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Guideline

American Society of Transplantation and Cellular Therapy Series, 1: Enterobacterales Infection Prevention and Management after Hematopoietic Cell Transplantation

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A B S T R A C T

The Practice Guidelines Committee of the American Society of Transplantation and Cellular Therapy partnered with its Transplant Infectious Disease Special Interest Group to update its 2009 compendium-style infectious diseases guidelines for hematopoietic cell transplantation (HCT). A completely fresh approach was taken, with the goal of better serving clinical providers by publishing each stand-alone topic in the infectious diseases series in a concise format of frequently asked questions (FAQs), tables, and figures [1]. Adult and pediatric infectious diseases and HCT content experts developed and then answered FAQs, and then finalized topics with harmonized recommendations that were made by assigning a strength of recommendation ranging from A to E paired with a level of supporting evidence graded I to III. The first topic in the series focuses on potentially life-threatening infections in HCT caused by Enterobacterales, relevant infection risk factors, and practical considerations regarding prevention and treatment of these infections in the setting of emerging multidrug resistance.

INTRODUCTION

Hematopoietic cell transplantation (HCT) recipients are at increased risk for potentially life-threatening bloodstream infections caused by Enterobacterales. This guideline is in the form of frequently asked questions (FAQs) and focuses on relevant risk factors for infection and multidrug resistance that are prevalent in many geographic regions, as well as on strategies to prevent and treat these common gram-negative infections.

EPIDEMIOLOGY

FAQ1: Which organisms compose the order Enterobacterales, and which are the most common pathogens after HCT?

Enterobacterales comprises multiple bacterial families, including the family Enterobacteriaceae that harbors the genera *Escherichia, Klebsiella*, and *Enterobacter* [2]. *Escherichia coli* and *Klebsiella pneumoniae* are the most common causes of post-transplantation gram-negative bacteremia [3-5].

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FAQ2: What are risk factors for developing an Enterobacterales infection after HCT?

Enterobacterales bacteremias most commonly occur before neutrophil engraftment. Risk factors include older age, receipt of a cord blood or mismatched donor graft, prolonged neutropenia, gastrointestinal (GI) mucositis, and lack of antibacterial prophylaxis [6-8]. Postengraftment, GI graft-versus-host disease (GVHD) is another risk factor due to bacterial translocation across a damaged colon [9,10].

FAQ3: What are the most problematic types of multidrug-resistant (MDR) Enterobacterales, and how frequently do they occur during HCT? (Table 1)

These can be dichotomized into third-generation cephalosporin-resistant/carbapenem-susceptible Enterobacterales, which include extended-spectrum β-lactamase (ESBL)-producing and AmpC-producing bacteria, as well as the category of carbapenem-resistant Enterobacterales (CRE). The former are most commonly *E coli* and *K pneumoniae* that have ESBL enzymes that hydrolyze penicillins, extended-spectrum cephalosporins, and aztreonam, but not carbapenems, thereby conferring resistance to many first-line agents for fever and neutropenia [11,12]. Depending on geographic region, 10% to

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Table 1
ESBL-Producing, AmpC-Producing, and Carbapenem-Resistant Enterobacterales: Epidemiology, Resistance Phenotypes, and Treatment Considerations

Parameter	Third-Generation Cephalosporin-Resistant/Carbapenem-Susceptible		
	ESBLs	**AmpCs**	**CREs**
Common species	*Escherichia coli* *Klebsiella pneumoniae* *Proteus mirabilis*	*Enterobacter* spp* *Klebsiella aerogenes* *Serratia marcescens* *Proteus vulgaris* *Morganella morganii* *Providencia* spp *Citrobacter freundii*	*Klebsiella pneumoniae* *Enterobacter* spp *Escherichia coli*
Common phenotypic susceptibility profile†	Ceftriaxone-resistant Carbapenem- and cefoxitin-susceptible	Ampicillin-, cefazolin-, and cefoxitin-resistant‡ Carbapenem- and cefepime-susceptible	Carbapenem-, cefepime-, and piperacillin-tazobactam-resistant • KPC: susceptible to new BL-BLIs§ • MBL (eg, NDM): resistant to new BL-BLIs • OXA-48: susceptible to ceftazidime-avibactam, but often resistant to other new BL-BLIs
Resistance mechanisms	Production of plasmid-encoded CTX-M and mutated TEM and SHV ß-lactamases	Production of chromosomally encoded ß-lactamases that can be derepressed on exposure to certain ß-lactam agents‖	Carbapenemase production (eg, KPC, NDM, OXA-48) or ESBL or AmpC production combined with loss or dysfunction of outer membrane porins
Preferred therapies	Carbapenems (**A-I**)	First-line: Carbapenems (**B-II**) Alternative: Cefepime (**B-II**)	• KPC: New BL-BLIs (**B-II**) • MBL: Ceftazidime-avibactam + aztreonam or polymyxin or aminoglycoside-based combination therapy • OXA-48: Ceftazidime-avibactam (**B-III**) • Noncarbapenemase producers: case-by-case depending on susceptibility testing results

* These organisms are frequently referred to as the "SPICE" organisms.
† Susceptibilities of ESBL- and AmpC-producing Enterobacterales to piperacillin-tazobactam and ceftazidime are variable.
‡ Hyperproduction of AmpC ß-lactamase typically also leads to resistance to third-generation cephalosporins and aztreonam.
§ Newly approved BL-BLIs with activity against KPC-producing organisms include ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam.
‖ Plasmid-encoded AmpC ß-lactamases have also been identified, but are less common than chromosomally-encoded enzymes.

40% of *E coli* and *K pneumoniae* bloodstream isolates in HCT recipients are ESBL producers [13].

Other Enterobacterales harbor *ampC* genes not normally expressed at sufficient levels to confer resistance to third-generation cephalosporins. However, after exposure to certain ß-lactam agents, including third-generation cephalosporins, *ampC* gene expression is induced, leading to sufficient AmpC β-lactamase production to hydrolyze third-generation cephalosporins and aztreonam [14]. Thus, isolates that initially appear susceptible to third-generation cephalosporins can quickly develop resistance on therapy [15]. *Enterobacter* spp and *Klebsiella* (*Enterobacter*) *aerogenes* most commonly harbor these genes, followed by other "SPICE" organisms *(Serratia marcescens, Proteus vulgaris, Morganella morganii, Providencia stuartii*, and *Citrobacter freundii)*.

CRE bacteremia after HCT is being increasingly reported, particularly in certain endemic areas outside of the United States [13,16,17]. It occurs from either bacterial carbapenemases alone or ESBL/AmpC β-lactamases combined with changes in outer membrane porins that limit antimicrobial access to penicillin-binding proteins. Carbapenemase-producing Enterobacterales are often resistant to all first-line agents for fever and neutropenia, with *K pneumoniae* carbapenemase (KPC) the most common [18]. Other major carbapenemases include OXA-48 ß-lactamases and New Delhi metallo-ß-lactamases (NDM).

FAQ4: What are risk factors for infection due to an Enterobacterales that is resistant to standard agents for fever and neutropenia in HCT recipients?

Risk factors include residence in a location with a high prevalence of MDR Enterobacterales, colonization with MDR Enterobacterales, prolonged hospitalization, receipt of allogeneic HCT, and previous antibacterial therapy [5,19]

FAQ5: Are clinical outcomes attributed to MDR Enterobacterales infections worse than those due to more susceptible pathogens?

Studies of neutropenic patients have generally demonstrated increased mortality after bacteremias caused by ESBL-producing Enterobacterales (ESBL-E) versus non-ESBL-E, in part because ESBL-E-infected patients frequently receive inadequate initial therapy [20-22]. CRE bacteremia during HCT has devastating consequences, with mortality >50% [13,16,17]. No firm conclusions can be established about the outcomes of bacteremias caused by AmpC-hyperproducing Enterobacterales in this population.

TREATMENT

FAQ6: Which antimicrobial agents are best to treat infections caused by ESBL-E and AmpC-producing Enterobacterales during HCT? (Table 1)

Carbapenems are recommended for treating invasive ESBL-E infections despite frequent in vitro susceptibility of ESBL-E to piperacillin-tazobactam (**A-I**). This is because mortality was increased by 3-fold when piperacillin-tazobactam was compared with a carbapenem in a randomized trial of ESBL-E bacteremia therapy in the general population [23]. The majority of ESBL-E are resistant to cefepime (fourth-generation cephalosporin) and even patients with a cefepime-susceptible ESBL-E infection have worse outcomes when treated with cefepime compared with carbapenems [24,25]. The newer agents ceftolozane-tazobactam and ceftazidime-avibactam are active against ESBL-E in vitro [24]. Although limited data suggest that

they have comparable clinical efficacy to carbapenems for ESBL-E infections in the general patient population [24,26-28], clinical data on the efficacy of these new agents in HCT recipients are needed.

Carbapenem therapy is also recommended for invasive *Enterobacter* spp and *K aerogenes* infections, because carbapenems are not readily hydrolyzed by their AmpC ß-lactamases **(B-II)** [14]. Third-generation cephalosporins (eg, ceftriaxone) should not be used to treat invasive *Enterobacter* infections, because resistance can develop on therapy **(D-II)** [15]. However, increasing observational data suggest that cefepime may be just as effective as carbapenems and thus can serve as an alternative agent for these infections **(B-II)** [14,29-31]. Depending on susceptibility results, fluoroquinolones and trimethoprim-sulfamethoxazole are potential oral step-down therapies after clinical improvement for both ESBL-E and AmpC-producing Enterobacterales infections **(B-III)** [32]. The optimal treatment of infections due to SPICE organisms other than *Enterobacter* (eg, *S marcescens*) is less clear, and treatment decisions can be based on in vitro susceptibility results.

FAQ7: Which antimicrobial agents are best for treating CRE infections during HCT?

This depends on the mechanism of carbapenem resistance (Table 1). Infections caused by KPC-producing CRE are best treated with novel ß-lactam/ß-lactamase inhibitors (BL-BLIs), such as ceftazidime-avibactam, meropenem-vaborbactam, or imipenem-relebactam, because of improved clinical outcomes and less toxicity compared with polymyxin-based regimens **(B-II)** [33-35]. CRE with OXA-48-like carbapenemases are frequently resistant to meropenem-vaborbactam and imipenem-relebactam but are typically susceptible to ceftazidime-avibactam, which is recommended for these infections **(B-III)** [36-38]. Metallo-ß-lactamase (MBL)-producing CRE (eg, NDM) are typically resistant to new BL-BLIs, and although optimal therapies for these infections remain undefined, potential options include ceftazidime-avibactam plus aztreonam and polymyxin- or aminoglycoside-based regimens. Other novel agents, such as eravacycline, plazomicin, or cefiderocol, also may be considered [39,40]. Consultation with an infectious diseases expert is recommended for the treatment of CRE infections [41].

FAQ8: For how long should Enterobacterales bacteremias be treated after HCT?

Although data on outcomes by treatment duration are limited, 10 to 14 days of appropriate antimicrobial therapy is generally recommended **(C-III)** [42]. One randomized trial of patients with uncomplicated gram-negative bacteremia demonstrated that 7 days was noninferior to 14 days of therapy, but immunocompromised patients were excluded from the study [43]. In uncomplicated central venous catheter (CVC)-related Enterobacterales bacteremia, a course as short as 7 days may be reasonable if management includes CVC removal, but other factors may warrant up to 14 days of therapy **(C-III)** [44].

HCT recipients who receive 14 days of therapy and remain neutropenic but without signs or symptoms of ongoing infection can often resume antibacterial prophylaxis or have antibacterial therapy discontinued [12]. This strategy is supported by a randomized trial that showed discontinuing antibacterial therapy is safe during neutropenia if patients are afebrile without signs or symptoms of infection [45]. Although we recommend initial i.v. therapy, those who improve clinically and do not have GI pathology that would impair systemic absorption can be transitioned to highly bioavailable oral therapies, such as fluoroquinolones or trimethoprim-sulfamethoxazole, depending on relevant susceptibility profiles **(B-III)**. Observational study results showing therapeutic equivalence for i.v.-to-oral step-down therapy versus continued i.v. therapy support this approach [32].

FAQ9: Should a CVC be removed for Enterobacterales bacteremia during HCT?

It depends. Enterobacterales bacteremia in HCT is more commonly due to gut translocation during chemotherapy-induced neutropenia or GI GVHD than from direct infection of a CVC [19,46-49]. In this setting of mucosal barrier injury, CVC removal is not associated with improved outcomes and is not routinely recommended **(D-III)** [46].

Conversely, if the Enterobacterales bacteremia develops when there is no mucosal barrier injury and no clear alternate source of infection, a central line-associated bloodstream infection (CLABSI) is more likely. CVC removal is associated with improved outcomes in this setting and should be considered **(B-III)** [44].

PREVENTION/EMPIRICAL THERAPY

FAQ10: Does antibacterial prophylaxis during neutropenia decrease the risk of Enterobacterales infections during HCT?

Yes in adults, but not clearly in children. Levofloxacin should be considered for adults during neutropenia after HCT to lower the risk of Enterobacterales bacteremia **(B-I)** [50]. A randomized, placebo-controlled trial in adult patients with cancer who were expected to have >7 days of neutropenia, of whom one-half were undergoing autologous HCT (allogeneic HCT recipients were excluded), demonstrated that levofloxacin prophylaxis significantly decreased the risk of gram-negative bacteremia [51]. Observational studies, primarily in autologous HCT recipients, reached similar conclusions [52-56]. A recent randomized trial in children undergoing autologous or allogeneic HCT showed a trend toward reduction in all-cause BSI with levofloxacin prophylaxis, but was not powered or designed to specifically assess Enterobacterales BSIs [57].

The degree to which increasing fluoroquinolone resistance among the most common Enterobacterales decreases the effectiveness of fluoroquinolone prophylaxis is unclear [58]. The decision whether to routinely administer levofloxacin prophylaxis after HCT should carefully weigh the benefit of potentially lowering the risk of bacteremia and fever and neutropenia against the risks of increasing antimicrobial resistance and levofloxacin-related adverse effects [59,60]. Levofloxacin prophylaxis may not only increase the risk of fluoroquinolone resistance among breakthrough Enterobacterales infections, but because of co-occurrence of fluoroquinolone and β-lactam resistance in prominent strains, may also increase the risk of ESBL-E bacteremia [19,55]. Thus, careful monitoring for increased rates of ESBL-E infections is warranted when using fluoroquinolone prophylaxis.

FAQ11: Should screening be used to identify HCT recipients colonized with MDR Enterobacterales to guide initial empirical therapy?

No definitive recommendations can be provided due to variable colonization rates. One multicenter study demonstrated that in HCT recipients colonized with carbapenem-resistant *K pneumoniae* (CR*Kp*), rates of post-transplantation CR*Kp* infection were 26% in the autologous setting and 39% in the allogeneic setting [16]. Thus, in transplantation centers where CRE

are prominent pathogens, screening for CRE colonization may have a role in guiding empirical therapy during post-transplantation neutropenia. When CRE are uncommon, limiting screening to patients referred from CRE-endemic areas is another reasonable strategy.

At one center where levofloxacin prophylaxis was administered, one-third of ESBL-E-colonized patients developed ESBL-E bacteremia during post-transplantation neutropenia [19]. Thus, screening for ESBL-E could identify HCT recipients who should be treated empirically with a carbapenem for fever and neutropenia. By contrast, other studies in hematologic malignancies in which antibacterial prophylaxis was not routinely used have reported lower rates of ESBL-E bacteremia in colonized patients [61-63].

FAQ12: Instead of a single approach for prophylaxis and empirical therapy, can an individualized approach be pursued during HCT?

One approach to tailoring prophylaxis and empirical antibiotic therapy in HCT recipients is to use an individualized antibiotic plan (IAP) [64]. Before transplantation, patients would undergo rectal screening for colonization with MDR bacteria. Patients not colonized by MDR bacteria would be assigned a standard 3-tiered IAP to guide their antibiotic management from conditioning through engraftment (eg, levofloxacin for prophylaxis; ceftazidime for fever, stable; and ceftazidime + vancomycin + gentamicin for fever, unstable). Patients colonized by MDR bacteria would be assigned a modified IAP regimen by an algorithmic approach according to the susceptibility phenotype of the isolate. The IAP would be entered into the electronic medical record before transplantation, readily visible and accessible to all providers, updated in the event of new microbiologic data, and inactivated at 100 days post-transplantation.

FAQ13: Should HCT recipients infected or colonized with MDR Enterobacterales be placed on contact precautions?

Contact precautions with gown and gloves are recommended in patients infected or colonized with CRE [65] and should be considered for patients with ESBL-E **(B-III)**. The rationale for this is that contact precautions may decrease the risk of transmission of these organisms on a transplantation unit, although data do not consistently support efficacy in preventing ESBL-E transmission [66,67].

FAQ14: Are there interventions to mitigate the risk of MDR Enterobacterales infection in HCT recipients who are colonized with these organisms?

Using oral antibiotics to decolonize HCT recipients with ESBL-E or CRE gut colonization is not routinely recommended **(D-III)**. Some randomized clinical trials have demonstrated marginal effectiveness in temporarily suppressing gut colonization with these organisms, but benefits are transient and major concerns include emergence of resistance to agents used for decolonization and negative effects on the gut microbiome [68-72].

Fecal microbiota transplantation (FMT) is another potential strategy to suppress or eradicate ESBL-E or CRE gut colonization. However, additional data are needed to evaluate the merits of FMT for this indication, particularly in immunocompromised HCT recipients, given the concern for transmission of infectious agents [73].

ADDITIONAL CONSIDERATIONS

FAQ15: Is the epidemiology of HCT infections caused by Enterobacterales different in children?

There are some differences. Risk factors for Enterobacterales infections in children include allogeneic HCT or myeloablative conditioning, prolonged neutropenia, and acute GI GVHD [74-76]. *E coli* was the most common cause of CLABSI reported from adult and pediatric oncology centers [77,78], but whereas *Klebsiella* spp were the second most common cause of CLABSI in pediatric oncology units, they were the fourth most common cause in adult oncology units.

Rates of resistance to extended-spectrum cephalosporins and carbapenems among CLABSI isolates of *E coli, Klebsiella* spp, and *Enterobacter* spp were similar between adult and pediatric oncology patients, but rates of fluoroquinolone resistance were lower among pediatric *E coli* (38%) than adult *E coli* (65%) [77,79]. In a study conducted primarily in Europe, gram-negative bloodstream isolates were less frequently resistant to anti-pseudomonal BL-BLIs and fluoroquinolones among pediatric allogeneic HCT recipients compared with adult allogeneic HCT recipients [5].

FUTURE DIRECTIONS

FAQ16: How can rapid diagnostics be incorporated into treating Enterobacterales bacteremias during HCT?

Multiplexed PCR/microarray-based platforms can diagnose the type of gram-negative infection and presence of selected resistance genes within 2 hours of blood culture bottles signaling positive growth [79,80]. When combined with antimicrobial stewardship interventions, the use of these assays optimizes pathogen-directed antimicrobial therapy and may decrease mortality [79,81]. These assays also rapidly detect certain carbapenemases, which can guide treatment decisions given that therapy choices for carbapenemase-producing infections depends on carbapenemase type (Table 1).

A limitation of these multiplexed PCR/microarray-based platforms is that they detect only a small number of genetic resistance determinants. In contrast, a new rapid phenotypic susceptibility testing platform identifies the organism and more comprehensive antimicrobial susceptibility results within 7 hours of blood cultures signaling positive [82]. An additional novel diagnostic test combines magnetic resonance and PCR-based amplification to detect 5 common bloodstream pathogens, including *E coli* and *K pneumoniae*, directly from whole blood within 6 hours of blood culture collection [83]. However, this test does not detect Enterobacterales species other than *E coli* and *K pneumoniae* and does not provide antimicrobial susceptibility information. Additional data are needed to better understand how to leverage these assays to improve outcomes of HCT recipients with Enterobacterales bacteremia.

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APPENDIX: GRADING STRENGTH OF RECOMMENDATION AND LEVEL OF EVIDENCE [1]

Recommendation	Grade
Which antimicrobial agents are best to treat infections caused by ESBL-E and AmpC-producing Enterobacterales during HCT?	
1. Carbapenems are recommended to treat invasive ESBL-E infections despite frequent in vitro susceptibility of ESBL-E to other ß-lactam agents [23,25].	A-I
2. Carbapenems are recommended for invasive *Enterobacter* spp and *Klebsiella* (*Enterobacter*) *aerogenes* infections because carbapenems are not hydrolyzed by their AmpC ß-lactamases [14].	B-II
3. Third-generation cephalosporins (eg, ceftriaxone) should not be used to treat invasive *Enterobacter* infections, because resistance can develop on therapy [15].	D-II
4. Cefepime may be an alternative option for invasive *Enterobacter* infections because of its stability against AmpC ß-lactamases [14,29-31].	B-II
5. Depending on susceptibility results, fluoroquinolones and trimethoprim-sulfamethoxazole are potential oral step-down therapies for ESBL-E and AmpC-producing Enterobacterales after clinical improvement [32].	B-III
Which antimicrobial agents are best to treat CRE infections during HCT?	
6. Infections caused by KPC-producing CRE are best treated with novel BL-BLIs, such as ceftazidime-avibactam, meropenem-vaborbactam, or imipenem-relebactam [33-35].	B-II
7. Ceftazidime-avibactam is recommended for the treatment of infections caused by CRE with OXA-48-like carbapenemases, which are frequently resistant to meropenem-vaborbactam and imipenem-relebactam [36-38].	B-III
For how long should Enterobacterales bacteremias be treated after HCT?	
8. In the absence of complications, 10 to 14 days of appropriate antimicrobial therapy is generally recommended [42].	C-III
9. In uncomplicated CVC-related Enterobacterales bacteremia, a course as short as 7 days may be reasonable if management includes CVC removal, but other factors may warrant up to 14 days of therapy [44].	C-III
Should a CVC be removed for Enterobacterales bacteremia during HCT?	
10. In the setting of Enterobacterales bacteremia during chemotherapy-induced neutropenia or GI GVHD, CVC removal is not routinely recommended, unless there are clear indications that the CVC is the source of the infection [46].	D-III
11. If Enterobacterales bacteremia develops without chemotherapy-induced neutropenia or GI GVHD, CVC removal should be considered in the absence of an alternate source of infection [44].	B-III
Should antibacterial prophylaxis be administered during neutropenia to decrease the risk of Enterobacterales infections during HCT?	
12. Levofloxacin prophylaxis should be considered for adults during neutropenia after HCT to lower the risk of Enterobacterales bacteremia [50-56].	B-I
Should HCT recipients infected or colonized with MDR Enterobacterales be placed on contact precautions?	
13. Contact precautions with gown and gloves are recommended in patients infected or colonized with CRE and should be considered for patients with ESBL-E [65,66].	B-III
Should oral antibiotics be used to decolonize HCT recipients who are colonized with MDR Enterobacterales?	
14. Using oral antibiotics to decolonize HCT recipients with ESBL-E or CRE gut colonization should not be performed routinely [68-72].	D-III

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