THE PREVALENCE OF EXTENDED SPECTRUM BETA-LACTAMASE (ESBL) IN THIRD GENERATION CEPHALOSPORIN USAGE AMONG SEPSIS PATIENTS IN THE DEPARTMENT OF INTERNAL MEDICINE RSUD DR. SOETOMO SURABAYA

Bramantono, Purwati, Hamidah
Department of Internal Medicine
Faculty of Medicine, Airlangga University
Dr Soetomo Teaching Hospital, Surabaya

ABSTRAK

*Insiden sepsis maupun kematian akibat sepsis terus meningkat setiap tahunnya. Antibiotika golongan beta-laktam paling banyak digunakan untuk mengatasi berbagai jenis infeksi. Banyaknya penggunaan antibiotika tersebut mengakibatkan munculnya enzim Extended Specrtum ß-lactamase (ESBL) yang dihasilkan oleh K. Ozaenae, dan sejak itu menyebar ke seluruh dunia dengan relatif cepat. Angka kejadian infeksi oleh karena bakteri penghasil ESBL di masing-masing negara sangat bervariasi. Di Indonesia, kejadian ESBL pada Enterobacteriaceae masih belum secara luas diketahui. Tujuan penelitian ini adalah untuk mengetahui besarnya angka kejadian ESBL pada penggunaan antibiotik sefalosporin generasi ke-3 pada penderita sepsis yang rawat inap di Instalasi Rawat Inap Medik Ruangan Penyakit Dalam RSUD Dr. Soetomo Surabaya. Penelitian cross-sectional ini dilakukan pada pasien yang rawat inap di RSUD Dr. Soetomo Surabaya antara tanggal 1 November 2011 - Februari 2012. Dari status penderita dilihat data demografi serta diagnosis saat MRS, selanjutnya dilakukan pemeriksaan spesimen untuk kultur kuman dan uji sensitivitas antibiotic, pemeriksan laboratorium darah lengkap, urin lengkap, tes faal hati dan faal ginjal. Data dianalisis menggunakan SPSS 18.0. Didapatkan 30 penderita dengan sepsis, 2 (6,66%) dengan ESBL positif. Kejadian ESBL positif didapatkan pada kelompok umur 41-50 tahun dan 61-70 tahun, dengan penderita semuanya laki-laki. Pneumonia dan penyakit hepatobilier merupakan kondisi penyakit yang mendasari. ESBL positif didapatkan pada isolat darah dan dahak. Kuman penghasil ESBL yang muncul adalah Klebsiella pneumoniae dan Enterobacter coxacie dengan uji sensitivitas terbanyak levofloxacin, imipenem dan meropenem.**(FMI 2013;49:244-251)***

Kata kunci: *Extended Spectrum Beta-Lactamase (ESBL), sefalosporin generasi ketiga, sepsis, RSUD Dr Soetomo*

ABSTRACT

*The incidence of sepsis and death caused by sepsis increases each year. Beta-lactam antibiotics is widely used to treat many types of infections because of its minimum side-effects. As a result of the widespread use of broad spectrum cephalosporin, an Extended Spectrum ß-lactamase (ESBL) enzyme produced by K. ozaenae has developed. Since then, other types of ESBL have been found and spread around the world relatively fast. The prevalence of infection caused by ESBL-producing bacteria varies in each country. In Indonesia, the incidence of ESBL in Enterobacteriaceae is still not widely known. This research aims to investigate the prevalence of ESBL in third generation cephalosporin usage among sepsis patients in The Department of Internal Medicine of RSUD Dr. Soetomo Surabaya. This crossectional study is conducted in The Department of Internal Medicine RSUD Dr. Soetomo Surabaya between November 1st 2011 and February 29th 2012. Demographic characteristics of patients and the basic diagnose were obtained from the medical record. Specimen were collected to examine bacterial culture and antibiotic sensitivity testing, complete blood laboratory examination, complete urine examinationm liver function tests and kidney function test. Data were analyzed using SPSS 18.0. Of the 30 sepsis patients, 2 were ESBL-positive (6.66%). ESBL-positive incidence were in the age group 41-50 and 61-70 years old, all male. Pneumonia and hepatobilliary disease were the underlying disease. ESBL-positive culture were obtained in blood and sputum isolates. ESBL-producing bacteria were Klebsiella pneumoniae dan Enterobacter coxacie with the most sensitivity towards levofloxacin, imipenem and meropenem.**(FMI 2013;49:244-251)***

Keywords: *Extended Spectrum Beta-Lactamase (ESBL), third generation cephalosporin, sepsis, RSUD Dr Soetomo*

Correspondence: Bramantono, Department of Internal Medicine, Faculty of Medicine, Airlangga University
Dr Soetomo Teaching Hospital, Surabaya

INTRODUCTION

Sepsis is a systemic inflammation syndrome with symptoms such as fever, hypothermia, shivering, tachypnea, tachycardia, hypotension, fast but weak pulse and decreased consciousness caused by microorganism (Suharto 2007a). Sepsis is a life-threatening condition because in the course of the disease, the majority of patients will fall into a septic shock condition, resulting in multi-organ failure and

death. Sepsis is still a main cause of death in critically ill patients despite the modern use of antibiotics and resuscitation therapy. The incidence of sepsis and death caused by sepsis increases each year. In The United States, from 500,000-700,000 cases of sepsis, the survival rate only reaches 55-65% despite the advanced development of intensive care unit and supportive therapy (Almog 2003, Riedemann et al 2003). This makes sepsis the tenth cause of death in The United States (Mortensen et al 2008)

Antibiotics are the main pillars of sepsis therapy and should be given as soon as the diagnosis of sepsis is suspected to prevent serious widespread of infection. Before antibiotic administration, microorganism culture from blood or other body fluid should be collected. However, antibiotic administration should not be postponed after the examination result (Nasronudin 2007, Suharto 2007a, Hadi 2005). Since the antibiotic era 50 years ago, marked by the discovery of penicillin, antibiotics has been a reliable medication for infectious diseases. However, several years later, *Staphylococcus aureus* became resistant towards penicillin by producing penicillinase. A broad spectrum penicillin and beta-lactam first generation cephalosporin was then introduced. But 20 years later, both became resistant, caused by the enzyme beta-lactamase produced by gram negative bacilli bacteria such as *E. coli* and *K. pneumoniae* (Medeiros 1997, Nordmann et al 2000, Aztal et al 2004). Beta–lactam antibiotics has broad spectrum and were relatively safe because of its minimum side effects. Therefore, the class became the most reliable antibiotics to overcome various infections (Livermore 1995). The introduction of third generation cephalosporin in the 1980s was considered the problem solving for beta-lactamase producing bacteria resistant to antibiotics. Third generation cephalosporin are not only effective against beta-lactam producing organism but are also less nephrotoxic compared to aminoglycosides and polymyxin. As a result of the widespread use of broad spectrum cephalosporin, in 1983 in Germany, an Extended Specrtum ß-lactamase (ESBL) enzyme produced by K. ozaenae has been isolated. Since then, other types of ESBL has been found and it spread around the world relatively fast (Shah et al 2004, Paterson et al 2004, Al-Jasser 2006)

ESBL are plasmid enzymes that mediate the hydrolysis and inactivation of beta-lactam antibiotics including third generation cephalosporin, penicillin and aztreonam (Aztal et al 2004, Al-Jasser 2006). The enzyme is primarily produced by *Klebsiella pneumoniae* and Escherichia coli. Moreover, it can be produced by other organisms such as Salmonella species, Pseudomonas aeruginosa, Morganella morganii, Erratia marcescens and other Enterobacteriaceae (Aztal et al 2004, Livermore 2004). ESBL enzymes are the result of a mutation of the TEM-1, TEM-2, and SHV-1. All three enzymes are beta-lactamases commonly found in the family Enterobacteriaceae. Normally TEM-1, TEM-2 and SHV-1 will provide high resistance to penicillin and first generation cephalosporin. The broad and unclear use of third generation cephalosporin and aztreonam, is believed to be the main cause of mutation of the enzyme. ESBL can also cause cross-resistance to other classes of antibiotics types, such as fluoroquinolones and aminoglycosides group (Chaudhary & Aggarwal 2004, Giamarellou 2005, Jacoby & Munoz-Price 2005, Weinbren & Borthwick 2005).

The prevalence of infection caused by ESBL-producing bacteria varies in each country. In The United States the number is 0-25% based on the institution, so is in Europe, excluding Netherlands (less than 1%) (Stobberingh et al 1999). In France, 40% ESBL-producing *K. pneumoniae* is resistant towards ceftazidime. While in Japan the prevalence is still low: 0.1% for *E. coli* and 0.3% for *K. pneumoniae*. In other Asian countries, the prevalence of ESBL produced by *E. coli* and *K. pneumoniae* varies: 4.8% in Korea, 8.5% in Taiwan and 12% in Hong Kong (Nordmann et al 2000, Ho et al 2000). In Indonesia, the incidence of ESBL in Enterobacteriaceae is still not widely known; however, an increase is estimated. Results of Antimicrobial Resistance in Indonesia study: prevalence and prevention (AMRIN Study) proved that *E. coli* found in the normal flora of patients exiting the hospital or after hospitalization for at least 5 days in RSU Dr. Soetomo and Hospital Dr. Kariadi Semarang experience increasing levels of resistance to cefotaxime and ciprofloxacin compared to the community. Kuntaman et al (2005a) in a research on clinical specimens found that the incidence of ESBL is quite high at 29% in *E. coli* and *K. pneumoniae* 36% (AMRIN Study 2006).

Meanwhile in RSUD Dr. Soetomo Surabaya, a clonal spread of *E. coli* and ESBL-producing *K. pneumoniae* from clinical specimens (January-April 2005) has been detected. The spread of identical clones of both bacteria to various rooms in Surgery, Pediatrics, Internal Medicine as well as Obstetrics and Gynecology Department has been proved (Kuntaman 2007). In some hospitals abroad, the first outbreak of infection that has been shifted by outbreaks of ESBL-producing organisms. This leads to increased patient mortality if antibiotics which are not effective against ESBL-producing bacteria are given. As a consequence, if bacteria culture contained ESBL-producing gram negative, empiric therapy should be replaced with imipenem, quinolones, or a combination of ß-lactam/ß-lactamase inhibitor. In some centers, it is associated with resistance in Pseudomonas aeruginosa and

Acinobacter baumannii and ESBL-producing organism itself. Endemic controls against ESBL-producing organisms are difficult, and only made possible after significant treatment and medical reorganization at a high cost (Paterson et al 2004).

This research aims to investigate the prevalence of ESBL in third generation cephalosporin usage among sepsis patients in The Department of Internal Medicine of RSUD Dr. Soetomo Surabaya. In addition to that, this research also aims to elucidate the distribution of sepsis patients with ESBL –producing bacteria based on sex, age, culture material and underlying disease, the types of ESBL-producing bacteria and results of antibiotic sensitivity tests in sepsis patients.

MATERIALS AND METHODS

Subjects in this cross-sectional study were 30 sepsis patients treated with third generation cephalosporin in The Internal Medicine Department of RSUD Dr. Soetomo Surabaya between November 1st 2011-February 29th 2012. The inclusion criteria were male and female sepsis patients aged 14-70 years old and were given third generation cephalosporin antibiotics before culture examination. Patients who were not treated with cephalosporin were excluded from the study.

Specimens were taken for germ culture examination and antibiotic sensitivity. Complete blood test, urine examination, liver function test, and renal function test was also conducted. Eligible patients were classified based on germ culture result and antibiotic sensitivity test result. Demographic data, diagnosis result and laboratory examination results were noted. Obtained data were analyzed by descriptive statistics methods to describe mean, standard deviation and frequency distribution. To investigate ESBL prevalence the number of affected individuals were divided with the total number of population.

RESULTS

General characteristics including vital sign, basic laboratory examination, liver function test and renal function test of the 30 subjects are given in Table 1. From urinalysis, 21 (70%) sepsis patients developed bacteriuria while 9 (30%) were negative. Details are given in table 2.

The type of third generation cephalosporin given to 23 (76.67%) of patients is ceftriaxone. 4 patients (13.33%) were given cefotaxime, while 3 (10%) were given ceftazidime. Of the two ESBL-positive patients, 1 was given ceftazidime, 1 was given ceftriaxone. Based on sex, as many as 20 (66.7%) patients were male and 10 (33.3%) were female. ESBL-positive patients were all male (2 men). Based on age group, ESBL-positive patients were in the age group 41-50 and 61-70 years old, one person in each age group.

Table 1. General characteristics of the patients

Variable	Mean ± SD	Minimum	Maximum
Age	48.07 ± 14.70	18	70
Vital Signs			
Systolic blood pressure	125.66 ± 24.02	100	210
Diastolic blood pressure	78.67 ± 12.24	60	110
Heart rate	99.73 ± 11.77	84	130
Respiratory rate	22.87 ± 4.09	18	36
Temperature	37.7 ± 0.77	36.0	39.5
Basic Laboratory			
Hemoglobin level	9.99 ± 3.06	3.3	16.1
Leukocytes	18.66 ± 21.19	3.0	123.6
Thrombocytes	250.30 ± 191.15	6.0	970.0
Segmen	82.76 ± 5.39	75.4	94.5
Clinical chemistry			
BUN	46.16 ± 56.87	6.0	227.6
Serum Creatinine	3.36 ± 5.56	0.4	21.9
AST	32.87 ± 19.64	10.0	87.0
ALT	25.63 ± 18.16	5.0	100.0

Table 2. Urinalysis results to determine bacteriuria.

Bacteriuria		Frequency	Percentage	Valid Percent	Cumulative Percent
Valid	(-)	9	30.0	30.0	30.0
	(+)	14	46.7	46.7	76.7
	(++)	6	20.0	20.0	96.7
	(+++)	1	3.3	3.3	100.0
	Total	30	100.0	100.0	

Table 3. Distribution of ESBL-positive sepsis patients based on underlying disease.

Diagnosis	Frequency	
	ESBL (+)	Non ESBL
Diabetes mellitus	0	6
Chronic Kidney Disease (CKD)	0	7
Hepatopancreatobilliary disease	1	2
Malignancy	0	6
Community-acquired Pneumonia (CAP)	1	0
Urinary tract Infection	0	1
Others	0	6
Total	2	28

Table 4. Distribution of ESBL-producing bacteria in culture materials

Culture result	Culture material			
	Blood	Urine	Sputum	Pus
ESBL bacteria growth positive	1 (3,33%)	0 (0%)	1 (3,33%)	0 (0%)
ESBL bacteria growth negative	29 (96,67%)	30 (100%)	3 (10%)	5 (16,67%)
Examination not conducted	0	0	26 (86,67%)	25 (83,33%)
Total	(100,0%)	(100,0%)	(100,0%)	(100,0%)

Based on underlying disease diagnosis, most sepsis patients were suffering Chronic Kidney Disease (CKD) (7 patients, 23.34%), followed by Diabetes Mellitus and Malignancy, each 6 patients (20%). Of the 2 ESBL-positive patients one had hepatobilliary disease and the other had Pneumonia (Table 3). In the majority of culture material from blood (29 specimen, 96.67%) and urine (30 specimen, 100%), growth of ESBL-producing bacteria was not found. Meanwhile examination was not done in most of the culture from sputum and pus. ESBL-positive bacteria growth was found in blood and sputum culture, one in specimen each (Table 4). ESBL-producing bacteria, *Enterobacter coxacie* was found in 1 culture material (blood) and Klebsiella pneumonia was found in 1 culture material (sputum). (Table 5)

Antibiotic sensitivity testing result in blood culture material showed high sensitivity towards levofloxacin, imipenem and meropenem. Culture from urine and pus were not tested for antibiotic sensitivity because there was no ESBL-producing bacteria growth. Meanwhile, most of the cultures from sputum were still sensitive to amikacin, tobramycin, gentamicin, cefoperazone-sulbactam, cotrimoxazol, tigercycline, ciprofloxacin, levofloxacin, imipenem and meropenem. Levofloxacin, imipenem, meropenem were the most sensitive antibiotics towards ESBL-producing bacteria in the blood and sputum culture. (Table 6)

Table 5. Distribution of ESBL-producing bacteria species based on culture material

ESBL bacteria	Culture material			
	Blood	Urine	Sputum	Pus
E. coli	0	0	0	0
Klebsiella pneumoniae	0	0	1	0
Klebsiella oxytoca	0	0	0	0
Enterobacter aerogenes	0	0	0	0
Enterobacter coxacie	1	0	0	0

DISCUSSION

Sepsis is the main cause of death in non-coronary diseases in the Intensive Care Unit and is ranked tenth in the cause of most deaths in the United States. The incidence of severe sepsis is ranged between 650,000 to 750,000 cases per year. More than 70% cases are in a co morbid condition and more than 60% occurred in people

aged 65 years old or older. It is estimated that the incidence of sepsis will increase by 8% per year. The incidence in male and female are equal. Infection by gram-positive bacteria is more common than gram-negative bacteria, while fungal infections are found in 6% of the cases (Russel 2006). Immediate and accurate treatment is needed to overcome sepsis patients in order to improve the patient's survival. Antibiotics are the main pillars of sepsis treatment. Early antibiotic therapy decision has always been empirical. Sensitivity pattern of local germs is a prerequisite to guide empirical antibiotic therapy (Nasronudin 2007, Suharto 2007b, Hadi 2008).

Table 6. Distribution of antibiotic sensitivity test towards ESBL-producing bacteria based on culture material

Antibiotics	Culture Material				Total
	Blood	Urine	Sputum	Pus	
Amikacin	0	0	1	0	1
Tobramycin	0	0	1	0	1
Gentamicin	0	0	1	0	1
Amoxiclav	0	0	0	0	0
Piperacillin-Tazobac	0	0	0	0	0
Ticarcillin-Clavulan	0	0	0	0	0
Cefoperazone-Sulbac	0	0	1	0	1
Cotrimoxazole	0	0	1	0	1
Tigercyclin	0	0	1	0	1
Ciprofloxacin	0	0	1	0	1
Levofloxacin	1	0	1	0	2
Minocyclin	0	0	0	0	0
Cefazolin	0	0	0	0	0
Imipenem	1	0	1	0	2
Meropenem	1	0	1	0	2
Doripenem	0	0	0	0	0
Fosfomycin	0	0	0	0	0
Nitrofurantoin	0	0	0	0	0

The introduction of third generation cephalosporin in the early 1980s was considered a miracle solving for antibiotic resistant beta-lactamase producing bacteria. As a result of the increasing use of this class of antibiotics, arises an Extended Spectrum ß-lactamase (ESBL) enzyme produced by K. ozaenae. Since then, various types of ESBL has been noticed and the global wide spread was relatively fast (Shah 2004, Paterson et al 2004, Al-Jasser 2006).

The prospective observational study by Paterson et al (2004) in 12 hospitals in several countries reported that the use of beta-lactam antibiotics containing oxymino components (cefuroxime, cefotaxime, ceftriaxone, ceftazidime, dan aztreonam) increases the risk of ESBL-organism related bacteremia with a relative risk of 3.9 (95% CI, 1,1 to 13,8).

Kuntaman et al (2005a) in Surabaya found the sensitivity pattern of ESBL-producing bacteria resistant to third generation cephalosporin, especially ceftazidime, cefotaxime dan ceftriaxone, with resistance level of 51% to 76%. In the retrospective cohort study conducted in Rome, Italy, has been reported that patients without adequate early antibiotic therapy has greater risks of bacteremia, needs longer treatment in hospital with higher mortality rate, and spent greater treatment costs compared to patients who were given adequate early antibiotic therapy (Tumbarello et al 2007).

ESBL-producing Enterobacteriaceae has become a main problem for patients treated in the hospital and patients who were not. This class of bacteria has been isolated from asbestos, blood, tip of catheter, lungs, peritoneal fluid, sputum and throat swab. The bacteria is involved in several infections such as urinary tract infection, septicemia, hospital acquired pneumonia (HAP), intra abdominal abscess, encephalic abscess, and infection caused by medical instruments application (Mumtaz et al 2007). Various factors that can lead to an increase in infections due to ESBL-producing organisms are: the use of medical instruments such as urinary catheters, intravenous use; surgery; usage of third generation cephalosporin antibiotics especially ceftazidime, fluoroquinolones and cotrimoxazole, treatment at home, duration of hospitalization and the severity of APACHE III (Livermore 2004, Jacoby & Munoz-Price 2005).

Prevalence of ESBL in sepsis patients treated with third generation cephalosporin.

Investigation of ESBL prevalence has been conducted in many countries in the world. In Malaysia in 1994, 36,343 bacteria were reported resistant in four year isolation in 6 hospitals. There has been found ceftazidime resistance in *E. coli* 5.5%, resistant *Klebsiella spp* 16.8% and Pseudomonas aeuriginosa 6.8%. Prevalence of ESBL caused by *Klebsiella spp* in Japan was 5.0%, Taiwan 21.7%, Philippines 31.3%, Malaysia/Singapore 38% and in Indonesia 33%. Prevalence of ESBL caused by *E. coli* in Japan 8.1%, Taiwan 16.7%, Philippines 13.3%, Malaysia/Singapore 5.6 % and Indonesia 23% (Ministry of Health Malaysia et al 2001, Kuntaman 2005a).

In Indonesia, the prevalence of ESBL in Enterobacteriaceae is still not widely known, but it is estimated that there will be an increase. Some hospitals overseas have mentioned an outbreak of ESBL-producing organisms. Meanwhile in RSUD Dr. Soetomo Surabaya, a clonal spread of *E. coli* and ESBL-producing *K. pneumoniae* from clinical specimens (January-April 2005) has been detected. The spread of identical clones of both bacteria to various rooms in Surgery, Pediatrics, Internal Medicine as well

as Obstetrics and Gynecology Department has been proved (Kuntaman 2007).

In this study we obtained the prevalence rate of 6.66%. This result is smaller than the research conducted by Kuntaman. Kuntaman et al (2005b) reported that in a study conducted in RSUD Dr. Soetomo between April and November 2004 against 5,636 clinical specimens (1,292 blood, 2,792 urine, 531 sputum, 880 wound swabs, 243 stool, 55 cerebrospinal fluid) successfully isolated 148 Escherichia coli and 431 *Klebsiella spp*. 55 ESBL strains (13.8%) was found in Escherichia coli and 53 strains (12.3%) in *Klebsiella spp*.

While Yip et al (2006) reported that in a study conducted in Tung Wah Hospital, Hong Kong for 10 years to patients undergoing CAPD, 1066 patients suffered peritonitis. 88 patients (35%) due to *E. coli* and 11 of them (12.5%) were ESBL-positive. Of the 11 patients, 7 of them received antibiotics prior to culture with the details 2 patients were given penicillin, 3 patients were given first-generation cephalosporin cefazolin and 2 patients were given a second generation cephalosporin cefuroxime. Difference in the results of this study could be caused by the small number of samples and the short duration of research. Therefore, the prevalence was smaller, the hospital services quality was better, and the usage of cephalosporin antibiotics was more rational so resistance of bacteria does not occur.

Distribution of ESBL-positive sepsis patients

By age and sex

In this study, patients with sepsis using 3rd generation cephalosporin with a positive ESBL was found in the age group 41-50 years in 1 patient (50%) and in the age group 61-70 years in 1 patient (50%). While based on sex, ESBL incidence is only found in male patients as many as 2 people (100%). The results of this study differ from other studies. Mumtaz et al (2007) reported that in a study of 165 ESBL-positive patients, the number of female patients (106, 64.3%) was greater than male patients (59, 35.7%). While other studies derived the number of male was more than in female (Shah et al 2004). The age group with the greatest ESBL prevalence was 61-70 years old (27.9%) and the least was 0-10 years and 31-40 years (5.5%). While the study of Shah et al. (2002) showed that the largest age group with ESBL was 50-60 years (48 %) and lowest was >60 years (6.6%). The difference is likely caused by the greater number of male samples than female samples, less random sample selection; the sample size was too small.

Based on diagnosis

The results of this study obtained 1 patient (50%) with hepatobiliary disease and 1 patient (50%) with pneumonia. These results differ from a study conducted by Martin et al (2003), where the figures obtained respectively Diabetes Mellitus (18.7%), malignancy (29%) and there are no data on CKD and pneumonia. Meanwhile, Rodríguez-Baño et al (2006), derived DM (29%), malignancy (57%) and CKD (5%). Other literatures stated that sepsis risks would increase in diabetic patients or other diseases that cause immunocompromised conditions and patients who received immunosuppressive therapy (Wheeler & Bernard 1999, Martin et al 2003, Rodríguez-Baño et al 2006, Chang 2010).

In this study, one patient had hepatobiliary disease (chronic hepatitis) and aged 70 years old. Therefore, the patient could be classified as immunocompromised despite not receiving immunosuppressant therapy. Both conditions allows infection and development of sepsis occur. Similar conditions were observed in the other patient who had Pulmonary Tuberculosis co morbidity and thrombocytopenia; both are immunocompromised condition.

Based on culture material

In this study, the ESBL-positive was derived from blood culture in 1 patient (50%) and sputum culture in 1 patient (50%). These results differ from a study conducted by Kuntaman et al (2005a) and Rodríguez-Baño et al (2006). Kuntaman (2005a) found that the culture material containing most ESBL-producing bacteria was urine. A similar result was also derived by Rodríguez-Baño et al (2006) who found that 38% of ESBL isolates were derived from urine. The difference is thought to be caused by the small number of samples, uneven distribution and differences in the pattern of underlying disease diagnosis, so that isolate materials were also different.

ESBL-producing bacteria causing sepsis and result of sensitivity test

ESBL-producing bacteria causing sepsis.

It this research, we obtained different bacteria from both patients: 1 *Klebsiella pneumoniae* from sputum culture and 1 *Enterobacter coxacie* from blood culture. The most frequent ESB-producing bacteria in this research are similar to the research by Kuntaman et al (2005a). Kuntaman derived 42.7% (*Klebsiella pneumoniae*). However this study differed from the study by Micek et al (2010) in which he derived 36% (*E. coli*) and 24.7%

(*Klebsiella pneumoniae*). This difference is likely caused by the difference in research location resulting in a different bacterial mapping. In addition, it could be caused by the small number of samples resulting in uneven distribution of bacteria.

Antibiotic sensitivity test result

In this study, antibiotic sensitivity test results against ESBL-producing bacteria was found in Meropenem by 2 isolates (100%), Imipenem 2 isolates (100%) and Levofloxacin 2 isolates (100%). All isolates were resistant to third generation cephalosporin antibiotics. In a study by Kuntaman (2005a) in Surabaya, there has been obtained sensitivity pattern of ESBL-producing bacteria which are resistant to third generation cephalosporins, especially ceftazidime, cefotaxime and ceftriaxone, with resistance level between 51% and 76%. Kuntaman et al (2005b) obtained a high level of resistance to ciprofloxacin (81.8%) and in cefepime (29%). The lowest resistance was towards meropenem and cefoperazone-sulbactam combination.

The results in this study are also different from the results of research conducted by Rodríguez-Baño et al (2006) which found sensitivity rate antibiotics: meropenem (100%), piperacillin-tazobactam (91%), and gentamicin (91%). These differences may occur because of the different ESBL strains that affect susceptibility to different antibiotics. ESBL-producing organisms differ in their susceptibility to different Oxymino lactams.

For TEM and SHV types of ESBL, sensitivity towards cefepime and piperracillin-tazobactam is the same. CTX-M type ESBL was resistant to cefepime but sensitive to cefamisine and carbapenam. OXA types ESBL are still sensitive to aztreonam. Infections caused by *E. coli* or Klebsiella producing ESBL showed good results with imipenem or meropenem (Chaudhary & Aggarwal 2004, Jacoby & Munoz-Price 2005).

CONCLUSIONS

The prevalence of ESBL in sepsis patients treated with third generation cephalosporin in The Internal Medicine Department of RSUD Dr.Soetomo is 6.66%. Only found in male patients (2 men) patients in the age group between 41-50 and 61-70 years old. The underlying disease diagnosis is mostly hepatobiliary disease and pneumonia. The ESBL-producing bacteria were found in culture from blood and sputum. Most types of ESBL-producing bacteria are *Klebsiella pneumoniae* and *Enterobacter coxacie* with the highest sensitivity test results are levofloxacin, imipenem and meropenem.

ACKNOWLEDGMENT

We are indebted to Yusuf Ibrahim for his assistance in making the layout of the manuscript.

REFERENCES

Al-Jasser AM (2006). Extended-spectrum beta-lactamases (ESBLs): a global problem. Kuwait Medical Journal 38, 171-185

Almog Y (2003). Statins, inflammation, and sepsis: hypothesis. Chest 124, 740-743

Aztal Z, Sharif FA, Abdallah SA, Fahd MI (2004). Extended spectrum beta lactamases in Escherichia coli isolated from community-acquired urinary tract infection in the Gaza Strip, Palestina. Ann Saudi Med 24, 55-57

Chang L (2010). Sepsis (Blood Infection) and Shock Septic. Available from http://www.medicinenet.com /script/main/art.asp?articlekey=98247. Accessed August 21, 2011

Chaudhary U and Aggarwal R (2004). Extended spectrum-lactamases (ESBL) - an emerging threat to clinical therapeutics. Indian J Med Microbiol 22, 75-80

Giamarellou H (2005). Multidrug resistance in Gram-negative bacteria that produce extended-spectrum ß-lactamases (ESBLs). Clin Microbiol Infect 11, 1-16

Hadi U (2005). Manajemen penggunaan antibiotika di rumah sakit. In: Hadi U, Nasronudin, Kuntaman (eds). Simposium Penyakit Infeksi dan Problema Resistensi Antimikroba 30 April 2005 Surabaya, p 46-50

Hadi U (2008). Terapi empiris antibiotik pada penderita bakteriemia/sepsis. In: Hadi U, Nasronudin, Bramantono, Triyono EA, Arfianto MV, Soewandojo E, Suharto (eds). Simposium Nasional Penyakit Tropik-Infeksi dan HIV & AIDS, 22-23 Maret 2008 Surabaya, p 28-31

Ho PL, Tsang DN, Que TL, Ho M, Yuen KY (2000). Comparison of screening methods for detection of extended-spectrum ß-lactamases and their prevalence among Escherichia coli and Klebsiella species in Hong Kong. APMIS 108, 237-240

Jacoby GA and Munoz-Price LS (2005). Mechanisms of disease the new β-lactamases. N Engl J Med 352, 380-391

Kuntaman (2007). Aspek mikrobiologi dari infeksi dan sepsis. In: Nasronudin (ed). Penyakit Infeksi di Indonesia Solusi Kini & Mendatang, Surabaya, Airlangga University Press, p 229-237

Kuntaman, Mertaniasih NM, Purwanta M (2005a). Bakteri penghasil ESBL dari spesimen klinik di RSU Dr Soetomo Surabaya. In: Hadi U, Nasronudin, Kuntaman (eds). Simposium Penyakit Infeksi dan

Problema Resistensi Antimikroba 30 April 2005 Surabaya, p 1-9

Kuntaman, Mertaniasih NM, van den Broek PJ and Verbrugh HA (2005b). Genetic analysis of multiresisten bacteria from Indonesia. Indonesia International Joint Research Grant Program, Final Progress Report, p 35, Presented in Jakarta February 8, 2006

Livermore DM (1995). Beta-lactamases in laboratory and clinical resistance. Clin Microbiol Rev 8, 557-584

Livermore DM (2004). ESBLs: global aspects and laboratory detection. SCIEH Weekly Report 38, 8-11

Martin GS, Mannino DM, Eaton S, Moss M (2003). The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 348, 1546-1554

Medeiros AA (1997). Evolution and dissemination of beta-lactamases accelerated by generations of ß-lactam antibiotics. Clin Infect Dis 24, S19-S45

Micek ST, Welch EC, Khan J, Pervez M, Doherty JA, Reichley RM, Kollef MH (2010). Empiric combination antibiotic therapy is associated with improved outcome against sepsis due to Gram-negative bacteria: a retrospective analysis. Antimicrob Agents Chemother 54, 1742-1748

Ministry of Health Malaysia, Academy of Medicine of Malaysia, Malaysian Society of Infectious Diseases and Chemotherapy (2001). Consensus Guidelines for The Management of Infections by ESBL-Producing Bacteria, Malaysia, Ministry of Health Malaysia

Mortensen EM, Restrepo MI, Anzueto A (2008). The potential role of statins in severe sepsis. In: Rello J and Restrepo MI (eds). Sepsis New Strategies for Management, Berlin, Springer, p 19-2

Mumtaz S, Ahmad M, Aftab I, Akhtar N, ul Hassan M, Hamid A (2007). Extended spectrum ß-lactamases in enteric gram-negative bacilli: related to age and gender. J Ayub Med Coll Abbottabad 19, 107-111

Nasronudin (2007). Imunopatogenesis sepsis dan prinsip penatalaksanaan. In: Nasronudin (ed). Penyakit Infeksi di Indonesia Solusi Kini & Mendatang, Surabaya, Airlangga University Press, p 238-245

Nordmann P, Poirel L, Kubina M, Casetta A, Naas T (2000). Biochemical-genetic characterization and distribution of OXA-22, a chromosomal and inducible class D ß-lactamase from Ralstonia (Pseudomonas) pickettii. Antimicrobial Agents and Chemotherapy 44, 2201-2204

Paterson DL, Ko WC, Von Gottberg A, Mohapatra S, Casellas JM, Goossens H, Mulazimoglu L, Trenholme G, Klugman KP, Bonomo RA, Rice LB, Wagener MM, McCormack JG, Yu VL (2004). International prospective study of *Klebsiella pneumoniae* bacteremia: implications of extended-spectrum beta-lactamase production in nosocomial infections. Ann Intern Med 140, 26-32

Riedemann NC, Guo RF, Ward PA (2003). The enigma of sepsis. J Clin Invest 112, 460-467

Rodríguez-Baño J, Navarro MD, Romero L, Muniain MA, de Cueto M, Ríos MJ, Hernández JR, Pascual A (2006). Bacteremia due to extended-spectrum beta - lactamase-producing Escherichia coli in the CTX-M era: a new clinical challenge. Clin Infect Dis 43, 1407-1414

Russell J (2006). Management of sepsis. N Engl J Med 355, 1699-1713

Shah AA, Hasan F, Ahmed S, Hameed A (2004). Characteristics, epidemiology and clinical importance of emerging strains of Gram-negative bacilli producing extended-spectrum ß-lactamases. Res Microbiol 155, 409-421

Stobberingh EE, Arends J, Hoogkamp-Korstanje JA, Goessens WH, Visser MR, Buiting AG, Debets-Ossenkopp YJ, van Ketel RJ, van Ogtrop ML, Sabbe LJ, Voorn GP, Winter HL, van Zeijl JH (1999). Occurrence of extended-spectrum ß-lactamases (ESBL) in Dutch hospitals. Infection 27, 348-354

Suharto (2007a). Dasar patogenesis dan pemberian obat antimikrobia. In: Nasronudin (ed). Penyakit Infeksi di Indonesia Solusi Kini & Mendatang, Surabaya, Airlangga University Press, p 246-255.

Suharto (2007b). Patofisiologi syok septik. In: Nasronudin (ed). Penyakit Infeksi di Indonesia Solusi Kini & Mendatang, Surabaya, Airlangga University Press, p 263-264

Tumbarello M, Sanguinetti M, Montuori E, Trecarichi EM, Posteraro B, Fiori B, Citton R, D'Inzeo T, Fadda G, Cauda R, Spanu T (2007). Predictors of mortality in patients with bloodstream infections caused by extended – spectrum – beta – lactamase - producing Enterobacteriaceae: importance of inadequate initial antimicrobial treatment. Antimicrob Agents Chemother 51, 1987-1994

Weinbren MJ and Borthwick MA (2005). Rapid detection of extended-spectrum β-lactamase (ESBL)-producing organisms in blood culture. J Antimicrob Chemother 55, 131-132

Wheeler AP and Bernard GR (1999). Treating patients with severe sepsis. N Engl J Med 340, 207-214

Yip T, Tse KC, Lam MF, Tang S, Li FK, Choy BY, Lui SL, Chan TM, Lai KN, Lo WK (2006). Risk factors and outcomes of extended-spectrum beta-lactamase-producing *E. coli* peritonitis in CAPD patients. Perit Dial Int 26, 191-197