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Causative bacterial pathogens of septic patients at emergency department of King Chulalongkorn Memorial Hospital

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Background : *Sepsis is a clinical syndrome associated with a high mortality rate. Antimicrobial therapy is one of the milestones in the treatment of sepsis. Knowing the distribution of pathogens and local susceptibility of antimicrobials would be beneficial for empirical antimicrobial usage.*

Objective : *To determine the prevalence and characteristics of causative bacterial pathogens in culture-positive septic patients admitted to the Emergency Department (ED) of King Chulalongkorn Memorial Hospital (KCMH).*

Study design : *Retrospective descriptive study.*

Setting : *The Emergency Department, KCMH, Bangkok, Thailand.*

Method : *We reviewed medical records and computer databases of adult patients admitted to the ED from January to June 2013 with culture-positive sepsis.*

Result : *This study included 300 culture-positive patients admitted to our ED for sepsis. Gram-negative bacteria were isolated in 251 patients (83.7%) while Gram-positive bacteria were isolated in 87 patients (29%). Among these patients, 204 (68.0%) had only Gram-negative infections; 43 (14.3%) had only Gram-positive infections, while 44 (14.7%) had mixed Gram-*

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positive and Gram-negative infections. Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa were the three most common bacteria isolated from 132 (44%), 57 (19%), and 34 (11.3%) patients, respectively. Third generation cephalosporin resistant E. coli, third generation cephalosporin resistant K. pneumoniae and Acinetobacter baumannii isolates were more common pathogens in healthcare-associated than community-acquired cases (26.5% vs 12.3%, 8.6% vs 2.2%, and 10.5% vs 3.6%; respectively; all p <0.05).

Conclusion : *Gram-negative bacteria were the predominant causative pathogens of sepsis in patients at the ED.E. coli, K. pneumoniae, and P. aeruginosa were the three most common bacterial pathogens. Third generation cephalosporin resistant microorganisms and A. baumanii were found more in healthcare-associated than community-acquired sepsis.*

Keywords : *Sepsis, pathogen, Acinetobacter baumannii, Emergency Department.*

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เหตุผลของการทำวิจัย : *Sepsis เป็นภาวะที่มีอัตราการเสียชีวิตที่สูง ยาต้านจุลชีพเป็นหนึ่งในการรักษาที่มีความสำคัญ ซึ่งการทราบเชื้อก่อโรคและความไวต่อยาต้านจุลชีพจะเป็นประโยชน์ต่อการเลือกใช้ยาต้านจุลชีพแบบคาดการณ์ของผู้ป่วย sepsis ในแผนกฉุกเฉินต่อไป*

วัตถุประสงค์ : *เพื่อศึกษาความชุกและลักษณะของเชื้อก่อโรคที่ให้ผลเพาะเชื้อเป็นบวกในผู้ป่วย sepsis ที่เข้ารับการรักษาในแผนกฉุกเฉิน โรงพยาบาลจุฬาลงกรณ์*

รูปแบบการวิจัย : *การวิจัยพรรณนาแบบย้อนหลัง*

สถานที่ทำการศึกษา : *แผนกฉุกเฉิน โรงพยาบาลจุฬาลงกรณ์*

วิธีการศึกษา : *ทำการเก็บข้อมูลของผู้ป่วย sepsis ที่เข้ารับการรักษาที่แผนกฉุกเฉิน โรงพยาบาลจุฬาลงกรณ์ และให้ผลเพาะเชื้อเป็นบวก ตั้งแต่เดือนมกราคม ถึงเดือนมิถุนายน พ.ศ. 2556 จากเวชระเบียนและฐานข้อมูลคอมพิวเตอร์*

ผลการศึกษา : *จากผู้ป่วย sepsis ที่เข้ารับการรักษาที่แผนกฉุกเฉินและมีผลเพาะเชื้อเป็นบวก 300 ราย พบผู้ป่วยติดเชื้อแบคทีเรียแกรมลบ 251 ราย (ร้อยละ 83.7) และแบคทีเรียแกรมบวก 87 ราย (ร้อยละ 29.0) ซึ่งเป็นการติดเชื้อแบคทีเรียแกรมลบอย่างเดียว 204 ราย (ร้อยละ 68.0) ติดเชื้อแบคทีเรียแกรมบวกอย่างเดียว 43 ราย (ร้อยละ 14.3) และติดเชื้อแบคทีเรียแกรมบวกร่วมกับแบคทีเรียแกรมลบ 44 ราย (ร้อยละ 14.7) เชื้อแบคทีเรียก่อโรคที่พบบ่อยที่สุด 3 ชนิดแรกคือ คือ Escherichia coli พบในผู้ป่วย 132 ราย (ร้อยละ 44) Klebsiella pneumoniae 57 ราย (ร้อยละ 19) และ Pseudomonas aeruginosa 34 ราย (ร้อยละ 11.3) และพบเชื้อ E. coli, K. pneumoniae ที่ดื้อต่อยากลุ่ม third generation cephalosporin และเชื้อ Acinetobacter baumannii ในผู้ป่วย healthcare-associated infection มากกว่าผู้ป่วย community-acquired infection อย่างมีนัยสำคัญทางสถิติ (26.5% vs 12.3%, 8.6% vs 2.2%, และ 10.5% vs 3.6%; ตามลำดับ)*

สรุปผล : *เชื้อก่อโรคส่วนใหญ่ในผู้ป่วย sepsis ที่มารับการรักษาในแผนกฉุกเฉินเป็นเชื้อแบคทีเรียแกรมลบ โดยเชื้อก่อโรคที่พบบ่อย 3 อันดับแรกคือ E. coli, K. pneumoniae, และ P. aeruginosa*

คำสำคัญ : *ภาวะพิษเหตุติดเชื้อ, เชื้อก่อโรค, Acinetobacter baumannii, แผนกฉุกเฉิน.*

Sepsis is defined as infection plus systematic inflammatory response syndrome (SIRS).[1] Sepsis is a major healthcare problem associated with economic burden and high mortality rates (20 - 50%).[2 - 6] Bacteria are the most common causative microorganisms in sepsis. Failure to administer antibiotics to which the pathogens are susceptible is associated with an increase in mortality rate.[7, 8] In addition, time to administer the first dose of appropriate antibiotics has also been shown to be a risk factor for hospital mortality.[9, 10]

Since epidemiological data of infection and susceptibility of bacteria are different in each endemic area, and antimicrobial-resistant bacteria tends to be increasing.[11 - 15] The objective of this study was to determine the prevalence and characteristics of causative bacterial pathogens in patients with culture-positive sepsis at the Emergency Department (ED) of King Chulalongkorn Memorial Hospital (KCMH) during January - June 2013.

Method

In this retrospective study, we reviewed and gathered data from medical records and computerized databases of septic patients consecutively showed up at our ED from January to June 2013. KCMH is a tertiary-care university hospital with 45,000 patient ED visits per year.[16]

The data collected included age, sex, co-morbid diseases, prior exposure to antibiotics, and related laboratory results. Site of infection according to final diagnosis and results of cultures were records. The diagnosis was classified in International Statistical Classification of Diseases and Related Health Problems (ICD-10). Antimicrobial cultures and susceptibility tests in KCMH were performed and interpreted according to Clinical and Laboratory Standards Institute (CLSI) of the United States.[17]

Subjects

This study included patients age ≥ 18 years with sepsis in the ED. In addition, eligible patients met the following criteria: (1) admitted in the hospital, (2) treated with empirical antimicrobials in the ED, and (3) had a positive culture specimen. Patients who were transferred from other institutions with sepsis, already received empirical antimicrobials prior to admission to our ED, or their complete medical history cannot be accessed were excluded. We also excluded patients with common bacterial contamination or colonization unless they were deemed clinically significant by their staff physicians, and those with microbiology proven fungal, viral, and parasitic infections.

Definitions

Sepsis was defined as the presence (probable or documented) infection with more than one of the following clinical finding: body temperature > 38 or< 36°C, heart rate > 90 beats/min, respiratory rate > 20 breath/min, and white blood cell (WBC) count > 12,000 or < 4,000 cell/mm^3 or normal WBC count with > 10% immature form.[18, 19] Severe sepsis was defined as sepsis plus sepsis induced organ dysfunction or tissue hypoperfusion.[18, 20] Septic shock was defined as sepsis-induced hypotension: a systolic blood pressure (SBP) < 90 mm Hg or mean arterial pressure (MAP) < 70 mm Hg or SBP decrease > 40 mm Hg form baseline[18], despite adequate fluid resuscitation (2 liters or 30 ml/kg over 30 min

period), in the absence of other causes for hypotension.[21] Community-acquired infection was defined as an infection present on admission to the hospital or which developed within 48 hours of admission.[9] Healthcare-associated infection was defined as an infection in the patient who had hospitalization for ≥ 2 days in the preceding 90 days, outpatient hemodialysis, home healthcare service, a resident in a nursing home, antibiotic within the previous 30 days from the onset of sepsis or had an immunosuppressive drug.[9, 22]

To ensure that any bacteria isolated were the cause of sepsis that resulted in ED admission, we defined causative bacterial pathogens in sepsis as the bacteria isolated in the cultured specimens collected within 48 hours after admission to the ED[10, 23], unless the medical staff judged and recorded in medical charts that the bacteria were colonizers or contaminants.

Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS version 17, SPSS Co., Ltd., Bangkok Thailand) software. We expressed categorical variables as number (percentage) and median (interquartile range) as appropriate. We compared categorical variables using Chi-square or Fisher's exact test. All tests for significance and resulting *p*-value were 2-sided, with the level of significance set at 0.05.

Result

From 1,112 septic patients admitted to the ED of KCMH between January and June 2013, 472 (42.4%) were culture-positive. Of these patients, 61 were not admitted in the hospital, 39 were not treated with empirical antimicrobials at the ED; 2 denied to receive any treatment; 6 were bacterial colonization; 6 were transferred from other hospitals and had already received antibiotics prior to visit our ED; and 58 had incomplete medical history. Therefore, this study included a total of 300 patients, 138 of them (46%) were community-acquired and 162 (54%) were healthcare associated. Table 1 describes their characteristics on admission to the ED. Median age of these patients were 69.5 (IQR: 56.3 - 79.0) years. Two-third of all patients were over 60 years old. Ninety-seven patients (32.3%) had a history of antibiotic usage within one month prior to the ED admission. According to the stage of severity, 44.3% had sepsis; 36% severe sepsis and 19.7% septic shock. We found that 104 patients (34.7%) were elderly with history of frequent hospital admissions, and 25 patients (8.3%) depended on home healthcare.

Table 2 lists the sites of infection. Of the 300 septic patients, bacteremia were the most common site of infection (43.7%), followed by the urinary tract (43%), and the respiratory tract (31.3%) as shown in Table 2. One-third of all patients had more than one site of infection; 90 (30%), 9 (3%), and 1 (0.3%) patients had 2, 3, and 4 sites of infection, respectively.

From the 300 patients, 1,206 specimens were collected within 48 hours after ED admission. Of these specimens, 429 cultures were positive. Blood were the most common positive culture specimen (44.7%), followed by urine (43%), and sputum (32.7%) as shown in Table 3.

A total of 632 bacteria isolates were identified. Simultaneous growth of at least two organisms took place in 91 patients (30.3%). Gram-negative bacteria

were isolated in 251 patients (83.7%) while Gram-positive bacteria were isolated in 87 patients (29%). Among these patients, 204 (68%) had only Gram-negative infections, 43 (14.3%) had only Gram-positive infections, while 44 (14.7%) had mixed Gram-positive and Gram-negative infections as shown in Table 4.

Table 5 features the microbiology. *Escherichia coli* was the most common isolated Gram-negative bacteria in both community-acquired (42%) and healthcare associated (45.7%) patients, followed by *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Tests for extended-spectrum beta-lactamase (ESBL) was not performed in this study. However, we found third generation cephalosporin (ceftriaxone, cefotaxime or ceftazidime) resistant *E. coli,* third generation cephalosporin (ceftriaxone, cefotaxime or ceftazidime) resistant *K. pneumoniae* were commoner pathogens in healthcare-associated than in community-acquired sepsis (26.5% vs 12.3%, 8.6% vs 2.2%, all p <0.05). There was also higher prevalence of *A. baumanii* in healthcare-associated than in community-acquired cases (10.5% vs 3.6%; respectively).

Table 1. Characteristics of patients on the day of ED admission.

Variable	Number (%)
Gender	
Male	164 (54.7)
Female	136 (45.3)
Medianage (Interquartile) in years	69.5 (56.3 - 79.0)
Underlying comorbidities	
Hypertension	133 (44.3)
Diabetes	98 (32.7)
Cancer	70 (23.3)
Nervous system disease	57 (19.0)
Dyslipidemia	55 (18.3)
Cardiovascular disease	46 (15.3)
Kidney disease	29 (9.7)
Genitourinary disease	26 (8.7)
Infection disease	24 (8.0)
Liver disease	18 (6.0)
Respiratory disease	14 (4.7)
No underlying disease	13 (4.3)
Hematologic malignancy	10 (3.3)
Unknown	7 (2.3)
Systemic lupus erythematous	2 (0.7)
Digestive disease	1 (0.3)

Table 2. Site of infection.

Site of infection[a]	Patient (%)
Bacteremia	131 (43.7)
Urinary tract	129 (43.0)
Respiratory tract	94 (31.3)
Gastrointestinal tract	28 (9.3)
Skin and soft tissue	18 (6.0)
Central nervous system	3 (1.0)
Device	3 (1.0)
Bones and joints	2 (0.7)
Bone marrow	1 (0.3)
Endocarditis	1 (0.3)
Genitalia	1 (0.3)

[a]Some patients had more than one site of infection.

Table 3. Positive culture specimen.

Specimens	Patient[a] (%)
Blood	134 (44.7)
Urine	129 (43.0)
Sputum	98 (32.7)
Pus, Wound	18 (6.0)
Bile	12 (4.0)
Stool	11 (3.7)
Body fluid	9 (3.0)
Tissue	4 (1.3)
Cerebrospinal fluid	3 (1.0)
Ascites fluid	3 (1.0)
Other[b]	8 (2.7)

[a]One patient may had more than one positive culture specimen.

[b]Tip catheter, cervical swab, bone marrow, bronchoalveolar lavage, synovial fluid, bleb

Table 4. Type of causative bacterial pathogens.

Causative bacterial pathogens	Number of patients (%)	CAI (n =138)	HAI (n =162)	P-value[a]
Single bacterial pathogen	209 (69.7)	103 (74.6)	106 (65.4)	0.084
Gram-negative bacteria	167 (55.7)	82 (59.4)	85 (52.5)	0.227
Gram-positive bacteria	36 (12.0)	17 (12.3)	19 (11.7)	0.875
Mycobacteria	6 (2.0)	4 (2.9)	2 (1.2)	0.419
Mixed pathogens	91 (30.3)	35 (25.4)	56 (34.6)	0.084
Mixed Gram-negative and Gram-positive bacteria	44 (14.7)	19 (13.8)	25 (15.4)	0.685
Mixed Gram-negative bacteria	37 (12.3)	11 (8.0)	26 (16.0)	0.034
Mixed Gram-positive bacteria	7 (2.3)	4 (2.9)	3 (1.9)	0.707
Mixed Gram-negative and Mycobacteria	3 (1.0)	1 (0.7)	2 (1.2)	1.000

[a]Comparisons between CAI and HAI; CAI, community-acquired infections; HAI, healthcare-associated infections

Table 5. Bacteria isolates.

Causative bacterial pathogens	Number of patients (%)	CAI (n=138)	HAI (n=162)	P-value[a]
Gram negative bacteria	251 (83.7)	113 (81.9)	138 (85.2)	0.441
Escherichia coli[b]	132 (44.0)	58 (42.0)	74 (45.7)	0.526
Klebsiella pneumoniae[c]	57 (19.0)	27 (19.6)	30 (18.5)	0.818
Pseudomonas aeruginosa	34 (11.3)	13 (9.4)	21 (13.0)	0.335
Acinetobacter baumannii	22 (7.3)	5 (3.6)	17 (10.5)	0.023
Proteus mirabilis[d]	12 (4.0)	8 (5.8)	4 (2.5)	0.143
Haemophilus influenza lactamas	7 (2.3)	3 (2.2)	4 (2.5)	1.000
Others	52 (17.3)	20 (14.5)	32 (19.7)	NA
Gram-positive bacteria	87 (29.0)	40 (29.0)	47 (29.0)	0.996
Coagulase negative staphylococcus	24 (8.0)	10 (7.2)	14 (8.6)	0.657
Enterococcus faecalis	17 (5.7)	8 (5.8)	9 (5.6)	0.928
Staphylococcus aureus	15 (5.0)	8 (5.8)	7 (4.3)	0.559
MSSA	12 (4.0)	6 (4.3)	6 (3.7)	0.777
MRSA	3 (1.0)	2 (1.4)	1 (0.6)	0.596
Enterococcus sp.	11 (3.7)	2 (1.4)	9 (5.6)	0.059
Others	40 (13.3)	18 (13.0)	22 (13.5)	NA

[a]Comparisons between CAI and HAI;

[b]*Escherichia coli* was resistant to either 3rd generation cephalosporin (ceftriaxone, cefotaxime or ceftazidime) 12.3% in CAI, 26.5% in HAI (p-value = 0.002);

[c]*Klebsiella pneumoniae* was resistant to either 3rd generation cephalosporin (ceftriaxone, cefotaxime or ceftazidime) 2.2% in CAI, 8.6% in HAI (p-value = 0.016);

[d]*Proteus mirabilis* were resistant to either 3rd generation cephalosporin (cefotaxime or ceftazidime) 0% in CAI, 0.6% in HAI (p-value = 1.000);

CAI, community-acquired infections; HAI, healthcare-associated infections; MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *S. aureus*; NA: not available

Discussion

To our knowledge, this is the first study of prevalence and characteristics of causative bacterial pathogens of sepsis in ED. in Thailand. Gram-negative bacteria were identified as causative microorganisms in 83.7% of our patients. Studies published in the last 10 years found that Gram-negative bacteria accounted for 47.9 - 62.2% of pathogens of sepsis in Thailand, Canada, United State, and China[9, 10, 24, 25] While other studies reported that more than 40.0 % of causative pathogens were Gram-positive bacteria.[5, 6]

In our population, 57.6% of patients with sepsis were culture-negative, while previous studies reported lower culture-negative rates (41.5 - 55.5%). It may be hypothesized that our high culture-negative rate was at least partly due to possibilities of a milder form of sepsis, prior antimicrobial exposure, sampling error, insufficient volume for blood cultures, poor transport conditions, and slow-growing or fastidious bacteria.

The most common causative microorganisms identified in our patients are *E. coli*, *K. pneumoniae*, and *P. aeruginosa*. These three pathogens, all together, caused septic cases accounted for 75% of our patients. Although we observed similar common causative bacterial pathogens among community-acquired and healthcare associated patients, there were higher prevalence of third generation cephalosporin (ceftriaxone, cefotaxime or ceftazidime) resistant *E. coli*, third generation cephalosporin (ceftriaxone, cefotaxime or ceftazidime) resistant *K. pneumoniae*, and *A. baumanii* in healthcare associated than in community-acquired cases (26.5% vs 12.3%, 8.6% vs 2.2%, and 10.5% vs 3.6%; respectively). Our findings are consistent with other previous studies which show that ESBL-producing *E. coli* and *A. baumanii* were found more frequently in healthcare-associated infection compared with community-acquired infection.[9, 26] Healthcare-associated patients whose identified pathogens were third generation cephalosporin resistant, including *E. coli*, *K. pneumoniae*, and *P. mirabilis* were accounted for 35.7% of all healthcare-associated patients. Meanwhile, the corresponding figure was only 14.5% in community-acquired patients. Our finding reemphasizes the trend of the increasing resistance to antimicrobial therapy especially in healthcare-associated infection.[22, 27] An adequate empirical antibiotic therapy to cover third generation cephalosporin resistant bacteria should be considered in healthcare-associated patients, since these bacteria were identified in more than one-third of this group of patients.

Though, it is still debatable to conclude that the inadequacy of empirical antibiotic therapy is an independent predictor of mortality in sepsis, it has been shown in earlier studies that the mortality rate of bacteremia could be reduced with an adequate use of antibiotics.[28, 29]

Emergency Department is the first place to identify and provide empirical antimicrobial therapy in septic patients came from outside hospital. It was demonstrated that actions implemented in the ED can improve the medical care of patients with sepsis.[30] Together with the knowledge of local antibiotic patterns of use and resistances, our data should be beneficial for empirical antibiotic selection in an effort to improve outcomes in sepsis.

Nevertheless, our study has some limitations. First, since this is a single-center study conducted at the ED, the details of its finding may not be extrapolated to all ED patients in other geographic areas. Second, our data were retrospectively collected and pathogens were only identified in culture-positive patients. Cases with no microbiological isolation were not evaluated. Further studies of culture-negative sepsis would be able to provide more in-depth information to improve knowledge in sepsis, both culture-positive and culture-negative.

Our strength is that we only included microorganisms that were deemed by the medical staff as pathogens since they opposed to colonizers or contaminants.

Conclusion

Gram-negative bacteria were the predominant causative pathogens of septic patients at the ED. (83.7%). *E. coli*, *K. pneumoniae,* and *P. aeruginosa* were the three most common bacterial pathogens. Third generation cephalosporin resistant *E.coli*, third generation cephalosporin resistant *K. pneumoniae* and *A. baumanii* were found in 45.6% of healthcare-associated sepsis and 18.1% of community-acquired sepsis.

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