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The prevention and management of infections due to multidrug resistant organisms in haematology patients

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Infections due to resistant and multidrug resistant (MDR) organisms in haematology patients and haematopoietic stem cell transplant recipients are an increasingly complex problem of global concern. We outline the burden of illness and epidemiology of resistant organisms such as gram-negative pathogens, vancomycin-resistant *Enterococcus faecium* (VRE), and *Clostridium difficile* in haematology cohorts. Intervention strategies aimed at reducing the impact of these organisms are reviewed: infection prevention programmes, screening and fluoroquinolone prophylaxis. The role of newer therapies (e.g. linezolid, daptomycin and tigecycline) for treatment of resistant and MDR organisms in haematology populations is evaluated, in addition to the mobilization of older agents (e.g. colistin, pristinamycin and fosfomycin) and the potential benefit of combination regimens.

Introduction

Multidrug resistant (MDR) organisms have emerged as significant pathogens in expanding haematology and haematopoietic stem cell transplant (HSCT) populations. Resistance to currently available drugs and a limited array of new pharmaceuticals necessitates novel pharmacological and non-pharmacological solutions. We review infections due to resistant and MDR gram-negative organisms, vancomycin-resistant *Enterococcus faecium* (VRE) and *Clostridium difficile*, which contribute significantly to the burden of healthcare-associated infections and poorer outcomes in haematology patients [1, 2]. Furthermore, we examine the role of infection prevention programmes, screening, restricted antibiotic prophylaxis and antimicrobial stewardship in controlling these infections.

Emerging resistant organisms in haematology patients

Multidrug resistant gram-negative organisms

The emergence of MDR gram-negative pathogens has resulted in adverse outcomes in haematology cohorts [1, 2]. Gram-negative bacilli contribute up to 71% of bacteraemia isolates in some haematology units, and may be responsible for outbreaks of infection in hospitalized patients [3]. Neutropenia and malignancy are independent risk factors for resistant *Escherichia coli* and *Klebsiella pneumoniae* bacteraemia [4]. Haematological malignancy has been identified as a risk factor for bloodstream infections due to extended-spectrum beta-lactamase (ESBL) gram-negative organisms.[5, 6] In countries with high rates of antibiotic resistance, ESBL or MDR gram-negative organisms contribute up to 13.7% of clinical isolates

[5, 7]. While high level plasmid mediated ampicillin and cephalosporin resistant gram-negative isolates (e.g. TEM, SHV) are widely reported, carbapenem-resistant Enterobacteriaceae (CRE) with a range of underlying resistance mechanisms (e.g. *Klebsiella pneumoniae* Carbapenemase (KPC)) are emerging in haematology populations, with associated mortality [8].

ESBL colonization has been reported in 3–32% of all HSCT patients [9–13], with the same organism isolated in 6% of bacteraemic patients in a recent German study [13]. ESBL bacteraemia in colonized patients has been reported in 2–9% in other studies [10, 12], and the relative risk of ESBL bacteraemia in a colonized patient has been estimated to be 4.5 [13].

Poor outcomes in MDR gram-negative infections are noted in febrile neutropenia and haematology cohorts [4]. MDR *Pseudomonas aeruginosa* in haematology patients is associated with a mortality rate of 35.8–83.3% [1, 14]. ESBL *E. coli* and MDR gram-negative infections are associated with ICU admission and increased mortality in haematology patients [5].

Vancomcyin-resistant enterococcus

Increasing rates of VRE acquisition have been reported in haematology patients, with VRE being responsible for up to 41.1% of all gram-positive bacteraemias [1, 15–17], and prevalence in many haematology units being consistent with endemnicity [18]. Factors common to haematology populations (neutropenia, central venous access, prolonged length of stay, intensive care unit (ICU) admission, allogenic-HSCT (allo-HSCT), AML diagnosis, antibiotic therapies) are known risk factors for VRE acquisition [18–21]. VRE isolation may be a marker of illness severity, especially if detected early in the post-allo-HSCT period [22].

VRE bacteraemia rates in colonized patients range from 0–34% [13, 15–17, 23, 24]. In HSCT VRE-colonized patients, risk factors for VRE bacteraemia include vancomycink use following VRE colonization, prolonged duration of neutropenia and immunosuppression [24].

The impact of VRE is significant. Infection is associated with prolonged hospital stay, increased costs, morbidity and mortality [17, 20, 25]. While attributable mortality for VRE bacteraemia is reportedly low (0–8%) [15, 16, 20, 22–24, 26], in neutropenic and allo-HSCT patients it has been associated with poorer outcomes, especially if bacteraemia is prolonged or occurs early in the post-transplant period [16, 22, 27–29].

Clostridium difficile

C. difficile infection (CDI) is increasingly observed in haematology and HSCT patients [30, 31], where rates have been estimated to be twice the rates observed in hospitalized non-haematology patients [24]. Incidence has been reported as 10–13% in patients with leukemia, 6–27% for HSCT recipients [30–34] and 5–7% for non-leukemic haematology patients [35]. Furthermore, up to one third of infections in haematology patients may present as severe disease [36]. Hyper-virulent strains (e.g. NAP-1, typically resistant to fluoroquinolone agents) are widespread in Europe and the US, and have been reported in HSCT recipients [30]. Treatment outcomes for CDI have been variably reported in haematology patients [34, 35], with a recent study suggesting response to metronidazole and vancomycin to be as low as 53.7% and 50%, respectively [36].

Risk factors for CDI have been identified. In patients with acute myeloid leukemia (AML), CDI has been associated with older age, longer duration of antibiotic therapy, ceftazidime use and prolonged neutropenia [31, 34, 37]. CDI in allo-HSCT patients is strongly associated with graft *vs*. host disease (GVHD). Increased risk of CDI in allo-HSCT recipients is associated with cord blood transplants, total body irradiation and acute grade 2 GVHD [38]. CDI has been associated with prior chemotherapy, receipt of broad-spectrum antimicrobial agents and previous VRE colonization in all HSCT recipients [30, 31].

Recipients of allo-HSCT are at higher risk for CDI than those who undergo autologous HSCT (auto-HSCT) [30], with an almost a two-fold increase in incidence for allo-HSCT groups compared with auto-HSCT [39, 40].

Infection prevention, antimicrobial stewardship and prophylaxis

Non-pharmacological measures are essential for control and management of MDR organisms in haematology and HSCT patients.

Cleaning, isolation and screening

Multimodal strategies including hand-hygiene, environmental cleaning/disinfection, isolation and surveillance form the backbone of effective prevention programmes [41]. Hand-hygiene programmes and electronic surveillance systems have been demonstrated in haematology centres to increase compliance and trend toward significant reductions of nosocomial transmission of organisms such as VRE [42, 43].

Bleach-based cleaning has resulted in significant reductions in newly-acquired VRE [44], supporting the previous success of intensive infection control measures to prevent VRE acquisition [45]. Chlorhexidine-impregnated washcloths have been associated with reduced VRE colonization in ICU patients [46, 47]. Although one study has not demonstrated a benefit in haematology-oncology patients [48], a recent multi-centre randomized trial (including HSCT patients) demonstrated an overall reduction in MDR organisms, but not bacteraemia with methicillin-resistant *Staphylococcus aureus* (MRSA)/VRE, with the daily use of chlorhexidine-impregnated washcloths [49]. Novel methods for environmental decontamination, such as ultraviolet disinfection [50], hydrogen

peroxide vapour [51] and copper alloy surfaces [52] require targeted evaluation in haematology units and cost-benefit analysis before incorporating into standard prevention strategies.

Although the benefits of screening for VRE colonization are widely recognized in haematology populations [41, 53], support for routine ESBL screening programmes is limited. One study of neutropenic cancer patients found an ESBL *E. coli* colonization rate of 31.8%, and a recent multicentre study demonstrated an ESBL faecal carriage rate of 29% [9, 12]. Notably, there was no link between ESBL carriage and subsequent ESBL bacteraemia or outcome [12]. This raises questions regarding the benefits and validity of ESBL screening in this population and the need for studies examining approaches to empirical antibiotic algorithms in ESBL-colonized patients [54].

Antimicrobial stewardship in haematology patients

In large hospitals, host factors and antibiotic exposure, rather than breaches in infection control, have been associated with VRE colonization in haematology patients [55]. Antimicrobial stewardship programmes therefore complement infection control strategies. Antimicrobial stewardship programmes are aimed at reducing MDR acquisition with specific recommendations for haematology populations [56, 57]. Reduction in use of broad-spectrum antimicrobials is vital to reducing CDI and VRE acquisition [21]. Given the risks of MDR infection associated with vancomycin therapy [18], vancomycin should be ceased at 48 h in the absence of suspected infection due to gram-positive organisms [58, 59].

Antimicrobial stewardship teams with dedicated staff reduce broad-spectrum prescribing, inappropriate vancomycin use and antibiotic resistance in gram-negative organisms [60–63]. Improved antimicrobial stewardship, focused on prescribing of high risk antibiotics (third generation cephalosporins, clindamycin, fluoroquinolones) significantly reduces CDI incidence [64]. Empiric therapies should be targeted to local epidemiology, which can be facilitated by a stewardship team. Antimicrobial cycling for neutropenic fever is not routinely recommended [57, 58, 65].

Interventions to modify gastrointestinal flora

To combat primarily gram-negative bacteraemia, selective digestive decontamination (SDD) has been used in some haematology and ICU units [66–68]. Aztreonam and colistin have previously been used for this purpose, with no difference in outcomes between the two drugs [69]. A multicentre cluster trial of ICU patients given SDD demonstrated decreases in mortality and bacteraemia [70, 71]. This trial was limited by a short period of follow-up, use in a low multiresistant prevalence setting and restricted broad-spectrum systemic antimicrobial agents [72]. A study of oral gentamicin to eliminate carriage of carbapenem-resistant *K. pneumoniae* reported a success of 66%, but lacked controls and microbiological follow-up for development of resistance beyond 5 months [73]. A recent meta-analysis of 35 studies demonstrated no short-term microbiological resistance [74]. Nonetheless, concerns of resultant increases in gram-negative resistance mean that SDD is therefore not widely practiced or recommended [75].

Reducing the density of MDR organism gastrointestinal colonization and manipulation of microbiota has been proposed to reduce VRE infection risk. Following antibiotic therapy, the microbiome in allo-HSCT patients demonstrated VRE dominance [76, 77]. While administration of probiotics has been proposed to eliminate VRE colonization in non-haematology populations [78], risk is recognized in haematology patients, where bloodstream infections have been associated with probiotic therapy [79]. The introduction of diverse intestinal microbiota via faecal transplantation, including *Barnesiella* spp., to heavily colonized mice reduced VRE colonisation [76, 77]. Clinical study in haematology populations is required.

Faecal microbiota transplantation (FMT), is increasingly used for refractory and recurrent CDI [80, 81], and has been shown to be superior to vancomycin therapy in non-haematology patients with recurrent CDI [82]. A single case of fulminant CDI in a haematology patient successfully treated with FMT has been reported [83].

Fluoroquinolone prophylaxis

Fluoroquinolone antibiotics have been used for antibacterial prophylaxis in patients with acute leukemia undergoing chemotherapy and allogenic HSCT recipients with profound neutropenia for ≥ 7 days [65, 84], and a reduction in febrile neutropenia events, bacteraemia, hospitalization and mortality has been demonstrated [85–87]. However, a meta-analysis of only randomized control trials demonstrated no statistically significant mortality benefit in patients with febrile neutropenia [88].

Despite perceived benefits, fluoroquinolone resistance rates exceeding 20% have been reported following uptake of fluoroquinolone prophylaxis in haematology patients [3, 86, 87, 89–93]. Significantly increased ciprofloxacin resistance has been reported by the European Centre for Disease Prevention and Control [94]. In addition, breakthrough bacteraemias with MRSA, MDR *E. coli* and *P. aeruginosa* have been associated with prophylaxis [95]. In patients with AML, higher rates of fluoroquinolone-resistant *E. coli* have been reported, when compared with isolates in patients not administered prophylaxis [96]. Notably, the use of fluoroquinolone prophylaxis may lead to subsequent increases in carbapenem prescribing [87, 97].

Fluoroquinolone prophylaxis can be targeted and limited by antimicrobial stewardship programmes [57]. Cessation of fluoroquinolone prophylaxis in one centre

resulted in a decline in fluoroquinolone-resistant Enterobacteriaceae from 85% to 17% ($P = 0.0078$) [98].

In our experience the cost of antibacterial prophylaxis with regard to evolving resistance is a major concern.[99, 100] Australian consensus guidelines for management of haematology patients recommended against routine antibacterial prophylaxis for gram-negative bacteraemia, in particular, fluoroquinolones [101].

Pharmacotherapy

To manage MDR infections adequately in haematology patients, new antimicrobial agents, re-consideration of older therapies (Table 1) and combination regimens are necessary.

Resistant gram-negative infections

To date, there are no published reports of randomized trials evaluating treatment options for MDR gram-negative infections in haematology patients. Current American and European febrile neutropenia practice guidelines for haematology patients either colonized or with previous MDR Enterobacteriaceae infections suggest empiric colistin and a beta-lactam agent (or one of tigecycline, aminoglycoside, fosfomycin).[58, 102]

Colistin Colistin (polymixin E) has been clinically available since 1959 and increasingly used as a treatment option for infections caused by MDR gram-negative pathogens [103]. However, data on colistin therapy in HSCT and haematology patients are limited. Despite renal toxicity (0–50%), it has been found to be safe in neutropenic patients.[104–106] and is recommended for treatment of carbapenem-resistant Enterobacteriaceae and *P. aeruginosa* [102]. Successful treatment of MDR *Pseudomonas* has been demonstrated in bacteraemic haematology patients, predominately in conjunction with a beta-lactam agent.[105, 107]

Tigecycline Tigecycline is a first-in-class glycylcycline with activity against MDR gram-negative infections, excluding *P. aeruginosa*, *Proteus/Morganella/Providencia* species [108]. Clinical utility has been limited by low peak serum concentrations, rapid post treatment resistance and increased mortality and failure rates [109–111]. In critically ill patients, tigecycline has been reported to have an overall success of 73%, highest in intra-abdominal infections (82%). In the same study, a 42% failure rate was noted in empirical febrile neutropenia therapy and 30% failure rate in bacteraemia even if the isolate was clinically susceptible [112]. In oncology patients (58% haematology, 28% neutropenic) an overall response rate of 64% has been reported [113]. A retrospective review of tigecycline as salvage therapy for febrile neutropenia has suggested an overall success rate of 43% [111]. Tigecycline is not recommended for empiric febrile neutropenia therapy [58]. Meta-analysis and systematic reviews highlight increased mortality and clinical failure. The USA Food and Drug Administration (FDA) recently issued a black box warning [114]. Therefore, tigecycline can only be recommended for salvage therapy or as a component of combination regimens for MDR gram-negative infections.[109, 110]

Combination regimens Successful combination therapies for MDR gram-negative infections have been demonstrated in predominately non-haematology patients and neutropenic gram-negative sepsis. [115–117] Colistin/rifampicin therapy has *in vitro* and *in vivo* synergy in small case studies of *Acinetobacter baumannii* infections [118, 119]. However, in a randomized trial the addition of rifampicin to colistin offered no benefit [120]. Colistin/carbapenem therapy has demonstrated a mortality benefit compared with colistin monotherapy in a retrospective review of MDR gram-negative infections, including haematology patients [121]. This was also demonstrated in solid-organ transplant recipients, where colistin/carbapenem therapy for drug-resistant *A. baumannii* was associated with survival [122]. A recent study of patients with carbapenem-resistant (KPC)-producing *K. pneumoniae* infections, including haematology patients, demonstrated survival benefit with combination therapy (colistin/carbapenem or colistin/tigecycline) without increased toxicity [123]. Despite the majority of studies including few haematology patients, the use of combination therapy including colistin/carbapenem should be considered for MDR gram-negative infections.

Resistant gram-positive infections

Daptomycin Daptomycin is a cyclic lipopeptide bactericidal antibiotic with *in vitro* activity against *S. aureus* (MSSA, MRSA, heterogeneous vancomycin-intermediate *Staphylococcus aureus;* hVISA) and *Enterococcus* spp. (vancomycin-sensitive enterococci; VSE, VRE).[124, 125] Infrequent elevations of creatine kinase have been associated with daptomycin, and limitations include the lack of an oral formulation, uncertain dosing (6–10 mg kg^{-1}) and inactivation by pulmonary surfactant. Although not formally evaluated in haematology patients, efficacy for gram-positive infections in neutropenic patients has been reported.[126–128] Treatment failure has been reported in central nervous system Staphylococcal infections [129].

Linezolid Linezolid is a synthetic oxazolidinone antibiotic with excellent oral bioavailability and intrinsic activity against streptococci, staphylococci (MSSA, MRSA, hVISA) and enterococci (*E. faecalis*, VSE, VRE) [124]. Toxicities include cytopenias, peripheral neuropathy and lactic acidosis, with limited toxicity and effect on engraftment observed with use early post allo-HSCT.[130, 131] A randomized study has demonstrated cure rates comparable with vancomycin (87.3% for linezolid, 82.5% for vancomycin) and fewer drug-related adverse events [132].

Table 1

A description of the pharmacology and clinical utility of colistin, pristinamycin and fosfomycin in haematology patients with mutli-resistant organisms

Antibiotic	Class	Mechanism of action	Formulation Oral bioavailability	Dosing Renal/hepatic adjustment	Clinical utility	Comments regarding treatment of multi-drug resistant (MDR) organisms in haematology patients
Colistin*	Polymyxin	Not completely understood; believed to interact with LPS on gram-negative membrane	i.v., i.m., inhaled NA	Loading and maintenance dosing calculations required† Renal adjustment required	MDR gram-negatives, including *Pseudomonas* spp. and *Acinetobacter* spp.	• Renal adjusted dosing safe in haematology and HSCT patients [104, 124]. • Successful treatment in a matched pair analysis of MDR *Pseudomonas aeruginosa*; median treatment duration 13 days, resolution of infection in 20/26 (76.9%). Single patient suffered renal failure [105]. • Case report/series data of successful colistin single agent and combination therapy for allogenic HSCT patients and haematology patients with MDR *Pseudomonas* spp [107, 149].
Pristinamycin	Streptogramin	Inhibit protein synthesis via binding peptidyl transferase of 50S subunit of 70S ribosomes	Oral Excellent	500 mg^{-1} to 1 g TDS No adjustment required	Resistant gram-positive cocci (streptococci, staphylococci > enterococci)	• Limited data specific to haematology cohorts. Majority of data for suppressive therapy for resistant CoNS, MRSA or VRE bone and joint infections [150, 151]. • In a retrospective review of 46 cases predominately suppression of VRE or staphylococci (58%) joint, bone or wound infections [152].
Fosfomycin	Phosphoenolpyruvate analogue	Bacterial cell wall inhibition by binding to and inactivating enzyme enolpyruvate transferase	Oral or i.v. Good‡ (excellent urinary levels)	• 3 g single dose (simple UTI) • 3 g alternate days (complicated UTI) • 8 g BD i.v. Renal adjustment if CL_{cr} <50 ml min^{-1}	MDR gram-negatives (except *Pseudomonas*) and gram-positive cocci (*S. aureus* and *Enterococcus* spp. except *E. faecalis*)	• No specific data for use in haematology patients. Usual clinical indication is gram-negative UTIs, soft tissue infections and surgical prophylaxis [153, 154]. • Primarily for MDR gram-negative UTI, not bacteraemia (*E.coli, Citrobacter, Proteus mirabilis* including ESBL, however excluding *Enterobacter* spp., *P. vulgaris, Providencia* spp., *Acinetobacter* spp., *Pseudomonas* spp., *Morganella morganii*) [153]. • *In vitro* and *in vivo* synergy with carbapenems, colistin, fluoroquinolones and tigecycline in 30–74% of gram-positive and gram-negative organisms [155, 156]. • Successful mono or combination therapy for suppression of chronic MDR gram-positive infections (e.g. *Staphylococcus aureus*, *Enterococcus* spp.) [153]

Adapted from Kucers'. The use of Antibiotics (6th edition) – For 'Class', 'Mechanism of action', 'Bioavailability', 'Dosing' sections [124]. *Colistin is commercially available in two forms: colistin sulphate (referred to in this publication as colistin) and sodium colistin methanesulphonate (CMS). CMS is 'less toxic' when administered intravenously and is present in all parenteral (and most inhaled) formulations. CMS undergoes conversion *in vivo* to form a mixture of partially sulphonmethylated byproducts and colistin [157]. †Colistin dosing dependent upon organism MIC and patient renal function. Loading dose of CBA (colistin based activity)(mg) = Colistin organism minimum inhibitory concentration (mg l^{-1}) × 2 × body weight (kg) (use lower of ideal or actual body weight). Maintenance dose of CBA (mg) = Colistin organism minimum inhibitory concentration (mg l^{-1}) × (1.50 × CL_{cr} + 30) [158]. ‡Bioavailability: 37–42%. Oral formulation has high levels in urine for 1–3 days post single dose (1053–4415 mg ml^{-1}). BD, twice daily; CoNS, Coagulase-negative Staphylococcus; CL_{cr}, creatinine clearance; ESBL, Extended-spectrum-beta-lactamase; HSCT, haematopoietic stem cell transplantation; i.m., intramuscular; i.v., intravenous; LPS, lipopolysaccharide; MDR, multidrug-resistant; MIC, minimum inhibitory concentration.; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not applicable; TDS, three times daily; UTI, urinary tract infection; VRE, vancomycin-resistant enterococcus.

Appropriate dosing and treatment duration are vital to prevent resistance for infections due to *E. faecium*, *S. epidermis* and *S. haemolyticus* [133].

These two agents are now used increasingly as targeted therapy for VRE bacteraemia in haematology patients. Teicoplanin therapy is also appropriate for vanB-VRE, although *vanA*-VRE is inherently resistant to this agent, and inducible resistance in vanB-VRE has been reported [134]. While safety and tolerability of teicoplanin has been demonstrated in haematology patients with VRE bacteraemia [135, 136], the use of empiric teicoplanin in vanB-VRE colonized haematology patients has not been studied, and clinical guidelines do not support this practice.

Daptomycin use for *Enterococcus* spp. bacteraemia was reported in a recent multicentre retrospective study (dosing: > 6 mg kg^{-1} day^{-1}, median 8.2 mg kg^{-1} day^{-1}), with an overall clinical success rate of 89%, together with low rates of creatine kinase elevation (3%) [137].

There are no randomized controlled trials comparing linezolid with daptomycin. One retrospective review of haematology and allo-HSCT patients found no difference in treatment success and outcome in patients treated with these agents [28]. Meta-analysis of nine studies demonstrated no difference in microbiological or clinical cure rates, with a trend towards increased survival with linezolid [138].

Clostridium difficile

Fidaxomicin First line therapy for CDI is oral metronidazole, with vancomycin reserved for severe or refractory cases. Data supporting alternative therapies for CDI are limited in haematology and HSCT patients. Fidaxomicin has been shown to be non-inferior to vancomycin therapy in oncology patients and to be associated with reduced CDI recurrence.[139, 140] In HSCT recipients with CDI, cure rates following fidaxomicin have been shown to be less than conventional treatments with vancomycin or metronidazole, although studied cases were more severe and likely to have had pre-treatment prior to fidaxomicin [141].

Older agents, pharmacokinetics and pharmacodynamics

In addition to colistin, antimicrobial agents previously curbed because of toxicity profiles have been re-examined as effective therapies for MDR infections. These include fosfomycin and pristinamycin. In particular, the need for effective suppressive therapies for chronic VRE, MRSA and MDR gram-negative infections where cure is impractical has led to the increased use of agents outlined in Table 1.

Pharmacokinetic (PK)/pharmacodynamic (PD) properties of antimicrobial agents may be unique in the haematology population and strategies based on maximizing these principles may form future pathways for treatment of multiresistant organisms. The potential utility of infusional beta-lactam antibiotics for febrile neutropenia has been reported [142, 143]. Whilst continuous infusions would increase time above mean inhibitory concentrations (MIC) in neutropenic fever when volume of distribution is altered [142, 144], prospective studies demonstrating improved cure rates or mortality benefit are still required before widespread implementation. Dosages provided in this review are based upon those used in clinical studies, and these are reflected in published clinical guidelines. However, during sepsis and those critically ill, the PK/PD of drugs such as meropenem are altered [145, 146]. A recent study demonstrated concentrations of meropenem were below typical gram-negative MIC values and time above MIC shorter in neutropenic sepsis patients *vs*. non-neutropenic patients [147]. Although computer based simulations suggest longer antibiotic infusions give greater time above MIC [146, 148], they do not include a significant haematology cohort. To evaluate adequately optimal dosage of antimicrobial agents across the spectrum of patient age, weight, renal and hepatic functions and presence of systemic inflammatory response syndrome, appropriate data must be captured by antimicrobial stewardship programmes and clinical endpoint studies with respect to variation of these variables.

Conclusion

The management of MDR infections in haematology patients is an increasingly complex problem involving pharmacological and non-pharmacological prevention and intervention strategies. The burden of illness arising from MDR gram-negative pathogens, VRE and *C. difficile* is expanding more rapidly than therapies are becoming available. Increased use of newer antimicrobial agents, such as daptomycin and linezolid, in conjunction with older antibiotics and combination regimens, are effective treatment strategies. Key principles that should underpin multidisciplinary services provided by infectious disease physicians, pharmacists, infection control consultants and haematologists include:

- limiting fluoroquinolone prophylaxis.
- a greater understanding of microbiological complications of SDD before routine use.
- implementing effective infection prevention strategies.
- evaluating the role of ESBL screening and impacts on empirical antibiotic therapy
- antimicrobial stewardship programmes aimed at reducing unnecessary cephalosporin, vancomycin and carbapenem use to limit further emergence of *C. difficile*, VRE and MDR gram-negatives.
- judicious use of new effective antimicrobials (fidaxomicin, linezolid, daptomycin) against MDR organisms in haematology patients.

- a return to older antimicrobials for MDR organisms (fosfomycin and pristinamycin) and exploration of new combination therapies involving colistin for resistant gram-negatives.
- exploring infusional beta-lactams for neutropenic sepsis to improve time above MIC and patient outcome.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

REFERENCES

1 Cattaneo C, Casari S, Bracchi F, Signorini L, Ravizzola G, Borlenghi E, Re A, Manca N, Carosi G, Rossi G. Recent increase in enterococcus, viridians streptococci, pseudomonas spp. and multi-resistant strains among haematological patients, with a negative impact on outcome. Results of a 3-year surveillance study at a single institution. Scand J Infect Dis 2010; 42: 324–32.

2 Haeusler GM, Mechinaud F, Daley AJ, Starr M, Shann F, Connell TG, Bryant PA, Donath S, Curtis N. Antibiotic-resistant gram-negative bacteraemia in pediatric oncology patients – risk factors and outcomes. Pediatr Infect Dis J 2013; 32: 723–6.

3 Bousquet A, Malfuson JV, Sanmartin N, Konopacki J, Macnab C, Souleau B, de Revel T, Elouennass M, Samson T, Soler C, Foissaud V, Martinaud C. An 8-year survey of strains identified in blood cultures in a clinical haematology unit. Clin Microbiol Infect 2014; 20(1): O7–O12.

4 Ortega M, Marco F, Soriano A, Almela M, Martinez JA, Munoz A. Analysis of 4758 *Escherichia coli* bacteraemia episodes: predictive factors for isolation of an antibiotic-resistant strain and their impact on the outcome. J Antimicrob Chemother 2009; 63: 568–74.

5 Gudiol C, Calatayud L, Garcia-Vidal C, Lora-Tamayo J, Cisnal M, Duarte R, Arnan M, Marin M, Carratalà J, Gudiol F. Bacteraemia due to extended-spectrum beta-lactamase producing Escherichia coli (ESBL-EC) in cancer patients: clinical features, risk factors, molecular epidemiology and outcome. J Antimicrob Chemother 2010; 65: 333–41.

6 Tumbarello M, Spanu T, Sanguinetti M, Citton R, Montuori E, Leone F, Fadda G, Cauda R. Bloodstream infections caused by extended spectrum beta-lactamase producing *Klebsiella pneumoniae*: risk factors, molecular epidemiology and clinical outcome. Antimicrob Agents Chemother 2006; 50: 498–504.

7 Gudiol C, Tubau F, Calatayud L, Garcia-Vidal C, Cisnal M, Sánchez-Ortega I, Duarte R, Calvo M, Carratalà J. Bacteraemia due to multidrug-resistant Gram-negative bacilli in cancer patients: risk factors, antibiotic therapy and outcomes. J Antimicrob Chemother 2011; 66: 657–63.

8 Satlin MJ, Jenkins SG, Chen L, Helfgott D, Feldman EJ, Kreiswirth BN, Schuetz AN. Septic shock caused by *Klebsiella pneumoniae* carbapenemase-producing *Enterobacter gergoviae* in a neutropenia patient with leukemia. J Clin Microbiol 2013; 51: 2794–6.

9 Calatayud L, Arnan M, Linares J, Dominquez MA, Gudiol C, Carratala J, Battle M, Ribera JM, Gudiol F. Prospective study of fecal colonization by extended-spectrum-beta-lactamase-producing *Escherichia coli* in neutropenic patients with cancer. Antimicrob Agents Chemother 2008; 52: 4187–90.

10 Reddy P, Malczynski M, Obias A, Reiner S, Jin N, Huang J, Noskin GA, Zembower T. Screening for extended spectrum beta-lactamase-producing Enterobacteriaceae among high-risk patients and rates of subsequent bacteraemia. Clin Infect Dis 2007; 45: 846–52.

11 Friedmann R, Raveh D, Zartzer E, Rudensky B, Broide E, Attias D, Yinnon AM. Prospective evaluation of colonization wit extended-spectrum beta-lactamase (ESBL) producing enterobacteriaceae among patients at hospital admission and of subsequent colonization with ESL-producing enterobacteriaceae among patients during hospitalization. Infect Control Hosp Epidemiol 2009; 30: 524–42.

12 Arnan M, Gudiol C, Calatayud L, Liñares J, Dominguez MÁ, Batlle M, Ribera JM, Carratalà J, Gudiol F. Risk factors for and clinical relevance of, faecal extended-spectrum beta-lactamase producing *Escherichia coli* (ESBL-EC) carriage in neutropenic patients with haematological malignancies. Eur J Clin Microbio Infect Dis 2011; 30: 355–60.

13 Liss BJ, Vehreschild JJ, Cornely OA, Hallek M, Fatkenheuer G, Wisplinghoff H, Seifert H, Vehreschild MJ. Intestinal colonisation and blood stream infections due to vancomycin-resistant enterococci (VRE) and extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBLE) in patients with haematological and oncological malignancies. Infection 2012; 40: 613–9.

14 Cattaneo C, Antoniazzi F, Casari S, Ravizzola G, Gelmi M, Pagani C, D'Adda M, Morello E, Re A, Borlenghi E, Manca N, Rossi GP. P. aeruginosa bloodstream infections among hematological patients: an old or new question? Ann hematol 2012; 91: 1299–304.

15 Matar MJ, Tarrand J, Raad I, Rolston KV. Colonization and infection with vancomycin-resistant Enterococcus among patients with cancer. Am J Infect Control 2006; 34: 534–6.

16 Weinstock DM, Conlon M, Iovino C, Aubrey T, Gudiol C, Riedel E, Young JW, Kiehn TE, Zuccotti G. Colonization, bloodstream infection and mortality caused by vancomycin resistant enterococcus early after allogenic hematopoietic stem cell transplant. Biol Blood Marrow Transplant 2007; 13: 615–21.

17 Kamboj M, Chung D, Seo SK, Pamer EG, Sepkowitz KA, Jakubowski AA, Papanicolaou G. The changing epidemiology of vancomycin-resistant Enterococcus (VRE) bacteraemia in allogenic hematopoietic stem cell transplant (HSCT) recipients. Biol Blood Marrow Transplant 2010; 16: 1576–81.

18 Worth LJ, Thursky KA, Seymour JF, Slavin MA. Vancomcyin resistant Enterococcus faecium infection in patients with hematologic malignancy: patients with acute myeloid leukemia are at high-risk. Eur J Haematol 2007; 79: 226–33.

19 Suntharam N, Lankford MG, Trick WE, Peterson LR, Noskin GA. Risk factors of acquisition of vancomycin-resistant enterococci among hematology-oncology patients. Diagn Microbiol Infect Dis 2002; 43: 183–8.

20 Peel T, Cheng AC, Spelman T, Huysmans M, Spelman D. Differing risk factors for vancomycin-resistant and vancomcyin-sensitive enterococcal bacteraemia. Clin Microbiol Infect 2012; 18: 388–94.

21 McKinnell JA, Kunz DF, Chamot E, Patel M, Shirley RM, Moser SA, Baddley JW, Pappas PG, Miller LG. Association between vancomycin-resistant Enterococci bacteraemia and ceftriaxone usage. Infect Control Hosp Epidemiol 2012; 33: 718–24.

22 Avery R, Kalaycio M, Pohlman B, Sobecks R, Kuczkowski E, Andresen S, Mossad S, Shamp J, Curtis J, Kosar J, Sands K, Serafin M, Bolwell B. Early vancomycin resistant enterococcus (VRE) bacteraemia after allogenic bone marrow transplantation is associated with a rapidly deteriorating clinical course. Bone Marrow Transplant 2005; 35: 497–9.

23 Bossaer JB, Hall PD, Garrett-Mayer E. Incidence of vancomycin-resistant enterococci (VRE) infection in high-risk febrile neutropenia patients colonized with VRE. Support Care Cancer 2010; 19: 231–7.

24 Kang Y, Vincente M, Parsad S, Brielmeier B, Psiano J, Lando E, Pettit NN. Evaluation of risk factors for vancomycin-resistant Enterococcus bacteraemia among previously colonized hematopoietic stem cell transplant patients. Transpl Infect Dis 2013; 15: 466–73.

25 Vydra J, Shanley RM, Geroge I, Ustun C, Smith AR, Weisdorf DJ, Young JAH. Enterococcal bacteraemia is associated with increased risk of mortality in recipients of allogenic hematopoietic stem cell transplantation. Clin Infect Dis 2012; 55: 764–70.

26 Zaas AK, Song X, Tucker P, Perl TM. Risk factors for development of vancomycin-resistant enterococcal bloodstream infection in patients with cancer who are colonized with vancomycin-resistant enterococci. Clin Infect Dis 2002; 35: 1139–46.

27 DiazGranados CA, Jernigan JA. Impact of vancomycin resistance on mortality among patients with neutropenia and enterococcal bloodstream infection. J Infect Dis 2005; 191: 588–95.

28 Kraft S, Mackler E, Schlickman P, Welch K, DePestel DD. Outcomes of therapy: vancomycin-resistant enterococcal bacteraemia in hematology and bone marrow transplant patients. Support Care Cancer 2011; 19: 1969–74.

29 Montassier E, Batard E, Gastinne T, Potel G, Cochetière MF. Recent changes in bacteremia in patients with cancer: a systematic review of epidemiology and antibiotic resistance. Eur J Clin Microbiol Infect Dis 2013; 32: 841–50.

30 Alonso CD, Treadway SB, Hanna DB, Huff CA, Neofytos D, Carroll KC, Marr KA. Epidemiology and outcomes of *Clostridium difficile* infections in hematopoietic stem cell transplant recipients. Clin Infect Dis 2012; 54: 1053–63.

31 Alonso CD, Dufresne SF, Hanna DB, Labbé AC, Treadway SB, Neofytos D, Bélanger S, Huff CA, Laverdière M, Marr KA. *Clostridium difficle* infection after adult autologous stem cell transplantation: a multicenter study of epidemiology and risk factors. Biol Blood Marrow Transplant 2013; 19: 1502–8.

32 Panichi G, Pantosti A, Gentile G, Testore GP, Venditti M, Martino P, Serra P. *Clostridium difficile* colitis in leukemia patients. Eur J Cancer Clin Oncol 1985; 21: 1159–63.

33 Chakrabarti S, Lees A, Jones SG, Milligan DW. *Clostridium difficile* infection in allogenic stem cell transplant recipients is associated with severe graft-versus-host disease and non-relapse mortality. Bone Marrow Transplant 2000; 26: 871–6.

34 Schalk E, Bohr UR, König B, Scheinpflug K, Mohren M. *Clostridium difficile*-associated diarrhoea, a frequent complication in patients with acute myeloid leukemia. Ann Hematol 2010; 89: 9–14.

35 Gorschlüter M, Glasmacher A, Hahn C, Schakowski F, Ziske C, Molitor E, Marklein G, Sauerbruch T, Schmidt-Wolf IG. *Clostridium difficile* infection in patients with neutropenia. Clin Infect Dis 2001; 33: 786–91.

36 Parmar SR, Bhatt V, Yang J, Zhang Q, Schuster M. A retrospective review of metronidazole and vancomycin in the management of *Clostridium difficile* infection in patients with hematologic malignancies. J Oncol Pharm Pract 2013; Jun 26. (Epub ahead of print).

37 van Kraaij MG, Dekker AW, Verdonck LF, van Loon AM, Vinjé J, Koopmans MP, Rozenberg-Arska M. Infectious gastro-enteritis: an uncommon cause of diarrhoea in adult allogeneic and autologous stem cell transplant recipients. Bone Marrow Transplant 2000; 26: 299–303.

38 Willems L, Porcher R, Lafaurie M, Casin I, Robin M, Xhaard A, Andreoli AL, Rodriguez-Otero P, Dhedin N, Socié G, Ribaud P, Peffault de Latour R. *Clostridium difficile* infection after allogeneic hematopoietic stem cell transplantation: incidence, risk factors, and outcome. Biol Blood Marrow Transplant 2012; 18: 1295–301.

39 Trifilio SM, Pi J, Mehta J. Changing epidemiology of *Clostridium difficile*-associated disease during stem cell transplantation. Biol Blood Marrow Transplant 2013; 19: 405–9.

40 Chopra T, Chandrasekar P, Salimnia H, Heilbrun LK, Smith D, Alangaden GJ. Recent epidemiology of *Clostridium difficile* infection during hematopoietic stem cell transplantation. Clin Transplant 2011; 25: E82–7.

41 Muto CA, Jernigan JA, Ostrowsky BE, Richet HM, Jarvis WR, Boyce JM, Farr BM, SHEA. SHEA guideline for preventing

nosocomial transmission of multidrug-resistant strains of *Staphylococcus aureus* and *enterococcus*. Infect Control Hosp Epidemiol 2003; 24: 362–86.

42 Venkatesh A, Lankford M, Rooney D, Blachford T, Watts C, Noskin G. Use of electronic alerts to enhance hand hygiene compliance and decrease transmission of vancomycin-resistant Enterococcus in a haematology unit. Am J Infect Control 2008; 36: 199–205.

43 Sodré da Costa LS, Neves VM, Marra AR, Sampaio Camargo TZ, Fátima Dos Santos Cardoso M, da Silva Victor E, Vogel C, Tahira Colman FA, Laselva CR, Pavão Dos Santos OF, Edmond MB. Measuring hand hygiene compliance in a hematology-oncology unit: a comparative study of methodologies. Am J Infect Control 2013; 41(11): 997–1000.

44 Grabsch EA, Mahony AA, Cameron DR, Martin RD, Heland M, Davey P, Petty M, Xie S, Grayson ML. Significant reduction in vancomycin-resistant enterococcus colonization and bacteraemia after introduction of a bleach-based cleaning-disinfection programme. J Hosp Infect 2012; 82: 234–42.

45 Ostrowsky B, Steinberg JT, Farr B, Sohn AH, Sinkowitz-Cochran RL, Jarvis WR. Reality check: should we try to detect and isolate vancomycin-resistant enterococci patients? Infect Control Hosp Epidemiol 2001; 22(2): 116–9.

46 Climo MW, Sepkowitz KA, Zuccotti G, Fraser VJ, Warren DK, Perl TM, Speck K, Jernigan JA, Robles JR, Wong ES. The effect of daily bathing with chlorhexidine on the acquisition of methicillin-resistant *Staphylococcus aureus*, vancomcyin-resistant Enterococcus, and healthcare-associated bloodstream infections: results of a quasi-experimental multicenter trial. Crit Care Med 2009; 37: 1858–65.

47 Vernon MO, Hayden MK, Trick WE, Hayes RA, Blom DW, Weinstein RA. Chlorhexidine gluconateto cleanse patients in a medical intensive care unit: the effectiveness of source control to reduce the bioburden of vancomycin resistant enterococci. Arch Intern Med 2006; 166: 306–12.

48 Bass P, Karki S, Rhodes D, Gonelli S, Land G, Watson K, Spelman D, Harrington G, Kennon J, Cheng AC. Impact of chlorhexidine-impreganted washcloths on reducing incidence of vancomycin-resistant enterococci colonization in hematology-oncology patients. Am J Infect Control 2013; 41: 345–8.

49 Climo MW, Yokoe DS, Warren DK, Perl TM, Bolon M, Herwaldt LA, Weinstein RA, Sepkowitz KA, Jernigan JA, Sanogo K, Wong ES. Effect of daily chlorhexidine bathing on hospital-acquired infection. N Engl J Med 2013; 368: 533–42.

50 Stibich M, Stachowiak J, Tanner B, Berkheiser M, Moore L, Raad I, Chemaly RF. Evaluation of a pulsed-xenon ultraviolet room disinfection device for impact on hospital operations and microbial reduction. Infect Control Hosp Epidemiol 2011; 32: 286–8.

51 Otter JA, Cummins M, Ahmad F, van Tonder C, Drabu YJ. Assessing the biological efficacy and rate of recontamination following hydrogen peroxide vapour decontamination. J Hosp Infect 2007; 67: 182–8.

52 Salgado CD, Sepkowitz KA, John JF, Cantey JR, Attaway HH, Freeman KD, Sharpe PA, Michels HT, Schmidt MG. Copper surfaces reduce the rate of healthcare-acquired infections in the intensive care unit. Infect Control Hosp Epidemiol 2013; 34: 479–86.

53 Calderwood MS, Mauer A, Tolentino J, Flores E, van Besien K, Pursell K, Weber SG. Epidemiology of vancomycin-resistant enterococci among patients on an adult stem cell transplant unit: observations from an active surveillance program. Infect Control Hosp Epidemiol 2008; 29: 1019–25.

54 Poon LM, Jin J, Chee YL, Ding Y, Lee YM, Chng WJ, Chai LY, Tan LK, Hsu LY. Risk factors for adverse outcomes and multidrug-resistant Gram-negative bacteraemia in haematology patients with febrile neutropenia in a Singaporean university hospital. Singapore Med J 2012; 53: 720–5.

55 Almyroudis NG, Lesse AJ, Hahn T, Samonis G, Hazamy PA, Wongkittircoh K, Wang ES, McCarthy PL Jr, Wetzler M, Segal BH. Molecular epidemiology and risk factors for colonization by vancomycin-resistant Enterococcus in patients with hematologic malignancies. Infect Control Hosp Epidemiol 2011; 32: 490–6.

56 Yong MK, Buising KL, Cheng AC, Thursky KA. Improved susceptibility of gram-negative bacteria in an intensive care unit following implementation of a computerized antibiotic decision support system. J Antimicrob Chemother 2010; 65: 1062–9.

57 Tverdek FP, Rolston KV, Chemaly RF. Antimicrobial stewardship in patients with cancer. Pharmacotherapy 2012; 32: 722–34.

58 Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR, Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2011; 52: 427–31.

59 Shaikh ZH, Osting CA, Hanna HA, Arbuckle RB, Tarr JJ, Raad II. Effectiveness of a multifaceted infection control policy in reducing vancomycin usage and vancomycin-resistant enterococci at a tertiary care cancer centre. J Hosp Infect 2002; 51: 52–8.

60 Paskovaty A, Pflomm JM, Myke N, Seo SK. A multidisciplinary approach to antimicrobial stewardship: evolution into the 21st century. Int J Antimicrob Agents 2005; 25: 1–10.

61 Cheng VC, To KK, Li IW, Tang BS, Chan JF, Kwan S, Mak R, Tai J, Ching P, Ho PL, Seto WH. Antimicrobial stewardship program directed at broad-spectrum intravenous antibiotics prescription in a tertiary hospital. Eur J Clin Microbiol Infect Dis 2009; 28: 1447–56.

62 Yeo CL, Chan DS, Earnest A, Wu TS, Yeoh SF, Lim R, Jureen R, Fisher D, Hsu LY. Prospective audit and feedback on antibiotic prescription in an adult hematology-oncology unit in Singapore. Eur J Clin Microbiol Infect Dis 2011; 31: 583–90.

63 Yeo CL, Wu JE, Chung GW, Chan DS, Fisher D, Hsu LY. Specialist trainees on rotation cannot replace dedicated consultant clinicians for antimicrobial stewardship of specialty disciplines. Antimicrob Resist Infect Control 2012; 17: 36.

64 Aldeyab MA, Kearney MP, Scott MG, Aldiab MA, Alahmadi YM, Darwish Elhajji FW, Magee FA, McElnay JC. An evaluation of the impact of antibiotic stewardship on reducing the use of high-risk antibiotics and its effects on the incidence of *Clostridium difficile* infection in hospital settings. J Antimicrob Chemother 2012; 67: 2988–96.

65 Dellit TH, Owens RC, McGowan JE Jr, Gerding DN, Weinstein RA, Burke JP, Huskins WC, Paterson DL, Fishman NO, Carpenter CF, Brennan PJ, Billeter M, Hooton TM, Infectious Diseases Society of America, Society for Healthcare Epidemiology of America. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 2007; 44: 159–77.

66 Stoutenbeek CP, van Saene HK, Miranda DR, Zandstra DF. The effect of selective decontamination of the digestive tract on colonisation and infection rate in multiple trauma patients. Intensive Care Med 1984; 10: 185–92.

67 Donnelly JP, Maschmeyer G, Daenen S. Selective oral antimicrobial prophylaxis for the prevention of infection in acute leukemia-ciprofloxacin versus co-trimoxazole plus colistin. The EORTC-Gnotobiotic Project Group. Eur J Cancer 1992; 28A: 873–8.

68 Maschmeyer G, Haralambie E, Gaus W, Kern W, Dekker AW, De Vries-Hospers HG, Sizoo W, König W, Gutzler F, Daenen S. Ciprofloxacin and norfloxacin for selective decontamination in patients with severe granulocytopenia. Infection 1988; 16: 98–104.

69 Bosi A, Fanci R, Pecile P, Guidi S, Saccardi R, Vannucchi AM, Longo G, Donnini E, Orsi A, Rossi-Ferrini P. Aztreonam versus colistin-neomycin for selective decontamination of the digestive tract in patients undergoing bone marrow transplantation: a randomized study. J Chemother 1992; 4: 30–4.

70 de Smet AM, Kluytmans JA, Cooper BS, Mascini EM, Benus RF, van der Werf TS, van der Hoeven JG, Pickkers P, Bogaers-Hofman D, van der Meer NJ, Bernards AT, Kuijper EJ, Joore JC, Leverstein-van Hall MA, Bindels AJ, Jansz AR, Wesselink RM, de Jongh BM, Dennesen PJ, van Asselt GJ, te Velde LF, Frenay IH, Kaasjager K, Bosch FH, van Iterson M, Thijsen SF, Kluge GH, Pauw W, de Vries JW, Kaan JA, Arends JP, Aarts LP, Sturm PD, Harinck HI, Voss A, Uijtendaal EV, Blok HE, Thieme Groen ES, Pouw ME, Kalkman CJ, Bonten MJ. Decontamination of the digestive tract and oropharynx in ICU patients. N Engl J Med 2009; 360: 20–31.

71 de Smet AM, Kluytmans JA, Blok HE. Selective digestive tract decontamination and selective oropharyngeal decontamination and antibiotic resistance in patients in intensive-care units: an open-label, clustered group-randomised, crossover study. Lancet Infect Dis 2011; 11: 372–80.

72 Vincent JL, Jacobs F. Effect of selective decontamination on antibiotic resistance. Lancet Infect Dis 2011; 11: 337–8.

73 Zuckerman T, Benyamini N, Sprecher H, Fineman R, Finkelstein R, Rowe JM, Oren I. SCT in patients with carbapenem resistant Klebsiella pneumoniae: a single center experience with oral gentamicin for the eradication of carrier state. Bone Marrow Transplant 2011; 46: 1226–30.

74 Daneman N, Sarwar S, Fowler RA, Cuthbertson BH, SuDDICU Canadian Study Group. Effect of selective decontamination on antimicrobial resistance in intensive care units: a systematic review and meta-analysis. Lancet Infect Dis 2013; 13: 328–41.

75 van der Meer JW, Vandenbroucke-Grauls CM. Resistance to selective decontamination: the jury is still out. Lancet Infect Dis 2013; 13: 282.

76 Ubeda C, Taur Y, Jenq RR, Equinda MJ, Son T, Samstein M, Viale A, Socci ND, van den Brink MR, Kamboj M, Pamer EG. Vancomycin-resistant Enterococcus domination of intestinal microbiota is enabled by antibiotic treatment in mice and precedes bloodstream invasion in humans. J Clin Invest 2010; 120: 4332–4.

77 Ubeda C, Bucci V, Caballero S, Djukovic A, Toussaint NC, Equinda M, Lipuma L, Ling L, Gobourne A, No D, Taur Y, Jenq RR, van den Brink MR, Xavier JB, Pamer EG. Intestinal microbiota containing Barnesiella species cures vancomycin-resistant *Enterococcus faecium* colonization. Infect Immun 2013; 81: 965–73.

78 Szachta P, Ignyś I, Cichy W. An evaluation of the ability of the probiotic strain *Lactobacillus rhamnosus* GG to eliminate the gastrointestinal carrier state of vancomycin-resistant enterococci in colonized children. J Clin Gastroenterol 2011; 45: 872–7.

79 Mehta A, Rangarajan S, Borate U. A cautionary tale for probiotic use in hematopoietic SCT patients-*Lactobacillus acidophilus* sepsis in a patient with mantle cell lymphoma undergoing hematopoietic SCT. Bone Marrow Transplant 2013; 48: 461–2.

80 Eiseman B, Silen W, Bascom GS, Kauvar AJ. Fecal enema as an adjunct in the treatment for pseudomembranous colitis. Surgery 1958; 44: 854–9.

81 Gough E, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent *Clostridium difficile* infection. Clin Infect Dis 2011; 53: 994–1002.

82 van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, Visser CE, Kuijper EJ, Bartelsman JF, Tijssen JG, Speelman P, Dijkgraaf MG, Keller JJ. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. N Engl J Med 2013; 368: 407–15.

83 Neemann K, Eichele DD, Smith PW, Bociek R, Akhtari M, Freifeld A. Fecal microbiota transplantation for fulminant *Clostridium difficile* infection in an allogenic stem cell transplant patient. Transpl Infect Dis 2012; 14: E161–5.

84 Wingard JR, Eldjerou L, Leather H. Use of antimicrobial prophylaxis in patients with chemotherapy-induced neutropenia. Curr Opin Hematol 2012; 19: 21–6.

85 Reuter S, Kern WV, Sigge A, Döhner H, Marre R, Kern P, von Baum H. Impact of fluoroquinolone prophylaxis on reduced infection-related mortality among patients with neutropenia and hematologic malignancies. Clin Infect Dis 2005; 40: 1087–93.

86 Gafter-Gvili A, Fraser A, Paul M, Leibovici L. Meta-analysis: antibiotic prophylaxis reduces morality in neutropenic patients. Ann Intern Med 2005; 144: 704.

87 Garnica M, Nouer SA, Pellegrino FL, Moreira BM, Maiolino A, Nucci M. Ciprofloxacin prophylaxis in high risk neutropenic patients: effects on outcomes, antimicrobial therapy and resistance. BMC Infect Dis 2013; 13: 356.

88 Imran H, Tleyjeh IM, Arndt CA, Baddour LM, Erwin PJ, Tsigrelis C, Kabbara N, Montori VM. Fluoroquinolone prophylaxis in patients with neutropenia: a meta-analysis of randomized control trials. Eur J Clin Microbiol Infect Dis 2008; 27: 53–63.

89 Baden LR. Prophylactic antimicrobial agents and the importance of fitness. N Eng J Med 2005; 353: 1052–54.

90 Therriault BL, Wilson JW, Barreto JN, Estes LL. Characterization of bacterial infections in allogenic hematopoietic stem cell transplant recipients who received prophylactic levofloxacin with either penicillin or doxycycline. Mayo Clin Proc 2010; 85: 711–8.

91 Schelenz S, Nwaka D, Hunter PR. Longitudinal surveillance of bacteraemia in haematology and oncology patients at a UK cancer centre and the impact of ciprofloxacin use on antimicrobial resistance. J Antimicrob Chemother 2013; 68: 1431–8.

92 Kern WW, Steib-Bauert M, de With K, Reuter S, Bertz H, Frank U, von Baum H. Fluoroquinolone consumption and resistance in haematology – oncology patients: ecological analysis in two university hospitals 1999–2002. J Antimicrob Chemother 2005; 55: 57–60.

93 Castagnola E, Haupt R, Micozzi A, Caviglia I, Testi AM, Giona F, Parodi S, Gimmenia C. Differences in the proportions of fluoroquinolone-resistant Gram negative bacteria isolated from bacteraemic children with cancer in two Italian centres. Clin Microbiol Infect 2005; 11: 5050–7.

94 European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe. Annual report 2010. Available at http://www.ecdc.europa.eu (last accessed September 2013).

95 Rangaraj G, Granwehr BP, Jiang Y, Hachem R, Raad I. Perils of quinolone exposure in cancer patients: breakthrough bacteremia with multidrug-resistant organisms. Cancer 2010; 116: 967–73.

96 Saini L, Rostein C, Atenafu EG, Brandwein JM. Ambulatory consolidation chemotherapy for acute myeloid leukemia with antibacterial prophylaxis is associated with frequent bacteremia and the emergence of fluoroquinolone resistant *E. coli*. BMC Infect Dis 2013; 13: 284.

97 Eleutherakis-Papaiakovou E, Kostis E, Migkou M, Christoulas D, Terpos E, Gavriatopoulou M, Roussou M, Bournakis E, Kastritis E, Efstathiou E, Dimopoulos MA, Papadimitriou CA. Prophylactic antibiotics for the prevention of neutropenic fever in patients undergoing autologous stem-cell transplantation: results of a single institution, randomized phase 2 trial. Am J Hematol 2010; 85: 863–7.

98 Saito T, Yoshioka S, Iinuma Y, Takakura S, Fujihara N, Ichinohe T, Ishikawa T, Uchiyama T, Ichiyama S. Effects on spectrum and susceptibility patterns of isolates causing bloodstream infection by restriction of fluoroquinolone prophylaxis in a haematology unit. Eur J Clin Microbiol Infect Dis 2007; 27: 209–16.

99 Lingaratnam S, Thursky KA, Slavin MA. Fluoroquinolone prophylaxis: a word of caution. Leuk Lymphoma 2011; 52: 5–6.

100 Haeusler GM, Slavin MA. Fluoroquinolone prophylaxis: worth the cost? Leuk Lymphoma 2013; 54: 677–8.

101 Slavin MA, Lingaratnam S, Mileshkin L, Booth DL, Cain MJ, Ritchie DS, Wei A, Thursky KA, Australian Consensus Guidelines 2011 Steering Committee. Use of antibacterial prophylaxis for patients with neutropenia. Australian Consensus Guidelines 2011 Steering Committee. Intern Med J 2011; 41 (1b): 102–9.

102 4th European Conference on infections in leukemia: bacterial resistance in haematology-ECIL 4. Accessed at http://www.ebmt.org/Contents/Resources/Library/ECIL/Documents/ECIL4%202011%20Bacterial%20resistance%20in%20Haematology.pdf (last accessed 10 September 2013).

103 Michalopoulos AS, Tsiodras S, Rellos K, Mentzelopoulos S, Falagas ME. Colistin treatment in patients with ICU-acquired infections caused by multiresistant Gram-negative bacteria: the renaissance of an old antibiotic. Clin Microbiol Infect 2005; 11: 115–21.

104 Averbuch D, Horwitz E, Strahilevitz J, Stepensky P, Goldschmidt N, Gatt ME, Shapira MY, Resnick IB, Engelhard D. Colistin is relatively safe in hematological malignancies and hematopoietic stem cell transplantation patients. Infection 2013; 41: 991–7.

105 Durakovic N, Radojcic V, Boban A, Mrsic M, Sertic D, Serventi-Seiwerth R, Nemet D, Labar B. Efficacy and safety of colistin in the treatment of infections caused by multidrug-resistant Pseudomonas aeurginosa in patients with hematologic malignancy: a matched pair analysis. Intern Med 2011; 50: 1009–13.

106 Hachem RY, Chemaly RF, Ahmar CA, Jiang Y, Boktour MR, Rjaili GA, Bodey GP, Raad II. Colistin is effective in treatment of infections caused by multidrug-resistant *Pseudomonas aeruginosa* in cancer patients. Antimicrob Agents Chemother 2007; 51: 1905–11.

107 Micol JB, de Botton S, Guieze R, Coiteux V, Darre S, Dessein R, Leroy O, Yakoub-Agha I, Quesnel B, Bauters F, Beaucaire G, Alfandari S. An 18-case outbreak of drug-resistant *Pseudomonas aeruginosa* bacteraemia in hematology patients. Haematologica 2006; 91: 1134–8.

108 Pankey GA. Tigecycline. J Antimicrob Chemother 2005; 56: 470–80.

109 Yahav D, Lador A, Paul M, Leibovici L. Efficacy and safety of tigecycline: a systematic review and meta-analysis. J Antimicrob Chemother 2011; 66: 1963–7.

110 Prasad P, Sun J, Danner RL, Natanson C. Excess deaths associated with tigecycline after approval based on noninferiority trials. Clin Infect Dis 2012; 54: 1699–709.

111 Schwab KS, Hahn-Ast C, Heinz WJ, Germing U, Egerer G, Glasmacher A, Leyendecker C, Marklein G, Nellessen CM, Brossart P, von Lilienfeld-Toal M. Tigecycline in febrile neutropenic patients with haematological malignancies: a retrospective case documentation in four university hospitals. Infection 2013; Aug 25. [Epub ahead of print].

112 Bassetti M, Nicolini L, Repetto E, Righi E, Del Bono V, Viscoli C. Tigecycline use in serious nosocomial infections: a drug use evaluation. BMC Infect Dis 2010; 10: 287.

113 Chemaly RF, Hanmod SS, Jiang Y, Rathod DB, Mulanovich V, Adachi JA, Rolston KV, Raad II, Hachem RY. Tigecycyline use in cancer patients with serious infections: a report on 110 cases from a single institution. Medicine (Baltimore) 2009; 88: 211–20.

114 FDA drug safety communication, 2013. Accessed at www.fda.gov/Drugs/DrugSafety.ucm369580.htm (last accessed 27 September 2013).

115 Kumar A, Zarychanski R, Light B, Parrillo J, Maki D, Simon D, Laporta D, Lapinsky S, Ellis P, Mirzanejad Y, Martinka G, Keenan S, Wood G, Arabi Y, Feinstein D, Kumar A, Dodek P, Kravetsky L, Doucette S, Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Research Group. Early combination antibiotic therapy yields improved survival compared with mono-therapy in septic shock: a propensity-matched analysis. Crit Care Med 1773; 38: 85.

116 Safdar N, Handelsman J, Maki DG. Does combination antimicrobial therapy reduce mortality in gram-negative bacteraemia? A meta-analysis. Lancet Infect Dis 2004; 4: 519–27.

117 Martínez JA, Cobos-Trigueros N, Soriano A, Almela M, Ortega M, Marco F, Pitart C, Sterzik H, Lopez J, Mensa J. Influence of empiric therapy with a beta-lactam alone or combined with an aminoglycoside on prognosis of bacteremia due to gram-negative microorganisms. Antimicrob Agents Chemother 2010; 54: 3590–96.

118 Hogg GM, Barr JG, Webb CH. In-vitro activity of the combination of colistin and rifampicin against multi drug resistant strains of *Acinetobacter baumannii*. J Antimicrob Chemother 1998; 41: 494–5.

119 Petrosillo N, Chinello P, Proietti MF, Cecchini L, Masala M, Franchi C, Venditti M, Esposito S, Nicastri E. Combined colistin and rifampicin therapy for carbapenem-resistant *Acinetobacter baumannii* infections: clinical outcome and adverse events. Clin Microbiol Infect 2005; 11: 682–3.

120 Durante-Mangoni E, Signoriello G, Andini R, Mattei A, De Cristoforo M, Murino P, Bassetti M, Malacarne P, Petrosillo N, Galdieri N, Mocavero P, Corcione A, Viscoli C, Zarrilli R, Gallo C, Utili R. Colistin and rifampicin compared with colistin alone for the treatment of serious infections due to extensively drug-resistant *Acinetobacter baumannii*: a multicenter, randomized clinical trial. Clin Infect Dis 2013; 57: 349–58.

121 Falagas ME, Rafailidis PI, Kasiakou SK, Hatzopoulou P, Michalopoulos A. Effectiveness and nephrotoxicity of colistin monotherapy vs. colistin-meropenem combination therapy for multidrug-resistant Gram-negative bacterial infections. Clin Microbiol Infect 2006; 12: 1227–30.

122 Shields RK, Clancy CJ, Gillis LM, Kwak EJ, Silveira FP, Massih RC. Epidemiology, clinical characteristics and outcomes of extensively drug-resistant *Acinetobacter baumannii* infections among solid organ transplant recipients. PLoS ONE 2012; 7: e52349.

123 Qureshi ZA, Paterson DL, Potoski BA, Kilayko MC, Sandovsky G, Sordillo E, Polsky B, Adams-Haduch JM, Doi Y. Treatment outcome of bacteraemia due to KPC-producing *Klebsiella pneumoniae*: superiority of combination antimicrobial regimens. AAC 2012; 56: 2108–13.

124 Grayson ML, Kucers A, Crowe SM, McCarthy J, Mills J, Mouton J, Norrby R, Paterson D, Pfaller M., eds. Kucers' The Use of Antibiotics: 6th Ed. London: CRC Press, 2010.

125 Vihena C, Bettencourt A. Daptomycin: a review of properties, clinical use, drug delivery and resistance. Mini Rev Med Chem 2012; 12: 202–9.

126 Rolston KV. New antimicrobial agents for the treatment of bacterial infections in cancer patients. Hematol Oncol 2009; 27: 107–14.

127 Rolston KV, Besece D, Lamp KC, Yoon M, McConnell SA, White P. Daptomycin use in neutropenic patients with documented gram-positive infections. Support Care Cancer 2014; 22(1): 7–14.

128 Barber GR, Lauretta J, Saez R. Case reports. A febrile neutropenic patient with Enterococcus gallinarum sepsis treated with daptomycin and gentamicin. Pharmacotherapy 2007; 27: 927–32.

129 Wahby KA, Alangaden GJ. Daptomycin failure in a neutropenic leukemia patient with Staphylococcus aureus meningitis. Leuk Lymphoma 2012; 53: 1610–2.

130 Kuter DJ, Tillotson GS. Hematologic effects of antimicrobials: focus on the oxalidinone linezolid. Pharmacotherapy 2001; 21: 1010–3.

131 Cohen N, Mihu CN, Seo SK, Chung D, Chou J, Heller G, Papanicolaou GA. Hematologic safety profile of linezolid in the early periengraftment period after allogenic stem cell transplantation. Bio Blood Marrow Transplant 2009; 15: 1337–41.

132 Jaksic B, Martinelli G, Perez-Oteyza J, Hartman CS, Leonard LB, Tack KJ. Efficacy and safety of linezolid compared with vancomycin in a randomized, double blind study of febrile neutropenic patients with cancer. Clin Infect Dis 2006; 42: 597–607.

133 Ramirez E, Gomez-Gil R, Borobia AM, Moreno F, Zegarra C, Munoz R. Improving linezolid use decreases the incidence of resistance among gram-positive microorganisms. Int J Antimicrob Agents 2013; 41: 174–8.

134 Holmes NE, Ballard SA, Lam MM, Johnson PDR, Grayson ML, Stinear TP, Howden BP. Genomic analysis of teicoplanin resistance emerging during treatment of vanB vancomycin-resistant *Enterococcus faecium* infections in solid organ transplant recipients including donor-derived cases. J Antimicrob Chemother 2013; 68: 2134–9.

135 Hahn-Ast C, Glasmacher A, Arns A, Mühling A, Orlopp K, Marklein G, Von Lilienfeld-Toal M. An audit of efficacy and toxicity of teicoplanin versus vancomycin in febrile neutropenia: is the different toxicity profile clinically relevant? Infection 2008; 36: 54–8.

136 de la Rubia J, Montesinos P, Martino R, Jarque I, Rovira M, Vázquez L, López J, Batlle M, de la Cámara R, Juliá A, Lahuerta JJ, Debén G, Díaz J, García R, Sanz MA. Imipenem/cilastatin with or without glycopeptide as initial antibiotic therapy for recipients of autologous stem cell transplantation: results of a Spanish multicenter study. Biol Blood Marrow Transplant 2009; 15: 512–6.

137 Casapao AM, Kullar R, Davis SL, Levine DP, Zhao JJ, Potoski BA, Goff DA, Crank CW, Segreti J, Sakoulas G, Cosgrove SE, Rybak MJ. Multicentre study of high-dose daptomycin for treatment of enterococcal infections. Antimicrob Agents Chemother 2013; 57: 4190–6.

138 Whang DW, Miller LG, Partain NM, McKinnell JA. Systematic review and meta-analysis of linezolid versus daptomycin for treatment of vancomcyin-resistant enterococcal blood stream infections. Antimicrob Agents Chemother 2013; 57: 5013–8.

139 Cornely OA, Miller M, Fantin B, Mullane K, Kean Y, Gorbach S. Resolution of Clostridium difficile-associated diarrhea in patients with cancer treated with fidaxomicin or vancomycin. J Clin Oncol 2013; 31: 2493–9.

140 Louie TJ, Miller MA, Mullane KM, Weiss K, Lentnek A, Golan Y, Gorbach S, Sears P, Shue YK, OPT-80-003 Clinical Study Group. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. N Engl J Med 2011; 364: 422–31.

141 Clutter DS, Dubrovskaya Y, Meri MY, Teperman L, Press R, Safdar A. Fidaxomicin versus conventional antimicrobial therapy in 59 recipients of solid organ and hematopoietic stem cell transplantation with *Clositridium difficile*-associated diarrhea. Antimicrob Agents Chemother 2013; 79: 4501–5.

142 Abbott IJ, Roberts JA. Infusional beta-lactam antibiotics in febrile neutropenia: has the time come? Curr Opin Infect Dise 2012; 25: 619–25.

143 Pea F, Viale P, Damiani D, Pavan F, Cristini F, Fanin R, Furlaut M. Ceftazidime in acute myeloid leukemia patients with febrile neutropenia: helpfulness of continuous intravenous infusion in maximizing pharmacodynamic exposure. Antimicrob Agents Chemother 2005; 49: 3550–3.

144 Crandon JL, Nicolau DP. Pharmacodynamic approaches to optimizing beta-lactam therapy. Crit Care Clin 2011; 27: 77–93.

145 Varghese JM, Roberts JA, Lipman J. Antimicrobial pharmacokinetic and pharmacodynamic issues in the critically ill with severe sepsis and septic shock. Crit Care Clin 2011; 27: 19–34.

146 Roberts JA, Kirkpatrick CM, Roberts MS, Robertson TA, Dalley AJ, Lipman J. Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution. J Antimicrob Chemother 2009; 64: 142–50.

147 Binder L, Schwörer H, Hoppe S, Streit F, Neumann S, Beckmann A, Wachter R, Oellerich M, Walson PD. Pharmacokinetics of meropenem in critically ill patients with severe infections. Ther Drug Monit 2013; 35: 63–70.

148 Li C, Kuti JL, Nightingale CH, Nicolau DP. Population pharmacokinetic analysis and dosing regimen optimization of meropenem in adult patients. J Clin Pharmacol 2006; 46: 1171–8.

149 Stanzani M, Turnietto F, Giannini MB, Bianchi G, Nanetti A, Vianelli N, Arpinati M, Giovannini M, Bonifazi F, Bandini G, Baccarani M. Successful treatment of multi-resistant *Pseudomonas aeruginosa* osteomyelitis after allogenic bone marrow transplantation with a combination of colistin and tigecycline. J Med Microbiol 2007; 56: 1692–5.

150 Ng K, Gosbell IB. Successful oral pristinamycin therapy for osteoarticular infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) and other Staphylococcus spp. J Antimicrob Chemother 2005; 55: 1008–12.

151 Ruparelia N, Atkins BL, Hemingway J, Berndt AR, Byren I. Pristinamycin as an adjunctive therapy in the management of gram-positive multi-drug resistant organism (MDRO) osteoarticular infection. J Infect 2008; 57: 191–7.

152 Reid AB, Daffy JR, Stanley P, Buising KL. Use of pristinamycin for infections by gram-positive bacteria: clinical experience at an Australian hospital. Antimicrob Agents Chemother 2010; 54: 3949–52.

153 Michalopoulos AS, Livaditis IG, Gougoutas V. The revival of fosfomycin. Int J Infect Dis 2011; 15: e732–9.

154 Falagas ME, Karageorgopoulos DE, Nordmann P. Therapeutic options for infections with Enterobacteriaceae producing carbapenem-hydrolyzing enzymes. Future Microbiol 2011; 6: 653–66.

155 Kastoris AC, Rafailidis PI, Vouloumanou EK, Gkegkes ID, Falagas ME. Synergy of fosfomycin with other antibiotics for Gram-positive and Gram-negative bacteria. Eur J Clin Pharmacol 2010; 66: 359–68.

156 Evren E, Azap OK, Çolakoğlu Ş, Arslan H. *In vitro* activity of fosfomycin in combination with imipenem, meropenem, colistin and tigecycline against OXA 48-positive Klebsiella pneumoniae strains. Diagn Microbiol Infect Dis 2013; 76: 335–8.

157 Bergen PJ, Landersdorfer CB, Lee HJ, Li J, Nation RL. 'Old' antibiotics for emerging multidrug-resistant bacteria. Curr Opin Infect Dis 2012; 7: e52349.

158 Garonzik SM, Li J, Thamlikitkul V, Paterson DL, Shoham S, Jacob J, Silveira FP, Forrest A, Nation RL. Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. Antimicrob Agents Chemother 2011; 55: 3284.