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RESEARCH ARTICLE

The impact of antimicrobial stewardship on reserve antibiotic use and procuring cost

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Abstract

Background: Antimicrobial Stewardship (AMS) is an intervention designed to optimise the appropriate use of antibiotics is expected to reduce selective pressure on microbes, control antimicrobial resistance, improve patient clinical outcomes, and cost reduction. **Objective**: The aim of this study is to analyse the impact of antimicrobial stewardship on "reserve" antibiotics use and procuring cost of antibiotics in hospitals. **Method**: The study was conducted at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. A retrospective observational design study to analyse trends of "*reserve*" antibiotics use and procuring cost before AMS implementation (January 2018-December 2019) and after AMS implementation (January 2020-December 2021). **Results**: The total meropenem consumption before AMS intervention in January 2018-December 2019 was 9950 DDD, and after AMS intervention in January 2020-December 2021 was 4639 DDD, showing a decrease of 53 %. Procuring Meropenem cost in 2018-2019 was Indonesian Rupiah (IDR) 1.490 billion and IDR 309 million between 2020 to 2021. Cost reduction positively impacts saving procurement costs in hospitals of IDR 1.18 billion (79%). **Conclusion**: The impact antimicrobial stewardship programs can reduce reserve antibiotic use with meropenem indicator and have a sustainable economic impact, saving the cost of procuring antibiotics in hospitals.

Introduction

The treatment of infectious diseases relies on the use of antimicrobials. Antibiotics are antimicrobials with several classes, each with a different work target. Unfortunately, the use of antimicrobials also triggers antimicrobial resistance (AMR) and is accelerated by inappropriate antibiotics (Abushaheen, 2020). The inappropriate use of antibiotics affects the patient's clinical outcomes, such as the prognosis for healing infectious diseases, the potential for side effects, and the length of treatment, and also becomes the dominant factor causing resistance so that the handling and treatment of infectious diseases are increasingly complicated, hospitalisation is longer and of course has an impact on the treatment costs of patients (World Health Organisation, 2016).

The Global Antimicrobial Resistance and Use Surveillance System (GLASS) report shows that the prevalence of multiple drug-resistant organisms (MDRO) with extended-spectrum Beta-lactamase (ESBL) producing bacteria indicators in 11 hospitals in Indonesia increased to an average of 66.7% (World Health Organisation, 2020). In addition, the results of surveillance on the use of antibiotics using a multicentre point prevalence survey method in six hospitals in Indonesia showed that out of 1602 inpatients, 993 (62.0%) received less than one antimicrobial, and the most prescribed antibiotic classes were third-generation cephalosporins 44.3%, fluoroquinolones 13.5%, carbapenems 7.4%, and penicillins with b-lactamase inhibitor 6.8% (Limato *et al.,* 2021).

In May 2015, the World Health Organisation launched the Global Action Plan on Antimicrobial Resistance (GAP-AMR) with five objective strategies adopted by various countries, including Indonesia, into the National Action Plan on Antimicrobial Resistance (NAP-AMR) (Parathon *et al.,* 2017). The fourth objective strategy is the optimisation of antimicrobial stewardship programs (AMS) to monitor and promote the prudent use of antibiotics at local and national levels according to standards to ensure the correct indication and choice as well as the correct dosage and duration regimen (Parathon *et al.,* 2017). The Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) recommend that pre-authorisation and/or prospective audits are effective interventions based on research evidence: strong recommendation and moderate- quality evidence (Barlam *et al.,* 2016). Pre-authorisation prescribing optimises initial antibiotic therapy, and prospective audits optimise further antibiotic therapy and can prevent unnecessary or excessive initiation of antibiotics (Tamma *et al.,* 2017).

The AWaRe Classification of antibiotics was developed in 2017 by the WHO Expert Committee on the selection and use of essential medicines as a tool to support antibiotic stewardship efforts at local, national, and global levels. Antibiotics are classified into three groups: Access, Watch, and Reserve (AWaRe), considering the impact of different antibiotics and antibiotic classes on antimicrobial resistance to emphasise the importance of their appropriate use (Sprenger, 2016; WHO, 2021b). In the list of national antibiotic guidelines, meropenem is a reserved category and antibiotic of choice for treating infections caused by extended-spectrum beta-lactamase (ESBL)-producing bacteria. However, its use is high and needs to be controlled and monitored (Ministry of Health Republic Indonesia, 2021). Based on this background, this study aims to analyse the impact of AMS implementation on controlling the consumption of reserve antibiotics and their procurement costs.

Methods

This study was conducted at Dr. Soetomo General Academic Hospital Surabaya, Indonesia, the main referral hospital in East Java province. The design of this study was retrospective observational by collecting data from pharmacy records in the period before the AMS implementation in 2018-2019 and the period after the AMS implementation in 2020-2021.

The intervention of antimicrobial stewardship programme through pre-authorisation of "reserve" antibiotic prescribing with indicators of prescribing meropenem. The AMS team will then review inpatients who start treatment with meropenem to obtain prescribing approval. The socialisation of the AMS implementation began in October 2019.

The variables analysed were meropenem consumption by measuring the total defined daily dose (DDD) and procurement costs (IDR) during the period of the year. This study is under ethical clearance issued by the ethical committee of Dr. Soetomo General Academic Hospital.

Results

Data collection from pharmacy records in the period before the implementation of AMS, the total consumption of meropenem in January 2018-December 2019 was 9950 DDD, and after the implementation of AMS in January 2020-December 2021, it was 4639 DDD. The total DDD consumption of meropenem showed a significant decrease of 53%. meropenem consumption data every month can be seen in Figure 1. The total procurement cost of meropenem in 2018-2019 was IDR 1.490 billion, and IDR 309 million in 2020-2021. The decrease in meropenem procurement costs by 79% (IDR 1.18 billion) has a positive impact on saving procurement costs in hospitals.

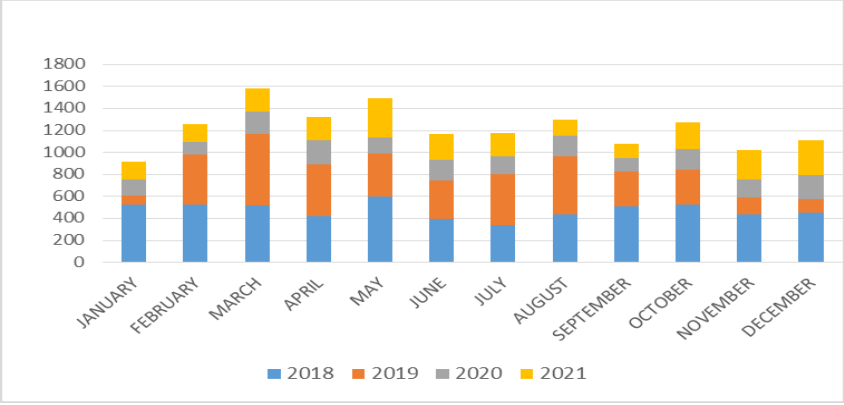

Figure 1: Total DDD of meropenem consumption

Discussion

Antibiotics are antimicrobial drugs used for the treatment of bacterial infections; if they lose their effectiveness, then medical procedures in surgical procedures such as heart surgery, cesarean section, joint replacement, and other surgical procedures can become too dangerous to perform, also in the treatment of patients with conditions immunocompromise such as chemotherapy for cancer with febrile neutropenia and critically ill disorders will become increasingly tricky (O'Neil, 2016). The magnitude of this resistance problem is estimated that the burden of death due to antimicrobial resistance will increase to 10 million people annually by 2050, and the cumulative loss to global economic output is 100 trillion USD (O'Neill J, 2016). The Lancet February 2022 reported the results of a systematic analysis that there was an estimated 4.95 million/year (3.62–6.57) deaths related to AMR in 2019, including 1.27 million/year (95% UI 0.911–1, 71) deaths caused by AMR (Antimicrobial Resistance Collaborators, 2022).

At the regional level, it is estimated that the all-age mortality rate from antimicrobial resistance is highest in western sub-Saharan Africa, with 27.3 million deaths per 100,000 (20.9–35.3), and lowest in Australia, at 6 5 million deaths (4.3–9.4) per 100,000. Lower respiratory tract infections accounted for more than 1.5 million resistance-related deaths in 2019 (Antimicrobial Resistance Collaborators, 2022).

The GLASS Report 2021 shows that the prevalence of MDRO indicators of *Escherichia coli* and *Klebsiella pneumoniae* bacteria producing extended-spectrum beta-lactamase (ESBL) multicentre surveillance in hospitals in Indonesia increased from 62.2% in 2019 to 66.7% in 2020 (WHO, 2021a). The dominant factor for the increasing prevalence of MDRO is the excessive use of antibiotics or no indication (Davies, 2017).

Carbapenems are practical options for treating severe infections caused by multidrug-resistant (MDR) Enterobacterales bacteria (Tompkins., 2021). The emergence of carbapenem resistance is a significant public health concern, and the World Health Organisation has identified carbapenem-resistant Enterobacterales as critical-priority bacteria (Tacconelli, 2018).

Meropenem is a carbapenem antibiotic for treating infections caused by ESBL-producing bacteria. Based on the WHO Access, Watch, Reserve (AWaRe) classification list, meropenem is included in the

"Watch" category (WHO, 2021b). Based on the national antibiotic guidelines Ministry of Health is included in the "Reserve" category, so its use must be controlled and monitored (Ministry of Health Republic Indonesia, 2021).

Antimicrobial Stewardship (AMS) is a strategic, systematic, integrated, and organised activity aimed at optimising the prudent use of antimicrobials in quantity and quality. IDSA and SHEA recommend that one intervention strategy for implementing effective antimicrobial stewardship, strong recommendation and moderate-quality evidence is restrictive interventions, limiting antibiotics use through pre-authorisation of antibiotic prescribing based on AWaRe categories [Mijović *et al.,* 2018].

Reserve antimicrobial consumption showed a declining trend after introducing the Reserve drug indent form (RDIF). Hence, the RDIF served as an important tool to combat inappropriate use, reducing the cost burden and also helping to improve the sensitivity to reserve drugs (Deepthi *et al.,* 2015).

The parameter of antibiotic consumption used to reflect antimicrobial usage accurately is the defined daily dose (DDD) promoted by the WHO. WHO defines DDD as the assumed average daily maintenance dose for a drug used for its main indication in adults. To estimate the total number of days of antimicrobial therapy, healthcare personnel divide the total grams of each antimicrobial used for a given period by the WHO-defined DDD for the individual antimicrobials. Because DDD is a standardised unit of measure, it allows comparisons with antimicrobial usage in other hospitals and countries (Septimus, 2014).

In this study at Dr. Soetomo General Academic Hospital since October 2019, an antimicrobial stewardship programme has been launched by applying a pre-authorisation policy on antibiotic prescribing in the reserved category with meropenem indicator. Inpatients who start Meropenem treatment will be reviewed by the AMS Team to get their prescribing approval, whether the Meropenem prescription is indicated or not. After AMS implementation through the pre-authorisation prescription for two years, the total DDD of meropenem consumption showed a significant decrease of 53% and 79% savings in procurement costs. The limitations of this study have not examined the impact on patient clinical outcomes.

Conclusion

The reserve antibiotics are used with the meropenem indicator and have a sustainable economic impact, saving the cost of procuring antibiotics in hospitals.

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References

Abushaheen, M. A., Muzaheed, Fatani, A.J., Alosaimi, M., Mansy, W., George, M., Acharya, S., Rathod, S., Divakar, D. D., Jhugroo, C., Vellappally, S., Khan, A. A., Shaik, J., Jhugroo, P. (2020). Antimicrobial resistance, mechanisms and its clinical significance. *Disease a Month*, **66**(6), 100971. https://doi.org/10.1016/j.disamonth.2020.100971.

Barlam, T. F., Cosgrove, S.E., Abbo, L. M., MacDougall, C., Schuetz, A.N., Septimus, E. J., Srinivasan, A., Dellit, T. H., Falck-Ytter, Y. T., Fishman, N. O., Hamilton, C. W., Jenkins, T. C., Lipsett, P. A., Malani, P. N., May, L. S., Moran, G. J., Neuhauser, M. M., Newland, J. G., Ohl, C. A., Samore, M. H., Seo, S. K., Trivedi, K. K. (2016). Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis*. **62**(10), e51-77. https://doi.org/10.1093/cid/ciw118

Center for Diseases Control and Prevention. (2019). *The Core Elements of Hospital Antibiotic Stewardship Programs*. Accessed: 20 May 2022. Available on: https://www.cdc.gov/antibiotic-use/core-elements/hospital.html

Shridhar. D. P., Anitha, K. B., Rai, M., Fernandes. (2015). A Reserve drug indent form and its impact on antimicrobial consumption and sensitivity pattern in the medical intensive care unit of a tertiary care hospital. *Journal of Clinical and Diagnostic Research*, **9**(2), FC05-https://doi.org/10.7860/JCDR/2015/10974.5593.

Antimicrobial Resistance Collaborators. (2022). Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis, **399**(10325), 629-655. https://doi.org/10.1016/S0140-6736(21)02724-0

Kelly, R., & Davies, S. C. (2017). Tackling antimicrobial resistance globally. *Medical Journal of Australia*, **207**(9), 371-373. https://doi.org/10.5694/mja17.00865.

Ministry of Health Republic Indonesia. (2021). *Regulation of the Minister of Health of the Republic of Indonesia number 28 of 2021 concerning Guidelines for the Use of Antibiotics*. Accessed: 20 May 2022. Available at https://www.iccc.or.id/wpcontent/uploads/2021/03/Minister-of-Health-Regulation-No.-10-of-2021-SSEK-Translations.pdf

Limato, R., Nelwan, E. J., Mudia, M., de Brabander, J., Guterres, H., Enty, E., Mauleti, I. Y., Mayasari, M., Firmansyah, I., Hizrani, M., Hamers, R. L. (2021). A multicentre point prevalence survey of patterns and quality of antibiotic prescribing in Indonesian hospitals. *JAC Antimicrobial Resistance*, **3**(2), dlab047. https://doi.org/10.1093/jacamr/dlab047

Mijović, B., Dubravac Tanasković, M., Račić, M., Bojanić, J., Stanić, S., & Banković Lazarević, D. (2018). Outcomes of intrahospital antimicrobial stewardship programs related to prevention of Clostridium difficile infection outbreaks. *Medicinski Glasnik*, **15**(2), 122-131. https://doi.org/10.17392/958-18.

Nathwani, D., Varghese, D., Stephens, J., Ansari, W., Martin S., & Charbonneau, C. (2119). Value of hospital antimicrobial stewardship programs [ASPs]: A systematic review. *Antimicrobial Resistance Infectious Control*, **8**, 35. https://doi.org/10.1186/s13756-019-0471-0

O'Neill, J. (2016). Tackling Drug-Resistant Infections Globally: Final Report And Recommendations. The review on AMR. Accessed: 20 May 2022. Available on: https://apo.org.au/node/63983,

Parathon, H., Kuntaman, K., Widiastoety, T. H., Muliawan, B. T., Karuniawati, A., Qibtiyah, M., Tawilah, J. F., Aditama, T., Tamlikitkul, V., & Vong, S. (2017). Progress Towards Antimicrobial Resistance Containment And Control In Indonesia. https://doi.org/10.1136/bmj.j3808

Peirano, G., Chen, L., Nobrega, D., Finn, T. J., Kreiswirth, B. N., DeVinney, R., & Pitout, J. D. D., (2022). Genomic Epidemiology of Global Carbapenemase-Producing Escherichia coli, 2015– 2017. Emerging Infectious Diseases, **28**, 5. https://www.cdc.gov/eid

Septimus, E. (2014). Antimicrobial stewardship-qualitative and quantitative outcomes: The role of measurement. *Current Infectious Disease Reports.* **16**(11), 433. https://doi.org/10.1007/s11908-014-0433-x.

Tacconelli, E., Carrara, E., Savoldi, A., Harbarth, S., Mendelson, M., Monnet, D. L., Pulcini, C., Kahlmeter, G., Kluytmans, J., Carmeli, Y., Ouellette, M., Outterson, K., Patel, J., Cavaleri, M., Cox, E.M., Houchens, C.R., Grayson, M. L., Hansen, P., Singh, N., Theuretzbacher, U., & Magrini, N. (2018). WHO Pathogens Priority List Working Group. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infect Dis,* **18**(3), 318-327. https://doi.org/10.1016/S1473- 3099(17)30753-3.

Tamma, P. D., Avdic, E., Keenan, J. F., Zhao, Y., Anand, G., Cooper, J., Dezube, R., Hsu, S., & Cosgrove, S. E. (2017). What Is the most effective antibiotic stewardship intervention: Preprescription authorisation or postprescription review with feedback? *Clinical Infectious Diseases*, **64**(5), 537-543. https://doi.org/10.1093/cid/ciw780.

Tompkins, K., & van Duin, D. (2021). Treatment for carbapenem- resistant Enterobacterales infections: Recent advances and future directions. *European Journal of Clinical*

Microbiology Infectious Diseases. **40**(10), 2053-2068. https://doi.org/10.1007/s10096-021-04296-1

World Health Organisation. (2021a). Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report. Accessed, 20 May 2022. Available on: https://www.who.int/initiatives/glass

World Health Organisation. (2021b). WHO Access, Watch, Reserve (AWaRe) Classification of antibiotics for evaluation and monitoring of use. Available on: https://apps.who.int/iris/handle/10665/345555