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PREVENTION AND TREATMENT OF INFECTIOUS COMPLICATIONS POST HSCT

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INTRODUCTION

The current version of the “Recommendations for the Prevention and Treatment of post-HSCT Infections” has been structured in tables and divided into the following sessions: 1) pre-transplant screening; 2) prophylactic measures; 3) laboratory monitoring; 4) management of febrile neutropenia; 5) empirical and preemptive antimicrobial therapies; 6) antimicrobial therapy for documented infectious events; and 7) post-transplant vaccination program.

In addition to the bibliographic update, new topics were added to the current version, such as the risk stratification for invasive fungal diseases, prophylaxis of CMV infection with letermovir, the debated topic of antibacterial prophylaxis during neutropenia, febrile neutropenia treatment duration, preemptive approach in adenovirus and HHV6 infections, and the reemer-

gence of yellow fever and measles as a consequence of low vaccine coverage. Concerning the revaccination program, we cite the introduction of PCV13 for adult patients and the recombinant herpes zoster vaccine only for autologous transplant recipients. The latter is currently only available in private vaccination clinics.

Lastly, we would like to highlight the important changes in the management of respiratory viruses due to the COVID-19 pandemic, with the implementation of contact and aerosol precautions in HSCT units. Complete information concerning SARS COV-2 and COVID-19 have been posted in the website of SBTMO and has been updated as needed.

The strength of recommendations and quality of evidence were based on the grading system of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) summarized in

FIGURE 1- Grading system of the ESCMID.

| STRENGTH OF RECOMMENDATION | QUALITY OF EVIDENCE |
|--|---|
| <ul style="list-style-type: none"> • Grade A: ESCMID strongly supports the recommendation for use • Grade B: ESCMID moderately supports the recommendation for use • Grade C: ESCMID marginally supports the recommendation for use • Grade D: ESCMID is against the use of the recommendation | <ul style="list-style-type: none"> • Level I: evidence from at least one properly designed randomised, controlled trial • Level II: evidence from at least one well designed clinical trial, without randomization; from cohort or case-controlled analytical studies (preferably from more than one centre); from multiple time series; or from dramatic results of uncontrolled experiments • Level III: evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees |

| 1. PRE-TRANSPLANT SCREENING FOR AUTOLOGOUS OR ALLOGENEIC HSCT | | REFERENCES |
|---|--|------------|
| 1.1. | <p>Assessment: Colonization by a multi-resistant germ (MDR). Method: Colonization surveillance swab for MDR (MRSA, VRE, CRE, ESBL). Comment (Evidence): Each center should propose a screening strategy appropriate to its epidemiology to reduce intra-hospital transmission, in conjunction with the local Infection Control Program. (BII)</p> | [1–3] |
| 1.2. | <p>Assessment: Previous bacterial infections. Method: Anamnesis, physical examination, imaging tests, and review of previous events. Comment (Evidence): Attention to recurrent infectious events, MDR pathogens, and latent infections. Previous infections by MDR agents will be considered when choosing the empirical drug at the time of febrile neutropenia (BII)</p> | [4,5] |
| 1.3. | <p>Assessment: Risk stratification for invasive fungal disease (IFD) Method: The level of risk for IFD in allogeneic HSCT recipients depends on several factors, including host characteristics, underlying hematological disease conditions and the type of transplantation that will be performed. Anamnesis, physical examination, imaging tests, and review of previous events. Risk factors: high doses of corticosteroids, prolonged neutropenia, IFD 6 months before transplantation. Allogeneic stem cell transplant patients are generally at high risk with factors such as GVHD, CMV disease, cord blood and haploidentical donors and active leukemia at time of transplant increasing the risk further. Patients who are not in complete remission pre-transplant are at higher risk of IFD post-transplant. Comments (Evidence): Risk stratification identifies those patients who will benefit most from mold active versus yeast active prophylaxis and those who can be safely managed with monitoring and clinically driven interventions for IFD (AII).</p> | [6–13] |
| 1.4. | <p>Assessment: Previous viral infection Method: Medical history and specific serologies (HSV, CMV, EBV, HIV, HCV, HBV, HTLV). Comments (Evidence): Order HBsAg, anti-HBs, anti-HBc, and anti-HCV serology for recipient and donor and NAT for the donor. It is crucial to screen viral hepatitis for the right prophylaxis or treatment (AII).</p> | [4,14] |
| 1.5. | <p>Assessment: Dengue, Chikungunya Zika. Method: Inquiry about the epidemiological risk. Serological screening for D / R is not recommended. Comment (Evidence): Check whether the candidate and/or donor come from an endemic or epidemic region; or had a recent travel to such regions. If symptomatic, collect NAT (and/or NS1 in the case of DENV). If positive, wait 30 days for stem cell (SC) harvesting or transplant (AII).</p> | [15] |
| 1.6. | <p>Assessment: Screening of respiratory virus infections. Method: Immunofluorescence assay or multiplex PCR in respiratory samples (nasopharynx swab or nasal wash) before admission. Comment (Evidence): With the emergence of COVID-19, the screening of respiratory viruses in asymptomatic patients became mandatory before admission to HSCT (AII).</p> | [16,17] |

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| 1.7. | <p>Assessment: Yellow Fever Method: There is no recommendation for serological screening for D/R. Consider vaccinating D and/or R before HSCT. Comment (Evidence): The whole country has recommendation of yellow fever vaccination. About 30% of the individuals vaccinated before transplantation maintain antibodies after HSCT (BII). Check if the donor has been vaccinated recently. If yes, wait 30 days for SC harvesting or HSCT.</p> | [18–22] |
| 1.8. | <p>Assessment: Latent tuberculosis infection (LTBI) Method: Investigate the occurrence of previous TB, TB in household contacts, or diagnose LTBI by tuberculin skin test (TST) or by interferon gamma release assays (IGRA), e.g., the QuantiFeron TB test (QTF-TB). Comment (Evidence): Previous history of TB, contact with TB, positive PPD or reactive QTF-TB indicate latent TB. Recipient with TST \geq 5mm is considered reactive (positive). In a population vaccinated with BCG, the IGRA is recommended because it does not cross-react with Mycobacterium bovis, present in BCG (BII).</p> | [23,24] |
| 1.9. | <p>Assessment: Chagas disease Method: Enzyme immune assay (EIA), immunofluorescent assay (FA) or hemagglutination inhibition assay (HIA). Perform two different tests. If discordant, repeat with Western blot or chemiluminescence. Comment (Evidence): Inquiry D/R about residence in an endemic area, houses that favors the presence of the vector, blood transfusion before 1992, having family members or a mother with Chagas positive serology. False negative serology may occur. In such cases, the information acquired in the survey must be valued and the recipient should be monitored after HSCT (AII).</p> | [18,25] |
| 1.10. | <p>Assessment: Toxoplasmosis Method: Toxoplasmosis serology (IgG and IgM) from donor and recipient. Comment (Evidence): More than 70% of cases are due to reactivation. Higher risk if D-/R+. Positive IgM or high levels of IgG may indicate recent infection. In such cases, PCR test should be performed and if positive, the patient should be treated (AII).</p> | [26] |
| | <p>Evaluation: Strongyloidiasis Method: Investigation by stool examination, and/or serology, or empirical therapy. Comment (Evidence): In general, the tests have low sensitivity. Empirical pre-HSCT therapy with ivermectin 200 mg/kg/d for 2 days is recommended. Repeat treatment after 2 weeks. Alternative schedule is albendazole 400 mg 12/12h for 7 days (AII).</p> | [27,28] |

| 2. PROPHYLACTIC MEASURES | | REFERENCES |
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| 2.1. | <p>Situation: Antibacterial prophylaxis in the neutropenic phase. Conduct: Ciprofloxacin or levofloxacin. Comment (Evidence): The consensus does not recommend using antibacterial prophylaxis in the routine, given the high prevalence of quinolone-resistant enterobacteria and the risk of selecting multidrug-resistant strains (MDR). Consider only in centers where the frequency of resistance to quinolones is low (<30%), a controlled MDR infection/colonization rate and high bloodstream infection prevalence. In other centers, the benefit is questionable and is not indicated. Antibacterial prophylaxis is not recommended in children during the neutropenia (DI) phase. Caution about QT prolongation toxicity, especially in situations with concomitant use of QT prolongations drugs (as voriconazole)</p> | [29–36] |
| 2.2. | <p>Situation: Antibacterial prophylaxis in late post-engraftment phase. Conduct: Oral penicillin. Alternatives: macrolides, quinolones, or 2nd generation cephalosporins. Comment (Evidence): Recommended only in patients with GVHD, for preventing S. pneumoniae, or in cases of recurrent respiratory infection and hypogammaglobulinemia. (BII)</p> | [23] |
| 2.3. | <p>Situation: Documented hypogammaglobulinemia (serum IgG <400 mg / dl). Conduct: Immunoglobulin replacement (IVIG) dose 500mg / kg / month. Comment (Evidence): Decreases the number of infectious episodes in patients who need replacement. It is not recommended in patients without documentation of hypogammaglobulinemia. (BIII)</p> | [37–39] |
| 2.4. | <p>Situation: Primary antifungal prophylaxis (PAP) at High risk Recommendation: Mold-active PAP is recommended. Posaconazole (AI); voriconazole (BI); caspofungin (CIII); micafungin (CIII). Children: voriconazole for patients >2 years of age (AII); or posaconazole in > 13 years (AII). Alternatives include liposomal amphotericin B (B-II); micafungin (B-II); and, with less strength of evidence, aerosolized liposomal amphotericin B (C-II) and caspofungin (C-II). If posaconazole and voriconazole are selected, TDM is recommended with target concentrations similar to those recommended for adults. Comment (Evidence): There are 3 phases after the transplant which reflect the risk of IFD: neutropenia (early), a-GVHD and the early immune recovery (late), and late a-GVHD or c-GVHD, together with late immunologic recovery (very late) High Risk patients (adaptated Girmenia 2014) Early phase from day 1 to 40: Active acute leukemia at the time of trans-plantation (AII), CB transplantation (AII), Grade III-IV a-GVHD after any type of transplantation (AII), Transplantation from MMRD or UD and 1 or more of the following additional risk factors: grade II a-GVHD, steroid dose >2 mg/kg/day for at least 1 week, CMV disease, recurrent CMV infection, prolonged neutropenia (PMN < 500/mL for more than 3 weeks), iron over- load (BIII) , Steroid refractory/dependent a-GVHD after any type of transplantation (AIII). Late Phase (from day 41 to 100): Acute grade III-IV GVHD after any type of transplantation (AII), Transplantation from MMRD or UD and 1 or more of the following additional risk factors: grade II a-GVHD, steroid dose > 2 mg/kg/day for at least 1 week, CMV disease, recurrent CMV infection, recurrent neutropenia (PMN < 500/mL for more than 1 week) (BIII), Steroid refractory/dependent a-GVHD after any type of transplantation (AIII) Very Late Phase after Transplantation (Day > 100) Persistent or late-onset grade III-IV a-GVHD (AII), Persistent or late-onset steroid refractory/ dependent a-GVHD after any type of transplantation (AII), Persistent or late-onset grade II a-GVHD after transplantation from MMRD or UD (BIII) Extensive c-GVHD when preceded by an a- GVHD (AII)</p> | [7,12,40–47] |
| 2.5. | <p>Situation: Primary antifungal prophylaxis (PAP) at standard risk. Recommendation: Candida active PAP is recommended. Fluconazole (AI); voriconazole (BI); micafungin (BI). In children fluconazole (AI). Comment (Evidence): Standard Risk: Early Phase after Transplantation (Day 0-40): All remaining patients not included in the high-risk category (AI) Late Phase after Transplantation (Day 41-100): All remaining patients not included in the high-risk category (BI). Very Late Phase after Transplantation (Day > 100): Limited c-GVHD in patients who receive only a nonsteroid immunosuppression and “de novo” c-GVHD (BIII).</p> | [7,12,45,48] |

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| 2.6. | <p>Situation: Primary Antifungal Prophylaxis (PAP) at low risk Recommendation: No prophylaxis Comment (Evidence): Early Phase after Transplantation (Day 0-40). Autologous HSCT: Fluconazole can be used in the phase of intense neutropenia to prevent Candida infections, especially in the presence of mucositis. No patient undergoing allogeneic HSCT is considered to be at low risk at this stage Late Phase after Transplantation (Day 41-100) No patient undergoing allogeneic HSCT may be considered at low risk for IFD during this phase. Very Late Phase after Transplantation (Day > 100) Absence of any type of GVHD and no steroid therapy (All).</p> | [7,12,45] |
| 2.7. | <p>Situation: Prophylaxis for herpes simplex virus (HSV) and varicella-zoster (VZV). Recommendation: Acyclovir or Valacyclovir. Comment (Evidence): Beginning in conditioning up to 1 year after BMT or up to 6 months after the end of immunosuppression, whichever comes last (allogeneic HSCT) (AI).</p> | [49,50] |
| 2.8. | <p>Situation: Prophylaxis for Cytomegalovirus (CMV). Recommendation: Letermovir. Comment (Evidence): Indicated for positive CMV IgG receptors. The benefit is more significant at high risk: cord, use of post-cyclophosphamide, HLA mismatch, and T cell depletion (e.g., ATG, alemtuzumab). Perform CMV qPCR before prophylaxis (less effective if DNAemia is present). Start as soon as possible and keep until D + 100 (AI). Pay attention to the dose adjusted for concomitant use of cyclosporine. There is no data in pediatrics for the use of letermovir. Prophylaxis with acyclovir or valacyclovir for HSV / VZV should be maintained (AI).</p> | [51] |
| 2.9. | <p>Situation: Prophylaxis for HBV Recommendation: lamivudine; alternative entecavir or tenofovir Comment (Evidence): Indicated in the following situations: AntiHBc + donor with negative HBV DNA; AntiHBc / AntiHBs + receptor with negative HBV DNA. For AntiHBc+ receptor with AntiHBs- and HBV DNA - recommended prophylaxis is entecavir 0.5mg/day. Follow-up with monthly transaminases when using prophylaxis, if increased, request HBV DNA. Prophylaxis duration: from the first conditioning day (if not in use) to 1 year after autologous HSCT and two years after allogeneic HSCT or six months after the end of immunosuppression (whichever comes later) (All).</p> | [14,52] |
| 2.10. | <p>Situation: Prevention of respiratory viruses (RV). Recommendation: HSCT should be postponed in symptomatic patients (All). Only patients who tested negative in pre-HSCT RV screening can be admitted for transplantation (All). Daily surveillance of respiratory symptoms is crucial (AIII). Rapid diagnosis and precautions implementation according to specific diagnosis (All). In units with HEPA rooms, the positive pressure should be reverted or turned off if respiratory viruses are diagnosed (All). Comment (Evidence): Only recipients of allogeneic HSCT <2 years of age with a high risk of progression to RSV pneumonia can be considered for treatment with palivizumab (CIII). Due to the current circulation of SARS CoV-2 worldwide, masks and contact precautions besides hand hygiene is strongly recommended in HSCT units (All).</p> | [17,53] |
| 2.11. | <p>Situation: Prevention of hemorrhagic cystitis (HC) caused by BK virus (BKV). Recommendation: Hyperhydration (BII) and bladder irrigation (CII). Comment (Evidence): HC prophylaxis is based on hyperhydration and bladder irrigation to reduce urothelial damage, which occurs mainly in myeloablative conditioning with cyclophosphamide, busulfan and total body irradiation. Asymptomatic BKV viruria is frequent after HSCT (> 60%) and there is no correlation between viral load and hematuria severity. Monitoring of BKV in urine or blood is not recommended. Fluoroquinolones are not recommended because ineffectiveness in viral replication and severity of CH, and the risk of increasing resistance to quinolones (DII).</p> | [54,55] |

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| 2.12. | <p>Situation: Tuberculosis prophylaxis Management: Prophylaxis with INH for 6 to 9 months for recipients with latent TB. An alternative is to enter prophylaxis if the recipient develops chronic GVHD (BIII). Comment (Evidence): Prophylaxis with INH has been controversial due to the late occurrence of TB and adverse events (in general, rare). Main risk factor is chronic GVHD. Maintain prophylaxis for 6 months or until the condition stabilizes (BII).</p> | [56,57] |
| 2.13. | <p>Situation: Prophylaxis for Toxoplasmosis and Pneumocystosis. Conduct: TMP/SMX. Comment (Evidence): TMP/SMX is active against T.gondii, P.jiroveci (All adults; AI children), Listeria and Nocardia. Although less effective, the alternative drug is dapsone 100 mg/day (AII). Half of the cases of toxoplasmosis occur before d+30. Thus, prophylaxis should be started soon after engraftment and maintained until d+180 or more in patients who continue to receive IS and/or have chronic GVHD. There is no evidence that prophylaxis can be safely stopped if CD4+ count is normal (as in HIV +) because other risk factors may persist (BIII).</p> | [26,58]5 |

| 3. Laboratory monitoring | | References |
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| 3.1. | <p>Situation: CMV monitoring. Method: Perform qPCR (AII) or pp65 antigenemia (BII) weekly. Comment (Evidence): In all CMV seropositive recipients (R+) at least 1x a week up to D + 100. R- / D- do not require monitoring. CMV monitoring should be done regardless of the use of prophylaxis with letermovir. CMV monitoring should be prolonged in HSCT with a mismatch, cord blood or haplo without Pt-Cy; in patients who reactivated up to d + 100; who had acute or chronic GVHD; with persistent immunodeficiency or who used prophylaxis with letermovir. When using qPCR, monitoring should be carried out keeping the same type of sample, the same method of DNA extraction and quantification (including WHO quantification standard) (AII), and the results must be available within 48 hours. Monitoring with AG should start after engraftment.</p> | [59] |
| 3.2. | <p>Situation: Monitoring of EBV. Method: quantitative PCR (qPCR) weekly Comment (Evidence): Recommended for groups at risk for post-HSCT lymphoproliferative disease (DLPT): cord, HLA mismatch; in vivo or in vitro depletion of T cells; mismatch in EBV serology; splenectomy and previous HSCT (AII). Monitoring starts in D+7 until D+100; may be extended, at least monthly, in case of GVHD using ISS or previous reactivation of EBV during the first year (BII).</p> | [60] |
| 3.3. | <p>Situation: Monitoring of HHV-6 reactivation. Method: quantitative PCR (qPCR) Comment (Evidence): Routine HHV-6 DNA screening is not recommended for pre-emptive or prophylactic therapy (DII)</p> | [86] |
| 3.4. | <p>Situation: Adenovirus monitoring (ADV). Method: qPCR in feces or blood weekly. Comment (Evidence): In high-risk groups e.g., children with cord blood HSCT or unrelated, severe GVHD (grade III-IV); severe lymphopenia (<200/L) (IIA children). Adults with cord or haploidentical HSCT; Severe GVHD (grade III-IV); severe lymphopenia (<200/L); alemtuzumab treatment (BII adults). In feces, viral load above 10⁶ copies/gram of feces predicts viremia and indicates the time to start blood monitoring. In the absence of stool screening, blood monitoring can begin immediately after transplantation and be maintained until D + 100 (BIII children, CIII adults).</p> | [61] |

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| 3.5. | <p>Situation: Aspergillosis Method: Serum Galactomannan (GM) by EIA, 2-3x/week during the early engraftment phase has a high sensitivity and negative predictive value (NPV) for IA (AII). Serial screening is not recommended in patients on mold-active prophylaxis (DII). Children: GM testing can be used both as a screening tool in pediatric patients considered at high risk for developing IA (B-II) as well as a diagnostic tool in pediatric patients suspected of having developed IA, e.g. those with clinical symptoms or imaging abnormalities (B-II). Comments (Evidence): Better performance of the test with 2 consecutive values above 0.5 (AI). Monitoring should be combined with imaging tests and clinical evaluation. After grafting, the risk of developing IFD by filamentous fungus is associated with GVHD and the use of corticosteroids. Serum monitoring is not recommended in patients who have filamentous fungus prophylaxis. (DII). Decrease of the ODI during the first two weeks of antifungal therapy is a reliable predictor of a satisfactory response in cancer patients</p> | [46,62–69] |
| 3.6. | <p>Situation: Control of response to the treatment of invasive aspergillosis (AII) Method: Galactomannan (GM) by EIA, 2-3x/week Comments (Evidence): In monitoring response to the treatment of invasive aspergillosis; the persistence of positive GM is indicative of a poor prognosis. The 1,3 beta D glucan test may be positive for several agents such as Candida, Aspergillus, P. jirovecii, without discriminating between them.</p> | [62] |
| 3.7. | <p>Situation: Monitoring of Chagas disease Method: Qualitative PCR in decreasing frequency. Comment (Evidence): In D+ and/or R+ for Chagas. PCR monitoring should start on admission, then weekly for 2 months, every other week between 2 and 6 months of HSCT and annually after 6 months. If benznidazole is introduced pre-emptively, monitor marrow and hepatic toxicity. There is no benefit of prophylaxis compared to preemptive therapy (BIII).</p> | [18,25] |

| 4. Febrile neutropenia (FN) management | | References |
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| 4.1. | <p>Situation: Diagnosis of febrile neutropenia. Method: Fever surveillance, clinical investigation, and blood culture collection. Comment (Evidence): During neutropenia, monitor for fever or other signs or symptoms suggestive of infection—detailed clinical examination, identifying signs of sepsis, infectious foci. Blood culture collections are mandatory before the start of antimicrobials (AII).</p> | [70] |
| 4.2. | <p>Situation: Introduction of empirical antimicrobials. Method: escalating or de-escalating antimicrobials. Escalation = monotherapy with piperacillin-tazobactam, or cefepime, or ceftazidime. De-escalation = β-lactam + aminoglycoside; β-lactam +/- aminoglycoside +/- tigecycline; association of polymyxin B / E; use of new drugs with spectrum for MDR. Comment (Evidence): An institutional management algorithm appropriate to the local antimicrobial profile is recommended. Empirical therapy should be started within 60 minutes after the onset of fever. This measure reduces mortality. If no hemodynamic instability, history of infection, or previous colonization by MDR pathogen, an escalation strategy is recommended. Carbapenems as an initial drug are discouraged due to their association with pseudomembranous colitis. The de-escalation strategy should be used in clinical instability situations, previous history of MDR, or epidemiological situation of MDR outbreak in the unit (AI).</p> | [5,70–77]h |

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| 4.3. | <p>Situation: Criteria for modifying antimicrobial therapy in FN. Method: Detection of microbiological and / or clinical failure. Comment (Evidence): Development of new clinical signs or hemodynamic instability during the initial empirical treatment. Persistent fever in the absence of clinical or microbiological documentation is not an indication of empirical modification in a stable patient. Persistent fever should be conducted with an intensification of the diagnostic approach. Therapy adjustment should be made according to the antibiogram of the isolated agent. The minimum spectrum of coverage for empirical therapy is enterobacteria and for Pseudomonas spp (All).</p> | [71,76,78,79] |
| 4.4. | <p>Situation: Treatment duration in the FN. Method: Consider the criteria for withdrawal. Comment (Evidence): The course of antimicrobial treatment should be guided by documentation of infection and neutrophil recovery (> 500 cells / mm³). In patients with fever resolution, no infection documentation, and stability, the empirical therapy may be suspended after 3 or 5 days. In cases of documented infection, the treatment duration will depend on the type of infection (All).</p> | [74,80,81] |

| 5. Empiric and Pre-emptive Therapies | | References |
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| 5.1. | <p>Situation: Empiric antifungal therapy Recommendation: Caspofungin (AI), Liposomal Amphotericin B (BI), voriconazole (BII) Comment (Evidence): Empirical therapy is indicated for neutropenic patients who persist with fever for more than 4 days using broad spectrum antibiotic therapy at places without quick access to diagnosis of IFD (e.g., galactomannan) or in high-risk epidemiological situations. (construction-related outbreaks, etc.). Children: This approach should be initiates in high-risk neutropenic patients after 96h of fever of unclear cause that is unresponsive to broad spectrum antibacterial agents (BII) and be continued until resolution of neutropenia in the absence of suspected or documented invasive fungal disease BII. Four prospective randomized clinical trials have been performed in pediatric haemato-oncologic populations.</p> | [82–85] |
| 5.2. | <p>Situation: Pre-emptive antifungal therapy Recommendation: Voriconazole; isavuconazole. Alternatives: Liposomal Amphotericin B or Amphotericin B lipidic complex Comments (Evidence): The preemptive strategy uses antigenic or molecular fungal markers (beta 1.3 glucan, galactomannan, or fungal PCR), surveillance of radiological changes (chest and sinus CT scans) and clinical data. This treatment strategy has already been shown to decrease the use of antifungals without impacting mortality related to fungal infection. The use of biomarkers has limitations in the case of prophylaxis for filamentous fungi, as it reduces the sensitivity of the test in this situation. False positive results may also occur in patients with intestinal GVHD and mucositis (adult All, CI children). Children: a diagnostic-driven treatment strategy can be recommended in children (A-II) if the diagnostic infrastructure allows timely access to CT imaging, GM testing and the ability to undertake bronchoscopies with bronchoalveolar lavage and appropriate microbiologic assessment.</p> | [69,86–93] |
| 5.3. | <p>Situation: Preemptive therapy for CMV Recommendation: Induction therapy with ganciclovir (GCV) or valganciclovir (VGV). Foscarnet can be used during neutropenia (AI). Comment (Evidence): Preemptive therapy should be introduced after CMV qPCR positive or AG positivity (≥ 1 positive / 300,000 cells). The cut-off of the viral load for the introduction of GCV must be defined locally according to the standardized kit and may vary according to the patient's risk. High risk = cord, haplo, T cell depletion, and HLA mismatch (lower cut-off). Low risk = remaining HSCTs or using letermovir (highest cut-off). If viremia is on the rise after two weeks, consider increasing the dose of GCV (CIII). The duration of preemptive therapy is ≥14 days and maybe suspended after that period with a negative qPCR result. G-CSF can be used in case of hematopoietic toxicity by GCV. During preemptive therapy, suspend prophylactic ACV. Oral valganciclovir should not be used in patients with severe GI GVHD (All)</p> | [94] |

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| 5.4. | <p>Situation: Pre-emptive therapy for EBV. Recommendation: Weaning/withdrawal of immunosuppression (All). In selected cases, consider weekly rituximab, from 1-4 doses, until negative EBV qPCR (All). Comment (Evidence): Post-transplant PTD risk groups are severe acute GVHD (refractory to corticosteroids), severe chronic GVHD, high or rising EBV viral load, and use of mesenchymal cells. To date, there are no studies that indicate a viral load cut-off to start preemptive therapy. Consider the dynamics of EBV viral load. If the viral load is high or increases, withdraw SI is desirable. If symptoms, or persistence of high CV, start therapy with rituximab (CIII).</p> | [60,95] |
| 5.5. | <p>Situation: Pre-emptive therapy for HHV-6. Recommendation: Consider therapy with GCV or FCV just in few conditions. Comments (Evidence): Pre-emptive therapy with GCV for 21 days in risk groups with HHV-6 positive DNAemia AND compatible neurological condition, excluding other causes, OR DNAemia with delayed engrafting/myelosuppression with no other explanation (CIII).</p> | [96] |
| 5.6. | <p>Situation: Pre-emptive therapy for ADV. Recommendation: Reduce immunosuppression (All) and cidofovir therapy (BII). Comment (Evidence): Patients with disseminated disease could receive therapy with cidofovir 3–5 mg/kg/week for 2–3 weeks; after that, every two weeks. Alternative scheme is cidofovir 1 mg / kg 3 times / week (BII). Hyperhydration and the use of probenecid can reduce nephrotoxicity.</p> | [61] |

| 6. Antimicrobial therapy for documented infections | | References |
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| 6.1. | <p>Situation: Bacterial infections. Conduct: Clinical and laboratory diagnosis of the disease; specific treatment. Comment (Evidence): The choice of therapy should be guided by syndrome and isolated agent (including susceptibility test). There is no indication of expanding the antimicrobial spectrum beyond what is necessary to treat documented infectious syndrome in non-neutropenic situations.</p> | [97] |
| 6.2. | <p>Situation: Candidemia or Acute Invasive Candidiasis Recommendation: Caspofungin; micafungin; anidulafungin. Alternatives: Liposomal Amphotericin B; Amphotericin B lipidic complex or voriconazole. Comments (Evidence): Therapy should be continued for 14 days after the first negative blood culture in the absence of other metastatic foci. Ocular fundoscopy and echocardiography are recommended for all patients. Central venous catheter (CVC) should be removed as early as possible when it is the source of infection. Specie confirmation is necessary to adequate therapy.</p> | [98,99] |
| 6.3. | <p>Situation: Invasive aspergillosis Recommendation: Voriconazole (AI); isavuconazole (AI); Liposomal Amphotericin B (BII); Amphotericin B lipidid complex (CIII). Children other than neonates: Voriconazole is recommended as the first line agent to treat IA in all children except neonates (All). L-Ampho B –(BII) Caspofungin (CII). Neonates: Liposomal Amphotericin B is the first choice in neonates (AIII). Comments (Evidence): Attention to drug interactions, renal impairment. Treatments with voriconazole should be monitored by serum voriconazole level. Treatment duration depends on clinical response and immune reconstitution or recovery from GvHD. Regions where the resistance rate is > 10% give preference to amphotericin or the combination of voriconazole and caspofungin.</p> | [46,62,100–104] |

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| 6.4. | <p>Situation: Mucormycosis. Recommendation: Liposomal Amphotericin B (All); Amphotericin B lipidic complex (no CNS involvement) (BIII); Isavuconazole (BII) Posaconazole oral suspension (CII) – not indicated as first therapy, only for post induction maintenance/secondary prophylaxis. Comments (Evidence): Local debridement of all necrotic tissue is strongly recommended. Posaconazole tablets or intravenous are not yet available in Brazil. Posaconazole is not allowed for children under than 13 years old.</p> | [105,106] |
| 6.5. | <p>Situation: Fusariosis Recommendation: Voriconazole (All); Liposomal Amphotericin B (BII); Amphotericin B Lipid Complex (CIII); isavuconazole (no data). Comments (Evidence): Combination therapy can be considered in persistently neutropenic patients with therapeutic failure. Surgical debridement of localized lesion should be considered. Monitoring serum levels of voriconazole. Few pediatric studies, most studies of invasive fusariosis in pediatric immunosuppressed patients used combination therapy based on azole.</p> | [107–111] |
| 6.6. | <p>Situation: CMV disease Recommendation: Intravenous Ganciclovir (All); foscarnet (if GCV resistance or toxicity) (AIII). Alternatives are cidofovir (2nd line) (BII) or foscarnet + GCV in full doses (3rd line) (CII). Comment (Evidence): The addition of intravenous immunoglobulin (IVIg) can be considered for the treatment of CMV pneumonia (CIII). For other manifestations of CMV disease, the addition of IgIV (IBD) is not recommended. Intravitreal injections of GCV or foscarnet can be used to treat CMV retinitis combined with systemic therapy (BII). Valganciclovir can be used in place of GCV IV or foscarnet, except in patients with severe gastrointestinal GVHD (BII). Doses need to be adjusted to the patient's renal function (All).</p> | [94] |
| 6.7. | <p>Situation: Disease due to EBV and PTLD. Recommendation: Reduce SI and rituximab weekly for up to 4 weeks (All). An alternative is the transfer of adaptive immunity by infusion of donor lymphocytes (DLI) if specific EBV (CII). Comment (Evidence): In cases of disease (hepatitis, pneumonitis, or CNS disease) due to suspected or confirmed EBV or PTLD (with biopsy), therapy should be started as soon as possible (All). Factors of good prognosis are age <30 years, benign disease, absence of acute GVHD, reduced ISS at diagnosis, and drop in viremia after initial therapy.</p> | [60,95,112,113] |
| 6.8. | <p>Situation: Influenza A or B. Recommendation: Oseltamivir. Comment (Evidence): The introduction of oseltamivir is recommended in all individuals with suspected or documented influenza infection (All). Oseltamivir may be withdrawn if diagnostic tests rule out influenza.</p> | [114] |
| 6.9. | <p>Situation: Respiratory syncytial virus (RSV) Recommendation: Supportive therapy consider the use of ribavirin at high risk (BIII). Consider IVIG as an adjuvant (BIII). Comment (Evidence): Consider immunodeficiency score for low risk (score 0-2), medium risk (3-6) and high risk (7-12). The following factors are considered in the score: neutropenia <500; lymphopenia <200; age > 40; GVHD using steroids; myeloablative conditioning and HSCT for <1 year (BII). High risk of complications comprises a patient with RSV or RSV pneumonia detected before grafting, lymphopenia <0.3 x 10⁹ / L (most important), GVHD using IS, or neutrophils <0.5 x 10⁹ / L.</p> | [115,116] |

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| 6.10. | <p>Situation: Parainfluenza, adenovirus, metapneumovirus, rhinovirus, coronavirus. Recommendation: If documented before HSCT, postpone conditioning (BII). Supportive therapy considers the use of IVIG if hypogammaglobulinemia (<400 mg / dL). Comment (Evidence): If recurrent or severe respiratory infections with IgG hypogammaglobulinemia <400mg / dL, IVIG replacement may be performed. Perform IgG dosage monthly.</p> | [46] |
| 6.11. | <p>Situation: BK virus hemorrhagic cystitis (BKV). Recommendation: Supportive treatment. Antiviral treatment is controversial. Comment (Evidence): There is no effective antiviral for BKV hemorrhagic cystitis. Treatment is based on supportive therapy (hyperhydration, bladder irrigation, platelet transfusions to reduce bleeding, and pain management). Treatment with cidofovir IV is controversial (absence of randomized controlled studies), but it may be an option although there is uncertainty regarding efficacy, doses, and risk-benefit in the face of renal side effects. Intravesical cidofovir can be used in severe cases with evaluation by an ID physician.</p> | [54,55] |
| 6.13. | <p>Situation: Tuberculosis Conduct: RHZE for 2 months + RH 4 months. In HSCT recipients, therapy may be prolonged according to clinical response. Comment (Evidence): The most common form is pulmonary, with symptoms similar to the immunocompetent host (fever, weight loss and persistent cough). Clinical suspicion can be masked in patients with lung GVHD (investigate TB always). Acid fast bacilli (AFB) shows low sensitivity (60%), and culture is the gold standard for TB diagnosis (but may take 30 days). Currently, PCR is most recommended yielding fast results and allowing prompt introduction of treatment. There are molecular tests that already detect resistance to rifampicin (AII).</p> | [117,118] |
| 6.14. | <p>Situation: Pneumocystosis. Conduct: Sulfamethoxazole-trimethoprim. Comment (Evidence): The consensus recommends diagnostic confirmation by specific tests. Full dose therapy should be administered for at least 14 days. Secondary prophylaxis should be maintained for the duration of IS (AII). Corticosteroid use may be necessary in cases of hypoxemia. Alternatives are pentamidine (BII), primaquine + clindamycin or atovaquone (CIII).</p> | [119] |
| 6.15. | <p>Situation: Toxoplasmosis Conduct: Sulfadiazine + pyrimethamine for 4 to 6 weeks (AII). Add leucovorin due to hematological toxicity of pyrimethamine. Comment (Evidence): Non-specific presentation. Investigate neurological and ocular conditions. Other presentations are fever with no apparent cause and interstitial pneumonia. Diagnosis by PCR for T. gondii or immunohistochemistry in biopsy or BAL. C-reactive protein or procalcitonin have no role in the diagnosis.</p> | [26,27] |

| 7. POST-TRANSPLANT REVACCINATION PROGRAM | | | | | | References (120–123) |
|--|---------|-------|----------------|---|-----------------|----------------------|
| Inactivated vaccines | | | | | | |
| Vaccine | Start | Doses | Interval | Chronic GVHD | Children | Autologous |
| PCV13 | 3-4 mo | 3 | 1 mo | 4th dose | Idem | Idem |
| PPV23 | 12 mo | 1 | >8 w after PCV | Idem | - | - |
| Hib | 3-4 mo | 3 | 1 mo | Idem | Idem | Idem |
| DTP-Hib | 6 mo | 3 | 1 mo | Idem | Idem | Idem |
| MCV | 6 mo | 2 | 1 mo | Idem | Idem | Idem |
| DTaP | 6 mo | 3 | 1-2 mo | Idem | Idem | Idem |
| IPV | 6 mo | 3 | 1-2 mo | Idem | Idem | Idem |
| INF | 6 mo | 1 | Annually | 2 doses | 2 doses (<9 yr) | Idem |
| HBV | 6 mo | 3 | 0-1-6 mo | Idem | Idem | Idem |
| HAV | 6-12 mo | 2 | 6 mo | Idem | Idem | Idem |
| HPV | 6-12 mo | 3 | 0-2-8 mo | Idem | Idem | Idem |
| HZV rec | d50-d70 | 2 | 1-2 meses | Recombinant vaccine. Only autologous HSCT | | |

| ATTENUATED VACCINES | | | | | | |
|---------------------|------------------------------------|-------|----------|-----------------|-----------|------------|
| Vaccine | Start | Doses | Interval | Chronic GVHD | Children | Autologous |
| LAVV | 24 mo | 1 | 1m | Contraindicated | 2 doses | Idem |
| LAZV | Contraindicated in HSCT recipients | | | | | |
| MMR | 24 mo | 1 | 1m | Contraindicated | 2 | Idem |
| YFV | 24 mo | 1 | - | Contraindicated | > 9 meses | Idem |

| OTHER SPECIFIC COMMENTS | |
|-------------------------|--|
| PCV13 | At Reference Centers for Special Immunobiological Agents (CRIEs) and at Basic Health Units (UBS), children under 5 yr may receive PCV10. In private clinics, PCV13 is preferred. In patients with chronic GVHD, a 4th dose of PCV13 may be administered 6 months after the 3rd dose. In general, children respond better to PCV13, but have more fever and local reactions than adults (AI). |
| PPV23 | Those who have already received PPV23, can take 1 dose of PCV13 after ≥ 6 months. If gammaglobulinemia $<3g/L$, severe GVHD, or rituximab for less than 6m, maintain with prophylactic antibiotics + IgIV and wait to perform PPV23 (BI). |
| Hib | Cord blood and non-myeloablative transplantation have the same response rate (BII). Chronic GVHD does not interfere in the response (AII). |
| DTaP | The adult formulation (dTaP) is poorly immunogenic. Use DTaP for adults and children (BII). |
| INF | Annually, for life, or at least up to 6 m after the end of IS. Children <9 years at the first vaccination or those with chronic GVHD should receive 2 doses (one month apart) (AII). |
| HAV | Serology (IgG) is recommended to evaluate specific antibodies and the need of vaccination. More than 90% of HSCT recipients maintain antibodies for up to 5 years. The response to HAV vaccine in HSCT recipients is poor ($\sim 30\%$) (CII). |
| HBV | R-/D-: vaccinate after 6-12 months of HSCT. R-/D antiHBc +: vaccinate before HSCT (0-10-21) and give HBIG (BII). R antiHBc +: vaccinate after 6 months of HSCT. If anti-HBs +, monitor monthly and vaccinate if anti-HBs $<10mIU / mL$ (BIII). In children, attention to the pediatric dose of the vaccine. Age and chronic GVHD decrease the response to HBV vaccine. |
| HZV rec | So far, only approved for autologous HSCT (AI). |
| Attenuated vaccines | Only after 24m of HSCT and in patients without IS and without chronic GVHD. |
| LAVV | More than 90% of HSCT recipients have had zoster after the 2nd year of HSCT. Therefore, chickenpox vaccine would benefit only a few patients (DII). The attenuated varicella vaccine may be indicated in children (2 doses) and in VZV seronegative adults (1 dose). |
| MMR | In case of measles outbreak, MMR can be anticipated to the 12th month of HSCT and in patients with mild IS (BII). |
| YFV | To date, there are no reports of serious adverse events in HSCT recipients vaccinated against YF. Consider vaccination before transplantation, since 30% of vaccinees maintain antibodies after HSCT (BIII). |

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