Therapeutic Advances in Infectious Disease
Review

Ther Adv Infectious Dis
2021, Vol. 8: 1–19
DOI: 10.1177/20499361211053480

Prevention and management of carbapenem-resistant Enterobacteriaceae in haematopoietic cell transplantation

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***Abstract*:** Carbapenem-resistant Enterobacteriaceae (CRE) infections are associated with high morbidity and mortality rates in haematopoietic cell transplantation (HCT) recipients. Factors like mucositis, neutropenia, prolonged hospital stay, and frequent use of prophylactic antimicrobials make HCT recipients especially susceptible to CRE infections. Low culture positivity rates, delay in microbiological diagnosis, and resistance to empirical antimicrobial therapy for febrile neutropenia are responsible for high mortality rates in HCT recipients infected with CRE. In this review we discuss the epidemiology, diagnosis, and management of CRE infections with particular emphasis on patients undergoing HCT. We emphasise the need for preventive strategies like multidisciplinary antimicrobial stewardship, and pre-emptive screening for CRE colonisation in prospective HCT patients as measures to mitigate the adverse impact of CRE on HCT outcomes. Newer diagnostic tests like polymerase chain reaction and matrix-assisted laser desorption ionisation-time of flight (MALDI-TOF) assay that enable earlier and better identification of CRE isolates are discussed. Antimicrobial agents available against CRE, including newer agents like ceftazidime-avibactam and meropenem-vaborbactam, have been reviewed. We also discuss the data on promising experimental treatments against CRE: phage therapy and healthy donor faecal microbiota transplant. Finally, this review puts forth recommendations as per existing literature on diagnosis and management of CRE infections in blood and marrow transplant (BMT) unit.

Keywords: arbapenem-resistant enterobacteriaceae, hematopoietic cell transplantation, febrile neutropenia, gut microbiome, fecal microbiota transplantation

Received: 21 June 2021; revised manuscript accepted: 28 September 2021.

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Introduction

Infections are one of the leading causes of mortality in haematopoietic cell transplantation (HCT) recipients. During 2018–2019, the Center for International Blood and Marrow Transplant Research (CIBMTR) reported infections to be the cause of early mortality (<100 days of HCT) after autologous transplant in 28% and 22% paediatric and adult patients respectively, and 16% after both paediatric and adult allogeneic transplants.[1] Gram-negative Enterobacteriaceae (*Klebsiella pneumoniae, Escherichia coli)*, and *Pseudomonas aeruginosa* account for majority of bloodstream infections (BSI) in HCT recipients. Hence, the current recommendation of empirical initiation of antimicrobial agents active against these bacteria in febrile neutropenia patients.[2] However, over the last decade, multidrug resistant bacteria (MDR), especially carbapenem-resistant Enterobacteriaceae (CRE), have increasingly become prevalent in haematology units in developing countries and CRE infections have emerged as a major cause of early mortality in HCT recipients.[3] The reasons for growing incidence of CRE infections in blood and marrow transplant (BMT) unit include wider, and often inappropriate, use of antimicrobials, longer hospital stays of haematology patients before and

Table 1. Characteristics of common carbapenemases in Enterobacteriales.[12]

Ambler class	Representative gene	Active site	Substrate	Inhibitors	Species of origin
A	KPC	Serine	Carbapenems, cephalosporins, penicillins	Clavulanic acid	*Klebsiella pneumoniae*
B	NDM-1	Zinc	Most β-lactams including carbapenems except monobactams	EDTA	*Klebsiella pneumoniae*
	IMP				*Serratia marcescens*
	VIM				*Pseudomonas aeruginosa*
D	OXA	Serine	Most β -lactams including carbapenems	Clavulanic acid	*Klebsiella pneumoniae*

EDTA, ethylenediamine tetraacetic acid; IMP, imipenem-hydrolysing metallo-β-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; VIM, Verona integron-encoded metallo-β -lactamase.

after their HCT.[4] In this review, we offer a BMT physician's perspective on diagnosis and management of CRE infections in HCT recipients. Early identification of CRE infection in HCT patients is important because it enables earlier initiation of specific antimicrobials and prevents transplant-related mortality (TRM). We also review data on newer strategies like faecal microbiota transplantation (FMT) and phage therapy in management of CRE infections in HCT recipients. Above all, the clinicians should ensure adherence to basic principles of hand hygiene, patient isolation and antibiotic stewardship to prevent CRE infections in their BMT unit.[5]

Microbiology of CRE

The Centers for Disease Control and Prevention (CDC) defines CRE as a group of Enterobacteriaceae resistant to at least one carbapenem antibiotic or producing a carbapenemase enzyme.[6] The CRE infection spectrum covers severe BSI, intra-abdominal infections (IAI), pneumonia, urinary tract infections (UTI) and device/implant-associated infections.[7]

Carbapenemase-producing CRE

The Ambler molecular classification divides β -lactamases into three groups (A, C and D) that use serine-mediated substrate hydrolysis and a fourth group B metalloproteinase using divalent zinc atoms for the same.[8] Characteristics of common carbapenemases are summarised in Table 1. The clinical relevance of Ambler class C is unknown.[9] The genes encoding these carbapenemases are located either on the chromosome or on mobile genetic elements (MGEs) like plasmids, transposons and integrons.[10,11] Rapid propagation of carbapenemase genes by MGEs among clinical isolates is a source of serious public health concern.

Epidemiology and risk factors

Predisposing factors for CRE bacteraemia in HCT recipients include conditioning regimen-associated mucosal barrier injury leading to BSI, protracted neutropenia (associated with breakthrough infections), prolonged hospital stay and frequent exposure to broad-spectrum antimicrobial therapy (Figure 1). Fluoroquinolone prophylaxis is associated with a high risk of bacteraemia in HCT recipients colonised with fluoroquinolone-resistant bacteria.[13] A CIBMTR study reported higher incidence of bacterial infections in HCT recipients after myeloablative conditioning (MAC) compared with reduced intensity conditioning (RIC). However, this was not specific for CRE infections. Other contributory

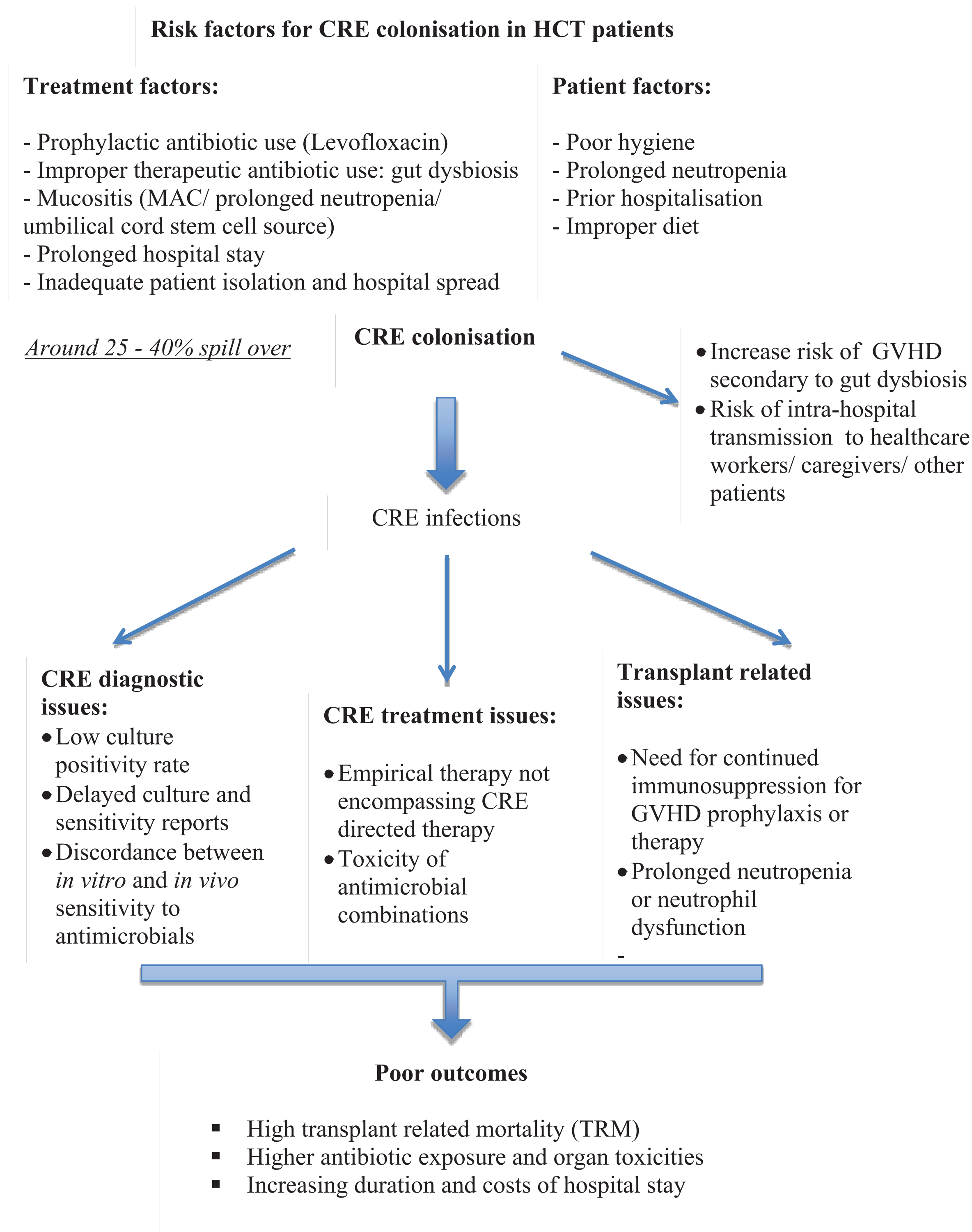

Figure 1. Risk factors for CRE colonisation in HCT patients.
CRE, carbapenem-resistant Enterobacteriaceae; GVHD, graft-*versus*-host disease; HCT, haematopoietic cell transplant; MAC, myeloablative conditioning; TRM, transplant-related mortality.

factors for bacterial BSI in HCT recipients are as follows: prior history of CRE infection, prolonged hospital stay before HCT, umbilical cord blood transplant, haploidentical donor HCT, prolonged time to neutrophil recovery, severe mucositis, acute graft-*versus*-host disease (GVHD) and immunosuppressive treatment in post-HCT period. While these risk factors are not CRE infection-specific, they do contribute significantly towards increased risk of CRE infections in colonised patients.[14–19]

In 2017, the CDC reported 13,100 cases of CRE infections with more than 1100 deaths among the hospitalised patients in the United States.[6] The prevalence of CRE in India, as per the 2019 Indian Council of Medical Research (ICMR) resistance surveillance network report, varies from 35% to 45% among all Enterobacteriaceae isolates (excluding urine and faeces specimens).[20] Of 136 acute leukaemia patients admitted at our centre, 61% were found to be colonised with CRE at the time of admission.[21]

The incidence of CRE infection in HCT recipients ranges from 1.6% to 3.4%.[22–24] Prior colonisation by CRE dramatically increases the CRE BSI rates in the post-HCT period.[3,16,25] While *Klebsiella pneumoniae* carbapenemase (KPC) is the most common CRE subtype isolated from bacteraemic HCT recipients, oxacillinase (OXA-48) and New Delhi metallo-β-lactamase (NDM) producing CREs are increasingly being reported.[26,27] Mortality rates in this subset of population due to CRE BSIs remain high (>50%).[3,28,29] Important studies on CRE in HCT recipients and in patients with haematological malignancies are highlighted in Table 2.

Microbiological diagnosis of CRE

Up to 50% of febrile neutropenia episodes have no identifiable infectious aetiology, and bacteraemia is documented in less than 30% of patients.[2,43–46] Conventional culture-based susceptibility tests lead to delay of up to 72 h, and an additional 24 h is required for reporting sensitivity. Hence, delay in diagnosis of CRE is one of the major reasons for higher mortality associated with this infection in HCT recipients as they often get initiated on empirical antimicrobials that provide poor to no coverage against CRE infections. Rapid molecular diagnostic tests for CRE are needed for timely initiation of effective antimicrobial therapy in immunosuppressed HCT recipients to avoid TRM.[47]

Rapid tests for detection of carbapenemases include molecular tests to detect the resistance mechanism (i.e. presence of carbapenemase gene) and novel phenotypic tests that detect *in vitro* activity of carbapenemase enzymes. Molecular methods like polymerase chain reaction (PCR) and microarray-based platforms allow for rapid detection of carbapenemase genes. However, high cost and technical requirements preclude their widespread use.[48,49] Rapid phenotypic tests for carbapenemase activity [e.g. Carba NP test, matrix-assisted laser desorption ionisation-time of flight mass spectrometry (MALDI TOF MS)] can be used as an alternative to molecular methods.[50,51] While these tests are relatively inexpensive, they do not differentiate between various classes of carbapenemases. Implementation of rapid diagnostic assays is associated with significant decrease in time to initiation of appropriate antimicrobial therapy and early discontinuation of inappropriate empirical antimicrobials.[50]

Prevention and treatment of CRE in BMT unit

Various professional groups have put forth recommendations on CRE infection prevention and management in HCT recipients. Recommendations from the recent guidelines by American Society of Transplantation and Cellular therapy (ASTCT), Infectious Diseases Society of America (IDSA) guidance on treatment of CRE infections and the 2015 Italian consensus statement on management of CRE infections in HCT recipients are enumerated in Table 3 along with our comments for practice in high-prevalence setting.[17,52,53] Salient CRE preventive strategies from these recommendations are elaborated below.

Gastrointestinal screening for CRE colonisation before HCT

Prior colonisation by CRE is an important predictor for subsequent infections. Colonisation by MDR organisms adversely impacts survival in early postallogeneic HCT period.[25,54,55] An Italian multicentre study showed CRE bacteraemia rates of 26% and 39% in CRE colonised autologous and allogenic HCT.[3] Preemptive detection of

Table 2. Summary of studies reporting CRE in patients undergoing HCT and patients with haematological malignancies.

Author	Study population	Study methodology	Number of patients	CRE prevalence	Comments
Hussein *et al.*[30]	All adult patients including HCT	BSI	317 patients	103 of 317 patients had CRKp	Higher mortality with CRKp BSI
Girmenia *et al.*[3]	HCT	BSI	10,477 patients	112 of 10,477 patients	Pre-HCT CRKp infection associated with an increased mortality in allo-HCT recipients who developed a CRKp infection
		Rectal swab for surveillance	5111 patients	82 of 5111 patients	
Kikuchi *et al.*[31]	HCT	BSI	122 patients	52% of all GNB BSI were CRE	N/A
Satlin *et al.*[32]	Haematologic malignancy including HCT	BSI	43 patients	43 of 1992 isolates	CRE-active empirical therapy was associated with a lower 30-day mortality rate
Stoma *et al.*[33]	HCT	BSI	135 patients	7 of 34 *Klebsiella* isolates were CRE	Higher mortality with CRE BSI
Trecarichi *et al.*[34]	Haematologic malignancy including HCT	BSI	161 patients	161 of 278 isolates	Higher overall 21-day mortality with CRKp BSI
Philip *et al.*[35]	AML	BSI	109 patients	14 patients	N/A
Kumar *et al.*[36]	Haematologic malignancy	Rectal swab for surveillance	93 patients	76 of 86 isolates	N/A
Jaiswal *et al.*[37]	Haematologic malignancy	Faecal culture for surveillance	225 patients	94 patients	100% mortality in patients with CRE BSI
		BSI		18 of the above 94 patients	
Kothari *et al.*[21]	Acute leukaemia	Rectal swab for surveillance	136 patients	83 patients	More chemotherapy interruptions More induction deaths
Gill *et al.*[38]	HCT	Faecal culture for surveillance	76 patients	18 patients	N/A
Korula *et al.*[39]	HCT	Faecal culture for surveillance	232 transplants	19 of 164 isolates	Higher 100-day risk of bacteraemia and mortality in MDR-positive patients
Barman *et al.*[40]	HCT	Faecal culture for surveillance	127 patients	48 patients	
		BSI	438 transplants	131 patients and 145 organisms: 22% GNB with 66.8% CRE	N/A
Kumar *et al.*[41]	Haematologic malignancy	Rectal swab for surveillance	200 patients	151 patients	N/A
Jain *et al.*[42]	AML	BSI	121 patients	14 patients	N/A

AML, acute myeloid leukaemia; BSI, bloodstream infections; CRE, carbapenem-resistant Enterobacteriaceae; CRKp, carbapenem-resistant *Klebsiella pneumoniae*; GNB, gram-negative bacillus; HCT, haematopoietic cell transplant; MDR, multidrug resistant; N/A, not available.

Table 3. Summary of grade recommendations adapted from ASTCT 2021, Italian 2015 multidisciplinary consensus and IDSA 2021 recommendations for CRE screening, prevention and treatment in patients with haematological malignancies.[17,52,53]

Recommendation	ASTCT 2021	IDSA 2021[a]	Italian consensus (for CRKp) 2015[b]	Rationale/comment
Screening for MDR colonisation in HCT recipients to guide initial antibiotic therapy	No definitive recommendation	N/A	Yes: **A-II** Centres in settings with known CRKp spread No: **B-III** Centres without significant CRKp spread	Allows isolation/cohorting of patients and nurses Enables early initiation of CRE-effective antimicrobial therapy Important for centres where CRE is highly prevalent
Screening site and frequency	N/A	N/A	Rectal swab: **A-II** Weekly screening: **A-II** (esp. if other patients found colonised in the same unit)	Serial monitoring might increase cost burden, though preferred
Contact precautions for CRE-infected patients	Yes: B-III	N/A	Yes: **A-II**	
Nursing staff education for infection control and prevent cross-transmission	N/A	N/A	Yes: **A-II** Hand hygiene: **A-I**	Preferred, given that such practices in general lead to lesser burden of infections
Role of fluoroquine prophylaxis on incidence of CRE bacteraemia	Decreases when used during neutropenia (adults): B-I	N/A	N/A	Increased risk of ESBL emergence with routine FQ prophylaxis
Selective digestive decontamination with oral gentamicin/colistin	Not routinely recommended: D-III		Yes: **C-III**	
CRE-directed antibiotic therapy				
With neutropenia but w/o fever	N/A	N/A	No: **C-III**	
Choice of antibiotic				
Cefta-avi (CA)/Mero-vabor (MV)	Yes: B-II	Yes (especially for non-UTI)	N/A	CA combination in CRE neutropenic fever should be strongly considered
OXA-48-like carbapenemase	Yes: B-III	Yes	N/A	
High-dose meropenem infusion ± second agent	No recommendation	Yes; In CRE cystitis (otherwise not recommended)	Combination therapy: meropenem + genta/tigecycline/colistin	Can be considered if CA is unavailable or infection with CRE is limited with soon expected neutrophil recovery
Duration of antibiotic therapy				
10–14 days in patients with progressive complications	Yes: C-III 7-day course with CVC-related uncomplicated CRE bacteraemia: C-III	N/A	N/A	Consider • Afebrile >72 h • Cardiovascular stability (if prior septic shock) • Cultures sterile • Neutrophil recovery
CVC should be removed during CRE bacteraemia		N/A	N/A	Evaluate for possible foci of infection. Important to have an adequate IV access during these episodes. No judicial removal of CVC should be avoided. Paired blood cultures from CVC and PB are a must to assess CLABSI.

(Continued)

Table 3. (Continued)

Recommendation	ASTCT 2021	IDSA 2021[a]	Italian consensus (for CRKp) 2015[b]	Rationale/comment
During non-neutropenic fever and with no other obvious source	Yes: B-III			
During chemotherapy-induced neutropenia, mucositis or GI GVHD	No: D-III			

ASTCT, American Society of Transplantation and Cellular therapy; CA, ceftazidime-avibactam; CLABSI, central line-associated bloodstream infection; CRE, carbapenem-resistant Enterobacteriaceae; CRKp, carbapenem-resistant *Klebsiella pneumoniae*; CVC, central venous catheter; ESBL, extended spectrum beta lactamase; FQ, fluoroquinolone; GI GVHD, gastrointestinal graft-*versus*-host disease; HCT, haematopoietic cell transplant; IDSA, Infectious Diseases Society of America; IV, intravenous; MDR, multidrug resistant; MV, meropenem-vaborbactam; N/A, not available; OXA, oxacillinase; PB, peripheral blood; UTI, urinary tract infection.
[a]The IDSA 2021 guidelines are not specific for HCT recipients.
[b]The Italian consensus statement 2015 was before CA/MV options became commonplace.

CRE colonisation is helpful in identifying patients who need early initiation of anti-CRE treatment during their febrile neutropenia episodes and may possibly benefit from gut microbiome restorative strategies before their HCT.[54,56,57]

As Enterobacteriaceae are one of the major gut commensals, CRE colonisation can be detected by screening for their faecal carriage. Various studies have found rectal swabs to be more sensitive for detection of CRE colonisation when compared with faecal culture.[58–60] The time points of surveillance for colonisation are also important. A regular and continuous screening strategy via faecal culture has been found to be more effective for detection for CRE carriage compared with one-time screening strategy.[24] Forcina *et al.*[23] reported substantial reduction in mortality due to carbapenem-resistant *Klebsiella pneumoniae* (CRKp) BSI at 1 year post-HCT when weekly surveillance cultures strategy was employed, with contact precautions, in carriers and early targeted therapy was initiated in febrile neutropenic carriers. The 2015 Italian multidisciplinary consensus statement on CRKp infection management in HCT recipients recommended monitoring for CRE colonisation before hospital admission for HCT, weekly post-HCT monitoring in the event of CRKp isolation from other patients in the same BMT unit and in patients who present with post-HCT intestinal complications, in particular GVHD.[52] The recent guidance from ASTCT recommends such screening to be restricted to patients referred from CRE endemic areas.[17] Beyond identification of CRE carriers who benefit from upfront CRE-effective therapy during their febrile neutropenia, screening can also be helpful in selecting prospective HCT patients for CRE decolonisation strategies like FMT. Hence, in HCT recipients, adopting a preemptive screening strategy leads to increased identification of CRE colonisers and a reduced progression to BSIs by timely initiation of CRE-effective antimicrobial therapy.[61]

Infection control strategies and management of CRE colonisers in the BMT unit

Recommendations for CRE prevention in health care settings stress on hand hygiene compliance, healthcare personnel education, antimicrobial stewardship and screening for CRE colonisers before their HCT in centres where CRE is highly prevalent. Infected or colonised patients with CRE need isolation (single rooms where feasible), and strict contact precautions with gown and gloves are recommended.[17,52,62] Initiation of effective antimicrobial therapy based on the susceptibility pattern of the colonising isolate at the onset of febrile neutropenia in CRE colonisers is strongly recommended. Surveillance data on CRE prevalence in hospitals should be regularly updated, and coordinated control effect involving various departments to prevent intrahospital transmission of CRE is recommended.[52]

Antimicrobial stewardship programme in BMT unit

Prior antimicrobial use such as carbapenem and aminoglycoside is an important risk factor for

CRKp infection.[63] Antimicrobial stewardship policies (ASP) play an important role in curtailing unnecessary antimicrobial usage, thus potentially reducing the prevalence of CRE.[64–67]

Although broad-spectrum antimicrobial therapy is often necessary in HCT recipients, transplant physicians should strive to implement the following recommended practices: early de-escalation of antimicrobial therapy and daily assessment for the need for continued antimicrobial therapy.[68] Multidisciplinary team involving transplant physicians, infectious disease specialists, microbiologists and pharmacists should regularly review the BMT unit's epidemiology and antibiogram and implement unit-specific antimicrobial therapy algorithms.[69] The IDSA recommends implementation of local and institution-specific clinical guidelines to improve judicious antimicrobial use.[64] A single-centre study on patients with haematological malignancies and HCT recipients demonstrated significant reduction in carbapenem use after implementation of revised antimicrobial policy recommending piperacillin-tazobactam with or without amikacin as the first-line treatment for febrile neutropenia.[70]

Major impediments to ASP implementation include lack of key personnel, limited antimicrobial options in settings with a high prevalence of MDR organisms and poor interpersonal and interdepartmental communication. These inevitably result in increased TRM rates, prolonged hospitalisation and high intensive care requirements.[71,72] Formulation of institution-specific protocols for antimicrobial use, regular training and motivation of all healthcare staff for compliance with ASP, multidisciplinary team collaboration and improving interpersonal communication can overcome these obstacles.

Escalation versus *de-escalation approaches in management of neutropenic sepsis in the BMT unit*

There is no clear consensus on escalation *versus* de-escalation strategy and treatment duration of antimicrobial therapy for neutropenic sepsis.

In escalation strategy initial empirical antimicrobial treatment provides cover for Enterobacteriaceae and *Pseudomonas aeruginosa* but not MDR bacteria like CRE. Coverage for the latter is provided by 'escalating' the initial antimicrobials to a broader spectrum combination regimen that is effective against these as well. A de-escalation strategy, on the contrary, provides upfront initial coverage for highly resistant pathogens. Therapy is 'de-escalated' later with subsequent focus on microbiology isolates.[73] We believe that de-escalation strategy is better suited for practice settings where CRE is highly prevalent. We further posit that screening for CRE colonisation in patients before their HCT permits identification of the subset who will benefit from de-escalation strategy of antimicrobial therapy in their febrile neutropenic episode. Timely initiation of CRE-active therapy in profoundly neutropenic HCT patients is the most effective strategy in preventing CRE bacteraemia-related deaths.[29]

An Italian multicentre survey on HCT patients reported 26% and 39% CRKp infections in autologous and allogeneic HCT recipients, respectively, colonised by CRKp.[3] Initial empirical therapy targeted against CRKp was associated with 2.67-fold increase in survival [hazard ratio (HR) range: 1.43–4.99; $p = 0.002$].

Treatment duration: The 2011 IDSA guidelines on febrile neutropenia recommend continuing the antimicrobial therapy until neutrophil recovery (absolute neutrophil count >500 cells/mm^3) or longer, if clinically necessary.[2] However, the European Conference on Infections in Leukaemia (ECIL-4) guidelines recommend stopping antimicrobials after defervescence in patients with no identifiable cause of infection who are afebrile for more than 48 h irrespective of the neutrophil count or the expected duration of neutropenia.[73] The 2021 National Comprehensive Cancer Network (NCCN) guidelines discuss both the options and suggest de-escalation to fluoroquinolone prophylaxis in patients who become afebrile.[74]

Several large retrospective studies on HCT recipients with febrile neutropenia without any identifiable infectious focus show that early cessation of antimicrobials has no adverse impact on mortality, rehospitalisation, clinical deterioration and recurrence of fever at ⩾72 h.[75–83] A multicentre, randomised controlled trial (HOW LONG study) evaluated cessation of antimicrobials before neutrophil recovery in febrile neutropenic patients without an aetiological diagnosis who are clinically recovered and apyrexic for >72 h and compared this approach with continual antimicrobials until neutrophil recovery to >500 cells/mm^3.[84] Almost a fourth of participants in this study were HCT recipients. Early cessation of empirical antimicrobial therapy was found to be associated with a significant increase in antibiotic-free days without an adverse impact on mortality and recurrence of fever.

Antimicrobial therapy for CRE

The effective antimicrobial armamentarium against CRE is still a work in progress. Monotherapy options against CRE are limited and not yet widely available. Hence, combination antimicrobial regimens incorporating high-dose extended-infusion meropenem, tigecycline, polymyxins and aminoglycosides remain in widespread use. Their use is complicated by multiple drug interactions, add-on organ toxicities and possibility of reduced effectiveness due to accrual of resistance.[85,86] There are promising data on newer CRE-effective β-lactam/β-lactamase inhibitors (BL-BLIs): ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam.[87–91] However, these agents are not uniformly active against all carbapenemases. For instance, ceftazidime-avibactam does not have activity against metallo-β-lactamase (MBL)-producing Enterobacteriaceae. Hence, for treatment of MBLs, either cefiederocol monotherapy or a combination of ceftazidime-avibactam with aztreonam is recommended, as the latter is not hydrolysed by MBLs and MBL-producing Enterobacteriaceae frequently coproduce other enzymes; KPC and OXA-48 against which aztreonam has no activity.[53,92,93] Table 4 summarises the available antimicrobials and their activity against various CRE. Management algorithm of CRE in HCT patients is illustrated in Figure 2.

Combination versus *monotherapy regimens in CRE sepsis*

The important clinical question of whether combination antimicrobial therapy is more or less efficacious against CRE compared with novel single CRE-active agents remains to be addressed in a prospective head-to-head comparative trial. While combination antimicrobial therapy has shown increased bactericidal activity *in vitro* compared with monotherapy, clinical studies assessing comparative efficacy of various CRE-effective therapies show conflicting results as majority of them were conducted before the novel BL-BLIs era.[96] Conclusions from the various studies are summarised below.

- Combination therapy comprising various CRE-effective antimicrobials: carbapenems, polymyxin, tigecycline, aminoglycoside and fosfomycin have been shown to be effective in treatment of CRE BSIs in critically ill patients in older studies before novel BL-BLIs era.[97–103]
- There is no added advantage of combining colistin with meropenem over single-agent colistin.[104] In fact, a recent guideline recommends against using polymyxin B and colistin for CRE infections as these have been shown to be associated with increased nephrotoxicity and mortality risk.[53,87,88,90,91]
- A recent meta-analysis by Onorato *et al.*[105] compared the efficacy of single-agent ceftazidime-avibactam against carbapenem-resistant gram-negative bacteria with combination therapy comprising colistin, tigecycline, aminoglycosides, fosfomycin and ciprofloxacin. No difference in mortality and microbiological cure rates was noted.

Based on existing evidence, combination therapy can no longer be recommended for treatment of CRE infections in HCT patients. Effective treatment against CRE is based on the mechanism of carbapenem resistance (Table 4). New CRE-effective antimicrobials like meropenem-vaborbactam and ceftazidime-avibactam assume a frontline role in modern recommendations.[53] Hence, it is prudent to prioritise the use of these novel CRE-effective agents when adopting a de-escalation strategy in HCT patients colonised with CRE and/or those getting treated in a centre with high CRE prevalence.

Important considerations for CRE antimicrobial therapy are as follows:[53,94,106]

1. Detailed clinical and diagnostic evaluation should be undertaken to identify the infection source and CRE in the bloodstream. Surveillance for CRE colonisation using rectal swab in HCT patient is helpful as

MANAGEMENT ALGORITHM FOR CRE IN HCT PATIENTS (40)

CRE suspected based on risk factors

EMPIRICAL THERAPY
(Carbapenemase status awaited or test not available)

Focus of Infection	Preferred Antimicrobial Agent	Alternative choice Antimicrobial Agent
Lower Urinary Tract (uncomplicated)	Ciprofloxacin/Levofloxacin *or* Trimethoprim - sulfamethoxazole *or* Amikacin/Gentamicin *or* nitrofurantoin	Colistin *or* Ceftazidime – Avibactam *or* Meropenem – Vaborbactum *or* Imipenem- Cilastatin- Relebactum *or* Cefiderocol
Others (including complicated lower UTI, Pneumonia etc)	Ceftazidime - Avibactam **plus** Aztreonam *or* Meropenem – Vaborbactum *or* Imipenem- Cilastatin- Relebactum Tigecycline* *or* Eravacycline *or*	Cefiderocol

DEFINITIVE THERAPY ONCE CARBAPENEMASE CLASS IDENTIFIED

CLASS A (Eg : KPC)	CLASS B (Eg :MBL)	CLASS D (Eg :OXA- 48)
Ceftazidime – Avibactam *or* Meropenem – Vaborbactum *or* Tigecycline* *or* Eravacycline *or* Imipenem- Cilastatin- Relebactum *or* Cefiderocol	Ceftazidime - Avibactam **plus** Aztreonam *or* Cefiderocol *or* Tigecycline* *or* Eravacycline	Ceftazidime - Avibactam *or* Tigecycline* *or* Eravacycline *or* Cefiderocol

CRE BUT NOT CARBAPANEMASE PRODUCER

Consider extended Meropenem infusion if sensitive to meropenem or continue Ceftazidime – Avibactam

Figure 2. Management algorithm for CRE in HCT patients.[53]
CRE, carbapenem-resistant Enterobacteriaceae; HCT, haematopoietic cell transplant; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; OXA, oxacillinase; UTI, urinary tract infection.
*Avoid single-agent tigecycline in ventilator or healthcare-associated pneumonia/isolated or primary CRE bacteraemia.

faecal carriage of CRE is a risk factor for CRE BSIs.

2. Early initiation of empirical CRE-effective therapy at onset of neutropenic fever in patients colonised by CRE.
3. Use pharmacokinetic data in administration of CRE-effective combination therapy. A combination therapy should only be used when there is no access to novel CRE-effective BL-BLIs.

Table 4. Available antimicrobial agents with activity against CRE.[29,47,94,95]

Older antimicrobials		
Drugs	**Dose**	**Comments**
Polymyxins • Colistin • Polymyxin B	9 million units loading followed by 4.5 million units i.v every 12 h 2.5 mg/kg loading dose, then 1.5 mg/kg i.v every 12 h	• Disadvantages: nephrotoxicity and neurotoxicity
Rifampin	600–900 mg i.v every 24 h	• Rifampicin addition may be considered to exploit synergism in colistin resistance • Disadvantage: drug interactions with conditioning regimes
Tigecycline	100 mg i.v loading f/b every 12 h Doses up to 100 mg every 12 h can be used	• Must be used in combination regimen with colistin and fosfomycin or aminoglycosides or rifampicin or carbapenams • Low bloodstream and urinary tract concentration. • Bacteriostatic drug. • Disadvantages: not good for BSI due to high lipophilic nature and gastrointestinal side effects
Aminoglycosides • Gentamycin • Amikacin	3–5 mg/kg/day i.v every 24 h 15 mg/kg every 12 h	• Variable CRE activity • Used in combination regimen • Nephrotoxicity and otovestibular toxicity
Fosfomycin	4 g i.v every 4 h	• Used as adjunctive therapy for CRE • Active against all classes of CRE • Low barrier to development of resistance
Carbapenems • Meropenem (high-dose prolonged infusion) Double carbapenems • Ertapenem + doripenem/meropenem	2 g i.v every 8 h 1 g i.v every 24 h (Ertapenem) 500 mg i.v every 8 h (Doripenem) 2 g i.v every 8 h (Meropenem)	• Can be used in CRKp infections with meropenem MIC ⩽8–16 mg/l • Must be used in combination regimen • Can be used in CRKp infections with meropenem MIC >8–16 mg/l

New antimicrobials				
Drugs	**Dose**	**Activity**		
		Class A (e.g. KPC)	**Class B (e.g. NDM)**	**Class D (e.g. OXA-48)**
Ceftazidime-avibactam	2.5 g i.v q8h	Yes	No	Yes
Aztreonam	2 g i.v q8h	No	Yes	No
Meropenem-vaborbactam	2 g i.v q8h	Yes	No	No
Imipenem-cilastatin-relebactam	1.25 g i.v q6h	Yes	No	No
Cefiderocol	2 g i.v q8h	Yes	Yes	Yes
Plazomicin	10–15 mg/kg i.v q24h	Yes	Variable[a]	Yes
Eravacycline	1 mg/kg i.v q12h or 1.5 mg/kg i.v q24h	Yes	Yes	Yes

BSI, bloodstream infections; CRE, carbapenem-resistant Enterobacteriaceae; CRKp, carbapenem-resistant *Klebsiella pneumoniae*; i.v, intravenous; KPC, *Klebsiella pneumoniae* carbapenemase; MIC, minimum inhibitory concentration; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase.
[a]Frequently inactive against strains that produce NDM-type metallo-β-lactamases.

- High-dose extended-infusion meropenem for treatment of CRE infections outside urinary tract if meropenem minimum inhibitory concentration is less than 16 mg/l
- Higher dose of tigecycline (200 mg/day) to be used as part of CRE-effective combination therapy.
- Frequent estimation of augmented renal clearance (ARC) is helpful in prevention against antimicrobial underdosing in critically ill patients.

4. Consider organ-specific antibiotic effectivity before initiation of therapy.
    - Parenteral polymyxin antibiotics are not effective against infections in lungs, central nervous system and skin/soft tissue.
5. Consider additive organ toxicities of antimicrobials, especially when using combination therapy in HCT patients who are on multiple drugs.
    - Concurrent administration of polymyxins, aminoglycosides, cyclosporine and amphotericin significantly increases the risk of nephrotoxicity.
6. Prioritise the use of newer CRE-effective antimicrobials:
    - Ceftazidime-avibactam with aztreonam
    - Meropenem-vaborbactam
    - Imipenem-cilastatin-relebactam
    - Cefiderocol

Future directions

Faecal microbiota transplant

Gut microbiota are a complex microbial ecosystem of bacteria, fungi, archaea, viruses and protozoa existing in a symbiotic or pathogenic relationship within the human gastrointestinal tract.[107,108] Recent studies have provided compelling evidence on adverse impact of reduced gut microbial diversity or dysbiosis on HCT outcomes viz. bacterial BSIs and acute GVHD.[109–111] Contributing factors to gut microbiota dysbiosis in HCT recipients include use of intensive conditioning radiation and chemotherapy, and frequent exposure to broad-spectrum antimicrobials.[112] Gut colonisation by MDR bacteria is a significant risk factor for MDR BSIs in HCT recipients.[16,18] Various studies have explored the safety and efficacy of healthy donor FMT as a gut microbiota restorative strategy.[56,113,114] Bilinski *et al.*[113] assessed the effectiveness of FMT in eradication of MDR bacteria gut colonisation in 20 patients with blood cancers. Of these, 75% overall achieved complete MDR bacteria decolonisation after their FMT procedure. Battipaglia *et al.*[56] reported a retrospective case series of 10 participants with haematological malignancies who underwent FMT for MDR decolonisation pre- and post-HCT. At a median of 13 months post-FMT, 6 out of 10 participants (60%) achieved sustained decolonisation of MDR bacteria. Concerns have been raised about the risk of transmission of infections through FMT when the procedure is performed close to HCT. It is logistically challenging to sequence FMT and HCT together keeping the safety concerns in mind.[115] It is unsafe to perform FMT in neutropenic patients or patients that are at risk of neutropenia within 2 weeks. It is possibly safer to sequence FMT at least 4 weeks before HCT procedure. However, this raises logistical challenges for HCT procedure as not all HCT indications permit delays. Other challenges that need to be addressed are HCT donor availability vis-à-vis FMT and exposure to new or ongoing antimicrobials.[114]

Phage therapy

Recent biotechnological advances have enabled the use of bioengineered bacteriophages against MDR bacteria. In contrast to antibiotics, phages tend to be species and strain specific. Given their narrow spectrum of activity, microbiota dysbiosis and emergence of resistant organisms are not of primary concern.[116]

Theoretically, this advantage makes phage therapy a potentially attractive alternative to healthy donor FMT for eradication of MDR bacteria from the gut in HCT patients. Lengthy development process and necessity for tailored phage cocktails in most patients restricts their use to treatment of chronic infections and precludes their use against CRE infections in neutropenic patients.[117] Another limitation is lack of understanding of phages' interaction with resident gut flora, and human host. At present, phage therapy is not an approved therapy and data on its effectiveness against MDR bacterial infections in humans remain restricted to case reports.[118–124]

Conclusion

CRE are increasingly being isolated from bloodstream of HCT recipients. Delay in initiation of

CRE-effective treatment in CRE-infected HCT recipients leads to dismal outcomes. Novel CRE-effective BL-BLIs like ceftazidime-avibactam and meropenem-vaborbactam have significantly improved CRE infection outcomes in HCT recipients. Combination antimicrobial therapy is recommended for treatment in settings without access to novel CRE-effective agents. A de-escalation approach incorporating early empirical initiation of CRE-effective antimicrobial therapy is effective in mitigating the mortality risk associated with these devastating superbug infections. De-escalation approach is especially useful in practice in high CRE-prevalence areas. Surveillance for CRE colonisation by rectal swabs is helpful as CRE carriage is predictive of CRE BSIs during periods of profound immunosuppression post-HCT. Pre-HCT screening for faecal carriage of CRE is additionally useful in delineating the group of patients who will benefit from de-escalation strategy during their febrile neutropenia. The importance of adequate hand hygiene, patient isolation, barrier nursing and antibiotic stewardship in prevention and management of CRE cannot be stressed enough. Eradication of CRE colonisation before HCT has the potential to improve transplant outcomes by decreasing the risk of post-HCT BSIs and acute GVHD. Early data on use of healthy donor FMT as gut microbiome restorative strategy in HCT patients colonised by CRE are promising. However, this enthusiasm has been dampened by the recently raised safety concerns associated with the procedure.

Author contributions

The authors confirm contribution to the article as follows: RD helped in conception and design of work. DSKS, JS and SN helped in data collection. MA and PK helped in data analysis and interpretation. DSKS, JS, AJ and AJ helped in drafting the article. SM, PR and PM helped in critical revision of the article. RD and MM helped in the final approval of the version.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The authors received no financial support for the research, authorship and/or publication of this article.

Ethics statement

Our study/research article does not require an ethical board approval because it does not contain human or animal trials.

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