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LITERATURE REVIEW

ANTIBIOGRAM

(Antibiogram)

Jeine Stela Akualing, IGAA Putri Sri Rejeki

ABSTRAK

Resistensi antibiotika telah menjadi masalah kesehatan global. Upaya yang dilakukan untuk mengatasi kegentingan resistensi antibiotika adalah melalui penggunaan antibiotika secara bijak. Salah satu strategi penggunaan antibiotika secara bijak adalah dengan menyusun dan menggunakan antibiogram. Antibiogram menuntun peklinik dalam memilih pengobatan antibiotika empiris terbaik sementara menunggu hasil kultur dan uji kepekaan antibiotika. Antibiogram dapat dijadikan dasar dalam penyusunan pedoman pengobatan antibiotika empiris dan dapat digunakan dalam mendeteksi serta memantau arah resistensi antibiotika. Laboratorium Mikrobiologi Klinik di setiap lembaga pelayanan kesehatan bertanggung jawab dalam menyusun antibiogram, menyebarkannya kepada peklinik, serta melakukan perbaikan setiap tahun. Telaah pustaka ini bertujuan untuk membahas antibiogram, termasuk cara menyusun dan menyajikan antibiogram, sehingga diharapkan dapat membantu setiap lembaga dalam membuatnya.

Kata kunci: *Antibiogram, resistensi antibiotika, penggunaan antibiotika bijak*

ABSTRACT

Antibiotic resistance has become a global health problem. An effort to resolve the global antibiotic resistance crisis is done through the use of antibiotics wisely. One of the strategies to use antibiotics wisely is performed by generating and using an antibiogram. Antibiogram guides the clinicians in the selection of the best initial empirical antibiotic therapy while waiting for culture and antibiotic susceptibility test results. Antibiogram can be used as a basic for formulating empirical antibiotic treatment guideline, as well as for the detection and monitoring resistance trends. The clinical microbiology laboratories in every healthcare institution is responsible for the generating of antibiogram, as well as distributing it to the clinicians and updating annually. The aim of this review was to know about antibiogram, regarding how to generate and present it, in order to help the institution for creating an antibiogram by explaining many aspects of discussions.

Key words: Antibiogram, antibiotic resistance, cumulative antibiogram

INTRODUCTION

Irrationally use of antibiotic has become a major problem in the world as well as in Indonesia. Inappropriate use of antibiotics leads to the emergence of resistancy to bacteria, increasing adverse effect and drug interaction, coinfected with other bacteria such as *Clostridium difficile*, increasing length and cost of hospitalization. Patients suffering from infections due to bacteria resistancy will be faced with delayed recovery, treatment failure and even death.[1]

The results of antibiotics resistance study in Indonesia between 2000–2004, at the Dr. Soetomo Hospital Surabaya and dr. Kariadi Hospital Semarang, showed multi-resistant bacteria such as *Methicillin Resistant Staphylococcus aureus* (MRSA) and *Extended Spectrum Beta Lactamases* (ESBL) producing bacteria. They also found the use of antibiotics without indication between 30−80%.[1] Based on the study at the Dr. Soetomo Hospital Surabaya in 2010, 5.6% pan-resistant bacteria from 554 isolates has been found. The collaboration study of PPRA-Litbangkes-World

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Health Organization (WHO), in 2013—2014, at six teaching hospitals in Indonesia, revealed an increment in the prevalence of ESBL producing bacteria resistant to the third generation of cephalosporin, which has become an important indicator for the risk of treatment failure of infectious diseases. The WHO through *Antimicrobial Resistance Global Report on Surveillance-of* 2014*,* reported an increment of bacteria resistance more than 50% for the routinely use of antibiotics.[2] The study results of *Antimicrobial Resistance in Indonesia (AMRIN-Study)* 2000–2005, which has been shown in 2494 community subjects, revealed that 43% of *Escherichia coli* has become resistant to various antibiotics, such as: ampicillin (34%), cotrimoxazole (29%) and chloramphenicol (25%). From the 781 hospitalized patients, 81% suffering from *Escherichia coli* became resistant to ampicillin (73%), cotrimoxazole (56%), chloramphenicol (43%), ciprofloxacin (22%) and gentamicin (18%).[3]

These data showed that those who develop antibiotic resistance become a crucial problem that need to be urgently resolved. One of the efforts to resolve this problem is done by using selected antibiotics wisely. World Health Organization (WHO) has proclaimed a programme as a resolution for the global crisis of antibiotic resistancy namely *Global Action Plan on Antimicrobial Resistance*. This programme focused on the improvement of awareness and understanding of antibiotic resistance and appropriate use of antibiotics.[4] WHO has prompted the healthcare institutions to generate antibiogram and distribute it to the clinicians as the one strategy in order to reach the goal. *The Centers for Disease Control and Prevention* has begun a campaign about preventing antibiotic resistance. This campaign prompted the healthcare worker to use local data and understand about antibiogram as the implementation of using antibiotics wisely.[4,5] The antibiogram is used as a basic for formulating and updating of empirical antibiotic therapy guidelines in all hospitals.[3]

Regarding to all that have been mentioned above, knowledge is important to understand deeply about antibiogram. So this review aimed to know about antibiogram, how to construct it and how to present it, in order to help the institution for creating their own antibiogram by explaining many aspects of discussions.

DISCUSSION

An antibiogram is an overall profile of antibiotic susceptibility testing results of a specific microorganism to a battery of antibiotic drugs. The cumulative antibiogram is a report which presents the percentage of susceptibility of an isolate to a particular antibiotic agent, at a certain institution over a defined period of time.[6–9] This antibiogram should be reported at least once a year. More frequent reporting can be considered if there are relevant changes in the pattern of susceptibility or if there is a substantial number of isolates. Cumulative antibiogram will be further translated into practical application, known as a formulation of the hospital empiric antibiotic policy.[7,8]

Antibiogram as a tabulation of frequency of antibiotic susceptibility to a specific bacteria can be made based on a certain hospital unit, such as antibiogram of *intensive care unit* (ICU), burn unit, or hospital wide program. The utility of antibiogram is to provide guidance to responsible clinicians for the application concerning empiric therapy of infection or as a direct therapy while waiting for the susceptibility test results, guiding the pharmacist on antibiotic utilization and preventing misuse of it, for monitoring resistance trends over time, and as a guidance to the formulation of the hospital empiric antibiotic policy.[7–9]

The recommendations for constructing antibiogram

Monitoring of emerging trends in the resistance at the local level of a healthcare unit can be started by making an antibiogram. There are several distinct approaches in summarizing results from a database of clinical isolates, ranging from the simplest to the complicated calculation method. Many laboratories use different calculation methods, causing the consequence, as well as the comparability of antimicrobial susceptibility statistics between institutions is poor. On the other hand, using the simplistic calculation method will lead to an overestimate of drug-resistance rates. Therefore, the Clinical and Laboratory Standard Institute (CLSI) has developed recommendations for the analysis and presentation of data on antibiogram.[10,11]

The first approved antibiogram guidelines is of M39-A document about the analysis and presentation of cumulative antimicrobial susceptibility test data, published by CLSI in 2002. The critical issues regarding constructing an antibiogram based on the recommendations of CLSI M39-A4, include the following regulations: the data should be analyzed and presented at least annually, include only final and verified results of at least 30 isolates, and

Table 1. The recommendations for constructing an antibiogram[7,10–13]

1.	Data should be analyzed and presented at least annually
2.	Include only final and verified test results
3.	Include only species with testing data at least 30 isolates
4.	Include only diagnostic isolates, whether isolates from surveillance cultures should not be included
5.	Eliminate duplication by including only the first isolate of a given species per patient per analysis period, regardless of the specimen sites, or overall antibiotic susceptibility testing profile
6.	Include the results for the antibiotics that are routinely tested
7.	Only calculate the percentage susceptible (%S) and not include the intermediate percentage (%I)
8.	For *Streptococcus pneumoniae,* list of % S for cefotaxime/ ceftriaxone/penicillin, using meningitis and non-meningitis breakpoint
9.	For *Streptococcus viridans*, list of % S dan % I for penicillin, based on minimun inhibitory concentration (MIC) of penicillin; because the treatment for infective endocarditis caused by *Streptococcus viridans* varies, even isolates that are 'I' can still be candidates for penicillin therapy
10.	For *Staphylococcus aureus*, list of % S for all isolates and the *methycilline resistant Staphylococcus aureus* (MRSA) subset.

only including isolates from the diagnostic testing (see Table 1).[7,10–13]

Frequency of data analysis and reporting according to CLSI's recommendations is at least annually. More frequent analysis and reporting can be considered if there are substantial numbers of isolates, significant changes in the percentage of susceptibility of certain bacteria, or if there is a new antibiotic that has been tested during the course of reporting period.[7,10,11,13]

The number of isolates that should be analyzed for each species is ≥30 isolates. When there are fewer than 30 isolates, a footnote like' organisms with n<30, must be interpreted with caution, because it may not have a statistically relevance to the susceptibility results. Some alternatives are by combining data from the previous year, or from several facilities located in the same geographical area, or from the same species (eg: *Klebsiella spp*).[8,10,11,13]

The selection of isolates and the handling of repeated isolates

Analysis of antibiogram include only data from the first isolate of a given species per patient per analysis period, irrespective of the specimen sites, antibiotic susceptibility testing profile or phenotypic characteristic.[7,10-13] In fact, one patient may have more than one isolates that had been cultured on multiple occasions. How to handle the repeated isolates still becomes the most controversial aspect when constructing an antibiogram.

A repeated isolate is defined as the same bacterial species which is isolated from an individual patient after an initial culture. The analysis of the data in which all isolates as well as repeat isolates are included, is the simplest calculating method, but it is not recommended by the CLSI. Because the results of several studies revealed that the data analysis using all isolates (isolate based) approach are often biased towards a larger percentage of antibiotic-resistance strains.[10,14,15]

There are several approaches for handling the repeated isolates, namely patient-based, episode-based and resistance of the phenotype-based algorithm. Patient-based algorithm, means that the calculation of susceptibility percentage is based only on the first isolate per patient. The episode-based algorithm focused on the relation with the episodes of infection, that include one isolate per one episode for analysis. The episode can be determined according to the interval of time between obtaining the isolates, that could be seven (7) days or 30 days from the initial isolate. Unfortunately, there is no agreement consensus on the definition of an episode. The resistance phenotype-based algorithm means that the data analysis is focused on certain phenotypic characteristic of the bacterial strains.[10,14,15]

The estimation of susceptibility percentage in using different algorithm resulting in different results, but a greater bias towards the resistance is experienced when applying all isolates based on the algorithm (see Table 2). According to CLSI's recommendation and supported by the results of several studies, the first isolate patient-based algorithm is better used to handle repeated isolates.[10-15] This algorithm requires good recording and reporting system of the microbiology laboratory where it will be applied.

The screening culture isolates should be excluded from the routine analysis of antibiogram. For example, the cultures from MRSA or vancomycin-resistant *Enterococcus* species (VRE) screening. It is aimed to avoid unrepresentative data, because the antibiogram only analyses the data from diagnostic isolates.[10,11,15]

The selection of antibiotics

Each antibiotic reported must be appropriate for the organism species. All antibiotics tested should be included in the analysis to prevent biases introduced by selective reporting practices. Intrinsic resistance to a particular antibiotic agents in antibiogram

Table 2. The example of the estimate results of susceptibility percentage for *Staphylococcus aureus* and *Pseudomonas aeruginosa* using different algorithm[10]

Pathogen, algorithm	No. of isolates	Susceptible isolates, %
S. aureus		
Patient based (first isolate per patient)	1439	55
Episode based (30-day interval)	1615	53
Phenotype based		
Major difference in oxacillin result	1467	55
Major difference in any antimicrobial result	1536	54
Isolate-based (all isolates)	2192	49
P. aeruginosa		
Patient based (first isolate per patient)	742	70
Episode based (30-day interval)	864	69
Phenotype based		
Major difference in ciprofloxacin result	767	69
Major difference in any antimicrobial result	919	66
Isolate based (all isolates)	1445	62

is highlighted using a black square or letter 'R' coding.[10–13]

The CLSI M39-A2 document showed recording of recommending both quantitative test measurement and qualitative test interpretation, in separate fields. The quantitative test measurement is based on the minimum inhibitory concentration (MIC) value using dilution method. The qualitative test interpretation means that isolates are classified as resistant, intermediate or susceptible.[10,13]

The percentage of susceptibility and data stratification

Antibiogram report should show present data as the susceptibility percentage of isolates (%S). Isolates with intermediate susceptibility must be excluded in the calculation of the percentage of isolates that are susceptible.[10]

The percentage of susceptibility is calculated based on the number of isolates that are susceptible to a certain antibiotic divided by the total number of isolates that have been tested. The percentage of susceptibility will statistically relevant if ≥ 30 isolates were analyzed.[7,10,13]

The data can be stratified based on the patient populations, hospital units, specimen types, or patient age. The susceptibility percentage between two units in the hospital may be different depending on the patient populations. An example from the study of Horvat *et al.*[16] *Staphylococcus aureus* isolates from intensive care units (ICU)'s patients revealed that only 52% were susceptible to oxacillin, whereas from non-ICU's patients the susceptibility was 70%. Therefore, the data stratification is useful to calculate the exact susceptibility percentage in order to determine the optimal empirical antibiotic therapy.[16]

Ensuring The quality of antibiogram

Before constructing an antibiogram, it has to be ensured that the microbiological test results that will be analyzed are accurate. This point correlated with the good quality control of microbiology laboratory, as well as good recording and reporting system. After completing the report, it is important to review the antibiogram and investigate for potential errors.[10]

The antibiogram report will be further distributed to the healthcare worker such as infectious disease specialists and other clinicians, pharmacists, and infection-control practitioners. The antibiogram will be reviewed by the group reviewers for evaluating the antibiotic resistance trends, assessing current therapy guidelines and more.[10]

The structure of antibiogram

An antibiogram should be presented in a tabular form, with color or letter coding. Antibiogram should be generated for Gram positive and negative bacteria. Antibiogram for Gram positive and negative can be separately reported or both in one table and clearly marked.

The components of an antibiogram comprise of basic and additional component. The basic components including the data of organism tested, number of isolates, antibiotic tested and susceptibility percentage (%S) (see Figure 1).[17,18] The additional components include additional information about antibiotics, hospital drug regulation, or information about body surface area.[17] The color and letter coding can be used to identify bacteria and antibiotics and distinguish

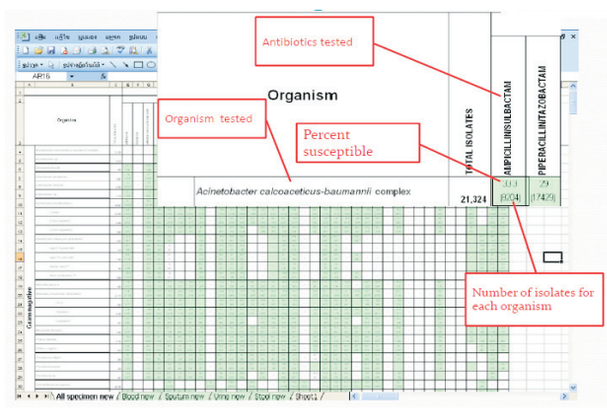

Figure 1. The structure of an antibiogram.[18]

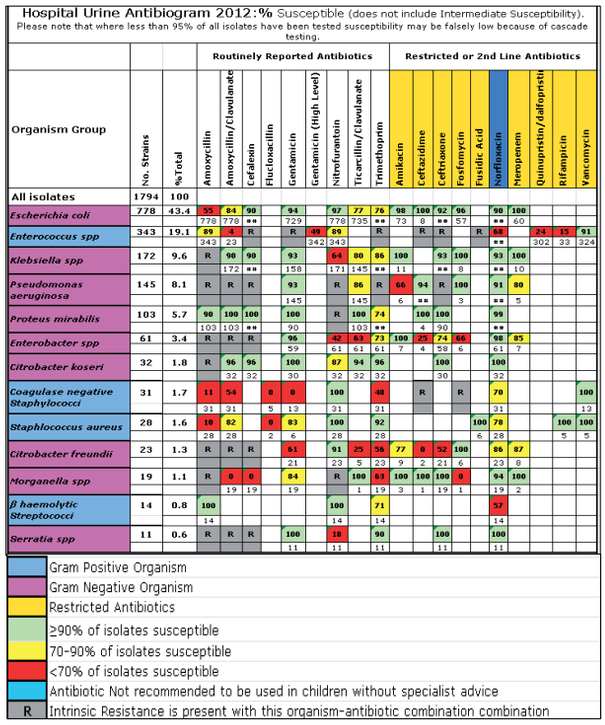

Figure 2. Example of an antibiogram.[19]

between Gram positive and Gram negative and their susceptibility percentage (see Figure 2).[19]

The name of antibiotic should be written in its generic name. The terminology for bacteria should be correctly written in Latin. The class of fluoroquinolone and tetracycline should not be administered to children, except on the specialist advice, so it can be emphasized in antibiogram by means such as a highlighted background color, or different font color. Certain antibiotics should only be reserved for specific purpose and not recommended for the usage as an empiric therapy (restricted antibiotics), such as carbapenem and fluoroquinolone. These antibiotics should be reserved for infections with organisms that the laboratory confirmed as resistance to alternative antibiotics, or when the patient has a significant allergy to a narrower spectrum antibiotics that would otherwise be appropriate.[19]

The susceptibility percentage is highlighted using different font colors, such as: green, yellow and red for each antibiotic that has been analyzed (Figure 1). There is no consensus regarding the range of %S for each color code such as green, yellow and red that has been reached so far. Some literatures use green code if >90% isolates are sensitive, yellow if 60–90% isolates are sensitive and red if <60% isolates are sensitive.[11,20] Other literatures use green code if >90% isolates are sensitive, yellow if 70-90% isolates are sensitive, and red if <70% isolates are sensitive.[19]

Gram-Negative Organisms	No. Strains	Amikacin	Ampicillin	Cefazolin	Cefotaxime	Ceftazidime	Ciprofloxacin	Nitrofurantoin[1]	Gentamicin	Meropenem	Piperacillin-tazobactam	Trimethoprim-sulfamethoxazole	Tobramycin
Acinetobacter baumannii	32	80	R	R	34	52	51	–	60	80	46	58	59
Citrobacter freundii	49	100	R	R	72	67	90	78	100	99	67	67	100
Enterobacter aerogenes	31	100	R	R	68	69	92	85	91	99	74	95	91
Enterobacter cloacae	76	99	R	R	61	62	92	81	90	99	77	84	90
Escherichia coli	1433	99	36	68	96	94	72	98	91	99	51	65	92
Klebsiella pneumoniae	543	99	R	72	91	92	84	74	94	95	86	81	94
Morganella morganii	44	100	R	R	85	81	99	R	100	99	64	75	100
Proteus mirabilis	88	100	87	80	99	99	89	R	90	100	70	73	93
Pseudomonas aeruginosa	397	97	R	R	R	76	75	R	80	80	85	R	83
Salmonella spp.	32	–	88	–	97	97	90	–	–	100	91	86	–
Serratia marcescens	50	100	R	R	82	94	95	R	94	99	94	91	89
Shigella spp.	33	–	64	–	100	100	95	–	–	100	84	69	–
Stenotrophomonas maltophilia	72	R	R	R	R	63	6	R	R	R	–	98	R

Figure 3. Using '(-)' and 'R' code in antibiogram.[11]

Dash (–) code or grey color is placed in the data box if an antibiotic agent is not tested, or is known to be clinically ineffective. 'R' code is placed in the data box when it is known that the bacteria is intrinsically resistant to the antibiotic agent (see Figure 3).[11]

The selection of antibiotic therapy based on antibiogram

The antibiogram can assist in the selection of antibiotic therapy for prophylaxis, empiric or directed-pathogens (see Table 3). An antibiogram is the basis for creating a clinical guideline for antibiotic selection in a healthcare unit.[21,22] So far, there is lack of literature that obviously mention about the reference of susceptibility percentage of antibiotic in showing antibiogram which is effective as the empiric therapy. The study of Boggan *et al*[23], revealed that in vitro susceptibility percentage of antibiotic (%S) >80% has the best effectiveness for an empiric therapy.[23]

Table 3. The role of antibiogram in the selection of antibiotic therapy[22]

The type of therapy	Description	Use of an antibiogram
Prophylaxis	Antibiotics used to prevent infection	Selection of antibiotic
Empiric	Organism is unknown but syndrome is known	Selection of antibiotic
Pathogen-directed	Organism is known but the susceptibility is unknown	Selection of antibiotic
Susceptibility-guided	Organism is known and the susceptibility is known	The antibiogram is not useful

The Limitation of the antibiogram

Antibiogram should not be used as the only tool to determine the treatment. There are some limitations of antibiogram, such as not including *minimum inhibitory concentration* (MIC) and not knowing the patient's condition. Such as the above can not determine cross reactivities with other antibiotics and the data can not be generalized.[24]

Minimum inhibitory concentration (MIC) is not included in the antibiogram, so it is difficult to detect the increase of MIC values that are still below the susceptible breakpoint. The history of infection or previous antibiotic therapy is also not included in the analysis of antibiogram. Cross reactivities with other antibiotic agents can not be determined because antibiogram may only present susceptibility percentage of a given bacteria-antibiotic combination. Meanwhile, there are several factors that can affect the data in an antibiogram, including the population of the patient, procedure of culture and the susceptibility testing, recording and reporting system and the intermittent outbreak.[24]

CONCLUSION

One of the efforts to resolve global antibiotic resistance crisis is done by using the antibiotics wisely. Antibiogram is very useful to guide the clinicians in the selection of the best initial empirical antibiotic therapy, as well as for the detection and monitoring the resistance trends. The Clinical Microbiology laboratory in every healthcare institution should be able to generate the antibiogram and distribute it to the clinicians and other healthcare workers.

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