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ORIGINAL ARTICLE

Isolated pathogens and clinical outcomes of adult bacteremia in the emergency department: A retrospective study in a tertiary Referral Center

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KEYWORDS
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Background: Approximately two-thirds of the patients with severe sepsis or septic shock are first encountered in the emergency departments (EDs) of western countries, in which bacteremia is present in about 50% of patients with severe sepsis. The situation of bacteremia presenting to the EDs in Taiwan is not well documented. The objective of this study was to examine the epidemiology and microbiology of bacteremia in adult patients who visited the ED of a medical center in southern Taiwan.
Methods: A retrospective observational study of the epidemiology and microbiology of bacteremia was conducted in the ED of a medical center involving 6,137 adult patients and 13,903 blood cultures.
Results: A total of 831 consecutive patients with 890 episodes of bacteremia were obtained from January 1 to December 31, 2004, indicating a positive culture rate of 13.5% (1,872/13,903). Among these episodes, 525 (59%) were defined as true community—acquired infections followed by 263 (29.5%) as health care—associated infections and 102 (11.5%) as nosocomial infections. Of the 972 isolates, 289 (29.7%) were gram-positive species and 683 (70.3%) were gram-negative species. Urinary tract infections (32.2%, 287/890) were most common in these patients, with *Escherichia coli* (30.8%, 299/972) being the most common pathogen. Bacteremia caused by *Staphylococcus aureus* was more common in nosocomial than true community—acquired infections (31.3% *vs.* 12%) and had significantly higher possibility of resistance to methicillin in infections not purely acquired from community (odds ratio = 24.92;

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95% confidence interval, 9.88—62.87). The overall crude mortality rate was 21% and nearly half of the mortalities occurred within 3 days of visiting the ED. All patients discharged inadvertently were uneventful ($n = 65$, two lost at follow-up).
Conclusions: Categories of bacteremia acquisition was associated with different distribution of pathogens, antimicrobial resistance, and clinical outcome. Traditional classification might overestimate the problem of drug resistance in community-acquired infections. The concept of health care—associated infection should be introduced to avoid overemphasis of drug-resistant problem in true community—acquired infection.
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Introduction

Fever is usually a sign of infection and is a major complaint of patients admitted to hospital emergency departments (EDs).[1—4] Usually, it takes about 24—48 hours[5] to obtain the blood culture results in this modern environment, where bacterial strains have become more and more antibiotic resistant.[6—8] Thus, ED physicians must identify the clinical and microbiologic features of the febrile patients as soon as possible to offer the most appropriate antibiotics empirically on the limited evidence available. The situation will be more complicated in the ED of tertiary hospitals, which deal with various nosocomial and community-acquired infections. Many studies showed clearly the importance of predicting the pathogenic species and risk factors for antimicrobial resistance[8—10] in the bacteremic patients so that appropriate empiric antibiotics can be administered.[11] However, most of them were either focused on specific species, diseases, and populations or using an old definition of bacteremia acquisition in study design.[12] Before the advent of reappraisal of community-acquired bacteremia advocated by Siegman-Igra et al.,[13] many health care—associated infections that could not be readily classified into either community or hospital-acquired category then were recognized as community acquired thus amplifying the severity of antimicrobial resistance in "true" community-acquired infections. Few large-scale comprehensive studies have had addressed this issue in the field of emergency medicine, particularly in Taiwan. Beside, we were also interested in the outcome of bacteremic patients, especially who were discharged inadvertently from the ED. That was why we conducted this retrospective observational study to describe the epidemiological and microbiologic characteristics of bacteremia in the adult patients admitted to the ED of a medical center in southern Taiwan and to review the blood culture results and the prognoses of these patients.

Materials and methods

Adult patients aged older than 14 years were collected in the study over a 1-year period, from January 1 to December 31, 2004. All cases enrolled were those who were sent to our ED and considered urgent to be planned for check for the causes of febricity. The adult patients were considered to require blood cultures for empiric antibiotic treatment by a consultant or attending physician on duty. This study protocol was approved by the Kaohsiung Veteran General Hospital (KSVGH) Ethics Committee for human investigation. In the study period, 67,240 adult patients visited our ED. Among them, 6,137 adult patients complained of febricity during 7,139 visits, and a total of 13,903 blood cultures were obtained. Those identified with true bacteremia were analyzed including demographic data, underlying diseases, classification of bacteremia acquisition, white blood cell (WBC) counts, etiologies and isolates of bacteremia, antimicrobial susceptibility, and clinical outcome. A blood culture consists of a pair of BACTEC PLUS aerobic/F and anaerobic/F bottles. Cultures were processed using the BACTEC 9240 system (Becton Dickinson, Sparks, MD, USA) and bacterial species identification (ID) and antimicrobial susceptibility test were performed using the BD Phoenix automated microbiology system (Becton Dickinson, Sparks, MD, USA). The Phoenix ID method uses modified conventional, fluorogenic, and chromogenic substrates. The ID side contains 45 wells with dried biochemical substrates and 2 fluorescent control wells. The ID broth was inoculated with bacterial colonies from a pure culture adjusted to a 0.5 McFarland standard by using a CrystalSpec nephelometer (BD Diagnostics Becton Dickinson, Sparks, MD, USA), according to the manufacturer's recommendations. The antimicrobial susceptibility test side of the combination panel contains up to 84 wells with dried antimicrobial panels and 1 growth control well. The assay is a broth-based microdilution test. The system uses a redox indicator for the detection of organism growth in the presence of an antimicrobial agent. The isolates of gram-negative bacteria including extended-spectrum β-lactamase (ESBL) producing strains, *Streptococcal* spp and gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant Enterococcus (VRE) were tested on the BD Phoenix NMIC/ID-4, SMIC/ID-9, and PMIC/ID-14 panels, respectively, following manufacturer's directions.

A bloodstream infection episode was diagnosed after a positive blood culture result or by any new positive blood culture result performed more than 48 hours after a previous positive result. For common contaminants (coagulase-negative staphylococci, α-hemolytic streptococci, *Corynebacterium* spp, *Bacillus* spp, *micrococci*, and *Propionibacterium acnes*), at least two positive blood culture results are required for a positive diagnosis. If there is only one positive blood culture, another positive culture should be obtained directly from an intravenous catheter or the clinical significance is otherwise evident.[5,14] Polymicrobial bacteremia was diagnosed after the ID of more

than one microorganism from a single blood culture or from different cultures that were taken within 48 hours. Bloodstream infections were classified following the idea of proposal Siegman-Igra and colleagues made for the spectrum of acquisition of bacteremia.[13] Bacteremia in patients who were recently discharged within 48 hours from the hospital was classified as "nosocomial." Bacteremia in patients who were hospitalized for more than 2 days, received hemodialysis, intravenous chemotherapy, or invasive procedures less than 3 months before a bacteremia episode, or who resided in a nursing home was classified as "health care associated." Bacteremia in patients who were excluded of nosocomial and health care–associated infection was classified as "true community acquired."

A peripheral WBC count of 4,000–10,000/μL, with neither band nor precursor forms, was considered normal. All patients' charts were reviewed by two physicians who are on the boards of emergency medicine and infectious diseases. All outcomes were followed for up to 30 days after ED visit and verified by chart review or telephone interviews. Crude mortality included all in-hospital death.

Statistical analysis was performed using SPSS version 11.0 (SPSS Inc., Chicago, IL, USA) for Windows. The χ^2 test was used to assess the associations among categorical variables. All tests were two-tailed and p values less than 0.05 were regarded as significant. The odds ratio (OR) and 95% confidence interval (CI) were calculated for risk estimates.

Results

Among 13,903 blood cultures, 1,872 (13.5%) were positive for bacteria. This result represented 1,549 (11.2%) cultures that were obtained from 831 patients with 890 episodes of bacteremia. And it left 323 blood cultures (2.3%) as "contaminated." The overall incidence of bacteremia in our ED was 1.3% (890 episodes/67,240 total visits) during 2004.

Among the 831 bacteremia patients, 493 were male (with 526 episodes, 59.1%) and 338 were female (with 364 episodes, 40.9%). One patient had two episodes of bacteremia within one visit, so there were totally 890 episodes in 889 visits. Among these episodes, 525 (59%) were defined as true community-acquired infections followed by 263 (29.5%) as health care–associated infections and 102 (11.5%) as nosocomial infections. Demographic data, disposition of underlying diseases, and classification of bacteremia acquisition of cases presented with bacteremia were seen in Table 1. Table 2 demonstrated the etiologies of these bacteremia, with urinary tract infections (287, 32.2%) being the most common bacterial infections, followed by intra-abdominal infection (199, 22.4%) and occult bacteremia (141, 15.8%). A total of 972 microorganisms were isolated and classified as bacteremic pathogens (see Table 3), which included 289 (29.7%) gram-positive and 683 (70.3%) gram-negative organisms. Anaerobic isolates accounted for 3.7% of all isolates (36/972). The incidence of polymicrobial bacteremia was 8% (72/890).

The most commonly encountered pathogens in various etiologies were *Escherichia coli* in urinary tract infection (59.2%, 170/287 episodes) and intra-abdominal infection (44.2%, 88/199 episodes); and *Klebsiella pneumoniae* in lower respiratory tract infection (25%, 17/68 episodes).

Table 1 Demographics, underlying diseases, and classification of 890 adult bacteremic episodes presenting to the Kaohsiung Veteran General Hospital emergency department in 2004

Variables	*n* (%)
Gender	
Male	526 (59.1)
Female	364 (40.9)
Age (yr)	
Mean ± SD	64.9 ± 16
Median (range)	69 (16–96)
Classification of bacteremia acquisition	
Nosocomial	102 (11.5)
Health care associated	263 (29.5)
True community acquired	525 (59.0)
Underlying diseases	
Hypertension	383 (30.1)
Diabetes mellitus	300 (23.6)
Malignancy	200 (15.7)
Liver cirrhosis[a]	130 (10.2)
Uremia	65 (5.1)
Chronic obstructive pulmonary diseases	63 (4.9)
Neurologic deficit[b]	58 (4.6)
Congestive heart failure	56 (4.4)
Autoimmune disorder	18 (1.4)

[a] Including alcoholic liver disease.
[b] Disability in bedridden status.
SD = standard deviation.

E coli and *K pneumoniae* accounted for up to 66% (365/538) pathogens of all urinary tract and intra-abdominal infections. *S aureus* were commonly isolated from cardiovascular infection (75%, 55/73 isolates) and soft tissue infection (35.8%, 39/109 episodes). The pathogens accounting for occult bacteremia were 59 different species isolated from 141 episodes and the most common specie, *S aureus*, accounted for 19.1% of them.

In all true community–acquired infections, the most common pathogen was *E coli*, accounting for 38.9% of episodes (204/525). The yield of *E coli* decreased to 28.5% (75/263) in health care–associated infections and 19.6% (20/102) nosocomial infections, respectively. To the contrary, *S aureus* was the most common pathogens in nosocomial infections (31.3%, 32/102) and its yield decreased to 15.9% (42/263) and 12% (63/525) in health care–associated infections and true community–acquired infections, respectively. Non-"true" community–acquired bacteremia significantly has a positive association with the acquisition of MRSA infections (OR = 24.92; 95% CI, 9.88–62.87, $p < 0.05$), but not methicillin-susceptible *S. aureus* (MSSA). The distribution of common pathogens in different categories of bacteremia acquisition was summarized in Table 4.

The resistance of all *E coli* and *K pneumoniae* isolates to cefazolin (a first-generation cephalosporin) was 11.7% (35/299) and 7.5% (12/161), respectively. Of 150 episodes

Table 2 Case numbers and mortality of different etiologies accounting for the bacteremic episodes in the Kaohsiung Veteran General Hospital emergency department in 2004

Etiologies	*n* (%)	Mortality,[a] *n* (%)[b]
Urinary tract infection	287 (32.2)	29 (10.4)
Intra-abdominal infection	199 (22.4)	39 (20)
Biliary tract infection	104 (11.7)	19 (18.6)
Liver abscess	42 (4.7)	4 (10)
Spontaneous bacterial peritonitis	18 (2.0)	7 (38.9)
Others	35 (3.9)	9 (25.7)
Unknown	141 (15.8)	41 (29.9)
Soft tissue infection	109 (12.3)	16 (15.2)
Respiratory tract infection	76 (8.5)	40 (54.7)
Lower	68 (7.6)	40 (61.5)
Upper	8 (0.9)	0 (0)
Cardiovascular infection	73 (8.2)	20 (27.4)
Central nervous system infection	5 (0.6)	2 (40)
Total (episodes)	890 (100)	187 (21.6)

[a] Crude in-hospital mortality.
[b] Case numbers lost at follow-up: nine in urinary tract infection, two in liver abscess and biliary tract infection, respectively, four in soft tissue infection and unknown origin, respectively, and three in lower respiratory tract infection.

Table 3 Isolated pathogens responsible for 890 bacteremic episodes in the Kaohsiung Veteran General Hospital emergency department in 2004

Organisms	*n* (%)
Gram-negative	683 (70.3)
Escherichia coli	299 (30.8)
Sensitivity to first-gen. cephalosporin	
Susceptible	264 (27.2)
Resistant	35 (3.6)
ESBL (+)	17 (1.7)
Klebsiella pneumoniae	161 (16.5)
Sensitivity to first-gen. cephalosporin	
Susceptible	149 (15.3)
Resistant	12 (1.2)
ESBL (+)	9 (0.9)
Proteus mirabilis	34 (3.5)
Salmonella spp	25 (2.6)
Pseudomonas aeruginosa	23 (2.4)
Others	141 (14.5)
Gram-positive	289 (29.7)
Staphylococcus spp	150 (15.4)
S aureus	137 (14.1)
Methicillin susceptible	71 (7.3)
Methicillin resistant	66 (6.8)
Coagulase negative	13 (1.3)
Streptococcus spp	101 (10.4)
S viridans	29 (3.0)
S agalactiae	21 (2.2)
S pneumoniae	17 (1.7)
S pyogens	13 (1.3)
Others	21 (2.2)
Enterococcus spp	27 (2.8)
Others	11 (1.1)
Total (isolates)	972 (100)

ESBL = extended-spectrum β-lactamase; First-gen. = first-generation.

of Staphylococcal bacteremia, MSSA accounted for 71 cases (47.3%), MRSA accounted for 66 cases (44%), and coagulase-negative isolates accounted for 13 cases (8.7%). No VRE isolate was found. The ESBL was detected in 28 isolates (3.1%), 17 of which were *E coli* and 9 were *K pneumoniae* with only 3 of 28 (10.7%) episodes being true community acquired.

Six episodes were lost at early follow-up (within 3 days) and 18 episodes were lost at late follow-up (Days 4—30). Excluding these episodes, the estimated early mortality rate (within 3 days) was 11% (97/884) and the late mortality rate (Days 4—30) was 8% (69/866). The overall in-hospital crude mortality rate was 21.6% (187/866) (Fig. 1). The mortality of different etiologies and classifications of bacteremia was seen in Tables 2 and 4, respectively. Infections with MRSA showed a higher mortality rate than those with MSSA [29/66 (44%) *vs.* 15/71 (21%), $p < 0.05$] (data not shown). Among the 65 patients who were discharged inadvertently, 2 were lost at follow-up and the rest of them survived. Most of their etiologies were unknown origin (47.7%, 31/65) or urinary tract infection (30.8%, 20/65) and *E coli* was the most common pathogens (41.5%, 27/65). The majority of them (70.7%, 46/65) are true community—acquired infections. There were 181 (20%) episodes of bacteremia cases presenting with normal white cell counts that were even more common (49.2%, 32/65) among those discharged inadvertently. The early mortality rate (within 3 days) of this group was 4% (7/177, 4 lost at follow-up).

Discussion

Approximately two-thirds of the patients with severe sepsis or septic shock are first encountered in the EDs,[15—17] in which bacteremia is present in about 50% of patients with severe sepsis. KSVGH is a government medical center built to provide health care to the community and the populace, who are mainly the veterans. So most of our patients were elderly males, with hypertension (43%), diabetes mellitus (33.7%), and malignancy (22.5%) being the most common underlying diseases. With relatively low mortality rate (9.4%), urinary tract infections (30.6%) were the most common bacterial infections in our patients. And when taking both intra-abdominal and urinary tract infections into consideration, they accounted for more than half of our cases (54.6%, 486/890) and the most common pathogen identified were *E coli*. and *K pneumoniae* (66%, 365/538). Because the resistance rate of these pathogen to the commonly used first-line antibiotic (e.g., first-generation cephalosporins) remained

Table 4 Comparison of mortality, comorbidity, and incidences of common pathogens[a] among nosocomial, health care-associated bacteremia, and true community-acquired bacteremia in the Kaohsiung Veteran General Hospital emergency department in 2004

	Nosocomial (n = 102)	Health care associated (n = 263)	True community acquired (n = 525)	p
	n (%)	n (%)	n (%)	
Mortality[b]	38 (39.2)	60 (23.3)	83 (16.1)	<0.05
Underlying diseases				
Diabetes mellitus	32 (31.4)	84 (31.9)	184 (35)	0.59
Malignancy	28 (27.5)	104 (39.5)	68 (13)	<0.05
Liver cirrhosis	12 (11.8)	48 (18.3)	70 (13.3)	0.12
Uremia	18 (17.6)	27 (10.3)	20 (3.8)	<0.05
Chronic obstructive pulmonary diseases	19 (18.6)	13 (4.9)	31 (5.9)	<0.05
Neurologic deficit	16 (15.7)	24 (9.1)	18 (3.4)	<0.05
Congestive heart failure	10 (9.8)	13 (4.9)	33 (6.3)	0.22
Autoimmune disorder	4 (3.9)	8 (3)	6 (1.1)	0.07
None[c]	19 (18.6)	57 (21.7)	195 (37.1)	<0.05
Isolates				
Escherichia coli	20 (19.6)	75 (28.5)	204 (38.9)	<0.05
Klebsiella pneumoniae	9 (8.8)	37 (14.1)	115 (22.0)	<0.05
ESBL (+)	13 (12.7)	12 (4.6)	3 (0.6)	<0.05
Staphylococcus aureus	32 (31.3)	42 (16.0)	63 (12.0)	<0.05
Methicillin resistant	29 (28.4)	29 (11.0)	8 (1.5)	<0.05
Methicillin susceptible	3 (2.9)	13 (4.9)	55 (10.5)	<0.05

[a] Common pathogens: leading three species (a total of 597 isolates, 61.4% of all).
[b] Five, six, and eleven episodes were lost at follow-up in nosocomial, health care associated, and true community–acquired categories, respectively.
[c] No underlying diseases listed in Table 1 except for hypertension.
ESBL = extended-spectrum β-lactamase.

low (around 10%), first-generation cephalosporins would still be proper empirical antibiotics for patients with urinary tract infection or intra-abdominal infection visiting ED. Bacteremia of unknown origins, which was usually the main etiology of the patients with severe infections[18–20] and made the treatments difficult, were the third common etiology (15.8%) in our series. The pathogens accounting for occult bacteremia were difficult to predict, because the most common specie, *S aureus*, accounted for only 19.1% of them, broad spectrum antimicrobial coverage is thus advised for severe infections of unknown origins whereas advanced microbiologic and epidemiologic studies are warranted to clarify the relationship between pathogens and occult infections.

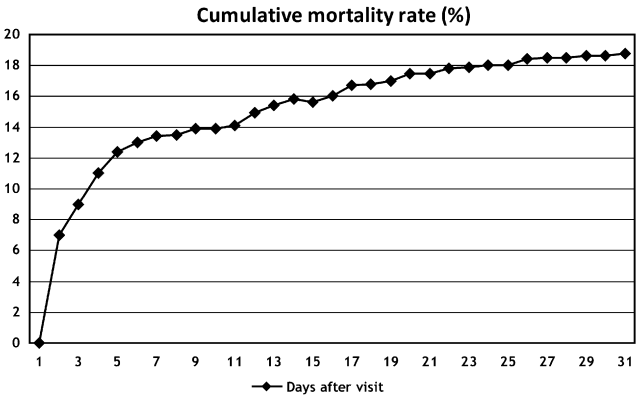

Figure 1. Cumulative mortality rate of bacteremic patients following visits to the Kaohsiung Veteran General Hospital emergency department in 2004.

It is possible for an ED physician to inadvertently discharge patients with subsequent bacteremia before disclosure of culture results, and this would then lead the physician to the embarrassing situations. Fortunately, these patients who were inadvertently discharged before prompt treatments had satisfactory outcomes without complications, and similar results were also observed by Epstein and colleagues.[21] Generally speaking, the common clues to advise febrile patients going home on emergency practice were benign presentation including normal laboratory result, unknown origin like viral infection without toxic signs, no comorbidity, and good response to treatment in observation unit. These probably could explain why most of the episodes (78.5%, 51/65) discharged inadvertently had either fever with unknown origin or urinary tract infection and half of them (49.2%) presenting with normal WBC counts. However, predictors for their favorable outcome warrant more comprehensive study design to evaluate. Other results of the study indicated that febrile patients with normal WBC counts should also be checked closely because many bacteremic episodes (181, 20%) occur in these patients. These cases were tended to be discharged

without further examinations or treatments. Fortunately, the early mortality rate (within 3 days) of this group was lower than average (4% *vs.* 11%).

An astonishing finding was that over half of the mortalities (97/187, 52%) occurred within 3 days. The effort made during this period may be crucial to improving the outcome of bacteremic patients. For example, the early goal-directed therapy advocated by Rivers et al.,[22] was focused on aggressive management at the early beginning of this period. A lot of factors were indicated to be associated with mortality of patents with serious infection, such as clinical presentation, underlying conditions, etiologies, pathogenic species and their presence of drug resistance, laboratory data, and adequacy of antimicrobial therapy.[23–25] In our study, we found the acquisitions of bacteremia were also associated with mortality, that was the highest fatality rate noted in nosocomial infections, whereas the lowest in true community—acquired infections. Patients in the nosocomial category had more items of ominous prognostic factors such as underlying conditions, comorbidity, and presence of drug-resistant pathogens than those in true community—acquired category, which might account for part of this outcome (Table 4).

In the study, many patients with bacteremic episodes (41%, 365 of 890) presented to our ED with at least one nosocomial or health care—associated factor, presumably because KSVGH is a tertiary hospital. Organisms isolated from patients with "true community—acquired bacteremia" were invariably more susceptible to antimicrobials.[13,26] Recent studies reported the percentage of MRSA in *S aureus* bacteremia ranged from 31% to 40%,[9,27] which was similar to the result of our study. And according to the previous reports,[9,27] anti-MRSA antibiotics (rather than penicillinase-resistant penicillins) should be the first choice for empirical treatments in the ED if staphylococcus infections are to be considered. Although up to 56% (37 of 66) MRSA by traditional classification in our series were community acquired, most of them were actually attributed to health care—associated infections (44%, 29/66), not true community—acquired infections (12%, 8/66). The result of our study indicated that the risk for MRSA infection is relatively low if nosocomial or health care—associated infection is unlikely, with only 8 of 66 (12%) MRSA bacteremia and 55 of 71 (77%) MSSA bacteremia being true community acquired. Univariate analysis also indicated that the non-"true" community—acquired bacteremia significantly has a positive association with the acquisition of MRSA infections (OR = 24.92; 95% CI, 9.88—62.87, $p < 0.05$), but not MSSA. One prospective multicenter study had reported that nafcillin was superior to vancomycin in efficacy in patients with MSSA bacteremia.[28] Furthermore, a delay in the use of an appropriate antibiotic (especially glycopeptides) before preliminary microbiological report might not adversely affect the outcome of patients with MRSA bacteremia.[29] Thus, penicillinase-resistant penicillins (such as methicillin) remain as reliable first-line antibiotics for patients who have not been exposed in hospital or health care settings.

Regarding the other drug-resistant strain, the incidence of VRE isolate in our study was none, and that of other emerging drug-resistant isolates such as ESBL producing stains was also low (3.1%, 28/890) and most of these (89.2%, 25/28) were isolated from the patients with either nosocomial or health care—associated bacteremia. So the empirical antibiotic treatments used for drug-resistant isolates should not necessarily be the first-line choice for true community—acquired bacteremia in our ED. If health care—associated exposure has been excluded, the probability to acquire drug-resistant bacteremia from the true community might be low. We believed that the use of the new classification of bacteremia acquisitions[13] would help to build a distinct epidemiologic, clinical, and bacteriologic characteristics, as well as distinct antimicrobial susceptibility profiles of the isolates truly acquired from community we frequently saw in the ED.

Category of bacteremia acquisition was associated with the distribution of pathogens, trend of antimicrobial resistance, and clinical outcome. The problem of drug resistance in community-acquired infections will be overestimated if it is defined using traditional classification. Purely true community—acquired drug-resistant bacteremia might not be that serious as thought, because a lot of episodes categorized as community acquired before were attributed to health care—associated infections. The concept of health care—associated bacteremia should be introduced for an early understanding of the epidemiology and microbiology of bacteremic patients to avoid over-emphasis of drug-resistant problem thus prevent antibiotic abuse in true community—acquired infection.

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