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 bodyattempts 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 treatmentis 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 apost-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 aretrospective 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.

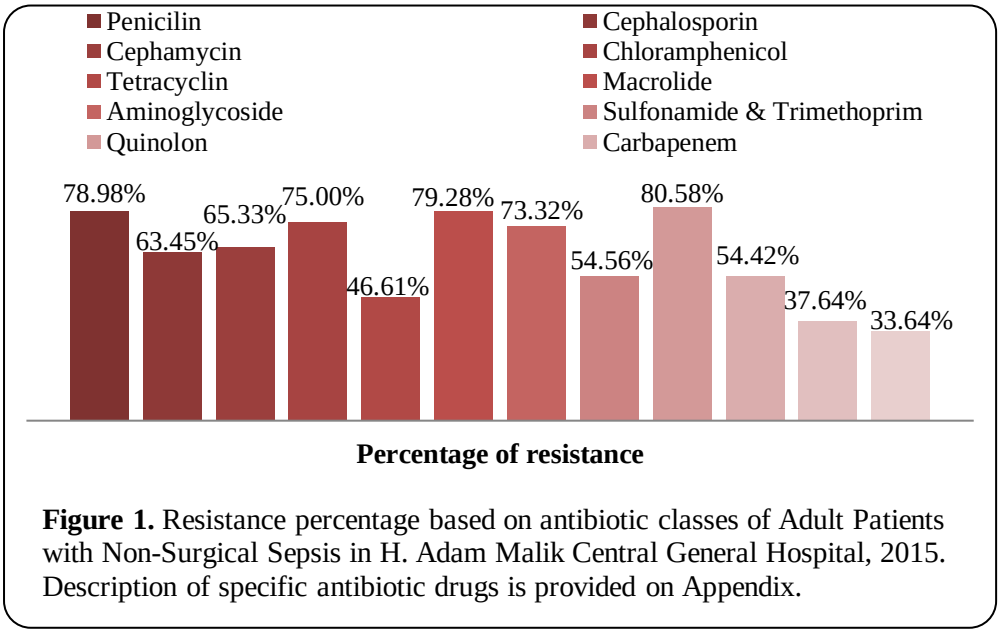

Figure 1. Resistance percentage based on antibiotic classes of Adult Patients with Non-Surgical Sepsis in H. Adam Malik Central General Hospital, 2015. Description of specific antibiotic drugs is provided on Appendix.

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.aeroginosa	12	6.98%
K.pneumoniae	20	11.63%
A.baumanii	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%
Gaffkya 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%**

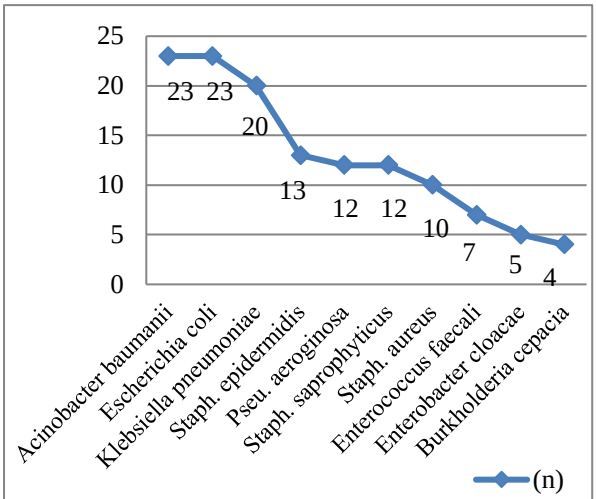

Figure 2. Most common isolates from adult patients with non-surgical sepsis in H. Adam Malik center general hospital, 2015.

4. Discussion

Total of bacteria isolates from adult patients' medical records of H. Adam Malik General Hospital Medical Center were 59 items and merged with 89 data from adult patients' culture data of Microbiology Laboratory of H. Adam Malik Central General Hospital. *Escherichia coli* isolate also found one of the most common bacterial infection in the Intensive Care Unit of Fatmawati Hospital, Jakarta from 2001 to 2002.[7] Among ten highest incidences of bacterial isolates in this research (Figure2), there were two pathogenic bacteria found (*Acinobacter baumani* and *Burkholderia cepacia*) and eight other isolations were normal flora bacteria. Nonetheless, if this normal flora escapes from their normal location, they can cause disease.[8] As one of the normal flora, The crucial lead of 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. Forinstance, 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 ithas 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 thepreferential 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 theavailable 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 themedical and public health community, as a support for informing strategic actions and program planning. It is best to continue relevant surveillanceannually in other centers for more reliable and presentative national data regarding antibiotic resistance phenomenon. And lastly, promoting theeducation 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.

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Appendix

Antibiotic Susceptibility Testing Distribution

Antibiotic	Resistant		Intermediate		Sensitive	
	(n)	(%)	(n)	(%)	(n)	(%)
Amikacin	19	13.19%	2	1.39%	123	85.42%
Amoxicillin	47	74.60%	11	17.46%	5	7.94%
AMC[a]	75	51.72%	25	17.24%	45	31.03%
Ampicilin	117	82.39%	9	6.34%	16	11.27%
SAM[b]	3	50.00%	0	0.00%	3	50.00%
Azlocillin	9	90.00%	0	0.00%	1	10.00%
Azythromycin	9	64.29%	0	0.00%	5	35.71%
Bacitracin	2	40.00%	0	0.00%	3	60.00%
Benzylpenicillin	19	95.00%	1	5.00%	0	0.00%
Carbenicillin	9	90.00%	0	0.00%	1	10.00%
Cefaclor	7	70.00%	0	0.00%	3	30.00%
Cefadroxil	7	70.00%	0	0.00%	3	30.00%
Cefalexin	7	70.00%	0	0.00%	3	30.00%
Cefalotin	7	77.78%	0	0.00%	2	22.22%
Cefamandole	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%
Cefditoren	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%
Cefmatazole	6	66.67%	0	0.00%	3	33.33%
Cefmenoxim	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/S[c]	21	22.34%	13	13.83%	60	63.83%
Ceforoxime	10	76.92%	0	0.00%	3	23.08%
Cefotamime	5	100.00%	0	0.00%	0	0.00%
Cefotaxime	80	81.63%	3	3.06%	15	15.31%
Cefotetan	8	66.67%	0	0.00%	4	33.33%
Cefoxitin	64	64.00%	2	2.00%	34	34.00%
Cefpirome	8	100.00%	0	0.00%	0	0.00%
Cefpodoxime	9	75.00%	0	0.00%	3	25.00%
Cefprozil	8	80.00%	0	0.00%	2	20.00%
Cefradine	8	72.73%	0	0.00%	3	27.27%
Ceftazidime	75	72.82%	5	4.85%	23	22.33%
Ceftibuten	8	100.00%	0	0.00%	0	0.00%
Ceftizoxime	8	72.73%	0	0.00%	3	27.27%
Ceftobiprole	0	0.00%	0	0.00%	3	100.00%
Ceftriaxone	87	82.08%	7	6.60%	12	11.32%
Cephapirin	8	72.73%	0	0.00%	3	27.27%
CHL[d]	6	75.00%	1	12.50%	1	12.50%
Ciprofloxacin	22	81.48%	0	0.00%	5	18.52%
Claritromycin	8	57.14%	0	0.00%	6	42.86%
Clindamycin	15	71.43%	1	4.76%	5	23.81%
Cloxacillin	7	70.00%	0	0.00%	3	30.00%
Cotrimoxazole	2	50.00%	0	0.00%	2	50.00%
Dicloxacillin	7	70.00%	0	0.00%	3	30.00%
Dirithromycin	1	100.00%	0	0.00%	0	0.00%
Doripenem	21	24.42%	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%
Flomoxef	8	100.00%	0	0.00%	0	0.00%
Flucloxacillin	7	70.00%	0	0.00%	3	30.00%
Fosfomycin	8	30.77%	1	3.85%	17	65.38%
Gentamicin	61	58.65%	2	1.92%	41	39.42%
HLG[e]	5	100.00%	0	0.00%	0	0.00%
Imipenem	31	29.52%	4	3.81%	70	66.67%
iCLI[f]	1	100.00%	0	0.00%	0	0.00%
Latamoxef	8	72.73%	0	0.00%	3	27.27%
Leftriaxone	1	100.00%	0	0.00%	0	0.00%
Levofloxacin	63	57.27%	11	10.00%	36	32.73%
Linezolid	3	15.79%	0	0.00%	16	84.21%
Loracarbef	8	72.73%	0	0.00%	3	27.27%
Meropenem	26	25.00%	8	7.69%	70	67.31%
Methicillin	7	70.00%	0	0.00%	3	30.00%
Metronidazole	0	0.00%	0	0.00%	1	100.00%
Mezlocilin	9	100.00%	0	0.00%	0	0.00%
Minocycline	0	0.00%	1	16.67%	5	83.33%
Moxifloxacin	14	82.35%	0	0.00%	3	17.65%
Nafcillin	7	70.00%	0	0.00%	3	30.00%
Netilmicin	8	88.89%	0	0.00%	1	11.11%
Nitrofurantoin	18	48.65%	3	8.11%	16	43.24%
Norfloxacin	20	90.91%	0	0.00%	2	9.09%
Ofloxacin	40	90.91%	1	2.27%	3	6.82%
Oxacilin	13	81.25%	0	0.00%	3	18.75%
Penicillin	1	50.00%	0	0.00%	1	50.00%
Piperacilin	15	88.24%	0	0.00%	2	11.76%
TZP[g]	45	47.37%	11	11.58%	39	41.05%
Polymyxin B	1	1.54%	2	3.08%	62	95.38%
Q/D[h]	5	29.41%	1	5.88%	11	64.71%
Rifampicin	3	27.27%	2	18.18%	6	54.55%
HLS[i]	5	100.00%	0	0.00%	0	0.00%
Tetracyclin	25	73.53%	0	0.00%	9	26.47%
TIM[j]	1	25.00%	0	0.00%	3	75.00%
Ticarcillin	10	83.33%	0	0.00%	2	16.67%
Tigecyclin	0	0.00%	0	0.00%	15	100.00%
Tobramycin	40	45.98%	12	13.79%	35	40.23%
Trimethoprim	14	73.68%	2	10.53%	3	15.79%
TMP/SMX[k]	6	40.00%	0	0.00%	9	60.00%
Vancomycin	7	33.33%	0	0.00%	14	66.67%

[a]Ampoxicillin-clavulanic acid
[b]Ampicillin-sulbactame
[c]Cefoperazone-sulbactam
[d]Chloramphenicol

[e]High level Gentamicin
[f]inducible-Clindamicin
[g]Piperacillin/Tazobactam
[h]Quinupristin/Dalfpor
[i] High level Streptomycin
[j]Ticarcilin/Clavulanic acid
[k]Trimethoprim-Sulfamethoxazole