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ORIGINAL ARTICLE

Antimicrobial susceptibility of bacteremic isolates from cancer patients with or without neutropenia at a medical center in southern Taiwan

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Background: Few studies focus on comparison of antimicrobial susceptibility for bacteremic isolates in neutropenic and nonneutropenic cancer patients. The purpose of this study was to elucidate the antimicrobial susceptibility of bacteremic isolates from cancer patients.
Methods: We collected bacterial isolates causing bloodstream infections in cancer patients at a tertiary care hospital from 2003 to 2005 and performed *in vitro* antimicrobial susceptibility of these pathogens by the disc diffusion method.
Results: A total of 588 bacterial isolates were identified from 476 episodes of bloodstream infections in cancer patients. Major pathogens were *Escherichia coli* (22.4%), *Klebsiella pneumoniae* (17.6%), and *Pseudomonas aeruginosa* (14.1%) in neutropenic patients and *E coli* (13.3%), *K pneumoniae* (10.1%), and *Staphylococcus aureus* (9.7%) in nonneutropenic patients. Of *S aureus*, 55.8% were resistant to methicillin, and of coagulase-negative *Staphylococcus* 87.0%. Cefepime, cefpirome, piperacillin/tazobactam, meropenem, or imipenem in combination with or without an aminoglycoside, were active against more than 85% of gram-negative bacilli (GNB). Ceftazidime, piperacillin, or ciprofloxacin plus an aminoglycoside were also active against more than 85% of GNB. The susceptibility rate of GNB or gram-positive cocci to any agent was not different between the isolates from neutropenic and nonneutropenic patients, but more GNB isolates from the former were susceptible to imipenem or meropenem plus an aminoglycoside.

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Conclusion: GNB remained dominant among bacteremic isolates in cancer patients. Antimicrobial agents, especially aminoglycoside-containing combination regimens, as recommended by Infectious Diseases Society of Taiwan for febrile neutropenia, were active against more than 85% of GNB isolates.

Introduction

Infection is the most common complication associated with febrile neutropenia and accounts for substantial length of stay, cost, morbidity, and mortality.[1–3] The principles guiding empirical antimicrobial therapy for patients with febrile neutropenia are based on species distribution and antimicrobial susceptibility of bacterial pathogens. Although bacteria causing bloodstream infections (BSIs) in cancer patients have not been uncommonly reported, little is known about difference in antibiotic susceptibilities in bacterial pathogens in cancer patients with and without neutropenia.[4–6] The availability of timely and accurate epidemiological information on causative pathogens is essential to the appropriate selection of empirical therapy.[7,8] This study was intended to understand bacterial pathogens that caused BSIs in cancer patients with or without neutropenia admitted between 2003 and 2005 at a medical center in Taiwan and to investigate the susceptibility profiles of these pathogens to antimicrobial agents recommended by the Infectious Diseases Society of Taiwan.[9] Such information may be useful for clinicians at starting empirical antimicrobial therapy for febrile cancer patients.

Materials and methods

Setting and source of data

There were approximately 900 beds, including 100 beds for cancer patients and 4 beds for bone marrow transplantation in National Cheng Kung University Hospital, a university-affiliated medical center in southern Taiwan. We collected consecutive bacteremic isolates from adults (aged ≧18 years) with cancer during study period. In cases of recurrent bacteremia caused by the same pathogen, only the isolates obtained from the first episode were included. Each set of blood culture consisted of two bottles, one for Standard Aerobic/F bottle and the other for Standard Anaerobic/F culture. The substitute Plus Aerobic/F and Anaerobic/F bottles were used if patients had received antibiotics. At least two sets of blood cultures were used, in which one contained at least 8–10 mL of blood collected from different vascular sites at 30 minutes apart. Common blood culture contaminant pathogens, such as coagulase-negative *Staphylococcus*, *Propionibacterium* sp, or undifferentiated aerobic Gram-positive bacilli, were excluded, unless they were isolated from at least two sets of blood cultures. These bacteremic isolates were stored at −70°C until tested for susceptibility.

Definition

Neutropenia was defined as an absolute neutrophil count equal to or less than 500 cells/mm^3 in peripheral blood. Episodes of polymicrobial bacteremia were those in which more than one organism was isolated from one or more blood cultures within a 72-hour period. Bacteremia was considered to be nosocomial, if it was present beyond 48 hour after admission, without evidence of infection at admission. Hematological malignancies included acute myeloid leukemia, acute lymphoblastic leukemia, non-Hodgkin's lymphoma, multiple myeloma, chronic myeloid leukemia, chronic lymphocytic leukemia, myelodysplastic syndrome, aplastic anemia, and others.

Microbiological studies and antimicrobial susceptibility

These blood cultures were incubated at BACTEC 9240 system (Becton Dickinson, Sparks, MD, USA) with tryptic soy agar with 5% sheep blood, eosin-methylene blue agar, Chocolate agar for aerobic, and CDC anaerobic blood agars for anaerobic cultures. All isolates were identified by standard methods and the VITEK or API identification system (bioMérieux, Marcy l'Etoile, France).[10,11] Antimicrobial susceptibility was determined by the disk diffusion method and the interpretive criteria of the Clinical and Laboratory Standards Institute[11] were followed. Not all causative pathogens and drugs had corresponding interpretive criteria recommended by the Clinical and Laboratory Standards Institute. Some modified strategies were adopted for such settings. Like tigecycline, Food and Drug Administration disk diffusion interpretive criteria are proposed for all strains.[12,13] For cefpirome, the breakpoints of ≧18 mm as being susceptible and ≦14 mm as being resistant were used.[14,15] The disk diffusion interpretive criteria in antibiotic susceptibility tests of Gram-negative bacilli (GNB) other than the members of *Enterobacteriaceae* were used for rarely encountered pathogens, such as *Actinobacilius* species, *Alcaligenes xylosoxidans*, *Brevundimonas vescularis*, *Chryseobacterium* species, *Kluyvera* species, *Pantoea agglomerans*, *Pasteurella multocida*, and *Stenotrophomonas maltophilia*.

Antimicrobial agents for susceptibility tests (BD BBL™ Sensi-Disc™, Sparks, MD, USA) in aerobic gram-positive organisms included vancomycin (30 μg), teicoplanin (30 μg), linezolid (30 μg), tigecycline (15 μg), ceftazidime (30 μg), cefepime (30 μg), cefpirome (30 μg), meropenem (10 μg), imipenem (10 μg), ciprofloxacin (5 μg), piperacillin (100 μg), piperacillin/tazobactam (100/10 μg), and gentamicin (10 μg). Oxacillin (1 μg) was tested on *Staphylococcus* species, and penicillin (10 μg) for *Streptococcus* species.

Antimicrobial agents for susceptibility tests in aerobic gram-negative organisms included tigecycline, ceftazidime, cefepime, cefpirome, meropenem, imipenem, ciprofloxacin, piperacillin, piperacillin/tazobactam, gentamicin, and amikacin (30 μg). Minimal inhibitory concentration of vancomycin for *Enterococcus* sp was performed by E-test method in isolates with reduced susceptibility to vancomycin.

Statistics

All statistical analyses were performed by the SPSS software version 13.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were compared by Student *t* test, whereas categorical variables were compared by χ^2 test or two-tailed Fisher's exact test. A *p* values less than 0.05 were considered to be statistically significant.

Results

During the study period, 588 isolates from 476 episodes of BSIs were collected. Of 476 episodes of BSIs, 275 occurred in patients with neutropenia and 201 in patients without neutropenia. There were 77 (22.6%) Gram-positive cocci (GPC) isolates and 263 (77.4%) GNB isolates obtained from neutropenic cancer patients, and 76 (30.6%) GPC and 172 (69.4%) GNB recovered from those without neutropenia. The proportions of GNB of bacteremic isolates were 73.5% in 2003, 69.7% in 2004, and 72.9% in 2005, respectively. There were 82 episodes of polymicrobial bacteremia, that is, 50 episodes in neutropenic patients and 32 in patients without neutropenia. Of 275 neutropenic patients, 62.9% had hematological malignancies; and of 201 nonneutropenic patients, only 34.3% had hematological malignancies.

The distribution of causative microorganisms classified according to neutropenia status among cancer patients was listed in Table 1. Among neutropenic patients with BSIs, *Escherichia coli* (22.4%), *Klebsiella pneumoniae* (17.6%), and *Pseudomonas aeruginosa* (14.1%) were the most common pathogens, more predominantly in neutropenic patients than nonneutropenic patients. The three leading bacteremic isolates in nonneutropenic groups were *E coli* (13.3%), *K pneumoniae* (10.1%), and *S aureus* (9.7%). Only *Acinetobacter baumannii* was more often recovered from nonneutropenic patients. The percentage of *Enterobacteriaceae* in neutropenic patients was higher than that in patients without neutropenia (51.4% *vs.* 38.7%; $p = 0.002$). Nosocomial pathogens were 411 bacteremic isolates. Three major nosocomial pathogens were the same in patients with or without neutropenia, that is, *E coli*, *K pneumoniae*, and *P aeruginosa*. The fourth and fifth nosocomial pathogens were *S aureus* and *Enterobacter cloacae*, and the ranking was in reverse order in community-onset bacteremia.

There is no difference in the prevalence of GPC bacteremia between cancer patients with or without neutropenia. *S aureus* bacteremia comprised 5.6% and 9.7% of all bacteremic isolates from patients with and without neutropenia, respectively. Of total 43 *S aureus* isolates, methicillin-resistant *S aureus* accounted for 55.8%. Methicillin resistance was found in 87.0% of 46 coagulase-negative *Staphylococcus* isolates and ampicillin resistance in 45.5% of 35 *Enterococcus* isolates. Only one *Enterococcus faecalis* isolate displayed a reduced susceptibility to vancomycin (minimal inhibitory concentration = 16 μg/mL) during this study period.

Antimicrobial susceptibility of monotherapy for bacteremic isolates from neutropenic cancer patients and those without neutropenia were not different. The ceftazidime, cefepime, cefpirome, piperacillin/tazobactam, meropenem, imipenem, and amikacin were *in vitro* active against more than 80% of GNB (Table 2). Of GPC, tigecycline, linezolid, teicoplanin, and vancomycin were active against more than 90% (Table 3).

Antimicrobial susceptibility of commonly prescribed antibiotics in combination with gentamicin or amikacin for cancer patients with or without neutropenia was listed in Table 4. Most antibiotics, except pipracillin, in combination with gentamicin in Table 4 were in *vitro* active against more than 85% GNB from cancer patients. In combination with amikacin, all drugs were *in vitro* active against more than 90% GNB from cancer patients regardless of neutrophil counts, as shown in Table 4. Imipenem or meropenem plus an aminoglycoside were more active for GNB isolates from cancer patients with neutropenia than those with non-neutropenia: gentamicin-containing regimens: 98.5% versus 94.8% ($p = 0.03$) and amikacin-containing regimens: 99.2% versus 95.3% ($p = 0.01$).

Discussion

How to choose appropriate antibiotics with less cost, less toxicity, little collateral damage, and more effective antimicrobial agents for sepsis in oncologic patients is always an important issue and a great challenge. Our study focuses on antimicrobial susceptibility in BSIs in bacteremic isolates from cancer patients with or without neutropenia. These

Table 1 The species distribution of bacteremic isolates from cancer patients with or without neutropenia

Bacteria	Isolate *n* (%)		*p*
	With neutropenia	Without neutropenia	
Escherichia coli	76 (22.4)	33 (13.3)	0.005
Klebsiella pneumoniae	60 (17.6)	25 (10.1)	0.009
Pseudomonas aeruginosa	48 (14.1)	20 (8.1)	0.022
Enterobacter cloacae	25 (7.4)	18 (7.3)	0.971
Staphylococcus species[a]	23 (6.8)	23 (9.3)	0.263
Staphylococcus aureus	19 (5.6)	24 (9.7)	0.064
Enterococcus species	17 (5.0)	18 (7.3)	0.261
Streptococcus species	15 (4.4)	12 (4.8)	0.804
Acinetobacter species[b]	13 (3.8)	14 (5.6)	0.306
Acinetobacter baumannii	10 (2.9)	23 (9.3)	0.001
Pseudomonas species[c]	5 (1.5)	1 (0.4)	0.236
Klebsiella oxytoca	4 (1.2)	2 (0.8)	0.698
Others	25 (7.3)	35 (14.1)	
Total	340 (100)	248 (100)	

[a] Coagulase-negative Staphylococcus.
[b] Acinetobacter species other than *Acinetobacter baumannii*.
[c] Pseudomonas species other than *Pseudomonas aeruginosa*.

Table 2 Antimicrobial susceptibility of Gram-negative bacilli from bloodstream of cancer patients with or without neutropenia

Drugs	Susceptible rate, %		*p*
	Isolates from patients with neutropenia, $n = 263$	Isolates from patients without neutropenia, $n = 172$	
Tigecycline	78.3	82.0	0.36
Ciprofloxacin	81.7	78.4	0.40
Ceftazidime	84.4	86.0	0.65
Cefepime	91.2	91.2	1
Cefpirome	85.2	85.4	0.94
Meropenem	97.0	93.6	0.11
Imipenem	96.6	93.6	0.16
Piperacillin	50.6	50.6	1
Piperacillin/tazobactam	86.3	87.8	0.66
Gentamicin	78.3	71.5	0.11
Amikacin	93.5	89.5	0.14

local data could be helpful in choosing appropriate antibiotics in patient care. The predominant etiology of BSIs in cancer patients with neutropenia has been reported to be gram-positive organisms in recent studies.[16–18] However, previous studies in Taiwan [6,19] and our data showed that GNB remain being responsible for most causative microorganisms of BSIs in cancer patients who were neutropenic or not.

A high prevalence of *Enterobacteriaceae* bacteremia in neutropenic cancer patients with BSIs, at least 51.4%, may be explained by breaking down of gastrointestinal mucosal barrier. However, the prevalence of *Pseudomonas aeruginosa* bacteremia in neutropenic patients was 14.1%, twice that in nonneutropenic cancer patients. Such a causative species discrepancy highlights the precaution in choosing empirical antibiotics for cancer patients with and without neutropenia.

As the study by Velasco et al.,[4] antimicrobial susceptibility of bacteremic isolates among GNB and GPC isolates from our cancer patients with and without neutropenia was not different. Substantial percentages of methicillin and ampicillin resistance were present in our *Staphylococcus* and *Enterococcus* isolates, respectively, either in neutropenic or nonneutropenic patients. It reminds us to pay attention to risky patients for GPC infections and the needs of glycopeptides, tigecycline, or linezolid for β-lactam-resistant gram-positive pathogens. Tigecycline, although *in vitro* active against GPC isolates, low serum concentrations of tigecycline will probably limit its therapeutic efficacy in treating BSIs. However, a recent meta-analysis revealed no benefit for the role of glycopeptides in the initial empirical treatment of febrile neutropenic cases, and the adverse effects, including nephrotoxicity, were higher in the group of empirical vancomycin treatment.[20] Further study is needed to determine the optimal choices and timing of empirical antibiotic use for β-lactam-resistant Gram-positive pathogens.

Table 3 Antimicrobial susceptibility of Gram-positive cocci from bloodstream of cancer patients with or without neutropenia

Drugs	Susceptible rate, %		*p*
	Isolates from patients with neutropenia, $n = 77$	Isolates from patients without neutropenia, $n = 76$	
Tigecycline	96.1	98.7	0.38
Teicoplanin	100	100	1
Vancomycin[a]	97.4	97.3	0.99
Linezolid	96.1	97.4	0.69
Ciprofloxacin	37.7	40.8	0.70
Ceftazidime	31.1	25.0	0.40
Cefepime	49.4	40.8	0.29
Cefpirome	45.4	36.8	0.29
Meropenem	53.2	46.1	0.38
Imipenem	63.6	60.5	0.70
Piperacillin	44.2	38.2	0.46
Piperacillin/tazobactam	70.1	63.2	0.37
Gentamicin	36.4	26.3	0.19

[a] The susceptible breakpoint of vancomycin using disk diffusion test was recommended by 2005 CLSI. However, in 2009, the CLSI deleted the susceptible disk diffusion breakpoint of vancomycin for staphylococci because of unreliable differentiation.
CLSI = Clinical and Laboratory Standards Institute.

Table 4 Susceptibility rates of Gram-negative bacillary bacteremic isolates from cancer patients with or without neutropenia to gentamicin-based/amikacin-based combination regimens

Combination regimens	Susceptible rate, %		*p*
	Neutropenic $n = 263$	Nonneutropenic $n = 172$	
Ceftazidime + gentamicin	92.0	89.0	0.29
Cefepime + gentamicin	95.4	92.4	0.20
Cefpirome + gentamicin	92.0	90.1	0.49
Meropenem + gentamicin	98.5	94.8	0.03
Imipenem + gentamicin	98.5	94.8	0.03
Piperacillin + gentamicin	81.0	78.0	0.44
Piperacillin/ tazobactam + gentamicin	94.3	91.9	0.33
Ciprofloxacin + gentamicin	89.0	86.6	0.46
Ceftazidime + amikacin	95.4	93.6	0.41
Cefepime + amikacin	96.6	93.6	0.16
Cefpirome + amikacin	95.8	92.4	0.14
Meropenem + amikacin	99.2	95.3	0.01
Imipenem + amikacin	99.2	95.3	0.01
Ciprofloxacin + amikacin	97.7	94.8	0.11
Piperacillin + amikacin	95.1	93.0	0.38
Piperacillin/ tazobactam + amikacin	97.3	97.1	0.87

Note: The effects of two antibiotics in combination were calculated as the concurrent susceptibilities against either of two drugs.

The recommended antimicrobial agents by the Infectious Diseases Society of Taiwan for patients with febrile neutropenia, including cefepime, a carbapenem, cefepime, or cefpirome plus gentamicin or amikacin, ceftazidime plus amikacin, a carbapenem plus gentamicin or amikacin, piperacillin/tazobactam plus gentamicin or amikacin,[9] were *in vitro* active against more than 90% of GNB causing BSIs in our cancer patients, irrespective of neutropenic status. The *in vitro* susceptibility data supported that these regimens can be appropriate choices in empirical use for febrile neutropenia in Taiwan. In a study by Sunil et al.,[21] routine combination of amikacin and a β-lactam agent can increase the adequacy of empirical coverage. For GNB sepsis, piperacillin or ciprofloxacin in combination with an aminoglycoside, especially amikacin, showed better *in vitro* antibacterial activity. Ciprofloxacin combined with an aminoglycoside can be considered when facing patients with febrile neutropenia and β-lactam allergy history.

In recent meta-analysis studies, monotherapy has been proved as effective as aminoglycoside-containing combinations for empirical treatment of febrile neutropenia.[22,23] The advantage of monotherapy included easier to administering, possibly cheaper than combination therapy, and low toxicity, especially nephrotoxicity. However, the mortality rate of *P aeruginosa* bacteremia would be significantly lower in patients treated by combination therapy or initial combination therapy followed by an adequate definitive monotherapy.[24,25] Combination therapy, including a fluoroquinolone either with an antipseudomonal β-lactam or amikacin, or an antipseudomonal β-lactam with an aminoglycoside, could *in vitro* minimize the risk of developing resistance.[26,27] In our study, *P aeruginosa* ranked the third in neutropenic patients and the sixth in nonneutropenic patients. It was reasonable to take combination strategy as an alternative choice in empirical therapy in febrile cancer patients with or without neutropenia.

Our study has at least three major limitations. The first is the samples collected from a single medical center; such results may be not bale to be generalized to other medical centers in Taiwan. The second limitation is the combination of two drugs. We did not evaluate the *in vitro* antibacterial effect of two drugs in combination but just simply counted the susceptibility data of causative pathogens to either of two antibiotics. The last limitation is the changing interpretative criteria of disk diffusion tests to certain pathogens, such as the vancomycin disk for methicillin-resistant *S aureus* or carbapenem disks for *Enterobacteriacea*. It highlights the need of frequent updating of such susceptibility profiles.

In conclusion, our data show GNB were the dominant organisms causing BSIs. Antimicrobial susceptibility data supported the recommended antimicrobial agents in febrile neutropenic patients by the Infectious Diseases Society of Taiwan. When GPC infections are suspected, a glycopeptide can be considered with the concern of β-lactam resistance.

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