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ORIGINAL ARTICLE

Emergence of MRSA in positive blood cultures from patients with febrile neutropenia—a cause for concern

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Abstract
Goals of work Febrile neutropenia (FN) causes considerable morbidity in patients on cytotoxic chemotherapy. Recently, there has been a trend towards fewer Gram-negative and more Gram-positive infections with increasing antibiotic resistance. To assess these patterns, data from a supra-regional cancer centre in Ireland were reviewed.
Patients and methods A 5-year review of all positive blood cultures in patients undergoing anti-cancer chemotherapy was carried out.
Main results Eight hundred and ninety-four patients were reviewed. The mean incidence of FN was 64.2 cases per year. Eight hundred and forty-six blood culture specimens were taken and 173 (20.4%) were culture positive. The isolated organisms were Gram positive (71.1%), Gram negative (27.8%) and fungal (1.1%). Of the Gram-positive organisms, 75.6% were staphylococci. Of these, 67.8% were coagulase-negative staphylococci and 30.1% were *Staphylococci aureus*. Amongst the *S. aureus*, 89.3% were methicillin-resistant (MRSA). Vancomycin-resistant enterococci were not identified as a cause of positive blood cultures.
Conclusions Amongst patients with cancer who develop FN in our hospital, Gram-positive bacteria account for the largest proportion. The high proportion of MRSA as a cause of positive blood cultures is of concern.

Keywords Febrile neutropenia · MRSA · VRE · Blood cultures

Abbreviations

FN	febrile neutropenia
MRSA	methicillin-resistant *Staphylococcus aureus*
VRE	vancomycin-resistant enterococci
CSFs	colony-stimulating factors
S. aureus	*Staphylococcus aureus*

Introduction

Febrile neutropenia (FN) causes considerable morbidity in patients on cytotoxic chemotherapy [1, 2]. Despite improvements in environmental controls, antibiotic prophylaxis and therapy, it remains a significant clinical problem [2, 3]. The mortality from FN may be up to 10%, depending on the population studied, and FN still accounts for the majority of chemotherapy-associated deaths [1, 4, 5]. Extensive investigations do not usually yield a causative organism and treatment remains empirical based on known patterns of infection [6–8].

Historically, Gram-negative infections were the commonest and most clinically important pathogens but in

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recent years there has been a trend towards fewer Gram-negative and more Gram-positive infections [1, 6, 9]. The exact reasons for this are unclear but are probably multifactorial and include the increasing use of broad-spectrum beta-lactams, quinolone prophylaxis, the persistence of oral mucositis as a clinical problem despite advances in supportive therapies and, importantly, the increased use of central venous access devices [1–3, 6].

Of particular concern in recent years has been the growing level of antibiotic resistance, particularly amongst Gram-positive bacteria, specifically the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) [1, 2, 4]. There is considerable geographic variation in the prevalence of MRSA but in some parts of Europe up to 43% of all *S. aureus* isolated from blood cultures are methicillin resistant [10–13]. In addition, the emergence of vancomycin-resistant enterococci (VRE) has led to the need to use new antimicrobials, such as the oxazolidinones, of which linezolid is the first commercially available [4].

We reviewed data from a supra-regional cancer centre in Ireland to assess the patterns of positive blood cultures, antibiotic resistance amongst our patient population, and the appropriateness of current antibiotic practices.

Patients and methods

Beaumont Hospital is a tertiary referral supra-regional cancer centre including the national centre for the treatment of central nervous system tumours. The Medical Oncology Service treats patients for a wide variety of solid organ malignancies and lymphomas. Colony-stimulating factors (CSFs) and prophylactic antibiotics during neutropenia are not routinely used in the majority of patients in line with international guidelines [14, 15]. The standard management of patients with FN involves first-line therapy with piperacillin–tazobactam in combination with the aminoglycoside, gentamicin. Vancomycin is used as standard second-line therapy and in first-line therapy when there is clinical concern about staphylococcal infection, including that caused by MRSA.

A 5-year review of all blood cultures in patients undergoing anti-cancer chemotherapy was carried out from 1st July 2000 to 30th June 2005. Laboratory data from all patients attending the Medical Oncology Service at Beaumont Hospital were retrospectively reviewed. Blood culture results were reviewed for the causative organisms and the patterns of antibiotic resistance. Laboratory data were reviewed to assess whether infection occurred in the setting of neutropenia or a normal neutrophil count. Neutropenia and febrile neutropenia were defined as per the National Cancer Institute common terminology criteria for adverse events version 3.0 [16]. The annual incidence of FN was calculated from the number of blood cultures taken in the setting of new episodes of neutropenia. Further clinical correlation was sought in the setting of positive blood cultures with multi-resistant pathogens such as MRSA and VRE.

Results

During the study period, 894 patients had one or more microbiological investigations performed and were included in the analysis. The mean incidence of FN was 64.2 cases annually with 62, 71, 69, 59 and 60 cases in each of five consecutive years. In total, 846 blood culture specimens were taken from patients with neutropenia. Of these, 173 (20.4%) were positive. These cultures represent the fact that over the 5 years 68 patients had 88 separate episodes of FN that were associated with positive blood cultures. Therefore, bacteraemia was documented in 27.4% of all cases of FN.

The pathogens causing positive blood cultures are outlined in Table 1. As some patients had several positive blood cultures, the numbers of patients with the corresponding isolates are also shown. Gram-positive bacteria accounted for 71.1% of positive blood cultures in patients with FN; Gram-negative were responsible for 27.8% and the remainder were fungal (*Candida glabrata* and *Geotrichum candidum*.). Of the Gram-positive bacteria isolated, 93 (75.6%) were staphylococci. Table 2 shows the breakdown of these staphylococci; in particular *S. aureus*, of which 89.3% were MRSA.

In consecutive years, MRSA was identified from one, one, five, one and zero patients with FN. Of these eight patients with MRSA isolated from blood cultures, four died, with three of the four patients admitted to the intensive care unit prior to death. VRE was not isolated from blood cultures in patients with FN.

Discussion

In the current study, 20.4% of blood cultures yielded an organism which is consistent with other reports where up to 30% of episodes of FN are associated with confirmed bacteraemia [1, 2, 8]. The most commonly isolated bacteria in our patients were coagulase-negative staphylococci, which accounted for 63 of 173 (36.4%) blood culture isolates, similar to other studies [6]. Overall, Gram-positive organisms accounted for nearly three-quarters (71%) of all blood culture isolates. These data support the documented high rates of Gram-positive infections in cancer patients with FN [1, 6, 9]. Gram-positive infections have now been more common than Gram-negative infections in FN for almost three decades [17].

Table 1 Organisms causing positive blood cultures in febrile neutropenic patients, 2001–2005

Gram-positive species	No of isolates (%)	No of patients (%)	Gram-negative species	No of isolates (%)	No of patients (%)
Staphylococci	93 (53.8%)	*40*	*E. coli*	21 (12.1%)	15
Enterococci	11 (6.4%)	*6*	*Pseudomonas aeruginosa*	13 (7.5%)	7
Streptococci	10 (5.8%)	*9*	*Klebsiella* spp.	5 (2.9%)	5
Clostridium spp.	3	*2*	*Enterobacter* spp.	3	3
Bacillus spp.	3	*2*	*Acinetobacter* spp.	2	1
Micrococcus spp.	2	*2*	*Stenotrophomonas maltophilia*	2	1
Corynebacterium spp.	1	*1*	*Serratia* spp.	1	1
			Other *Enterobacteriaceae*	1	1
Total	123 (71.1%)	62 (63.9%)	Total	48 (27.8%)	34 (35.1%)
Fungal	2 (1.1%)	1			

Spp Species

A worrying trend is the high level of methicillin resistance noted amongst *S. aureus* isolates, 89.3%. This is much higher than might be expected, given known patterns of resistance, which exhibit marked geographical variation [2, 10–12]. In addition, there is marked variation in the resistance pattern of *S. aureus* between studies depending on the population studied and the clinical specimen. It is estimated that in the US and in many European countries about 30% of all isolates of *S. aureus* are methicillin resistant [18]. In some centres, this may be greater than 50% and in Japan may be as high as 70% [2, 18].

The prevalence of MRSA-positive blood cultures is monitored by the European Antimicrobial Resistance Surveillance System [13]. A recent review of 29 laboratories across the UK and Ireland suggested that up to 42% of *S. aureus* isolates from blood were MRSA [12]. Most recent data suggest that in Ireland this rate has stabilised at 43% [13]. It therefore appears that bacterial resistance is important in our unit with the prevalence of methicillin resistance at 89% amongst *S. aureus*, though the total numbers are relatively small.

Other studies have specifically looked at rates of MRSA amongst positive blood cultures in patients with cancer. In 2000, Gopal et al. [19] examined a series of patients with cancer, *S. aureus* isolated from blood cultures and normal neutrophil counts in a tertiary referral centre in the US and found that 32% of isolates of *S. aureus* were MRSA. More recently, a series of 309 patients with FN and haematological malignancies in Venezuela showed 23.1% of *S. aureus* were MRSA [20]. Allowing for geographic variations and other confounding factors such as the patient populations, the reported rates of methicillin resistance amongst *S. aureus* cultures in patients with cancer are considerably less than in our study (89.3%).

Table 2 Staphylococci from blood cultures in febrile neutropenic patients, 2001–2005

	No. of isolates	% of isolates
Coagulase-negative staphylococci	63	67.8
Staphylococcus saprophyticus	2	2.1
Staphylococcus aureus	28	30.1
MRSA	25	89.3
Methicillin sensitive	3	10.7

In our study, half of the eight patients with MRSA infection died, although the overall numbers are low. Three of the four patients who died were treated in the intensive care unit although further clinical correlation was not included in the study. Because of the retrospective nature of this study, it is unclear whether this finding highlights the danger of isolating MRSA from blood cultures itself or the association between MRSA and the intensive care unit and the presence of a recent or current malignancy. In a prospective study of *S. aureus* isolates from blood cultures in patients with cancer by Figuera Esparza et al. [20], MRSA was not associated with a higher mortality than methicillin-sensitive *S. aureus*. Patients in this study, however, had normal neutrophil counts compared to our study of patients with cancer and FN [19].

This study has several limitations. It was retrospective and did not assess the effect of CSFs, prophylactic antibiotics and other clinical factors that may have contributed to the development of FN, e.g. the underlying malignancy, chemotherapy-related issues, the severity of neutropenia, the presence or otherwise of indwelling central venous catheters and drains. By focussing on blood culture isolates only, we may have underestimated the impact of Gram-negative bacteria, which may be more likely to cause tissue-specific infections such as pneumonia, urinary tract infections and soft tissue infections [1, 2].

First-line therapy for FN was piperacillin–tazobactam in combination with the aminoglycoside, gentamicin. This antibiotic policy remained unchanged throughout the duration of the study but is currently being reviewed. Despite clinical concerns about growing antibiotic resistance, the fact that no patients with FN had VRE isolated

from blood culture suggests that current antibiotic protocols are largely appropriate, but the inclusion of an aminoglycoside may be unwarranted [21].

Given the rate of methicillin resistance amongst blood culture isolates of *S. aureus*, there may be a need to incorporate glycopeptides into first-line treatment, particularly in patients with a known history of MRSA or at clinical risk of MRSA, such as those patients with indwelling central venous devices. The use of glycopeptides such as vancomycin as part of first-line therapy for FN remains controversial because of the associated rise in VRE but requires further evaluation [1]. To date, studies have not shown any benefit from the addition of vancomycin to first-line therapy in the absence of clinical suspicion or documented microbiological infection with resistant Gram-positive organisms [1, 22].

We have confirmed the predominance of Gram-positive over Gram-negative bacteria as the documented cause of positive blood cultures associated with FN. The emergence of MRSA, with death in 50% of patients, is of major concern although the overall numbers are small and there is no clinical correlation in this study. This highlights the need to enhance infection prevention and control measures in our unit, e.g. more isolation rooms, and to consider reviewing our empirical antibiotic approach to treating FN.

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