrel monotherapy are MI, ischemic stroke/TIA and PAD.[12] Recent evidence has also supported the use of combination therapy for ST-segment elevation myocardial infarction (STEMI).[18,19]

For patients with multiple visits, we chose the most recent visit as the date to determine the indication for clopidogrel use. Patient's diagnosis was collected if it was written in the medical records. However, if the diagnosis was not recorded, we retrospectively reviewed all previous visits in which clopidogrel was prescribed. As it was possible that patient's diagnosis was not documented, we specifically reviewed for information regarding sign and symptoms, laboratory findings and physical examinations to determine whether they were consistent with the diagnostic guideline of American College of Cardiology/American Heart Association (ACC/AHA).[1–5] Two cardiologists were consulted to determine whether the guideline is applicable and used in the hospital where data collection took place. In addition, to determine whether clopidogrel was used in accordance to the recommended fashion set by AHA/ACC guidelines, we also looked at the pattern of drug use including dosage regimen, duration of therapy, as secondary outcome measures.

### *Statistical analysis*

Data were analysed using descriptive statistics. The percentage of patients using clopidogrel with certain indications was reported. For sample size estimation, we calculated that 95 patients were required to estimate the proportion of 56% for using clopidogrel



DOI: 10.1002/pds

with FDA-approved indications with the acceptable level of error of 10% and confidence level of 95 (alpha = 0.05).[22,24] The sample size required plus 15% addition to compensate for missing medical records was 110 patients.

## RESULTS

A total of 191 patients were included in our final data analysis. Among these patients, 95 medical charts were from the inpatient department (IPD) and 96 medical charts were from the outpatient department (OPD) (Figure 1).

Patients' characteristics were shown in Table 1. The mean age of our study population was 68.9 ± 11.4 years. The most common co-morbidities were hypertension (61.8%), diabetes (44.5%) and dyslipidemia (39.8%). Approximately 75% of this population had a history of documented vascular disease including ischemic heart disease (103/191 or 53.9%) and ischemic stroke (40/191 or 20.9%). Based on these data, our study population can be considered as a high-risk group for serious cardiovascular events. The most common types of health insurance were the Civil Servant Medical Benefit Scheme (73.8%) and Universal Coverage Scheme (22%). Background therapies are also listed in Table 1.

Combination of clopidogrel and aspirin was more commonly used in the IPD group compared with the OPD group (75.8% vs. 35.4%). In contrast, clopidogrel monotherapy was more commonly used in the OPD group compared with the IPD group (64.6% vs. 24.2%). The pattern of clopidogrel use was presented in Table 2. The majority of clopidogrel use was 75 mg daily.

### *Indications for the use of clopidogrel*

About 82.7% (158/191) of clopidogrel use was based on Thai FDA-approved indications or medically justified indications. A total of 20 patients (10.5%) used clopidogrel because of STEMI; a new medically justified indication without FDA approval, while the remaining 138 patients (72.2%) received clopidogrel based on FDA-approved indications. These indications included ischemic stroke (31.2%: 43/138), post-myocardial infarction (1.4%: 2/138), acute coronary syndrome (53.6%: 74/138) and percutaneous intervention (13.8%: 19/138; Table 3).

There were 93 patients who were diagnosed with acute coronary syndrome or underwent PCI, conditions where combination therapy of clopidogrel and aspirin was warranted. However, we found that 71 patients received such combination, while clopidogrel monotherapy was used in 22 (24%) patients. Among patients receiving clopidogrel monotherapy, only 14 patients had documented history of aspirin intolerance, which might be a potential justification for the usage of clopidogrel monotherapy.

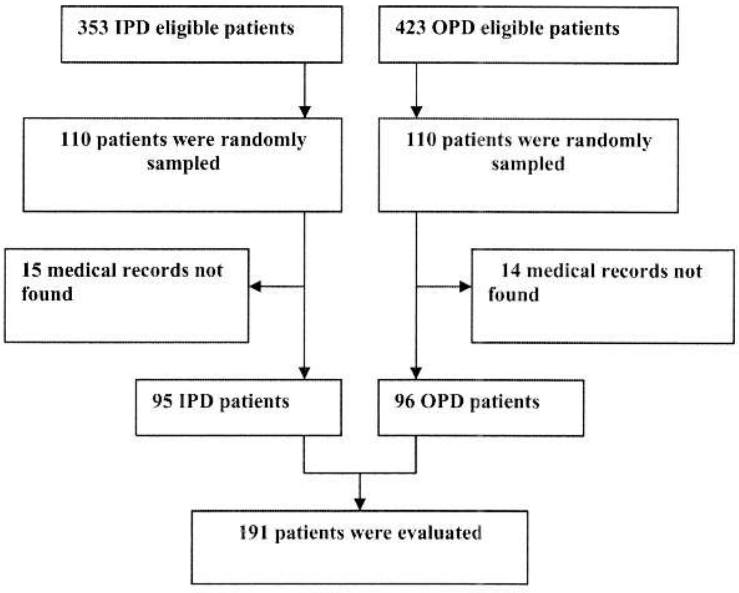


Figure 1. Study profile



DOI: 10.1002/pds

Table 1. Demographic data

| | Overall ($n = 191$) | IPD ($n = 95$) | OPD ($n = 96$) |
|---|---|---|---|
| Age (years) | 68.9 (11.4) | 68.2 (11.2) | 69.6 (11.6) |
| Males *n* (%) | 105 (55%) | 60 (63.2%) | 45 (46.9%) |
| Health insurance *n* (%) | | | |
| Civil servant medical benefit scheme | 141 (73.8%) | 55 (57.9%) | 86 (89.6%) |
| Universal coverage scheme | 42 (22%) | 36 (37.9%) | 6 (6.3%) |
| Social security insurance scheme | 4 (2.1%) | 3 (3.2%) | 1 (1.0%) |
| Others | 3 (1.6%) | 1 (1.1%) | 2 (2.1%) |
| Medical history *n* (%) | | | |
| Hypertension | 118 (61.8%) | 61 (64.2%) | 57 (59.4%) |
| Diabetes | 85 (44.5%) | 39 (41.1%) | 46 (47.9%) |
| Dyslipidemia | 76 (39.8%) | 38 (40%) | 38 (39.6%) |
| Congestive heart failure | 34 (17.8%) | 25 (26.3%) | 9 (9.4%) |
| Hemorrhagic stroke | 3 (1.6%) | 0 (0.0%) | 3 (3.1%) |
| Atrial fibrillation | 4 (2.1%) | 4 (4.2%) | 0 (0.0%) |
| Atherothrombotic diseases *n* (%) | | | |
| Ischemic heart disease | 103 (53.9%) | 46 (48.4%) | 57 (59.4%) |
| Ischemic stroke | 40 (20.9%) | 9 (9.5%) | 31 (32.3%) |
| Medication | | | |
| Beta blockers | 92 (48.2%) | 46 (48.4%) | 46 (47.9%) |
| Calcium channel blockers | 27 (14.1%) | 7 (7.4%) | 20 (20.8%) |
| Angiotensin converting enzyme inhibitors | 71 (37.2%) | 43 (45.3%) | 28 (29.2%) |
| Angiotensin II receptor blockers | 39 (20.4%) | 11 (11.6%) | 28 (29.2%) |
| Nitrate | 108 (56.5%) | 66 (69.5%) | 42 (43.8%) |
| Statins | 134 (70.2%) | 71 (74.7%) | 63 (65.6%) |
| Fibrate | 4 (2.1%) | 1 (1.1%) | 3 (3.1%) |
| Aspirin | 106 (55.0%) | 75 (75.8%) | 34 (35.4%) |

IPD, inpatient department; OPD, outpatient department.

Out of 45 patients with indications for clopidogrel monotherapy (ischemic stroke and post-myocardial infarction), 22% (10/45) received combination therapy of clopidogrel and aspirin. Only two patients had a documented history of recurrent ischemic stroke or MI, while the other eight patients had no information indicating the potential need for combination therapy. For the other 35 patients, 60% (21/35) had no history of aspirin intolerance or recurrent events of stroke or MI while on aspirin therapy, situations where the use of clopidogrel as an alternative to aspirin would be justified.

### *Medically justified indications for clopidogrel*

Out of 20 patients using clopidogrel under an indication of STEMI, 17 patients received combination therapy whereas the remaining three patients received clopidogrel alone. All three patients had documentation of having current bleeding during the hospitalisation.

Table 2. Pattern of clopidogrel used

| Clopidogrel regimen | Overall ($n = 191$) | IPD ($n = 95$) | OPD ($n = 96$) |
|---|---|---|---|
| Clopidogrel with aspirin *n* (%) | | | |
| 300 mg then 75 mg OD | 29 (15.2%) | 29 (30.5%) | 0 (0.0%) |
| 150 mg then 75 mg OD | 1 (0.5%) | 1 (1.1%) | 0 (0.0%) |
| 75 mg OD | 76 (39.8%) | 42 (44.2%) | 34 (35.4%) |
| All | 106 (55.5%) | 72 (75.8%) | 34 (35.4%) |
| Clopidogrel monotherapy *n* (%) | | | |
| 300 mg then 75 mg OD | 2 (1.0%) | 2 (2.1%) | 0 (0.0%) |
| 150 mg then 75 mg OD | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| 75 mg OD | 83 (43.5%) | 21 (22.1%) | 62 (64.6%) |
| All | 85 (44.5%) | 23 (24.2%) | 62 (64.6%) |

IPD, inpatient department; OPD, outpatient department.



DOI: 10.1002/pds

Table 3. Indication for Clopidogrel

| Indication | Overall ($n = 191$) | IPD ($n = 95$) | OPD ($n = 96$) |
|---|---|---|---|
| FDA-approved *n* (%) | | | |
| Ischemic stroke | 43 (22.5%) | 12 (12.6%) | 31 (32.3%) |
| Acute coronary syndromes | 74 (38.7%) | 49 (51.6%) | 25 (26.0%) |
| PCI | 19 (10.0%) | 7 (7.4%) | 12 (12.5%) |
| Post-myocardial infarction | 2 (1.0%) | — | 2 (2.1%) |
| ALL | 138 (72.2%) | 68 (71.6%) | 70 (72.9%) |
| Medically justified *n* (%) | | | |
| STEMI | 20 (10.5%) | 18 (18.9%) | 2 (2.1%) |
| FDA-approved and STEMI *n* (%) | 158 (82.7%) | 86 (90.5%) | 72 (75.0%) |

ACS, acute coronary syndromes; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; IPD, inpatient department; OPD, outpatient department.

### *Clopidogrel use without FDA-approved or medically justified indications*

Thirty-three of 191 patients (33/191, 17.3%) received clopidogrel with neither FDA-approved indication nor STEMI. All 33 patients had indications for the use of aspirin such as coronary heart disease, hypertension and diabetes. However, only 13 patients had documented potential contraindications to aspirin therapy or history of aspirin intolerance. These conditions included gastrointestinal bleeding (5), peptic ulcer (3), dyspepsia (4) and hemorrhagic stroke (1).

## DISCUSSION

Our findings demonstrated that the majority of clopidogrel use was consistent with FDA-approved indications or supported by current clinical evidence. However, there are certain areas for improvement that are of major importance both in the clinical and cost-effectiveness aspects.

Although clopidogrel has an approved indication in the reduction of MI, ischemic stroke and vascular death among patients with history of MI, ischemic stroke/TIA and PAD, its use as first-line therapy in the absence of documented history of aspirin intolerance may not be appropriate. In the CAPRIE study, clopidogrel reduced nonfatal and fatal cardiovascular events, compared to aspirin, with the relative risk reduction of 8.7%.[13] Numerous clinical practice guidelines have clearly indicated that aspirin should be used as first-line therapy in patients with ischemic stroke or PAD for the secondary prevention of cardiovascular thrombotic events.[4–8,25] Clopidogrel was recommended as an option in patients having contraindications for the use of aspirin. Our study found that a large proportion (21/35) of clopidogrel monotherapy was used in patients without clear contraindications to aspirin therapy. Policy makers and clinicians may have to consider identifying the exact place of therapy of clopidogrel under this condition.

Since most of the inappropriate use of clopidogrel monotherapy was found in outpatient services, the introduction of prescribing guidelines for clopidogrel monotherapy may be of benefit. Such guidelines should focus on promoting the appropriate use of clopidogrel by introducing measure to ascertain clear or documented contraindication to aspirin prior to prescribing clopidogrel monotherapy. Once such guidelines are implemented, a formal evaluation should be performed to assess the appropriateness of the practice model.

The usage pattern of clopidogrel/aspirin combination is of significant importance. As reported in this study, significant portion of patients did not receive such combination when indicated, despite having no clear contraindication to aspirin. As a result, clinical effect may not be achieved optimally. This is of major clinical implication especially for patients undergoing PCI with stent implantation, a condition where dual antiplatelet therapy is mandatory to avoid acute and subacute thrombosis.

On the contrary, certain patient population received combination therapy where the risk may outweigh benefits. There were 10 patients for whom secondary prevention of ischemic stroke was listed as indication for clopidogrel/aspirin combination. However, as recently shown in the Management of Atherothrombosis with Clopidogrel in High-risk patients (MATCH) study, such combination did not provide extra protection than clopidogrel alone and may indeed increase the risk of major bleeding.[26] In this



DOI: 10.1002/pds

situation, clinicians may have extrapolated the clinical use of medications to indications not supported by current clinical trial evidence despite being theoretically sound. Alternatively, clinicians may use combination therapy because they are not aware of the recent findings from the MATCH study. This points out the importance of clinicians and policy makers keeping themselves up to date regarding clinical evidence and utilising it as part of evaluation tools to improve patient outcome.

The results in our study are consistent with another published study. Kubler *et al.*[22] found that most of the use of clopidogrel was evidence-based but not appropriate according to prescribing guidelines. Our study is the first utilisation review conducted to determine whether the use of clopidogrel is supported by current evidence. The exploration of clopidogrel usage pattern helps us to understand the potential room for improvement to support rational use of this important drug.

Certain limitations exist in this study. A concern regarding the quality of data collected by retrospective study design is of importance for the validity of the study. A common problem with retrospective chart review is incomplete documentation of medical records. However, we have made our best attempt to solve the missing data problem especially in some patients with missing Thai FDA-approved indications by specifically reviewing clinical information consistent with the current diagnostic guideline to revive the missing diagnosis. However, it must be noted that our efforts may not be completely successful.

To our knowledge, this study is the first utilisation review of clopidogrel in Thailand. It provides clinicians and hospital policy makers with the current pattern of clopidogrel usage in a hospital in Thailand. It is important to note that there has not been a guideline for clopidogrel use developed in the study setting. Our findings would provide a direction for clinicians to develop strategies to promote the appropriate use of this agent to improve outcomes. It is undeniable that these results might not be generalisable to other hospitals in Thailand. It, at least, prompts the policy makers in other settings to consider conducting a study to assess its use and compare the pattern across hospitals in the country.

Because of scarcity of resources in Thailand, policy makers have to consider the best ways to allocate resources to maximise outcomes of the population. At the time the study was conducted, prices of 1-month supply of enteric-coated aspirin and clopidogrel in Thailand were approximately 2 and 60 USD, respectively. The pricing difference of this magnitude is important considering the nationwide impact on healthcare budget. Clopidogrel is one of the examples of medications with high budget impact in a hospital. The 2005 annual expenditure of clopidogrel at a hospital was about 8.5 million baht (242 857 USD). If we count the number of cases receiving clopidogrel monotherapy based FDA-approved indication without contraindications of aspirin, as unnecessary conditions, the use of clopidogrel in 54 patients was not needed. It was estimated that the expenditure will be reduced by a quarter or 2.4 million baht (68 571 USD) per year, if clopidogrel could have been used in only cases needed. Hospital policy makers and clinicians might want to consider forming a team to develop criteria of its use and implement it strategically to improve rationale use of drug. A formal cost-effectiveness study might provide information critical to the team for deciding in what kind of population clopidogrel is needed.

While the results of this study shed some light on the issue of clopidogrel use, another side of the coin should also be explored. There might be some other patients whose condition requires clopidogrel therapy either as monotherapy or combination therapy but do not receive it. However, since the use of clopidogrel was one of our inclusion criteria, this issue has not been answered by our study. This may be a potential research question to be explored.

While the reason to use a medication is important, the way the medication is used is also of great importance. Usage pattern of clopidogrel including the loading dose in acute setting, the timing of loading dose, the duration of clopidogrel use especially in patients with drug-eluting stent, may have significant impact on patient outcomes. These issues deserve further analysis, which may help us to understand more the usage compliance by the healthcare system of such an important medication.

In conclusion, our study showed that the majority of clopidogrel use was deemed appropriate based on FDA-approved indication and for medically justified indication. However, significant number of patients received clopidogrel instead of aspirin while no aspirin intolerance was documented. Therefore, efforts should be continued to promote the appropriate use of this agent to improve patient outcomes.

## ACKNOWLEDGEMENTS

This study is supported by a grant from the Thailand Research Fund and an unrestricted grant from Sanofi-Aventis (Thailand). We would like to thank Dr. Tomorn Tongsri and Dr. Poj Jianmongkol for their assistance and Mrs Nopawan Jeanpeerapong for providing assistance regarding access to medical records.

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Original Article

# การวิเคราะห์ต้นทุน-ประสิทธิผลของการดูแลผู้ป่วยเบาหวานชนิดที่ 2 แบบการบริหารจัดการโรคในบริบทโรงพยาบาลชุมชน โดย CORE Diabetes Model

# Cost-Effectiveness Analysis of Type 2 Diabetes Disease Management in District Hospital Context: An Analysis Using CORE Diabetes Model

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*Received: 2 April, 2007* *Accepted: 14 June, 2007*

## Abstract

Type 2 diabetes is a chronic disease which is a major health problem. Currently, the American Diabetes Association published clinical practice recommendations for diabetes care, prevention and management of complications and treatment goal. However, diabetes care in Thailand has not been complied with the guideline particularly in district hospitals due to limited resource. More than 50% of diabetic patients do not achieve target goal. The aims of this study were to calculate the projected long term clinical outcomes and cost-effectiveness analysis of diabetes disease management compared with diabetes usual care. CORE Diabetes Model was used to calculate life expectancy, quality-adjusted life expectancy (QALY), incidence of diabetes complications, lifetime cost and incremental cost-effectiveness ratio (ICER) using time frame of 35 years and health care provider perspective. Over a 35 year period, life expectancy were 9.52 and 8.39 years which were equivalent to 6.59 and 5.73 QALYs for disease management and usual care, respectively. An ICER of disease management as compared with usual care was 12,607 Baht per QALY. Moreover, disease management can decrease incidence of complications and improve time alive and free of complication. Sensitivity analysis showed that improvement in hemoglobin A1c, systolic blood pressure and coverage of renal replacement therapy led to improve cost-effectiveness. In conclusion, type 2 diabetes disease management is considered the cost-effectiveness management in district hospital context.

**Keywords:** Disease management, diabetes, cost-effectiveness

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## บทคัดย่อ

โรคเบาหวานชนิดที่ 2 เป็นโรคเรื้อรังที่เป็นปัญหาทางสาธารณสุขที่สำคัญ ปัจจุบันมีหลักฐานการศึกษาสนับสนุนถึงประสิทธิผลการดูแลผู้ป่วยเบาหวานโดยแนวทางการรักษาของ American Diabetes Association (ADA) 2006 ได้แนะนำการดูแลผู้ป่วยเบาหวานและเป้าหมายในการรักษาเพื่อป้องกันการเกิดโรคแทรกซ้อนจากเบาหวาน อย่างไรก็ตามการดูแลผู้ป่วยเบาหวานในประเทศไทยยังไม่เป็นไปตามแนวทางการรักษา และมีผู้ป่วยมากกว่าร้อยละ 50 ที่มีผลลัพธ์การรักษาต่ำกว่าเป้าหมายการรักษาโดยเฉพาะในโรงพยาบาลชุมชนที่มีทรัพยากรจำกัดกว่าโรงพยาบาลขนาดใหญ่ การศึกษานี้จึงมีวัตถุประสงค์เพื่อทำนายผลลัพธ์ทางคลินิกและวิเคราะห์ต้นทุน-ประสิทธิผลของการดูแลผู้ป่วยเบาหวานแบบ disease management เปรียบเทียบกับ usual care ในผู้ป่วยเบาหวานชนิดที่ 2 อายุมากกว่าหรือเท่ากับ 40 ปี ในบริบทโรงพยาบาลชุมชน โดยใช้ CORE Diabetes Model ในการคำนวณอายุคาดของผู้ป่วย (life expectancy) จำนวนปีชีพที่ปรับด้วยคุณภาพชีวิต (quality-adjusted-life-expectancy, QALY) อุบัติการณ์ของการเกิดภาวะแทรกซ้อน ต้นทุนตลอดชีพ (lifetime cost) และอัตราส่วนต้นทุนที่เพิ่มขึ้นต่อหน่วยประสิทธิผล (incremental cost-effectiveness ratio, ICER) ของการดูแลแบบ disease management เปรียบเทียบกับ usual care ภายใต้มุมมองของผู้ให้บริการทางสุขภาพ กำหนดกรอบระยะเวลาในการศึกษา คือ 35 ปี ผลการศึกษาพบว่าอายุคาดของผู้ป่วยที่ได้รับการดูแลแบบ disease management และ usual care เท่ากับ 9.52 และ 8.39 ปี หรือมีจำนวนปีชีพที่ปรับด้วยคุณภาพชีวิตเท่ากับ 6.59 และ 5.73 QALYs ตามลำดับ ค่า ICER ของการดูแลแบบ disease management เปรียบเทียบกับ usual care เท่ากับ 12,607 บาท/QALY โดยการดูแลแบบ disease management สามารถลดอุบัติการณ์ของการเกิดภาวะแทรกซ้อน และเพิ่มระยะเวลาการมีชีวิตที่ไม่เกิดภาวะแทรกซ้อนเมื่อเปรียบเทียบกับ usual care การวิเคราะห์ความไวพบว่าความคุ้มค่าทางเศรษฐศาสตร์จะเพิ่มขึ้นเมื่อประสิทธิผลของการลด hemoglobin A1c ความดันโลหิต และมีการเข้าถึงการรักษาทดแทนไตได้มากขึ้น สรุปได้ว่าการดูแลผู้ป่วยเบาหวานชนิดที่ 2 แบบ disease management ในบริบทของโรงพยาบาลชุมชนมีความคุ้มค่าทางด้านเศรษฐศาสตร์

**คำสำคัญ:** การบริหารจัดการโรค เบาหวาน การวิเคราะห์ต้นทุน-ประสิทธิผล

## บทนำ

โรคเบาหวานชนิดที่ 2 เป็นโรคเรื้อรังที่เป็นปัญหาทางสาธารณสุขที่สำคัญ และมีการขยายตัวของปัญหาเพิ่มขึ้น เนื่องจากโรคเบาหวานเป็นสาเหตุสำคัญของการเกิดภาวะแทรกซ้อนของหลอดเลือดขนาดเล็กและขนาดใหญ่ และการเสียชีวิตเมื่อเปรียบเทียบกับประชากรทั่วไป มีผลทำให้ต้องสูญเสียค่าใช้จ่ายในการดูแลรักษาเป็นมูลค่ามหาศาล โดยจำนวนของผู้ป่วยเบาหวานทั่วโลกในปี ค.ศ. 2000 มีการคาดประมาณว่ามีจำนวน 172 ล้านคน และจะเพิ่มจำนวนอีกเท่าตัวในปี ค.ศ. 2030 (Wild et al, 2000) สำหรับประเทศไทยมีความชุกของผู้ป่วยเบาหวานร้อยละ 9.6 ของประชากรที่มีอายุตั้งแต่ 35 ปีขึ้นไป หรือประมาณ 2.4 ล้านคน (Aekplakorn et al, 2003) จากการสำรวจการสูญเสียปีสุขภาวะ (Disability Adjusted Life Year, DALY) ของประเทศไทย พบว่าผู้ป่วยเบาหวานมีจำนวนปีสุขภาวะคิดเป็น 435,749 DALY ซึ่งเป็นสาเหตุอันดับ 3 ของการสูญเสีย DALY ในเพศหญิง และอันดับ 5 ในเพศชาย (สุวิทย์, 2549)

โรคเบาหวานเป็นโรคเรื้อรังที่การให้การดูแลรักษาที่เหมาะสมสามารถลดอัตราการเสียชีวิตและการเกิดโรคแทรกซ้อนได้ ในปัจจุบันมีหลักฐานการศึกษายืนยันประสิทธิผลของการรักษาและการป้องกันการเกิดโรคแทรกซ้อนของหลอดเลือดขนาดเล็กและขนาดใหญ่ ได้แก่ การควบคุมระดับน้ำตาล การลดปัจจัยเสี่ยงต่างๆ เช่น ภาวะไขมันในเลือดสูง ความดันโลหิตสูง และการสูบบุหรี่ การใช้ยากลุ่ม angiotensin converting enzyme inhibitor (ACEI) และ aspirin เป็นต้น แนวทางการรักษาของ ADA (2006) ได้กำหนดเป้าหมายของการรักษาให้ควบคุมระดับ hemoglobin A1c (HbA1c) ให้มีค่า <7% ความดันโลหิต

<130/80 mmHg ระดับไขมัน low density lipoprotein cholesterol (LDL-C) <100 mg/dl ระดับ high density lipoprotein cholesterol (HDL-C)>40 mg/dl และ triglyceride (TG) <150 mg/dl และแนะนำให้มีการตรวจคัดกรองปัจจัยเสี่ยงและโรคแทรกซ้อนอย่างสม่ำเสมอ เช่น การตรวจจอประสาทตา การตรวจคัดกรองภาวะ microalbuminuria เป็นต้น

ประเทศไทยมีการดูแลผู้ป่วยเบาหวานในรูปแบบคลินิกเบาหวาน คุณภาพของการบริการในแต่ละโรงพยาบาลมีความแตกต่างกันขึ้นกับปัจจัยในด้านต่างๆ เช่น บุคลากร เครื่องมือ และงบประมาณ โรงพยาบาลชุมชนเป็นหน่วยบริการที่มีบทบาทสำคัญในการดูแลผู้ป่วยเบาหวานส่วนใหญ่ของประเทศ และมีความสำคัญต่อการสนับสนุนการจัดบริการในระดับปฐมภูมิ อย่างไรก็ตามด้วยข้อจำกัดในด้านต่างๆ พบว่าผลการตรวจประเมินคุณภาพการดูแลผู้ป่วยโรคเบาหวานของหน่วยบริการที่ขึ้นทะเบียนเป็นคู่สัญญากับสำนักงานหลักประกันสุขภาพแห่งชาติ ปี 2548 โดยการตรวจสอบจากเวชระเบียนจากโรงพยาบาล 61 จังหวัด โรงพยาบาลชุมชนมีการตรวจประเมินและเฝ้าระวังภาวะแทรกซ้อนอย่างน้อย 1 ครั้งต่อปี ต่ำกว่าโรงพยาบาลในระดับอื่นโดยมีเพียงร้อยละ 3.3 ที่มีการตรวจ HbA1c ร้อยละ 12.9 มีการตรวจจอประสาทตา ร้อยละ 19.4 มีการตรวจแผลที่เท้า ร้อยละ 25.4 มีการตรวจโปรตีนในปัสสาวะ และร้อยละ 22.4 มีการตรวจไขมันในเลือด เปรียบเทียบกับโรงพยาบาลระดับใหญ่กว่า ได้แก่ โรงพยาบาลทั่วไป โรงพยาบาลศูนย์ และโรงพยาบาลมหาวิทยาลัย ที่ร้อยละ 21.1-62.1 มีการตรวจ HbA1c ร้อยละ 34.5-35.8 มีการตรวจจอประสาทตา ร้อยละ 20.6-27.0 มีการตรวจแผลที่เท้า ร้อยละ 33.9-51.7 มีการตรวจโปรตีนในปัสสาวะ และร้อยละ 33.4-66.7 มีการตรวจไขมันในเลือด (พงษ์พิสุทธิ์, 2549) และเมื่อพิจารณาข้อมูลการศึกษาผลลัพธ์ทางคลินิกในการดูแลผู้ป่วยเบาหวานของโรงพยาบาลและหน่วยบริการปฐมภูมิจำนวน 44 หน่วย 18 เครือข่ายทั่วประเทศ ของผู้ป่วยเบาหวานจำนวน 5,903 คน ซึ่งได้ดำเนินการในปี 2548 พบว่าเมื่อพิจารณาตามเป้าหมายการรักษาของ ADA (2006) มีผู้ป่วยเพียงร้อยละ 39.7 ที่สามารถควบคุมระดับน้ำตาลได้ตามเกณฑ์ HbA1c < 7% ผู้ป่วยร้อยละ 62 มีระดับ LDL-C > 100 mg/dl ร้อยละ 31.3 มี HDL-C < 40 mg/dl และร้อยละ 56.9 ที่มี TG > 150 mg/dl (สุพัตรา และคณะ, ม.ป.ป.)

การบริหารจัดการโรค (disease management) เป็นแนวคิดหนึ่งของระบบการดูแลสุขภาพแบบผสมผสานซึ่งมีองค์ประกอบหลักประกอบด้วย การคัดกรองผู้ป่วยที่มีความเสี่ยงเพื่อให้ได้รับการดูแลที่เหมาะสม การใช้แนวทางการรักษาที่มีหลักฐานเชิงวิชาการ การสนับสนุนให้ทีมบุคลากรทางการแพทย์มีการรักษา การติดตาม หรือตรวจคัดกรองภาวะแทรกซ้อน การจัดรูปแบบบริการเพื่อเพิ่มความรู้ความสามารถในการดูแลตนเองและความร่วมมือในการรักษาของผู้ป่วย และการเก็บรวบรวมข้อมูลเพื่อประเมินผลลัพธ์ของการจัดการทั้งในด้านคลินิกและเศรษฐศาสตร์ (Disease Management Association of America, 2006) แนวคิดนี้ได้นำมาใช้ในการบริหารจัดการของประกันสุขภาพเอกชนและในบางรัฐของประเทศสหรัฐอเมริกา และยุโรปบางประเทศ สำหรับประเทศไทยการนำแนวคิดนี้มาใช้ในการดูแลผู้ป่วยเบาหวานเป็นทางหนึ่งที่จะช่วยส่งเสริมคุณภาพการรักษาและส่งผลลัพธ์ที่ดีต่อผู้ป่วย อย่างไรก็ตามยังส่งผลต่อการเพิ่มงบประมาณในการบริหารจัดการเช่นกัน อีกทั้งปัจจุบันการประเมินผลลัพธ์ของการดูแลผู้ป่วยเบาหวานทั้งในทางคลินิกและต้นทุนเป็นเพียงในระยะสั้น ดังนั้นการทำนายหรือคาดประมาณผลลัพธ์ทางคลินิกและการวิเคราะห์ต้นทุน-ประสิทธิผลของการดูแลผู้ป่วยเบาหวานแบบ disease management เปรียบเทียบกับ usual care ในบริบทของโรงพยาบาลชุมชนในระยะยาวจึงอาจเป็นข้อมูลหนึ่งที่มีความสำคัญในการกำหนดแนวทางและสนับสนุนการดูแลผู้ป่วยเบาหวานให้มีความเหมาะสมมากยิ่งขึ้น

## วัตถุประสงค์

1. เพื่อทำนายผลลัพธ์ทางคลินิกของการดูแลผู้ป่วยเบาหวานชนิดที่ 2 อายุ 40 ปีขึ้นไป แบบ disease management เปรียบเทียบกับการดูแลแบบ usual care ในบริบทของโรงพยาบาลชุมชน โดยแสดงอยู่ในรูปอายุคาดของผู้ป่วย (life expectancy)

และการเกิดภาวะแทรกซ้อน

2. เพื่อวิเคราะห์ต้นทุน-ประสิทธิผลของการดูแลผู้ป่วยเบาหวานชนิดที่ 2 ซึ่งมีอายุ 40 ปีขึ้นไป โดยแสดงผลอัตราส่วนต้นทุนที่เพิ่มขึ้นต่อหน่วยประสิทธิผล (incremental cost-effectiveness ratio, ICER) ในรูปของต้นทุนตลอดชีพ (lifetime cost) ที่เพิ่มขึ้นต่อจำนวนปีชีพที่ปรับด้วยคุณภาพชีวิต (quality-adjusted- life-expectancy, QALY) จากการดูแลแบบ disease management เปรียบเทียบกับ usual care

## วิธีการศึกษา

การวิจัยนี้ใช้ CORE Diabetes Model ในการคำนวณผลลัพธ์ของการวิจัย โดย CORE Diabetes Model เป็นตัวแบบจำลอง (simulation model) ทางคอมพิวเตอร์แบบ internet based ของผู้ป่วยเบาหวาน มีลักษณะเป็น Markov model และ Monte Carlo simulation ประกอบด้วย 15 ตัวแบบย่อยที่จำลองการเกิดภาวะแทรกซ้อนที่สัมพันธ์กับเบาหวาน ภายในตัวแบบย่อยประกอบไปด้วยสถานะสุขภาพ (health state) ของการเกิดภาวะแทรกซ้อน ดังตารางที่ 1 มีระยะเวลาในการเปลี่ยนสถานะสุขภาพในแต่ละรอบเท่ากับ 1 ปี โดยผู้ป่วยหนึ่งคนสามารถเกิดภาวะแทรกซ้อนได้มากกว่าหนึ่งชนิด (Palmer et al, 2004)

ข้อมูลความน่าจะเป็นในการเปลี่ยนสถานะสุขภาพ (transitional probability) ใช้ค่าที่กำหนดจาก CORE Diabetes Model (รายละเอียดแสดงใน Palmer et al, 2004) โดยได้มีการปรับเปลี่ยนข้อมูลอัตราการเสียชีวิตตามกลุ่มอายุและเพศให้เหมาะสมกับประเทศไทย โดยใช้ข้อมูลอัตราตายตามกลุ่มอายุ จำแนกตามเพศ พ.ศ. 2548 (สำนักนโยบายและยุทธศาสตร์, 2006) และอัตราการเสียชีวิตจากการทำ dialysis จากการศึกษาต้นทุนประสิทธิผลของยากลุ่ม thiazolidinedione (TZD) ซึ่งใช้ CORE Diabetes Model ในบริบทของประเทศไทยก่อนหน้านี้ (Chirakup, 2006) กรอบระยะเวลาในการศึกษานี้ คือ 35 ปี (ตารางที่ 1)

**ตารางที่ 1** สถานะสุขภาพภายในตัวแบบจำลองการเกิดภาวะแทรกซ้อน

| ตัวแบบย่อย | สถานะทางสุขภาพ |
|---|---|
| Myocardial infarction | No history of MI, history of MI, death following MI |
| Angina | No angina, history of angina |
| Congestive heart failure | No CHF, history of CHF, death following CHF |
| Stroke | No history of stroke, history of stroke, death following stroke |
| Peripheral vascular disease | No PVD, PVD |
| Neuropathy | No neuropathy, neuropathy |
| Foot care | No foot ulcer, un infected ulcer, infected ulcer, healed ulcer, uninfected recurrent ulcer, infected recurrent ulcer, gangrene, history of amputation, death |
| Retinopathy | No retinopathy, BDR, PDR, SVL |
| Macular edema | No macular edema, macular edema |
| Cataract | First cataract with operation, second cataract with operation |
| Nephropathy | No renal complication, microalbuminuria, gross proteinuria, ESRD, death following ESRD |
| Hypoglycemia | Alive, death (due to hypoglycemia) |
| Ketoacidosis | Alive, death (due to ketoacidosis) |
| Lacticacidosis | Alive, death (due to lactic acidosis) |
| Nonspecific mortality | Alive and death |

MI, myocardial infarction; CHF, congestive heart failure; PVD, peripheral vascular disease; BDR, background diabetic retinopathy; PDR, peripheral diabetic retinopathy; SVL, severe vision loss; ESRD, end stage renal disease

## กลุ่มตัวอย่าง

Base case ในการวิจัยนี้ คือ ผู้ป่วยเบาหวานชนิดที่ 2 อายุ 40 ปีขึ้นไปในบริบทโรงพยาบาลชุมชน ลักษณะของกลุ่มตัวอย่างที่ใช้เป็นตัวแทนอาศัยฐานข้อมูลจากโครงการวิจัยเพื่อพัฒนาและติดตามประเมินผลระบบบริการสุขภาพปฐมภูมิในประเทศไทยเป็นหลัก (สุพัตรา และคณะ, ม.ป.ป.) ซึ่งเป็นการวิจัยที่มีการสุ่มตัวอย่างผู้ป่วยเบาหวานจากโรงพยาบาลและหน่วยบริการปฐมภูมิจำนวน 44 หน่วย 18 เครือข่ายทั่วประเทศ จำนวน 5,903 คน มีเพศหญิง ร้อยละ 70.76 เมื่อจำแนกตามช่วงอายุประกอบด้วย ร้อยละ 18.38 อายุ 40-49 ปี ร้อยละ 32.45 อายุ 50-59 ปี ร้อยละ 30.98 อายุ 60-69 ปี และร้อยละ 18.19 อายุ 70 ขึ้นไป ภายใน CORE Diabetes Model ผู้วิจัยสามารถใส่ข้อมูลลักษณะพื้นฐานของกลุ่มเป้าหมายที่จะทำการศึกษาได้ ประกอบด้วยหลายตัวแปรที่มีผลในการทำนายผลลัพธ์ทางคลินิก ตัวแปรที่อาศัยข้อมูลจากโครงการวิจัยนี้ ได้แก่ เพศ ค่าเฉลี่ยของอายุ ดัชนีมวลกาย (body mass index, BMI) ระยะเวลาได้รับการวินิจฉัยเบาหวาน HbA1c total cholesterol HDL-C LDL-C TG สัดส่วนของผู้สูบบุหรี่ สัดส่วนผู้ป่วยที่มี microalbuminuria และ macroalbuminuria

สำหรับตัวแปรค่าเฉลี่ย systolic blood pressure (SBP) จำนวนบุหรี่ที่สูบเฉลี่ยต่อวัน ปริมาณการบริโภคแอลกอฮอล์ สัดส่วนของผู้ป่วยที่มีประวัติ angina myocardial infarction (MI) atrial fibrillation (AF) congestive heart failure (CHF) stroke peripheral vascular disease (PVD) left ventricular hypertrophy (LVH) end stage renal disease (ESRD) การเกิดภาวะแทรกซ้อนทางตา ได้แก่ background diabetic retinopathy (BDR) proliferative diabetic retinopathy (PDR) macular edema (ME) cataract และ severe vision loss สัดส่วนผู้ป่วยที่มี peripheral neuropathy active ulcer healed ulcer และ history of amputation ข้อมูลดังกล่าวใช้ข้อมูลจากหลายแหล่งเนื่องจากการศึกษาข้อมูลระบาดวิทยาของผู้ป่วยเบาหวานในประเทศไทยในภาพรวมมีจำกัด ดังตารางที่ 2 ทั้งนี้ตัวแปรใดที่มีความแปรปรวนของข้อมูลจะทำการวิเคราะห์ความไวของการเปลี่ยนแปลงค่าตัวแปรที่มีผลต่อผลการศึกษาในภายหลัง (ตารางที่ 2)

**ตารางที่ 2** ลักษณะพื้นฐานของ base case

| Characteristic | Model simulation population | Data sources | Sensitivity analysis |
|---|---|---|---|
| Age (yr), mean±SD | 60.05±9.89 | สุพัตรา และคณะ (ม.ป.ป.) | - |
| Female (%) | 70.76 | สุพัตรา และคณะ (ม.ป.ป.) | - |
| BMI (kg/m$^2$), mean±SD | 25.21 | สุพัตรา และคณะ (ม.ป.ป.) | - |
| SBP (mmHg), mean±SD | 127.06±18.03 | สิริวรรณ (2549) | - |
| Duration (yr), mean±SD | 6.54±5.75 | สุพัตรา และคณะ (ม.ป.ป.) | - |
| HbA1c (%), mean±SD | 7.79±1.78 | สุพัตรา และคณะ (ม.ป.ป.) | - |
| Total cholesterol (mg%), mean±SD | 200.63±45.42 | สุพัตรา และคณะ (ม.ป.ป.) | - |
| HDL-C (mg%), mean±SD | 46.06±11.92 | สุพัตรา และคณะ (ม.ป.ป.) | - |

**ตารางที่ 2** ลักษณะพื้นฐานของ base case (ต่อ)

| Characteristic | Model simulation population | Data sources | Sensitivity analysis |
|---|---|---|---|
| LDL-C (mg%), mean±SD | 115.86±38.42 | สุพัตรา และคณะ (ม.ป.ป.) | - |
| TG (mg%), mean±SD | 204.06±140.21 | สุพัตรา และคณะ (ม.ป.ป.) | - |
| Smoking (%) | 9.01 | สุพัตรา และคณะ (ม.ป.ป.) | - |
| Alcohol consumption (Oz/d) | 8.69 | จุรีย์ และเศรณีย์ (2548) | - |
| Cigarette/day | 10.8 | สำนักงานสถิติแห่งชาติ (ม.ป.ป.) | - |
| Myocardial infarction (%) | 4.2 | Chirakup (2006) | 1.5-4.2 |
| Angina (%) | 4.3 | Chirakup (2006) | 1.5-14.4 |
| Peripheral vascular disease (%) | 3.9 | เพชร และคณะ (2547) | 1.5-5.8 |
| Stroke (%) | 4.4 | เพชร และคณะ (2547) | 2.1-5.4 |
| Congestive heart failure (%) | 3.0 | Chirakup (2006) | 1.5-6* |
| Atrial fibrillation (%) | 1.7 | Chirakup (2006) | 0.85-3.4* |
| Left ventricular hypertrophy (%) | 13.0 | Sriratanasathavorn et al (2000) | 6.5-26* |
| Microalbuminuria (%) | 36.1 | สุพัตรา และคณะ (ม.ป.ป.) | - |
| Gross proteinuria (%) | 10.8 | สุพัตรา และคณะ (ม.ป.ป.) | - |
| End stage renal disease (%) | 0.0014 | วิโรจน์ และคณะ (2544), อนุตตร (2545) | - |
| Background diabetic retinopathy (%) | 19.2 | Nitiapinyasakul (1999) | 12.0-27.3 |
| Prolipherative diabetic retinopathy (%) | 2.6 | Nitiapinyasakul (1999) | 2.6-9.4 |
| Severe vision loss (%) | 5.34 | Nitiapinyasakul (1999) | 0.5-6.5 |
| Macular edema (%) | 5.28 | Nitiapinyasakul (1999) | 2.20-5.28 |
| Cataract (%) | 58.2 | Nitiapinyasakul (1999) | 18.1-58.2 |
| Infected ulcer (%) | 0.5 | Chetthakul et al (2006) | - |
| Healed ulcer (%) | 4.4 | Chetthakul et al (2006) | - |
| History of amputation (%) | 1.0 | Chetthakul et al (2006) | - |
| Neuropathy (%) | 16.8 | Chetthakul et al (2006) | 9.0-35.6 |

*แปรผันค่าในการทำ sensitivity analysis 50-200% จาก base case

## องค์ประกอบของการดูแลผู้ป่วยเบาหวาน

องค์ประกอบของการดูแลผู้ป่วยเบาหวานในกลุ่ม disease management และ usual care สำหรับการวิจัยนี้มีความแตกต่างกันดังนี้ (ตารางที่ 3)

การดูแลผู้ป่วยเบาหวานแบบ disease management ในบริบทของโรงพยาบาลชุมชน หมายถึง การดูแลผู้ป่วยเบาหวานตามแนวทางการรักษาของ ADA

**ตารางที่ 3** องค์ประกอบของการรักษาเบาหวานและการป้องกันการเกิดโรคแทรกซ้อน

| การรักษาเบาหวานและการป้องกันการเกิดโรคแทรกซ้อน | ร้อยละของผู้ป่วยที่ได้รับการดูแล | |
|---|---|---|
| | Disease management | Usual care |
| 1. การให้ยาป้องกันชนิดปฐมภูมิ | | |
| aspirin | 100 | 24 |
| ACEI ในผู้ป่วยตรวจพบ microalbuminuria และ macroalbuminuria | 100 | 28 |
| statin ในผู้ป่วยที่มี LDL-C > 100 mg/dl | 100 | 23 |
| 2. การให้ยาป้องกันชนิดทุติยภูมิ | | |
| aspirin | 100 | 36.5 |
| ACEI | 100 | 36.1 |
| statin | 100 | 45.7 |
| 3. การตรวจ HbA1c 1 ครั้ง/ปี | 100 | 3.3 |
| 4. การตรวจไขมันในเลือด 1 ครั้ง/ปี: total cholesterol, HDL-C, LDL-C, TG | 100 | 14.8 |
| 5. การตรวจคัดกรองภาวะแทรกซ้อนทางไต 1 ครั้ง/ปี: microalbuminuria และ gross proteinuria | 100 | 25.4 |
| 6. การตรวจคัดกรองภาวะแทรกซ้อนทางตา 1 ครั้ง/ปี | 100 | 12.9 |
| 7. การให้ยากลุ่ม TZD | 1.14 | 0 |
| 8. การให้ยากลุ่ม ARB | 0.05 | 0 |
| 9. การตรวจเท้าและการให้คำแนะนำในการดูแลเท้า | 100 | 19.4 |

(2006) โดยมีการปรับจำนวนครั้งของการตรวจประเมินและคัดกรองภาวะแทรกซ้อนเป็น 1 ครั้ง/ปี และกำหนดให้ได้รับยาในกลุ่ม TZD และ angiotensin receptor blocker (ARB) เมื่อไม่สามารถรักษาด้วยยาอื่น รายละเอียดมีดังนี้

1. การให้ยาป้องกันชนิดปฐมภูมิ ประกอบด้วย การให้ยา aspirin ในผู้ป่วยทุกราย การให้ยา ACEI ในผู้ป่วยที่ตรวจพบ microalbuminuria และ macroalbuminuria ที่ไม่มีข้อห้ามใช้ และการให้ statin ในผู้ป่วยที่มี LDL-C>100 mg/dl สัดส่วนของผู้ป่วยที่มีภาวะข้างต้นใช้ข้อมูลจาก โครงการวิจัยเพื่อพัฒนาและติดตามประเมินผลระบบบริการสุขภาพปฐมภูมิในประเทศไทย (สุพัตรา และคณะ, ม.ป.ป.) โดยกำหนดให้ผู้ป่วยเบาหวานที่มี serum creatinine มากกว่าหรือเท่ากับ 2 เป็นผู้ป่วยที่มีข้อห้ามใช้ของ ACEI

2. การให้ยาป้องกันชนิดทุติยภูมิ ได้แก่ การให้ยา aspirin ACEI และ statin

3. การตรวจ HbA1c 1 ครั้ง/ปี

4. การตรวจระดับไขมัน 1 ครั้ง/ปี

5. การตรวจคัดกรองภาวะแทรกซ้อนทางไต 1 ครั้ง/ปี

6. การตรวจคัดกรองภาวะแทรกซ้อนทางตา 1 ครั้ง/ปี

7. การให้ยากลุ่ม TZD ในผู้ป่วย insulin resistance ที่ไม่สามารถฉีดอินซูลินได้ กำหนดสัดส่วนผู้ป่วยที่ได้รับยาเท่ากับ 1.2 % อ้างอิงจาก

ฐานข้อมูลอิเล็กทรอนิกส์โรงพยาบาลลำปลายมาศ จังหวัดบุรีรัมย์ที่มีการใช้ TZD ตามข้อบ่งใช้นี้ ในปีงบประมาณ 2549

8. การให้ยากลุ่ม ARB ในผู้ป่วยที่ทนผลข้างเคียงจาก ACEI ไม่ได้ กำหนดสัดส่วนของผู้ป่วยเท่ากับ 0.05% (Gerstein et al., 2000)

9. การตรวจเท้าและการให้คำแนะนำในการดูแลเท้า 1 ครั้ง/ปี

การดูแลแบบ usual care ในบริบทของโรงพยาบาลชุมชนสำหรับการวิจัยนี้ หมายถึง การดูแลผู้ป่วยเบาหวานของโรงพยาบาลชุมชนแบบปกติในปัจจุบัน ซึ่งอาศัยข้อมูลจากหลายแหล่งเพื่อเป็นตัวแทนของ usual care ได้แก่ การตรวจประเมินและคัดกรองภาวะแทรกซ้อน ได้แก่ การตรวจ HbA1c การตรวจจอประสาทตา การตรวจเท้า และการตรวจไขมันในเลือด ใช้ข้อมูลจากรายงานผลการตรวจประเมินคุณภาพการดูแลผู้ป่วยโรคเบาหวานและความดันโลหิตสูง (พงษ์พิสุทธิ์, 2549) การกำหนดสัดส่วนของผู้ป่วยที่ได้รับการป้องกันชนิดปฐมภูมิด้วยยา aspirin และ ACEI และการคัดกรองภาวะ microalbuminuria ใช้ข้อมูลก่อนการให้ intervention จากการศึกษาของ สิริวรรณ (2549) สัดส่วนที่ได้รับยา statin สำหรับการป้องกันชนิดปฐมภูมิ ใช้ข้อมูลพื้นฐานของผู้ป่วยจากการศึกษาของ ปิยวรรณ (2549) สัดส่วนที่ได้รับการป้องกันชนิดทุติยภูมิด้วยยา aspirin, ACEI และ statin ใช้ข้อมูลจากการศึกษาของ Chirakup (2006) และกำหนดให้ผู้ป่วยในกลุ่มนี้ไม่ได้รับการรักษาด้วยยากลุ่ม TZD และ ARB

## การวิเคราะห์ประสิทธิผล

การวิเคราะห์ข้อมูลประสิทธิผลที่เกิดขึ้นในอนาคตจะทำการปรับลดด้วยอัตราลด (discount rate) 3% ต่อปี การวิจัยนี้กำหนดให้การดูแลแบบ diasease management สามารถควบคุมระดับ HbA1c และ SBP ในผู้ป่วยแต่ละรายได้ดีกว่ากลุ่ม usual care โดยให้มีค่า HbA1c ไม่เกิน 7% และ SBP ไม่เกิน 130 mmHg สำหรับกลุ่ม usual care กำหนดให้มี HbA1c และ SBP ไม่เปลี่ยนแปลง ดังนั้นผลของการดูแลแบบ disease management ต่อ HbA1c และ SBP ที่ใช้ในตัวแบบจึงมีค่าเท่ากับค่าเฉลี่ยของผลต่างระหว่างกลุ่มในผู้ป่วยแต่ละราย ซึ่งประสิทธิผลจากการลด HbA1c และ SBP การให้ยา aspirin ACEI และ statin การตรวจเท้าและให้คำแนะนำในการดูแลเท้า ใช้ข้อมูลจาก CORE Diabetes Model สำหรับอัตราการเกิด hypoglycemia เนื่องจากการดูแลแบบ disease management มีการควบคุมระดับ HbA1c เข้มงวดกว่า usual care ดังนั้นจึงมีความเสี่ยงต่อการเกิด hypoglycemia ได้มากกว่า การวิจัยนี้ใช้ข้อมูลจากการศึกษา UKPDS 33 (1998) โดยกลุ่ม disease management ใช้ข้อมูลกลุ่ม intensive ที่รักษาด้วย insulin ซึ่งมีการเกิด hypoglycemia ร้อยละ 1.8 ในกลุ่ม usual care ใช้ข้อมูลจากกลุ่ม conventional ซึ่งมีการเกิด hypoglycemia ร้อยละ 0.7

ภายใน CORE Diabetes Model ผู้ป่วย ESRD จะถูกกำหนดให้ได้รับการรักษาทดแทนไตด้วยการทำ hemodialysis (HD) peritoneal dialysis (PD) และ kidney transplant (KT) แต่เนื่องจากในขณะนี้โครงการประกันสุขภาพถ้วนหน้ายังไม่ครอบคลุมการรักษาทดแทนไตในผู้ป่วยไตวายเรื้อรังระยะสุดท้าย นอกเหนือจากสวัสดิการข้าราชการที่สามารถเบิกค่าใช้จ่ายได้และผู้ประกันตนตามพระราชบัญญัติประกันสังคมที่ให้สิทธิในการเบิกค่าใช้จ่ายได้บางส่วน ทำให้ผู้ป่วยส่วนหนึ่งต้องรับผิดชอบค่าใช้จ่ายเอง การวิจัยนี้ได้กำหนดสัดส่วนผู้ป่วยที่สามารถเข้าถึงบริการเท่ากับร้อยละ 23.2 (วิโรจน์ และคณะ, 2543) และคำนวณสัดส่วนของผู้ป่วยไตวายเรื้อรังระยะสุดท้ายให้ได้รับการทำ HD PD และ KT โดยใช้ข้อมูลจากรายงานโครงการ Thailand renal replacement therapy registry (อนุตตร, 2545)

สำหรับข้อมูลคุณภาพชีวิตของผู้ป่วยเบาหวานในแต่ละสถานะสุขภาพกำหนดให้มีค่าอยู่ระหว่าง 0-1 ในลักษณะของ utility weight ใช้ข้อมูลจาก CORE Diabetes Model

## การวิเคราะห์ต้นทุนค่ารักษาพยาบาล

การวิเคราะห์ต้นทุนรวมของการวิจัยนี้ใช้มุมมองของผู้ให้บริการสุขภาพ (health care provider perspective) ดังนั้นองค์ประกอบของต้นทุนจะพิจารณาเฉพาะต้นทุนทางตรงด้านสุขภาพ (direct health care cost) เท่านั้น ไม่รวมถึงต้นทุนทางตรงที่ไม่เกี่ยวข้องกับการแพทย์ (direct non-health care cost) เช่น ค่าเดินทาง ค่าพาหนะของผู้ป่วย และ

ต้นทุนทางอ้อม (indirect cost) เช่น รายได้ที่สูญเสียไปจากการหยุดงานเนื่องจากการป่วย เป็นต้น ค่าของเงินที่ใช้แสดงค่าใช้จ่ายเป็นค่าของเงินบาทในปี พ.ศ. 2549 สำหรับ base case โดยทำการปรับลดค่าใช้จ่ายในอนาคตที่จะเกิดขึ้นด้วยอัตราลด (discount rate) 3% ต่อปี

องค์ประกอบของต้นทุนประกอบด้วย 2 ส่วน คือ ต้นทุนในการรักษาเบาหวานและการป้องกันการเกิดโรคแทรกซ้อน และต้นทุนในการรักษาโรคแทรกซ้อนจากเบาหวาน

1. การรักษาเบาหวานและการป้องกันการเกิดโรคแทรกซ้อน

ราคายาต่อหน่วยใช้ค่ามัธยฐานของราคาจัดซื้อปกติของโรงพยาบาลในสังกัดกระทรวงสาธารณสุข ปีงบประมาณ 2549 (ศูนย์ข้อมูลข่าวสารด้านเวชภัณฑ์, 2549) โดยขนาดยา aspirin statin และ ACEI ที่กำหนดในการวิจัยใช้ขนาด usual dose ตามแนวทางการรักษา (ADA, 2006) ต้นทุนในการตรวจ HbA1c การตรวจระดับไขมัน การตรวจ microalbuminuria และ gross proteinuria ใช้ข้อมูลจากอัตราค่าบริการสาธารณสุขเพื่อใช้สำหรับการเบิกจ่ายค่ารักษาพยาบาลในสถานพยาบาลของทางราชการ (กรมบัญชีกลาง, 2549) ต้นทุนของการตรวจคัดกรอง diabetic retinopathy ใช้ข้อมูลจากการศึกษาของ สุภาพร (2548) ดังตารางที่ 4 สำหรับการดูแลรักษาอื่นๆ เช่น การให้ยาลดระดับน้ำตาลในเลือด และการรักษาโรคร่วมอื่นๆ กำหนดให้ทั้งสองกลุ่มไม่มีความแตกต่างกัน (ตารางที่ 4)

2. การรักษาโรคแทรกซ้อนจากเบาหวาน

ต้นทุนการรักษาที่เกิดขึ้นในแต่ละสถานะทางสุขภาพอาศัยค่ามัธยฐานของต้นทุนการรักษาในผู้ป่วยเบาหวานจากการศึกษาของ Chirakup (2006) โดยสถานะสุขภาพ PVD after healed ulcer healed ulcer history of amputation post cataract operation และ blindness ถูกกำหนดให้ไม่มีค่าใช้จ่ายการรักษา สำหรับการรักษา standard uninfected ulcer ใช้ค่า percentile ที่ 25 ของต้นทุนในการรักษา ulcer จากการศึกษาข้างต้น (ตารางที่ 5)

**ตารางที่ 4** ต้นทุนต่อปีของการให้ยา และการตรวจคัดกรองภาวะแทรกซ้อนจากโรคเบาหวาน

| | **Base case** | **ต้นทุนต่อปี (บาท)** | **Sensitivity analysis** |
|---|---|---|---|
| Statin | simvastatin 20 mg/d | 548 | 10-80 mg |
| Aspirin | aspirin 120 mg/d | 55 | - |
| ACEI | enalapril 20 mg/d | 376 | 10-80 mg |
| TZD | rosiglitazone 8 mg | 29,254 | 4 mg |
| ARB | valsartan 160 mg | 11,709 | 80-320 mg |
| Screening for microalbuminuria | 1 ครั้ง/ปี | 270 | - |
| Screening for gross proteinuria | 1 ครั้ง/ปี | 20 | - |
| Eye screening | 1 ครั้ง/ปี | 118 | - |
| HbA1c | 1 ครั้ง/ปี | 150 | - |
| Lipid profile screening: Total cholesterol, HDL-C, LDL-C, TG | 1 ครั้ง/ปี | 200 | - |

**ตารางที่ 5** ต้นทุนของการรักษาภาวะแทรกซ้อน

| ภาวะแทรกซ้อน | | ต้นทุนการรักษา (บาท) |
|---|---|---|
| Myocardial infarction | Annual cost of first year | 41,603 |
| | Annual cost of following years | 27,447 |
| Angina | Annual cost of first year | 28,777 |
| | Annual cost of following years | 12,653 |
| Congestive heart failure | Annual cost of first year | 39,076 |
| | Annual cost of following years | 7,246 |
| Stroke | Annual cost of first year | 20,797 |
| | Annual cost of following years | 9,058 |
| Hemodialysis | Annual cost of first year | 352,665 |
| | Annual cost of following years | 331,165 |
| Peritoneal dialysis | Annual cost of first year | 408,083 |
| | Annual cost of following years | 361,416 |
| Kidney transplant | Annual cost of first year | 333,228 |
| | Annual cost of following years | 91,329 |
| Neuropathy | Annual cost of first year | 8,618 |
| | Annual cost of following years | 8,971 |
| Major hypoglycemia | | 7,677 |
| Laser treatment | | 1,756 |
| Cataract operation | | 11,403 |
| Amputation | | 48,602 |
| Amputation prosthesis | | 2,900 |
| Gangrene treatment (cost per month) | | 38,926 |
| Infected ulcer (cost per month) | | 2,496 |
| Standard uninfected ulcer (cost per month) | | 687 |

## การวิเคราะห์ความไว

การวิจัยนี้เป็นการวิเคราะห์ข้อมูลที่อาศัยตัวแบบจำลองจากตัวแปรหลายตัวซึ่งมีความไม่แน่นอน ดังนั้นค่า ICER ที่ได้อาจผันแปรตามการเปลี่ยนแปลงของตัวแปรที่สำคัญจึงได้ทำการวิเคราะห์ความไว (sensitivity analysis) ของ ICER ซึ่งอาจขึ้นกับความเปลี่ยนแปลงในกรณีดังต่อไปนี้

1. Baseline complication ได้แก่ สัดส่วนของผู้ป่วย MI angina PVD stroke BDR PDR SVL และ cataract จะผันแปรตามข้อมูลที่มีจากการศึกษาในประเทศไทย สำหรับ CHF AF LVH ME infected ulcer healed ulcer history of amputation และ neuropathy จะแปรผันค่าตั้งแต่ 50%-200% จาก base case

2. สัดส่วนของการเข้าถึงการรักษาทดแทนไต 100%

3. ผลของการลด HbA1c เปลี่ยนแปลงจาก base case ± 0.5% และ ±1% และผลของการลด SBP ผันแปรตั้งแต่ 30-200%

4. ขนาดยาในการรักษาและราคาต่อหน่วยของยา simvastatin และ enalapril

## ผลการศึกษา

ผลลัพธ์ภายใต้กรอบระยะเวลา 35 ปี ของการดูแลแบบ disease management มี life expectancy 9.52±5.51 ปี หรือมีจำนวนปีชีพที่ปรับด้วยคุณภาพชีวิตเท่ากับ 6.59±3.91 QALYs มีระยะเวลามากกว่า usual care ที่มี life expectancy 8.39±5.04 ปี หรือจำนวนปีชีพที่ปรับด้วยคุณภาพชีวิตเท่ากับ 5.73±3.52 QALYs โดยที่การดูแลแบบ disease management จะมีระยะเวลาการมีชีวิตที่ไม่เกิดภาวะแทรกซ้อน (time alive and free of complication) ยาวนานกว่า usual care (ตารางที่ 6) และสามารถลดอุบัติการณ์ในการเกิดภาวะแทรกซ้อนต่างๆ เมื่อเปรียบเทียบกับ usual care (ตารางที่ 7) แต่เป็นที่น่าสังเกตว่าการเกิด stroke cataract และการเสียชีวิตจาก ESRD CHF และ stroke ของการดูแลแบบ disease management สูงกว่า usual care ในขณะที่ disease management สามารถยืดระยะเวลาการมีชีวิตที่ไม่เกิด stroke และ cataract ได้ยาวนานกว่า รวมถึงมีการเกิด ESRD และ CHF ที่ต่ำกว่า ผลลัพธ์ดังกล่าวอาจเนื่องมาจากการดูแลแบบ disease management ที่ทำให้มี life expectancy ยาวนานกว่าจึงมีการเกิดภาวะแทรกซ้อนที่สัมพันธ์กับอายุได้มากกว่า usual care

เมื่อพิจารณาต้นทุนรวมเฉลี่ยที่กรอบระยะเวลา 35 ปี ของการดูแลแบบ disease management และ usual care มี lifetime cost เฉลี่ย 110,717±153,071 บาท และ 99,908±157,185 บาท ตามลำดับ โดยต้นทุนเฉลี่ยในการรักษาทั้งของสองกลุ่มที่ระยะเวลาต่างๆ แสดงดังตารางที่ 8 และเมื่อเปรียบเทียบการดูแลแบบ disease management และ usual care พบว่าค่า ICER ของการดูแลแบบ disease management จะเท่ากับ 9,518 บาทต่อหนึ่งปีชีพ หรือ 12,607 บาท/QALY

**ตารางที่ 6** ระยะเวลาการมีชีวิตที่ไม่เกิดภาวะแทรกซ้อน (time alive and free of complication)

| Complication | ระยะเวลาการมีชีวิตที่ไม่เกิดภาวะแทรกซ้อน, ปี | |
|---|---|---|
| | Disease management | Usual care |
| Any complications | 0.50 | 0.38 |
| Background diabetic retinopathy | 6.18 | 4.97 |
| Proliferative diabetic retinopathy | 11.01 | 9.37 |
| Microalbuminuria | 6.37 | 5.45 |
| Gross proteinuria | 10.76 | 8.97 |
| End stage renal disease | 12.28 | 10.46 |
| 1st Ulcer | 11.03 | 9.11 |
| Amputation | 12.03 | 10.20 |
| Neuropathy | 7.99 | 6.43 |
| Peripheral vascular disease | 11.52 | 9.78 |
| Congestive heart failure | 11.78 | 9.93 |
| Angina | 11.48 | 9.89 |
| Myocardial infarction | 11.73 | 9.77 |
| Stroke | 12.13 | 10.36 |
| Cataract | 4.87 | 4.13 |
| Macular edema | 8.69 | 7.12 |
| Severe vision loss | 10.61 | 9.01 |

**ตารางที่ 7** Cumulative incidence of complication (%)

| Complication | Cumulative incidence (%) | |
|---|---|---|
| | Disease management | Usual care |
| Background diabetic retinopathy | 40.34 | 45.61 |
| Prolipherative diabetic retinopathy | 3.84 | 5.30 |
| Macular edema | 36.44 | 38.66 |
| Severe vision loss | 14.15 | 14.43 |
| Cataract | 7.62 | 6.52 |
| Microalbuminuria | 15.00 | 17.75 |
| Gross proteinuria | 7.93 | 11.08 |
| End stage renal disease | 2.16 | 2.64 |
| ESRD death | 0.94 | 0.90 |
| First ulcer | 16.06 | 18.36 |
| First amputation | 4.64 | 5.64 |
| Recurrent amputation | 1.50 | 2.06 |
| Congestive heart failure | 24.66 | 27.36 |
| Angina | 6.33 | 5.65 |
| Myocardial infarction | 11.18 | 24.54 |
| Stroke | 7.70 | 7.22 |
| Neuropathy | 32.34 | 36.33 |
| Peripheral vascular disease | 6.76 | 7.10 |
| Death due to CHF | 22.04 | 21.96 |
| Death due to MI | 9.28 | 19.66 |
| Death due to stroke | 10.20 | 10.00 |
| Non-specific mortality | 45.94 | 37.10 |

**ตารางที่ 8** ต้นทุนรวมเฉลี่ยต่อรายของการดูแลแบบ disease management และ usual care ที่ระยะเวลาต่างๆ

| Years | Total cost (Baht) | |
|---|---|---|
| | Disease management | Usual care |
| 1 | 7,504 | 6,618 |
| 5 | 36,039 | 33,798 |
| 10 | 67,872 | 64,545 |
| 15 | 88,993 | 83,746 |
| 20 | 100,929 | 93,958 |
| 25 | 106,823 | 97,955 |
| 30 | 109,698 | 99,432 |
| 35 | 110,717 | 99,907 |

เมื่อจำแนกต้นทุนตามองค์ประกอบ พบว่าต้นทุนในการรักษาและการป้องกันในกลุ่ม disease management เฉลี่ยเท่ากับ 21,067 บาท สูงกว่า usual care ซึ่งมีค่าเท่ากับ 4,060 บาท แต่พบว่า disease management สามารถลดต้นทุนในการรักษาภาวะแทรกซ้อนของหัวใจและหลอดเลือด ภาวะแทรกซ้อนทางไต ภาวะแทรกซ้อนของระบบประสาทและการเกิดแผล โดยมีต้นทุนในการรักษาเท่ากับ 37,721 13,085 และ 33,371 บาท เมื่อเปรียบเทียบกับ usual care ซึ่งมีค่าเท่ากับ 42,794 13,085 และ 33,371 บาท ตามลำดับ อย่างไรก็ตามพบว่ากลุ่ม disease management มีค่าใช้จ่ายในการรักษา major hypoglycemia และภาวะแทรกซ้อนทางตาสูงกว่า โดยมีค่าใช้จ่ายเท่ากับ 3,989 และ 1,484 บาทตามลำดับ เปรียบเทียบกับ usual care ซึ่งมีค่าใช้จ่ายเท่ากับ 1,167 และ 954 บาท ตามลำดับ

## ผลการวิเคราะห์ความไว

เมื่อเปลี่ยนแปลงสัดส่วนของ baseline complication พบว่าค่า ICER มีค่าผันแปรในช่วง 4,296-19,257 บาท/QALY และเมื่อกำหนดให้สัดส่วนของการเข้าถึงการรักษาทดแทนไตเป็น 100% พบว่ามี ICER ลดลงจาก base caseเป็น 10,646 บาท/QALY ซึ่งพบแนวโน้มของค่า ICER ที่ลดลงเมื่อสัดส่วนของผู้ป่วยที่มีประวัติ stroke ลดลง

กรณีที่ประสิทธิผลในการดูแลมีการเปลี่ยนแปลงจาก base case โดยลด HbA1c เพิ่มขึ้น 0.5% และ 1% พบว่าการดูแลแบบ disease management จะมี life expectancy เพิ่มขึ้นเป็น 9.55 และ 9.69 ปี ตามลำดับ และมีค่า ICER ลดลงเท่ากับ 5,789 บาท/QALY และ 4,412 บาท/QALY ตามลำดับ และเมื่อผลต่อการลด HbA1c มีค่าลดลงพบว่าทำให้ life expectancy ลดลงในขณะที่ค่า ICER มีแนวโน้มเพิ่มขึ้น ในขณะที่การเปลี่ยนแปลงผลในการลด SBP 30-200% จาก base case จะทำให้ค่า ICER มีค่าผันแปรตั้งแต่ 9,874-13,474 บาท/QALY โดยพบว่าการลด SBP ได้เพิ่มขึ้นจะมีผลทำให้ค่า ICER มีแนวโน้มลดลง สำหรับขนาดยาและราคาต่อหน่วยของยา simvastatin และ enalapril พบว่าไม่มีผลต่อการเปลี่ยนแปลงค่า ICER

## สรุปและวิจารณ์ผลการศึกษา

การคาดประมาณผลลัพธ์ทางคลินิก และต้นทุนในการดูแลผู้ป่วยเบาหวานชนิดที่ 2 อายุ 40 ปีขึ้นไปของการดูแลแบบ disease management เปรียบเทียบกับการดูแลแบบ usual care ในบริบทของโรงพยาบาลชุมชน พบว่ามีค่า ICER 12,607 บาท/QALY โดยการดูแลแบบ disease management สามารถลดอุบัติการณ์ของการเกิดภาวะแทรกซ้อน และเพิ่มระยะเวลาการมีชีวิตที่ไม่เกิดภาวะแทรกซ้อนเมื่อเปรียบเทียบกับ usual care และเมื่อผลของการควบคุม HbA1c SBP และการเข้าถึงการรักษาทดแทนไตเพิ่มขึ้นจะมีผลให้ความคุ้มค่าทางเศรษฐศาสตร์เพิ่มมากขึ้น ในขณะที่ข้อมูล baseline complication ที่เป็นข้อจำกัดของการศึกษานี้ เมื่อทำ sensitivity analysis พบว่าทำให้ค่า ICER มีค่าผันแปรอยู่ในช่วงที่ไม่ทำให้ข้อสรุปด้านความคุ้มค่าทางเศรษฐศาสตร์เปลี่ยนแปลงไปมากนัก ICER ที่คำนวณได้จากการศึกษานี้ไม่ได้รวมต้นทุนของการดูแลผู้ป่วยเบาหวานในการมาติดตามการรักษาแต่ละครั้งที่นอกเหนือจากองค์ประกอบของต้นทุนในการศึกษานี้ เช่น ค่าตรวจ fasting plasma glucose ค่ายาลดระดับน้ำตาลในเลือด ค่ายาลดความดันโลหิต เป็นต้น ซึ่งจะทำให้มีค่า ICER สูงเพิ่มขึ้น ในการทำ sensitivity analysis ของการวิจัยนี้เป็นลักษณะ one-way sensitivity analysis และข้อมูลที่ใช้ในการวิเคราะห์ต้นทุน-ประสิทธิผลทั้งในส่วนความน่าจะเป็นในการเปลี่ยนสถานะทางสุขภาพประสิทธิผลของการลด HbA1c และ SBP ตลอดจนค่า utility ในการวิจัยนี้เป็นข้อมูลที่เป็นค่าเดียว (point estimate) จึงเป็นข้อจำกัดที่ไม่ได้ทำ probabilistic uncertainty analysis

เมื่อพิจารณาตามเกณฑ์ของ World Bank (1993) ที่กำหนดความคุ้มค่าทางเศรษฐศาสตร์ไว้ที่ 2-3 เท่าของรายได้เฉลี่ยต่อคนต่อปี การดูแลแบบ disease management ในผู้ป่วยเบาหวานชนิดที่ 2 จัดว่ามีความคุ้มค่าทางด้านเศรษฐศาสตร์ และเมื่อเปรียบเทียบกับการดูแลเฉพาะในด้านต่างๆ ในผู้ป่วยเบาหวานชนิดที่ 2 การดูแลแบบ disease management ยังอาจถือว่ามีความคุ้มค่าทางด้านเศรษฐศาสตร์ เช่น การตรวจคัดกรองพยาธิสภาพจอประสาทตาจากโรค

เบาหวาน มีค่า ICER เท่ากับ 85,976 บาทต่อการป้องกันตาบอดได้หนึ่งตา เมื่อเปรียบเทียบกลุ่มผู้ป่วยที่ได้รับการตรวจคัดกรองทุก 4 ปี กับกลุ่มผู้ป่วยที่ไม่ได้รับการตรวจคัดกรอง และผู้ป่วยที่ได้รับการตรวจคัดกรองทุก 3 ปี เปรียบเทียบกับ 4 ปี ทุก 2 ปี เปรียบเทียบกับทุก 3 ปี และทุกปีเปรียบเทียบกับทุก 2 ปี มีค่า ICER เท่ากับ 62,806 70,553 และ 95,865 บาทต่อการป้องกันตาบอดได้หนึ่งตา ตามลำดับ (สุภาพร, 2548) การศึกษาการใช้ statin สำหรับการป้องกันการเกิดภาวะแทรกซ้อนของโรคหลอดเลือดและหัวใจชนิดปฐมภูมิ มีค่า ICER เท่ากับ 20,608 บาท/QALY เมื่อเปรียบเทียบกับการไม่ได้รับยา statin (ปิยะวรรณ, 2549) การศึกษาการรักษาด้วยยา ACE-Inhibitors สำหรับโรคไต พบว่ามีค่า ICER 148,500 บาท/QALY เมื่อเปรียบเทียบการตรวจคัดกรองและใช้ยาในระยะ microalbuminuria กับการตรวจคัดกรองและใช้ยาในระยะ macroalbuminuria (พรรณทิพา, 2545) นอกจากนั้นกา ดูแลแบบ disease management มีความคุ้มค่าทางเศรษฐศาสตร์มากกว่าการรักษาเมื่อเกิดภาวะแทรกซ้อนแล้ว โดยที่การรักษาทดแทนไตด้วยการฟอกเลือดด้วยเครื่องไตเทียมและการล้างช่องท้องอย่างต่อเนื่องเปรียบเทียบกับการรักษาแบบประคับประคอง มีค่า ICER 7.7-8.5 แสนบาท/QALY และ 5.2-5.7 แสนบาท/QALY ตามลำดับ (Teerawattananon et al., 2007)

การนำแนวคิด disease management มาปรับใช้ในการดูแลผู้ป่วยเบาหวานเป็นวิธีหนึ่งที่จะช่วยเพิ่มคุณภาพและประสิทธิภาพในการดูแลผู้ป่วย และให้ผู้ป่วยสามารถเข้าถึงบริการได้อย่างเหมาะสม การสนับสนุนโรงพยาบาลชุมชนให้มีศักยภาพในการตรวจคัดกรองเพื่อเฝ้าระวังโรคแทรกซ้อนและให้การรักษาเพิ่มขึ้น การพัฒนาระบบฐานข้อมูลของผู้ป่วยเพื่อใช้สำหรับการประเมินผลลัพธ์ของการดูแลผู้ป่วยเบาหวานทางคลินิกและเศรษฐศาสตร์ในระยะยาว เป็นองค์ประกอบสำคัญที่จะทำให้การดูแลแบบ disease management มีประสิทธิภาพมากขึ้น รวมถึงการจัดรูปแบบบริการเพื่อเพิ่มความรู้ความสามารถในการดูแลตนเองและความร่วมมือในการรักษาของผู้ป่วยเป็นส่วนสำคัญที่จะสนับสนุนให้ผลลัพธ์ในการรักษาถึงเป้าหมายในขณะที่งบประมาณที่ใช้ในการจัดบริการไม่มากนักเมื่อเปรียบเทียบกับการให้บริการในด้านอื่น ซึ่งจะส่งผลให้การดูแลแบบ disease management มีความคุ้มค่าทางเศรษฐศาสตร์มากยิ่งขึ้น

## กิตติกรรมประกาศ

ได้รับทุนสนับสนุนจากทุนอุดหนุนและส่งเสริมการทำวิทยานิพนธ์ ปีการศึกษา 2549 จากบัณฑิตวิทยาลัย มหาวิทยาลัยขอนแก่น

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# A cost-effectiveness analysis of a community pharmacist-based smoking cessation programme in Thailand

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*Tob. Control* 2008;17;177-182; originally published online 19 Feb 2008; doi:10.1136/tc.2007.022368

# A cost-effectiveness analysis of a community pharmacist-based smoking cessation programme in Thailand

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Received 17 June 2007
Accepted 5 February 2008
Published Online First 19 February 2008

## ABSTRACT

**Objective:** To estimate the incremental cost-effectiveness ratio of a structured community pharmacist-based smoking cessation programme compared with usual care.

**Design:** A cost-effectiveness study using a healthcare system perspective

**Population:** Two simulated cohorts of smokers: male and female aged 40, 50 and 60 years who regularly smoke 10–20 cigarettes per day.

**Intervention and comparator:** A structured community pharmacist-based smoking cessation (CPSC) programme compared to usual care.

**Main outcome measure:** Cost per life year gained (LYG) attributable to the smoking cessation programme.

**Results:** The CPSC programme results in cost savings of 17 503.53 baht (£250; €325; $500) to the health system and life year gains of 0.18 years for men and; costs savings of 21 499.75 baht (£307; €399; $614) and life year gains of 0.24 years for women. A series of sensitivity analyses demonstrate that both cost savings and life year gains are sensitive to variations in the discount rate and the long-term smoking quit rate associated with the intervention.

**Conclusion:** From the perspective of the health system, the CPSC programme yields cost savings and life year gains. This finding provides important information for health policy decision-makers when determining the magnitude of resources to be allocated to smoking cessation service in community pharmacy.

Smoking is associated with increases in morbidity, mortality and healthcare costs worldwide.[1–3] It has also been recognised as an important cause of deaths and chronic diseases in Thailand. Annually, approximately 52 000 residents in Thailand die from smoking-related diseases.[4 5] Over 79% of lung cancer and 88% of chronic obstructive pulmonary diseases are caused by smoking.[6] In 1999, it was estimated that $6 million or 0.1% of Thai total healthcare expenditure was incurred for management of smoking-related diseases.[7]

Smoking cessation has been accepted as a crucial strategy in tobacco control because such intervention reduces the incidence and impact of a range of costly chronic diseases, improves health-related quality of life and yields savings in healthcare cost.[8–12] Evidence has consistently demonstrated the effectiveness of various health professional-based smoking cessation interventions.[13–19] However, in Thailand, a recent survey in 2005 revealed that less than 70% of smoking cessation clinics still provided services for Thai smokers who seek professional help.[20]

A community pharmacy provides an excellent setting in which to provide a smoking cessation programme, as the pharmacy would have regular contact with residents of the area.[21] In Thailand, more than 1000 community pharmacists were trained and provide smoking cessation services.[22] Based on a recent review of the literature, community pharmacist-based smoking cessation programmes have been shown to be cost effective.[23–32] However, several cost-effectiveness studies[30–32] calculated life years saved for successful quitters' estimates based on US population estimates.[33] We believe that such methods and estimates may not be applicable to the long-term outcomes of smoking cessation programmes in Thailand. Strictly speaking, these studies were conducted in countries that are different from Thailand in terms of life expectancy of population, healthcare system and medical costs of smoking-related diseases. Therefore, cost-effectiveness evidence of smoking cessation programmes in Thailand is still needed. The main purpose of this study is to determine the incremental cost-effectiveness ratio of a structured community pharmacist-based smoking cessation (CPSC) programme compared to a usual care in order to assist health policy decision-makers in determining whether resources should be allocated to support community pharmacist-based smoking cessation services in Thailand.

## METHODS

### Overall description

This analysis compares a structured CPSC programme and usual care. The CPSC programme includes systematic identification and documentation of smoking status; provision of a personalised and supportive advice on smoking cessation; an assessment a smoker's interest in quitting and level of nicotine dependence; and the provision of appropriate therapy with self-help materials and seven scheduled 10-minute follow-up visits. Usual care consists of discussion on smoking status, assessment of motivation and nicotine dependence, provision of brief advice and support as well as provision of therapy without follow-up care.

We use standard techniques in economic evaluation and decision analysis in order to assess the costs and effectiveness of a CPSC programme. A decision tree is used to depict the consequences of smoking cessation for those who continuously abstain from smoking for 12 months. These long-term outcomes are derived by applying a Markov

model of disease state transition to a simulated cohort of Thai residents. The Markov model links long-term smoking cessation to reductions in the risk of developing various important smoking related diseases comprising chronic obstructive pulmonary disease (COPD), lung cancer, stroke and cardiovascular diseases. In the base-case analysis, we have used a hypothetical cohort of Thai men and women aged 40 years, who regularly smoke 10–20 cigarettes per day. We use this base population because it is typical of Thai smokers.[34]

The healthcare system perspective is used in our analysis; hence only direct medical costs are included. The cost-effectiveness ratio is expressed as the incremental costs per life year saved. In this study, all analyses are performed using Microsoft Office Excel 2003. The Markov model simulates a hypothetical cohort according to age, sex and smoking status. All participants begin in a healthy state before transition to other health states. The model uses a cycle length of one year. Transitional probabilities are conditional on age, sex and smoking status. The absorbing state is death. The time horizon used in this study is the lifetime for a Thai resident.

### Likelihood of events

Event probabilities used in the model are shown in table 1. The likelihood of successful quitting was derived from a systematic review of randomised controlled trial data that assessed individuals who had stopped smoking for 12 continuous months.[35] The reported continuous quit rate was 14.3% in the CPSC group and 2.7% in the usual care group. Relapse rate and natural quit rate were not considered in our analysis because the existing cost-effectiveness study indicated they had a slight effect on the results.[30] In this study, we assumed that smokers who are abstinent at one year remain abstinent for life.

Risks of developing smoking-related diseases were based on international published studies. Based on a 10-year prospective cohort study,[36] the annual risk of COPD for smokers and ex-smokers was 1.22% and 0.34%, respectively. The risk of lung cancer, derived from an 8-year multi-ethnic cohort study,[37] was 0.24% for smokers and 0.08% for ex-smokers. We estimated the annual probabilities of developing coronary heart diseases (CHD) and stroke from the Framingham's risk equation as performed in Johannesson *et al*.[38] The equation yields the risk of cardiovascular disease using blood pressure and total cholesterol levels for Thai residents as derived from the InterASIA study.[39] We adopted a method developed by Johansson *et al*[40] to estimate transition probabilities for each sub-CHD health state. The transition probabilities for CHD were based on the proportion of the distribution of each health state within CHD (acute myocardial infarction, myocardial infarction unrecognised, chronic heart failure, angina and sudden death).

Age-specific mortality for the Thai population[6] was used as the transition probability from a healthy state to death. Probabilities of dying from smoking-related diseases were based on estimates in the Thai and international literature. In order to calculate the mortality rate from COPD, the age-specific Thai mortality rate was multiplied by the hazard ratio (or relative risk) of dying from COPD.[41] The lung cancer mortality rate was based on data from a 5-year cohort study[42] that followed lung cancer patients at 14 large hospitals in Thailand. The annual mortality rate for diseases within CHD were based on mortality estimates derived from the Framingham's equation using a similar approach to that used by Johanesson.[38]

### Costs

The total cost of smoking cessation interventions by community pharmacists were based on the summation of the pharmacists' training costs, the pharmacists' fee and the cost of medications. Cost of the pharmacists' training course was acquired from the Thai Pharmacy Network for Tobacco Control (PNTC).[22] Pharmacists' fees were taken from a costing study of 40 Thai community pharmacies conducted by Nantamongkol *et al*.[43] The cost of drugs aiding smoking cessation were based on estimates offered by the Drug and Medical Supply Information Center (DMSIC).[44]

The disease-specific treatment costs were derived from recently published Thai studies. The cost of lung cancer was taken from estimates of the economic cost of lung cancer at Siriraj Hospital and the National Cancer Institute.[45] Lung cancer costs were 53 980.96 baht per person per year. The cost of COPD was derived from the average direct cost of COPD at Ramathibodi Hospital over the period July 2000–June 2001.[46 47] Such cost estimates were 59 721.30 baht per person per year. The cost of acute myocardial infraction, the cost of chronic heart failure and the cost of angina were obtained from a study concerning diabetes complication costs from Buddhachinaraj Hospital database.[48] In our study, cost of unrecognised myocardial infarction was assumed to be zero. The annual cost of acute myocardial infarction, angina and chronic heart failure were 31 911, 22 892 and 29 738 baht per person per year, respectively. Cost of stroke was taken from the cost for patients receiving care at Prasat Neurological Institute during 1999.[49]

**Table 1** Probabilities of events and costs plugged in the model

| Parameters | Base case (range) | | References |
|---|---|---|---|
| | CPSC | Usual care | |
| Efficacy of smoking cessation programme | 0.1430 (0.101–0.185) | 0.0270 (0.006–0.048) | 27 |
| Cost of smoking cessation programme (baht) | 6039.18 (2825.82–10 238.88) | 2701.48 (0.00–6746.46) | 22 |
| Cost of lung cancer (baht) | 53 980.96 (40 485.72–67 476.20) | | 45 |
| Cost of COPD (baht) | 59 721.30 (44 790.98–74 651.63) | | 46, 47 |
| Cost of acute myocardial infarction (baht) | 31 911.00 (7317.36–33 330.24) | | 48 |
| Cost of chronic heart failure (baht) | 29 738.00 (6055.20–29 260.08) | | 48 |
| Cost of angina (baht) | 22 892.00 (6004.80–29 257.92) | | 48 |
| Cost of stroke (baht) | 50 331.50 (37 748.63–62 914.38) | | 48 |
| Discount rate (%) | 3 (0–10) | | – |

COPD, chronic obstructive pulmonary disease; CPSC, community pharmacist-based smoking cessation programme.
1000 baht = £16; €20; $32.

**Table 2** Incremental cost and life years gained associated with a community pharmacist-based smoking cessation programme compared to usual care by age and sex

| | Incremental cost (baht) | | Life years gained (year) | |
|---|---|---|---|---|
| Age | Male | Female | Male | Female |
| 40 | −17 503.53 | −21 499.75 | 0.1810 | 0.2440 |
| 50 | −16 355.62 | −20 073.98 | 0.1520 | 0.2050 |
| 60 | −12 387.18 | −14 889.16 | 0.1210 | 0.1610 |

This annual cost of stroke was 50 331.50 baht per person per year. All costs in this study were adjusted to 2005 Thai baht using the medical and personal care consumer price index for Thailand 1994–2005.[50] The exchange rate used to convert Thai baht to US dollars is 35 baht per US dollar.

### Analysis

The incremental cost-effectiveness ratio was estimated to determine whether the benefits derived from the CPSC programme, measured by life years gained, offered value for money. This intervention programme was compared to usual care. In the base-case analysis, a discount rate of 3% was used to adjust both costs and outcomes using standard discounting conventions.[51–54]

Sensitivity analysis using Monte Carlo simulation was conducted in order to assess the effects of varying assumptions on the study findings. The decision analysis model was simulated on 1000 iterations. A cost-effectiveness acceptability curve was plotted based on the results derived form the Monte Carlo simulation. In addition, a series of one-way sensitivity analyses, two-way sensitivity analysis and threshold analyses were also undertaken to investigate the effects of altering parameters including discount rate, continuous abstinence rate, cost of smoking cessation programme and cost of smoking-related diseases. Discount rates on cost and outcome of 0%, 3%, 5% and 10% were used. Quit rates were varied by their 95% confidence interval, and intervention costs were altered from low to high estimates of resources use.

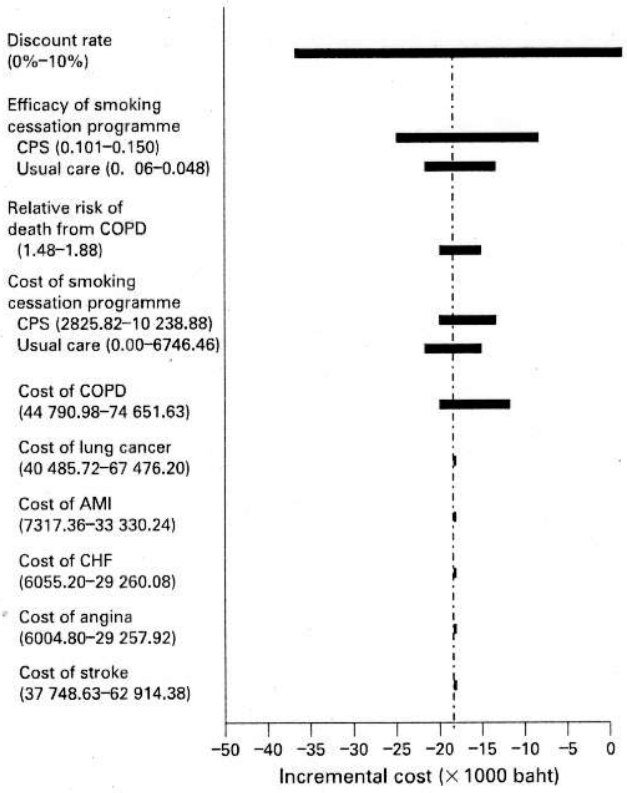


**Figure 1** A series of sensitivity analyses for incremental cost (in baht). AMI, acute myocardial infarction; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; CPS, community pharmacist-based smoking cessation programme.

### Main assumptions

There were four main assumptions that warrant emphasis: (1) The risk of smoking related diseases were uniform over time. (2) Smokers will only experience, at most, one disease over their lifetime. (3) In each cycle of the Markov model, the transition to next health state is irreversible. (4) Smokers will receive only one smoking cessation programme during their lifetime.

## RESULTS

### Costs and outcomes

In the base-case analysis, compared with the usual care, the CPSC programme results in cost savings of 17 503.54 baht ($500) and 21 499.75 baht ($614) for men and women, respectively. Furthermore, CPSC also leads to increases in life expectancy of 0.181 years for men and 0.244 years for women. Thus, the CPSC programme rather than usual care results in cost savings and gains in life years. The estimated incremental cost and life year gained for participants aged 40, 50 and 60 years are depicted in table 2.

### Sensitivity analysis

A series of one-way analyses, based on a 40 year old male smoker, demonstrated that incremental costs were influenced by the discount rate and the 12-month abstinence rate (fig 1). Incremental life expectancy was sensitive to the 12-month abstinence rate (fig 2). Using the 95% CI for the 12-month abstinence rate, total cost savings and life expectancy gains ranged from 9827.17 to 24 919.09 baht and from 0.115 to 0.246 years, respectively.

In the two-way sensitivity analyses, if the long-term quit rate resulting from the CPSC programme was more than usual care by 0.02 or greater, cost savings were maintained. The CPSC programme continues to result in life years gained as long as long-term quit rate from the CPSC programme is more than the quit rate from usual care by 0.001 or greater. In 84% of the 1000 Monte Carlo simulations, the CPSC programme led to cost savings and life years gained (fig 3). Moreover, the results of the probabilistic sensitivity analysis are also presented by cost-effectiveness acceptability curve (CEAC) (fig 4). The CEAC indicates the probability that a community pharmacist-based smoking cessation programme is cost effective compared with a usual care, over a range of the decision-maker's willingness to pay or maximum acceptable ceiling ratio ($\lambda$). If $\lambda$ is 315 000 baht

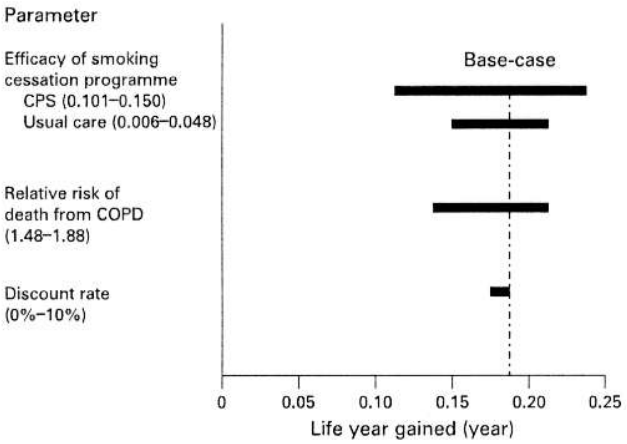


**Figure 2** A series of sensitivity analyses for life year gained. COPD, chronic obstructive pulmonary disease; CPS, community pharmacist-based smoking cessation programme.

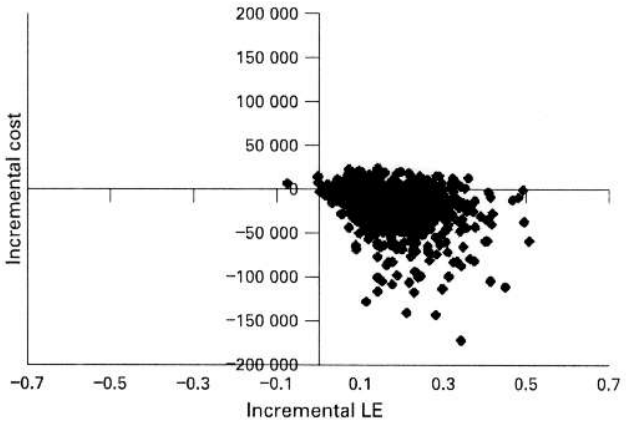


**Figure 3** Probabilistic sensitivity analysis in a cost-effectiveness plane. LE, life expectancy.

per life year gained, which is three times of Thai GDP per capita, the probability that a structured CPSC programme is cost effective is found to be 0.996.

## DISCUSSION

The community pharmacist-based smoking cessation (CPSC) programme results in gains in life expectancy and cost saving. These findings are important pieces of information to aid policy-makers in planning budget allocations to support smoking cessation services for Thai smokers. This study is the first conducted to estimate the long-term effects of CPSC using a disease based model for Thailand.

Our approach is different from previous cost-effectiveness studies of CPSC interventions.[30–32] Those studies calculated the expected increase in life expectancy associated with smoking cessation from the US published data.[33] Unfortunately, that approach is not applicable to Thailand as basic demographic and socioeconomic characteristics of the Thai population deviate from those jurisdictions.

Our findings suggest that the CPSC programme is cost saving. This is because of the lower cost of the programme compared to the cost of smoking-related diseases. In the near future, if a smoking cessation training programme for community pharmacists is included in the curriculum for Thai pharmacy students, the training programme costs would be reduced substantially. Therefore, CPSC programmes should result in even more cost saving.

Our cost-saving results are quite different from those found in the current literature.[30–32] Those studies reported CPSC programmes were not cost saving; however, the cost increase was relatively small compared to the gains in life years. The cost-saving findings were absent in these studies because they did not take into account the costs of smoking-related diseases. There has been continuing debate regarding the difference in lifetime medical costs between smokers and non-smokers. Some studies[55–57] have indicated that lifetime costs of smokers were not different from non-smokers while others provide counter-arguments because of the greater life expectancy of non-smokers.[7 58] Instead of adopting either of these assumptions, we included the cost of smoking-related diseases in our model because excluding these costs led to a significant underestimate of the benefits of smoking cessation.

Our findings are consistent with the results reported in cost-effectiveness studies of other smoking cessation interventions using disease-based approach. Feenstra *et al*[59] reported the one-year implementation of minimal general practitioners counselling in the Dutch population would save healthcare costs for smoking-related diseases by €5700 and yield 1.4 life years comparing to current practice. Johansson *et al*[60] estimated that a "quit-and-win" contest for mothers of pre-school children provided cost-savings of Swedish krona (SEK) 20 000–35 000 per quitter and offered gains of 0.42 to 0.53 life years. In addition, the Health and Economic Consequence of Smoking model (HECOS)[61] illustrated quitting by three standardised interventions in the United Kingdom, pharmacological treatment, general practitioner advice and group therapy resulted in reduction in cost of smoking related diseases of £4.5 million to £36 million.

Because of the uncertainty of data used in the model, we explore possible variability in our outcomes using sensitivity analyses. The cost savings were sensitive to both the discount rate and the cessation rate while gains in life years were sensitive to the cessation rate, relative risk of death from COPD and the discount rate. These influential parameters are similar to what has been reported in the existing cost-effectiveness

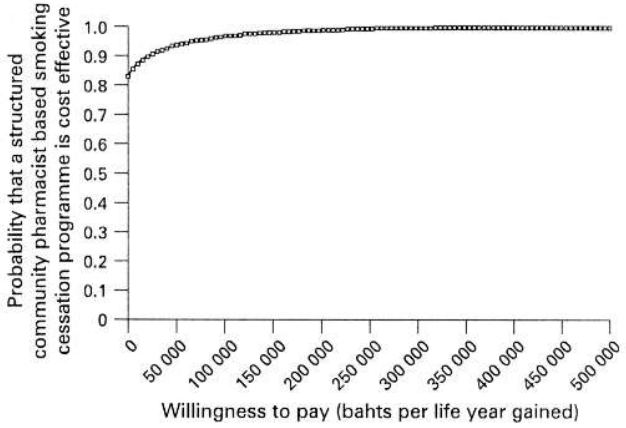


**Figure 4** Cost-effectiveness acceptability curve showing the probability that a structured community pharmacist-based smoking cessation programme (CPSC) is cost-effective compared with usual care.

literature concerning smoking cessation programmes provided by community pharmacists.[30–32] Furthermore, we also assess the uncertainty of combination parameters on our findings using probabilistic sensitivity analysis (PSA), which offers a complete picture of the impact of parameter uncertainty on the findings. The cost-effectiveness acceptability curves suggest that the probability that the CPSC programme is cost saving compared to usual care is approximately 0.84.

Our study has some limitations that should be addressed. First, owing to the limitation of epidemiological and utility parameters in Thailand, we considered only tobacco-related diseases that had the highest prevalence among smokers[6] and had significant impacts in Thailand, although smoking causes a number of serious diseases. In addition, we estimated long-term effects of the smoking cessation programme in terms of life years saved rather than quality adjusted life year (QALYs). Second, in our analysis, relapse rate and natural quit rate were not considered because of the scarcity of these data in Thailand. Moreover, the existing cost-effectiveness study also indicated that both relapse rate and natural quit rate had a slight effect on the cost-effective results.[30] Third, since we obtained cost parameters from various references in the existing Thai literature, it might be argued that different sources of costs data may lead to inaccurate costs estimation. Nevertheless, all cost parameters were obtained from the best available studies. Fourth, owing to scarcity and difficulty in accessing data, the risk of CHD and stroke were estimated from the Framingham risk equation[38] while the one-year transition probability of COPD was calculated from the 10-year cumulative incidence in the Swedish population.[36] Furthermore, the likelihood of lung cancer was derived from an eight-year cumulative risk of lung cancer in a Japanese-American cohort study.[37] With regard to the background mortality, we did not adjust the age-specific mortality for the inclusion of cardiovascular, lung cancer and COPD deaths. We used Thai age-specific mortality rate to estimate probability of death of the healthy population. It should be noted that using unadjusted background mortality rate from smoking-related diseases may lead to overestimation of the probability of death among the population. However, this lack of adjustment is unlikely to change the overall point estimate much as it is applied to both cohorts: smokers and quitters. For risk of death from COPD, risk of death from CHD and stroke, these estimates were drawn from an international study.[38] It might be argued that evidence from international studies cannot accurately depict the impact of smoking cessation for the Thai population. Nevertheless, we believe that all of our input parameters are derived from the best available sources of information. In future, should there be improved evidence regarding smoking-related morbidity or mortality, this model is amenable to the incorporation of such data.

Our study shows the cost savings and gains in life years resulting from a CPSC programme. These findings are very favourable and could be interpreted by policy-makers as paramount evidence to strongly endorse the decision to support the programme; however, most of the decision-making cannot generally be based solely on a cost-effectiveness analysis. Before deciding to reimburse smoking cessation programmes, decision-makers may be interested in knowing other important issues about the characteristics of the populations that benefit from the programme. In addition, it is crucial to review the existing reimbursement system for smoking cessation programme in other countries in order to develop appropriate systems for introduction into the Thai context. Moreover, policy-makers may need to know how the implementation of reimbursement affects behaviour of healthcare professionals, care recipients as well as to gauge the impact on the total healthcare budget. Lastly, before policy-makers decide to reimburse for this cessation service, there might be a need to develop the standards for quality control of the provision of smoking cessation services in community pharmacies.

### What this paper adds

- A community pharmacist-based smoking cessation (CPSC) programme is an effective way to increase access to cessation assistance for smokers interested in quitting. Several cost-effectiveness studies were conducted, but none of them focused on developing countries. In addition, the life expectancy calculated in all studies was based US population estimates; these were not applicable to Thai population.
- This cost-effectiveness study found that the CPSC programme resulted in gains in life expectancy and cost savings. These findings provide the best Thai-specific data available for health policy decision-makers as they plan allocation of resources for smoking cessation.

## CONCLUSION

In summary, a CPSC programme yields cost savings and provides life year gains. In future, if this programme were supported by the government, it will allow a number of Thai smokers with an interest in quitting to have access to a smoking cessation programme that would help them to become a successful quitter.

**Acknowledgements:** We thank Dr Piyarat Nimpitakpong and Dr Peter C Coyte for their critical comments of this manuscript. In addition, we acknowledge the technical assistance of Dr Chuanchom Thananitisak during the initial stage of this research project.

**Funding:** This study was supported, in part, by a grant from the Thailand Research Fund and Thai Pharmacy Network for Tobacco Control (through the Thai Health Promotion Foundation).

**Competing interests:** None.

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Volume 11 • Supplement 1 • 2008
VALUE IN HEALTH

# Cost-Effectiveness Analysis of Thiazolidinediones in Uncontrolled Type 2 Diabetic Patients Receiving Sulfonylureas and Metformin in Thailand

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## ABSTRACT

**Objective:** The national essential drug committee in Thailand suggested that only one of thiazolidinediones be included in hospital formulary but little was know about their cost-effectiveness values. This study aims to determine an incremental cost-effectiveness ratio of pioglitazone 45 mg compared with rosiglitazone 8 mg in uncontrolled type 2 diabetic patients receiving sulfonylureas and metformin in Thailand.

**Methods:** A Markov diabetes model (Center for Outcome Research model) was used in this study. Baseline characteristics of patients were based on Thai diabetes registry project. Costs of diabetes were calculated mainly from Buddhachinaraj hospital. Nonspecific mortality rate and transition probabilities of death from renal replacement therapy were obtained from Thai sources. Clinical effectiveness of thiazolidinediones was retrieved from a meta-analysis. All analyses were based on the government hospital policymaker perspective. Both cost and outcomes were discounted with the rate of 3%. Base-case analyses were analyzed as incremental cost per quality-adjusted life year (QALY) gained. A series of sensitive analyses were performed.

**Results:** In base-case analysis, the pioglitazone group had a better clinical outcomes and higher lifetime costs. The incremental cost per QALY gained was 186,246 baht (US$ 5389). The acceptability curves showed that the probability of pioglitazone being cost-effective was 29% at the willingness to pay of one time of Thai gross domestic product per capita (GDP per capita). The effect of pioglitazone on %HbA1c decrease was the most sensitive to the final outcomes.

**Conclusions:** Our findings showed that in type 2 diabetic patients who cannot control their blood glucose under the combination of sulfonylurea and metformin, the use of pioglitazone 45 mg fell in the cost-effective range recommended by World Health Organization (one to three times of GDP per capita) on average, compared to rosiglitazone 8 mg. Nevertheless, based on sensitivity analysis, its probability of being cost-effective was quite low. Hospital policymakers may consider our findings as part of information for the decision-making process.

*Keywords:* cost-effectiveness analysis, pioglitazone, rosiglitazone, thiazolidinediones.

## Introduction

Diabetes is a chronic disease associated with increases in morbidity, mortality, and health-care expenditures worldwide [1]. Prevalence of diabetes diseases in Thailand is also high. The estimated national prevalence of Diabetes in Thai adult (age over 35) in year 2000 was up to 9.6% or 2.4 million people [2]. The Diabetes Registry Project 2003 [3] reported that among 9419 diabetes patients in Thailand had blindness due to diabetes (1.5%), history of amputation (1.6%), coronary diseases (8.5%) and cerebral vascular diseases (4.5%). In 2002, diabetes was one of the four leading chronic diseases that caused 29 million deaths worldwide [4]. The health-care expenditure on treatment of diabetes is high in many countries. In Japan, the health-care expenditures on diabetes are $ 8 billions or 4% of total health-care expenditures of the government in 1996 [5] and up to $ 98 billion in the USA in 1997 [6].

The main goal of treating diabetic patients is to prevent macro- and microvascular complications by controlling blood glucose level. The United Kingdom Prospective Diabetes Study (UKPDS) [7] indicated that controlling blood glucose level could delay the progress of microvascular complications in type 2 diabetes. Although nonpharmacologic treatment can

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10.1111/j.1524-4733.2008.00366.x

 1098-3015/08/S43 S43–S51

**Table I** Clinical effectiveness of the treatment used in the analysis

| Interventions | HbA1c (%) | HDL (mg/dL) | Tot Chol (mg/dL) | Ref. |
|---|---|---|---|---|
| Pioglitazone 45 mg (combination*) Mean (95% CI) | −1.56 (−1.16 to −1.96) | +4.55 (+3.61 to +5.48) | −0.09 (−0.13 to +0.13) | [17] |
| Rosiglitazone 8 mg (combination*) Mean (95% CI) | −1.26 (−1.48 to −1.04) | +2.71 (+2.01 to +3.42) | +21.3 (+17.7 to +24.9) | [17] |

*Combination means the use of thiazolidinediones combined with either sulfonylurea or metformin.
HDL, high density lipoprotein; Ref., references; Tot Chol, total cholesterol.

improve the glycemic control, the UKPDS reported that not more than 8% of diabetes patients can control their blood glucose with nonpharmacologic therapy within 9 years. Oral hypoglycemic drug treatment should be used in the next step.

Thiazolidinedione is an oral antihyperglycemic agent that can reduce insulin resistance in peripheral tissues and decrease hepatic glucose production [8]. There are two drugs in this class currently available in the market: rosiglitazone and pioglitazone. In the large clinical trial of pioglitazone, the PROactive (the Prospective Pioglitazone Clinical Trial in Macrovascular Events) [9], the use of pioglitazone could significantly reduce a composite secondary end point of all-cause mortality, stroke, and myocardial infarction with the relative risk reduction of 16%. Therefore, adding thiazolidinedione may help delay the progression of macrovascular diseases including myocardial infarction and stroke which the combination of sulfonylurea and metformin cannot [7].

From the hospital policymaker perspective, both cost and effectiveness of the interventions should be considered when a decision to include an intervention into hospital formulary needs to be made. There are many cost-effectiveness studies in thiazolidinediones conducted in other countries, but not in Thailand [10–15]. Only two studies compared the cost-effectiveness between rosiglitazone and pioglitazone [12,15], but both studies did not base their effectiveness on meta-analysis. In addition, the results in one country cannot be applied to other countries because of the differences in health-care systems and resource utilization pattern. A cost-effectiveness study of thiazolidinediones has not been conducted in Thailand. In this study, we determined an incremental cost-effectiveness ratio of the maximal dose of pioglitazone compared with the maximal dose of rosiglitazone in patients who cannot control their blood sugar with sulfonylureas and metformin. We adapted the Center for Outcome Research (CORE) diabetes model by Thai data to use as an analytical instrument in this study.

## Methods

### *CORE Diabetes Model*

The CORE diabetes model is the analytical tool that was used in this study. The model consists of 15 submodels including angina, cataract, congestive heart failure, foot ulcer and amputation, hypoglycemia, ketoacidosis, lactic acidosis, macular edema, myocardial infarction, nephropathy, neuropathy, peripheral vascular disease, retinopathy, stroke, and nonspecific mortality. Each submodel is a Markov model using Monte Carlo simulation using probabilities derived from published sources. The model can predict the long-term costs and outcomes in diabetes patients based on many large clinical and epidemiological studies that are currently available [16]. The model analyses data by taking into account of baseline characteristics of a cohort, clinical effectiveness and costs of intervention, and transition probabilities of each diabetes complication progressions. The final outcomes are reported as life expectancy, quality-adjusted life expectancy, cumulative incidence of each diabetes complications, and total lifetime costs of the diabetes populations.

### *Interventions Compared*

The interventions compared in this study are pioglitazone and rosiglitazone used in type 2 diabetic patients who cannot control their blood glucose under the combination of sulfonylurea and metformin. The dose regimen of pioglitazone was 45 mg orally taken once daily, while the dose regimen of rosiglitazone was 8 mg taken orally once daily. These two regimens were the full dose of each thiazolidinedione which are capable of achieving the best glycemic control level of each product. Clinical effectiveness of both regimens were derived form a meta-analytic study conducted by Chiquette and colleague (Table 1) [17].

### *Cohort*

Baseline characteristics of our hypothetical cohort were based on Thai Diabetes Registry Report (TDRP) [3]. This project is a multicenter registry of 9419 diabetic patients receiving medical care in diabetic clinics of 11 tertiary centers in Bangkok and major provinces. The registry data were collected from April to December 2003. Almost all patients (94.6%) were type 2 diabetic patients. Some characteristics that were not reported in TDRP were retrieved from other publication related with Thai population (Table 2).

### *Costs and Perspective*

The government policymaker perspective was taken in this study by considering only direct medical costs of

**Table 2** Base line characteristics of the Thai diabetic population

| | Baseline characteristics | | |
|---|---|---|---|
| | Mean | SD | Ref. |
| Start age | 59.43 years | 13.52 years | [3] |
| Duration of diabetes | 10 years | 7.61 years | [3] |
| Proportion of male | 0.34 | | [3] |
| | Mean: | SD: | |
| HbA1c | 7.75% | 0.56% | Expert opinions |
| Systolic blood pressure | 126.3 mmHg | 0 mmHg | [2] |
| Total cholesterol | 197.1 mg/dL | 42.52 mg/dL | [3] |
| High density lipoprotein cholesterol (HDL) | 53.9 mg/dL | 15.31 mg/dL | [3] |
| Low density lipoprotein cholesterol (LDL) | 114.5 mg/dL | 35.76 mg/dL | [3] |
| Triglyceride | 150.7 mg/dL | 105.4 mg/dL | [3] |
| Body mass index | 25.6 kg/m$^2$ | 4.3 kg/m$^2$ | [3] |
| | Proportion | | |
| Proportion of myocardial infarction | 0.42 | | [3], database* |
| Proportion of angina | 0.43 | | [3], database* |
| Proportion of peripheral vascular disease | 0.039 | | [3] |
| Proportion of stroke | 0.044 | | [3] |
| Proportion of congestive heart failure | 0.03 | | Database* |
| Proportion of atrial fibrillation | 0.017 | | Database* |
| Alcohol consumption | 35 oz/week | | [32] |
| Proportion of smoker | 0.141 | | [3] |
| Cigarettes/day | 10.8 | | [33] |
| Proportion of left ventricular hypertrophy | 0.13 | | [34] |
| Proportion of micro albuminuria | 0.178 | | [3] |
| Proportion of gross protienuria | 0.178 | | [3] |
| Proportion of end state of renal disease | 0.083 | | [3] |
| Proportion of background diabetic retinopathy | 0.213 | | [3] |
| Proportion of proliferative diabetic retinopathy | 0.094 | | [3] |
| Proportion of severe vision loss | 0.015 | | [3] |
| Proportion of macular edema | 0.022 | | [35] |
| Proportion of cataract | 0.428 | | [3] |
| Proportion of uninfected ulcer | 0.059 | | [3] |
| Proportion of healed ulcer | 0.044 | | [36] |
| Proportion of history of amputation | 0.016 | | [3] |
| Proportion of neuropathy | 0.168 | | [36] |

*Buddhachinaraj hospital database.
Ref., references.

each competing treatment. The direct medical costs include cost of medications, cost of laboratory monitoring, and cost of managing diabetes-related complications incurred either inpatient or outpatient services. The estimated costs of diabetes-related complications in Thailand were derived from different sources. Most of diabetic complication costs were calculated from Buddhachinaraj hospital's database (Phitsanulok, Thailand). A total of 12,902 type 2 diabetic patients were identified by ICD-10 (International Classification of Disease version 10) diagnosis or the use of medications specific for diabetes between June 2001 and July 2005. Other complication costs that could be not calculated from the hospital database were derived from Thai published literature, expert opinions, and DRGs (Diagnosis-Related Groups) guidebook (Table 3). Based on the average cost derived from the Drug and Medical Supply information center [18], the daily cost of pioglitazone and rosiglitazone was 107.87 baht (US$3.12) and 86.08 baht (US$2.49), respectively. All costs were adjusted to 2004 value. To present the results in US$, we used the currency exchange rate of April 23, 2007, 34.56 baht/US$1 [19] refer to Bank of Thailand website (http://www.bot.or.th/bothomepage/index/index_e.asp).

### *Transition Probabilities*

Most of diabetic complication transition probabilities were based on the CORE model default [16] except probability value of nonspecific mortality and death related to hemodialysis and peritoneal dialysis. Nonspecific mortality probability values in the model were replaced by age-specific mortality data in Thai population [20]. Probabilities values of death related to hemodialysis and peritoneal dialysis were derived from Thai renal registry project 2003 [21].

### *Time Horizon*

Time horizon of the simulation was 40 years. We used 40 years to confirm that the simulation would cover the average life time of our cohort.

### *Discounting*

Costs and clinical outcomes were discounted at 3% annually in base-case analysis, according to

**Table 3** Thai diabetes-related costs used in the CORE diabetes model

| Description of event or state | Cost per event or state (baht) | References |
|---|---|---|
| Annual cost of screening for microalbuminuria | 150 | Expert opinion* |
| Annual cost of screening for gross proteinurea | 10 | Expert opinion* |
| Annual cost of eye screening | 118 | [37] |
| Myocardial infarction, year of event | 67,653 | Database† |
| Myocardial infarction, each subsequent year | 27,447 | Database† |
| Angina, year of event | 67,192 | Database† |
| Angina, each subsequent year | 32,323 | Database† |
| Congestive hear failure, year of event | 60,801 | Database† |
| Congestive hear failure, each subsequent year | 24,779 | Database† |
| Stroke, year of event | 63,984 | Database† |
| Stroke, each subsequent year | 31,996 | Database† |
| Cost of hemodialysis (HD), year of event | 352,665 | [31,38] |
| Annual costs HD, each subsequent year | 331,165 | [31,38] |
| Cost of peritoneal dialysis (PD), year of event | 408,083 | [31] |
| Annual costs of PD, each subsequent year | 361,416 | [31] |
| Cost of renal transplant (RT), year of event | 333,228 | [39] |
| Annual costs RT each subsequent year | 91,329 | [39] |
| Major hypoglyceamic event | 12,472 | Database† |
| Ketoacidosis event | 42,375 | Database† |
| Lactic acid event | 40,510 | Database† |
| Cost of eye laser treatment | 1,756 | [37] |
| Cost of cataract operation | 11,403 | [40] |
| Neuropathy, year of event | 21,515 | Database† |
| Neuropathy, each subsequent year | 24,034 | Database† |
| Amputation (event-based) | 76,688 | Database† |
| Amputation Prosthesis (event-based) | 2,900 | Expert opinion* |
| Gangrene treatment (monthly-based) | 62,245 | Database† |
| Standard uninfected ulcer (monthly-based) | 8,371 | Database† |

*Albuminuria screening costs got from an expert opinion who had worked as the head of Chemical clinic laboratory department, Buddhachinaraj hospital. Amputation prosthesis cost was cost of artificial limb that got from the opinions of two experts who had worked at the artificial limb center at Buddhachinaraj hospital.
†Data were average costs calculated from diabetic patients in Buddhachinaraj hospital database between June 2001 and July 2005.
CORE, Center for Outcome Research.

World Health Organization (WHO) guide of cost-effectiveness analysis [22].

### *Data Analysis*

In the model simulation, each of 1000 nonidentical patients with different baseline characteristics was run for 1000 times. The mean incremental costs versus mean incremental effectiveness of 1000 simulations of each 1000 patients were used to generate a scatter plot. Mean of the mean incremental costs versus mean incremental effectiveness of 1000 patients was reported as the incremental cost-effectiveness ratio.

### *Sensitivity Analysis*

The sensitivity analyses were done by varying some variables including effects of pioglitazone on %HbA1c decreasing, effects of pioglitazone on lipid profiles, time horizon that used to run the simulation, drug treatment costs of the pioglitazone group, and the discounting rate. In the HbA1c sensitivity analysis, we use %HbA1c change from baseline in pioglitazone group between −1.16 and −1.96 (upper bound and lower bound of the confident interval of %HbA1c changing in pioglitazone treatment report in the Chiqutte's Meta-analysis [17]). Effects of pioglitazone on lipid profiles were also varied by using upper bound and lower bound of 95% confidence interval from the Meta-analysis. Drug treatment cost of the pioglitazone group was varying by +25% of the pioglitazone treatment cost in base-case. For the sensitivity analysis of discounting rate, we use the recommendation from WHO [22] including 0% discount costs and clinical effects, 0% discount clinical effects and 6% discount costs, and 6% discount cost and clinical effects. Finally, we vary time horizon from 10 years to 30 years.

## Results

### *Base-Case Analysis*

The results from the base-case analysis showed that patients in the pioglitazone group had slightly lower cumulative incidence of diabetes complications than those in the rosiglitazone group. The incidence of proliferative diabetic retinopathy, end stage renal disease, amputation ulcer, and myocardial infarction in the pioglitazone group compared to the rosiglitazone group was 1.11% versus 1.19%, 5.07% versus 5.42%, 6.64% versus 6.70%, and 15.90% versus 18.50%, respectively. In addition, patients in the pioglitazone group had longer life expectancy and quality-adjusted life expectancy compared to the rosiglitazone group. Life expectancy and quality-adjusted life expectancy in the pioglitazone group was 0.16 and 0.14 years higher than those in the rosiglitazone group, respectively. At the end of the 40 years

**Table 4** Summary of cost and incremental cost-effectiveness analysis in base-case results

| | Pioglitazone group | Rosiglitazone group |
|---|---|---|
| Average total lifetime cost (baht) (SD) | 491,457 (16,202) | 465,839 (16,136) |
| Average life expectancy (years) | 9.62 (0.171) | 9.47 (0.177) |
| Average quality adjusted life year (years) | 6.69 (0.124) | 6.55 (0.123) |
| Incremental cost per life expectancy (baht per life year gained) | 161,777 | |
| Incremental cost per quality adjusted life expectancy (baht per quality adjusted life year gained) | 186,246 | |

simulation, the survival rate of the pioglitazone group was 0.3% and rosiglitazone group was 0.1%.

The total costs in the pioglitazone group were higher than the total costs in the rosiglitazone group. An incremental cost-effectiveness ratio showed that we had to pay 161,777 Baht (US$ 4681) for one life year gained or pay 186,246 Baht (US$ 5389) for an additional quality-adjusted life year (QALY) earned (Table 4).

The incremental cost-effectiveness scatter plot of 1000 sample generated from mean incremental costs versus mean incremental effectiveness of 1000 simulation of each 1000 patients (Fig. 1) showed that majority of the cost-effectiveness ratio fell in the upper right quadrant. This indicates that most simulations showed that the pioglitazone treatment is both higher costs and more effective than the rosiglitazone treatment.

When we used the scatter plot to generate an acceptability curve (Fig. 2), the acceptability curve show how likely it will be that the pioglitazone treatment is cost-effective for any particular willingness to pay value. With a willingness to pay value of 110,000 and 33,000 Baht per QALY gained, there is a 29% and 64% probability that the pioglitazone treatment will be cost-effective compared to the rosiglitazone treatment, respectively.

### *Sensitivity Analyses*

Sensitivity analyses showed that the most influential variable was the effect of %HbA1c change. When varying the effect of %HbA1c change (Fig. 3), the incremental cost per QALY gained varied from 79,586 to 951,204 baht (US$ 2302–US$ 27,523)/QALY. When %HbA1c change from pioglitazone using was −1.16% (lower bound of the confidence interval of %HbA1c change from pioglitazone used in the base-case analysis) and %HbA1c change from rosiglitazone using was −1.26% as in the base-case analysis, the pioglitazone group remained dominant to rosiglitazone.

Varying other variables for the sensitivity analysis also affected the final outcome but the effects were less than the effect of %HbA1c change. The cost-effectiveness values, when using varying discount rates, fell between 130,224 and 262,681 Baht (US$ 7600)/QALY. Varying the pioglitazone drug costs by + 25% showed the incremental cost per QALY fell between 64,329 (US$ 1861) and 308,163 Baht (US$ 8916)/QALY. The incremental cost-effectiveness ratio was slightly changed when we varied the effects of pioglitazone on lipid profiles (Fig. 3). The effects of pioglitazone on low density lipoprotein (LDL) and triglyceride did not affect the cost-effectiveness values. Varying time horizontal showed that using thiazolidinediones for 40 years was more cost-effective than 10 years and 20 years.

## Discussion

Our base-case findings showed that using pioglitazone, compared to rosiglitazone, resulted in reduced incidence of long-term complications, improved life

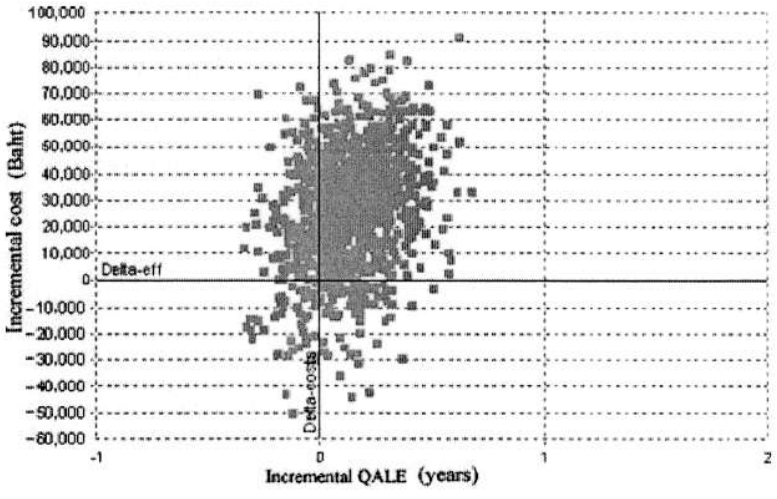


**Figure 1** The incremental cost per quality adjusted life expectancy scatter plot. QALE, quality adjusted life expectancy.

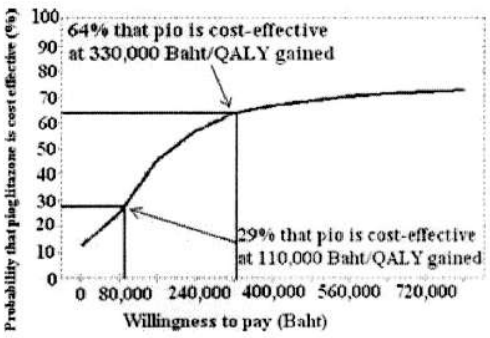


**Figure 2** Acceptability curve. QALY, quality-adjusted life year.

expectancy and QALY in type 2 diabetic patients who have previously failed on treatment with sulfonylurea or metformin. These clinical benefits of pioglitazone over rosiglitazone are mostly derived from the better lipid profile and glycemic control [17] although the higher cost in the pioglitazone group is mostly due to the medication cost.

In addition, the sensitivity analysis results demonstrated that the effects of pioglitazone on %HbA1c changes from base line were the most sensitive to the final outcomes. This is not surprising as glycemic level is a strong predictor of developing microvascular and macrovascular complications [7,23]. In a scenario when the effects of glycemic control of pioglitazone were inferior to rosiglitazone (%HbA1c change of −1.16% vs. −1.26%), the incremental cost per QALY gained was 951,204 baht (US$ 27,523) per QALY gained or five times higher than the incremental cost per QALY gained in the base-case analysis. The glycemic control results were affected directly with our interventions. Although life style modification was also a potential effect on glycemic control in a clinical practice, it did not affect to the results of our analysis. We assumed that the life style modification in both the pioglitazone group and the rosiglitazone group were not different. Therefore, our final incremental effectiveness was reflected from the difference of effectiveness between both thiazolidinediones only.

Based on the WHO recommendation regarding the cost-effectiveness thresholds criteria [24–26], an intervention with an incremental cost-effectiveness ratio less than one or falling between one to three times of gross domestic product per capita (GDP per capita) would be deemed very cost-effective and potentially cost-effective, respectively. On the other hand, an intervention with a cost-effectiveness ratio beyond the three times of GDP per capita would be interpreted as not cost-effective. Based on the results of this study, the incremental cost per QALY gained in our base-case analysis was 186,246 baht (US$ 5389) per QALYs which was about 1.7 times of the Thai GDP per capita (110,000 baht per year) in 2005 fiscal year. The results fell between one to three times GDP per capita. When we applied the criteria based on WHO recommendation, the incremental cost-effectiveness ratio in our study showed that using pioglitazone was likely to be cost-effective, compared with rosiglitazone.

When taken into account the join probability of values of the incremental cost and effectiveness simultaneously, the cost-effectiveness acceptability curve graphically presents the probability of being cost-effective as a function of the maximal willingness to pay value. The cost-effectiveness acceptability curves in our study illustrated that the probability per QALY gained was only 29% at 110,000 baht per QALY gained and 64% at 330,000 baht per QALY gained (a value of one and three times of GDP per capita, respectively). This way of presenting findings is easy to understand and provides more meaningful interpretation, compared to the base-case analysis.

Our cost-effectiveness results were different from the findings in previous cost-effectiveness studies [12,15]. Based on a dossier submission, reported in the article of Veenstra and colleagues [15], using pioglitazone resulted in cost-savings of US$ 6057 in year 2000. Nevertheless, the analysis was performed for comparing pioglitazone 30 mg and rosiglitazone 4 mg

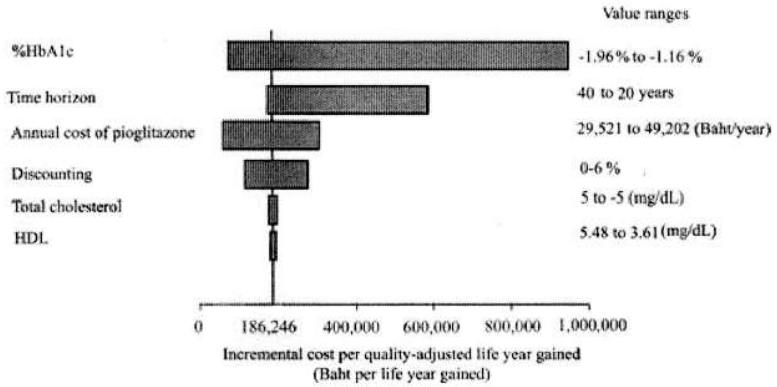


**Figure 3** Tornado diagram of the sensitivity analyses.* *Effect of pioglitazone on %HbA1c, total cholesterol (T-Chol), and HDL were varied in the sensitivity analysis, when effect of rosiglitazone on each parameters were set as constant as the base case analysis. HDL, high density lipoprotein.

in combination with metformin or sulfonylurea [15], which was different from our study in which a maximal dose of pioglitazone 45 mg and rosiglitazone 8 mg was studied. Henrikson [12] determined a cost-effectiveness of thiazolidinedione using Swedish perspective. The study compared pioglitazone 30 mg versus rosiglitazone 8 mg in combination with metformin and found that the incremental cost-effectiveness ratio was SEK$ 148,561/life years gained [12]. Both studies were not interpreted cost-effectiveness by WHO criteria. The cost-effectiveness interpretation was not a problem in Veenstra et al. study because they stated that using pioglitazone was cost-saving [15]. Henrikson study stated that Sweden authorities were not set threshold values for cost-effectiveness in health-care expenditure. Henrikson applied data from the Swedish Road Safety Office for the cost-effectiveness threshold to interpret his result. The value that could be interpreted as cost-effective in Henrikson study was not more than SEK$ 430,000 per life years gained [12]. It was important to note the model used in both studies was based on the diabetes model, developed by the Institute for Medical Informatics and Biostatistics (IMIB), which was the original model version of CORE diabetes model [27].

One limitation of our study was that we calculated diabetes complication costs mainly from a hospital. As this hospital is a teaching, tertiary care, government hospital, the cost estimates may be different in other hospitals. Kunaratanapruk and colleagues [28] reported that the charge was different between the government hospital in Bangkok and the government hospital in other provinces in 1995. Total charges of the accident treatment in out-patient visit in the government hospital in Bangkok were two times higher than that in the government hospital in outside of Bangkok [28]. In addition, missing value is commonly seen in the hospital database [29]. Nevertheless, after we found that 90% of inpatient room charge was missing, we could replace the room charge by calculating average room charges in each year of the hospital and multiplied it with the length of stay of each patient to replace the missing data. Coding error was another problem that can occur in the database. This problem is also commonly found in the database of other countries [6]. Given that almost 10,000 observations were included in our analysis, the effect of wrong coding was unlikely to be large.

We believe that our results are valid for Thai population because of several reasons. First, the transition probabilities of diabetes complication progression that used in the model were based on two large, longitudinal cohort studies, The Framingham cohort and UKPDS studies. These studies had a follow-up period more than 10 years. They were landmark studies which the relationship of glycemic control, lipid profiles, and other factors and the risk of developing diabetes complications were derived from. Second, the CORE diabetes model is one of a few models that have been validated in several clinical studies using different population including for Asians [30]. Last, many of Thai specific data were used to input in our analysis including baseline characteristic of diabetes patients, age-specific mortality, renal replacement therapy specific mortality, diabetes complication costs and associated medical costs.

Several crucial issues need to be considered, when decision-makers interpreted our findings. First, our study determines the effect of maximum dose of pioglitazone combination and maximum dose of rosiglitazone combination only. Second, this study was performed using the hospital perspective. The incremental cost-effectiveness ratio may be lower if the societal perspective is considered. Third, we have to consider many factors when we decide to choose a treatment for our organization including the ethical, and health equity issue. For example, a study of cost-utility analysis of renal replacement therapy in Thailand by Teerawattananon [31] demonstrated that peritoneal dialysis and hemodialysis are considered not cost-effective, according to WHO threshold recommendation. This does not mean that the hospital policymakers should discard the renal replacement therapy in their organization for budget saving. On the other hand, government has decided to allow peritoneal dialysis and hemodialysis to be used in a certain situation despite the findings of non–cost-effective.

## Conclusion

To our knowledge, this study is the first to evaluate the cost-effectiveness of pioglitazone, compared to rosiglitazone, in terms of long-term health outcomes and economic consequences in the context of Thai health-care system. Although the base-case analysis found that the use of pioglitazone fell in the cost-effective range recommended by WHO cost-effective as threshold criteria (one to three times of GDP per capita), the acceptability curves demonstrated probability that the use of pioglitazone was cost-effective were between 29% and 64% at the one time and three times of GDP per capita, respectively. Nevertheless, if we considered using pioglitazone in diabetic patients with higher risk of cardiovascular diseases, the incremental cost-effectiveness ratio comparing pioglitazone and rosiglitazone may be lowered.

Source of financial support: A grant from Thailand Research Fund.

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Volume 11 • Supplement 1 • 2008
VALUE IN HEALTH

# Factors Affecting Health-Care Costs and Hospitalizations among Diabetic Patients in Thai Public Hospitals

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## ABSTRACT

**Objective:** The study investigated the factors affecting health-care costs and hospitalizations among diabetic patients in Thai public hospitals.

**Methods:** A retrospective study was conducted by using administrative claims data obtained from diabetic patients during October 1, 2002 and September 30, 2003. Dependent variables were total health-care costs and the occurrence of hospitalizations. Independent variables included demographic factors, health-care utilizations, complications, comorbidities, and payment methods. Multivariate statistical analyses were applied.

**Results:** The results of this study suggested that demographic factors of patients (i.e., age and male sex), payment methods (i.e., capitation, fee-for-service, and out-of-pocket) were significantly associated with higher health-care costs and probability of hospitalization. Patients receiving treatment from teaching hospitals significantly consumed higher health-care costs. In addition, the more health-care utilizations (i.e., occurrence of hospitalization, number of outpatient visit, and insulin utilization), the higher health-care costs the patients significantly had. Diabetic patients taking insulin had significantly higher health-care costs and risk of hospitalization. Furthermore, comorbidities (e.g., hypertension and cancer) and diabetes-related complications (e.g., nephropathy, neuropathy, retinopathy, coronary artery disease, cardiovascular disease, and peripheral vascular disease) were significantly associated with an increase in health-care costs and hospitalization.

**Conclusion:** Factors affecting health-care costs and hospitalizations may help health-care providers intervene to improve patient management and possibly reduce health-care costs in the future.

*Keywords:* diabetes, health-care costs, hospitalizations, risk factors.

## Introduction

Diabetes is a common, serious, and chronic disease causing major long-term complications and comorbidities. For all age groups worldwide, the prevalence of diabetes was estimated at 2.8% in 2000 and 4.4% in 2030 [1]. Especially in the economically developing countries, it is predicted to have the greatest increase [2]. Among Thai people, the prevalence of diabetes was estimated at 2.4% in 1995 and 3.5% in 2025 [2]. The rise in prevalence of diabetes leads to an increase in prevalence of diabetic complications (e.g., retinopathy [23%], nephropathy [24%], amputation [1.6%], coronary disease [8.2%], and stroke [4.4%]) and diabetic comorbidities (e.g., hypertension [63.6%] and dyslipidemia [73.3%]) [3]. Diabetic-related complications and comorbidities largely affect patient outcomes and health-care costs. In the United States, the total cost of diabetes was $132 billion (i.e., direct [69.7%] and indirect cost [30.3%]) [4]. In Thailand, there have been few studies estimating the cost of diabetes. Based on the study determining the costs of patients with diabetes in seven Thai government hospitals located in four regions of Thailand and Bangkok, the annual average direct medical cost per diabetic patient was 6017 baht, which was significantly higher than those without diabetes [5]. In addition, the annual average total health-care cost per diabetic patient was 13,751 baht (i.e., direct medical and nonmedical cost [82.26%] and indirect cost [17.74%]) [6]. The average direct medical cost per outpatient visit was about 1206 baht per diabetic patient [7]. Recently, seven studies performed in the United States or Taiwan have investigated the impact of factors such as demographic characteristics, number of diabetic complications, number of health-care utilization, length of stay (LOS), and payment methods on health-care costs or hospitalizations [8–14]. In Thailand, only two studies have

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10.1111/j.1524-4733.2008.00369.x

 1098-3015/08/S69 S69–S74

determined the factors associated with direct medical costs, but no study has ever investigated the association between factors and the occurrence of hospitalization [6,15]. Therefore, the objective of this study was to investigate the factors associated with total health-care costs and the occurrence of hospitalization. Knowledge of these factors may help health-care providers intervene to improve patient management and possibly reduce health-care costs in the future.

## Methods

### *Data Source*

A retrospective study was conducted by using administrative databases obtained from four Thai government hospitals during October 1, 2002 and September 30, 2003. These data were allowed to be used in this study by hospital administrators. Data included demographic characteristics, medical history of illness, health-care utilizations, and medical costs. Medical cost data were all charges of patients' underpayment methods such as capitation (i.e., social security scheme [SSS] and universal coverage [UC]), fee-for-service (FFS) (i.e., civil servant medical benefits scheme [CSMBS]), and out-of-pocket. The social security office pays a fixed amount of money per year to hospitals for covering health-care benefits of employees who enrolled under SSS. Under CSMBS, the government provides full health-care coverage for government officers and their dependents (e.g., parents, spouse, and up to three children). Regarding the UC, the national health security office pays a fixed amount of money per year to hospitals for covering health-care benefits of patients who enrolled under UC, and patients also pay 30 baht per visit ($US 1 = 35 baht) [16]. Out-of-pocket means that patients pay all health-care costs by themselves. Although patients under capitation payment method did not actually pay for their total charges, their medical charge data were still recorded on hospitals' databases.

### *Patient Selection*

Diabetic patients must have at least one claim with the primary, secondary, or tertiary diagnostic code of diabetes mellitus based on the International Statistics Classification Diagnostics and Health Problem tenth revision (ICD-10 codes = E10-E14).

### *Statistical Analysis*

Data were transformed to a patient-level or cross-sectional data. Univariate and multivariate statistical analyses (i.e., ordinary least square (OLS) regression and logistic regression analyses) were applied. SPSS program version 11.0 was used for statistical analyses. Multiple linear regression analysis and log transformation were used when a dependent variable was total health-care costs. Total health-care costs were the summation costs of both diabetic and nondiabetic-related resource use (e.g., drugs, medical supplies, laboratory tests, surgeries, hospitalizations, and other health-care services) incurred by patients with diabetes. Logistic regression analysis was applied when the occurrence of hospitalization was a dependent variable. Nevertheless, the occurrence of hospitalization was used as one of independent variables when a dependent variable was total health-care costs. Other independent variables included demographic factors (e.g., age, female), payment methods such as capitation (i.e., SSS and UC), FFS (i.e., CSMBS), and out-of-pocket, hospital characteristics (e.g., teaching hospital), health care and drug utilizations (e.g., outpatient visits and insulin utilization), comorbidities (e.g., hypertension, hyperlipidemia, and cancer), microvascular complications (e.g., retinopathy, nephropathy, and neuropathy), and macrovascular complications (e.g., coronary artery disease [CAD], cardiovascular disease [CVD], and peripheral vascular disease [PVD]). Comorbidities and complications were identified by ICD-10 codes. All variables used in the analysis and the reference categories of dummy variables are presented in Table 1.

**Table 1** Variables used in the analysis

| Variables | Type (reference category) |
|---|---|
| Dependent variables | |
| Health-care costs | Continuous (baht) |
| Hospitalization | Dummy (yes = 1, no = 0) |
| Independent variables | |
| Demographics: | |
| Age | Continuous (years) |
| Female | Dummy (female = 1, male = 0) |
| Payment method: | |
| Capitation (i.e., SSS or UC) | Dummy (yes = 1, no = 0) |
| FFS (i.e., CSMBS) | Dummy (yes = 1, no = 0) |
| Out-of-pocket | Dummy (yes = 1, no = 0) |
| Hospital characteristics: | |
| Teaching hospital | Dummy (teaching hospital = 1, nonteaching hospital = 0) |
| Health-care utilization: | |
| Number of outpatient visits | Continuous |
| Insulin utilization | Dummy (insulin users = 1, noninsulin users = 0) |
| Comorbidity: | |
| Hypertension | Dummy (yes = 1, no = 0) |
| Hyperlipidemia | Dummy (yes = 1, no = 0) |
| Cancer | Dummy (yes = 1, no = 0) |
| Microvascular complications: | |
| Retinopathy | Dummy (yes = 1, no = 0) |
| Nephropathy | Dummy (yes = 1, no = 0) |
| Neuropathy | Dummy (yes = 1, no = 0) |
| Macrovascular complications: | |
| CAD | Dummy (yes = 1, no = 0) |
| CVD | Dummy (yes = 1, no = 0) |
| PVD | Dummy (yes = 1, no = 0) |

CAD, coronary artery disease; CVD, cardiovascular disease; CSMBS, civil servant medical benefits scheme; FFS, fee-for-service; PVD, peripheral vascular disease; SSS, social security scheme; UC, universal coverage.

**Table 2** Descriptive statistics of the sample

| Variables | Statistical values (N = 24,051) |
|---|---|
| Demographics: | |
| Average age (years) | 59 (SD = 13.14) |
| Female sex | 66% |
| Type II diabetes | 99% |
| Payment method: | |
| Fee-for-service | |
| Civil servant medical benefit scheme | 19% |
| Capitation | 34% |
| Universal coverage | 28% |
| Social security scheme | 6% |
| Out-of-pocket | 47% |
| Hospital characteristics: | |
| Number of patients in teaching hospitals | 61% |
| Number of patients in nonteaching hospitals | 39% |
| Health-care costs and utilization: | |
| Average annual cost per person (baht) | 19,299 baht or $551 (SD = 64,754 baht or $1850) |
| Median annual cost per person (baht) | 5658 baht or $162 (IQR = 14,209 baht or $406) |
| Average annual length of stay per person (day) | 2.52 (SD = 9.10) |
| Average annual number of hospitalizations per person | 0.35 (SD = 0.89) |
| Average annual number of outpatient visits per person | 7.39 (SD = 6.20) |
| Number of patients with only outpatient visits | 77% |
| Number of patients admitted to hospitals | 21% |
| Average annual number of hospitalizations per person | 1.63 (SD = 1.26) |
| Insulin utilization: | |
| Number of diabetic patients taking insulin | 12% |
| Comorbidity: | |
| Number of diabetic patients with coronary artery diseases | 6.15% |
| Number of diabetic patients with cardiovascular diseases | 1.46% |
| Number of diabetic patients with peripheral vascular diseases | 0.59% |
| Number of diabetic patients with hyperlipidemia | 12.79% |
| Number of diabetic patients with hypertension | 33.33% |
| Number of diabetic patients with cancer | 4.10% |
| Complication: | |
| Number of diabetic patients with nephropathy | 1.77% |
| Number of diabetic patients with neuropathy | 3.95% |
| Number of diabetic patients with retinopathy | 8.67% |

## Results

Table 2 shows the results of the descriptive statistics of the sample. There were 24,051 patients with diabetes with average age of 59 years old (standard deviation [SD] 13.14). Sixty-six percent of patients with diabetes were female and 99% had type II diabetes. In this study, diabetic patients were under capitation (34%) (i.e., SSS [6%] and UC [28%]), FFS (i.e., CSMBS [19%]), and out-of-pocket (47%). Moreover, 61% of patients received their treatment at teaching hospitals. The average annual total health-care cost per person was 19,299 baht or $551 (SD 64,754 baht or $1,850). The median annual total health-care cost per person was 5,658 baht or $162 (Interquartile Range, IQR = 14,209 baht or $406). The annual LOS per person was 2.52 (SD 9.10) days. The average annual number of hospitalizations per person was 0.35 (SD 0.89), and the average annual number of outpatient visits per person was 7.39 (SD 6.20). In this analysis, there were 77% of patients who had only outpatient visits. Only 21% of patients were admitted to the hospitals and the average annual number of hospitalizations per person of these patients was 1.63 (SD 1.26), which was higher than that of total patients (0.35 [SD 0.89]). In addition, 12% of diabetic patients took insulin.

Tables 3 and 4 shows the results of OLS and logistic regression analyses, respectively. Age (parameter

**Table 3** Results of multiple linear regression analysis

Dependent variable = log of total health-care costs

| Independent variables | Parameter estimates | *P*-value |
|---|---|---|
| Age | 0.006 | <0.001* |
| Female | −0.019 | 0.002* |
| Capitation | 0.083 | <0.001* |
| Fee-for-service | 0.211 | <0.001* |
| Out-of-pocket | 0.057 | <0.001* |
| Teaching hospital | 0.359 | <0.001* |
| Hospitalization | 0.615 | <0.001* |
| Outpatient visit | 0.041 | <0.001* |
| Insulin utilization | 0.344 | <0.001* |
| Hypertension | 0.096 | <0.001* |
| Hyperlipidemia | 0.029 | 0.002* |
| Cancer | 0.154 | <0.001* |
| Nephropathy | 0.016 | <0.001* |
| Neuropathy | 0.064 | <0.001* |
| Retinopathy | 0.035 | <0.001* |
| Coronary artery disease | 0.141 | <0.001* |
| Cardiovascular disease | 0.058 | 0.024* |
| Peripheral vascular disease | 0.213 | <0.001* |

*Statistically significant at $P < 0.05$.
Model significant at $P < 0.001$; Adjusted *R*-square = 0.54.

**Table 4** Results of logistic regression analysis

Dependent variable = occurrence of hospitalization (yes = 1)

| Independent variables | Parameter estimates | Odds ratio | *P*-value |
|---|---|---|---|
| Female | −0.116 | 0.89 | 0.006* |
| Capitation | 2.163 | 8.69 | <0.001* |
| FFS | 2.365 | 10.64 | <0.001* |
| Out-of-pocket | 1.502 | 4.49 | <0.001* |
| Teaching hospital | −1.600 | 0.20 | <0.001* |
| Outpatient visit | −0.029 | 0.97 | <0.001* |
| Insulin utilization | 1.308 | 3.70 | <0.001* |
| Hypertension | 0.751 | 2.12 | <0.001* |
| Hyperlipidemia | 0.027 | 1.03 | 0.687 |
| Cancer | 1.525 | 4.60 | <0.001* |
| Nephropathy | 2.845 | 17.21 | <0.001* |
| Neuropathy | 1.790 | 5.99 | <0.001* |
| Retinopathy | 0.523 | 1.69 | <0.001* |
| CAD | 1.964 | 7.13 | <0.001* |
| CVD | 0.324 | 1.38 | 0.024 |
| PVD | 1.233 | 3.43 | <0.001* |

*Statistically significant at $P < 0.05$; Model significant at $P < 0.001$.
CAD, coronary artery disease; CVD, cardiovascular disease; FFS, fee-for-service; PVD, peripheral vascular disease.

estimates [PE] = 0.006, $P < 0.001$) or male sex (PE = –0.019, $P < 0.002$) had a significant impact on an increase in health-care costs. Payment methods (e.g., capitation [PE = 0.083, $P < 0.001$], FFS [PE = 0.211, $P < 0.001$], and out-of-pocket [PE = 0.057, $P < 0.001$]) had a significant positive effect on an increase in health-care costs. In addition, diabetic patients under capitation (PE = 2.163, odds ratio [OR] = 8.69, $P < 0.001$), FFS (PE = 2.365, OR = 10.64, $P < 0.001$) were more likely to have higher hospitalizations compared to those paid by out-of-pocket (PE = 1.502, OR = 4.49, $P < 0.001$). Diabetic patients receiving treatment from a teaching hospital had significantly higher health-care costs (PE = 0.359, $P < 0.001$), but they were less likely to have hospitalizations (PE = –1.600, OR = 0.20, $P < 0.001$).

Patients admitted to hospital (PE = 0.615, $P < 0.001$) were significantly associated with an increase in health-care costs. Patients with more outpatient visits significantly consumed higher health-care costs (PE = 0.041, $P < 0.001$). Insulin users significantly had higher health-care costs (PE = 0.344, $P < 0.001$) and were about four times more likely to have hospitalizations compared to noninsulin users (PE = 1.308, OR = 3.70, $P < 0.001$).

Diabetic patients with comorbidities (e.g., hypertension [PE = 0.096, $P < 0.001$]), hyperlipidemia (PE = 0.029, $P = 0.002$), and cancer (PE = 0.154, $P < 0.001$)] had significantly higher health-care costs than those without comorbidities. In addition, diabetic patients with hypertension (PE = 0.751, OR = 2.12, $P < 0.001$) or cancer (PE = 1.525, OR = 4.60, $P < 0.001$) also were about two or four times more likely to hospitalize compared to those without hypertension or cancer, respectively. Nevertheless, there was no statistical significant association between an increase in risk of hospitalization and having hyperlipidemia (PE = 0.027, OR = 1.03, $P < 0.687$). Furthermore, patients with microvascular complications (e.g., nephropathy [PE = 0.016, $P < 0.001$]), neuropathy (PE = 0.064, $P < 0.001$), and retinopathy (PE = 0.035, $P = 0.001$)] had a positive impact on health-care costs. Especially, diabetic patients with nephropathy (PE = 2.845, OR = 17.21, $P < 0.001$), neuropathy (PE = 1.790, OR = 5.99, $P < 0.001$), or retinopathy (PE = 0.524, OR = 1.69, $P < 0.001$) were about 18, 6, or 2 times more likely to have hospitalizations than those without microvascular complications, respectively. Diabetic patients with macrovascular complications (e.g., CAD [PE = 0.141, $P < 0.001$]), CVD (PE = 0.058, $P = 0024$), and PVD (PE = 0.213, $P < 0.001$)] were positively associated with higher health-care costs. In addition, diabetic patients with CAD (PE = 1.964, OR = 7.13, $P < 0.001$), CVD (PE = 0.325, OR = 1.38, $P < 0.001$), or PVD (PE = 1.223, OR = 3.39, $P < 0.001$) were 7, 1, or 3 times more likely to hospitalize compared to those without CAD, CVD, or PVD, respectively. Multiple linear and logistic regression models were significant ($P < 0.001$) and the adjusted $R^2$ was 54%, meaning that all significant factors in the model were able to explain 54% of the variation in total health-care costs.

## Discussion

The results of this study suggested that demographic factors, payment methods, hospital characteristics, health-care utilizations, comorbidities, and complications were significantly associated with higher health-care costs and hospitalizations. All previous studies supported the finding that older age patients had higher health-care costs and hospitalizations [8–15]. Moreover, male patients were more likely to have higher costs and hospitalizations than female patients. Krop et al. [8] found the same result, whereas the study of Bhattacharyya [11] showed that female patients were more likely to consume higher health-care costs and utilization.

Regarding the payment methods, particularly patients under FFS (i.e., CSMBS) or capitation (i.e., SSS or UC) significantly had higher health-care costs and hospitalizations compared to those paid by out-of-pocket. In contrast to previous studies, there was no impact of payment method factor on health-care costs. Whether patients were enrolled in the FFS or capitation systems did not have any significant effect on the total direct costs of diabetes [10,12]. In addition, there was no statistically significant difference in patients under FFS plan on hospitalization use [11]. In this study, it could be explained that because all health-care costs of patients under FFS were covered by the government and patients under capitation would pay only some amount of copay for their health-care costs, these patients could easily acquire their treatments as much as they needed and would not be worried about the affordability of health-care expenses. Therefore, they tended to consume higher health-care costs and hospitalizations. This could suggest that patient's eligible benefits could be an important indicator of health-care cost drivers in patients with diabetes in Thailand. Most patients under SSS were the working-age adults who were likely to be healthier than the patients under UC, so that they tended to consume less health-care costs and hospitalizations.

For hospital characteristic factor (e.g., teaching hospitals), patients receiving treatment from teaching hospitals significantly consumed higher health-care costs but had less probability of hospitalization. This could explain that most patients with higher disease severity from nonteaching hospitals were usually referred to a teaching hospital. These patients mostly had only outpatient visits and might not be able to admit to a teaching hospital due to the lack of space. The results reveal that more patients receiving treat-

ment at a teaching hospital had only outpatient visits (86%) compared to those receiving treatment at nonteaching hospitals (61%). In addition, there were fewer patients admitted to teaching hospital (11%) compared to those admitted to nonteaching hospitals (37%).

The results show that the more health-care utilizations (e.g., hospitalization, outpatient visit, and insulin utilization), the higher health-care costs the patients significantly had. Moreover, diabetic patients taking insulin had significantly higher risk of hospitalization. Similar results were also found in the studies of Bhattacharyya [11] and Guo et al. [14].

Furthermore, diabetic patients with comorbidities (e.g., hypertension, hyperlipidemia, and cancer) had significantly higher health-care costs, and diabetic patients with hypertension or cancer tended to have higher hospitalizations. Patients with diabetes and microvascular complications (e.g., nephropathy, neuropathy, and retinopathy) had significantly higher health-care costs and hospitalizations. Diabetic patients with macrovascular complications (e.g., CAD, CVD, and PVD) had significantly higher health-care costs and hospitalizations. Similar to the studies of Bhattacharyya [11] and Bhattacharyya and Else [12], diabetic complications (e.g., retinopathy, nephropathy, and neuropathy) and comorbidities (e.g., hypertension, hyperlipidemia, CAD, and CVD) also had a significant positive impact on health-care costs and hospitalizations.

Two limitations have been addressed in this study. First, the administrative claims data used might be limited. In Thailand, there has been no standardized claims data collection system and standardized data coding excluding ICD-10 codes across hospitals yet, so that different hospitals have different types of claims data collected and data coding. This study used the claims data obtained from four public hospitals and combined into one data set, therefore, unmatched variables were not able to be used for the analysis. Some different coding of administrative claims data would not allow us to identify which type of health-care cost was either diabetic or nondiabetic-related treatment. Thus, in this study, all health-care costs consumed by patients with diabetes were used instead of the costs related to diabetic-related treatment only. Last, like any other retrospective claims data analysis, clinical information such as blood glucose level and other laboratory values would have been highly associated with health-care costs and hospitalizations. Without these clinical measures, assessing the perfect association between factors and health-care costs and hospitalizations might not be possible. Nevertheless, the finding may still be useful information for health-care providers and health policymakers because significant factors in this analysis were able to explain 54% of the variation in total health-care costs.

Based on the results of this study, it is suggested that health-care providers and health policymakers may need to focus on the factors associated with an increase in health-care costs and hospitalizations, such as patients with older age, male sex, comorbidities, complications, patients under capitation or FFS system, and patients taking insulin. Health-care providers may set up the interventions such as diabetic patient counseling, pharmaceutical care, or disease management to delay the progression of comorbidities or complications that diabetic patients may possibly have in the future [17,18]. Although patients under capitation or FFS system have significantly higher health-care costs and hospitalization, these patients may not be at risk. This factor signals the eligible benefits rather than the potential prognostic factors of health-care costs and utilizations. This may relatively indicate the issue of inequity in health care rather than disease severity. It may be used as the information for health policymakers to solve the inequity problem. An investigation of factors associated with health-care costs and hospitalizations may help health-care providers and administrators intervene to improve patient management and possibly reduce health-care costs in the future.

## Acknowledgment

This study is supported by a grant from the Thailand Research Fund. We would like to give particular thanks to the Department of Pharmacy, Mahidol University and the Health Intervention and Technology Assessment Program (HITAP) supported by the Thai Health Foundation, the National Health System Research Institute (HSRI) and the Bureau of Health Policy and Strategy, Ministry of Public Health.

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