# 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);** subcon junctival, 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*