Research Article

Microbial and Resistance Profile in Isolate from Adult Sepsis Patients: An Observational Study at an Indonesian Private Hospital during 2009-2012

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ABSTRACT

Sepsis is a systemic infection with a high mortality rate. The common pathogen that is found in sepsis is a bacterial pathogen, therefore, appropriateness in antibiotic use is very important to decrease the mortality and morbiditys rate in patients with sepsis. The selection of antibiotics requires information about the location of source infection, the common pathogen that develops into an infection, and the local sensitivity pattern of antibiotics. This study aimed to analyze the pattern of the infection source, the organism isolated from various specimens, and the local resistance of antibiotics in adult patients with sepsis in order to support the rational of antibiotics use in septic patients. An observational retrospective study was conducted at a Bandung private hospital in Indonesia from March to May 2012. Data were collected from the hospital medical record department on the adult patient population diagnosed with sepsis during January 2009-March 2012. Thirty-nine patients met the criteria as subject population with 67% on the mortality rate. Respiratory source infection (36%) was the highest source infection that developed to sepsis in the subject population. Microbial culture showed that only 50% tested positive. *Escherichia coli, Streptococcus viridans*, and *Candida sp* were the highest microbials that were detected in culture. Of the subject population, 37.14% showed a level of antibiotic resistance ≥50%, there were levofloxacine, ceftriaxone, doripenem, ciprofloxacine, cefotaxime, cefepime, gentamiycine, and canamycine. A policy on the use of antibiotics with a high resistance level and a collaboration among medical doctors, clinical pharmacists, microbiologists and nurses are needed to increase the rational use of antibiotics in patients with sepsis.

Keywords: Antibiotic resistance, bacteremia, sepsis.

INTRODUCTION

Sepsis is a systemic inflamatory response syndrome that is caused by an infection[1]. Around the world, 13 million people have sepsis each year and as many as 4 million people have died from sepsis [2]. In 1996, there were 4.774 patients admitted to a teaching hospital in Surabaya, Indonesia and 504 patients were diagnosed with sepsis, with a mortality rate of 70.2% [3]. In another study at a teaching hospital in Yogyakarta, Indonesia, there were 631 cases of sepsis in 2007, with a 48.96% mortality rate[4].

Gram-negative bacteria is the major pathogen in the septic patient, but since 1987 until 2000, Gram-positive bacteria has been the major cause of sepsis with an increasing rate of 26.3%[5]. A study at an Indonesian teaching hospital reported that *Staphylococcus coagulase negative, Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* were the high organisms that were detected from various specimens in adult septic patients[4]. In addition to bacteria, *Candida sp* is another organism that was commonly found in septic patients [6].

Therapeutic management of sepsis, severe sepsis, and septic shock requires a systematical approach which combines an accurate diagnosis, rationality of antibiotic use, as well as a rapid and right treatment[7]. A retrospective study demonstrated that the appropriateness of antibiotic therapy in septic patients can reduce the mortality rate[8]. It shows the importantance of antibiotics selection in septic patients, therefore a systematic approach of antibiotic selection is needed by considering the location of infection sources, the common pathogen that develops to sepsis, and the local pattern of antibiotic sensitivity[6]. This study aimed to analyze the pattern of the infection source, to isolate the organism from various specimens and to identify the antibiotics that are locally resistant in the adult septic patients so as to support the rational use of antibiotics in sepsis patients.

MATERIALS AND METHODS

An observational retrospective study was conducted in a Bandung private hospital in Indonesia. The data were collected from the medical record department with the adult population of sepsis patients who were hospitalized from January 2009 to March 2012. Inclusion criteria of the subject population were adult sepsis patient (15-50 years old) who have been diagnosed by a medical doctor and have been admitted to the hospital from January 2009 to March 2012. The data that were collected included identity, diagnosis, comorbidities, source of infection, results of microbial culture, results of antimicrobial sensitivity testing, antibiotic use, length of stay, and clinical outcome. The various culture specimens were processed according to the Minimum Inhibitory Concentration methods in the hospital microbiology laboratory [9]. No growth in the inoculated blood culture media indicated a negative result.

RESULTS AND DISCUSSION

A total of 106 patients, 48 males and 58 females, were diagnosed with sepsis during the study period with a mortality rate of 62.12%. The highest mortality rate was found in the age group ≥65 years. Incidence of mortality in patients diagnosed with sepsis during the study period can be observed in Figure 1.

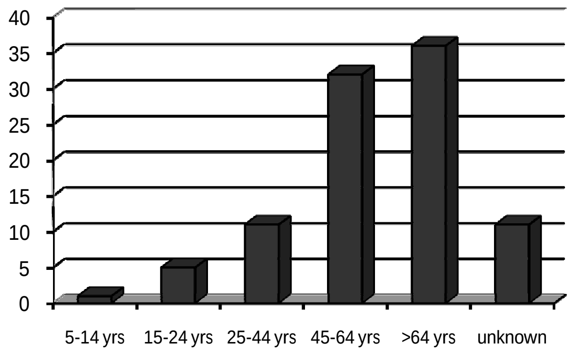

Figure 1 : Percentage of mortality incidence according to age group of sepsis patients during 2009 January- 2012 March at an Indonesian private hospital (*n* = 106)

The influence of gender on the incidence and mortality rate in sepsis patients is still under debate [10]. The study demonstrated a higher incidence of sepsis in men compared to women [5,11,12], but the other study had conflicting results [3,13,14]. In terms of mortality rate, Schroder, et al show a higher mortatlity rate in men than in women[13], but the other studies demonstrated the contrary result[3,13,14]. Although still in debate, a study by Adrie et al. concluded that, in a group of severe sepsis patients of 50 years of age, women have a lower mortality risk than men[15]. The differences of incidence and mortality rate between male and female is due to hormonal and non-hormonal factors that influence the immune system. Women have more estrogen production than men, which influences greater activity of the immune system[10]. Increasing age and body mass index (BMI) in women can affect the production of estrogen by increasing aromatase activity in adipose tissue, and increasing estrogen, which provides better protection through the action of the immune system [10]. Women also showed higher secretion of cytokines by peripheral blood mononuclear cells [10]. Other factors that influenced the immune system are non-hormonal factors such as the production of interleukin-6 and LPS-stimulated tumor necrosis, social factors, economic factors, levels of physical activity, the source of infection, and hormonal modification factors [10,15-17].

The study showed that patients in the age group of 65 years have the highest mortality rate. Similiar results were also shown by several studies[3,11,12,14]. The high incidence of sepsis in elderly patients is affected by aging factors that cause the decline in body systems such as metabolism, cardivascular, visual, genitourinary, immune, nervous system, and drug response. The elderly patient also presents with many symptoms, thus affecting the diagnosis and making it more difficult to make an early diagnosis and to provide therapeutic management [18].

Characteristics of the subject population

Out of 106 patients, 39 met the criteria as a subject population, with a mortality rate of 66.6%. The characteristics of the subject population can be observed in Table 1.

Table 1: Characteristics of the subject population (*n* = 39)

Characteristic	Quantity (%)
Ages	
18-44	13 (33)
45-59	26 (67)
Clinical outcomes	
Died > 48 hours	15 (39)
Died < 48 hours	11 (28)
Not recovered	1 (3)
Recovered	1 (3)
Improvement	8 (20)
Unknown	3 (7)

Source of infection

There were five sites of infection that developed into sepsis, of which 9 patients had an unknown source of infection. Respiratory tract infection is the most common source of infection that developed to sepsis in the subject population, and pneumonia is a major complication from respiratory tract infection. The frequency of infection sites that developed into sepsis is shown in Table 2.

Table 2. Infection site that can develop to sepsis (*n*=42)

No	Infection site	Quantity (%)
1	**Respiratory tract**	**15 (35.70)**
	CAP (*Community Acquired Pneumonia*)	4 (9.52)
	HAP (*Hospital-acquired pneumonia*)	3 (7.14)
	Tuberculosis	3 (7.14)
	Bronchopneumonia	2 (4.76)
	Pneumonia	2 (4.76)
	HCAP (*Healthcare associated pneumonia*)	1 (2.38)
2	**Intra-abdominal**	**11 (26.18)**
	Abdominal infection	4 (9.55)
	Gastroenteritis	3 (7.14)
	Sepsis *E. coli*	2 (4.76)
	Abdominal tuberculosis	1 (2.38)
	Candidiasis gastrointestinal	1 (2.38)
3	**Skin and soft tissue**	**5 (11.90)**
	Abscess	2 (4.76)
	Cellulitis	1 (2.38)
	Fungal infection	1 (2.38)
	Others	1 (2.38)
4	**Urinary tract**	**2 (4.76)**
	UTI (*Urinary Tract Infection*)	2 (4.76)
5	**Unknown**	**9 (21.43)**

The study shows that respiratory infection is the most common infection that develops to sepsis, with the highest incidence being pneumonia. Other studies show the same results[11,12,19]. The common organisms isolated from patients with respiratory tract infections are *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Pseudomonas sp*, and *Haemophilus sp* [20,21]. Another site of infection that leads to sepsis is intrabdominal infection. Intra-abdominal sepsis usually occurs after trauma or surgical resection, or intrinsic disease of the intestine, which includes appendicitis, peritonitis, diverticulitis or biliary tract infection, cholecystitis, and cholangitis [22]. The common organisms isolated from patients with intra-abdominal infections are *Staphylococcus aureus*, *Streptococcus group D*, *Escherichia coli,* and *Candida sp* [21]. Intravascular catheter-related bacteremia can be set as the source of infection when the patient does not know the source of sepsis infection [23]. The common organisms isolated from the blood specimen are *Methicillin-Resistant Staphylococcus Aureus* (MRSA), *Staphylococcus aureus*, *Streptococcus pneumoniae, Escherichia coli, Klebsiella*, and *Proteus* [24].

Microbial culture and susceptibility pattern

Twenty subjects (51.28%) had the microbial culture from various specimens, of which 50% were positive results. Thirty-four organisms were detected from the various specimens, such as blood, sputum, urine, pus, and ascites fluid. *Escherichia coli, Streptococcus viridans*, and *Candida sp.* were the highest organisms detected. The pattern of the organisms isolated from the various specimens can be observed in Table 3.

Table 3: Organisms isolated from the various specimens (*n* = 68)

No	Organism	%
1	*Escherichia coli*	4.41
2	*Streptococcus viridans*	4.41
3	*Candida sp.*	4.41
4	*Streptococcus pneumoniae*	2.94
5	*Streptococcus pyogenes*	1.47
6	*Staphylococcus aureus*	1.47
7	*Staphylococcus epidermidis*	1.47
8	*Pseudomonas aeruginosa*	1.47
9	*Pseudomonas oryzihabitans*	1.47
10	*Klebsiella pneumoniae*	1.47
11	*Enterobacter cloacae*	1.47
12	*Acinobacter baumanii*	1.47
13	Fungi	1.47
14	Gram positive bacterial	11.76
15	Gram negative bacterial	8.82
16	Negative results	50

The study shows that *E. coli* is the most common organism detected from the microbial culture. Vincent et al, demonstrated the same results, with most microorganisms in Europe septic patients being the bacteria *Escherichia coli* and *Streptococcus viridans*, and the fungi *Candida sp* [12]. *Escherichia coli* is a bacteria that commonly causes intestinal and extraintestinal infections, including Gram-negative extraintestinal infections such as urinary tract infections, neonatal meningitis, and septicemia.

Contamination of extraintestinal pathogenic *E. coli* (ExPEC) is usually due to contamination of the urinary catheter or other catheters [25]. In addition to *E. coli*, *Candida* species, especially *C. albicans* is a normal flora of the human body and can be found in the respiratory tract, gastrointestinal tract, urinary tract, skin, and mucous membranes. In patients who were hospitalized with low immune system, *Candida* can become opportunistic pathogens that cause infections and develop into a systemic infection [26].

Two *Streptococcus* species found in an isolated organism were *Streptococcus viridans* and *Streptococcus pneumonia*. *Streptococcus viridans* is part of the normal microbial flora in humans, which are found in the oral cavity, upper respiratory tract, female genital tract, gastrointestinal tract, and skin. *Streptococcus viridans* can cause endocarditis, meningitis, and pneumonia, which can be life-threatening. The study shows an increase in bacteremia cases caused by *Streptococcus viridans* during 1972-1989 [27].

The other *Streptococcus* species that was detected in an isolated organism is *Streptococcus pneumoniae*. *Streptococcus pneumoniae* is a Pneumococcus bacteria that can lead to infection, such as pneumonia, meningitis, endocarditis, septic arthritis, osteomyelitis, brain abscess, and peritonitis. The mortatlity rate in adult patients with pneumococcus pathogens achieved 14-42%, with the common disesase being pneumonia, meningitis, and upper respiratory tract infection [28]. Knowledge of the common pathogens that develop into sepsis based on the site of infection can help us in choosing the appropriate antibiotics and improving the quality of life of septic patients.

Pattern of microbial resistance and antibiotic use

We conducted susceptibility tests from the organism that was detected from the various specimens, and 22 antibiotics showed a resistance level <50% and 19 antibiotics showed a resistance level ≥50%. The antibiotic resistance pattern is shown in Table 4.

Table 4: The level of antibiotic resistance based on susceptibilty test of the subject population

No	Antibiotics	N	S	I	R	Eficacy (%)	Resistance (%)
1	Clindamycin	4	4	0	0	100	0
2	Linezolid	5	5	0	0	100	0
3	Cefoxitin	1	1	0	0	100	0
4	Tobramycin	2	2	0	0	100	0
5	Doxycycline	1	1	0	0	100	0
6	Netylmycin	1	1	0	0	100	0
7	Tigecycline	9	7	1	1	89	11
8	Chlorampenicol	12	9	1	2	83	17
9	Amikacin	9	5	2	2	78	22
10	Ampicillin/sulbactam	11	5	3	3	73	27
11	Tazobactam / piperacillin	10	7	0	3	70	30
12	Amoxicillin	3	2	0	1	67	33
13	Imipenem	9	6	0	3	67	33
14	Meropenem	12	7	1	4	67	33
15	Cefixime	3	0	2	1	67	33
16	Moxifloxacin	3	2	0	1	67	33
17	Erythromysin	6	4	0	2	67	33
18	Oxacillin	3	0	2	1	67	33
19	Vancomycin	3	2	0	1	67	33
20	Cefoperazone	5	2	1	2	60	40
21	Ceftazidime	10	4	2	4	60	40
22	Cephalotin	9	4	1	4	56	44
23	Amoxicillin / clavulanic acid	10	5	0	5	50	50
24	Cefepime	10	5	0	5	50	50
25	Doripenem	4	2	0	2	50	50
26	Ceftriaxone	11	4	1	6	45	55
27	Aztreonam	7	2	1	4	43	57
28	Penicillin	7	3	0	4	43	57
29	Cefotaxime	12	4	1	7	42	58
30	Gentamycin	10	4	0	6	40	60
31	Levofloxacin	13	2	3	8	38	62
32	Ciprofloxacin	11	2	2	7	34	64
33	Cotrimoxazole	11	2	2	7	36	64
34	Ampicillin	11	3	0	8	27	73
35	Tetracyclin	11	2	0	9	18	82
36	Norfloxacin	2	0	0	2	0	100
37	Ofloxacin	1	0	0	1	0	100
38	Kanamycin	1	0	0	1	0	100
39	Cefprozil	1	0	0	1	0	100
40	Carbenicillin	1	0	0	1	0	100
41	Ticarcillin/ clavulanic acid	1	0	0	1	0	100

* N: number of susceptibility test; S: sensitive; I: intermediate; R: resistant; Efficacy (%) = (S+I)/N x 100%;Resistance (%) = R/N x 100% [3]

The increased resistance is a result of many factors, but the foremost cause is the overall volume of antibiotic consumption [29], therefore the high use of antibiotics should be monitored for their level of resistance. The study shows that meropenem still has a high efficacy of 66.67%, but levofloxacin and ceftriaxone have a low efficacy of 38% and 45%, respectively. Although the resistance level of meropenem is still low, meropenem should be used strictly. The use of the antibiotic and its level of resistance must be monitored regularly in order to prevent the development of resistance to meropenem. Meropenem is a suitable choice for the indication of sepsis with broad spectrum activity against Gram-negative and Gram-positive culture[30].

A total of 31 antibiotics were admistered to the subject population with meropenem, levofloxacine, and ceftriaxone being the three major ones. Based on the sensitivity test from the subject population specimens, eight antibiotics that demonstrated a resistance level ≥50% were levofloxacine, ceftriaxone, doripenem, ciprofloxacine, cefotaxime, cefepime, gentamiycine, and canamycine. The pattern of antibiotic use with their resistance level at an Indonesian private hospital 2008-2012 can be observed in Table 5.

The antibiotics which have high resistance levels were levofloxacin, ceftriaxone, doripenem, ciprofloxacin, cefotaxime, cefepime, gentamycin, and canamycin. The highly used antibiotics with high resistance levels required a policy to prevent the development of resistance. Seven strategies for antibiotic resistance prevention, as suggested by Kollef, 2005, include: (1) Creating formal protocol and guidelines; (2) Hospital formulary restriction; (3) Use of narrow spectrum antibiotics; (4) Combination antibiotic therapy; (5) Shorter courses of antibiotic treatment; (6) Antibiotic heterogeneity; and (7) Optimizing pharmacokinetic/ pharmacodynamic principles[30]. There are three strategies in antibiotic heterogeneity: antibiotic cycling or antibiotic rotation, scheduled antibiotic changes, and antibiotic mixing. Antibiotic cycling is a fixed pattern for the predominant use of antibiotic class or classes, followed by their repeated removal and reintroduction over time. Its strategy differs from a scheduled antibiotic change. In a scheduled antibiotic change, changing of antibiotic is based on the changing patterns of antimicrobial sensitivity and is not simply time based. The other strategy is antibiotic mixing. Antibiotic mixing is a strategy whereby all or most available antimicrobial classes are employed to minimize undue presure for the emergence of resistance from having a single or limited number of antibiotic class available[31].

The most successful strategy to combat antibiotic resistance is multidisciplinary, involving the cooperation of the pharmacists, the infection control staff, the nursing staff, the treating physicians, as well as the microbiology laboratory and infectious disease consultants. Such programs should also focus on promoting infection control practices and employing rational antibiotic utilization aimed at minimizing future emergence of resistance [32].

Table 5: Pattern of antibiotic use with their resistance level at an Indonesian private hospital, 2009-2012

No	Antibiotics	Level of use (%)	Resistance level (%)
1	Meropenem	14.29	33
2	Levofloxacin	14.29	62
3	Ceftriaxone	10.48	55
4	Ceftazidime	3.81	40
5	Doripenem	3.81	50
6	Moksifloxacin	3.81	33
7	Ciprofloxacin	3.81	64
8	Ethambutol	3.81	-
9	INH	3.81	-
10	Pyrazinamide	3.81	-
11	Rifampicin	3.81	-
12	Fluconazole	3.81	-
13	Piperacillin/ tazobactam	2.86	30
14	Cefpirome	2.86	-
15	Cefotaxime	1.90	58
16	Chloramphenicol	1.90	17
17	Clindamycin	1.90	0
18	Metronidazole	1.90	-
19	Teicoplanin	1.90	-
20	Azithromycin	0.95	-
21	Cefepime	0.95	50
22	Cefixime	0.95	33
23	Cefoperazone	0.95	40
24	Cefoperazone/ Sulbactam	0.95	-
25	Ertapenem	0.95	-
26	Gentamicin	0.95	60
27	Imipenem	0.95	33
28	Kanamycin	0.95	100
29	Ketoconazole	0.95	-
30	Pyrimethamine	0.95	-
31	Terbinafine	0.95	-

CONCLUSION

Respiratory infection is the most common infection that is found in sepsis patient. *E coli*, *Streptococcus viridans,* and *Candida sp* is the most widely isolated organisms that were detected in septic patients. A policy of antibiotic use with a high resistance level and a collaboration among medical doctors, clinical pharmacists, microbiologists and nurses are needed in order to increase the rational use of antibiotics and to prevent the development of resistance in sepsis patients.

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REFERENCES

1. Levy MM, MP Fink, JC Marshall, E Abraham, D Angus, D Cook, J Cohen, SM Opal, JL Vincent, G Ramsay, 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med, 31, 2003, 1250-53.
2. Levy MM, Introduction. In : R Daniels, T Nutbeam, ed. ABC of Sepsis, Wiley-Blackwell, Chichester, 2010, 1.
3. Sudjito, Usman H, Joewono S, Suharto, Eddy S, The Prognostic Factors in Sepsis, Folis Medica Indonesiana, XXXIV, 1998, 14-20.
4. Pradipta IS. Antibiotic Use Evaluation at Ward of Internal Medicne dr. Sardjito Hospital November-December 2008 [Thesis]. Faculty of Pharmacy, Universitas Gadjah Mada, Indonesia, 2009, 48-55.
5. Marti GS, DM Mannino, S Eaton, M Moss, The Epidemiology of Sepsis in the United States from 1979 through 2000, New Engl J Med, 348, 2003, 1546–50.
6. Kang-Birken SL, JT Dipiro, Sepsis and Septic Shock, In : JT Dipiro, ed, Pharmacotherapy A Pathophysiologic Approach, Seventh Edition, McGraw-Hill Companies, United States of America, 2008, 1943-1944.
7. Bochud PY, T Calandra, Pathogenesis of Sepsis : New Concepts and Implications for Future Treatment, BMJ, 326, 2003, 262-266.
8. Sutton SS, Sepsis and Septic Shock. in Chisholm Burns, Marie A, Wells, Barbara G, Schwinghammer, Terry L., Malone, Patrick M., Kolesar, Jill M., Rotschafer, John C., and DiPiro, Joseph T, ed. Pharmacotherapy Principles and Practice, McGraw-Hill, New York, 2008, 1190-1192.
9. Clinical and Laboratory Standard Institute, Performance standard for Antimicrobial Susceptibility testing. Fifteenth Informational Supplement, CLSI- M110-S15 Villanova, PA, 2005.
10. Berkowitz DM, GS Martin, Sepsis and Sex: Can We Look Beyond Our Hormones?, CHEST, 132, 2007, 1752-1757.
11. Angus DC, RS Wax, Epidemiology of Sepsis: An Update, Crit Care Med, 29, 2001, S109-S114.
12. Vincent JL, Y Sakr, CL Sprung, VM Ranieri, K Reinhart, H Gerlach, R Moreno, J Carlet, JRL Gall, D Payen, Sepsis in European Intensive Care Units: Results of SOAP study, Crit Care Med, 34, 2006, 344-51.
13. Schröder, JV Kahlke, KH Staubach, P Zabel, F Stüber, Gender Differences in Human Sepsis, Arch Surg, 133, 1998, 1200-5.
14. Eachempati SR, L Hydo, PS Barie, Gender-based Differences in Outcome in Patients with Sepsis, 1999, Arch Surg, 1342-47.
15. Adrie C, Azoulay E, Francais A, Clec'h C, Darques L, Schwebel C, et al. Influence of gender on the outcome of severe sepsis: A reappraisal, CHEST, 132, 2007, 1786-93.

16. Danai, Pajman A, Marc Mass, David MM, Greg SM, The Epidemiology of Sepsis in Patients With Malignancy, CHEST, 126, 2006, 1432-1440.

17. Michael C, Reade, Angus DC, Epidemiology of sepsis and Non-infectious SIRS. In: Cavaillon, Jean-Marc, Chrisptophe Adrie, ed, Sepsis and Non-Infection Systemic Inflammation, From Biology to Critical Care, Wiley-VCH Verlag GMbH & Co.KGaA, Weinheim, 2009, 13-27.

18. Destarac LA, EW Ely, Sepsis in Older Patients: An Emerging Concern in Critical Care, Adv Sepsis, 2, 2002, 15-22.

19. Engel C, FM Brunkhorst, HG Bone, R Brunkhorst, H Gerlach, S Grond, et al., Epidemiology of sepsis in Germany: results from a national prospective multicenter study, Intensv Care Med, 33, 2007, 606-618.

20. Kollef MH, Bench to bedside review: Antimicrobial strategies aimed at preventing the emergence of bacterial resistance in the intensive care unit, Crit Care, 9, 2005, 459-464.

21. Volakli E, C Spies, A Michalopoulos, ABJ Groeneveld, Y Sakr, JL Vincent, Infections of respiratory or abdominal origin in ICU patients: what are the differences?, Crit Care, 14, 2010, R32.

22. Podnos YD, JC, Jimenez, SE Wilson, Intra-abdominal Sepsis in Elderly Persons, Clin Infect Dis, 35, 2002, 62-68.

23. Vallés, J, C León, F Alvarez-Lerma, Nosocomial Bacteremia in Critically Ill Patients: A Multicenter Study Evaluating Epidemiology and Prognosis, Clin Infect Dis, 24, 1997, 387-88.

24. Ramphal, R. The Sepsis Syndrome. In: F.S. Southwick. ed, Infectious Diseases in 30 days, McGraw-Hill, New York, 2003, 86-87.

25. Conceição RA, MS Ludovico, Andrade, Yano. Human sepsis-associated Escherichia coli (SEPEC) is able to adhere to and invade kidney epithelial cells in culture, Braz. J. Med. Biol. Res, 45, 2012, 417-24.

26. Singhi S, A Deep, Invasive Candidiasis in Pediatric Intensive Care Units, Indian J. Pediatr, 76, 2009, 1033-44.

27. Tunkel A, KA Sepkowitz, Infections Caused by Viridans Streptococci in Patients with Neutropenia, Clin Infect Dis, 34, 2002, 1524-1529.

28. Dhillon SS, C Watanakunakorn, Pneumococcal Bacteremia Associated with an Infected Central Venous Catheter, CHEST, 117, 2000. 1515-1516.

29. Kotwani, Holloway, Trends in antibiotic use among outpatients in New Delhi, India, BMC Infect Dis, 11, 2011, 99.

30. Roberts JA, CMJ Kirkpatrick, MS Roberts, TA Robertson, AJ Dalley, J Lipman, Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing stimulations and subcutaneous tissue distribution, JAC, 64, 2009,142-50.

31. Kollef MH, Is antibiotic cycling the answer to preventing the emergence of bacterial resistance in the intensive care unit ?, Clin Infect Dis, 43, 2006, S82-88.

32. Kollef MH, Optimizing antibiotic therapy in the intensive care unit setting, Crit Care, 5, 2001, 189-95.

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