ORIGINAL RESEARCH REPORT

Bacterial Pattern among Sepsis Patients in Internal Medicine Inpatient Ward Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

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ABSTRACT

Background: Bacteria remain the primary cause of bacterial sepsis. Gram-negative bacteria are the most commonly isolated from sepsis patients. However, gram-positive bacterial infections have also increased recently. **Objective**: To identify the pattern of bacterial infection in sepsis patients in Internal Medicine inpatient ward Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. **Material and Method**: This retrospective study reviewed the medical records of all sepsis patients in Internal Medicine Ward Dr. Soetomo General Academic Hospital, Surabaya, Indonesia from January 1 – December 31, 2016. All patients were divided according to bacterial species into two groups: patients with gram-positive and gram-negative infection. The collected data were statistically analyzed using SPSS ver. 16.0 to find out the frequency. **Result**: From 179 eligible data reviewed, there were 103 (57.5%) patients with gram-positive bacterial infection and 76 (43.5%) patients with a gram-negative bacterial infection. The major isolates of gram-positive bacteria were *Staphylococcus hominins* (30 isolates) and gram-negative bacteria was *Escherichia coli* (30 isolates), 43 isolates showed multi-drug resistant organisms; *Escherichia coli ESBL* 23 isolates, *Klebsiella pneumoniae ESBL* 3 isolates, *Klebsiella oxytoca ESBL* 2 isolates and *Methilcillin Resistance Staphylococcus aureus* 5 isolates. **Conclusion**: The most common causative agent in bacterial sepsis was gram-positive bacteria. The major isolated gram-positive bacteria are *Staphylococcus hominis* and gram-negative bacteria were *Escherichia coli*. The species of multi-drug resistant organisms found are Methilcillin-Resistant *Staphylococcus aureus* (MRSA), *Escherichia coli ESBL*, *Klebsiella pneumonia* ESBL and *Klebsiella oxytoca* ESBL. Among the patients with multi-drug resistant organism infection, *Escherichia coli ESBL* were the most prevalent one.

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BACKGROUND

Sepsis is the most common cause of death among critically ill patients in non-coronary intensive care units (ICU). The incidence of sepsis has increased and contributes to high mortality in hospital. In Asia, the mortality of severe sepsis reaches 44.5% (Phua, et al., 2011). Sepsis staging is based on the second consensus in 2001, in which there are sepsis, severe sepsis and septic shock. Sepsis is defined as SIRS with proof of infection, while severe sepsis is sepsis with organ dysfunction, and septic shock is sepsis with hypotension, even though the resuscitation liquid has been given (Mayr, et al., 2014). Causative organisms are identified from blood culture, so the blood culture must be accurate. Bacterial culture is important in sepsis because it not only gives us information about the species of microorganism, but also the sensitivity of antibiotics (Parija, 2012; Snyder, et al., 2012). Agents of infection are bacteria, viruses or fungi, but the bacteria are the majority. Nowadays, gram-positive bacteria are the most causative agent of sepsis (Mayr, et al., 2014). Both gram-positive and gram-negative bacteria have different virulence factors. Gram-positive bacteria with lipoteichoic acid and gram-negative bacteria with their lipopolysaccharide lead to different immune responses when they reach the human body (Mayr, et al., 2014; Surbatovic, et al., 2015). Sepsis is complex because of many factors that contribute to developing the disease. Comorbidity and nosocomial infections play role in developing its severity and outcome (Martin, 2012).

The problem in the treatment of sepsis is challenging with the presence of bacterial resistance known as multidrug resistance organism (MDRO). *Methilcillin Resistance Staphylococcus aureus (MRSA)* is a resistant organism from gram-positive bacteria species *Staphylococcus aureus* which is resistant to methicillin and related to poor clinical outcomes (Hassoun, , 2017). Gram-negative bacteria also have a resistant organism known as ESKAPE pathogen (*Escherichia coli, Klebsiella pneumonia, Acinetobacter spp. Pseudomonas aeroginosa, and Enterobacter spp.).* This condition makes the use of cephalosporin antibiotics ineffective and the therapeutic alternative becomes limited. It also leads to an increasing risk of death in bacterial sepsis (Pop-Vicas & Opal, 2014). Sepsis problems become more complex because they also involve the policies of antibiotic treatment. The presence of resistant microorganisms needs a wise decision to create an effective therapy, so, it is important to determine the etiology of bacterial sepsis.

OBJECTIVE

This study aimed to identify the pattern of bacterial infection in sepsis patients in Internal Medicine inpatient ward Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, and the sepsis epidemiology due to multi-drug resistant organisms (MDRO). The identification would be very helpful for clinicians to detect patients requiring a broader spectrum of antibiotics or as a consideration to make guidelines in antibiotic therapy.

MATERIALS AND METHODS

We reviewed medical records of sepsis patients who were admitted to the Internal Medicine Inpatient Ward Dr. Soetomo General Academic Hospital, Surabaya, Indonesia during the period January 1 - December 31, 2016. The inclusion criteria for this study were patients diagnosed with sepsis. From medical records, the demography and clinical data were collected by analysis of patient medical records such as age, sex, blood pressure, respiratory rate, temperature, leukocytes, thrombocytes level, serum creatinine, bilirubin level, and lactate level. Based on the clinical manifestation, sepsis is classified into 3: sepsis, severe sepsis, and septic shock based on the consensus statement from the American College of Chest Physicians and the Society of Critical Care Medicine 2001.

Patients were classified into sepsis when meeting both two of the following: a. Body temperature of >38°C or <36°C, tachycardia (>90 beats per min), tachypnea (>20 breaths per min or an arterial CO_2 pressure of <32 mm Hg), leukocytosis or leukopenia (white blood cell count of >12,000 cells/mm^3 or <4,000 cells/mm^3) or >10% immature forms. b. A documented source of infection. Patients who met the criteria for the sepsis above and met one of the criteria for organ failure were classified as severe sepsis. The organ failure criteria were: hypoxemia (PaO2/FiO2 <300), acute oliguria (urine output <0.5 mL/kg/hr persisting two hours or longer), serum creatinine >2.0 mg/dL, coagulation

disorder (PT-INR >1.5), thrombocytopenia (PLT <100,000/mL), hyperbilirubinemia (Total Bilirubin >2.0mg/dL), and hyperlactatemia (blood lactate >18 mg/dL). Patients with severe sepsis with a systolic pressure of 90 mmHg or lower that was persistent with appropriate fluid resuscitation and required a vasopressor were classified into septic shock group (Martin, 2012).

All positive blood cultures were identified by gram staining reaction and their characteristics. They were divided into two groups, gram-positive and gram-negative bacteria according to the bacterial species detected. Incomplete medical records and subjects with negative blood cultures were excluded from this study. The collected data were statistically analyzed to find the frequency. Statistical analysis was perform using SPSS ver. 16.0.

RESULTS

Between January 1, 2016 and December 31, 2016, as many as 715 patients diagnosed with sepsis were admitted to the Internal Medicine Wards, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. From all medical records of those patients, 88 were not found and 26 were incomplete. Positive blood culture was confirmed for 179 of 601 medical records. After eliminating those meeting the exclusion criteria, the remaining 179 culture-positive samples were included in the study.

After reviewing the medical records, it was found that gram-positive bacterial infection was predominant in the blood culture, which were found in 103 from 179 patients (57.5%), mostly *Staphylococcus hominis* (30 isolates). Gram-negative bacterial infection was present in 69 of 179 patients (42.5%), with *Escherechia coli* as the predominant infection (30 isolates). The species of the isolated bacteria among sepsis patients were shown in Table 1.

Table 1. Frequency of bacterial etiologies among sepsis patients

Bacteria	Frequency
Gram-positive bacteria	**103 (57.5%)**
Basil	**13 (12.6%)**
Enterococcus faecalis	4 (3.96%)
Streptococcus spp	3 (2.91%)
Corynebacterium amycolatum	2 (1.94%)
Bacillus megatorium	1 (0.97%)
Brevibacterium spp.	1 (0.97%)
Brevibacil brevis	1 (0.97%)
Corynebacterium bovis	1 (0.97%)
Coccus	**90 (87.4%)**
Staphylococcus hominis	30 (29.13%)
Staphylococcus haemolyticus	18 (17.48%)
*Staphylococcus aureus**	16 (15.53%)
Staphylococcus epidermidis	15 (14.56%)
Staphylococcus spesies lain	9 (8.74%)
Enterococcus faecum	1 (0.97%)
Micrococcus lylae	1 (0.97%)
Gram-negative bacteria	**76 (42.5%)**
Escherichia coli[#]	30 (39.47%)
Acinetobacter spp.	13 (17.09%)
Klebsiella pneumoniae[+]	9 (11.84%)
Pseudomonas spp	5 (6.58%)
Enterobacter spp	4 (5.26%)
Salmonella spp	3 (3.95%)
Empedobacter brevis	2 (2.63%)
Burkholderia cepacian	2 (2.63%)
Klebsiella oxytoca ESBL	2 (2.63%)
Pantoea agglomerans	1 (1.31%)
Proteus vulgaris	1 (1.31%)
Providencia rettgeri	1 (1.31%)
Cedecea lapagei	1 (1.31%)
Raoultella ornithinolytica	1 (1.31%)
Stenotrophomonas maltophilia	1 (1.31%)

*5 from 16 *Staphylococcus aureus* were MRSA, [#]23 from 30 isolate E. Coli were *Escherechia coli* ESBL 23,[+]3 from 9 isolates *Klebsiella pneumonia* were *Klebsiella pneumoniae* ESBL

This study showed that there was Multi-Drug Resistant Organism (MDRO) isolated from the patient. Methilcillin Resistance *Staphylococcus aureus* (MRSA) was isolated from gram-positive bacteria. It

was 31.25% of all the *Staphylococcus aureus* species. *Escherechia coli* ESBL was 76.66% from all *Escherechia coli* isolated. It means almost all *Escherechia coli* species isolated from the Internal Medicine Ward produced ESBL. *Klebsiella pneumoniae* was 33.33% and all isolates of *Klebsiella oxytoca* were producing ESBL.

Table 2. Frequency of multi-drug resistance organism among sepsis patients

Bacteria	Frequency
Methilcillin Resistance Staphylococcus aureus	5 (31.25%)*
Escherichia coli ESBL	23 (76.66%)*
Klebsiella pneumoniae ESBL	3 (33.33%)*
Klebsiella oxytoca ESBL	2 (100%)*
Total	43

*from the same species which was isolated

DISCUSSION

In previous studies, the incidence of gram-positive infection was higher than gram-negative bacteria in bacterial sepsis. There was a different pattern from the past when the highest incidence of bacterial sepsis was among the gram-negative bacteria (Martin, 2012; Mayr, et al., 2014; Ramachandran, 2014). The predominant species of gram-positive bacteria was *Staphylococcus hominis*. *Staphylococcus hominis* is commensal that usually infects immunocompromised patients such as cancer or HIV and has been associated as a causal agent of bacteremia, septicemia, and endocarditis (Mendoza-Olazarán., et al., 2013). The commensal bacteria can contaminate blood culture due to inappropriate disinfection procedure of phlebotomy, but it can also be bacteremia. Clinical assessment must be considered in differentiating between contamination and bacteremia, but a microbiological method can be performed. In a previous study by (Osaki, et al., 2020) Time to Positivity (TTP) method can be used to differentiate between bacteremia and contamination. TTP has shown that was bacteremia when the time from the start of blood culture to the detection of positivity test was shorter than it was when contamination occurred (Osaki et al., 2020). Other species in gram-positive bacterial sepsis were *Staphylococcus haemolyticus, Staphylococcus aureus*, and *Staphylococcus epidermidis*. The previous study by Bramantono, (2010) reported that the bacterial pattern was CoNS (coagulase-negative *Staphylococcus*), *Staphylococcus spp*, and *Streptococcus*. In 2012, CoNS (coagulase-negative *Staphylococcus), Staphylococcus aureus, Streptococcus, Corynaebacterium* and *Enterococcus* (Vitanata, et al., 2012). It was indicated that there was not much difference in bacterial patterns in Internal Medicine Wards in 2010, 2012 and 2016. *Staphylococcus hominis, Staphylococcus haemolyticus*, and *Staphylococcus epidermidis* as the most predominant species found in this study were coagulase-negative *Staphylococcus* (CoNS) group (Becker, et al., 2014). CoNS also relates to indwelling medical devices and nosocomial infection. Among CoNS, *Staphylococcus hominis* is one of the three most frequently identified isolates from the blood of neonates and immunosuppressed patients (Mendoza-Olazarán, et al., 2013).

The most frequently gram-negative bacterial infection in 2016 was *Escherichia coli, Acinetobacter spp. Klebsiella pneumonia* and *Pseudomonas spp*. In 2010, gram-negative bacterial infections were *Klebsiella spp, Escherechia coli, Acinetobacter spp, Enterobacter spp*, and *Pseudomonas spp*. Meanwhile, in 2012, *Acinetobacter spp, Eschericia coli, Pseudomonas spp, Acinetobacter baumanii, Pseudomonas aeruginosa, Enterobacter cloacae* (Vitanata, et al., 2012). The most predominant gram-negative bacterial infection in the Internal Medicine Wards was *Escherichia coli* (30 isolates). *Escherichia coli* is one of the most commonly isolated bacteria in the bloodstream and is most frequently isolated in adult patients with bacteremia. *Escherichia coli* is also associated with the severity and mortality of sepsis. Even though it is commensal bacteria in gastrointestinal, some strains are pathogenic (Mora-Rillo, et al., 2015).

In this study, from 179 blood cultures, there were 43 cultures found with multidrug-resistant organisms. There were *Methilcillin Resistance Staphylococcus aureus* and Extended Beta-Lactamase

producing bacteria. There were 5 MRSA which were identified from 16 species of *Staphylococcus aureus*. Another study reported that 39% of sepsis patients with gram-positive bacterial infection was MRSA (Yilmaz, et al., 2016). The prevalence of MRSA may different around the world. A review of 15 studies reported about 13 and 74% of *Staphylococcus aureus* infections are MRSA. The common sites of MRSA colonization are the anterior nares and the throat. It can develop an MRSA invasive infection and bacteremia. MRSA is related to healthcare-associated bacteremia. Patients with MRSA related to the healthcare-associated bacteremia frequently have comorbidities such as diabetes, decubitus ulcers, chronic renal disease, stroke, or dementia (Hassoun, et al., 2017).

This study also found that almost all *Escherichia coli* isolated were producing ESBL. It reached 76.66%. These data were similar to the previous study reported by (Irawan, et al., 2012), during January 1 - June 30, 2011, in which 64 patients in Internal Medicine Inpatient Ward of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia were found to be infected with ESBL (Irawan, et al., 2012). (Fitri, et al.,(2015) also reported that 27 of 36 *Escherichia coli* were producing ESBL in the same internal medicine inpatient ward (Fitri, et al., 2015). Other specific MDRO found in this study were *Klebsiella pneumonia* ESBL and *Klebsiella oxytoca* ESBL. A previous study by Bramantono, (2012) reported that MDRO in Internal Medicine Ward of Dr. Soetomo Hospital were *Acinetobacter baumanii*, *Klebsiella pneumonia, MRSA,* and *Pseudomonas* (Vitanata, et al., 2012). The primary source of bacteremia may be different between the pathogens. *Escherichia coli* was mostly found in urinary tract infection. *Klebsiella pneumoniae* was associated with surgical site infection (SSI), lower respiratory tract infection (LRTI) and unknown origin (Sakellariou, et al., 2016).

In some studies, MDRO infection is an independent risk factor for mortality, whereas in others it is a risk factor for inappropriate antibiotic therapy being the independent risk factor mortality. Besides, MDRO infection patients often have some comorbidities and a longer medical history (Capsoni, et al., 2019). The important thing in bacterial sepsis therapy was antibiotics. The use of inappropriate antibiotics was high and it contributes to developing bacterial-resistance. MDRO infection and inappropriate empirical antibiotic therapy are greatly correlated one to the other (Hadi, et al., 2013; Capsoni, et al., 2019). Some factors also reported as risk factors for MDRO infection such as nursing home, hospitalization for ≥2 days in the preceding 90 days, antimicrobial therapy in the preceding 90 days, home infusion therapy (including fluid or antibiotics), home wound care, indwelling urine catheter, indwelling intravascular medical devices, chronic renal failure, chronic dialysis at least during the prior 30 days, short hospital attendance for infusion therapy or blood transfusions, and immune-compromised patient (Capsoni, et al., 2019).

This study had limitations. It was performed retrospectively and did not assess the sensitivity of antibiotics for each bacterial species. The study only analyzed the patients in internal medicine inpatient ward which may not represent all bacterial patterns in Dr. Soetomo Hospital. We suggest to analyze the bacterial pattern, including the sensitivity of antibiotics for further research.

CONCLUSION

Gram-positive bacterial infection is the most predominant in bacterial sepsis. The species is *Staphilococcus hominis*. The most frequent gram-negative bacterial infection was *Escherichia coli*. Almost all infections of *Escherichia coli* produced ESBL. The MDRO in the gram-positive bacteria was the MRSA and in the gram-negative bacteria were *Escherichia coli ESBL, Klebsiella pneumonia ESBL,* and *Klebsiella oxytoca ESBL*. The bacterial pattern is important as a consideration in therapeutic antibiotic decisions. Antibiotics as an important therapy for bacterial sepsis should be used wisely to prevent bacterial resistance.

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Conflict of Interest
All authors declare that the research was conducted without any commercial relationship that could be considered as a potential conflict of interest.

Ethics Consideration

This study was approved by the Research and Ethical Committee of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia approval No. 645/Panke.KKE/XI/2017, approved on November 17, 2017.

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Author Contribution

IDT involved in conceptualization, collecting data, statistical analysis, and writing manuscript. MR involved in conceptualization, review, and supervision. JN involved in conceptualization, data review, and supervision.

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