Antimicrobial Resistance and Its Control Policy Implementation in Hospital in Indonesia

Resistensi Antimikroba dan Penerapan Kebijakan Pengendalian di Rumah Sakit di Indonesia

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Abstract

Antimicrobial Resistance (AMR) is a serious issue because it may reduce treatment effectiveness, increase infection transmission and health care costs. This article aims to identify the problems and the implementation of the AMR control program in hospital. Method : Data were collected by reviewing study results in journals and proceedings, books/literature on AMR at universities and hospitals in Jakarta and Bandung, regulation on the distribution and use of antimicrobials at NADFC, control policy on AMR of MoH RI, as well as data of nosocomial infections from National Survey on Health Facility (Rifaskes 2011). We also conducted consensus decision making which discusses strategic plan and policy for controlling AMR as well as how to optimize or strengthen the strategy with participants involving type A hospital AMR Control Committee as keynote speakers and Directorate of Referral Health Services, Directorate of Health Service Facility, Directorate of Pharmacy Services, Private and Public Hospital Directors in DKI Jakarta, Hospital Accreditation Commission (KARS), others researchers and academicians as stake holders. In Indonesia AMR control program has been started in some hospitals, but there are still many obstacles either from the management, facilities or infrastructures and practitioners. The policies related to AMR control in Indonesia are stated in Law No. 36 of 2009, Law No. 44 of 2009 and the Ministry of Health Decree No. 8 of 2015. There is also a guideline of the Ministry of Health for Infection Control Program in hospital. These policies should be implemented and used as a tool to increase the commitment of the hospital management. Compliance with the guidelines should be strictly implemented, besides the rational prescription of antimicrobials, completing facilities and infrastructures for controlling AMR and the establishment of surveillance of antibiotic use.

Keywords: resistance, antimicrobials, hospital

Abstrak

komitmen pihak manajemen rumah sakit dalam pengendalian AMR. Kepatuhan pada pedoman program pengendalian AMR harus ditekankan, selain peresepan antimikroba yang rasional, pemenuhan sarana dan prasarana untuk pengendalian dan pembentukan surveilans penggunaan antibiotik.

Kata kunci: resistensi, antimikroba, rumah sakit
Introduction

Infectious diseases is one of the biggest health problem and the leading cause of death in the world.\textsuperscript{1,2} The main infectious disease medications are antimicrobial. Based on the type of microorganisms, there are diverse antimicrobials, including antibiotic (antibacterial), antiviral, antifungal and the most often used is antibiotics.

The discovery of antibiotics was initiated by Paul Ehrlich who found Salvarsan to combat syphilis. Then followed by the Alexander Fleming who accidentally discovered penicillin to treat infections of Staphylococcus aureus. Other antibiotics, sulfa was discovered by Gerhard Domagk that pave the way for the anti-TB drug discovery, isoniazid. In 1943, streptomycin was discovered by Selkman Wakzman and Albert Schatz. Wakzman also the first person to introduce the terminology of antibiotics. Since that time antibiotics have been widely used by clinicians to handle a variety of infectious diseases.\textsuperscript{2,3}

During 1940 to 1970 period, many new antibiotics had been found such as Chloramphenicol, Framycetin, Bacitracin, Spiramycin, Nystatin, Cephalosporin, Rifamycin, Nebramycin, Streptomycin and others, but starting from 1980 to 2000 new antibiotics had been rarely found. Even the last 14 years there is no invention of brand new antibiotics, but simply replication/third generation.\textsuperscript{4}

Method

Data were collected by reviewing study results in journals and proceedings, books/literature on AMR at universities and hospitals in Jakarta and Bandung, regulation on the distribution and use of antimicrobials at NADFC, control policy on AMR of MoH RI, as well as data of nosocomial infections from National Health Facility Research (Rifaskes 2011). We also conducted consensus decision making which discusses strategic plan and policy for controlling AMR and that has already been done including the results, as well as how to optimize or strengthen the strategy with participants involving type A hospital AMR Control Committee as keynote speakers and Directorate of Referral Health Services, Directorate of Health Service Facility, Directorate of Pharmacy Services, Private and Regional Hospital Directors in DKI Jakarta, Hospital Accreditation Commission (KARS), Jakarta Health Office, others researchers and academicians as stake holders.

The antimicrobial resistance

Resistance can be defined as no inhibition of the growth of bacteria by administering antibiotics systemically with normal doses. While the multiple drug resistance is defined as the resistance to two or more drugs or drug classifications and cross resistance is resistance to a drug that is followed by other medications that have never been exposed.\textsuperscript{3}

Factors that favor the occurrence of resistance, among other things:

1. Inappropriate use (irrational)
   Example: use of antibiotics for a time too short, too low a dose, wrong early diagnosis, inadequate potential.

2. Wrong knowledge of the patient
   The wrong patient knowledge that considers antibiotics can cure a variety of infectious diseases, including infections caused by viruses, such as flu, cough-cold and fever are encountered in the community. Patients with good financial capability will ask for the most recent and costly antibiotic therapy even though not required. Moreover, patients can buy antibiotics without prescription (self-medication). While patients with low financial capability can hardly afford to complete the therapy regimen.

3. Prescription
   Antibiotics are often already prescribed, although the diagnosis is still uncertain. Clinicians often met difficulties in determining the proper antibiotics because of the lack of training in terms of infectious diseases and antibiotic treatment.

4. The use of monotherapy
   The use of monotherapy poses resistance more easily compared with the use of combination therapy.

5. Use of antibiotics in hospitals
   The existence of endemic or epidemic infection triggers a more massive use of antibiotics in an inpatient ward especially in the intensive care unit. The combination of more intensive and longer antibiotic used for patients who are very sensitive to infections, facilitates the occurrence of nosocomial infections.
6. Antibiotics use for animals and cattle

In farms, a large amount of antibiotic is used in routine supplement as prophylaxis or to stimulate the growth of farm animals. When used in a sub therapeutical dose, it will increase the occurrence of resistance.

7. Commercial promotion and the massive sales by pharmaceutical companies makes the amount of available antibiotic in abundance.

8. Research

The discovery of a new antibiotic study is languishing that no new antibiotics found.

9. The supervision

Weak government control over the distribution and use of antibiotics, such that anyone can easily get antibiotics without a doctor’s prescription

ISSUES

The problem of antibiotic resistance is an important issue because:

- Infections caused by resistant bacteria are often cannot be successfully treated using the standard treatment of antibiotics. Consequently, it will cause longer periods of hospitalization in a hospital (length of stay), raise morbidity and mortality rates and health costs.

- Antibiotic resistance will decrease the effectiveness of treatment and enhance the occurrence of infection to others. When treatment failed, the patient become infectious for several extended periods (carrier). This provides a greater opportunity for resistant strains to spread to others. The development of transportation technology will accelerate the spread of antimicrobial resistance whilst no new antibiotics found and the rise of antibiotic resistance would lead to a situation like at the time of the pre-antibiotic era. Therefore, it is very appropriate Slogan of the WHO on World Health Day in 2011, “Combat Drug Resistance, No Action today, No Cure tomorrow” The purpose of this study is to identify the types of resistant microbes, its control and problems in the implementation of the Antibiotic Resistance Control Program (ARCP) in the hospital.

FINDING AND DISCUSSION

a. The Situation of Antimicrobial Resistance in Various Countries

The success of penicillin therapy did not last long with the emergence of resistant strains containing gene blaZ that decode the beta-lactamase enzymes i.e., an enzyme that is able to degrade penicillin. At the end of the 1950s, this problem can be overcome by administering antibiotics resistant to beta-lactamase i.e. methicillin. About a year after the use of methicillin, strains of S. aureus resistant methicillin called MRSA emerged. The main resistance determinant on MRSA is gen mecA in the Staphylococcal Cassette Chromosome mec (SCCmec). MRSA outbreaks first occurred in Europe in the era of the 1960s, then spread rapidly to numerous hospitals worldwide, so that MRSA is often also called Healthcare-Associated MRSA (HA-MRSA). These bacteria are multiresistant. The average prevalence of MRSA in hospitals in the world ranges between 20-40 percent. In 1998 in the United States the existence of a new strain of MRSA was reported, that is Community-Associated MRSA (CA-MRSA) which is non-multiresistant but more virulent than HA-MRSA. The spread of MRSA was further expanded both in the hospital and in the community. In the United States, about 25 percent of isolates of S. aureus causing infection in hospital is MRSA. Prevalence lower than 5% can be found in the Netherlands and some Scandinavian countries, where the use of antibiotics is very constricted. This is one of the keys to the success of MRSA infection control in those countries.

Testing the sensitivity of strains from 1824 patients with sputum TB positive by Yan Shao et al in Jiangsu Province, China, against rifampicin, isoniazid, ethambutol and streptomycin suggests that 1077 (59.05%) MTB strains are sensitive to antibiotics and 747 (40.95%) strains are resistant to at least medication. The proportion of resistance to one drug is 28.73% to isoniazid, 19.41% to rifampicin, 29.33% to streptomycin, and 13.98% to ethambutol. The prevalence of MDR-TB is 16.61%, and significantly different between new cases (7.63%) and cases with previous treatment (33.07%). Patients with previous treatment had MDR TB risk 5 times (adjusted OR: 6.14, 95% CI: 4.61-8.17), compared to no previous treatment. High prevalence...
of drug resistance is a big challenge in controlling TB. Resistant TB prevention and control should be emphasized with the revised program DOTS (directly observed therapy, short term) through early case detection, good routine sensitivity testing for patients with a high risk of resistance, programmatic management with first and second-line drugs as well as systematic observation of treatment with priority on high MDR-TB setting Case-control study of the causes of anti-tuberculosis drug resistance in Bandung shows that previous inadequate treatment history factor is the leading cause.

b. The Situation of Antimicrobial Resistance in Indonesia

Currently Indonesia has not had a proper antibiotic resistance map. Existing resistance data from various studies are still sporadic in nature, location and time of study are different, as well as the number of samples, methods, and types of antimicrobial used is varying. Noviana reported that MRSA prevalence based on sensitivity test to various antimicrobials in Jakarta’s Atmajaya Hospital in 2003 reached 47 percent, likewise Yuwono also reported that MRSA incidence in RSU Dr. Mohammad. Hoesin, Palembang reached 46 percent. Currently only vancomycin and a small kind of antibiotics that can be used to treat MRSA infections.

The results of the study by Krisni Subandiyah for 1 January 1999 until 31 December 2003 on 563 patients suspect a urinary tract infection (UTI) in RSU Dr. Saiful Anwar, Malang shows that ciprofloxacin, cefotaxim, and amikasin are still sensitive to P. aeruginosa, E. coli, A. anitratus, A. hydrophilia, E. aerogenes, E. angleromers, E. gingivae, P. mirabilis, S. coagulase negative, whereas ampicillin is only sensitive to S. coagulase negative and nitrofurantoin is only sensitive to E. Coli. Research by Keni Istasaputri M. et al between 19 September and October 31, 2011 on 22 patients with atopic dermatitis (DA) in Clinic of skin and sex of RSU Hasan Sadikin showed that S. aureus nurtured in as many as 17 of the 22 patients and there was a growth of MRSA strains in 3 patients. Gentamycin, tetracycline and neomycin have been already resistant to S. aureus on 6 of 17 patients with S. aureus, just like 3 patients with MRSA strains.

The study of Usman Hadi stated that:
1) Infection with ESBL-producing bacteria had increased in hospitals and had reached a critical point that raises serious concerns.
2) Prevalence of ESBL varied between hospitals and the specimen due to differences in the use of antibiotics and policies.
3) Between Escherichia coli and Klebsiella pneumoniae, the average prevalence of resistance ranged from 26 to 56%.
4) The pattern of antibiotic sensitivity indicated there was only a small choice of antibiotics for treatment of ESBL-producing bacterial infection such as amikacin, phosphomycin, meropenem, tigecycline.
5) The main challenge of implementation of Antimicrobial Resistance Control Programs (ARCP) was the rise of wisely used antibiotics and adherence to SOPs.

Laboratory examination in National Center General Hospital Cipto Mangunkusumo during the years 2010 - 2012 indicates that there have been many antibiotics that have the sensitivity lower than 50%. They are among others, piperacillin/tazobactam, sulbactam, cefoperazone/cefpirone, tetracycline, cephalothin, and others from the class of tetracycline, penicillin, cephalosporin, aminoglycoside, macrolide, quinolone, and carbapenem.

c. Antimicrobial Resistance Control Program in Various Hospitals

The implementation of the Antimicrobial Resistance Control Program (ARCP) in hospitals, aims to improve the quality of health services, particularly in handling of infection case in the hospital, reducing the antimicrobial resistance, preventing toxicity due to antimicrobial use, lowering costs due to unwise use of the antimicrobials and lowering the risk of nosocomial infections, as well as enabling to minimize the risk of occurrence of medical errors in the hospital. It is estimated that 50 percent of prescriptions given to patients is not necessary because it is usually only for the treatment of colds, coughs and viral infections.

Controlling antimicrobial resistance requires the collaboration of various health professions, among others, a doctor, a nurse, a pharmacist, and a
microbiologist. In Canada, antimicrobial resistance control efforts began in 1997 that included 3 things, namely antimicrobial management, surveillance to monitor the trends of resistance as well as the prevention and control of infection. Implementation of healthcare related infection surveillance (Healthcare Associated Infections/HI) performed by most European countries and the United States has been shown to reduce the incidence of infections in Europe and the United States, despite differences or variations in the methods of surveillance. Implementation of healthcare related infection surveillance has been shown to reduce the incidence of infections in Europe and the United States, despite differences or variations in the methods of surveillance.

The commitment of the United Kingdom (UK) to address antimicrobial resistance and to respond to the AMR 2011 EU Strategic Action Plan and 2012 EU Council Conclusions, emphasizes several areas for the next actions at hospitals amongst others an increase in infection prevention and control practices, optimization of prescribing practices, an upgrade of professional education, training and public engagement, better access and use of surveillance data, improved identification and prioritization of AMR studies and stronger international cooperation.

The Government of India has also set policy on antimicrobial resistance (National policy for the containment of AMR India) which aims to:

- a. Understand the incidence and spread of antimicrobial resistance and the affecting factors.
- b. Establish a well-coordinated national antimicrobial resistance control program.
- c. Rationalize the use of antimicrobials.
- d. Reduce antibiotic selection pressure with adequate control measures.
- e. Increase the discovery of newer and more effective antimicrobial.
- f. Diagnose precisely infections and infectious diseases

The implementation of the policy is, among other things the establishment of surveillance program, the increase of rational use of antimicrobials, infection control and prevention programs, studies on antimicrobials, and monitoring and evaluation.

C.1. Antimicrobial Resistance Control Program in Hospitals in Indonesia

Legal basic

Article 5 paragraph 2 states that everyone bears the right to receive health services that are safe, high quality, and affordable. The Government is responsible for the availability of all forms of health care efforts that are high quality, secure, efficient, and affordable (article 19). As one form of administering health services that are safe and of good quality, the Government was supposed to make regulations that require hospitals to do ARCP.

- Law of the Republic of Indonesia No. 44 of 2009 about hospital.
One purpose of making a hospital to conduct services is to ensure the safety of patient, community, environment and human resources in hospital (article 3). A hospital has an obligation to provide health services that are safe, high quality, indiscriminate, and effective in accordance with standard services, as well as mandatory standards of patient safety.25
- Decree of MoH Republic of Indonesia no. 382/ Menkes/SK/III/2007 on guidelines for the prevention and control of Infection in hospital and other health facilities.

These guidelines are expected to be a reference to implement prevention and control of hospital infection, so as to protect health workers and the public from the spread of infectious diseases (Emerging Infectious Diseases).26
- Decree of MoH Republic of Indonesia no. 2406/ MENKES/PER/XII/2011 on General Guidelines on the use of Antibiotics

Aside from being a national reference in setting up policies and guidelines of antibiotic use for hospital and other health care facilities, these guidelines set the need for assessment of antibiotic use in hospital and antimicrobial stewardship program in health care facilities.5
- Decree of MoH Republic of Indonesia no. 8 of 2015 about Antimicrobial Resistance Control Program (ARCP).

The decree is used as a reference for hospital in an attempt to control the resistance so that the ARCP in hospital takes place in standardized, scalable and integrated manner.27 Some large (type A) hospital as National Center General Hospital Cipto Mangunkusumo, Dr. Sutomo and Hasan Sadikin hospital has formed an ARCP Team. The main task of the ARCP team is to help the leadership of the hospital to:

a. Set up a policy for controlling antimicrobial resistance at the hospital.
b. Establish implementation of ARCP in hospital.
c. Disseminate and enhance understanding of antimicrobial resistance control in hospital, which is closely related to proper use of antimicrobial wisely and implementation of the principles of infection control.
d. Develop integrated research related to antimicrobial resistance control in hospital.
e. Monitoring and evaluation of the implementation of the ARCP intensively.

In running the task, ARCP team always coordinate with the Medical Committee, the Hospital Patient Safety Committee (KPRS), the Infection Control Committee (DALIN), the Pharmacy and Therapeutics Committee, the Clinical Microbiology Installation and the Hospital Pharmacy Installation28

c.1.1. ARCP in Cipto Mangunkusumo National Center General Hospital

An ARCP team of National Center General Hospital Cipto Mangunkusumo has already been formed since July 2009 but ARCP implementation in the hospital is not yet satisfactory. As a result, improved quality of antimicrobial use has not seemed significant. The pattern of resistance germs also hasn’t decreased noticeably, but the rationality of antimicrobial use began to appear. Starting from February 2012 each patient who are treated with antibiotics has been recorded in the monitoring card for antibiotic use that are attached to the medical record. The role of the ARCP working group at the department level is still lacking.

Dissemination and socialization is not optimal yet. Responses of clinical doctors both for doctors in charge of services and for specialist residents are still lacking, perhaps due to such a heavy workload that ARCP is often overlooked. This suggests that the importance of controlling antimicrobial resistance has not been well understood. Therefore, the promotion and dissemination of ARCP among clinicians are crucial, especially for gaining similar conception in order to develop an attitude and behaviour that supports the success of ARCP. The next target of the promotion and dissemination are medical students at the clinical level, paramedics as well as others associated with infections in the hospital. Accreditation by Joint Commission International (JCI) is actually a good momentum since antimicrobial resistance control is also used as a benchmark for performance indicators.28,29

Barriers to ARCP is a bed occupancy rate (BOR) that often exceeds capacity, difficulty in coordination to perform ARCP, the role of the ARCP working group at the department level is still inadequate, dissemination and socialization are too slow, the unresponsiveness of clinician/physician as well as a very heavy workload.29
c.1.2. ARCP in Dr. Sutomo Provincial Hospital

Since its formation in 2009, ARCP team has gained results, among others:
1. Increased awareness of clinicians to examine culture, namely 29.75% to 64.56%.
2. Data turnaround time that describes the performance of microbiological examination is better so the patient can immediately get microbiological results to improve or ensure the diagnosis made by clinicians.
3. Improvement of the appropriateness of antibiotics uses from 52.94% to 65%.
4. Save antibiotic expenditures amounting to Rp. 203,000 per patient during hospitalization.
5. Increase the awareness of the clinicians to examine culture.

c.1.3. ARCP in Dr. Hasan Sadikin Provincial Hospital

Since it was formed in 2009, ARCP has shown progresses, among others antibiotic policy & antibiotic guideline (guideline for controlling antibiotic resistance), pattern of germs data, antibiotic used record, quantitative and qualitative audit results of antibiotic and surveillance of hospital infections (SIRS).

However, there are still obstacles i.e. human resources, formularies enactment, antibiotic restriction.

In addition, in the year 2012 an ARCP pilot project at 20 hospitals was conducted by ARCP working group of the Ministry of Health Republic of Indonesia. The results of the pilot project include:
- Determination of policy on ARCP implementation is conducted by 59.1% hospital, whereas the determination of long, medium and short term ARCP by 22.7% hospital.
- ARCP coordination meetings are done by 31.8% hospital, and direction of hospital executive at an ARCP coordination meeting by 27.3%.
- Establishment of the hospital ARCP team organization that at least involves elements of clinicians, microbiology laboratory, pharmacy, Pharmacy and Therapeutics Committee and Infection Prevention and Control Committee is done by 68.2% hospital, while determination of organizational structure that describes operational and coordination function by 40.9% and determination of descriptions of tasks, functions, authority, responsibility of the ARCP, in written form, by 45.5% hospital.
- The establishment of working program and schedule of activities by 40.9% hospital, ARCP socialization, coordination meetings, study cases of infectious diseases forum conducted by 22.7% hospital.
- Policy on antibiotic use control set by the leadership of 18.2% hospital and antibiotic use guidelines endorsed by the leadership of the hospital amounted to 6.8%.
- The existence of competent personnel in microbiology (clinical microbiologist or clinical pathologist or well-trained doctor or well-trained analysts) is 50%, microbiological examination, including painting and/or culture examination and antibiotic sensitivity testing is performed by 43.2% and existing data is 36, 4%, while communication between clinicians and laboratory microbiology in the treatment of infectious diseases is only done by 6.8% hospital.
- Warrant the availability of appropriate antibiotics in guideline and formulary conducted by 38.6% hospital, whereas clinical pharmacy activities and reports findings of Drug Related Problems concerning antibiotic use and the logging of antibiotics use recorded completely in written form is only done by 9.1% hospital. As for communication and consultation between the pharmacist, clinicians, microbiology laboratory staff and nurses on treatment of infectious cases is only done by 6.8% hospital.
- Implementation of the Prevention and Control of Infection (PPI) which consist of the existence of committees/subcommittee assigned by the hospital leadership (81.8%), the availability of means of communication and administration, which support the activities of PPI (54.6%), the presence of PPI manual and guide on outbreak management confirmed by the hospital leadership (50%), the availability of facilities for infection prevention and control as well as hand-washing guidelines and APD (27%), the existence of hospital infection surveillance activities and follow-up at regular intervals (24.2%).
• Periodic evaluation of antibiotic use is still very low (< 10%), whereas education and training is even lower (< 5%). Furthermore, periodic meeting of infectious diseases is not done in all hospitals that became the pilot project.31

Based on the above findings shows that many hospitals are not yet ready to conduct PPI, especially in terms of infrastructure, clean water sterilization and processing waste, mostly hospitals of classes C and D. Sewage treatment is important in the control or prevention of spread of antimicrobial resistance. This program gives many benefits especially in preventing the occurrence of total resistance or back to the era before antibiotics.32

Conclusion
Microbial resistance from a variety of research results and data in the hospital is already alarming. On the other hand, the government hospitals are not ready to do an ARCP in terms of human resources, facilities and infrastructure. The commitment of the hospital leadership is lacking to fully support the ARCP.

Recomendation
These policies should be implemented and used as a tool to increase the commitment of the hospital management. Compliance with the guidelines should be strictly implemented, besides the rational prescription of antimicrobials, completing facilities and infrastructures for controlling AMR and the establishment of surveillance of antibiotic use.

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