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GUIDELINES

Bacterial infection prevention after hematopoietic cell transplantation

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In addition to general recommendations regarding bacterial infections, this section provides specific recommendations with regard to *Streptococcus pneumoniae,* viridans streptococci (mainly the *S. mitis* and *S. anginosus* groups), *Haemophilus influenzae* type b (Hib) and central line-associated bloodstream infections (CLABSI). Recommendations regarding specific nosocomial infections, including those from *Legionella* species, methicillin-resistant *Staphylococcus aureus, Staphylococcus* species with reduced susceptibility to vancomycin, vancomycin-resistant *Enterococcus* and *Clostridium difficile* are found in the Infection Prevention and Control in Healthcare Facilities section.

General recommendations

Preventing exposure

Healthcare workers and others in contact with hematopoietic cell transplant (HCT) recipients should routinely follow appropriate hand hygiene practices to avoid exposing recipients to bacterial pathogens (AIII) (see Infection Prevention and Control in Healthcare Facilities). Additional precautions for patients colonized with certain contagious pathogens (for example, methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*) and for special situations (for example, diarrhea or respiratory diseases), and instructions with regard to visitors, pets and plants are described in the Infection Prevention and Control in Healthcare Facilities section and in the 2007 Centers for Disease Control (CDC) guidelines.[144] Guidelines for the management of neutropenic fever are published elsewhere.[145]

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Preventing early disease (0–100 days after HCT)

Antibacterial prophylaxis with a fluoroquinolone (that is, levofloxacin) to prevent bacterial infections should be strongly considered for adult HCT patients with anticipated neutropenic periods of 7 days or more (BI)[146–150] (Appendix 1). Owing to lack of data, there are currently no antimicrobial prophylactic regimens that can be recommended for children. Some experts use levofloxacin for pediatric antibacterial prophylaxis (CIII). Antibacterial prophylaxis is generally started at the time of stem cell infusion and is continued until recovery from neutropenia or initiation of empirical antibacterial therapy for fever during neutropenia.[148–152] Prophylaxis should not be continued after recovery from neutropenia. Local epidemiological data should be carefully considered before applying fluoroquinolone prophylaxis and once it is applied, the emergence of resistance in bacterial pathogens should be monitored closely because of increasing quinolone resistance worldwide among Gram-negative bacteria (for example, *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*)[153] and staphylococci;[154–157] plasmid-mediated quinolone resistance in Enterobacteriaceae that is closely related to the beta lactamases that inactivate third-generation cephalosporins;[158–160] and quinolone-related development of a hypervirulent strain of *C. difficile* (AIII).[161]

The addition of an anti-Gram-positive agent to the prophylaxis regimen is not indicated (DIII).[151] Specifically, glycopeptides (for example, vancomycin and teicoplanin) should not be used for routine bacterial prophylaxis, either systemically or for the prevention of catheter-related infections (DIII). These agents lack benefit for prophylaxis and their use may promote the emergence of resistant microorganisms.[151]

Growth factors (for example, GM-CSF and G-CSF) shorten the duration of neutropenia after HCT[162,163] and may slightly reduce the risk of infection[164,165] but have not been shown to reduce mortality.[164,165] Therefore, the routine use of growth factors after HCT is controversial and no recommendation for their use can be made (CI).

Prophylaxis with metronidazole has been shown to reduce anaerobic bacterial growth in the gut and was associated with a reduction in acute GVHD in recipients of transplants from HLA-identical sibling donors (but not from other donors) in one open-label randomized trial.[166] However, the evidence is insufficient to recommend routine gut decontamination for HCT candidates, either with metronidazole or with nonabsorbable antibiotics (DIII).

Although i.v. Ig has been recommended for use in producing immune system modulation for GVHD prevention, i.v. Ig should not be routinely administered to HCT recipients for prophylaxis of bacterial infection within the first 100 days after transplantation (DI). Some centers check total IgG levels in high-risk HCT recipients (for example, those with unrelated marrow grafts). For patients with severe hypogammaglobulinemia (that is, IgG <400 mg per 100 ml) i.v. Ig prophylaxis may be considered (Appendix 1) (CIII). The i.v. Ig dose and frequency for a hypogammaglobulinemic HCT recipient should be individualized to maintain trough serum IgG concentrations >400 mg per 100 ml, as the half-life of i.v. Ig among HCT recipients (generally 1–10 days) is much shorter than the half-life among healthy adults (generally 18–23 days) (BII).[167–169]

Preventing late disease (>100 days after HCT)
Prolonged antibiotic prophylaxis is recommended only for preventing infection with *S. pneumoniae* among allogeneic recipients with chronic GVHD for as long as active chronic GVHD treatment is administered (AIII).[170] Antibiotic selection should be guided by local antibiotic resistance patterns.

In the absence of severe hypogammaglobulinemia (that is, IgG levels <400 mg per 100 ml, which might be associated with bacteremia or recurrent sinopulmonary infections), routine monthly i.v. Ig administration to HCT recipients >100 days after allogeneic or autologous HCT is not recommended (DI)[171,172] as a means of preventing bacterial infections.

Recommendations for preventing late bacterial infections are the same among pediatric or adult HCT recipients.

Recommendations regarding CLABSI

Catheter-associated infections are a leading cause of bloodstream infections in HCT recipients, particularly during the preengraftment phase and in patients with GVHD.[173,174] These infections often result in catheter removal and, much less commonly, in death.[175,176]

In HCT recipients, all central venous catheters, whether tunneled or nontunneled, should be inserted using maximal sterile barrier precautions (AI).[177] The preferred approach is the CLABSI prevention bundle, which consists of hand hygiene, full barrier precautions, cleaning the insertion site with chlorhexidine, avoiding femoral sites for insertion and removing unnecessary catheters.[178] Although the efficacy of the CLABSI prevention bundle has not been studied in HCT recipients, all five elements of the bundle are recommended for this patient population (AII).

Other measures to decrease the risk of CLABSI have been studied. Catheters impregnated with minocycline/rifampin[179–181] have been shown to decrease CLABSI in patients requiring nontunnelled subclavian central venous access, including HCT patients. In one retrospective study, minocycline/rifampin-impregnated catheters did not affect the susceptibility of staphylococci to tetracyclines or rifampin.[181] For HCT centers with high CLABSI rates (more than 1 per 1000 catheter days), despite effective implementation of CLABSI bundle elements, use of additional interventions, such as minocycline/rifampin antimicrobial-impregnated catheters, to prevent CLABSIs should be considered (BIII).[182]

Additional prevention strategies (for example, catheter-site dressing regimens, antimicrobial/antiseptic ointments and antimicrobial lock prophylaxis) have been evaluated but not extensively assessed among the HCT patient population. A review found a similar risk of infection regardless of whether catheter dressings consisted of a transparent, semipermeable polyurethane dressing or of sterile gauze and tape.[183] Povidone-iodine ointment, mupirocin ointment and other antimicrobial ointments applied at the catheter insertion site have failed to show a consistent advantage when compared with no antimicrobial ointment. Recently, data have shown in non-HCT patients that chlorhexadine-impregnated sponges decreased the rates of catheter-related infections.[184,185] Topical antimicrobials should be avoided because of the risk of antimicrobial resistance or increased fungal colonization in immunosuppressed HCT patients (DIII).

Antimicrobial lock prophylaxis using antimicrobial solutions, including those that contain vancomycin, has been studied in patients with long-term venous access devices and who develop neutropenia. A meta-analysis of prospective, randomized trials testing the vancomycin-lock solution reported a decreased rate of bloodstream infections with vancomycin-susceptible organisms and a delay in the onset of the first bloodstream infection. However, the use of vancomycin-containing locks is not recommended, because of the increased risk of selecting for staphylococci with reduced vancomycin susceptibility[186] (DIII). Other alternatives, including lock solutions containing minocycline/EDTA, taurolidine citrate or ethanol, have shown success in preventing CLABSI and salvaging vascular access.[187–190] These approaches, although promising, cannot be recommended in routine catheter care until further investigation is completed (DIII).

When adopting prevention practices such as these, HCT programs should institute prospective data collection and reporting that allows for the analysis of the success of practices. HCT teams can also make use of a systemic review that defines benchmark rates of CLABSI for a wide range of catheter types.[191] Although not all of the studies included in the meta-analysis were conducted exclusively among HCT patients, HCT teams can use the results to assess their own center's relative performance, as an aspect of quality improvement efforts.

Recommendations regarding *S. pneumoniae*

Preventing exposure
Standard precautions should be taken with hospitalized patients infected with *S. pneumoniae* (AIII), including patients with infection caused by drug-resistant strains.[192]

Table 5 Vaccinations recommended for both autologous and allogeneic HCT recipients

Vaccine	*Recommended for use after HCT*	*Time post-HCT to initiate vaccine*	*No. of doses*[a]	*Improved by donor vaccination (practicable only in related-donor setting)*
Pneumococcal conjugate (PCV)	Yes (BI)	3–6 months	3–4[b]	Yes; may be considered when the recipient is at high risk for chronic GVHD
Tetanus, diphtheria, acellular pertussis[c]	Yes Tetanus–diphtheria: (BII) Pertussis (CIII)	6–12 months	3[d]	Tetanus: likely Diphtheria: likely Pertussis: unknown
Haemophilus influenzae conjugate	Yes (BII)	6–12 months	3	Yes
Meningococcal conjugate	Follow country recommendations for general population (BII)	6–12 months	1	Unknown
Inactivated polio	Yes (BII)	6–12 months	3	Unknown
Recombinant hepatitis B	Follow country recommendations for general population (BII)	6–12 months	3	Likely[e]
Inactivated influenza	Yearly (AII)	4–6 months	1–2[f]	Unknown
Measles–Mumps–Rubella[g] (live)	Measles: All children and seronegative adults Measles: BII Mumps: CIII Rubella: BIII EIII (<24 months post HCT, active GVHD, on immune suppression)	24 months	1–2[h]	Unknown

Abbreviations: DtaP = diphtheria tetanus pertussis vaccine; HCT = hematopoietic cell transplant; PCV = pneumococcal conjugate vaccine; Tdap = tetanus toxoid-reduced diphtheria toxoid-reduced acellular pertussis vaccine.
[a]A uniform specific interval between doses cannot be recommended, as various intervals have been used in studies. As a general guideline, a minimum of 1 month between doses may be reasonable.
[b]Following the primary series of three PCV doses, a dose of the 23-valent polysaccharide pneumococcal vaccine (PPSV23) to broaden the immune response might be given (BII). For patients with chronic GVHD who are likely to respond poorly to PPSV23, a fourth dose of the PCV should be considered instead of PPSV23 (CIII).
[c]DTaP is preferred, however, if only Tdap is available (for example, because TDaP is not licensed for adults), administer Tdap. Acellular pertussis vaccine is preferred, but the whole-cell pertussis vaccine should be used if it is the only pertussis vaccine available. (See text for more information.)
[d]See text for consideration of an additional dose(s) of Tdap for older children and adults.
[e]Significant improvement of recipient response to hepatitis B vaccine post transplant can be expected only if the donor receives more than one hepatitis vaccine dose before donation.
[f]For children <9 years of age, two doses are recommended yearly between transplant and 9 years of age.[306]
[g]Measles, mumps and rubella vaccines are usually given together as a combination vaccine. In females with pregnancy potential, vaccination with rubella vaccine either as a single or a combination vaccine is indicated.
[h]In children, two doses are favored.

Preventing disease

Invasive pneumococcal infection (IPI) is a life-threatening complication that may occur months to years after HCT. The annual incidence of IPI is 8.23 out of 1000 transplants among allogeneic HCT recipients, and is still higher among those with chronic GVHD (20.8 out of 1000 transplants).[193] Although IPI occurs less frequently in autologous HCT recipients (annual incidence, 3.8 out of 1000 transplants), the risk remains much higher than that in an immunocompetent population.[193] Efforts to prevent IPI should include active immunization and prophylactic antibiotics (Table 5 and Appendix 1). Vaccination against *S. pneumoniae* is recommended for all HCT recipients, preferably with pneumococcal 7-valent conjugate vaccine (BI) (see HCT Recipient Vaccinations).

Antibiotic prophylaxis against pneumococcal infection is indicated in patients with chronic GVHD and in those with low IgG levels (AIII). Antibiotic prophylaxis should be administered even to patients who have received pneumococcal vaccine, as not all strains are included in the vaccines, as the immunogenicity of vaccines against the vaccine strains in HCT patients is only, at the most, about 80%[194,195] and because of the theoretic concern that strains not included in the vaccine will replace vaccine strains. Oral penicillin remains the preferred choice, but antibiotic selection depends on the local pattern of pneumococcal resistance to penicillin and other antibiotics (that is, second-generation cephalosporins, macrolides and quinolones).[196–199] Early empirical antibiotic treatment is required in any HCT patient with suspected IPI, regardless of the time since transplant, the immunization status and the use of chemoprophylaxis (AIII).[193]

Recommendations regarding viridans streptococci

Preventing exposure

Viridans streptococci are normal commensals, primarily of oral surfaces. Hence, preventive efforts must focus on preventing systemic infection and disease rather than preventing exposure.

Preventing disease

Chemotherapy-induced oral mucositis is a potential source of viridans streptococcal bacteremia and sepsis. Consequently, before the start of conditioning, dental consults should be considered for all HCT candidates to assess the state of their oral health and to perform any needed dental procedures to decrease the risk for oral infections after

transplant (AIII).[200] Many experts recommend that antibiotics active against viridans streptococci be given from the time of transplantation until a minimum of day +21 afterward (CIII). However, this approach has not been systematically studied. Penicillin-, quinolone- and vancomycin-resistant strains of viridans streptococci have been reported.[201,202] Empirical treatment of any HCT recipient with fever, severe mucositis and neutropenia should include an agent active against viridans streptococci to prevent complications from this potentially fatal infection.[203]

Recommendations regarding Hib

Preventing exposure
Vaccination campaigns have markedly reduced the incidence of Hib disease. However, in the rare event of a patient being hospitalized with Hib, standard precautions are recommended, with droplet precautions added for the first 24 h after initiation of appropriate antibiotic therapy (BIII).[144,204]

Preventing disease
Vaccination against Hib is recommended for all HCT recipients, as at least one-third of HCT recipients do not have protective Ab levels of Hib capsular polysaccharide Abs after HCT, and the Hib conjugate vaccine has excellent efficacy among HCT recipients (BII)[194,205] (see HCT Recipient Vaccinations).

All HCT recipients who are exposed to persons with Hib disease should receive prophylaxis with 4 days of rifampin,[204] or with an alternative antimicrobial agent if rifampin is likely to interfere with other prophylactic agents that the patient is receiving (for example, extended-spectrum azoles) (BIII) (Appendix 1). Antibiotic prophylaxis is especially indicated for allogeneic HCT recipients with chronic GVHD, who are at increased risk for developing infections from Hib and other encapsulated organisms (see section on *S. pneumoniae*).[206]

Recommendations regarding *Bordetella pertussis*

Preventing exposure
Hematopoietic cell transplant recipients may be exposed to persons with pertussis, as this disease is increasingly frequent in the general community. Pertussis in an adolescent recipient of an unrelated cord blood transplant has been reported.[207] In addition to standard precautions, droplet precautions should be used in patients hospitalized with pertussis; droplet precautions are recommended for 5 days after initiation of effective therapy or, if antibiotic treatment is not given, until 3 weeks after the onset of paroxysmal cough (BIII).[208]

Preventing disease
All HCT recipients who are exposed to persons with pertussis should receive prophylaxis with azithromycin or another macrolide (trimethoprim–sulfamethoxazole may be an alternative antimicrobial agent), regardless of age and immunization status (BIII).[208] After HCT, all HCT recipients should receive vaccination with acellular pertussis (see HCT Recipient Vaccinations).