

Epidemiology of bloodstream infections in patients with haematological malignancies with and without neutropenia

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SUMMARY

All bacterial isolates from 7058 patients admitted to haemato-oncology wards at National Taiwan University Hospital between 2002 and 2006 were characterized. In total 1307 non-duplicate bloodstream isolates were made from all patients with haematological malignancy; 853 (65%) of these were from neutropenic patients. Gram-negative bacteria predominated (60%) in neutropenic isolates with *Escherichia coli* (12%), *Klebsiella pneumoniae* (10%), *Acinetobacter calcoaceticus-baumannii* complex (6%), and *Stenotrophomonas maltophilia* (6%) the most frequent. Coagulase-negative staphylococci (19%) and *Staphylococcus aureus* (4%) were the most common Gram-positive pathogens. Resistance to ciprofloxacin was found in 50% of *E. coli* and 20% of *K. pneumoniae* isolates from neutropenic patients. Extensively drug-resistant *A. calcoaceticus-baumannii* complex and vancomycin-resistant enterococci were also found during the study period. Emerging antimicrobial resistant pathogens are an increasing threat to neutropenic cancer patients.

Key words: Antimicrobial resistance, epidemiology, febrile neutropenia, haematological malignancy.

INTRODUCTION

The development of targeted molecular therapies for cancer treatment in recent years has significantly decreased the risk of neutropenia in this group of patients [1, 2] and new chemotherapeutic approaches for patients with solid tumours have substantially decreased neutropenia-related toxicity. However,

most cancer patients still receive conventional chemotherapy as part of their treatment regimen. The majority of patients with haematological malignancy are at high risk of neutropenic infection post-chemotherapy and febrile neutropenia remains a major complication [3, 4]. Febrile neutropenia is associated with high morbidity and mortality in these patients and the overall prognosis is dependent on timely and adequate empirical antibiotic therapy [1, 5].

Although several guidelines for the management of febrile neutropenia in cancer patients have been developed [6–8], the epidemiology of microbial pathogens and antimicrobial resistance may differ by

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geographical region [9–11], and thus impact on their universal applicability. Studies from the USA and Europe show that Gram-positive microorganisms are the predominant isolates from blood cultures [12, 13], but the spectrum of bacteraemic pathogens in patients of febrile neutropenia with haematological malignancy in Taiwan, where Gram-negative organisms predominate, is clearly different from that in Western countries [10, 14]. In addition, Taiwan has witnessed the emergence of fluoroquinolone-resistant *Escherichia coli* and *Klebsiella pneumoniae* between 1996 and 2001 [10]. Antimicrobial resistance has serious consequences in neutropenic cancer patients contributing to high rates of treatment failure, prolonged infections, morbidity and mortality. Indeed, the emergence of fluoroquinolone-resistant *E. coli* and *K. pneumoniae*, carbapenem-resistant *Acinetobacter* spp., *Stenotrophomonas maltophilia* as well as vancomycin-resistant *Enterococcus faecium* have all been reported in neutropenic patients [10, 15–18]. It follows that regular monitoring of the epidemiology of bacterial infections allows evaluation of antibacterial strategies and their adaptation to lessen the impact of emerging pathogens [19].

In this study, we examined the spectrum of bloodstream isolates from patients with haematological malignancies attending a medical centre in Taiwan between 2002 and 2006 and correlated the pathogens recovered with clinical characteristics and antimicrobial resistance.

PATIENTS AND METHODS

Setting and patients

National Taiwan University Hospital (NTUH) is a 2000-bed teaching hospital in metropolitan Taipei that provides both primary and tertiary care. The medical records of patients admitted to the haematology wards of the hospital between 1 January 2002 and 31 December 2006 were reviewed. All patients with haematological malignancies were enrolled into the study, including acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL), non-Hodgkin's lymphoma, multiple myeloma (MM), chronic myeloid leukaemia (CML), chronic lymphocytic leukaemia (CLL), myelodysplastic syndrome (MDS), aplastic anaemia (AA), and others. Patients with solid cancers and non-cancer patients were excluded. Most patients were admitted to receive induction or consolidation chemotherapy or were

undergoing haematopoietic stem cell transplantation. Other patients were admitted for the treatment of complications of malignancy such as infectious disease or bleeding.

A complete physical examination was performed at baseline and at least once daily during therapy for malignancy. Imaging by computed tomography scan, ultrasound and other examinations were performed if indicated according to clinical conditions. Before the start of antibiotic therapy, full blood count, liver biochemistry, renal function test, and chest X-ray, were undertaken. Two or three sets of blood cultures (aerobic and anaerobic bottles) with at least one from a peripheral vein were set up using the Bactec 9240 system (Becton Dickinson, USA). Urinalysis and urine culture were also performed. Bacteria and fungi were isolated by conventional methods and, if necessary, species identity was confirmed by the Phoenix identification systems (Becton Dickinson). Routine anti-bacterial or anti-fungal prophylaxis was not prescribed for patients receiving chemotherapy at NTUH during the study period.

Definitions

Febrile neutropenia was defined according to the criteria of the Infectious Disease Society of America [6]. Fever was defined as an axillary temperature of ≥ 38.3 °C on one occasion or of > 38.0 °C on two or more occasions during a 12-h period. Neutropenia was a neutrophil count < 500 cells/mm³ or a count < 1000 cells/mm³ with a predicted decrease to < 500 cells/mm³. Infections were classified as community acquired if fever developed within 72 h of admission, while development of fever after this time indicated nosocomial infection.

Antimicrobial susceptibility

Data on the susceptibilities of bloodstream isolates determined by the disk diffusion method [20] during the study period were retrieved from the annual summary document. Non-duplicate isolates of each species with identical resistance profiles recovered from each patient within 7 days were noted to calculate resistance rates. Detection of extended-spectrum β -lactamase (ESBL) phenotypes in *E. coli*, *K. pneumoniae*, *Proteus mirabilis*, and *K. oxytoca* isolates began in 2003 using methods in accordance with the Clinical and Laboratory Standards Institute (CLSI) [20, 21]. Isolates with intermediate resistance or fully

resistant to antimicrobial agents were classified as a resistant phenotype. Extensively drug-resistant *Acinetobacter calcoaceticus-baumannii* complex (XDRAB), isolates were defined as being resistant to all agents tested, including ampicillin-sulbactam, ceftazidime, cefepime, piperacillin-tazobactam, aztreonam, imipenem, meropenem, ciprofloxacin, levofloxacin, gentamicin, and amikacin, with the exception of colistin. A broth microdilution method was used for susceptibility testing of colistin and classified according to CLSI guidelines (susceptible $\leq 2 \mu\text{g/ml}$, resistant $\geq 4 \mu\text{g/ml}$) [21].

Antimicrobial prophylaxis and treatment

Prophylactic use of an oral fluoroquinolone (levofloxacin or moxifloxacin) was recommended in high-risk populations (e.g. acute leukaemia and bone marrow transplantation) in whom chemotherapy-induced neutropenia (< 500 neutrophils/ mm^3) was expected to last > 7 days. Antifungal prophylaxis was not routinely used after chemotherapy. Empirical antibiotic treatment for patients with febrile neutropenia followed published guidelines [22, 23].

Statistics

Statistical comparisons were made with χ^2 test using SPSS for Windows, version 13.0 (SPSS Inc., USA). A P value of < 0.05 was considered to indicate a significant difference.

RESULTS

Underlying haematological diagnosis

There were 7058 admissions to the haemato-oncology wards during the 5-year study period, including 3974 (56%) patients with haematological malignancies and 1032 (15%) patients with solid cancers. Seventy-eight percent of all admissions were patients with acute leukaemia (28% AML, 9% ALL) and lymphoma (41%).

Microbial aetiology

A total of 1307 non-duplicate isolates was recovered from blood cultures in patients with haematological malignancy admitted during the study period; 853 (65%) were isolated from patients with neutropenia. Figure 1 shows that over the study period Gram-negative infections in neutropenic patients peaked in

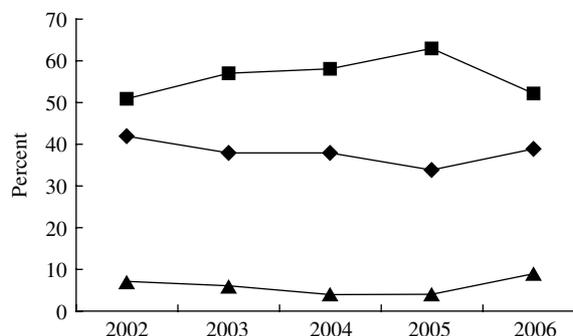


Fig. 1. Aetiological trends of bloodstream infections in febrile neutropenic adults with haematological malignancy at National Taiwan University Hospital from 2002 to 2006. χ^2 trend analysis ($P=0.255$). \blacklozenge —, Gram-positive pathogens; \blacksquare —, Gram-negative pathogens; \blacktriangle —, fungus.

2005 at 65% but fell in 2006 to frequencies similar to the start of the study. On the other hand infections with Gram-positive organisms ranged from 35% to 45% ($P=0.255$) and *Candida* spp. from 5% to 9%. There was a similar range and frequency of species recovered from all patients with and without neutropenia (Table 1). The leading Gram-negative pathogens were *E. coli*, *K. pneumoniae*, *A. calcoaceticus-baumannii* complex and *S. maltophilia*. The number of *A. calcoaceticus-baumannii* complex and *S. maltophilia* isolates increased over the study period and were more common than *Enterobacter cloacae* and *Pseudomonas aeruginosa*. Coagulase-negative staphylococci, including *Staphylococcus epidermidis*, were the most commonly isolated Gram-positive bacteria in both groups of patients; *S. aureus* comprised 4% and 5% of isolates from neutropenic and all patients, respectively, and 56% of these were oxacillin resistant and thus classified as MRSA. A similar patient distribution was observed for *Streptococcus* spp. with the majority being viridans streptococci (83% neutropenic, 90% all patients). Equal numbers of *Enterococcus faecalis* and *E. faecium* were isolated from neutropenic patients. Episodes of *Candida* bloodstream infections accounted for 6% and 5%, respectively, of neutropenic with all patients with *C. tropicalis* and *C. albicans* being the most frequent.

The distribution of microbial species in neutropenic patients according to type of haematological malignancy is shown in Table 2. Patients with AML accounted for over half (52%) of all pathogens recovered despite the fact that they represented just over a quarter (1093/3974, 27.5%) of all admissions. Similarly, patients with ALL represented 9.4% (375/3974)

Table 1. Pathogens isolated from blood in patients with haematological malignancy with and without neutropenia at National Taiwan University Hospital from 2002 to 2006

Bacteria	Number (%) of isolates		Total patients
	Haematological malignancy with neutropenia	Haematological malignancy without neutropenia	
Gram-negative	516 (60)	718 (55)	885 (54)
<i>Escherichia coli</i>	103 (12)	124 (9)	168 (10)
<i>Klebsiella pneumoniae</i>	86 (10)	148 (11)	152 (9)
<i>Acinetobacter baumannii</i>	54 (6)	101 (8)	128 (8)
<i>Pseudomonas aeruginosa</i>	47 (6)	64 (5)	76 (5)
<i>Enterobacter cloacae</i>	38 (4)	54 (4)	70 (4)
<i>Stenotrophomonas maltophilia</i>	48 (6)	67 (5)	69 (4)
<i>Salmonella</i> spp.	5 (1)	19 (1)	24 (1)
Other species*	135 (16)	141 (11)	198 (12)
Gram-positive	285 (33)	524 (40)	670 (41)
<i>Staphylococcus epidermidis</i>	73 (9)	121 (9)	141 (9)
Other coagulase-negative staphylococci	86 (10)	147 (11)	189 (12)
<i>Staphylococcus aureus</i>	36 (4)	65 (5)	85 (5)
<i>Streptococcus</i> spp.	31 (4)	40 (3)	52 (3)
<i>Enterococcus faecalis</i>	19 (2)	30 (2)	49 (3)
<i>Enterococcus faecium</i>	19 (2)	24 (2)	26 (2)
Other species†	21 (2)	97 (7)	128 (8)
Fungi	52 (6)	65 (5)	94 (5)
<i>Candida albicans</i>	14 (2)	23 (2)	40 (2)
<i>Candida parapsilosis</i>	5 (1)	9 (1)	9 (1)
<i>Candida tropicalis</i>	28 (3)	28 (2)	34 (2)
Other <i>Candida</i> spp.‡	5 (0)	5 (0)	11 (0)
Total	853 (100)	1307 (100)	1649 (100)

* Including *Proteus mirabilis*, *Serratia marcescens*, *Acinetobacter Iwoffii*, *Aeromonas hydrophila*, and *Sphingomonas paucimobilis*.

† Including *Corynebacterium* spp., *Bacillus* spp., and *Micrococcus*.

‡ Including *Candida krusei*, *C. glabrata*, and *C. guilliermondii*.

of those admitted during the study period with haematological malignancies but accounted for only 20% of all isolates from neutropenic patients. A similar picture was observed for non-Hodgkin's lymphoma patients, i.e. 41% of admissions, 17% of blood isolates from neutropenia.

ANTIBIOTIC SUSCEPTIBILITY

There were no statistically significant differences between the patient groups with regard to antimicrobial susceptibility (Table 3). The only notable resistance was that 50% of *E. coli* and 20% of *K. pneumoniae* isolates from neutropenic patients were resistant to ciprofloxacin. Similar rates of resistance were also observed for those without neutropenia. Production of ESBLs was detected in 12% and 3%, respectively,

of *E. coli* and *K. pneumoniae* from patients with neutropenia.

Isolates of *E. cloacae* were on the whole susceptible to amikacin (84%), and piperacillin-tazobactam (89%) but exhibited variable susceptibility to ceftaxime; however, all isolates were susceptible to imipenem. *P. aeruginosa* from both groups of patients were invariably susceptible to all antipseudomonal agents while most of *A. calcoaceticus-baumannii* complex isolates from all patients were susceptible to imipenem, piperacillin-tazobactam and amikacin; however, 6% of isolates of this complex from neutropenic patients and 4% of the control group were found to be multiresistant to all antimicrobials (XDRAB). *S. maltophilia* isolates were susceptible to sulfamethoxazole-trimethoprim (>90%) but less so to ceftazidime, and levofloxacin. Of the

Table 2. Distribution of bloodstream pathogens in patients according to haematological malignancies

Bacteria	Haematological malignancies						
	AML	ALL	NHL	CML	CLL	MM	MDS/AA
No. of total admissions ...	1093	375	1611	100	81	503	170
Gram-negative	266	109	93	7	2	22	17
<i>Escherichia coli</i>	56	23	13	1	1	7	2
<i>Klebsiella pneumoniae</i>	49	17	11	3	0	1	5
<i>Acinetobacter baumannii</i>	17	13	17	0	0	3	4
<i>Pseudomonas aeruginosa</i>	27	9	8	0	1	2	0
<i>Enterobacter cloacae</i>	21	9	6	1	0	0	1
<i>Stenotrophomonas maltophilia</i>	25	10	7	1	0	3	2
Other species*	71	28	31	1	0	6	3
Gram-positive	156	43	50	4	4	20	8
<i>Staphylococcus aureus</i>	18	8	7	0	0	3	0
Coagulase-negative staphylococci	96	20	24	3	3	10	3
<i>Streptococcus</i> spp.	16	5	7	0	0	2	1
<i>Enterococcus faecalis</i>	10	1	4	0	0	3	1
<i>Enterococcus faecium</i>	9	4	6	0	0	0	0
Other species†	12	5	2	1	1	2	3
Fungi	25	17	6	0	0	3	1
<i>Candida albicans</i>	8	3	1	0	0	1	1
<i>Candida parapsilosis</i>	4	1	0	0	0	0	0
<i>Candida tropicalis</i>	10	12	4	0	0	2	0
Other <i>Candida</i> spp.	3	1	1	0	0	0	0
Total pathogen isolated	447	169	149	11	6	45	26

AA, Aplastic anaemia; AML, acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; MDS, myelodysplastic syndrome; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma.

* Other species of Gram-negative bacteria: *Serratia marcescens*, *Acinetobacter Iwoffii*, *Aeromonas hydrophila*, *Proteus mirabilis*, and *Sphingomonas paucimobilis*.

† Other species of Gram-positive bacteria: *Corynebacterium* spp., *Bacillus* spp., and *Micrococcus* spp.

Gram-positive isolates oxacillin resistance was exhibited by over half (56%) of *S. aureus* from neutropenic patients and was marginally reduced for other patients (49%). Penicillin resistance in viridians streptococci was 14% in both patient groups and 21% of *E. faecium* isolates were vancomycin resistant.

Clinical characteristics and mortality

Most patients admitted to the haemato-oncology wards received chemotherapy and developed fever during neutropenic episodes; 5% of these were blood culture-positive within 72 h of admission. Although most patients required frequent admissions for chemotherapy or supportive care, only one isolate of *A. calcoaceticus-baumannii* complex and none of *S. maltophilia* were found in patients with community-acquired infection. *C. tropicalis* was the most common fungal infection in patients with febrile

neutropenia, but only two patients with community-acquired infection grew *C. albicans*. Overall, there was no significant difference in microbiological spectrum between patients with community-acquired and nosocomial infection. There were 193 (23%) isolates from patients with one episode of febrile neutropenia and this rose to 660 (77%) from patients with two or more febrile episodes. *K. pneumoniae* was less common in the latter group.

A total of 102 (12%) of 853 pathogens was isolated within 14 days from patients who died. The median duration between isolate positive blood culture and death was 5 days. *E. coli* (6%) and *S. maltophilia* (35%) isolates were identified within 14 days before mortality. The 14-day outcome for neutropenic patients with *E. coli* was better than that for neutropenic patients with other microbial species ($P=0.036$). By contrast, the outcomes for neutropenic patients with *S. maltophilia* bloodstream infections were significantly worse than for other patients ($P<0.001$).

Table 3. Susceptibilities of isolates from patients with haematological malignancy with and without neutropenia during 2002–2006

Bacteria (no. of susceptible isolates from patients with febrile neutropenia)	Number (percentage) of isolates susceptible to antibiotic									
	Cefotaxime	Ceftazidime	Cefepime	Amikacin	Piperacillin-tazobactam	Ciprofloxacin	Imipenem	Ticarcillin-clavulanate	SXT	
Isolates from patients with febrile neutropenia										
<i>Escherichia coli</i> (103)	88 (85)	n.a.	93 (90)	102 (99)	95 (92)	52 (50)	103 (100)	n.a.	n.a.	
<i>Klebsiella pneumoniae</i> (86)	82 (95)	n.a.	83 (97)	85 (99)	76 (88)	69 (80)	86 (100)	n.a.	n.a.	
<i>Enterobacter cloacae</i> (38)	22 (58)	n.a.	33 (87)	32 (84)	34 (89)	35 (92)	38 (100)	n.a.	n.a.	
<i>Pseudomonas aeruginosa</i> (47)	n.a.	46 (98)	47 (100)	46 (98)	43 (91)	44 (94)	43 (91)	n.a.	n.a.	
<i>Acinetobacter baumannii</i> (54)	n.a.	41 (76)	39 (72)	45 (83)	44 (81)	40 (74)	47 (87)	n.a.	n.a.	
<i>Stenotrophomonas maltophilia</i> (48)	n.a.	36 (75)	8 (17)	3 (6)	13 (27)	34 (71)*	2 (4)	33 (69)	45 (94)	
Isolates from total patients with haematological malignancy										
<i>Escherichia coli</i> (124)	109 (88)	n.a.	114 (92)	120 (97)	114 (92)	72 (58)	124 (100)	n.a.	n.a.	
<i>Klebsiella pneumoniae</i> (148)	138 (93)	n.a.	141 (95)	141 (95)	130 (88)	121 (82)	148 (100)	n.a.	n.a.	
<i>Enterobacter cloacae</i> (54)	28 (52)	n.a.	48 (89)	46 (86)	48 (89)	48 (89)	54 (100)	n.a.	n.a.	
<i>Pseudomonas aeruginosa</i> (64)	n.a.	46 (97)	63 (99)	62 (97)	58 (91)	59 (92)	62 (97)	n.a.	n.a.	
<i>Acinetobacter baumannii</i> (101)	n.a.	41 (75)	81 (80)	84 (83)	82 (81)	80 (79)	99 (98)	n.a.	n.a.	
<i>Stenotrophomonas maltophilia</i> (67)	n.a.	31 (64)	11 (16)	5 (7)	18 (27)	48 (72)*	3 (3)	42 (63)	61 (91)	

n.a., Not available; SXT, sulfamethoxazole-trimethoprim.

* For *S. maltophilia* isolates, levofloxacin was tested instead of ciprofloxacin.

DISCUSSION

This retrospective study disclosed several important points. First, Gram-negative bacteria were the predominant pathogens (60%) and fungal infections were relatively uncommon (6%) in bloodstream infections in patients with neutropenia. Second, the number of *Acinetobacter* and *Stenotrophomonas* infections increased from 2002 to 2006 and were the third (7%) and fourth (6%) most frequent after *E. coli* and *Klebsiella*. Last, an increasing burden of antimicrobial resistance was noted in several pathogens; >40% quinolone resistance and 12% of ESBL producers in *E. coli* isolates, 6% of *A. calcoaceticus-baumannii* complex isolates exhibiting resistance to several agents and 21% of *E. faecium* with vancomycin resistance.

Several studies in recent years have reported a shift from Gram-negative infections towards Gram-positive infections in cancer patients with febrile neutropenia [18, 24–27]. However, Gram-negative bacteria have predominated in such patients in most reported studies from Taiwan [10, 14]. The reasons why Gram-negative pathogens have continued to be the most prevalent in NTUH in the last 10 years compared to the previous survey from 1996 to 2001 [10] remain unknown. These findings underline the need for regular surveillance of the epidemiology and antimicrobial resistance of pathogens in different geographic areas to determine appropriate empirical antibiotic treatment for neutropenic cancer patients.

A. calcoaceticus-baumannii complex and *S. maltophilia* in bloodstream isolates of neutropenic patients represent around 1–3% in the USA and Europe [27, 28]. However, in some areas the frequency of *A. calcoaceticus-baumannii* complex in neutropenic patients is reportedly higher at 6–9% [10, 16, 29] and several studies have noted an increasing frequency of *S. maltophilia* infection in these patients [15, 17, 30].

We found no significant difference in the microbiological spectrum between neutropenic patients with community-acquired and nosocomial infection and this might be explained by the fact that these patients have frequent admissions for chemotherapy or supportive care and thus the distinction between community-acquired and nosocomial infection is less rigid.

The emergence of quinolone-resistant *E. coli* in neutropenic cancer patients has been observed in several institutions in Europe since 1994 [18, 31] and in our hospital increased from 33% to 50% between 1996–2001 and 2002–2006. Ciprofloxacin-resistant *K. pneumoniae* isolation also increased (13–20%) over

the two periods. This may reflect the more widespread use of quinolones for prophylaxis in high-risk populations. Nevertheless, during this study period, the susceptibility of *E. cloacae* to cefotaxime, amikacin, and piperacillin-tazobactam increased from 38% to 58%, 71% to 84%, and 75% to 89%, respectively. Ceftazidime and carbapenems remained effective agents for *P. aeruginosa* infection. There was a decrease in the activity of antibiotics against *A. baumannii* isolates over the two periods (83–94% susceptible in 1996–2001 and 72–87% in 2002–2006). Carbapenem resistance in this complex has been reported to have risen in the USA from 9% in 1995 to 40% in 2004 [32]. We found no extreme resistance in this group in the first survey [10] unlike the current study. Multiresistant *Acinetobacter* infections tend to occur in immunocompromised patients, those with serious underlying diseases, and in those subjected to invasive procedures and/or treated with broad-spectrum antibiotics [33, 34].

Patients with prolonged neutropenia, exposure to broad-spectrum antibiotics such as the carbapenems, and those requiring mechanical ventilation are at increased risk of *S. maltophilia* infection [15]. Our neutropenic patients with positive blood cultures of *S. maltophilia* had significantly worse 14-day outcome than other groups and 76% of *S. maltophilia* isolates were recovered from neutropenic patients with refractory disease status. Further studies are necessary to clarify the relationship between *S. maltophilia* infection and poor outcome in patients with haematological malignancy taking into account other variables potentially associated with poor outcome.

In conclusion, several opportunist pathogens, some exhibiting significant antimicrobial resistance, are increasing as the causes of infection in neutropenic cancer patients. Regular monitoring of bacterial epidemiology and antimicrobial resistance in these patients are crucial and will help to inform the suitability of local policies for the use of antimicrobial agents and the choice of agents for empirical antibiotic therapy, and prophylaxis in high-risk patients.

DECLARATION OF INTEREST

None.

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