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Emerging problem pathogens: A review of resistance patterns over time

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Summary Despite the advances in chemotherapy for cancer patients, infectious complications remain an important cause of mortality and morbidity. Surveillance data report not only a shift in the aetiology of infections and resistance patterns in this patient population, but also important differences between regions and countries. Viridans streptococcal bacteraemias are common among cancer patients being second only to the coagulase-negative staphylococci. However, in certain centres in Europe Gram-negative bacilli have once again become the predominant infecting pathogens. The problems associated with emerging resistance have been widely documented in the literature. In some institutions methicillin-resistance among coagulase-negative staphylococci has reached 75%, and in others the incidence of extended-spectrum beta-lactamase producing Gram-negative bacilli has risen markedly. These shifts in antimicrobial susceptibility are important in guiding the choice of agents for febrile neutropenia. Antibiotic use and prophylaxis have both been associated with changes in susceptibility, and prescribing habits may influence emerging resistance. In this context, the choice of empirical antibiotic therapy and the use of prophylaxis should be driven by a sound understanding of local circumstances.

Introduction

Despite advances in antimicrobial therapy, infectious complications remain an important cause of mortality and morbidity among febrile neutropenic patients. Important regional differences in the aetiology of infection exist. Surveillance data from the International Antimicrobial Therapy Group (IATG) of the European Organisation for Research and Treatment of Cancer (EORTC) show a shift in the aetiology of infection and in the patterns of resistance (Figure 1). Before the mid-1980s Gram-negative bacilli were the predominant pathogens associated with bacteraemia. In trials undertaken during the late 1980s there was a shift to Gram-positive cocci which became the dominant isolates until the turn of the century when the

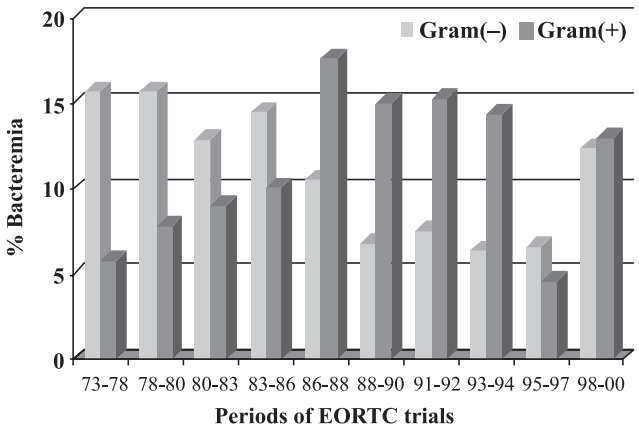

Figure 1. Single agent bacteraemia in EORTC–IATG trials (1972–2000) [1].

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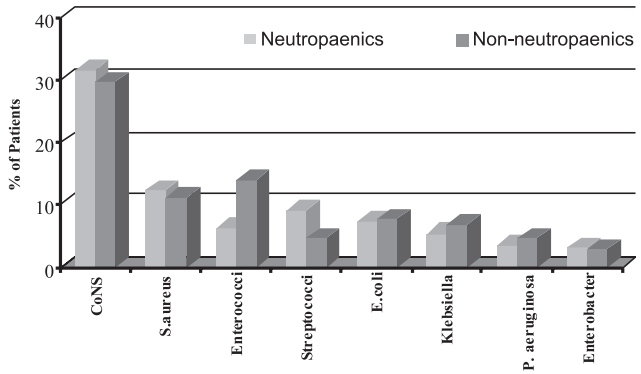

Figure 2. Predominant pathogens reported in US cancer patients (SCOPE) 1995–2000 [2].

Gram-negative bacilli re-emerged, notably *Pseudomonas aeruginosa*, *Escherichia coli* and the other enteric Gram-negative bacilli. This shift may be partially explained by a decrease in the use of fluoroquinolone as prophylaxis. A comparison of data from IATG–EORTC reported a significant decline in overall mortality (P = 0.001) and mortality associated with single agent Gram-positive bacterial infections (P = 0.009) between Trial V (1986) [3] and Trial XIV (2000) [4]. However, mortality associated with infections due to single species Gram-negative bacilli over the same period did not change. This re-emergence of Gram-negative bacilli has important implications for managing these patients; though, these trends are not found globally.

In the USA, data from the Surveillance and Control of Pathogens of Epidemiologic Importance (SCOPE) Project reports Gram-positive bacteria as the predominant pathogens in both neutropenic and non-neutropenic patients [2]. Between 1995 and 2000 these isolates have significantly increased (P = 0.001), with coagulase-negative staphylococci (CoNS) and *Staphylococcus aureus* predominating. In cancer patients without neutropenia, SCOPE has reported an increase in enterococci during this time. Importantly, among patients with severe neutropenia viridans streptococci were the third most commonly isolated pathogen (Figure 2), accounting for 1 in 10 isolates. In terms of Gram-negative bacilli, SCOPE data reports *E. coli*, *Klebsiella* spp. and *P. aeruginosa* as the most commonly isolated organisms. There were also high levels of resistance to methicillin amongst CoNS (77%) and *S. aureus* (29%), to vancomycin among *Enterococcus faecium* (VRE) (56%), to cephalosporins among the Enterobacteraceae (42%) but relatively low levels of cephalosporin (7%) and carbapenem-resistance (6%) amongst isolates of *P. aeruginosa*. However, resistant patterns differ between regions, countries and between institutions, which is an important consideration in terms of managing this patient group.

Epidemiology of infections in cancer patients

In a review of the incidence of bacteraemia among haematopoietic stem cell transplant recipients over a 7-year period, a shift in the aetiology of infection

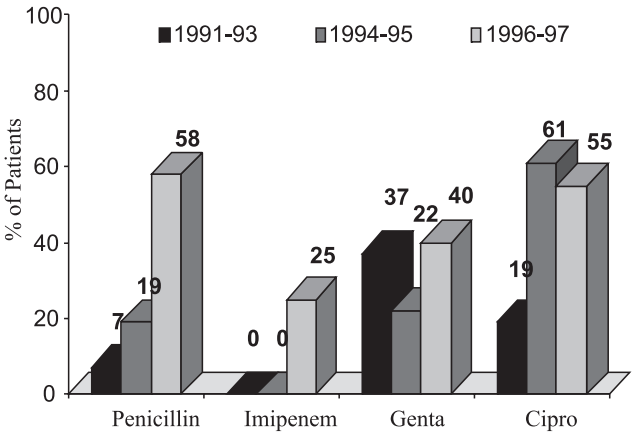

Figure 3. Resistance rates of *Streptococcus* spp. in BMT patients 1991–1997 [5].

was noted, although the overall infection rate fell [5]. During the first 5 years of this survey the Gram-positive cocci predominated, although the ratio of Gram-positive to Gram-negative bacteria declined from 2.7 to 1.3. Viridans streptococci, primarily *Streptococcus mitis* and *Streptococcus sanguis*, accounted for 49% of Gram-positive bacteria, followed by CoNS (20%) and *S. aureus* (6%), whilst *E. coli* and *Klebsiella* spp. were the most commonly isolated bacteria accounting for over half of the Gram-negative bacilli isolated. A significant increase in resistance to penicillin, ciprofloxacin and imipenem among the streptococci was noted during this time (Figure 3), and 40–45% of *Enterobacter* spp., *Serratia* spp. and *Citrobacter* spp. were resistant to ceftazidime and piperacillin, 50% of *E. coli* and *Klebsiella* spp. isolates were resistant to piperacillin and 15% of *P. aeruginosa* isolates were resistant to ceftazidime and tobramycin. EORTC data show a similar increase in the incidence of streptococcal infections, rising from 12% (1973–78) [6,7] to 47% (1998–2000) [4].

An earlier study also reported a predominance of Gram-positive bacteraemias among Italian paediatric cancer patients over a one-year period [8]. Of these, 123 (64%) occurred in neutropenic and 68 (36%) in non-neutropenic patients. Gram-positive cocci caused 45% (85/191) of the episodes, Gram-negative bacilli 41% (78/191), and fungi 9% (18/191). The remaining 5% (10/191) of episodes were poly-microbial infections. A 12-year survey in a single Italian tertiary centre reported that single-species Gram-positive bacteraemia accounted for 79/153 episodes (52%), single-species Gram-negative bacteraemia for 64 (42%), polymicrobial bacteraemia for 5 (3%) and isolated fungaemia for 5 (3%) episodes, respectively [9]. CoNS, viridans streptococci and *S. aureus* were the most commonly isolated Gram-positive bacteria [26/84 (31%), 25/84 (30%) and 19/84 (23%), respectively] and *Klebsiella*, *Enterobacter*, *Serratia* group, *E. coli* and *P. aeruginosa* the most commonly isolated Gram-negative bacilli [19/70 (27%), 15/70 (21%) and 14/70 (20%), respectively]. These data all confirm the importance of viridans streptococci as a risk factor for patients with febrile neutropenia. The intensity of chemotherapy was an associated risk factor for infection in this patient group. Data from IATG–EORTC Trials IX and XI show that

Table 1
Sites of infection in cancer patients (September 2001 – February 2002) [10]

Type of infection	Incidence of infections in patients with			
	Haematological malignancy		Solid tumours	
	N	(%)	N	(%)
Pneumonia	93	(38)	99	(26)
Bloodstream	88	(35)	74	(20)
Urinary tract	27	(11)	85	(22)
Skin and soft tissue	17	(6)	65	(17)
Gastrointestinal	16	(6)	38	(10)
Other	12	(4)	17	(5)
Total	253	(100)	378	(100)

15% (129/836) of the evaluable patients developed a secondary infection, of which half were attributable to Gram-positive bacteria and 42% (54/129) were attributable to a fungal infection [11]. CoNS accounted for 44% (11/25) of the Gram-positive isolates.

Analysis of data from Turkey over an 18-year period shows a similar increase in single species Gram-positive bacteraemia among cancer patients [12]. In 2004, CoNS accounted for ~70% of infections and enterococci for 13%. Interestingly the incidence of *S. aureus* infections had fallen from 47% (1991–94) to 9.6% in 2004. In single agent Gram-negative infections, *E. coli* had fallen from 58% in 1994 to 30% in 2004, *Enterobacter* spp. from 27% to 8%, whilst *Klebsiella* spp. and *P. aeruginosa* had increased from 7% to 23% and 11% to 23%, respectively. This shift in aetiology towards the Gram-positives was associated with an increase in the number of patients undergoing haematopoietic stem cell transplantation at Hacettepe University Hospital. A sub-analysis of all isolates from 2004 showed that the Gram-negative bacilli were the dominant isolates accounting for 52% (243/468) of all-cause infections, whereas they accounted for only 41.5% of bacteraemias. Among haematopoietic stem cell transplant recipients and/or those with indwelling intravascular catheters, the Gram-positive cocci were the dominant pathogens accounting for 59% (135/229) during the same period.

New data presented at the 16th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) from MD Anderson Cancer Centre at Houston, Texas, in the USA reported a rise in Gram-positive bacteria causing bacteraemia among cancer patients from 73% of 1055 in 1998 to 82% of 1025 in 2004 [13]. Amongst Gram-negative bacilli *E. coli* and *P. aeruginosa* accounted for 24% and 19%, respectively, and other Enterobacteriacae and non-fermenting Gram-negative bacilli for 32% and 25%, respectively. A sharp increase was noted in rates of isolation of *Stenotrophomonas maltophilia*, i.e. 6% in 1994 vs 16% in 2004 ($p < 0.01$). Compared with the Gram-positive infections reported by this group, a significant proportion of the Gram-negative bacteraemia were high-grade (18% vs 39% in 1998, and 7% vs 44% in 2004; $P < 0.001$).

A recent letter pointed out that focussing only on monomicrobial nosocomial bacteraemia may be misleading as this presents only part of the picture associated with infections in cancer patients [10]. This group reported that these bacteraemias accounted for only 35% of infections among patients with haematological malignancies and 20% of infections among patients with solid tumours (Table 1). The National Cancer Institute has also reported that the number of polymicrobial infections has dramatically increased since the 1970s and accounts for 23–31% of documented bacterial infections, with ~80% of these infections having a Gram-negative bacillary component and ~33% being caused exclusively by multiple Gram-negative bacilli.

Emerging resistance and problem pathogens

Methicillin resistance among CoNS has reached an incidence of 75% in some institutions [14]. Some isolates also have intermediate susceptibility to vancomycin, and occasionally vancomycin-resistant coagulase-negative staphylococci have been described [15]. The emergence of methicillin-resistance has been widely documented in the literature. Methicillin-resistant *S. aureus* is associated with significant mortality and morbidity [16]. However, an unexpectedly high mortality rate (33.4%) related with CoNS infections was reported in the SCOPE trial [2]. The same data indicated relatively lower mortality rates associated with infections caused by methicillin-resistant *S. aureus* (17.7%).

The increasing levels of resistance, particularly amongst viridans streptococci, is also of concern in cancer patients. Multi-drug resistance in this group of streptococci was first reported in 1996 [17], and the frequency of isolation of viridans streptococci from the blood of neutropenic patients with cancer has significantly increased over the course of the last 10–20 years. Risk factors in this patient population include severe neutropenia, oral mucositis, administration of high-dose cytosine arabinoside, and antimicrobial prophylaxis with either trimethoprim-sulfamethoxazole or a fluoroquinolone. Figure 3 illustrates the rise in penicillin resistance between 1991–1997 in a single centre trial with haematopoietic stem cell transplant recipients [9]. Table 2 shows the rates of resistance to various antimicrobials reported in three different studies conducted between 1995 and 2002. Similar trends have also been reported in data from the USA [2,18]. Recently, Han et al. [18] reported 28% (7/25) *S. mitis* strains isolated from cancer patients to be resistant to penicillin (MIC > 4 μg/mL). These strains were also significantly more resistant to fluoroquinolones and to ⩾3 classes of antibiotics. Young and elderly patients have higher levels of bacteraemia associated with *S. mitis* and a significant level of septic shock is caused by *S. mitis* ($P = 0.007$) in these patients.

The incidence of extended-spectrum β-lactamases (ESBLs) has increased in many institutions [19] and has also been reported in the isolates from Hacettepe University Hospital, where the incidence of ESBLs has reached ~50% in patients with ventilator-associated pneumonia. Among

Table 2
Percentage resistance of viridans Streptococci in patients with cancer 1995–2002

Antibiotic	1995[a]	2000[b]	2002[c]
Penicillin	56	40	79
Cefotaxime	45	24	-
Ceftriaxone	-	22	47
Ceftazidime	74	56	47
Cefepime	-	34	58
Imipenem	30	7	-
Erythromycin	40	36	-
Rifampin	0	-	-
Vancomycin	0	0	-

[a] Carratala (1995) [20]; [b] Marron (2000) [21]; [c] Bruckner (2002) [22].

cancer patients 31% of *E. coli* and 25% of *Klebsiella* spp. were shown to be ESBL producers, and the incidence among blood culture isolates was 36% and 29%, respectively [12]. Data from MYSTIC surveillance (1997–99) reported the incidence of ESBLs in Europe to be 23.4%, 2.8% and 1.5% and AmpC beta-lactamase producers to be 13.2%, 18.1% and 12.5% among isolates from neutropenic patients over the three years reported [23]. A study of the incidence of ESBL-producing *K. pneumoniae* among febrile neutropenic paediatric patients conducted in Kuala Lumpur in 1996–97 reported that 51.6% of isolates were ESBL producers [24]. Infections associated with these isolates were associated with a significantly longer duration of hospitalisation (21.9 versus 4.3 days, P = 0.003), and identified prior cephalosporin use within the previous two weeks to be a risk factor for colonisation with ESBL producers. Sepsis-related mortality was also significantly higher in children infected with resistant strains (50.0% versus 13.3%, P = 0.002).

Siu and co-workers [25] reported data from 13 paediatric patients who presented with 16 episodes of bacteraemia between 1993 and 1997 from an oncology ward with a high level of resistance among Gram-negative bacilli. Intermediate susceptibility to cefotaxime was reported for all isolates, and molecular characterisation identified two *K. pnuemoniae* and three *E. coli* to be carrying both SHV-5 and TEM-1 genes while the isolate of *K. pneumoniae* carried both SHV-2 and SHV-5 genes. Although there are a lot of data in the literature relating to the incidence of ESBLs, there is a paucity of information among febrile neutropenic patients. However the few publications cited above suggest that these pathogens should be considered when initiating treatment of cancer patients when there is a high-incidence of ESBL bacilli isolated from the general hospital population.

Fluoroquinolone prophylaxis and resistance

In response to the emerging resistance in Gram-negatives, particularly *E. coli*, the use of fluoroquinolone prophylaxis has declined. Data from 14 centres participating in EORTC XI and XIV shows a fall in the use of fluoroquinolone prophylaxis from 55% to 28% [26]. The incidence of fluoroquinolone-resistant *E. coli* dropped from 38% to 20% between the two studies. However, the incidence of Gram-negative bacteraemia increased from 6.2% (24/386) to 9.6% (32/332) in patients receiving fluoroquinolone prophylaxis and 9.2% (35/386) to 14.5% (48/332) in patients who had not received prophylaxis between the two trials.

A recent randomised controlled study of fluoroquinolone prophylaxis versus placebo among 760 neutropenic cancer patients reported a lower rate of microbiologically defined infections (absolute difference in risk, - 17 percent; 95% confidence interval [CI]: - 24% to - 10%; P < 0.001), bacteraemias (difference in risk, - 16 percent; 95% CI: - 22% to - 9%; P < 0.001), and single-species Gram-negative bacillary bacteremias (difference in risk, - 7%; 95% CI: - 10% to- 2%; P < 0.01) in the levofloxacin arm [27]. Gram-negative bacilli were isolated from 3% of patients receiving the drug versus 1% of those receiving placebo. Amongst the Gram-negative bacteraemias, 77% (10/13) versus 17% (4.24) of isolates were resistant to levofloxacin in the treated and placebo groups, respectively, as were 91% (31/34) and 64% (28/44) of Gram-positive isolates. Methicillin-resistant CoNS was the most frequently isolated Gram-positive species and all were resistant to levofloxacin.

A German study investigating the epidemiologic evolution of fluoroquinolone resistance of *E. coli* in a haematology-oncology unit recommending fluoroquinolone prophylaxis during episodes of neutropenia reported a dramatic decline in the levels of resistance after withdrawing fluoroquinolone prophylaxis, from 56% to 15% (P = 0.002; Figure 4) [28]. There was no significant difference in the incidence of fever per neutropenic episode during the three study periods (7/1997-1/1998, 2/1998-7/1998 and 8/1998-1/1999), however during the period when prophylaxis was withdrawn, more patients developed bacteraemias (34%) than in the periods prior- and post-study intervention (28% and 19%, respectively). More polymicrobial infections were also reported in the period with no prophylaxis, 8% versus 3% and 1%, respectively. A recent meta-analysis of clinical trials comparing fluoroquinolone prophylaxis with placebo (22 trials) or other antibiotics (35 trials) was presented at the 16th ECCMID [29].

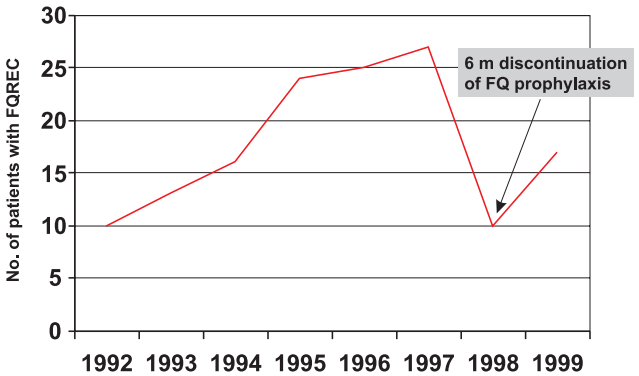

Figure 4. Quinolone-resistant *E. coli* bacteraemia in haematology-oncology patients. Adapted from Kern et al., 2005 [28].

Surveillance data were available for 28 of the studies. When fluoroquinolones were compared to placebo or no intervention, there was a trend to colonisation with resistant *E. coli* among those receiving a fluoroquinolone (RR 1.68, 95% CI: 0.71–4.0), however the rate of infection did not increase significantly. These authors concluded that the reduction in mortality associated with the use of fluoroquinolones probably outweighs the risk of the development of resistance.

Summary

Gram-negative bacilli have re-emerged as the dominant pathogens in some European centres treating cancer patients, whereas in the USA and elsewhere the Gram-positive cocci still predominate. Changes in the aetiology of infection among neutropenic patients and the increase in β-lactam resistance make it imperative to give careful consideration to the choice of drug for empirical therapy. There is also evidence that bacteraemia due to viridans streptococci, particularly among haematopoietic stem cell transplant recipients, may be increasing and that this is also associated with an increase in antibiotic resistance, morbidity and mortality. This again has implications for antimicrobial management. As for fluoroquinolone prophylaxis, this also increases the rate of resistance but further studies are needed to quantify the benefit or harm of prophylaxis with these agents in this patient group.

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