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Analisis Restriksi Penggunaan Vankomisin di RS Sebelum, Selama dan Setelah Implementasi Program Pengendalian Resistensi Antimikroba (PPRA)

Analysis of the Restriction of Vancomycin Use in Hospitals Before, During and After the Implementation of the Antimicrobial Resistance Control Program (ARCP)

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Abstrak

Latar Belakang: Kebijakan pembatasan vankomisin merupakan pilot project implementasi Program PengendalianResistensiAntimikroba (PPRA) di RSUD Nusa Tenggara Barat pada tahun 2018. Terdapat tiga tahapan PPRA di rumah sakit yaitu persiapan, pelaksanaan, dan pemantauan. Penelitian ini bertujuan untuk mengevaluasi kualitasperesepan vankomisin sebelum, selama dan setelah penerapan PPRA 2017-2019. **Metode**: Analisis deskriptif keseluruhan resep vankomisin sebelum, selama dan setelah penerapan PPRA pada tahun 2018. Semua rekam medis kasus yang meminta resep vankomisin selama masa penelitian dievaluasi: karakteristik pasien, hasil kultur, diagnosis klinis. Kualitas resep vankomisin dinyatakan sebagai: "Resep vankomisin hanya ditujukan untuk infeksi yang disebabkan oleh patogen Gram-positif terutama *Staphylococcus aureus* yang resisten methicillin (MRSA), Enterococcus sp (Vancomycin-Sensitive Enterococci)" dievaluasi. **Hasil**: Enam puluh satu kasus peresepan vankomisin; 21 perempuan dan 40 laki-laki, usia rata-rata 23 tahun (0-82 tahun). Secara keseluruhan, ada 41 kultur positif, 5 kultur negatif, dan 15 tidak ada data kultur. Diagnosis dengan infeksi sedang - berat: sepsis, pneumonia, pasca operasi, infeksi SSP, berat badan lahir rendah, syok septik dan penyakit paru obstruktif kronik. Presentasi infeksi saluran kemih sebagai infeksi ringan. Indikator kualitas resep 'vankomisin yang diresepkan hanya untuk infeksi sedang – berat' dan 'hanya diresepkan untuk patogen Gram-positif' semuanya meningkat. **Kesimpulan**: Terdapat perbaikan kualitas resep vankomisin setelah penerapan kebijakan pembatasan vankomisin.

Kata kunci: Program Pengendalian Resistensi Antimikroba, kebijakan pembatasan vankomisin.

Abstract

***Background**: A policy restricting the use of vancomycin was a pilot project for the implementation of the Antimicrobial Resistance Control Program (ARCP) in RSUD Nusa Tenggara Barat in 2018. There were three phases of the ARCP in hospitals, namely preparation, execution, and monitoring. This research aimed to evaluate the quality of vancomycin prescribing before, during, and after the implementation of ARCP in 2017–2019. **Method**: Descriptive analysis was conducted of all the vancomycin prescriptions before, during, and after the implementation of ARCP in 2018. All medical records of cases requiring vancomycin prescriptions during the research period was evaluated: patient characteristics, culture test results, and clinical diagnoses. The quality of vancomycin prescriptions, which was expressed as follows:*

"Vancomycin prescriptions are intended only for infections caused by Gram-positive pathogens, particularly Staphylococcus aureus, that are resistant to methicillin (MRSA), Enterococcus sp (Vancomycin-sensitive enterococci)" was evaluated. ***Results****: There were sixty-one cases of vancomycin prescribing; 21 female and 40 male patients, with a mean age of 23 years (0–82 years). Overall, there were 41 positive cultures, 5 negative cultures, and 15 no-cultures. The diagnoses were moderate to severe infections: sepsis, pneumonia, post-surgery infections, CNS infections, low birth weight, septic shocks, and chronic obstructive lung diseases. The urinary tract infection was present as a mild infection. The prescription quality indicators 'vancomycin is prescribed only for moderate to severe infections' and 'prescribed only for Gram-positive pathogens' altogether increased.* ***Conclusion****: There was improvement in the vancomycin prescription quality after the implementation of the vancomycin restriction policy.*

Keywords*: Antimicrobial Resistance Control Program, vancomycin restriction policy.*

Background

Antimicrobial stewardship program (ASP) in hospital is currently becoming a part of assessment component in National Standard of Hospital Accreditation in 2018. The history of ASP implementation in Indonesian hospital started when Indonesia – Netherlands Joint Program is made. The program called,Scientific Programme Indonesia – Netherlands (SPIN) with 4 main areas of research: 1) Antimicrobial Resistance in Indonesia (AMRIN study); 2) Typhoid fever; 3) Tuberculosis and 4) Dengue Haemorrhagic Fever. AMRIN study is conducted in Indonesia involving: 1) Universitas Diponegoro/ Dr Kariadi referral hospital, Semarang; 2) Universitas Airlangga/ Dr Soetomo referral hospital, Surabaya; 3. Leiden University Medical Center, Leiden; 4. Erasmus Medical Center, Rotterdam and 5) Nijmegen University Medical Center, Nijmegen. AMRIN study produce 16 publications, 4 PhDs and National Policy: 1) Verse 19 about hospital antimicrobial stewardship program committee of Presidential Decree No. 77 "Hospital Organization" and 2) Health Minister of Health Regulation No 8 "Antimicrobial Stewardship Program" in 2015.[1][2][3]

The manual of ASP in hospital is limited to initial assessment, which promote each hospital to develop afterward, depends on local situation.[4][5][6] ASP implementation in West Nusa Tenggara Hospital (WNTH) is vancomycin restriction policy which started in 2018 due to internal analysis of high demand of vancomycin prescription to moderate to severe infectionswithout prior microbial culture request. The study aimed to describe vancomycin restriction of ASP in WNTH.

Methods

All vancomycin prescription is summarized in 2017, 2018 and 2019 and its refer to medical record data. The goal of vancomycin prescription restriction is 'only indicated to moderate

to severe infection caused by Gram-positive pathogens especially methicillin-resistant *Staphylococcus aureus*, vancomycin-susceptible *Enterococcus spp*'. Inclusion criteria were: 1) Vancomycin prescription as second line therapy/substitute previous therapy, 2) Vancomycin prescriptions with bacterial culture request in the study period. Second line chemotherapy in the study is defined as substitute therapy of any given therapy for at least three days administered. The quality of vancomycin prescription was measured by two indicators: 1) The proprotion of vancomycin prescription only for moderate-severe infections; 2) The proportion of vancomycin prescription for Gram-positive pathogens

Result

In total, there were 576 vancomycin prescription in 2017, 2018 and 2019. Vancomycin prescription in 2017 was the highest (n=232), followed by 2018 (n=185) and 2019 (n=159). As much as 223 (38.7%) prescriptions were first line therapy and 353 (61.3%) prescriptions were second line therapy. Of 353 prescriptions, only 61 prescriptions were requested for bacterial culture, which met inclusion criteria (fig.1).

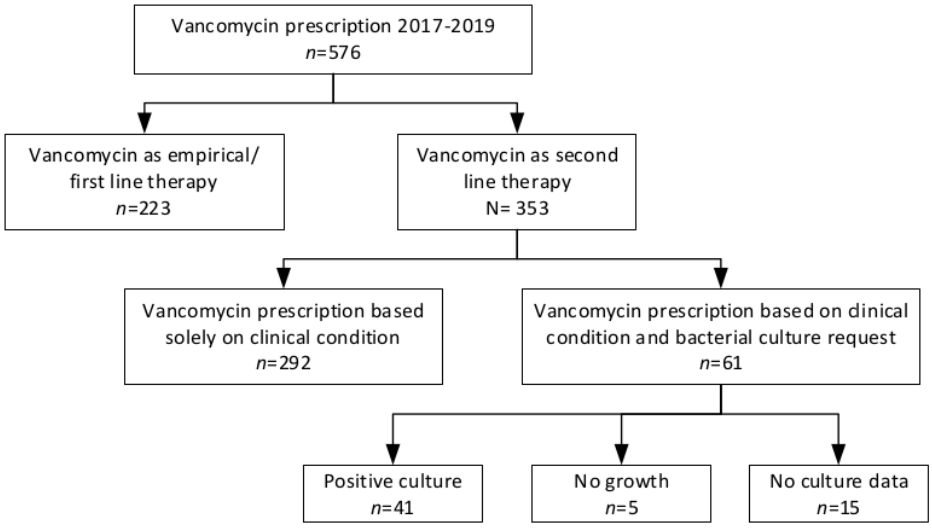

Figure 1. Flowchart of vancomycin prescription met inclusion criteria.

Sixty one subjects then traced from 61 prescriptions. Subjects consist of 21 females and 40 males with median age of 23 years old (0-82).There was a wide spectrum of infections: sepsis 21, pneumonia 18, post surgery 7, central nervous system (CNS) infections 6, low birth weight 3, septic shock 3, urinary tract infections 2, chronic obstructive pulmonary disease (COPD) 1. Seven cases were having comorbid disease of either diabetes or tuberculosis (table 1).

Table 1. Diagnosis and comorbidity. CNS= central nervous system; COPD= chronic obstructive pulmonary disease

Diagnosis	n(%)	Comorbidity	n(%)
Sepsis	21 (34,4)	Type 2 diabetes	2
Pneumonia	18 (29,5)	Tuberculosis	5
Post surgery	7 (11,4)		
CNS infections	6 (9,8)		
Low birth weight	3 (4,9)		
Septic shock	3 (4,9)		
Urinary tract infection	2 (3,2)		
COPD	1 (1,6)		

Microbiology culture result

Microbiology culture result based on Gram-stain characteristics: Gram-positives 31, Gram-negatives 10, no growth 5, no culture data 15 (table 2).

In 41 positive culture (table 2) Gram-positive organisms consist of: *Staphylococcus haemolyticus* 23, *Streptococcus epidermis* 3, *Staphylococcus aureus* 2, *Enterococcus faecialis* 2 and *Streptococcus agalactiae* 1. Gram-negative organisms are: *Klebsiella pneumoniae* 3, *Acinetobacter species* 3, *Proteus mirabilis* 1, *Enterobacter cloacae* 1 (table 3).

Table 2. Microbiology culture result based on Gram-stain characteristic

Culture	2017	2018	2019	Sub total
Gram-positive	10	7	14	31
Gram-negative	5	4	1	10
No growth	1		4	5
No culture results	3	8	4	15
Total	19	19	23	61

Table 3. Bacterial identification results

Bacterial	2017	2018	2019	Total
Staphylococcus haemolyticus	7	7	9	23
Streptococcus epidermis	-	-	3	3
Staphylococcus aureus	2	-	-	2
Enterococcus faecialis	1	-	1	2
Streptococcus agalactiae	-	-	1	1
Klebsiella pneumoniae	3	-	-	3
Acinetobacter species	-	3	-	3
Proteus mirabilis	1	-	-	1
Enterobacter cloacae	-	-	1	1

Quality indicator of vancomycin prescription

Quality indicator of vancomycin prescription stated as: "The prescription of vancomycin is dedicated only for an infection that is caused by Gram positive pathogens, especially methicillin-resistant *Staphylococcus*

aureus (MRSA), *Enterococcus sp* (Vancomycin-Sensitive *Enterococci*)". There were 2 quality indicators developed in this study: 1) Prescribed only for moderate-severe infections; 2) Prescribed for Gram-positive pathogens.

Table 4. Quality indicator used in the study

Quality indicator	2017	2018	2019	Comments
Prescribed only for moderate-severe infection	17/19 (89.5%)	19/19 (100%)	23/23 (100%)	Higher percentage is better output
Prescribed only for Gram positive pathogens	10/19 (52.6%)	7/19 (36.8%)	14/23 (60.8%)	Higher percentage is better output

Discussion

Antimicrobial stewardship program initiation in WNTHG is vancomycin restriction policy. It was started in 2018 due to internal evaluation to antibiotic spending budget and obvious irrational use of antibiotics.

Vancomycin is a glycopeptide antibiotic that had a bactericidal effect by inhibiting peptidoglycan bond formation (polymerization) in the bacterial cell wall. The bacterial cell wall contains a rigid peptidoglycan layer which has a cross-linked structure consisting of long polymers of N-acetylmuramic acid (NAM) and N-acetylglucosamine (NAG). Vancomycin binds to D-alanil D-alanine, which inhibits glucosyltransferase (peptidoglycan synthase) and P-phospholipid carriers, thereby preventing the synthesis and polymerization of NAM and NAG in the peptidoglycan layer. This inhibition weakens the bacterial cell wall and eventually causes leakage of the intracellular components, resulting in bacterial cell death. The cell wall peptidoglycan possessed by Gram-positive bacteria is thicker than Gram-negative bacteria, so Vancomycin also called Gram-positive antibiotics.[7][8]

The use of vancomycin should be used cautiously, because its activity is limited to Gram positive bacteria and is indicated to severe infections caused by methicillin resistant Staphylococcus aureus and vancomycin sensitive Enterococcus spp. Thus, indications of severe infection alone without knowledge of the causative agent are irrational.

Irrational use of vancomycin in hospitals may increase the number of cases of Vancomycin-resistance Enterococcus (VRE)[9] and the number cases of *Clostridium difficile* infection.[10] The clinical diagnosis of sepsis was being the most common

diagnosis (34.4%) showed severe infections lead clinician tend to prescribe vancomycin, which taking into account other clinical factors. Indications for use of vancomycin in infectious disease according to the Food and Drug Administration (FDA): *Clostridium difficile*-associated diarrhea (oral administration), Staphylococcus enterocolitis, Pseudomembranous colitis, Endocarditis: *diphtheroid*, Enterococcal, Staphylococcal, and Streptococcal species, Staphylococcal infections: septicemia, skin and soft tissue infections, bone infections, lower respiratory tract infections.[11][12][13]

The study findings showed that the causative agent of severe infections is not Gram positive bacteria alone, but also Gram negative bacteria; which determined that the use of vancomycin based solely on a clinical diagnosis of severe infection is irrational. Most of the pathogens that cause severe infectious disease are multidrug resistant.[14]

Staphylococcus aureus bacteria, which are also known as normal flora bacteria in the nasal, axillary and inguinal cavities have the ability to adapt to evolution and cause severe infections, according to a study by Young et al.[15]

Vancomycin restrictions are not only limited to confirming the criteria for prescribing approval but also need to be accompanied by infection prevention and control policy in hospitals such as increasing compliance with hand washing, appropriate washing of medical devices, vaccination, laboratory examinations, enforcement of clinical practice guidelines and application of a comprehensive ASP program.[16][17]

This ASP implementation analysis showed improvement vancomycin prescription year to year. Clinical indication for moderate to severe infections was improved from 2017 to 2018 (89.5% to 100%), and the indication for Gram positive pathogens was increased from 2018 to 2019 (36.8% to 60.8%) (table 4).

Limitation of the study is limited number of subjects to be analyzed. Improvement of quality of vancomycin prescription may affected by multi factors, not solely by vancomycin restriction policy, such as continuing professional development of clinician.

Conclusion

There was an improvement of quality vancomycin prescription after vancomycin restriction policy implementation.

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