

The Impact of New Antibiotic Stewardship Program and Vancomycin Susceptibility Pattern of Group D Enterococci: Experience in the Specialized Neurological Hospital

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(Received: October 19, 2020; Revised: March 5, 2021; Accepted: March 12, 2021)

บทคัดย่อ: ผลของการเปลี่ยนแนวทางการใช้ยา vancomycin ต่อแบบแผนความไวของเชื้อ group D enterococci: ประสบการณ์ในโรงพยาบาลเฉพาะทางด้านระบบประสาท

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ภูมิหลัง: การควบคุมกำกับดูแลการใช้ยาต้านจุลชีพอย่างเหมาะสม (antibiotic stewardship program; ASP) เป็นกระบวนการที่สำคัญอันหนึ่งในการลดอัตราการดื้อยาของเชื้อก่อโรคในโรงพยาบาล ในอดีตที่ผ่านมา ได้เคยมีการใช้วิธีตรวจสอบการใช้ยาต้านจุลชีพย้อนหลัง (retrospective audit) และเสนอแนะแนวทางที่เหมาะสม (feedback) แต่จากรายงานแบบแผนความไวของเชื้อต่อยาต้านจุลชีพในเวลาต่อมาพบว่า อัตราการใช้ vancomycin ยังเพิ่มขึ้นอย่างมีนัยสำคัญ ร่วมกับความไวต่อยาต้านจุลชีพของเชื้อแบคทีเรียกลุ่ม D enterococci ก็ลดลงจาก 100 เปอร์เซ็นต์เป็น 96 เปอร์เซ็นต์ **วัตถุประสงค์:** ศึกษาวิธีการควบคุมยาปฏิชีวนะ (ASP) ที่สามารถลดอัตราการดื้อยา vancomycin และช่วยเพิ่มความไวต่อยาต้านจุลชีพ vancomycin ของเชื้อ group D enterococci **วิธีการ:** เป็นการศึกษาย้อนหลังโดยการสังเกตเชิงพรรณนา ในผู้ป่วยจำนวน 442 ราย ที่เข้ารับการรักษา ในโรงพยาบาลตั้งแต่ 1 มกราคม 2557 ถึง 31 ธันวาคม 2560 ที่ได้รับ vancomycin injection โดยกลุ่มที่ได้ยาตั้งแต่ 1 มกราคม 2557 ถึง 31 พฤศจิกายน 2558 จำนวน 215 ราย จะถูกตรวจสอบ การใช้ยาต้านจุลชีพย้อนหลัง (retrospective audit) และเสนอแนะแนวทางที่เหมาะสม (feedback) ส่วนกลุ่มที่ได้รับยาตั้งแต่ 1 ธันวาคม 2558 ถึง 31 ธันวาคม 2560 จำนวน 227 ราย จะถูกหยุดยาโดย อัตโนมัตินาน 72 ชั่วโมงหลังเริ่มยา (timeout) หลังจากนั้นหากต้องการใช้ยาต่อ จะต้องขออนุมัติ การใช้ยาจากแพทย์อายุรกรรมก่อน (pre-authorized) แล้วเปรียบเทียบ vancomycin susceptibility ของเชื้อ gr D enterococci และ define daily dose (DDD) ก่อนและหลังการปรับเปลี่ยน **ผล:** หลังจากปรับเปลี่ยน วิธีการใช้ยาเป็นแบบ timeout with pre-authorization พบว่าปริมาณการใช้ยา vancomycin ซึ่งวัดเป็น DDD ต่อ 1,000 วันนอนโรงพยาบาล ลดลงจาก 32.1 และ 44.5 ต่อ 1,000 วันนอนโรงพยาบาล ในปี 2557 และ 2558 เป็น 34.4 และ 39.3 ต่อ 1,000 วันนอนโรงพยาบาล ในปี 2559 และ 2560 ในขณะเดียวกัน แบบแผนความไวของเชื้อ gr D enterococci ต่อยาต้านจุลชีพ vancomycin เพิ่มขึ้นจากร้อยละ 96 และ 95 ตั้งแต่ 2557 และ 2558 เป็นร้อยละ 100 ในปี 2559 และ 2560 **สรุป:** วิธีการควบคุมกำกับดูแลการใช้ยา vancomycin อย่างเหมาะสม ด้วยวิธีหยุดจ่ายยาอัตโนมัติหลังใช้ 72 ชั่วโมง หลังจากนั้นหากต้องการใช้ยาต่อ จะต้องขออนุมัติก่อนจ่ายยา น่าจะเป็นหนึ่งในวิธีการที่มีประสิทธิภาพสำหรับการควบคุมการดื้อยาของเชื้อ gr D enterococci.

คำสำคัญ: การควบคุมกำกับดูแลการใช้ยาต้านจุลชีพอย่างเหมาะสม การหยุดยา vancomycin อัตโนมัติ การขออนุมัติก่อนจ่ายยา group D Enterococci, โรงพยาบาลเฉพาะทางด้านประสาทวิทยา

Abstract

Background: The Antibiotic Stewardship Program (ASP) is an important process to reduce rate of drug-resistance of pathogens in hospitals. In the past, we used retrospective audit process to monitor antibiotics usage, before providing feedback for specific usage suggestion. We collected broad-spectrum antibiotics usage data through antibiotic request forms and Defined Daily Dose (DDD) records. Recent data from antimicrobial susceptibility pattern report shown that the vancomycin usage significantly increased while the antimicrobial susceptibility pattern of group D enterococci decreased from 100 percent to 96 percent. These undesirable trends could lead to higher rate of drug-resistance of pathogens in our hospital. **Objective:** To study the alternative ASP intervention that can reduce vancomycin usage and improve antimicrobial susceptibility of group D enterococci to the vancomycin. **Method:** This study was a descriptive observation study. We collected data from 442 admitted patients who filled the request forms to use vancomycin during January 1st, 2014 to December 31st, 2017. The 215 patients who received vancomycin during 2014-2015 were treated under retrospective audit and feedback (previous ASP). The remaining 227 patients who received vancomycin during 2016-2017 were implemented the antibiotics automatic timeout and pre-authorized intervention (new / alternative ASP). With this new ASP, the vancomycin usage will be automatically stopped after 72 hours of initial use and will require pre-authorization from internal medicine staffs to continue the usage afterward. After that, we evaluated impact of this new ASP by comparing changes of the vancomycin usage and the antimicrobial susceptibility pattern of gram-positive resistant bacteria from microbiological laboratories annual reports. **Result:** After implementing the new antibiotics automatic timeout and pre-authorized intervention, the DDD decreases from 32.1 per 1,000 inpatient-day in 2014 and 44.5 per 1,000 inpatient-day in 2015 to 34.4 per 1,000 inpatient-day in 2016 and 39.3 per 1,000 inpatient-day in 2017. Meanwhile, the antimicrobial susceptibility of group D enterococci to vancomycin improves from 96 percent in 2014 and 95 percent in 2015 to 100 percent in both 2016 and 2017. **Conclusion:** This new ASP intervention which combines the vancomycin automatic timeout with pre-authorization (after the timeout) is proven to be more

effective method to control vancomycin resistant group D enterococci.

Keywords: Antibiotic stewardship program, Vancomycin time out, Prior authorization, Group D Enterococci, Specialized Neurological Hospital.

Introduction

Infection in hospitalized patients can cause many serious complications and may lead to disabilities in many patients. The problem will be worse for the hospital-acquired infections from drug-resistant organisms¹⁻⁷ since we have less choice of antibiotics² for their treatment. Therefore, the Antimicrobial Resistant (AMR) management are crucially important to prevent the infections caused by these drug-resistant organism^{3,4}. Examples of AMR management techniques widely-adopted include handwashing before and after touching patients, wearing personal protective equipment when exposing to infected patients, isolating personal items used by patients, rapid weaning from mechanical ventilator, removing invasive tube and lines as soon as they are not needed, applying aseptic surgical techniques and infectious control program for broad-spectrum antibiotics usage.

The AMR management for controlling the use of broad-spectrum antibiotics, called Antibiotic Stewardship Program (ASP)⁵, is one of the most important processes to control and reduce rate of drug-resistance pathogens in hospitals. Core elements of the ASP include hospital leaders interventions, pharmacy-driven interventions, and infectious syndromes specific interventions. Detailed implementation of the ASP in each hospital will be different depending on management structure, available medical resources, and treatment policy of the hospital⁶

Gr D enterococci are normal intestinal flora commonly found inside human body. Whenever infected patients are treated with broad-spectrum antibiotics, gr D enterococci may outgrowth to be the drug-resistant strain⁷⁻¹⁰, which will lead to high rates of morbidity and mortality⁸⁻¹⁴. The Prasat Neurological Institute (PNI) is a specialized neurological hospital where nosocomial infections from drug-resistant bacteria can be commonly found. According to the National Antimicrobial Resistance Center, Thailand (NARST), nationwide antimicrobial resistance rate of enterococci spp. increases from 1.7 percent in 2014 to 2.3 percent in 2019⁹. Meanwhile,

the PNI microbiological laboratory also reported that antimicrobial resistance rate of group D enterococci to vancomycin increases from 0 percent in 2013 to 5 percent in 2015. With these alarming trends, we, medical staffs at the PNI hospital, have been working together to study an alternative ASP intervention that can increase antimicrobial susceptibility of group D enterococci to the vancomycin.

Materials and Method

This study was a descriptive study. We collected data from 442 admitted patients who filled the request forms to use vancomycin during January 1st, 2014 to December 31st, 2017. The 215 patients who received vancomycin during January 1st, 2014 to November 30th, 2015 were treated under retrospective audit and feedback (previous ASP). During December 1st, 2015 to December 31st, 2017, the new / alternative ASP intervention on vancomycin was applied to 227 patients by setting automatic timeout of vancomycin usage at 72 hours after empirical treatment to all the patients, and demanding re-evaluation from internal medicine staffs for appropriateness of further vancomycin usage beyond 72 hours. After that, we evaluated the impact of this new ASP by comparing changes of the antimicrobial susceptibility pattern of gr D enterococci and other gram-positive resistant bacteria from the annual reports published by the PNI microbiological laboratories.

Statistical analysis: The collected data were analyzed using SPSS Statistics 16.0 (SPSS Inc, Chicago, Ill). Baseline characteristics of the patients were presented as means and standard deviations. The differences of baseline characteristics between two groups, pre and post intervention included sex, treatment indication and hospital acquired infection site were analyzed by chi-squared tests, while age group was analyzed by independent t-test.

Result

Baseline characteristics of patients who used vancomycin before and after implementing intervention was shown in table 1. It found that, there were difference in terms of sex, treatment indication and hospital acquire infection site. The number of female patients were greater than male before intervention, it was in contrast with after intervention. ($p = 0.035$). The mean age before and after the intervention was 56 and 54 years. The most age groups were 61-75 and 46-60 years in the pre and post intervention group, respectively. The empirical treatment was commonly used more than specific treatment indication after intervention ($p < 0.001$). Most three hospital acquired infection sites before intervention were pneumonia, CNS infection and surgical site infection sequentially whereas most common three indications after intervention were CNS infection, surgical site infection and pneumonia respectively ($p = 0.043$).

Table 1 Baseline characteristics of patients using vancomycin before and after implementing intervention

Variables	Before intervention Year 2014 -2015	After intervention Year 2016 -2017	p-value
n	215	227	
Male; n (%)	93 (43.3)	121 (53.3)	0.035*
Age (mean; yrs)	56	54	
Age group; n (%)			
<15	10 (4.7)	6 (2.6)	0.310
16-30	15 (7.0)	26 (11.5)	
31-45	29 (13.5)	32 (14.1)	
46-60	56 (26.0)	63 (27.8)	
61-75	74 (34.4)	62 (27.3)	
>75	31 (14.4)	38 (16.7)	

Table 1 Baseline characteristics of patients using vancomycin before and after implementing intervention (continue)

Variables	Before intervention Year 2014 -2015	After intervention Year 2016 -2017	p-value
Treatment indication; n (%)			
Empirical Tx	144 (66.9)	183 (80.6)	<0.001*
Specific Tx	46 (21.5)	39 (17.2)	
Not filled form	25 (11.6)	5 (2.2)	
Hospital Acquired Infection site; n (%)			
BSI	10 (4.8)	8 (3.4)	0.043*
CNSI	54 (25.8)	73 (31.2)	
Pneumonia	56 (26.8)	53 (22.6)	
Sepsis	2 (1.0)	9 (3.8)	
UTI	13 (6.2)	7 (3.0)	
Periop prophylaxis	5 (2.4)	0 (0.0)	
SSI	51 (24.4)	65 (27.8)	
Other	18 (8.6)	19 (8.1)	
Not filled form	17	1	

Abbreviation: Tx; treatment, BSI; blood stream infection, CNSI; Central nervous system infection, UTI; urinary tract infection, periop; perioperative prophylaxis, SSI; surgical site infection.

*p<0.05

The defined daily dose (DDD) per 1,000 inpatient-day of patients using vancomycin and the antimicrobial susceptibility pattern of gr D enterococci and the other gram-positive resistant bacteria since January 1st, 2012 - December 31st, 2017 according to the table 2.

The DDD per 1,000 inpatient-day increased from 19.5 per 1,000 inpatient-day in 2012 and 23.3 per 1,000 inpatient-day in 2013 to 32.1 per 1,000 inpatient-day

in 2014 and 44.5 per 1,000 inpatient-day in 2015. After implementing intervention, the DDD per 1,000 inpatient-day decreased from previous rate to 34.4 in 2016 and 39.3 in 2017. Meanwhile, the antimicrobial susceptibility pattern of group D enterococci to vancomycin improved from 96 percent in 2014 and 95 percent in 2015 to 100 percent in both 2016 and 2017.

Table 2 Vancomycin usage and percent susceptibility of drug resistant gram-positive organisms since 2012 to 2017

Year	Before intervention				After intervention	
	2012	2013	2014	2015	2016	2017
Vancomycin usage (gram)	2,238.0	2,360.0	3,187.0	4,796.5	3,322.0	3,686.5
IPD hospital-days	57,278	49,568	49,683	53,462	48,336	46,887
DDD vancomycin/1,000 hospital-days	19.5	23.3	32.1	44.9	34.4	39.3

Table 2 Vancomycin usage and percent susceptibility of drug resistant gram-positive organisms since 2012 to 2017 (continue)

Year	Before intervention				After intervention	
	2012	2013	2014	2015	2016	2017
Organisms						
Gr D enterococci	100	100	96	95	100	100
Streptococcus pneumoniae	100	100	100	100	100	100
Staphylococcus aureus (MRSA)	100	100	100	100	100	100
Staphylococcus epidermidis (MRS)	100	100	100	100	100	100

Abbreviation: IPD; in-patient department, DDD; defined daily dose, Gr D enterococci; Group D enterococci, MRSA; methicillin resistant staphylococcus aureus, MRS; methicillin resistant staphylococcus epidermidis.

Discussion

It has been observed that after implementing this new ASP, vancomycin tends to be used more for empirical treatment before clinician receives culture and antimicrobial susceptibility results from microbiological laboratory. In the meantime, we found that the vancomycin usage for treatment of CNS infection and surgical site infection increases while the use for pneumonia treatment decreases. We believe that after implementing this intervention, vancomycin usage patterns have been changed to mainly use for more serious infections such as the CNS infection. Meanwhile, we experience that the vancomycin usage in uncleared infections such as prophylaxis surgical wound infection was dropped to low level.

Following the Centers of Disease Control and Prevention (CDC) guidelines¹⁰, the use of board-spectrum antibiotics for empirical treatment should be de-escalated after pathogens are identified from culture and antimicrobial susceptibility reported. This strategy can help reduce the rate of drug-resistant of pathogens. Furthermore, studies have shown that the

retrospective or prospective audit^{11,12,13} with feedback cannot effectively reduce improper use of antibiotics comparing to the automatic timeout^{14,15} and/or pre-authorized^{16,17} intervention. This study has also proven effectiveness of the antibiotic automatic timeout and pre-authorized intervention through the reductions of DDD and antimicrobial resistant rate in our patients.

Lastly, we would like to note that the automatic timeout and/or pre-authorization will require more attention and additional workload from medical staffs comparing to the retrospective or prospective audit with feedback intervention. Therefore, the health care facilities who want to implement this ASP intervention should have necessary manpower and additional resources prepared in advance.

Conclusion

The ASP intervention which combine vancomycin automatic timeout with pre-authorized (after the timeout) intervention is proven to be an effective method to control vancomycin resistant group D enterococci.

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