Bacterial Infections

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36.1 Introduction

Bloodstream infections (BSI) are the most frequent bacterial infections in HSCT patients; they occur in 5–10% of auto-HSCT and 20–50% of allo-HSCT patients, with higher rates before engraftment, and are associated with increased morbidity and mortality (Tomblyn et al. 2009; Girmenia et al. 2017; Weisser et al. 2017; Mikulska et al. 2018a). Microbiological documentation of skin and soft tissue infection, pneumonia, and typhlitis is frequently missing.

Patient-related risk factors for bacterial infections include older age, comorbidities, low functional capacity, and high-risk hematological disease (active malignancy, aplastic anemia).

Transplant-related risk factors are specific to the post-HSCT period. During the early pre-engraftment phase, neutropenia and disruption of anatomical barriers (mucosal damage and vascular devices) predispose to infections resulting from Gram-positive cocci (GPC) and Gram-negative bacilli (GNB)—mainly bacteremia/sepsis, pneumonia, sinusitis, proctitis, and cellulitis. In regimens with minimal myelosuppression and mucosal toxicity, as with some non-myeloablative protocols, the risk of infection in the immediate post transplant period is reduced. Conversely, CBT is associated with slower engraftment delayed immune reconstitution, and higher infection risks. During the intermediate phase, starting at engraftment (days +30 to +100), the main risk factors are CVC, GVHD-related organ damage and its treatment, and lack of immune reconstitution. Later, incompetent humoral and cellular immunity (resulting from GVHD, among other factors) predisposes to encapsulated pathogen-associated infections (*Streptococcus pneumoniae* and *Haemophilus influenzae*).

36.2 Epidemiology of Bacteremia

GNB has become an increasingly common cause of bacteremia. They almost equal GPC in a review of studies and ECIL-4 survey (2011) on bacteremia surveillance in European centers. A remarkable variation between centers was shown, from 85%/15% to 26%/74% GPC to GNB ratio (Mikulska et al. 2014). Attribute mortality and TRM are usually higher in patients with GNB-BSI compared with GPC-BSI (Girmenia et al. 2017; Mikulska et al. 2018a).

Emergence of antibacterial resistance complicates treatment of infections. An increase in infections caused by multidrug-resistant (MDR) bacteria (non-susceptible to ≥1 agent in ≥3 therapeutically relevant antimicrobial categories) has been observed in some centers.

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Extensively, drug-resistant bacteria (susceptible to ≤2 antimicrobial categories) have also been reported (Averbuch et al. 2017). Prevalence of resistance is influenced by local antibiotic use policies in prophylaxis and treatment, infection control measures, as well as local resistance patterns throughout the specific hospital and countrywide.

In this session, we address infections caused by the most frequent GPC and GNB.

36.3 Gram-Positive Infections

Coagulase-negative Staphylococcus (CoNS) is the most frequent etiology of BSI (Mikulska et al. 2014). True CoNS BSI, defined as at least two consecutive positive blood cultures, is usually CVC-related. Methicillin resistance is frequent (>50%), prompting treatment with glycopeptides. The prognosis is usually good.

Staphylococcus aureus is rare, reported in a median 6% of HSCT patients, and its attribute mortality is high (12–40%). Cefazolin and oxacillin are the therapeutic mainstays against methicillin-susceptible *Staphylococci*. Methicillin-resistant *Staphylococcus aureus* (MRSA) is frequent; these bacteria are usually susceptible to glycopeptides (vancomycin and teicoplanin). Reduced vancomycin susceptibility has, however, been reported (VISA). Other active agents include daptomycin, linezolid, and tigecycline. The main disadvantages of these agents include:

(a) Linezolid: myelosuppression.
(b) Daptomycin: inactivation by surfactant, it should not be used to treat pneumonia; reduced susceptibility among VISA.
(c) Tigecycline: monotherapy for BSI is not recommended due to low blood levels. Increased mortality has been reported, in comparison with other agents for treating severe infections; a better outcome has been, however, reported with loading and increased daily dosages.

Some newer antibiotics are active against MRSA: ceftaroline, ceftobiprole, dalbavancin, oritavancin, telavancin, and tedizolid.

Enterococci cause a median 5–8% of BSI in HSCT patients, usually occurring later after HSCT, near the time of neutrophil recovery; *E. faecium* is more common than *E. faecalis* (Satlin and Walsh 2017). VRE is an increasing threat in some centers. Previous colonization, mucositis, and broad-spectrum antimicrobial exposure predispose to VRE BSI, which typically occurs in patients in poor clinical condition, perhaps explaining high associated mortality. Main treatment options include linezolid and daptomycin, with VRE sometimes susceptible to quinupristin–dalfopristin (*E. faecium* only), tigecycline, fosfomycin, tedizolid, oritavancin, dalbavancin, and telavancin. Reduced daptomycin susceptibility was reported among VRE; thus, increased dosage (>8 mg/kg/day) is recommended.

Streptococcus viridans (VS) (Freifeld et al. 2011) causes median 5–13% of BSI, usually occurring soon after HSCT (median 4 days); ARDS and septic shock accompany 7–39% of episodes. Mucositis, especially following cytarabine, exposure to fluoroquinolone or ceftazidime, antiacids, MAC, and haploidentical HSCT predispose to VS infections. VS is usually susceptible to most β-lactams used in empirical therapy for febrile neutropenia, with the exception of ceftazidime. The possibility of β-lactam-resistant VS infections, mainly observed after exposure to β-lactams or in nosocomial BSI, justifies addition of vancomycin in neutropenic patients with septic shock.

HSCT patients are at risk for *invasive pneumococcal disease* (IPD), mainly bacteremia and pneumonia, late (median 17 months, range 4 months to 10 years) after HSCT (Engelhard et al. 2002), with a mortality rate of 13–20%. Predisposing factors include allo- versus auto-HSCT, BM versus PBSCT, hypogammaglobulinemia, specific antipneumococcal antibody, and IgG2 deficiency; memory cell defects, as in cGVHD, may also affect the response to vaccines.

36.4 Gram-Negative Infections (Averbuch et al. 2013a, b, 2017; Mikulska et al. 2014, 2018a; Trecarichi et al. 2015; Girmenia et al. 2017)

GNB infecting HSCT patients include *Enterobacteriaceae* (~70%) and non-fermentative GNB (NFGNB, ~24%); others are rare. GNB infections may present with bacteremia, sepsis, enterocolitis, soft tissue infections, such as ecthyma gangrenosum (typically associated with *Pseudomonas aeruginosa*), and septic shock; death may occur within hours in the absence of appropriate supportive and antibiotic treatment.

Several studies report an increase in MDR-GNB infections in HSCT patients, leading to inadequate empirical therapy and increased mortality. In the multinational prospective EBMT study, half of GNB were resistant to non-carbapenem β-lactams, the first-line treatment for febrile neutropenia; 18.5% (40% in some south-western regions) were carbapenem-resistant (CR); and 35% were MDR (Averbuch et al. 2017). Higher rates of resistance were reported in allo- versus auto-HSCT patients and in the south-eastern Europe, as compared with the northwest. The main risk factors for CRGNB are previous colonization, breakthrough on carbapenems, and hospitalization in an ICU. The main Gram-negatives and their resistance pattern are:

36.4.1 Broad-Spectrum β-Lactamase-Producing *Enterobacteriaceae*

The main resistance mechanism to empirical therapy in *Enterobacteriaceae* is broad-spectrum β-lactamase production. This includes (a) extended-spectrum β-lactamase (ESBL), reported in 2–44% of *Enterobacteriaceae* in HSCT patients, and (b) AmpC enzymes, typically produced by *Serratia*, *Providencia*, *Proteus*, *Citrobacter*, and *Enterobacter* spp. These can be induced by non-carbapenem β-lactam treatment. ESBL- or AmpC-producing organisms may appear susceptible in vitro to third-generation cephalosporins (e.g., ceftazidime) or inhibited by β-lactam/β-lactamase inhibitors (BLBLI: sulbactam, clavulanate, tazobactam) yet still be functionally resistant to these agents (Satlin and Walsh 2017). They are frequently fluoroquinolone-resistant. Carbapenems should be the preferred option for treating severely ill patients with broad-spectrum β-lactamase-producing organisms. High-dose prolonged BLBLI infusion can be used under close clinical monitoring in certain stable patients infected with ESBL+ bacteria, susceptible in vitro to BLBLI (Perez et al. 2014; Gudiol et al. 2017).

36.4.2 Carbapenemase-Producing *Enterobacteriaceae* (CPE) (Averbuch et al. 2013a, 2017; Satlin and Walsh 2017; Bassetti et al. 2018)

The main carbapenem resistance mechanism in *Enterobacteriaceae* is production of carbapenemases, including *Klebsiella pneumoniae* carbapenemase (KPC), New Delhi metallo-β-lactamase (NDM), and OXA-type enzymes. Among *Enterobacteriaceae*, carbapenem resistance is more frequent in *Klebsiella pneumoniae*. Delay in appropriate therapy can explain high mortality (~60%) in CPE infections in the allo-HSCT setting. CPE are frequently resistant to "last resource" antibiotics, e.g., fluoroquinolones (in 80%), amikacin or gentamicin (~40%), tigecycline (30%), and colistin (18%). Colistin/polymyxin B is active against a majority of GNB but not *Proteus*, *Serratia*, and *Providencia* spp. Increased mortality has been demonstrated in some retrospective studies, in comparison with other appropriate regimens. Its main side effects include nephrotoxicity and neurotoxicity. Adequate dosing is important (9 million IU loading dose; 4.5 million IU BID maintenance dose). Emergence of plasmid-associated colistin resistance challenges its utility.

Fosfomycin is in vitro active against some resistant GNB. Intravenous formulation is, however, unavailable in some countries; resistance can develop on treatment.

Two or more active agent combinations, including aminoglycosides, polymyxins, tigecycline, fosfomycin, and high-dose (2 g TID), prolonged infusion meropenem (if MIC is ≤8 mg/L), should be preferred in severely ill patients with CPE infections (Gutierrez-Gutierrez et al. 2017). Other treatment modalities include:

- For KPC-CPE infections:
  - TDM-guided meropenem treatment for more resistant bacteria (MIC >8 mg/L)
  - Double carbapenem therapy (ertapenem + meropenem/doripenem)
  - Ceftazidime/avibactam (also active against some OXA-producing GNB); resistance can, however, develop during treatment
  - Meropenem-vaborbactam
- For NDM-producing GNB: aztreonam + ceftazidime/avibactam

36.4.3 *Pseudomonas aeruginosa* (PA) (Mikulska et al. 2014; Averbuch et al. 2017; Satlin and Walsh 2017)

PA Causes 5–15% of BSI, carrying 39–79% mortality, especially in ICU-acquired and resistant PA infections. In a multicenter Italian study, <40% of patients with MDR PA BSI survived longer than 4 months following HSCT (Girmenia et al. 2017). PA in HSCT patients is frequently resistant to fluoroquinolones, aminoglycosides, and β-lactams; 25–71% are MDR. As prognosis is poor, combination therapy, using β-lactam with aminoglycoside or fluoroquinolone, is frequently used in treating severe PA infections, at least initially until the patient is stabilized. Nephrotoxicity is, however, a concern, and no survival benefit of combination therapy has been demonstrated by meta-analysis (Vardakas et al. 2013). A high-dose extended β-lactam infusion regimen was associated with better survival. Ceftolozane-tazobactam was successfully used in severely ill patients with carbapenem-resistant PA.

36.4.4 Other NFGNB

Other NFGNR rarely cause infections in HSCT patients. *Stenotrophomonas maltophilia* is intrinsically resistant to carbapenems and frequently resistant to aminoglycosides and β-lactams. While TMP/SMX should be considered as the primary therapeutic agent, resistance has been reported, and the sulfonamide can be poorly tolerated. Experience with alternative agents, such as ticarcillin-clavulanate, ceftazidime, fluoroquinolones, and minocycline, is limited. Combination of TMP/SMX with either ticarcillin/clavulanate or ceftazidime can be considered in severely ill patients.

MDR *Acinetobacter* infections have been associated with 49–95% mortality rate in HSCT patients. These bacteria can be susceptible to ampicillin/sulbactam, colistin, and tigecycline. Combination therapy was not associated with decreased mortality.

36.5 Bacterial Infection Syndromes

36.5.1 Central Line-Associated BSI (CLABSI)

CVC infections should be suspected when blood cultures are persistently positive, at the presence of exit site or tunnel infection and when fever and chills develop during CVC flushing. This can be proved by a differential time to positivity of >120 min in blood cultures simultaneously drawn from the CVC and a vein. Catheter removal, in addition to systemic antimicrobial therapy, is recommended for tunnel or port pocket site infection, septic thrombosis, endocarditis, hemodynamic instability, persistently positive (>72 h) blood cultures under appropriate antibiotics, and CLABSI caused by *S. aureus*, *P. aeruginosa*, fungi, or mycobacteria (Freifeld

et al. 2011). CVC salvage can be attempted by antimicrobial lock.

36.5.2 Pneumonia

Bacterial pneumonia during the neutropenic phase is due to GNB (including PA) and GPC typical to this stage. Specific entities include *Stenotrophomonas maltophilia* hemorrhagic pneumonia, *VS*-associated ARDS, and nosocomial legionellosis. In the late post-engraftment phase, IPD and *Haemophilus influenzae* should be considered. Symptoms and signs can be atypical and scarce, rapid progression can nonetheless occur. Hypoxemia can be the sole finding and should prompt chest CT; diagnostic bronchoscopy, if feasible; and immediate antibiotic therapy. Empirical therapy should reflect the history of colonization with resistant bacteria.

36.5.3 Diarrhea

Clostridium difficile-associated infection (CDI) is a typical bacterial toxin cause of diarrhea, occurring in 5–30% of HSCT patients following exposure to broad-spectrum antibiotics and chemotherapy. Clinical manifestation may paradoxically be mild. Severe complications, such as toxic megacolon and perforation, can, however, occur. Treatment choice is determined by the severity of CDI, patient's ability to take oral treatment, and recurrence (Debast et al. 2014).

Bacterial diarrhea due to *Shigella*, *Salmonella*, *Yersinia*, *Campylobacter* spp., and enterohemorrhagic *E. coli* is rare and usually occurs in a community-acquired setting. Routine stool culture is, thus, recommended for patients with diarrhea only within 3 days of admission.

36.5.4 CNS Infections

Bacteria rarely cause brain abscess (*Streptococcus epidermidis*, *Staphylococcus aureus*, *Klebsiella pneumonia*) or meningoencephalitis (*Listeria*, IPD). Clinical manifestations include fever, headache, altered mental state, and focal neurological signs and seizures. MRI is more sensitive than CT in identifying brain lesions.

36.6 Improving Management of Bacterial Infection (Averbuch et al. 2013a, b; Satlin and Walsh 2017)

Empirical therapy for febrile neutropenia should be individualized using escalation/de-escalation approach based on local epidemiology and patients' risk factors for infection with resistant bacteria and for complicated course. Early initiation of appropriate therapy improves prognosis and can be achieved by:

(a) Monitoring local department bacterial resistance patterns.
(b) Monitoring colonization with resistant bacteria and empirical administration of active antibiotics in colonized or previously infected febrile neutropenic patients, such as carbapenems in patients colonized with ESBL-GNB. Therapy streamlining, de-escalation, and discontinuation of unnecessary antibiotics should follow culture and susceptibility results.
(c) Novel laboratory techniques (e.g., matrix-assisted laser desorption/ionization–time of flight, MALDI-TOF) that reduce the time for pathogen identification and antibiotic susceptibility testing.

Antibiotic therapy should be optimized in line with pharmacokinetic/pharmacodynamic principles:

1. A loading dose, followed by prolonged or continuous infusion of time-dependent antibiotics, such as β-lactams, has been associated with lower mortality than short-term infusion.
2. Once-daily infusion for concentration-dependent drugs, such as aminoglycosides or daptomycin.

3. A loading dose, when appropriate (tigecycline and colistin).

36.7 Prevention of Bacterial Infection (Tomblyn et al. 2009; Tacconelli et al. 2014; Cordonnier et al. 2015; ECIL-meeting 2017)

General measures to prevent infection include patient's personal hygiene, safe diet, bathing with chlorhexidine-impregnated washcloths, and use of single-patient rooms. Important infection control measures include standard precautions, especially hand hygiene, use of gloves and gowns when soiling is likely, and environmental cleaning. Multifaceted interventions should be practiced to prevent MDR bacteria spread, including patient's screening for colonization in the epidemic setting, using contact precautions, isolation, and cohorting of colonized and/or infected patients and staff (this last, for CPE-colonized patients). Routine CPE-targeted decolonization with nonabsorbable oral antibiotics is not supported; it can select for resistance to the last treatment options.

Antimicrobial stewardship should aim to limit unnecessary antibiotic exposure and to optimize antimicrobial therapy, e.g., using escalation empirical approach (non-carbapenem monotherapy) for stable febrile patients without previous MDR bacteria colonization/infection.

CLABSI prevention includes sterile insertion by a specialized team, avoiding femoral sites, chlorhexidine cleaning during use, and removal of unnecessary catheters.

Fluoroquinolone prophylaxis is recommended in high-risk neutropenic patients with expected neutropenia ≥7 days (Freifeld et al. 2011). Meta-analysis of studies published prior to 2010 demonstrated significantly reduced all-cause mortality, fewer febrile episodes, and reduced GNB-BSI in patients receiving prophylaxis (Gafter-Gvili et al. 2012). Currently, prophylaxis benefit may be less, as fluoroquinolone resistance rates among GNB are high (Averbuch et al. 2017). Meta-analysis of studies published during 2006–2014 does not demonstrate reduction in mortality on fluoroquinolone prophylaxis. The possible benefits of prophylaxis should be weighed against its potential harm, including CDI risk, side effects, and association with colonization or infection with fluoroquinolone- or multidrug-resistant strains (Mikulska et al. 2018b).

Table 36.1 Vaccination schedule (against bacterial infections)

Vaccine	Start after HSCT (months)	Interval between doses (months)	Doses
Pneumococcal conjugate vaccine, PCV13	3	1	3–4[a]
Pneumococcal polysaccharide vaccine, PPV23[b]	12	6 months after last PCV13	1
Haemophilus influenzae B[c]	3–6	1	3
DTP vaccines	6–12	1–2	3
MenC or MCV4[d]	6–12	2	≥2
Men-B[d]	6–12	1–6	2

[a]A fourth dose (6 months after the third dose) if there is GVHD
[b]If no GVHD
[c]Can use combination vaccines
[d]According to country recommendations

Late infection prevention (>100 days post-HCT), targeting mainly encapsulated bacteria, includes:

1. Oral prophylaxis with penicillin (or other agents, according to local antibiotic resistance patterns) in patients with cGVHD or hypogammaglobulinemia
2. IVIg in patients with severe hypogammaglobulinemia (serum IgG level <400 mg/dL)
3. Vaccinations (Table 36.1; also see Chap. 29)

Key Points

- GNB increasingly cause infections in HSCT patients; prognosis is frequently poor.
- Resistant bacteria, such as broad-spectrum β-lactamase-producing (mainly ESBL) *Enterobacteriaceae*, carbapenemase-producing *Enterobacteriaceae* (CPE), MDR *Pseudomonas aeruginosa*, and VRE, are causing an increased number of infections, leading to delay in appropriate therapy and increased mortality.
- Targeted therapy against the main resistant bacteria includes:
  - Linezolid and daptomycin against VRE
  - Carbapenem preferred against severe ESBL+ infections
  - Combination therapy (colistin, aminoglycoside, and carbapenem if low-level resistance) preferred against severe CPE infections
  - β-Lactam with aminoglycoside or fluoroquinolone combination preferred for initial treatment of severe *Pseudomonas aeruginosa* infections
- Antimicrobial stewardship is aimed to individualize empirical approach (escalation vs. de-escalation) to patients with suspected infection, limit unnecessary antibiotic use, and optimize treatment based on pharmacokinetic/pharmacodynamic principles.
- Infection control is crucial to limit the spread of MDR pathogens.
- Fluoroquinolone prophylaxis is recommended for high-risk neutropenic patients; its efficacy, however, can be reduced.
- Encapsulated bacteria (*Streptococcus pneumoniae* and *Haemophilus influenzae*) cause infections during late post-engraftment period; preventive measures include oral prophylaxis, IVIg, and vaccinations.

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