Consensus in infection complications

Luiza de Souza Santos Milaré[1], Laura de Almeida Lanzoni[2], Fabianne Altruda de Moraes Costa Carlesse[3]

1. Grupo de Pesquisa e Assistência ao Câncer Infantil – Sorocaba (SP), Brazil.
2. Grupo de Apoio ao Adolescente e à Criança com Câncer – São Paulo (SP), Brazil.
3. Hospital Pequeno Príncipe – Curitiba (PR), Brazil.

***Corresponding author:** fabiannecarlesse@gmail.com

Section editor: Fernando Barroso Duarte

Received: Sept. 25, 2025 • **Accepted:** Dec. 13, 2025

ABSTRACT

Infectious complications remain a leading cause of morbidity and mortality in pediatric recipients of hematopoietic stem cell transplantation (HSCT). In Brazil, the access to effective therapies for multidrug-resistant bacterial, invasive fungal, and viral infections is frequently limited in the public healthcare system (SUS), posing significant challenges to optimal clinical management. This consensus-based review, endorsed by the Brazilian Society of Cellular Therapy and Bone Marrow Transplantation, focuses on selected pediatric infectious complications in HSCT for which access to appropriate antimicrobial therapy remains particularly restricted. We summarize recommended antimicrobial agents for multidrug-resistant bacterial infections, invasive fungal diseases, and viral infections, highlighting discrepancies between evidence-based treatment strategies and drug availability in the SUS.

Keywords: Hematopoietic Stem Cell Transplantation. Drug Resistance. Virus Diseases. Delivery of Health Care.

INTRODUCTION

Infectious complications are responsible for high morbidity and mortality in patients undergoing hematopoietic stem cell transplantation (HSCT). Treatment for multidrug-resistant bacterial, viral, and fungal infections is highly prevalent, often prolonged, costly, and frequently unavailable at our public healthcare system, SUS, especially for pediatric patients[1].

The Brazilian Society of Cellular Therapy and Bone Marrow Transplantation includes a chapter on the consensus for the diagnosis and treatment of infections in HSCT recipients, which is endorsed by our group. In this chapter, we chose to highlight the pediatric infectious complications for which access to appropriate treatment remains particularly challenging.

The tables summarize antimicrobial therapies for multidrug-resistant bacterial, fungal, and viral infections in pediatric HSCT recipients. For bacterial infections, agents such as ceftazidime-avibactam, aztreonam, tigecycline, and linezolid are highlighted, although most are not available through the Brazilian public health system (SUS), with the exception of polymyxin B and, in specific situations, linezolid[2,3].

In Brazil, antifungal therapy through the SUS is restricted to proven fungal infections and is dispensed only upon formal request from public institutions registered in SIES/SISMAT. To obtain antifungal treatment, the Ministry of Health requires a fully completed antifungal request form, laboratory confirmation of active fungal infection,

HIV serology, and institutional eligibility[4]. Antifungals are not provided for empirical treatment or prophylaxis. For aspergillosis, SUS makes available itraconazole, voriconazole, isavuconazole, lipid complex amphotericin B, and—when there is proven central nervous system (CNS) involvement—liposomal amphotericin B. For invasive candidiasis, the drugs accessible through SUS include fluconazole, anidulafungin, lipid complex amphotericin B, liposomal amphotericin B (for CNS disease), voriconazole, amphotericin B deoxycholate (in selected situations), and flucytosine (for CNS involvement)[5,6]. For mucormycosis, SUS provides liposomal amphotericin B as first-line therapy, with alternatives including lipid complex amphotericin B, isavuconazole, and posaconazole for consolidation[7]. Drug release is tied strictly to confirmed diagnosis—including cultures, histopathology, polymerase chain reaction, or compatible imaging—, ensuring access only for documented invasive fungal disease.

For viral infections, newer agents such as nirsevimab, palivizumab, letermovir, maribavir, and cidofovir are discussed for respiratory syncytial virus (RSV), cytomegalovirus (CMV), adenovirus, and BK virus prophylaxis or treatment. Among respiratory viruses, RSV is a major pathogen in immunosuppressed children[8,9]. Passive immunization is recommended for children younger than 2 years old, and two monoclonal antibodies are currently available: palivizumab (short-acting) and nirsevimab (long-acting). Immunocompromised children under 2, including those with hematological malignancies or undergoing HSCT, may benefit from pre-exposure prophylaxis with either agent during the RSV season[10]. However, palivizumab is not recommended for children older than 2 or for adults. Because nirsevimab targets the prefusion F0 protein and has a longer half-life, it is expected to offer superior efficacy compared with palivizumab[11]. In the SUS, nirsevimab is available only for high-risk groups: premature infants (< 37 weeks) and children up to 2 with comorbidities such as chronic lung disease of prematurity, hemodynamically significant congenital heart disease, severe immunosuppression, Down syndrome, cystic fibrosis, neuromuscular disease, and congenital airway anomalies, and may be used even when maternal vaccination occurred if the mother is immunosuppressed or if delivery took place within 14 days of vaccination[12] No recommendations can be made regarding nirsevimab or other investigational agents (*e.g.*, motavizumab, motavizumab-YTE, suptavumab, clesrovimab) in adults with hematological malignancies or undergoing HSCT due to the absence of data on dose, timing, efficacy, and safety.

CMV remains one of the most significant infectious complications after HSCT because of its high mortality[13,14]. Letermovir, a viral terminase inhibitor with proven efficacy for CMV prophylaxis in adult HSCT recipients, was recently approved by the U.S. Food and Drug Administration for pediatric use, but data in children remain limited, and it is not approved for pediatric patients in Brazil yet[15–18]. Maribavir, indicated for refractory or resistant CMV infection, has been incorporated into the SUS only for adult post-transplant patients (≥ 18 years old) who have failed prior antiviral therapies (ganciclovir, valganciclovir, cidofovir, or foscarnet), and is not available for pediatric patients[19,20]. Additionally, cidofovir still requires international importation[21–23] (Tables 1, 2 and 3).

Table 1. Multidrug-resistant bacterial infections.

Drug	Dosage	Activity	Indication	How to get
Ceftazidime avibactam (CAZ-AVI)	50 mg/kg/dose of the ceftazidime (62.5 mg/kg/ dose of CAZ-AVI), maximum 2 g/dose (or 2.5 g of CAZ-AVI) 8/8 hours	Broad spectrum Gram-negative bacteria, including highly resistant strains, such as ESBL, AmpC, and serine carbapenemase producing Enterobacterales (CPE) and *P. aeruginosa*, but no activity against metalo b-lactamase (MBL) producers	Severe infections due to carbapenem resistant Enterobacterales — ECR (*e.g.*: KPC) For children > 3 months old	Not available at SUS

Continue...

Continuation.

Aztreonam	30 mg/kg/dose, maximum 2,000 mg/dose Infusion intravenously over 3 hours 6/6 hours	*Klebsiella pneumoniae* producing ESBL, KPC, AmpC, OXA-48 and MBL. *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, including MBL, producing strains	Combine (simultaneous use) with ceftazidime avibactam. For children > 1 month old	Not available at SUS
Polymyxin B	Neonatal and infants: 15,000 to 40,000 units/kg/day Intravenously 12/12 hours Children and adolescents: 15,000 to 25,000 units/kg/day 12/12 hours	Susceptible aerobic Gram-negative pathogens when less toxic drugs are ineffective or contraindicated	Serious infections Obs.: Electrolyte abnormalities, potential nephrotoxicity, skin turns progressively gray when used for several days	SUS: treatment of serious infections due to aerobic Gram-negative pathogens
Tigecycline	Loading 4 mg/kg (maximum 200 mg) once followed by 2–3.2 mg/kg (maximum 100 mg/dose) Infusion intravenously over 1 hour 12/12 hours	Susceptible organisms	Complicated skin and soft-tissue and complicated intra-abdominal infections, community acquired pneumonia	Not available at SUS
Linezolid	< 12 years old: 10 mg/kg/dose 8/8 hours > 12 years old: 10 mg/kg/dose 12/12 hours, maximum: 600 mg/dose	Vancomycin resistant *Enterococcus faecium*; *Staphylococcus aureus* (MSSA or MRSA); *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus agalactiae*	Complicated skin infections without osteomyelitis; community acquired pneumonia including bacteremia	SUS: serious infections by MRSA

ESBL: extended-spectrum b-lactmases; MBL: metallo-b lactamase; MSSA: methicillin-susceptible *Staphylococcus aureus*; MRSA: methicillin resistant *Staphylococcus aureus*; SUS: Unified Health System; AmpC: AmpC b-lactamase; ECR: enterobacterales carbapenem-resistant; CPE: carbapenemase-producing enterobacterales; KPC: *Klebsiella pneumoniae* carbapenemase. Source: Elaborated by the authors.

Table 2. Invasive fungal infections.

Drug	Dosage	Indication	How to get
Liposomal amphotericin B	3–5 mg/kg Intravenously, once daily	Empirical therapy of IFI. Children > 1 month old	SUS: proved CNS IFI and induction treatment for mucormycosis
Amphotericin lipidic complex	5 mg/kg Intravenously, once daily	Preemptive therapy	SUS: proved IFI
Voriconazole	9–12 mg/kg/dose Intravenously or orally 12/12 h Monitor serum levels	Aspergillosis and Fusariosis	SUS: proved invasive aspergillosis
Isavuconazole	Loading dose (48 h) > 37 kg: 200 mg/dose < 37 kg: 5.4 mg/kg/dose Intravenously, 8/8 hours Maintenance (> 48 h) > 37 kg: 200 mg/dose < 37 kg 5.4 mg/kg/dose Intravenously, once daily	Aspergillosis and mucormycosis	SUS: consolidation phase of mucomycosis on patients older than 18 years old
Micafungin	Neonate: 10 mg/kg/dose Intravenously once daily Infants: 4–6 mg/kg/dose Intravenously, once daily Maximum: 150 mg	Invasive candidiasis	Not available at SUS
Anidulafungin	Loading dose: 3 mg/kg/dose Intravenously, one daily dose Maintenance: 1.5 mg/kg/dose Intravenously, once daily	Invasive candidiasis	SUS: invasive candidiasis

IFI: Invasive fungal infection; SUS: Unified Health System; CNS: central nervous system. Source: Elaborated by the authors.

Table 3. Viral infections.

Drug	Dosage	Indication	How to get
Niversimab	< 5 kg: 50 mg; > 5 kg: 100 mg	RSV prophylaxis during seasonality up to 24 months of age	SUS: available only for high-risk groups
Letermovir	> 30 kg: 480 mg/day; 18–30 kg: 240 mg/day; < 18 kg: 120 mg/day Orally or intravenously Obs.: reduce dose by 50% if concomitant cyclosporine (but *not* tacrolimus or sirolimus). < 12 years old and > 30 kg: 120 mg letermovir (with and without concomitant cyclosporine)	Started between D+7 and D+28 and maintain until D+100 for CMV prophylaxis in patients with a positive serology prior to transplant undergoing allogeneic HSCT	Not available at SUS
Maribavir	≥ 12 years old and ≥ 35 kg: 400 mg Orally, 12/12 hours	Refractory CMV DNAemia or disease (with or without resistance to traditional agents)	Not available at SUS
Cidofovir	3–5 mg/kg once a week intravenously *with* probenecid *OR* 1 mg/kg intravenously three times a week (with or without probenecid)	Adenovirus BK virus	Not available at SUS Not available in Brazil. It is necessary to import it

RSV: respiratory syncytial virus; SUS: Unified Health System; HSCT: hematopoietic stem cell transplantation; CMV: cytomegalovirus. Source: Elaborated by the authors.

CONFLICT OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable.

AUTHORS' CONTRIBUTIONS

Substantive scientific and intellectual contributions to the study: Milaré LSS, Lanzoni LA and Carlesse FAMC. **Conception and design:** Milaré LSS. **Analysis and interpretation of data:** Milaré LSS, Lanzoni LA and Carlesse FAMC. **Technical procedures:** Milaré LSS. **Statistics analysis:** Milaré LSS, Lanzoni LA and Carlesse FAMC. **Manuscript writing:** Milaré LSS, Lanzoni LA and Carlesse FAMC. **Final approval:** Carlesse FAMC.

FUNDING

Not applicable.

ACKNOWLEDGEMENTS

Not applicable.

REFERENCES

1. Brasil. Ministério da Saúde. Obter medicamentos para a população do estado ou município. Brasília: Ministério da Saúde; 2025. Available at: https://www.gov.br/pt-br/servicos/obter-medicamentos-para-a-populacao-do-estado-ou-municipio
2. Hoshino WT, da Silva AMPS, Pignatari AC, Gales AC, Carlesse F. Experience in Ceftazidime-Avibactam for treatment of MDR BGN infection in oncologic children. Braz J Infect Dis. 2025;29(2):104515. https://doi.org/10.1016/j.bjid.2025.104515

3. Paul M, Carrara E, Retamar P, Tängdén T, Bitterman R, Bonomo RA, de Waele J, Daikos GL, Akova M, Harbarth S, Pulcini C, Garnacho-Montero J, Seme K, Tumbarello M, Lindemann PC, Gandra S, Yu Y, Bassetti M, Mouton JW, Tacconelli E, Rodríguez-Baño J. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European Society of Intensive Care Medicine). Clin Microbiol Infect. 2022;28(4):521–47. https://doi.org/10.1016/j.cmi.2021.11.025

4. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde e Ambiente. Departamento de HIV/AIDS, Tuberculose, Hepatites Virais e Infecções Sexualmente Transmissíveis. Coordenação-Geral de Vigilância da Tuberculose, Micoses Endêmicas e Micobactérias não Tuberculosas. Nota informativa nº 9/2023-CGTM/DATHI/SVSA/MS. Orientações acerca da disponibilidade dos medicamentos antifúngicos para o tratamento das micoses endêmicas e oportunistas e o fluxo para requisição dos medicamentos. Brazil: Ministério da Saúde; 2023.

5. Donnelly JP, Chen SC, Kauffman CA, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clin Infect Dis. 2020;71(6):1367–76. https://doi.org/10.1093/cid/ciz1008

6. Kobayashi C, Hanadate T, Niwa T, Hirano Y, Yoshiyasu T, So M, Matsui K. Safety and efficacy of micafungin for prophylaxis against invasive fungal infections in Japanese patients undergoing hematopoietic stem cell transplantation: Results of a post-marketing surveillance study. J Infect Chemother. 2015;21(6):438–43. https://doi.org/10.1016/j.jiac.2015.01.016

7. Fernández Ledesma B, Mendoza-Palomar N, Melendo Pérez S, Fernández-Polo A, Renedo Miró B, Pau Parra A, Luque Pardos S, Grau Cerrato S, Vima Bofarull J, Martín-Gómez MT, Pujol Jover M, Benítez-Carbante MI, Díaz de Heredia C, Soler-Palacin P. Isavuconazole use and TDM in real-world pediatric practice. Antimicrob Agents Chemother. 2023;67(12):e0082923. https://doi.org/10.1128/aac.00829-23

8. Von Lilienfeld-Toal M, Khawaja F, Compagno F, Robin C, Piñana JL, Cesaro S, Einsele H, Ljungman P, Navarro D, Boeckh M, Chemaly RF, Hirsch HH. Community-acquired respiratory virus infections in patients with haematological malignancies or undergoing haematopoietic cell transplantation: updated recommendations from the 10th European Conference on Infections in Leukaemia. Lancet Infect Dis. 2025:S1473-3099(25)00365-2. https://doi.org/10.1016/S1473-3099(25)00365-2

9. Ruiz-Galiana J, Cantón R, De Lucas Ramos P, García-Botella A, García-Lledó A, Hernández-Sampelayo T, Gómez-Pavón J, González Del Castillo J, Martín-Delgado MC, Martín Sánchez FJ, Martínez-Sellés M, Molero García JM, Moreno Guillén S, Rodríguez-Artalejo FJ, Rodríguez Fernandez R, Kestler M, Bouza E. Respiratory syncytial virus: A new era. Rev Esp Quimioter. 2024;37(2):134–48. https://doi.org/10.37201/req/147.2023

10. Jones JM, Fleming-Dutra KE, Prill MM, Roper LE, Brooks O, Sánchez PJ, Kotton CN, Mahon BE, Meyer S, Long SS, McMorrow ML. Use of nirsevimab for the prevention of respiratory syncytial virus disease among infants and young children: recommendations of the Advisory Committee on Immunization Practices - United States, 2023. MMWR Morb Mortal Wkly Rep. 2023;72(34):920–5. https://doi.org/10.15585/mmwr.mm7234a4

11. Domachowske J, Hamrén UW, Banu I, Baronio R, Basavaraju B, Koen A, Leach A, Mankad VS, Pannaraj PS, Soler-Palacin P, Takas T, Mori M, Villafana T; MUSIC Study Group. Safety and pharmacokinetics of nirsevimab in immunocompromised children. Pediatrics. 2024;154(4):e2024066508. https://doi.org/10.1542/peds.2024-066508

12. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde e Ambiente. Departamento de HIV/AIDS, Tuberculose, Hepatites Virais e Infecções Sexualmente Transmissíveis. Coordenação-Geral de Vigilância da Tuberculose, Micoses Endêmicas e Micobactérias não Tuberculosas. Nota técnica nº 7/2024-CGTM/DATHI/SVSA/MS. Brazil: Ministério da Saúde; 2024.

13. Piret J, Boivin G. Management of cytomegalovirus infections in the era of the novel antiviral players, letermovir and maribavir. Infect Dis Rep. 2024;16(1):65–82. https://doi.org/10.3390/idr16010005

14. Khawaja F, Zamora D, Yong MK, Hakki M, Goscicki BK, Danziger-Isakov L, Lin A, Carpenter PA, Boeckh M, Papanicolaou GA, Dadwal SS, Chemaly RF. American Society for Transplantation and Cellular Therapy Series #11: Updated Cytomegalovirus Guidelines in Hematopoietic Cell Transplant and Cellular Therapy Recipients. Transplant Cell Ther. 2025;31(10):727–41. https://doi.org/10.1016/j.jtct.2025.06.025

15. Vendemini F, De Lorenzo P, Romani F, Malandrin SMI, Verna M, Bonanomi S, Valsecchi MG, Lucchini G, Balduzzi A. Letermovir primary and secondary prophylaxis in pediatric recipients of allogeneic haematopoietic stem cell transplant. Transplant Cell Ther. 2025;31(9):699.e1–e11. https://doi.org/10.1016/j.jtct.2025.05.021

16. Aldalati AY, Hussein AM, Balbaa E, Hammadeh BM, Idrees M, Aloudat O, Albliwi M, Abuassi M, Sultan I. Efficacy and safety of letermovir for cytomegalovirus prophylaxis in pediatric hematopoietic stem cell transplantation recipients: a systematic review, meta-analysis, and meta-regression. Transpl Infect Dis. 2025;27(2):e70006. https://doi.org/10.1111/tid.70006

17. Körholz KF, Füller MA, Hennies M, Holterhus M, Hagedorn S, Ahlmann M, Thorer H, Burkhardt B, Groll AH. Letermovir for prophylaxis and pre-emptive therapy of cytomegalovirus infection in paediatric allogeneic haematopoietic cell transplant patients. Paediatr Drugs. 2023;25(2):225–32. https://doi.org/10.1007/s40272-022-00547-6

18. Kuhn A, Puttkammer J, Madigan T, Dinnes L, Khan S, Ferdjallah A, Kohorst M. Letermovir as cytomegalovirus prophylaxis in a pediatric cohort: a retrospective analysis. Transplant Cell Ther. 2023;29(1):62.e1–e4. https://doi.org/10.1016/j.jtct.2022.10.005

19. Valencia Deray KG, Danziger-Isakov LA, Downes KJ. Current and emerging antiviral agents in the prevention and treatment of cytomegalovirus in pediatric transplant recipients. J Pediatric Infect Dis Soc. 2024;13(Suppl.1):S14–S21. https://doi.org/10.1093/jpids/piad059

20. Piret J, Boivin G. Management of cytomegalovirus infections in the era of the novel antiviral players, letermovir and maribavir. Infect Dis Rep. 2024;16(1):65–82. https://doi.org/10.3390/idr16010005

21. Cesaro S, Porta F. Adenovirus infection in pediatric hematopoietic cell transplantation: a challenge still open for survival. J Clin Med. 2022;11(16):4827. https://doi.org/10.3390/jcm11164827

22. Thomas SJ, Young RT, Steinbach WJ, Lugo DJ. Risks and outcomes of adenovirus disease in pediatric hematopoietic stem cell transplant recipients-Comparison of current antiviral treatment options. Transpl Infect Dis. 2021;23(2):e13505. https://doi.org/10.1111/tid.13505

23. Grasa C, Monteagudo-Vilavedra E, Pérez-Arenas E, Falces-Romero I, Mozo Del Castillo Y, Schüffelmann-Gutiérrez C, Del Rosal T, Méndez-Echevarría A, Baquero-Artigao F, Zarauza Santoveña A, Serrano Fernández P, Sainz T, Calvo C. Adenovirus infection in hematopoietic and solid organ paediatric transplant recipients: treatment, outcomes, and use of cidofovir. Microorganisms. 2023;11(7):1750. https://doi.org/10.3390/microorganisms11071750