Prevalence of antibiotic resistance in adult septic patients of H. Adam Malik central general hospital, Medan under Indonesia’s mandatory health scheme

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Abstract. Sepsis is a severe bacterial infection whose treatment still varies in preference. However, for more than 60 years, antibiotics have been regarded as the panacea, as long as they are used wisely and timely. Antibiotic resistance has escalated in recent years, resulting in an accelerating global health security emergency, that is rapidly outpacing available treatment options. In January 2014, the new mandatory health insurance scheme (JKN) was introduced, whose treatments must comply with National Formulary (FORNAS) policy. We aimed to systematically review the prevalence of antibiotic resistance to FORNAS policy’s preferential treatments in adult septic patients who had been in the non-surgical wards. Based on an overall view, 76 out of 90 kinds of antibiotics which had undergone antibiotic susceptibility test (AST) had alarming resistance rate and preferential antibiotics in the current JKN scheme may have become ineffective.

1. Introduction

Effective 1 January 2014, Indonesia’s government launched an ambitious project: to establish a compulsory national health insurance system. The scheme (JKN), was implanted by the newly-formed social security administrator for health, Badan Penyelenggara Jaminan Kesehatan (BPJS). JKN covers medical and non-medical benefits, that is mandatory for all Indonesian citizens and residents. The benefits, however, are limited to “basic needs.” Furthermore, since 2015, the implementation of preferential treatment has to follow the scheme of National Formularies (FORNAS) guideline, which is somewhat contradictory.[1]

Sepsis is a life-threatening medical condition that arises when the body attempts to fight an infection. This response, designed to protect us, for which may cause widespread inflammation resulting in organ damage.[2] In spite of the fact that sepsis management comes in various modalities, antibiotics have been regarded as the panacea in combating the attack of microorganisms. Sepsis treatment is by administrating broad-spectrum antibiotic within the first hour of recognition. However, if the blood culture sample has identified the pathogen isolate, physicians can choose empirical antibiotics which target specific organism(s).[3-5] Due to non-prescribed of antibiotic use, it would...
provoke inadequate eradication of bacteria which eventually cause mutation; this is primarily contributing to antibiotic resistance. This phenomenon has become a worldwide problem with consequences on the treatment of infectious diseases. Moreover, for over the last 30 years, no new types of antibiotics have been developed. Without urgent action, we are heading to a post-antibiotic era where common infections and minor injuries can once again kill.[4-6] Some resistant infections may require increased recovery time, demands alternative drugs which might be less effective, more toxic, and tend to incur increased medical expenses.[6]

2. Method
This research was a descriptive survey with an retrospective approach to observing the prevalence of antibiotic resistance of adult patients with non-surgical sepsis (from non-surgical departments: Internal Medicine, Pulmonology and Respiratory Medicine, ICU, Cardiology, Neurology, and ENT) in the year of 2015. This research was in H. Adam Malik Central General Hospital, which is a tertiary referral hospital as a representative of medical surveillance in North Sumatra starting from January to December of 2015. Samples were entire adult patients population collected from the hospital’s medical records and microbiology laboratory, who had undergone blood culture against AST.

In this era of JKN scheme, every installation in H. Adam Malik hospital follows the FORNAS guideline relating management therapy of certain diseases. Therefore, results of this study will be compared to FORNAS preferential antibiotic treatment policy.

3. Results
Out of 8422 non-surgical patients who had admitted to H. Adam Malik General Hospital, 390 (4.6%) patients were diagnosed with sepsis.

Based on bacterial isolates finding, total sample was 172 isolates which 107 (62.21%) cases were gram-negative bacteria, and 65 (37.79%) cases were gram-positive bacteria with no discovery of obligate anaerobic bacteria (0%). The most common isolates were Acinobacter baumanii and Escherichia coli with 23 (13.37%) incidences found in each isolation.

The resistance profile of certain antibiotic class is in Figure 1. Research findings showed Quinolone was the highest resistance (80.58%). The susceptible levels of each antibiotic, however, are provided in the appendix.

![Percentage of resistance](image)

**Figure 1.** Resistance percentage based on antibiotic classes of Adult Patients with Non-Surgical Sepsis in H. Adam Malik Central General Hospital, 2015. Description of specific antibiotic drugs is provided on Appendix.
Table 1. Bacterial isolates distribution.

| Variable              | Frequency (n) | Percentage (%) |
|-----------------------|---------------|----------------|
| **Gram-Negative Bacteria** |               |                |
| P. oryzihabitans      | 1             | 0.58%          |
| Hafnia alvei 1        | 1             | 0.58%          |
| K. terrigena          | 1             | 0.58%          |
| O. anthropi           | 1             | 0.58%          |
| Pantoea ssp 1         | 1             | 0.58%          |
| Prevotella buccae     | 1             | 0.58%          |
| Proteus vulgaris      | 1             | 0.58%          |
| ovidencia stuartii    | 1             | 0.58%          |
| P. fluorescens        | 1             | 0.58%          |
| P. putida             | 1             | 0.58%          |
| Serratia fonticola    | 1             | 0.58%          |
| S. liquefaciens       | 1             | 0.58%          |
| S. marcescens         | 1             | 0.58%          |
| Serratia rubidaea     | 1             | 0.58%          |
| C. freundii           | 2             | 1.16%          |
| E. aerogenes          | 2             | 1.16%          |
| K. oxytoca            | 2             | 1.16%          |
| B. cepacia            | 4             | 2.33%          |
| E. cloacae            | 5             | 2.91%          |
| P. aeruginosa         | 12            | 6.98%          |
| K. pneumoniae         | 20            | 11.63%         |
| A. baumannii          | 23            | 13.37%         |
| Escherichia coli      | 23            | 13.37%         |
| **Total**             | **107**       | **62.21%**     |
| **Gram-Positive Bacteria** |           |                |
| Bacillus cereus       | 1             | 0.58%          |
| C. sporogen           | 1             | 0.58%          |
| E. gallinarum         | 1             | 0.58%          |
| Leuconostoc pseudomone| 1             | 0.58%          |
| Strep. constellatus   | 1             | 0.58%          |
| Strep. mitis          | 1             | 0.58%          |
| Gafkya tetragena      | 2             | 1.16%          |
| Staph.hominis         | 2             | 1.16%          |
| S. maltophilia        | 2             | 1.16%          |
| Strep.agalactie       | 2             | 1.16%          |
| Strep. viridans       | 2             | 1.16%          |
| Strep.pyogenes        | 3             | 1.74%          |
| Staph. haemolyticus   | 4             | 2.33%          |
| E. faecali            | 7             | 4.07%          |
| Staph. aureus         | 10            | 5.81%          |
| Staph. saprophyticus  | 12            | 6.98%          |
| Staph.epidermidis     | 13            | 7.56%          |
| **Total**             | **65**        | **37.79%**     |
gram-negative infection is *Pseudomonas aeruginosa* especially for patients with compromised host defense mechanisms. It is the most general pathogen isolated from patients who have been hospitalized more than 1 week, and it is a usual cause of nosocomial infections.[9]

Preferential antibiotics to treat bacterial infection by FORNAS guideline[10] with sufficient sensitive percentage (>70%)[11] were Metronidazole (100%), Polymyxin B (95.38%), and Amikacin (85.42%). However, skewed data might be present from the result. For instance, Metronidazole is indicated for anaerobic bacterial infections, but the microbiology laboratory of H. Adam Malik hospital has not yet been providing anaerobic bacteria culture in which this situation may lead to misinterpretation. Polymyxin B is indicated for resistant gram-negative infections although it has not yet manufactured nor distributed in Indonesia. This antibiotic in FORNAS guideline was a form of combination with antibiotic bacitracin, while the available data from this research has no finding for the combination. Therefore, it is not surprising that the sensitivity numbers were remarkably high. Amikacin, on the other hand, is available in Indonesia as an indication for gram-negative bacterial infections that are resistant to gentamycin which is manufactured by five pharmacy brands in Indonesia and could be one of the choices for an empirical antibiotic for sepsis.

Other empirical antibiotics findings outside the FORNAS policy were Ceftobiprole (100%), Tigecycline (100%), Linezolid (84.21%), Minocycline (83.33%), and Doripenem (73.26%). Ceftobiprole is the fifth generation of cephalosporin antibiotic class, but it has not been in Indonesia. Based on data from MIMS Indonesia, Minocycline is only available in capsule, while sepsis management is primarily given intravenously. Meanwhile, Tigecycline, Linezolid, and Doripenem are available in Indonesia.[12] However, these drugs charges will be borne to patients. To ensure compliance with the JKN scheme, BPJS operates Indonesia Case Base Groups (INA-CBGs) package payment system, with the intention that charges can be covered by JKN scheme, which is only possible after obtaining a recommendation from the chairman of the pharmaceutical committee with the approval of the medical committee and the hospital CEO. Proposing this “not-recommended” drugs must be formerly done by filling out an application form which would cost lots of time where antibiotic therapy urge to be given to septic patients in the first critical hour.[13] Therefore, although several antibiotics were found sensitive from this research, it may not be exploited for sepsis treatments in current Indonesia’s scheme. In spite of the verdict, authors personally have high hopes for the program to be continued, because an improvement for some sections in Indonesian health service has been demonstrated.
Caution is necessary for interpreting the available data, the proportions of resistant antibiotics are determined based on results from AST. This study describes the situation of overall resistance rate but lacks in patients’ characteristics (clinical diagnosis & source of infection) which play a role as risk factors. Qualified samples were merely from adult patients with sepsis based on limited and skewed medical records, which are not likely to be representative of the general situation. But, this research provides useful insight into the current status of antibiotic resistance in H. Adam Malik Central General Hospital.

5. Conclusion
Practice guidelines advocate first-line antibiotics based on resistance rates above 30%, which most of the preferential antibiotic drugs by FORNAS policy had passed over. Based on the overall resistance; out of 90 antibiotics which had undergone AST, 76 antibiotics exceeded the resistance threshold. These results showed that most of the available drugs; both FORNAS policy and Indonesia’s available treatment have to offer, had become inadequate and the antibiotic resistance in H. Adam Malik Central General Hospital has reached to an alarming situation. The study is intended to provide information primarily for public health policy-makers and managers, and for the medical and public health community, as a support for informing strategic actions and program planning. It is best to continue relevant surveillance annually in other centers for more reliable and presentative national data regarding antibiotic resistance phenomenon. And lastly, promoting the education of antibiotic use for both clinicians and society should remain to be continued to increase public knowledge and to raise the awareness to improve Indonesia’s public health.

References
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### Antibiotic Susceptibility Testing Distribution

| Antibiotic | Resistant (%) | Intermediate (%) | Sensitive (%) |
|------------|---------------|------------------|---------------|
| Amikacin   | 19 (1.39%)    | 2 (0.15%)        | 123 (85.42%)  |
| Amoxicillin| 47 (13.30%)   | 11 (3.10%)       | 5 (1.40%)     |
| Ampicillin | 117 (8.23%)   | 9 (0.63%)        | 45 (33.80%)   |
| AMP³       | 3 (0.00%)     | 0 (0.00%)        | 3 (0.00%)     |
| Azlocillin | 9 (0.00%)     | 0 (0.00%)        | 1 (0.00%)     |
| Aztreomycin| 9 (6.49%)     | 0 (0.00%)        | 5 (3.57%)     |
| Bactinacin | 2 (0.00%)     | 0 (0.00%)        | 3 (0.00%)     |
| Benzylpenicillin | 19 (95.00%) | 1 (5.00%) | 0 (0.00%) |
| Carbenicillin | 9 (100.00%) | 0 (0.00%) | 1 (10.00%) |
| Cefadroxil | 7 (100.00%)   | 0 (0.00%)        | 3 (30.00%)    |
| Cefalexin | 7 (100.00%)   | 0 (0.00%)        | 3 (30.00%)    |
| Cefalotin | 7 (77.78%)    | 0 (0.00%)        | 2 (22.22%)    |
| Cefmanadole | 8 (72.73%)  | 0 (0.00%)        | 3 (27.27%)    |
| Cefazolin | 10 (76.92%)   | 0 (0.00%)        | 3 (23.08%)    |
| Cefdinir | 8 (72.73%)    | 0 (0.00%)        | 3 (27.27%)    |
| Cefidoren | 8 (72.73%)    | 0 (0.00%)        | 3 (27.27%)    |
| Cefepime | 10 (71.43%)   | 0 (0.00%)        | 4 (28.57%)    |
| Cefetamet | 8 (100.00%)   | 0 (0.00%)        | 0 (0.00%)     |
| Cefixime | 8 (100.00%)   | 0 (0.00%)        | 0 (0.00%)     |
| Cefmenoxime | 7 (100.00%) | 0 (0.00%) | 0 (0.00%) |
| Cefonicid | 7 (70.00%)    | 0 (0.00%)        | 3 (30.00%)    |
| Cefoperazone | 7 (77.78%) | 0 (0.00%) | 2 (22.22%) |
| C/S⁴      | 21 (22.34%)   | 13 (13.83%)      | 60 (63.83%)   |
| Cefoxime | 10 (76.92%)   | 0 (0.00%)        | 3 (23.08%)    |
| Cefotiamine| 5 (100.00%)   | 0 (0.00%)        | 0 (0.00%)     |
| Cefotaxime | 80 (81.63%)   | 3 (3.06%)        | 15 (13.31%)   |
| Cefotetan | 8 (66.67%)    | 0 (0.00%)        | 4 (33.33%)    |
| Cefoxitin | 64 (64.00%)   | 2 (2.00%)        | 34 (34.00%)   |
| Cephrimic | 8 (100.00%)   | 0 (0.00%)        | 0 (0.00%)     |
| Cepodoxime | 9 (75.00%)    | 0 (0.00%)        | 3 (25.00%)    |
| Ceprozil | 8 (80.00%)    | 0 (0.00%)        | 2 (20.00%)    |
| Cefradine | 8 (72.73%)    | 0 (0.00%)        | 3 (27.27%)    |
| Cefetamidone | 75 (72.82%)  | 5 (4.85%) | 23 (22.33%) |
| Cefdinone | 8 (100.00%)   | 0 (0.00%)        | 0 (0.00%)     |
| Cefditoxime | 8 (72.73%)  | 0 (0.00%) | 3 (27.27%) |
| Cefetobiprole | 0 (0.00%) | 0 (0.00%) | 100.00%    |
| Cefixime | 87 (82.08%)   | 7 (6.60%)        | 12 (11.32%)   |
| Cepaprin | 8 (72.73%)    | 0 (0.00%)        | 3 (27.27%)    |
| CHL⁵       | 6 (75.00%)    | 1 (12.50%)       | 1 (12.50%)    |
| Ciproflaxacin | 22 (81.48%) | 0 (0.00%) | 5 (18.52%) |
| Clarithromycin | 8 (57.14%)  | 0 (0.00%) | 6 (42.86%) |
| Clindamycin | 15 (71.43%)   | 1 (4.76%)        | 5 (23.81%)    |
| Cloxacillin | 7 (100.00%)   | 0 (0.00%)        | 3 (30.00%)    |
| Cotrimoxazole | 2 (50.00%) | 0 (0.00%) | 2 (50.00%) |
| Dicloxacin | 7 (100.00%)   | 0 (0.00%)        | 3 (30.00%)    |
| Diritrimocin | 1 (100.00%)  | 0 (0.00%) | 0 (0.00%)  |
| Doripenem | 21 (24.22%)   | 2 (2.33%)        | 63 (73.26%)   |
| Doxycyclin | 61 (66.30%)   | 6 (6.52%)        | 25 (27.17%)   |
| Ertapenem | 9 (100.00%)   | 0 (0.00%)        | 0 (0.00%)     |
| Erythromycin | 15 (75.00%) | 0 (0.00%) | 5 (25.00%)  |
| Faropenem | 9 (75.00%)    | 0 (0.00%)        | 3 (25.00%)    |

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¹Amoxicillin-clavulanic acid  
²Ampicillin-sulbactame  
³Cefoperazone-sulbactam  
⁴Chloramphenicol  
⁵High level Gentamicin  
⁶Inducible-Clindamycin  
⁷ Piperacillin/Tazobactam  
⁸Quinupristin/Dalfopris  
⁹High level Streptomyacin  
⁸Ticarcillin/Clavulanic acid  
⁸Trimethoprim-Sulfamethoxazole

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*Appendix*

from: [http://www.nims.indonesia.html](http://www.nims.indonesia.html)

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