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MEETING REPORT

The emerging problem of bacterial resistance in cancer patients; proceedings of a workshop held by MASCC "Neutropenia, Infection and Myelosuppression" Study Group during the MASCC annual meeting held in Berlin on 27–29 June 2013

Bernardo Rapoport[1] · **Jean Klastersky**[2] · **Harry Raftopoulos**[3] · **Allison Freifeld**[4] · **Mickael Aoun**[2] · **Stephen H. Zinner**[5,6] · **Kenneth V.I. Rolston**[7]

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Introduction

Over the past several decades, the successful treatment of fever and presumed infections in neutropenic patients with cancer has been based on the selection of a number of empiric regimens that contain one or more antibiotics. However, today, the successful treatment of these patients is becoming ever more challenging due to the emergence and dissemination of antibiotic-resistant Gram-positive and Gram-negative bacteria. This review summarizes and updates the proceedings of a workshop organized by the MASCC "Neutropenia, Infection and Myelosuppression" Study Group that was presented at the MASCC annual meeting in Berlin 27–29 June 2013.

✉ Bernardo Rapoport
brapoport@rosebankoncology.co.za

[1] Medical Oncology Centre of Rosebank, Johannesburg, South Africa

[2] Institut Jules Bordet, Centre des Tumeurs de l'Université Libre de Bruxelles, Brussels, Belgium

[3] Merck and Co, Kenilworth, NJ 07033, USA

[4] Nebraska Medical Center, Omaha, NE, USA

[5] Department of Medicine, Mount Auburn Hospital, Cambridge, MA, USA

[6] Harvard Medical School, Boston, MA, USA

[7] Infectious Disease Department, MD Anderson Cancer Center, Houston, TX, USA

Bacterial infections in cancer patients: spectrum of bacterial pathogens

Over the past several decades, substantial shifts in the spectrum of bacterial bloodstream isolates have occurred. Gram-positive cocci, including coagulase-negative staphylococci (CoNS) primarily, and also *Staphylococcus aureus*, viridans group streptococci, and enterococci predominated in the 1980s and 1990s. Gram-negative bacteria including *Enterobacteriaceae* (*Escherichia coli*, *Klebsiella* sp., *Enterobacter* sp.) and the non-fermenters (*Pseudomonas aeruginosa*, *Acinetobacter* spp., *Stenotrophomonas maltophilia*) were less commonly isolated. Two recent systematic reviews of bacteremia in febrile neutropenic (FN) patients at several global sites have documented three emerging trends in these patients: (1) Gram-negative isolates are becoming nearly as prevalent (or more so in some areas) as Gram-positives, (2) Gram-positive and Gram-negative bacteria that are resistant to empirically recommended β-lactam antibiotics are increasing worldwide, and (3) substantial geographic/regional differences exist in patterns of bloodstream isolates from FN patients [1, 2].

Emergence of antibiotic-resistant pathogens

The majority of drug-resistant infections in hospitalized patients have been grouped under the acronym ESKAPE, which stands for *Enterococcus faecium*, *S. aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *P. aeruginosa*, and *Enterobacter* spp. [3]. To adapt this framework to the neutropenic patient, *E. coli* and *S. maltophilia* also should be included, yielding the "ESKAPEES" acronym [4]. Of these six Gram-negative and two Gram-positive species with a

propensity for antibiotic resistance, rates of resistance vary widely among regional and even local institutions. For a given FN patient at risk for bacteremia, the background level of antibiotic resistance in the local environment is the most important risk factor for acquisition of resistant pathogens. Thus, physicians must familiarize themselves with local antibiograms for their particular hospital(s) and choose drugs accordingly. Notably, among 1148 episodes of bacteremia in cancer patients from a prospective multicenter study in Spain, 392 (34 %) were caused by ESKAPE pathogens (*E. coli* and *Stenotrophomonas* excluded in this study), and 54 episodes (4.7 %) were due to antibiotic-resistant ESKAPE strains [5]. In most studies, *E. coli* and *Klebsiella* spp. remain the most frequent causes of bacteremia in FN patients in the current era and an increasing proportion carry resistance plasmids coding for enzymes that destroy the cornerstone antibiotics for empiric therapy of FN—cephalosporins and carbapenems.

Mechanisms of resistance: Gram-positive organisms

The Gram-positive pathogens most commonly isolated from neutropenic patients include coagulase-negative staphylococci (CoNS), *S. aureus*, *Enterococcus* species, and the viridans group streptococci (VGS) or alpha-hemolytic streptococci [6]. Due to the production of beta-lactamases, virtually all strains of CoNS and *S. aureus* are resistant to natural penicillins, aminopenicillins, and anti-pseudomonal penicillins The *mec*A gene encoding low-affinity penicillin-binding protein PBP2a confers resistance to methicillin and other beta-lactams. Currently >90 % of CoNS isolates and 40 to 80 % of *S. aureus* isolates are methicillin-resistant. Resistance to other antimicrobial classes (fluoroquinolones, macrolides, tetracyclines, rifampin, and aminoglycosides) also occurs. Resistance to linezolid is conferred primarily by the *cfr* gene [7]. The mechanisms of daptomycin resistance in *S. aureus* are varied and include accumulation of single-nucleotide polymorphisms in the multipeptide resistance factor gene (*mpr* F) and cell wall thickening [8]. The mechanism of high-level resistance to vancomycin among *S. aureus* isolates (VISA–MIC ≥64.0 μg/mL) involves the horizontal transfer of a transposon containing *van*A and associated genes from vancomycin-resistant enterococci (VRE). Vancomycin resistance among *Enterococcus* species (primarily *E. faecium*) is mediated by two classes of related gene clusters (*van*A and *van*B), which produce resistance by altering the target for vancomycin from D-alanine-D-alanine to D-alanine-D-lactate [9]. Penicillin resistance is not uncommon in VGS and *Streptococcus pneumoniae*, but has not been demonstrated in group A beta-hemolytic streptococci [10]. Tolerance (MBC ≥ 32 times the MIC) to vancomycin and other agents is also an emerging problem [11].

With the emergence of methicillin-resistant *S. aureus* (MRSA) and penicillin-resistant streptococci, vancomycin has become the agent of choice for the treatment of these and other resistant Gram-positive pathogens in neutropenic patients. Recent changes including the so-called upward "MIC creep" and the development of heteroresistant organisms have undermined the therapeutic potential of this agent. Fortunately, several newer agents with potent Gram-positive activity including linezolid, tedizolid, daptomycin, telavancin, dalbavancin, oritavancin, and ceftaroline have been introduced, and several more are in various stages of development.

Mechanisms of resistance: Gram-negative organisms

The Gram-negative pathogens most frequently isolated from neutropenic patients include *E. coli*, *Klebsiella* species, other *Enterobacteriaceae*, *P. aeruginosa*, and other nonfermentative Gram-negative bacilli (NFGNB) [12, 13]. Antimicrobial agents commonly used for empiric and/or targeted therapy of these infections include the extended-spectrum cephalosporins (e.g., cefepime) and the carbapenems (imipenem, meropenem, and, to a lesser extent, doripenem) and combination agents such as piperacillin/tazobactam. The aminoglycosides are used much less often. The fluoroquinolones are still widely used for chemoprophylaxis in neutropenic patients. Resistance to aminoglycosides results from the production of various aminoglycoside-modifying enzymes that produce acetylation, adenylation, and phosphorylation. Quinolone resistance among *E. coli*, *P. aeruginosa*, and other Gram-negative bacilli has been reported from multiple institutions that use these agents for prophylaxis [14]. Mutations in the *gyr*A and *par*C genes are the most common mechanisms involved in high-level quinolone resistance.

Resistance to the β-lactams is mediated primarily through the production of a variety of β-lactamases including Ambler class C (AmpC) beta-lactamases, and the extended-spectrum β-lactamases (ESBLs). ESBLs are derived from older, plasmid-mediated hydrolyzing enzymes, primarily the TEM and SHV types, through genetic mutations that broaden their activity spectrum. Co-carriage of other antibiotic resistance coding genes (i.e., to fluoroquinolones, amioglycosides, macrolides, carbapenems, etc.) on the same plasmid can confer a multidrug resistance phenotype in a subset of these pathogens [15].

The carbapenems, previously considered the last line of defense against organisms resistant to other β-lactams, are currently under threat because of the development and rapid spread of carbapenemases, which belong to Ambler classes A, B, and D [16]. Examples of these carbapenemases include the *Klebsiella pneumoniae* Carbapenemase (KPC) and the metallo-beta-lactamases New-Delhi-1 and New-Delhi-2, VIM, IMP, and OXA-48. Multiple resistance mechanisms may be present in the same isolate. A detailed discussion of the various resistance mechanisms is outside the scope of this manuscript (common mechanisms of resistance have been

summarized in Table 1). Nevertheless, the rapid spread of these organisms globally, aided by the convenience of air travel, and the increasing rates of medical tourism, is of great concern. The conduct of periodic surveys to detect epidemiologic changes and the emergence of newer mechanisms of resistance cannot be stressed enough, particularly since institutional and geographic variations are relatively common.

A new gene mediating resistance to colistin (*mcr-1*) has been described recently on a multidrug-resistant plasmid [17]. This development could prove very dangerous to neutropenic patients infected with multidrug-resistant Gram-negative bacteria.

Epidemiology of resistant Gram-positive bacterial infections

Methicillin-resistant *S. aureus* (MRSA) has been increasing in prevalence over the past two decades. In the USA, community-acquired MRSA is responsible for 80 % or more of skin and soft tissue infections. Most of these infections are caused by a single clone, the most common of which is Strain Type USA 300 (ST USA300) [18]. These strains are currently causing hospital-acquired as well as community-acquired infections in America. This organism is less common in Europe, but a systematic review of data from the mid to late 2000s among 14 hematology/oncology centers in eight countries shows over half of all bacteremic *S. aureus* isolates were MRSA, but the range was 18 to 100 % in adults and 0 to 26 % in children [2]. The risk of MRSA infection in neutropenic patients should be assessed according to the clinical presentation and local epidemiology [19]. Regarding outcomes, a single-center study at MD Anderson in Texas, of 223 cases of MRSA bacteremia in cancer patients, reported a 12 % mortality rate and a 52 % vancomycin treatment failure rate. There was a significant association between mortality rates and vancomycin MIC ≥2 μg/mL [20].

Vancomycin-resistant enterococci (VRE) are an important cause of bacteremia in neutropenic patients with allohematopoietic stem cell transplantation (HSCT) and hematologic malignancy (HM) [21]. The majority are caused by *E. faecium* and less frequently by *Enterococcus faecalis* or other enterococci. Prior colonization (OR 3.88; 95 % CI 1.5–10.4; $p = 0.005$) and T cell depletion (OR 10.89; 95 % CI 1.30–91.35; $p = 0.028$) are important risk factors. Attributable mortality varies between 9 and 14 %.

Antibiotic resistance among viridans group streptococci (VGS) varies between institutions and countries. Recent studies in neutropenic patients with HM or HSCT reported 4 to 14 % of VGS isolates being highly resistant to penicillin [22, 23]. *Streptococcus mitis* is most consistently resistant to penicillin. It is more frequent in children, where 50 to 86 % of strains were found to be penicillin-resistant [24].

Table 1 Common resistance mechanisms among Gram-positive and Gram-negative bacteria causing infections in cancer patients

Organisms	Antimicrobial agents	Resistance mechanisms
Staphylococcus species—including CoNS and *S. aureus*	Penicillin	Beta-lactamase production
	Methicillin	Altered PBP2 binding site
	Vancomycin	Multiple mutations, thickened cell wall, *vanA*- or *vanB*-mediated resistance
	Daptomycin	Cell membrane mutations, cell wall thickening, reduced surface binding, polymorphism in the *mprF* gene
	Linezolid	Mutations at the 23S rRNA binding site, efflux pump (*cfr*)
Enterococcus species	Penicillin/ampicillin	Altered transpeptidase binding sites, overexpression of PBP5
	Gentamicin	Aminoglycoside modifying enzymes, diminished drug entry
	Vancomycin	*vanA*- or *vanB*-mediated resistance (alteration from D-alanine-D-alanine to D-alanine-D-lactate)
	Linezolid	23S rRNA mutations, *cfr* plasmid-mediated resistance
Enterobacteriaceae—including *E. coli*, *Klebsiella* species, *Enterobacter* species, and other *Enterobacteriaceae*	Beta-lactams including penicillins, cephalosporins, and carbapenems	Altered PBPs, augmented drug efflux, hyperproduction or derepression of Amber class C (AmpC), beta-lactamases, carbapenemase (amber classes A, B, and D) production
Non-fermentative Gram-negative bacilli (NFGNB) including *Acinetobacter* species, *Pseudomonas aeruginosa*, S*tenotrophomonas maltophilia*		
	Aminoglycosides	Diminished drug entry, aminoglycoside modifying enzymes
	Fluoroquinolones	Point mutations at topoisomerase binding sites (gyr A or par C)

Epidemiology of resistant Gram-negative bacterial infections

Over the last decade, *Enterobacteriaceae* carrying ESBL-bearing plasmids (primarily *E. coli* and *Klebsiella* spp.) have become the dominant cause of resistance in Gram-negative bacteria (GN) in both hospital and community settings [25]. Several specific ESBL-carrying plasmids, named CTX-Ms, currently represent the most predominant mechanism of resistance among GNB and are endemic in much of Asia, Europe, and South America [26]. Data from a large retrospective survey (2005 to 2011), primarily among European centers, revealed that ESBLs accounted for 34 % of Gram-negative bacteremic episodes in adult cancer patients, although regional incidence varied widely throughout Europe [2]. A recent study of 350 cases of *E. coli* bacteremia in cancer patients revealed that the overall 30-day mortality rate was higher among patients with ESBL *E. coli* bacteremia than for those with susceptible *E. coli* strains (22.1 vs. 12.2 %; $p = 0.02$) [27]. In a study from South Korea, ESBL-associated bacteremia was identified as an independent risk for mortality in patients with hematologic malignancies and associated with a 30-day mortality of almost 45 % [28]. Although many ESBLs produced by *E. coli* are inhibited by β-lactamase inhibitors such as tazobactam, piperacillin is not consistently active and carbapenems remain the treatment of choice for ESBL-related infections; delay of early adequate antibiotic therapy still correlates with increased mortality outcomes [25, 29–31]. Unfortunately, frequent co-carriage of other antibiotic resistance genes on ESBL-expressing plasmids has led to increasing multidrug resistance including the fluoroquinolones [32].

Carbapenem-resistant *Enterobacteriaceae* or CREs (primarily *K. pneumoniae* and *E. coli*) are most commonly isolated and include the *K. pneumoniae* carbapenemases (KPCs). Metallo-β-lactamases (NDM, VIM, IMP, OXA) are another group of plasmid-mediated carbapenemases that have emerged in *K. pneumoniae* and *E. coli*. *P. aeruginosa*- and *Acinetobacter* spp.-containing carbapenemases are often multidrug resistant [33]. Alarmingly, CREs and other carbapenemases can hydrolyze all penicillins, cephalosporins, and aztreonam, as well as the carbapenems. Usually, they remain susceptible only to colistimethate and tigecycline. One report from New York City documented a 56 % mortality rate among 18 patients with HM who developed CRE bacteremias [34]. In a systematic literature review evaluating pathogens causing bacteremias in oncology patients, Mikulska et al. [2] found that 20 % (11–72 %) of Gram-negative isolates were resistant to carbapenems, including 44 % (3–66 %) of *P. aeruginosa* isolates. Two recent publications from Turkey and Greece describe high rates of 30-day mortality among cancer patients who developed CRE bacteremias [35, 36].

Multidrug resistance

Multiple drug-resistant (MDR) Gram-negative isolates in cancer patients are frequent among the "non-fermenters," *P. aeruginosa*, *Acinetobacter* spp., and *S. maltophilia* (the last being intrinsically resistant to carbapenems). MDR is now defined as resistance to at least one antibiotic in three different classes. A recent study reported by Cattaneo et al. included 441 episodes of bacteremia in neutropenic patients with HM occurring between 2004 and 2010, 66 were due to *P. aeruginosa*, among which 33 % were MDR [37]. Inadequate empiric treatment was associated with a mortality rate of 83 % in these cases. In a multivariate analysis, history of chronic obstructive pulmonary disease and carbapenem use were identified as risk factors for developing MDR *P. aeruginosa* infection [38].

In a prospective study of cancer patients at a Spanish referral center, Guidol et al. found that 13.7 % of bacteremia episodes were due to MDR Gram-negative organisms, although their definition included resistance to only two antibiotic classes [39]. In this study, the occurrence of MDR GNB was an independent risk factor for increased 30-day mortality (OR 3.5, 95 % CI 1.4–9.1). Substantial variation in the frequency of MDR isolation by geographic location within Europe was reported [2], with rates among GNB being significantly higher in eastern and southern European countries, including Greece, Italy, Spain, Turkey, Russia, Romania, Hungary as well as Israel. Not surprisingly, MDR pathogens are often found to occur as "breakthrough infections" in patients currently or recently receiving antibiotics [39–41]. In the USA, Rangaraj et al. [41] reported that MDR Gram-negative bacteria, including *P. aeruginosa* and *E. coli*, accounted for approximately 10 % of breakthrough bacteremias among cancer patients who were receiving antibiotics. The observed high all-cause mortality among cancer patients with invasive CRE infections is linked to limited antimicrobial options for treatment. *A. baumannii* infection is uncommon, but resistance to antimicrobials is very high, with MDR strains representing more than 80 % in some cases. The incidence of *S. maltophilia* is very low but has increased in some institutions, especially in the presence of prolonged neutropenia, mechanical ventilation, and selective pressure by carbapenems [42].

Risk factors for bacteremia caused by antibiotic-resistant bacteria

Colonization with resistant organisms, immunosuppressed status, and recent exposure to broad-spectrum antibiotics are major risk factors for development of invasive disease. Specifically, in a study by Bodro et al., factors independently associated with resistant ESKAPE bacteremia included medical comorbidities, prior antibiotic therapy, a urinary catheter, and a urinary tract source [5]. In a German prospective study

among HM and oncology patients, ESBLs or VRE stool colonization was associated with subsequent ESBL bloodstream infection (BSI) [RR 4.5, 95 % CI 2.89–7.04] and VRE BSI (RR 10.2, 95 % CI 7.87–13.32), respectively [21]. Acute myelogenous leukemia and prior treatment with fluoroquinolones were identified as independent risk factors for ESBL BSI in colonized patients. In other studies, risk factors associated with the development of ESBL-associated bacterial infections also include prior use of cephalosporins or fluoroquinolones, as well as severe illness and recent hospitalization [27, 28, 43]. Risk factors for MDR in neutropenic patients with HM or HSCT include the presence of medical comorbidities, prior antibiotic therapy, and the presence of a urinary catheter [39]. Unfortunately, all these risk factors are quite common and provide little specificity to identify which patients will most likely develop invasive-resistant bacterial infections.

Treatment options: Gram-positive bacterial infections

Methicillin-resistant *S. aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE), vancomycin-resistant *Enterococcus* species (VRE), and viridans group streptococci are among the most important pathogens that cause serious infections in at-risk patients. MRSA infections are most frequently treated with vancomycin, and this agent also has been combined with several antibiotics in the search for in vitro synergism or enhanced activity, including oxacillin, nafcillin, cefazolin, ceftaroline, imipenem, rifampin, gentamicin, quinupristin/dalfopristin, and clindamycin. There is some evidence that vancomycin plus linezolid might be antagonistic [44]. Although vancomycin plus rifampin might be attractive because of pharmacodynamic considerations (e.g., vancomycin acting extracellularly and rifampin intracellularly), there is concern that rifampin resistance might arise during therapy and that rifampin might prolong bacteremia and increase both hepatic adverse effects and drug interactions [45].

Daptomycin is finding increasing use in neutropenic patients [46] and has been studied in combination with cloxacillin, nafcillin, oxacillin, ceftaroline, rifampin, gentamicin, clarithromycin, fosfomycin, and trimethoprim-sulfamethoxazole. Yang et al. have described a "seesaw" effect with daptomycin plus oxacillin where the development of daptomycin resistance in MRSA was accompanied by a decrease in oxacillin resistance [47]. A clinical report suggested that anti-staphylococcal β-lactam drugs in combination with daptomycin might enhance clearance of bacteremia due to daptomycin-resistant strains [48]. Another report showed enhanced bacterial clearance of a daptomycin non-susceptible MRSA strain with daptomycin plus ceftaroline in a patient with bacterial endocarditis [49].

Linezolid has been studied in various models in combination with a carbapenem, high-dose daptomycin, rifampin, and doxycycline against MRSA, MRSE, and enterococci [50], but clinical studies are limited. New drugs for use against MRSA infections include telavancin, ceftobiprole, tedizolid, oritavancin, and dalbavancin, some of which are in various stages of development in different countries.

Vancomycin-resistant enterococci may be amenable to treatment with high-dose daptomycin (>6 mg/kg/day), fosfomycin, quinupristin/dalfopristin, linezolid (bacteriostatic), tigecycline (bacteriostatic), and possibly ceftaroline and oritavancin [51].

Treatment options: Gram-negative bacterial infections

In the face of increasing resistance among GNB in FNP, continued re-evaluation of the traditional empiric approach will be necessary. It is possible that monotherapy might not be adequate for these patients and novel combinations will be needed [52].

Multiple drug-resistant (MDR) Gram-negative bacteria pose the greatest risk to neutropenic and other immunocompromised patients. Treatment of carbapenem-resistant Gram-negative infections is complex and poorly understood. Experience is limited and is based on retrospective studies in non-neutropenic patients. It shows that a combination of two or more active drugs (i.e., colistin, tigecycline, or fosfomycin) with a carbapenem is associated with a better outcome [53].

Definitive controlled studies in neutropenic patients are lacking, but CREs have been studied in vitro with antibiotic combinations including colistin or polymyxin B with an aminoglycoside, tigecycline, doxycycline, rifampin, fosfomycin, and daptomycin. A recent retrospective study from three Italian centers that included 126 patients with KpC bacteremia (non-neutropenic) showed lower mortality with the triple combination of colistin plus tigecycline plus meropenem than with single-agent treatment (34 vs. 54 %, $p = 0.02$) [54]. Fosfomycin may show in vitro synergism against CRE with carbapenems, colistin, aminoglycosides, and tigecycline [55].

An intriguing suggestion from in vitro and experimental models implies that a double carbapenem combination might hold promise for the treatment of MDR Gram-negatives including CRE. Bulik and Nikolau [56] combined ertapenem (a carbapenem with little or no activity against these organisms, but for which these organisms' carbapenemase has a high affinity) with the more active doripenem. Ertapenem acted as a "decoy" target for the carbapenemase, leaving doripenem relatively more able to act against the organisms. A preliminary report from this group at the 2013 ECCMID meeting suggested that this combination produced better clinical results against KpC bacteremia than the combination of colistin plus doripenem [57].

With the increasing dissemination of MDR and XDR Gram-negative bacteria around the world, the development of new agents potentially active against these organisms is becoming critically important. Boucher et al. [58] have summarized the

current candidate drugs under development including ceftaroline/tazobactam, ceftozolane/tazobactam, ceftaroline/avibactam, ceftazidime/avibactam, imipenem/MK-7655 (a new beta-lactamase inhibitor), plazomycin, eravacycline, and brilacidin. Some of these drugs have already been introduced but there are little or no published data about use in FNP.

Novel approaches are needed

Until clinical trials of newly introduced antibiotics are established in febrile neutropenic patients, it is important to optimize the use of currently available antimicrobial agents. Optimizing pharmacodynamics (effect of drugs on the organisms) has been studied in in vitro pharmacokinetic models with the goal of identifying the clinical dose that will provide maximal antimicrobial effect and minimal selection of bacterial resistance [59].

In some difficult clinical situations, strategies such as prolonged or continuous infusions of antibiotics and the use of aerosolized antibiotics applied directly to the respiratory tract deserve consideration, although results from the very few prospective trials are inconsistent.

Beyond these considerations, there are a series of new developments that could provide some hedge against the increasing threat of resistant organisms that might not be solved with the use of combinations of presently available antibiotics or by pharmacological manipulation of these drugs. These include drugs that can attenuate the virulence of bacteria in vivo, chemoprotectants, retinoid receptor agents, and chemokine receptor-4 agonists. Better understanding of natural immunity and its possible enhancement could represent another approach. As an example, antimicrobial proteins and anti-infective peptides from mammalian leukocytes have been developed as potential therapeutic agents and have entered clinical trials.

Conclusions

We are facing a major challenge as a result of the continued emergence of multiresistant microorganisms, and we risk returning to the pre-antibiotic era with few or limited active agents. As new agents with activity against resistant Gram-positive and Gram-negative bacteria are introduced, they should be carefully studied in febrile neutropenic infections. As these developments are awaited, we urge consideration of local antibiotic susceptibility data in selecting empiric combination therapy that will provide the most active agents for the resistant pathogens discussed in this review. Pressure on the pharmaceutical industry to discover and evaluate novel agents that might be active against multidrug-resistant pathogens should continue in an attempt to mitigate the adverse outcomes in these fragile patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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