Infectious diseases in allogeneic haematopoietic stem cell transplantation: prevention and prophylaxis strategy guidelines 2016

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Abstract
Infectious complications after allogeneic haematopoietic stem cell transplantation (allo-HCT) remain a clinical challenge. This is a guideline provided by the AGIHO (Infectious Diseases Working Group) of the DGHO (German Society for Hematology and Medical Oncology). A core group of experts prepared a preliminary guideline, which was discussed, reviewed, and approved by the entire working group. The guideline provides clinical recommendations for the preventive management including prophylactic treatment of viral, bacterial, parasitic, and fungal diseases. The guideline focuses on antimicrobial agents but includes recommendations on the use of vaccinations. This is the updated version of the AGHIO guideline in the field of allogeneic haematopoietic stem cell transplantation utilizing methods according to evidence-based medicine criteria.

Keywords
Infections · Viral · Fungal · Bacteria

Introduction
Infectious complications remain a clinical challenge in the setting of allogeneic haematopoietic stem cell transplantation (allo-HCT). Particular during the early phase after allo-HCT,
mortality rates for infections are high [1, 2]. After the first publication of recommendations from our group in 2003, [3] numerous new results of trials have been published and implemented into daily patient care. With this updated guideline, AGIHO (Infectious Diseases Working Group) of the DGHO (German Society for Hematology and Medical Oncology) pursues a step forward to include the entire patient history up right from the beginning of the preparation of patients through the entire post allo-HCT time period.

This guideline focuses on the adult patient population only and is partitioned into four parts: (a) general precautions and prevention measures, (b) pre-transplantation (screening) phase, (c) prophylactic treatment, and (d) immunization strategies.

Methods

Several steps were undertaken to develop the updated guideline: The first step was defining a group of specialists. They were enlisted by the AGIHO of the DGHO with a designated coordinator. The coordinator was responsible to manage the efforts of the group. The group of authors consisted of 14 certified internists, including 13 certified haematologists, and 5 certified infectious diseases specialists. Four authors are triple certified in internal medicine, infectious diseases, and haematology/oncology.

Predefined topics were elaborated by subgroups and then presented to the entire group for discussions. This included several face-to-face meetings, which were complemented by conference calls. Once the group had consensus with their results, the preliminary recommendations of the group were presented to the entire AGIHO assembly for review, discussions, modification, and final approval. All recommendations were made on the basis of available data providing evidence-based medicine. The guideline utilized the latest version of the strength of recommendation and quality of evidence published by the ESCMID (Table 1) [4]. Specific topics related to cord blood or haplo-identical transplant recipients are not addressed by this guideline.

General precautions

An allo-HCT requires certain assessment procedures, which are basically standardized (e.g. JACIE by the EBMT). Herein, we touch off on a few basic standardized requirements.

Patients’ rooms should be equipped with air-filtered systems to keep spore counts low and, thus, preventing nosocomial fungal diseases (BII) [5–9]. Further, nearby construction activities should be kept to a minimum (AII) [10]. Isolation of the stem cell recipients in a single hospital room under conditions of laminar airflow or positive pressure HEPA filtration (>12 exchanges per hour) is generally recommended. However, randomized controlled trials focusing on HEPA filter efficacy against viral infections are lacking. Especially respiratory virus outbreaks, including seasonal pathogens such as respiratory syncytial virus (RSV) and influenza, are not prevented by HEPA filtrations [11]. Genotyping of RSV outbreaks demonstrated that more than two thirds were hospital acquired [12–15]. These results underscored the important necessity of infection control measures (i.e. barrier precautions) to prevent exposure directly at the patients’ site (AII).

Some debate usually arises on the topic of appropriate dietary needs for patients after allo-HCT. The rule of thumb “cook it, peel it, or forget it” is easy to understand. However, there is a lack of appropriate literature on this specific topic. On the other hand, the evidence is clearer for the prevention of specific infections, e.g. listeria or other agents

| Strength of a recommendation | AGIHO strongly supports a recommendation for use |
|------------------------------|------------------------------------------------|
| Grade A                      | AGIHO moderately supports a recommendation for use |
| Grade B                      | AGIHO marginally supports a recommendation for use |
| Grade C                      | AGIHO supports a recommendation against use |
| Grade D                      | Evidence from at least 1 properly designed randomized, controlled trial |
| Quality of evidence          | Evidence from at least 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments |
| Level I                      | Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies |
| Level II                     | Evidence from at least 1 properly designed randomized, controlled trial |
| Level III                    | Evidence from at least 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments |

* Added index: | meta-analysis (or systematic review of RCT); | transferred evidence i.e., results from different patients ‘cohorts’ or similar immune status situation; | comparator group: historical control; | uncontrolled trials; | published abstract (presented at an international symposium or meeting)
causing infectious diarrhea (BII) [16, 17]. Contact precautions and hand disinfection (incl. repeated teaching on this matter) can prevent nosocomial infection (AII) [18]. Healthcare workers (HCW) with transmissible diseases (e.g. herpes, infectious gastroenteritis, respiratory tract infections) should be restrained from direct patient care to prevent any nosocomial spread of their disease (AIII) [19]. Some hospital facilities have recovered microbes (e.g. Legionella spp.) from their drinking water. In order to prevent transmission in high-risk patients, water filters provide a protective solution though regular testing remains a necessity (AII) [20–22].

**Pre-transplantation (screening) phase**

A comprehensive pre-transplant assessment of the allo-HCT recipient for infectious complications is a valuable tool to identify patients at increased risk for distinct infectious diseases.  
Syphilis, tuberculosis, *Toxoplasma gondii*, HIV, hepatitis B and C viruses, and *Herpes viridae* usually persist lifelong in the host after primary infection and can be reactivated under certain conditions. As a consequence, all candidates for allo-HCT should undergo a test for IgG antibodies specific for viral diseases, syphilis, and toxoplasmosis. False negative results particularly could occur in the context of CLL, multiple myeloma, previous antibody treatment (e.g. rituximab), or might be false positive after IVIG application or blood product transfusion. In any case, all patients tested IgG-seronegative strictly remain on preventive measures to avoid de novo infection prior to allo-HCT and afterwards.

**Specific viruses**

*Herpes viridae*

All candidates for allo-HCT should be tested for CMV, EBV, and VZV IgG antibodies to determine their risk for reactivation or de novo infection (AIII) [23–25]. Due to the high prevalence of HSV in the patient population, further antibody testing for HSV is not mandatory (CII) [26].

*Hepatitis B*

Prior to allo-HCT, besides hepatitis B virus (HBV) antibody panels, additional testing for hepatitis B surface antigen (HBsAg) should be performed [27, 28]. If tested positive for HBsAg or for anti-HBc, further HBV-DNA assessment for active replication is crucial (AII). If considered to be diagnosed with active hepatitis (e.g. viral replication), initiation of antiviral treatment prior to allo-HCT should be considered (AIII) [29].

There is a reported risk of up to 50 % for reverse seroconversion after allo-HCT if a patient is anti-HBc positive but has no detectable viral replication (resolved HBV infection) [30–32]. HBV-vaccination after allo-HCT might alleviate this risk [33].

**Hepatitis C**

Serologic testing for hepatitis C virus (HCV) is recommended. Serologically positive patients should receive quantitative testing for HCV-RNA viral load (AIII). Patients with chronic hepatitis C should receive a further diagnostic assessment, e.g., fibroscan or a liver biopsy to rule out liver fibrosis or cirrhosis. In case of liver cirrhosis or fibrosis, the conditioning regimen should try to avoid TBI, oral busulfan, or cyclophosphamide to minimize risk of hepatic sinusoidal occlusion syndrome (SOS) (BIII) [34–37].

**Hepatitis E**

Hepatitis E virus (HEV) is detected in immunocompromised patients. Limited information is available on the real incidence of HEV infection in recipients of allo-HCT [38, 39]. Mostly self-limited reactivation cases are published though chronic forms have been described as well. Serologic testing for HEV prior to allo-HCT is recommended (BIII). HEV should be considered as a differential diagnosis in patients after allo-HCT with elevated liver function tests [39–41].

**HIV**

HIV testing prior to allo-HCT is recommended. HIV-infected patients should be carefully evaluated for allo-HCT. Though HIV seropositivity per se is not a contraindication for allo-HCT [42]. If allo-HCT seems feasible, a donor screening for CCR5-Delta 32 deletion could be considered in patients with CCR5 tropism to potentially control HIV infection post-allo-HCT (BIII) [43, 44]. Toxicity permitting, antiretroviral therapy should be continued throughout the post-transplantation phase (AII) [45]. However, recurring interruptions with low drug levels may induce viral resistance, and an interrupted treatment should not be reinstated until the patient has sufficiently recovered to allow stable tablet intake (BIII).

*Syphilis*

Serologic testing for syphilis is recommended. Frequently TPHA/TPPA or VDRL are utilized. Important are the combinations of nontreponemal (e.g VDRL) and treponemal tests. If a nontreponemal test is positive, confirmation of infection with treponemal test (e.g. TPPA or TP-EIA) should be performed. In case of an active infection or unclear whether the
patient received an adequate treatment in the past, a treatment with penicillin should be instituted (BII) [46].

Toxoplasmosis

All candidates for allo-HCT should undergo serologic testing for toxoplasmosis. If the serology testing for toxoplasmosis IgG is positive, patients have a risk of toxoplasmosis reactivation, especially if the donor is serologically negative for toxoplasmosis [47]. Some centres propagate regular PCR testing [48]. Since the incidence in Europe is very low, regular toxoplasmosis DNA through PCR screening is not recommended (DIII). This is of course different in patients with clinical symptoms.

Tuberculosis

Thorough evaluation of the medical history can identify patients at risk for latent or active tuberculosis infection (AIII). As most candidates have received chemotherapy or immuno-suppressive treatment prior to evaluation for allo-HCT, a tuberculin skin test might be false negative and therefore cannot be recommended in this setting (DIII). If the medical history is suggestive of prior tuberculosis exposure, an interferon-gamma-release assay (IGRA) can be considered (BII) [49]. However, a reduced sensitivity in immunocompromised patients has been demonstrated as well [50, 51].

Prophylaxis and prevention

Prevention of bacterial infections (screening for bacterial colonization)

In this era of easy accessibility of antibiotics, clinicians are facing the growing challenge of multi-resistant bacteria (e.g. vancomycin-resistant Enterococci (VRE), methicillin-resistant Staphylococcus aureus (MRSA), extended-spectrum beta-lactamase producing bacteria (ESBL), metallo-β-lactamase-producing bacteria (MBL)). Colonization with certain multi-resistant bacteria is predictive for developing bloodstream infection, and knowledge of colonization status may therefore guide empirical antibiotic treatment, although this strategy has not been demonstrated to improve outcomes [52, 53]. We recommend screening procedures for multi-resistant bacteria, especially in institutions with a known high prevalence (BII) [54, 55]. Since the sensitivity of the screening methods is low, repeated testing (e.g. weekly rectal swabs) would be required [56–58]. Contact precautions between medical staff and patients remain to be necessary and separate sanitary facilities need to be guaranteed to exclude cross-patient transfer of multi-resistant bacteria [59, 60].

Antibiotic prophylaxis (e.g. ciprofloxacin) demonstrated its efficacy by reducing the incidence of Gram-negative sepsis during neutropenia without any significant change in mortality [61, 62]. All-cause mortality was reduced only in meta-analysis [63]. At institutions with a low rate of multi-resistant gram-negative bacteria, antibacterial prophylaxis remains a reasonable choice to reduce the incidence of Gram-negative sepsis during neutropenia (AIIc) [62, 64–67]. Encapsulated bacteria such as Streptococcus pneumoniae or Haemophilus influenzae often cause severe bacterial infections in the late phase after transplantation [68–70]. In patients with chronic GVHD (graft-versus-host disease) on immunosuppressive therapy, antibiotic prophylaxis against these bacteria for disease prevention might be useful until immunizations can be applied (BII). Antibiotic selection should be guided by local antibiotic resistance patterns. In patients without chronic GVHD, systemic antibiotic prophylaxis is not recommended after reconstitution of the neutrophils (DIII).

The value of selective gut decontamination is frequently debated and the literature points out that sepsis rates are increased and mortality outcomes were significantly worse in patients with lower intestinal diversity; therefore, no recommendation was made [71–74].

Prophylaxis against Pneumocystis pneumonia

Pneumocystis jirovecii (previously named Pneumocystis carinii) pneumonia has been noted in allo-HCT recipients with an incidence of approximately 5–16 % without adequate prophylaxis and occurred at a median of 9 weeks after allo-HCT. Despite intensive treatment, mortality rates are as high as 89 % during the first 6 months and approximately 40 % after the first 6 months following allo-HCT [75, 76].

Prophylaxis against Pneumocystis jirovecii pneumonia is recommended for at least first 6 months after allo-HCT to prevent Pneumocystis jirovecii pneumonia-associated death (AIIc). However, patients might require prophylaxis for prolonged periods of time. Recommended prophylactic regimens are similar to regimens in HIV/AIDS patients. Therefore, patients on immunosuppressive medications or active GVHD should remain on prophylaxis [77]. Once immunosuppressive medications are discontinued or no active GVHD is noted, prophylaxis may be discontinued assuming a CD4+/CD3+ lymphocyte count of 200/μL or higher (BII). Thus monitoring of CD4+/CD3+ lymphocytes could be continued until the threshold is confirmed by repeated testing (BII) [78]. The CD4+/CD3+ lymphocyte count of 200/μL as a discontinuation criterion is not confirmed in the allogeneic setting, and therefore, an individual decision to discontinue can be considered (CIII).

The prophylactic treatment of choice is the fixed combination of trimethoprim (80 mg) and sulfamethoxazole (400 mg) once daily thrice weekly (AII) [79–82]. In case of intolerance
to the trimethoprim/sulfamethoxazole therapy, aerosolized pentamidine (300 mg) every 4 weeks (BII) or atovaquone (750 or 1500 mg daily) (BII) is recommended [83–89]. Dapsone (100 mg) cannot be recommended (DIIt) [90]. Protective efficacy against Pneumocystis appears to be less with these alternative drugs compared to trimethoprim/sulfamethoxazole [84, 86, 90–93].

**Antifungal prophylaxis in allo-HCT**

Invasive fungal diseases (IFDs) are severe complications associated with prolonged hospital length of stay, costs, long-term treatment, and high mortality [94]. Approximately two thirds of the IFD develop in allo-HCT patients after leukocyte recovery [95, 96]. Furthermore, intensifying immunosuppression for treatment of transplant rejection or GvHD and CMV infection impose an imminent risk for IFD [97, 98].

The incidence of invasive aspergillosis (IA) varies between reports and may reach 23 % [94, 99]. Primary prophylaxis is highly recommended since diagnostic tools do not present with sufficient sensitivity numbers. This is mirrored in studies with a significant number of post-mortem diagnoses of fungal diseases [100–102]. In patients diagnosed with IA, mortality rates of up to 60 % have been reported despite adequate treatment [103]. Secondary prophylaxis is recommended prior to allo-HCT (BII) [104].

Invasive candidiasis, predominantly manifesting as candidemia, is the second most frequent IFD in allo-HCT patients. Invasive candidiasis/candidemia typically manifests in patients with underlying conditions after being exposed to additional risk factors, e.g. intravascular devices, broad-spectrum antibiotic treatment, total parenteral nutrition, or Candida colonization [105–107].

The currently largest cohort of IFDs shows an 8 % share of mucormycosis in all IFDs in allo-HCT, followed by a number of other rare mould infections [94]. Approximately half of the patients diagnosed with mucormycosis are patients after allo-HCT [108]. The share of rare IFDs like those caused by the order of Mucorales or Fusarium spp. appear to be increasing [94, 109]. Newer agents like isavuconazole demonstrated favorable response rates in primary treatment against moulds; however, larger prophylaxis studies are still needed [110–112].

In Table 2, prophylactic recommendations are summarized. Our group recently published recommendations for the treatment (i.e. targeted therapy) of fungal diseases [113].

**Herpes simplex virus 1/2 prevention**

*Herpes viridae* persist in the host after primary infection. Up to 80 % of adults are HSV-seropositive and especially during immunosuppression HSV may begin to replicate. Without prophylaxis allo-HCT recipients have a risk of approximately 80 % to reactivate during the early phase mainly during the first 4 weeks after allo-HCT [19, 137, 138]. Dissemination may lead to severe illness with substantial morbidity and mortality. As a consequence, patients should receive acyclovir early on for the prevention of disease to reduce mortality (A) [138–141] (Table 3).

The duration of prophylaxis should last for up to 30 days after allo-HCT (AI) [139, 141]. However, exceptions are defined by recurrent episodes of HSV disease or risk of *Varicella zoster* disease. In these situations, duration of acyclovir prophylaxis to prevent disease is prolonged to a year or longer especially during intensified immunosuppressive therapy (BII) [142].

Resistance to acyclovir is a rare event and mainly caused by reduced activity or mutations of viral thymidine kinase resulting in reduced activation of acyclovir in infected cells [143, 144]. Breakthrough infections are noted but are usually described as clinically resistant since prophylaxis failure is explainable by decreased bioavailability of acyclovir. In cases of real acyclovir-resistant HSV, foscarnet susceptibility remains, and this agent is considered as an alternative treatment option for acyclovir-resistant disease (BII). However, it cannot be recommended for routine prophylaxis due to its significant toxicity (DII) [145].

It is presumed that valacyclovir and famciclovir are effective for the prevention of HSV reactivation; however, there are no clinical trials in allo-HCT to better support a recommendation (CIII) [146, 147].

**Varicella zoster virus prevention**

Since *Varicella zoster* virus (VZV) is highly contagious, patients with VZV disease should be isolated to prevent nosocomial spreading of viruses until all lesions are crusted (AIII) [148, 149]. Patients should be informed of the easy transmission of VZV. Allo-HCT recipients without adequate antiviral prophylaxis are at risk for disease, since up to two thirds develop herpes zoster, which mainly occurs 3 to 12 months after allo-HCT [150]. VZV seronegative family members, healthcare workers, other contact persons of allo-HCT recipients, or children without a history of *Varicella* or immunization, should be advised to receive a vaccination against VZV ideally at least 4 weeks prior to planned allo-HCT (BII) [151].

Primary infection is rare and is associated with a high rate of mortality caused by frequent dissemination (e.g. encephalitis, pneumonia, visceral, or hepatitis) [150, 152, 153]. Therefore, exposure of seronegative recipients to chickenpox, zoster or vaccinated persons who experience a rash after vaccination should be avoided to prevent primary disease or VZV-associated death (BIII). If exposure to persons with chickenpox or zoster...
occurs, passive immunization with anti-VZV hyperimmunoglobulin (Ig) within 96 h after exposure is considered optional (CIII), as efficacy has not been proven [154, 155]. Antiviral therapy with valacyclovir 1 g po tid or acyclovir 800 mg qid should be administered (BIII) immediately to prevent disease in seronegative recipients. Main antiviral prophylaxis recommendations are summarized in Table 3. Various authors [156–159] noted that even prolonged administration for approximately 1 year or longer is considered safe and there was no higher incidence of disease after drug discontinuation. Longer than 12-month periods appears to be beneficial as long as patients remain on intensified immunosuppressive therapy (BIII).

If resistance to acyclovir is suspected, foscarnet or cidofovir are alternative agents (BIII) [160]. Brivudine is contraindicated in patients receiving 5-fluoropyrimidine derivatives and was not assessed in immunocompromised patients (DIII). (http://www.bfarm.de/SharedDocs/Risikoinformationen/Pharmakovigilanz/EN/RHB/2012/rhb-zostex.html, last accessed May 1, 2016)

### CMV disease prevention

All CMV-seronegative recipients ideally should receive a CMV-seronegative donor graft to prevent infection and reduce mortality (AII) [25, 161, 162]. To further prevent disease, CMV-seronegative recipients transplanted from a negative donor should only receive blood products from CMV-negative donors upon availability. Blood banks without a sufficient pool of CMV-negative donors should deliver only leukocyte-depleted red blood cells and thrombocytes (AII) [163]. However, data from various studies suggest if blood products are leukocytes reduced, testing for CMV-negative blood products is not needed for HSCT recipients (AII) [163–165]. Noteworthy, irradiation to prevent transfusion-associated GvHD does not inactivate CMV [164, 166–170]. Special risk factors for CMV infection or disease are T cell-depleted graft, HLA-mismatched transplantation, steroid treatment, and acute or chronic GvHD [171–173]. All patients at risk for CMV disease should be screened regularly for pp65 antigenemia or by nucleic acid detection methods after allo-HCT (AII) [174].

Table 2  Antifungal prophylaxis

| Intention                                    | Intervention                        | SoR | QoE | Comments                                                                 | Ref          |
|----------------------------------------------|-------------------------------------|-----|-----|--------------------------------------------------------------------------|--------------|
| Prevent mould infection in patients without GvHD, day 1–100 | Voriconazole 200 mg bid oral or iv<sup>b</sup> | C   | I   | No difference seen in the trial in comparison to fluconazole           | [114]        |
|                                              | Posaconazole (suspension) 200 mg tid<sup>b</sup> | B   | II,| Improved overall survival in AML/MDS induction during neutropenia, new formulations (tablet and iv, 300 mg qid) provide a better bioavailability | [115–117]   |
|                                              | Micafungin 50 mg/day                | C   | I   | Only during neutropenia, morbidity advantage                             | [118]        |
|                                              | Itraconazole suspension 2.5–7.5 mg/kg or capsules | C   | I   | Administered up to 180 days if GVHD was diagnosed; higher toxicity in comparison to fluconazole, TDM: cutoff at 500 mg/mL (AII) | [119–121]   |
| Prevent invasive Candida disease in patients without GvHD, day 1–100 | Fluconazole 400 mg/day              | A   | I   | Improved survival, note rising incidence of resistant Candida species since studies were published | [122–124]   |
|                                              | Voriconazole 200 mg bid oral or iv<sup>b</sup> | B   | II,| Also active against moulds, but no difference seen in the trial between voriconazole and fluconazole | [114]        |
|                                              | Posaconazole (suspension) 200 mg tid<sup>b</sup> | B   | II,| Also effective against moulds, new formulations (tablet and iv, 300 mg qd) provide a better bioavailability | [115, 117]  |
|                                              | Micafungin 50 mg/day                | B   | II,| Also effective against moulds, only during neutropenia, morbidity advantage | [118]        |
|                                              | Itraconazole suspension 2.5–7.5 mg/kg or capsules<sup>b</sup> | C   | I   | See above                                                                 | [119–121]   |
| Prevent invasive Aspergillosis during GvHD   | Posaconazole (suspension) 200 mg tid<sup>b</sup> | A   | I   | Improved survival (lower attributable mortality), new formulations (tablet and iv, 300 mg qd) provide a better bioavailability | [117, 125]  |
| Prevent fungal disease relapse (previous IFD)| Voriconazole<sup>b</sup>            | B   | II  | considered as secondary antifungal prophylaxis, dosages as above        | [126]        |
| Prevent fungal diseases<sup>a</sup>          | Amphotericin B deoxycholate         | D   | II  | Inacceptable toxicity                                                   | [129–131]   |

<sup>a</sup>other formulations and various dosages and application regimens of Amphotericin B have been evaluated with different results in small studies, all would need further evaluation to provide any kind of recommendation [132–134]

<sup>b</sup>Consider TDM, serum levels of efficacy in prophylaxis are still debated, e.g. posaconazole [135]
The current standard to improve morbidity and lower mortality is the early initiation of a preemptive therapy against CMV (AII) [174]. Duration of screening is usually defined by the time period of the application of immunosuppressive agents or GVHD.

Anti-CMV prophylaxis can only be considered as an option. The long-term administration of ganciclovir resulted in a delay of recovery from CMV-specific T cell immunity [175]. Valganciclovir is so far not officially approved in allo-HCT patients but has been applied in randomized trials [176, 177]. In a randomized controlled trial, valganciclovir prophylaxis was not superior in reducing the incidence of CMV disease or death when compared with PCR-guided preemptive therapy. Delay in virus-specific T cell reconstitution was not observed in patients receiving prophylaxis [177]. Administration of human immune

### Table 3: Antiviral prophylaxis

| Intention | Intervention | SoR | QoE | Comments | Ref |
|-----------|--------------|-----|-----|----------|-----|
| HSV | | | | | |
| Prevent HSV disease | Acyclovir 400 mg tid/day | A | II | Up to 30 days post allo-HCT (various dosages) | [139, 141, 233] |
| | Valacyclovir 500 mg bid /day | A | II | | [234] |
| | Acyclovir any dosage | D | III | Beyond 30 days if patient is also VZV seronegative | |
| VZV | VZV disease prevention in VZV seropositive recipients | Acyclovir 800 mg bid | A | I | Up to 1 year after allo-HCT | [156] |
| | | Acyclovir 400 mg/day | B | II | | [158, 159, 235] |
| | | Valacyclovir 500 mg bid | B | II | | [236, 237] |
| | | Acyclovir 200 mg/day | B | II | More than 365 days if continued on immunosuppressive therapy | [233, 238] |
| | Prevent VZV in seronegative patients | No prophylaxis | C | II | | |
| | Prevent VZV in seronegative patients if exposed | Passive immunization | C | II | Within 96 h post exposure, optional | [155] |
| | | Acyclovir or other VZV-active antiviral | C | III | If patient is not on acyclovir (or any other VZV active antiviral), a short duration of therapy is an option. | |
| CMV | | | | | |
| Preemptive strategy recommended over prophylaxis/treatment | Ganciclovir, valganciclovir, or foscarnet | A | I | | [177, 239–242] |
| Reduce incidence of CMV infection/disease, if a center does not follow a preemptive strategy | Long term acyclovir 800 mg/day | C | II | | [180] |
| | Valacyclovir 500 mg qid/day | B | I | | [182] |
| | Ganciclovir 2.5–5 mg/kg bid/day | C | II | Caution: myelotoxicity | [243, 244] |
| | Valganciclovir 900 mg bid | A | II | Caution: myelotoxicity | [177] |
| | CMV-specific CTLs | C | II | Not available at every site (considered experimental) | [245] |
| HBV | Prevent disease in HBsAG seropositive recipients | Lamivudine 100 mg/day | A | II | Monitor HBV DNA closely, duration until anti-HBs is detected (and HBV-DNA is negative) | [210, 246, 247] |
| | | Entecavir 0.5–1.0 mg/day | A | II | | [248–250] |
| | | Tenofovir 245 mg/day | C | III | | [251, 252] |
| | Prevent disease in HBsAG seropositive recipients with HBsAG seronegative donors | Additionally vaccinate donor | B | III | Requires long term planning | [253] |
| | Prevent reactivation in recipients who are anti-HBeAG seropositive, DNA viral load: positive | Lamivudine 100 mg/day | B | III | | [209] |
| | Prevent reactivation and disease in recipients who are anti-HBeAG seropositive, DNA viral load: negative | Lamivudine 100 mg/day | C | III | | [254] |
| | | HBV-DNA/HBsAG monitoring | B | III | | |
globulins for prophylaxis or therapy of CMV disease is generally not recommended (DII) [178, 179]. Some investigators published efficacy of high-dose acyclovir or its prodrug valacyclovir in the prevention of CMV disease [180–183]. However, acyclovir failed to prevent CMV disease in autologous transplantation and therefore, is not recommended for prophylaxis (DIII) [184].

Newer antiviral agents have been evaluated mainly in phase II trials. Maribavir, an oral antiviral agent was studied for prophylaxis. Maribavir inhibits the UL97 viral protein-kinase of human CMV. Despite promising results in a phase II study, a phase III study could not confirm a benefit [185–187]. Another antiviral agent named CMX001 is an orally bioavailable lipid acyclic nucleoside phosphonate and is converted intracellularly to cidofovir diphosphate. Brincidofovir (CMX001) is active in vitro against CMV, including ganciclovir-resistant strains and was assessed in a phase II trial with promising results in prophylaxis [188]. Letermovir (previously known as AIC246) is another anti-CMV agent with a novel mechanism of action targeting the viral terminase subunit pUL56, a component of the terminase complex. This agent demonstrated dose-dependent prophylactic efficacy in a phase II trial [189]. If the ongoing phase III trials confirm these results, a paradigm shift may occur in the future.

New DNA-based vaccination strategies against CMV are being evaluated in clinical trials [190].

Main antiviral recommendations are noted in Table 3.

**Epstein-Barr virus disease prevention**

Factors associated with an enhanced risk for Epstein-Barr virus (EBV) replication and therefore infection after allo-HCT are a selective T cell depletion of the graft, a HLA-mismatched transplantation, the choice of an unrelated donor (especially haploidentical transplant recipients), and the use of T cell depleting antibodies, e.g. alemtuzumab or ATG during conditioning [191, 192]. Early EBV-disease after transplantation is extremely rare. Primary or secondary prophylactic use of antiviral agents is not effective against EBV and therefore not recommended (DII) [193, 194]. Close EBV viral load monitoring and rituximab application can be considered as a preemptive therapeutic approach for the prevention of EBV-associated PTLD after allo-HCT in special high-risk patients (CIII) [195–197]. Still considered experimental is the application of cytotoxic T cells for the prevention and treatment of Epstein-Barr virus-induced lymphoma in allogeneic transplant recipients [198, 199].

**Toxoplasmosis prophylaxis**

Trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis, administered to most transplant patients to prevent *Pneumocystis jirovecii* pneumonia, is also efficacious in preventing toxoplasmosis disease [200, 201].

Clinical reactivation of toxoplasmosis may occur in the late phase after transplantation in seropositive patients under immunosuppression. However, the risk is considerably low and no primary prophylaxis is recommended (DIII) [47, 202, 203]. After a successful therapy of toxoplasmosis, secondary prophylaxis should be administered for at least 3 months (AI) [204–206] (Table 4).

**Hepatitis A prevention**

The incidence of infections due to hepatitis A varies widely. Prevention of hepatitis A by vaccination of seronegative patients or donors follows general vaccination recommendations. A previous exposure to hepatitis A has no impact on transplant-related complications, thus only serologic testing is recommended. In case of IgM seropositivity of the donor and/or recipient, allo-HCT might be postponed since a high risk of transmission or hepatic complications are associated with acute hepatitis A. Additional prevention of infection of the recipient can be achieved by avoiding potentially contaminated food. If exposed, passive immunization has been discussed controversially even in non-transplant patients.

Following patients’ post allo-HCT, a continuous loss of acquired hepatitis A antibodies has been described over a median time of 48 months, especially in those older than 18 years. Thus, hepatitis A vaccination should be recommended later in adult transplanted patients at risk (BII) [207].

**Hepatitis B prevention (Table 3)**

Hepatitis B infection or reactivation contributes to liver-related morbidity and mortality. This is a frequent problem, which occurs in 21–53 % of patients with immunosuppression [208].

**Table 4 Secondary prophylaxis after toxoplasmosis disease**

| Intention                          | Intervention                                   | SoR | QoE | Comments                                      | Ref    |
|-----------------------------------|-----------------------------------------------|-----|-----|-----------------------------------------------|--------|
| To prevent relapse of CNS toxoplasmosis | Pyrimethamine (25 mg/day) + sulfadiazine (orally, 30 mg/kg/d) | A   | II c| Minimum duration for 3 months, many cases longer | [204, 206] |
|                                   | Pyrimethamine (25 mg/d) + clindamycin (intravenously, 1200 mg/d) | B   | II c|                                               | [255–257] |
|                                   | Atovaquone 750 mg qid                          | B   | II c| In patients intolerant to conventional toxoplastic encephalitis therapies | [206] |

*Should be combined with folinic acid*
HCV-RNA should be considered (if time permitted) to receive antiviral treatment, if possible (AIII). All HBsAG-positive patients awaiting chemotherapy or immunosuppressive therapy should receive antiviral prophylaxis with a nucleoside analogue, regardless of HBV-DNA levels. In anti-HBe positive patients with no detectable viral replication (resolved HBV infection), there is a serious risk (up to 50%) of reverse seroconversion after allo-HCT [211]. These patients should be monitored for HBV replication on a regular basis and receive preemptive antiviral treatment with lamivudine (AII) or entecavir (AII) once HBV DNA levels are positive (more details: Table 3). It is recommended that antiviral treatment should be continued until at least 6 months after the cessation of immunosuppression (BIII) [29]. Prophylactic treatment of anti-HBe-positive patients without any viral load during the first months after allo-HCT is optional since no data are published in this patient population (CIII).

Hepatitis C prevention

Patients tested positive for HCV-RNA have a significantly higher risk of developing sinusoidal obstruction syndrome (SOS) [34]. Therefore, patients tested positive for HCV-RNA should be considered (if time permitted) to receive highly active antiviral treatment (BII) [212]. In allo-HCT, data is lacking; however, Mahale et al. reported that patients who have successfully eliminated HCV are not at risk of reactivation at least 6 months after conventional chemotherapy [212]. Detailed therapy recommendations cannot be provided since at this time many promising trials with new drugs are being published demonstrating eradication of HCV [213].

Allo-HCT from an HCV-RNA-positive donor should be avoided since the incidence of transmission remains high (DII). If timing permitted and no alternative donor options are available, the donor should be treated accordingly to prevent hepatic complications (AIII) [214].

Prevention of diseases caused by respiratory viruses

In recent years, an increasing number of reports on respiratory viral infections after allo-HCT are noted, which are in part attributable to improved diagnostic tools and better awareness. RSV followed by influenza, parainfluenza, metapneumovirus, and adenovirus are the main viruses causing severe diseases [215]. These viruses can contribute significantly to morbidity after allo-HCT; however, mortality rates seem to be mixed due to heterogeneity of various risk situations [216]. The main recommendation is to avoid infections with these viruses through adequate exposure prevention (AIII) [217, 218]. Visitors and staff with signs and symptoms of respiratory infections must avoid visiting the wards to prevent further disease (AIII). Additionally, annual influenza vaccination is strongly recommended for healthcare workers, all persons living with allo-HCT candidates or patients to prevent transmission (AIII) [219]. If vaccination was carried out during an influenza outbreak, a 2-week course of antiviral chemoprophylaxis could follow until immune response is effective (BIII) [19, 220].

There is no published data confirming clinical efficacy of prophylactic administration of respiratory syncytial virus (RSV) immune globulin (RSVIG); therefore, this approach is discouraged (DII) [221].

Intravenous immune globulin for prophylaxis

There is an ongoing controversy about the benefit, dosing, and optimum preparation (hyperimmune or polyclonal) of intravenous immune globulins (IVIG) in allo-HCT [222]. Older studies have demonstrated prevention of infection, interstitial pneumonia (IP), or GVHD [223, 224]. Large meta-analyses demonstrated no clinical benefit, except for a decrease of IP and an increase of sinusoidal obstruction syndrome (SOS) with high-dose IVIG [225, 226].

In a recent multicenter trial, 200 patients received different doses of IVIG or placebo weekly starting day –7 till day +100, but no differences were observed in regards to infections, interstitial pneumonia, treatment-related mortality, and overall survival. However, higher doses of immune globulin were again associated with deleterious SOS [227]. Therefore, the routine prophylactic substitution of immune globulin is not recommended if the IgG level is >4 g/L (DI) [227, 228].

Nevertheless, a retrospective study reported patients with severe hypogammaglobulinemia (e.g. IgG <4 g/L) were at risk for decreased survival [229]. This compares well with the IgG substitution recommendations by the IDSA [220] and the guidelines for patients with the common variable immunodeficiency (CVID) syndrome to substitute low-dose immune globulin if IgG <4 g/L [230]. According to an analysis by the Cochrane group, the use of IVIG may be considered in patients with hypogammaglobulinemia associated with CLL or multiple myeloma and recurrent infections. IVIG can significantly decrease the number of infections [225, 226].

Therefore, immune globulin should be replaced in patients with low serum IgG levels and recurrent infections associated with hypogammaglobulinemia to lower the incidence of infections (BII).
## Table 5  Vaccination recommendations for allo-HCT recipients

| Intention                      | Vaccine                                                                 | Interventions (timing of 1st application after allo-HCT) | SoR | QoE | Comments                                                                 | Ref            |
|--------------------------------|-------------------------------------------------------------------------|----------------------------------------------------------|-----|-----|--------------------------------------------------------------------------|----------------|
| Provide immunity               | *Pneumococcus* (combination of conjugate and polysaccharide vaccines)  | X (after day +100)                                        | A   | IIi | Post allo-HCT 6 months; 3 applications of 13-valent pneumococcal conjugate vaccine (PCV13, 4 weeks apart). After 1 year post allo-HCT use 23-valent polysaccharide pneumococcal vaccine; no data for non-myeloablative, haplo-identical, or DLI protocol regimes. | [258, 269–270, 310] |
|                                |                                                                         | X (after 6–12 months)                                    |     |     |                                                                           |                |
|                                |                                                                         | X (after 24 months)                                      |     |     |                                                                           |                |
|                                | *Pneumococcus* (polysaccharide vaccine) 23-valent (PPV23)               | (X)                                                      | D   | II  |                                                                           |                |
|                                |                                                                         |                                                         |     |     |                                                                           |                |
|                                | Influenza                                                               | X (after 6–12 months)                                    | A   | II  | Consider to vaccinate patient after 4 weeks again (BII) if still early after transplantation; Include next of kin and healthcare workers (HCW) to receive vaccination as well (AIIm). Consider quadrivalent vaccine (BIII). | [266, 271–276] |
|                                |                                                                         |                                                         |     |     |                                                                           |                |
|                                | *Bordatella pertussis* (acellular)*b                                    | X (after 6–12 months)                                    | A   | III | Antibody levels do not reflect effective vaccination.                    | [276–278]      |
|                                | *Diphtheria and tetanus toxoid*b                                         | X (after 6–12 months)                                    | A   | II  | First diphtheria and tetanus vaccination after 12 months; only data available beyond 12 months; for diphtheria higher dose possibly better (child dosage) but not approved (BIII). | [279–281, 310] |
|                                |                                                                         |                                                         |     |     |                                                                           |                |
|                                | *TBE* (Tick-borne encephalitis)                                         | X (after 6–12 months)                                    | B   | IIi | Only in endemic areas                                                    | [282]          |
|                                | *Poliovirus* a, b                                                       | X (after 6–12 months)                                    | A   | II  | Inactivated vaccine only                                                 | [281, 283–288] |
|                                | *Haemophilus influenza* (HI)*a, b                                        | X (after 6–12 months)                                    | B   | II  | Incidence of HI type B (vs. non type B) infections after allo-HCT is relatively low. | [269, 288–295, 310] |
|                                | *Meningococcal conjugate vaccine against serogroups A, C, W135, Y and Meningococcal vaccine for serogroup B| X (after 6–12 months)                                    | B   | IIi | Europe, North America and Canada register high rates of meningococcal disease by serogroup B. Therefore, both vaccines are recommended equally. | [295–297]      |
|                                | *Hepatitis A and B (HAV and HBV)*a, b                                   | X (after 6–12 months)                                    | B   | IIi | Only in patients at risk for hepatitis. Combination vaccination possible. Patients with a previous history of HBV need to be revaccinated (AII). | [33, 207, 298–300] |
|                                |                                                                         |                                                         |     |     |                                                                           |                |
|                                | *MMR* (mumps, measles, and rubella; live attenuated vaccine)*a, b        | X (after 6–12 months)                                    | B   | II  | Live attenuated vaccine after 24 months post allo-HCT and no GVHD or immunosuppressive therapy. Less than 24 months: DII. Consider occupational risks and household. | [301–303]      |
|                                |                                                                         |                                                         |     |     |                                                                           |                |
|                                | *VZV* (varizella zoster virus, live attenuated vaccine) *a               | X (after 6–12 months)                                    | B   | II  | As MMR but no history of VZV disease and seronegative                     | [304–307]      |

*a* Consider antibody measurements  

*b* Consider combination vaccines
**Granulocyte transfusion for prophylaxis**

A small matched pair analysis of nine neutropenic patients at high risk for recurrence of a previous fungal infections after allo-HCT demonstrated that prophylactic administration of granulocyte transfusions could reduce the incidence and shorten the duration of fever as well as the duration of neutropenia compared to the control group [231]. Oza et al. performed a “biological randomization” in 151 stem cell recipients dependent on ABO- and CMV-compatibility of their donor. There was a significant decrease in the number of febrile days and the use of intravenous antibiotics; however, no difference in the length of hospital stay or 100-day survival was noted [232]. So far, prophylactic granulocyte transfusion remains an experimental approach and is considered more a therapeutic option.

**Immunization (Tables 5 and 6)**

Protection against vaccine-preventable infections should be a part of the post-transplantation medical care management. Ideally, trials should provide evidence for the protection against diseases. However, a study powered for protective efficacy is not necessary if a sponsor of a vaccine study can justify the use of immunological data to predict protection against infection [233]. If it is not feasible to perform an efficacy study and there is no immunological correlation of protection, it may sometimes be justifiable to gauge the likely efficacy of a vaccine by comparison of immunological responses with those seen in past studies of similar vaccines with proven protective efficacy (e.g., acellular pertussis vaccines) [233].

In allo-HCT recipients, antibody titers against vaccine-preventable infections decline, leading to an increased risk of developing a disease [259]. For this reason, an early vaccination schedule would be warranted. However, during the first 3 to 6 months after transplantation, a sufficient specific immune system response to vaccination cannot be expected [259]. Depending on different factors such as pre- and post-transplant treatment, age, type of transplantation, or presence of chronic GVHD, recovery of the immune system is delayed [259]. Additionally, limited information about vaccine response exists for patients after reduced-intensity conditioning or with umbilical cord blood grafts. Administration of rituximab can suppress humoral immune response as long as 6 months after the last dose. Delayed vaccination schedules should be considered in these patients (BII) [260–262].

### Table 6  Immunization schedule

| Vaccine                        | SoR/QoE | Relative to day of allo-HCT | 12 months after first vaccination | Refresher | Comments | Ref |
|-------------------------------|---------|-----------------------------|----------------------------------|-----------|----------|-----|
|                               |         | Day 100 | Month +6 | Month +7 | Month +8 |     |                 |          |
| Pneumococcus                  | BII     |          |          | X       | X       | X   | None            |          |
| Influenza                     | AII     |          |          | X       | X       | X   | None            |          |
| Polio inactivated*            | All     |          |          | X       | X       | X   | None            |          |
| Pertussis (acellular)*        | All     |          |          | X       | X       | X   | None            |          |
| Diphtheria and tetanus toxoid*| All     |          |          | X       | X       | X   | None            |          |
| Haemophilus influenzae*       | BII     |          |          | X       | X       | X   | None            |          |
| Meningococcal conjugate 4 valent and serogroup B | BII | X | X | X | None | | |
| TBE                           | BII     |          |          | X       | X       | X   | None            |          |
| Hepatitis B                   | CII     |          |          | X       | X       | X   | None            |          |
| Mumps, measles, rubella      | BII     |          |          | X       | X       | X   | None            |          |
| Varicella zoster virus (VZV)  | BII     |          |          | X       | X       | X   | None            |          |

*a combination vaccination possible*
Pneumococcal and meningococcal immunization with the conjugated vaccine seems to provide a more stable immune response than the polysaccharide-based vaccine in immature or altered immune systems, but comparative trials are still missing [263].

MMR (measles, mumps, rubella) and Varicella vaccines are live attenuated vaccines that should not be given within the first 2 years after transplantation or during active GVHD (DIII). A significant risk of disease and side effects in the immunocompromised patient were observed. However, 24 months after transplantation without evidence of chronic GVHD and immunosuppression, MMR vaccine appears safe to be administered (BIII).

Routine VZV-vaccination is currently not indicated in seropositive patients for the prevention of herpes zoster (DIII). A newer inactivated VZV vaccine is being developed providing adequate VZV-specific antibody titers in most patients [264]. This new vaccine has the potential to change this recommendation in the future.

Additional immunizations against hepatitis A virus, human papillomavirus, yellow fever, cholera, typhus, rotavirus, or pre-exposure rabies virus vaccination are not routinely indicated in adults. Decision-making should follow the recommendations of general population and country-specific policy. Degree of immune suppression against live attenuated vaccines especially in the allo-HCT population needs special attention.

Little is known whether vaccinations can induce GVHD, since viral infections are known to do so [265]. On the other hand, clinical data demonstrate response to vaccination despite GVHD [266, 267]. A group of European experts published results of a consensus conference on vaccination in GVHD [268]. The conference attendees were more cautious about immune suppression. In patients receiving prednisone ≥0.5 mg/kg bodyweight per day as part of a combination therapy or a three-agent immunosuppressive treatment is given; vaccination may be postponed until immunosuppression is reduced to a double combination or prednisone <0.5 mg/kg bodyweight daily in order to achieve a better vaccine response (BIII) [268].

Antibody titer testing prior to and after immunization can be recommended for many vaccines. Decision-making based on a titer is not recommended for all vaccinations to document efficacy except for VZV, HAV, or HBV. Basically, titer determination provides some insight on vaccination success and should be considered as optional (CIII). Testing for sufficient antibody response after immunization is indicated in hepatitis B one month or later after the third vaccine dose (BIII). Revaccination with a second series of hepatitis B vaccine should be considered in non-responders (CIII).

In review of the available literature, clearly more studies are needed to provide more information on the safety and efficacy of vaccination schedules in allo-HCT.

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References

1. Tabbara IA et al (2002) Allogeneic hematopoietic stem cell transplantation: complications and results. Arch Intern Med 162(14):1558–1566

2. Hiemenez JW (2009) Management of infections complicating allogeneic hematopoietic stem cell transplantation. Semin Hematol 46(3):289–312

3. Einsele H et al (2003) Infectious complications after allogeneic stem cell transplantation: epidemiology and interventional therapy strategies—guidelines of the Infectious Diseases Working Party
(AGHKO) of the German Society of Hematology and Oncology (DGHO). Ann Hematol 82(Suppl 2):S175–S185
4. Ullmann AJ et al (2012) ESCMID* guideline for the diagnosis and management of Candida diseases 2012: developing European guidelines in clinical microbiology and infectious diseases. Clin Microbiol Infect 18(Suppl 7):1–8
5. Comet M et al (1999) Efficacy of prevention by high-efficiency particulate air filtration or laminar airflow against Aspergillus airborne contamination during hospital renovation. Infect Control Hosp Epidemiol 20(7):508–513
6. Eckmanns T, Ruden H, Gastmeier P (2006) The influence of high-efficiency particulate air filtration on mortality and fungal infection among highly immunosuppressed patients: a systematic review. J Infect Dis 193(10):1408–1418
7. Oren J et al (2001) Invasive pulmonary aspergillosis in neutropenic patients during hospital construction: before and after chemophylaxis and institution of HEPA filters. Am J Hematol 66(4):257–262
8. Kruger WH et al (2003) Effective protection of allogeneic stem cell recipients against Aspergillus by HEPA air filtration during a period of construction—a prospective survey. J Hematother Stem Cell Res 12(3):301–307
9. Vokurka S et al (2014) The availability of HEPA-filtered rooms and the incidence of pneumonia in patients after haematopoietic stem cell transplantation (HSCT): results from a prospective, multicentre, eastern European study. J Clin Nurs 23(11–12):1648–1652
10. Humphreys H (2004) Positive-pressure isolation and the prevention of invasive aspergillosis. What is the evidence? J Hosp Infect 56(2):93–100, quiz 163
11. Hayes-Lattin B, Leis JF, Maziarz RT (2005) Isolation in the allogegeneic transplantation unit. J Clin Microbiol 39(2):801–803
12. McCann S et al (2004) Outbreaks of infectious diseases in stem cell transplant units: a silent cause of death for patients and transplant programmes. Bone Marrow Transplant 33(5):519–529
13. Harrington RD et al (1992) An outbreak of respiratory syncytial virus in a bone marrow transplant center. J Infect Dis 165(6):987–993
14. Whimbey E et al (1995) Combination therapy with aerosolized ribavirin and intravenous immunoglobulin for respiratory syncytial virus disease in adult bone marrow transplant recipients. Bone Marrow Transplant 16(3):393–399
15. Taylor GS, Vipond IB, Caul EO (2001) Molecular epidemiology of outbreak of respiratory syncytial virus within bone marrow transplantation unit. J Clin Microbiol 39(2):801–803
16. McWilliam Leitch EC et al (2001) Dietary effects on the microbiological safety of food. Proc Nutr Soc 60(2):247–255
17. Boyle NM et al (2014) Bacterial foodborne infections after hematopoietic cell transplantation. Biol Blood Marrow Transplant 20(11):1856–1861
18. Allegraunzi B, Pittet D (2009) Role of hand hygiene in healthcare-associated infection prevention. J Hosp Infect 73(4):305–315
19. CE1-7 (2000) Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. MMWR Recomm Rep 49(RR-10):1–25
20. Daeschlein G et al (2007) Hygienic safety of reusable tap water filters (Germlyser) with an operating time of 4 or 8 weeks in a haematological oncology transplantation unit. BMC Infect Dis 7:45
21. Zhou ZY et al (2014) Removal of waterborne pathogens from liver transplant unit water taps in prevention of healthcare-associated infections: a proposal for a cost-effective, proactive infection control strategy. Clin Microbiol Infect 20(4):310–314
22. Cervia JS et al (2010) Point-of-use water filtration reduces healthcare-associated infections in bone marrow transplant recipients. Transpl Infect Dis 12(3):238–241
23. Kelsey SM, Newland AC (1989) Cytomegalovirus recoversion in patients receiving intensive induction therapy prior to allogeneic bone marrow transplantation. Bone Marrow Transplant 4(5):543–546
24. Hamadani M et al (2010) How we approach patient evaluation for hematopoietic stem cell transplantation. Bone Marrow Transplant 45(8):1259–1268
25. Schmidt-Hieber M et al (2013) CMV serostatus still has an important prognostic impact in de novo acute leukemia patients after allogeneic stem cell transplantation: a report from the Acute Leukemia Working Party of EBMT. Blood 122(19):3359–3364
26. Stewart JA et al (1995) Herpesvirus infections in persons infected with human immunodeficiency virus. Clin Infect Dis 21(Suppl 1):S114–S120
27. Liang R, Lau GK, Kwong YL (1999) Chemotherapy and bone marrow transplantation for cancer patients who are also chronic hepatitis B carriers: a review of the problem. J Clin Oncol 17(1):394–398
28. Hammond SP et al (2009) Hepatitis B virus reactivation following allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 15(9):1049–1059
29. Liang R (2009) How I treat and monitor viral hepatitis B infection in patients receiving intensive immunosuppressive therapies or undergoing hematopoietic stem cell transplantation. Blood 113(14):3147–3153
30. Knoll A et al (2004) Reactivation of resolved hepatitis B virus infection after allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 33(9):925–929
31. Mikulaska M et al (2014) Hepatitis B reactivation in HBsAg-negative/HBeAb-positive allogeneic hematopoietic stem cell transplant recipients: risk factors and outcome. Clin Microbiol Infect 20(10):O694–O701
32. Pompili M et al (2015) Prospective study of hepatitis B virus reactivation in patients with hematological malignancies. Ann Hepatol 14(2):168–174
33. Takahata M et al (2014) Hepatitis B virus (HBV) reverse seroconversion (RS) can be prevented even in non-responders to hepatitis B vaccine after allogeneic stem cell transplantation: long-term analysis of intervention in RS with vaccine for patients with previous HBV infection. Transpl Infect Dis 16(5):797–801
34. Peffault de Latour R et al (2008) Allogeneic hematopoietic cell transplant in HCV-infected patients. J Hepatol 48(6):1008–1017
35. de Latour Peffault R (2004) Long-term outcome of hepatitis C infection after bone marrow transplantation. Blood 103(5):1618–1624
36. Locascelli A et al (1989) Predictability before transplant of hepatic complications following allogeneic bone marrow transplantation. Transplantation 48(1):68–72
37. Lee JH et al (2005) Decreased incidence of hepatic veno-occlusive disease and fewer hemostatic derangements associated with intravenous busulfan vs oral busulfan in adults conditioned with busulfan + cyclophosphamide for allogeneic bone marrow transplantation. Ann Hematol 84(5):321–330
38. van der Eijk AA et al (2014) Hepatitis E virus infection in hematopoietic stem cell transplant recipients. Curr Opin Infect Dis 27(4):309–315
39. Versluis J et al (2013) Hepatitis E virus: an underestimated opportunistic pathogen in recipients of allogeneic hematopoietic stem cell transplantation. Blood 122(6):1079–1086
40. Le Coutre P et al (2009) Reactivation of hepatitis E infection in a patient with acute lymphoblastic leukemia after allogeneic stem cell transplantation. Gut 58(5):699–702
41. Bettinger D et al (2014) Chronic hepatitis E virus infection following allogeneic hematopoietic stem cell transplantation: an important differential diagnosis for graft versus host disease. Ann Hematol 94(2):359–360
80. Hughes WT et al (1977) Successful chemoprophylaxis for Pneumocystis carinii pneumonia. N Engl J Med 297(26):1419–1426
81. Stein DS et al (1991) Use of low-dose trimethoprim-sulfamethoxazole thrice weekly for primary and secondary prophylaxis of Pneumocystis carinii pneumonia in human immunodeficiency virus-infected patients. Antimicrob Agents Chemother 35(9):1705–1709
82. Stern A et al (2014) Prophylaxis for Pneumocystis pneumonia in non-HIV immunocompromised patients. Cochrane Database Syst Rev 10:CD005590
83. Lytvikainen O et al (1996) Late onset Pneumocystis carinii pneumonia following allogeneic bone marrow transplantation. Bone Marrow Transplant 17(6):1057–1059
84. Vasconcelles MJ et al (2000) Aerosolized pentamidine as Pneumocystis prophylaxis after bone marrow transplantation is inferior to other regimens and is associated with decreased survival and an increased risk of other infections. Biol Blood Marrow Transplant : J Am Soc Blood Marrow Transplant 6(1):35–43
85. Green H et al (2007) Prophylaxis for Pneumocystis pneumonia (PCP) in non-HIV immunocompromised patients. Cochrane Database Syst Rev 3:CD005590
86. Colby C et al (1999) A prospective randomized trial comparing the toxicity and safety of atovaquone with trimethoprim/sulfamethoxazole as Pneumocystis carinii pneumonia prophylaxis following autologous peripheral blood stem cell transplantation. Bone Marrow Transplant 24(8):897–902
87. Link H et al (1993) Pentamidine aerosol for prophylaxis of Pneumocystis carinii pneumonia after BMT. Bone Marrow Transplant 11(5):403–406
88. Marras TK et al (2002) Aerosolized pentamidine prophylaxis for Pneumocystis carinii pneumonia after allogeneic marrow transplantation. Transpl Infect Dis 4(2):66–74
89. Chan C et al (1999) Atovaquone suspension compared with aerosolized pentamidine for prevention of Pneumocystis carinii pneumonia in human immunodeficiency virus-infected subjects intolerant of trimethoprim or sulfonamides. J Infect Dis 180(2):369–376
90. Souza JP et al (1999) High rates of Pneumocystis carinii pneumonia in allogeneic blood and marrow transplant recipients receiving capsonze prophylaxis. Clin Infect Dis 29(6):1467–1471
91. Tomonari A et al (2008) No occurrence of Pneumocystis jiroveci (carinii) pneumonia in 120 adults undergoing myeloablative unrelated cord blood transplantation. Transpl Infect Dis 10(5):303–307
92. Hughes W et al (1993) Comparison of atovaquone (566C80) with trimethoprim-sulfamethoxazole to treat Pneumocystis carinii pneumonia in patients with AIDS. N Engl J Med 328(21):1521–1527
93. El-Sadr WM et al (1998) Atovaquone compared with capsonze for the prevention of Pneumocystis carinii pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. Community Program for Clinical Research on AIDS and the AIDS Clinical Trials Group. N Engl J Med 339(26):1889–1895
94. Kontoyiannis DP et al (2010) Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. Clin Infect Dis 50(8):1091–1100
95. Martino R et al (2002) Invasive fungal infections after allogeneic peripheral blood stem cell transplantation: incidence and risk factors in 395 patients. Br J Haematol 116(2):475–482
96. Ballay V, Chignard M (2009) The innate immune response to Aspergillus fumigatus. Microbes Infect 11(12):919–927
97. Zhang P et al (2010) Risk factors and prognosis of invasive fungal infections in allogeneic stem cell transplantation recipients: a single-institution experience. Transpl Infect Dis 12(4):316–321
98. Garcia-Vidal C et al (2008) Epidemiology of invasive mold infections in allogeneic stem cell transplant recipients: biological risk factors for infection according to time after transplantation. Clin Infect Dis 47(8):1041–1050
99. Post MJ et al (2007) Invasive fungal infections in allogeneic and autologous stem cell transplant recipients: a single-center study of 166 transplanted patients. Transpl Infect Dis 9(3):189–195
100. Lewis RE et al (2013) Epidemiology and sites of involvement of invasive fungal infections in patients with haematological malignancies: a 20-year autopsy study. Mycoses 56(6):638–645
101. Sinko J et al (2008) Invasive fungal disease in allogeneic hematopoietic stem cell transplant recipients: an autopsy-driven survey. Transpl Infect Dis 10(2):106–109
102. Chamilos G et al (2006) Invasive fungal infections in patients with hematologic malignancies in a tertiary care cancer center: an autopsy study over a 15-year period (1989–2003). Haematologica 91(7):986–989
103. Cordonnier C et al (2006) Prognostic factors for death due to invasive aspergillosis after hematopoietic stem cell transplantation: a 1-year retrospective study of consecutive patients at French transplantation centers. Clin Infect Dis 42(7):955–963
104. Cordonnier C et al (2010) Voriconazole for secondary prophylaxis of invasive fungal infections in allogeneic stem cell transplant recipients: results of the VOSIFI study. Haematologica 95(10):1762–1768
105. Ostrosky-Zeichner L (2004) Prophylaxis and treatment of invasive candidiasis in the intensive care setting. Eur J Clin Microbiol Infect Dis 23(10):739–744
106. Papahiotou NI, Ostrosky-Zeichner L, Rex JH (2005) Rules for identifying patients at increased risk for candidal infections in the surgical intensive care unit: approach to developing practical criteria for systematic use in antifungal prophylaxis trials. Med Mycol 43(3):235–243
107. Wenzel RP, Gennings C (2005) Bloodstream infections due to Aspergillus and other filamentous fungi (SECURE): a phase 3, primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. Lancet 367(9520):760–769
108. Chamilos G et al (2006) Invasive fungal infections in patients with hematologic malignancies in a tertiary care cancer center: an autopsy study over a 15-year period (1989–2003). Haematologica 91(7):986–989
109. Marty FM et al. (2016) Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case–control analysis. Lancet Infect Dis. doi:10.1016/S1473-3099(16)00071-2
110. Maertens JA et al (2016) Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. Lancet 387(10020):760–769
111. Marty FM et al. (2016) Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case–control analysis. Lancet Infect Dis. doi:10.1016/S1473-3099(16)00071-2
112. Marty FM et al. (2016) Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case–control analysis. Lancet Infect Dis. doi:10.1016/S1473-3099(16)00071-2
113. Mousset S et al (2014) Treatment of invasive fungal infections in cancer patients-updated recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). Ann Hematol 93(1):13–32
114. Wingard JR et al. (2010) Randomized double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection (IFI) after allo hematopoietic cell transplantation (HCT). Blood 116(24):5111–5118
Cornely OA et al (2007) Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 356(4):348–359

Duarte RF et al (2014) Phase 1b study of new posaconazole tablet for prevention of invasive fungal infections in high-risk patients with neutropenia. Antimicrob Agents Chemother 58(10):5758–5765

Cornely OA et al. (2016) Phase 3 pharmacokinetics and safety study of a posaconazole tablet formulation in patients at risk for invasive fungal disease. J Antimicrob Chemother 71(6):1747

van Burik JA et al (2004) Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. Clin Infect Dis 39(10):1407–1416

Marr KA et al (2004) Itraconazole versus fluconazole for prevention of fungal infections in patients receiving allogeneic stem cell transplants. Blood 103(4):1527–1533

Glasmacher A et al (1998) Antifungal prophylaxis with itraconazole in neutropenic patients with acute leukemia. Leukemia 12(9):1338–1343

Glasmacher A et al (1999) Breakthrough invasive fungal infections in neutropenic patients after prophylaxis with itraconazole. Mycoses 42(7–8):443–451

Goodman JL et al (1992) A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. N Engl J Med 326(13):845–851

Marr KA et al (2000) Prolonged fluconazole prophylaxis is associated with persistent protection against candidiasis-related death in allogeneic marrow transplant recipients: long-term follow-up of a randomized, placebo-controlled trial. Blood 96(6):2055–2061

Slavin MA et al (1995) Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation—a prospective, randomized, double-blind study. J Infect Dis 171(6):1545–1552

Ullmann AJ et al (2007) Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med 356(4):335–347

Cordonnier C et al (2004) Secondary antifungal prophylaxis with voriconazole to adhere to scheduled treatment in leukemic patients and stem cell transplant recipients. Bone Marrow Transplant 33(9):943–948

de Fabritiis P et al (2007) Efficacy of caspofungin as secondary prophylaxis in patients undergoing allogeneic stem cell transplantation with prior pulmonary and/or systemic fungal infection. Bone Marrow Transplant 40(3):245–249

Gupta S et al (2007) Successful treatment of disseminated fusariosis with posaconazole during neutropenia and subsequent allogeneic hematopoietic stem cell transplantation. Transpl Infect Dis 9(2):156–160

Wingard JR et al (1999) Clinical significance of nephrotoxicity in patients treated with amphotericin B for suspected or proven aspergillosis. Clin Infect Dis 29(6):1402–1407

Bates DW et al (2001) Mortality and costs of acute renal failure associated with amphotericin B therapy. Clin Infect Dis 32(5):688–693

Ullmann AJ et al (2006) Prospective study of amphotericin B formulations in immunocompromised patients in 4 European countries. Clin Infect Dis 43(4):e29–e38

Ullmann AJ et al (2004) Itraconazole prophylaxis in patients with prolonged neutropenia: results from a randomized, single-center trial. Ann Oncol 17(8):1306–1312

Behre GF et al (1995) Aerosol amphotericin B inhalations for prevention of invasive pulmonary aspergillosis in neutropenic cancer patients. Ann Hematol 71(6):287–291

Luu Tran H et al. (2014) Tolerability and outcome of once weekly liposomal amphotericin B for the prevention of invasive fungal infections in hematopoietic stem cell transplant patients with graft-versus-host disease. J Oncol Pharm Pract 22(2):228–234

Cornely OA, Ullmann AJ (2011) Lack of evidence for exposure-response relationship in the use of posaconazole as prophylaxis against invasive fungal infections. Clin Pharmacol Ther 89(3):351–352

Kawamura K et al (2014) Prophylactic role of long-term ultra-low-dose acyclovir for varicella zoster virus disease after allogeneic hematopoietic stem cell transplantation. Int J Infect Dis 19:26–32

Meyers JD, Flournoy N, Thomas ED (1980) Infection with herpes simplex virus and cell-mediated immunity after marrow transplant. J Infect Dis 142(3):338–346

Saral R et al (1981) Acyclovir prophylaxis of herpes-simplex virus infections. N Engl J Med 305(2):63–67

Gluckman E et al (1983) Prophylaxis of herpetic infections after bone-marrow transplantation by oral acyclovir. Lancet 2(8352):706–708

Wade JC et al (1982) Intravenous acyclovir to treat mucocutaneous herpes simplex virus infection after marrow transplantation: a double-blind trial. Ann Intern Med 96(3):265–269

Wade JC et al (1984) Oral acyclovir for prevention of herpes simplex virus reactivation after marrow transplantation. Ann Intern Med 100(6):823–828

Ljungman P et al (1986) Long-term acyclovir prophylaxis in bone marrow transplant recipients and lymphocyte proliferation responses to herpes virus antigens in vitro. Bone Marrow Transplant 1(2):185–192

Sauerbrei A et al (2011) Novel resistance-associated mutations of thymidine kinase and DNA polymerase genes of herpes simplex virus type 1 and 2. Antivir Ther 16(8):1297–1308

McLaren C, Sibrack CD, Barry DW (1982) Spectrum of sensitivity of acyclovir of herpes simplex virus clinical isolates. Am J Med 73(1A):376–379

Piret J, Boivin G (2011) Resistance of herpes simplex viruses to nucleoside analogues: mechanisms, prevalence, and management. Antimicrob Agents Chemother 55(2):459–472

Mertz GJ et al (1997) Oral famciclovir for suppression of recurrent genital herpes simplex virus infection in women. A multicenter, double-blind, placebo-controlled trial. Collaborative Famciclovir Genital Herpes Research Group. Arch Intern Med 157(3):343–349

Tyring SK, Baker D, Snowden W (2002) Valacyclovir for herpes simplex virus infection: long-term safety and sustained efficacy after 20 years’ experience with acyclovir. J Infect Dis 186(Suppl 1):S40–S46

Garner JS (1996) Guideline for isolation precautions in hospitals. The Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol 17(1):53–80

Josephson A, Gombert ME (1988) Airborne transmission of nosocomial varicella from localized zoster. J Infect Dis 158(1):238–241

Koc Y et al (2000) Varicella zoster virus infections following allogeneic bone marrow transplantation: frequency, risk factors, and clinical outcome. Biol Blood Marrow Transplant 6(1):44–49

Ramke HC et al (2011) Immunogenicity and safety of a measles-mumps-rubella-varicella vaccine following a 4-week or a 12-month interval between two doses. Vaccine 29(22):3842–3849

Han CS et al (1994) Varicella zoster infection after bone marrow transplantation: incidence, risk factors and complications. Bone Marrow Transplant 13(3):277–283

Locksley RM et al (1985) Infection with varicella-zoster virus after marrow transplantation. J Infect Dis 152(6):1172–1181

Weinstein DM, Boeckh M, Sepkowitz KA (2006) Postexposure prophylaxis against varicella zoster virus infection among
hematopoietic stem cell transplant recipients. Biol Blood Marrow Transplant 12(10):1096–1097

155. Zaia JA et al (1983) Evaluation of varicella-zoster immune globulin: protection of immunosuppressed children after household exposure to varicella. J Infect Dis 147(4):737–743

156. Boeckh M et al (2006) Long-term acyclovir for prevention of varicella zoster virus disease after allogeneic hematopoietic cell transplantation—a randomized double-blind placebo-controlled study. Blood 107(5):1800–1805

157. Erard V et al (2007) Use of long-term suppressive acyclovir after hematopoietic stem-cell transplantation: impact on herpes simplex virus (HSV) disease and drug-resistant HSV disease. J Infect Dis 196(2):266–270

158. Thomson KJ et al (2005) The effect of low-dose aciclovir on reactivation of varicella-zoster virus after allogeneic haematopoietic stem cell transplantation. Bone Marrow Transplant 35(11):1065–1069

159. Kanda Y et al (2001) Long-term low-dose acyclovir against varicella-zoster virus reactivation after allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 28(7):689–692

160. Gilbert C, Bestman-Smith J, Boivin G (2002) Resistance of herpesviruses to antiviral drugs: clinical impacts and molecular mechanisms. Drug Resist Updat 5(2):88–114

161. Kroger N et al (2001) Patient cytomegalovirus seropositivity with or without reactivation is the most important prognostic factor for survival and treatment-related mortality in stem cell transplantation from unrelated donors using pretransplant in vivo T-cell depletion with anti-thymocyte globulin. Br J Haematol 113(4):1060–1071

162. Boeckh M, Nichols WG (2004) The impact of cytomegalovirus serostatus of donor and recipient before hematopoietic stem cell transplantation in the era of antiviral prophylaxis and preemptive therapy. Blood 103(6):2003–2008

163. Thiele T et al (2011) Transmission of cytomegalovirus (CMV) infection by leukoreduced blood products not tested for CMV antibodies: a single-center prospective study in high-risk patients undergoing allogeneic hematopoietic stem cell transplantation (CME). Transfusion 51(12):2620–2626

164. Nairvis AB et al (2005) Transfusion of leukoreduced cellular blood components from cytomegalovirus-unscreened donors in allogeneic hematopoietic transplant recipients: analysis of 72 recipients. Bone Marrow Transplant 36(6):499–501

165. Kekre N et al (2013) Is cytomegalovirus testing of blood products still needed for hematopoietic stem cell transplant recipients in the era of universal leukoreduction? Biol Blood Marrow Transplant 19(12):1719–1724

166. Bowden RA et al (1991) Use of leukocyte-depleted platelets and cytomegalovirus-seronegative red blood cells for prevention of primary cytomegalovirus infection after marrow transplant. Blood 78(1):246–250

167. Bowden RA et al (1995) A comparison of filtered leukocyte-reduced and cytomegalovirus (CMV) seronegative blood products for the prevention of transfusion-associated CMV infection after marrow transplant. Blood 86(9):3598–3603

168. Miller WJ et al (1991) Prevention of cytomegalovirus infection following bone marrow transplantation: a randomized trial of blood product screening. Bone Marrow Transplant 7(1):227–234

169. De Witte T et al (1990) Prevention of primary cytomegalovirus infection after allogeneic bone marrow transplantation by using leukocyte-poor random blood products from cytomegalovirus-unscreened blood-bank donors. Transplantation 50(6):964–968

170. Narvios AB, Lichtiger B (2001) Bedside leukoreduction of cellular blood components in preventing cytomegalovirus transmission in allogeneic bone marrow transplant recipients: a retrospective study. Haematologica 86(7):749–752

171. Zaia JA et al (1997) Late cytomegalovirus disease in marrow transplantation is predicted by virus load in plasma. J Infect Dis 176(3):782–785

172. Nagler A et al (1994) Cytomegalovirus pneumonia prior to engraftment following T-cell depleted bone marrow transplantation. Med Oncol 11(3–4):127–132

173. Schmidt-Hieber M et al (2010) Immune reconstitution and cytomegalovirus infection after allogeneic stem cell transplantation: the important impact of in vivo T cell depletion. Int J Hematol 91(5):877–885

174. Einsele H et al (1991) Polymerase chain reaction to evaluate antiviral therapy for cytomegalovirus disease. Lancet 338(8776):1170–1172

175. Li CR et al (1994) Recovery of HLA-restricted cytomegalovirus (CMV)-specific T-cell responses after allogeneic bone marrow transplant: correlation with CMV disease and effect of ganciclovir prophylaxis. Blood 83(7):1971–1979

176. O’Brien S et al (2008) Valganciclovir prevents cytomegalovirus reactivation in patients receiving alemtuzumab-based therapy. Blood 111(4):1816–1819

177. Boeckh M et al (2015) Valganciclovir for the prevention of complications of late cytomegalovirus infection after allogeneic hematopoietic cell transplantation: a randomized trial. Ann Intern Med 162(1):1–10

178. Ruutu T et al (1997) No prevention of cytomegalovirus infection by anti-cytomegalovirus hyperimmune globulin in seronegative bone marrow transplant recipients. the Nordic BMT Group. Bone Marrow Transplant 19(3):233–236

179. Zitos P et al (1998) A randomized trial of high dose polyvalent intravenous immunoglobulin (HDlgG) vs. Cytomegalovirus (CMV) hyperimmune IgG in allogeneic hematopoietic stem cell transplants (HSCT). Haematologica 83(2):132–137

180. Meyers JD et al (1988) Acyclovir for prevention of cytomegalovirus infection and disease after allogeneic marrow transplantation. N Engl J Med 318(2):70–75

181. Winston DJ et al (2003) Randomized comparison of oral valacyclovir and intravenous ganciclovir for prevention of cytomegalovirus disease after allogeneic bone marrow transplantation. Clin Infect Dis 36(6):749–758

182. Ljungman P et al (2002) Randomized study of valacyclovir as prophylaxis against cytomegalovirus reactivation in recipients of allogeneic bone marrow transplants. Blood 99(8):3050–3056

183. Vusirikala M et al (2001) Valacyclovir for the prevention of cytomegalovirus infection after allogeneic stem cell transplantation: a single institution retrospective cohort analysis. Bone Marrow Transplant 28(3):265–270

184. Boeckh M et al (1995) Failure of high-dose acyclovir to prevent cytomegalovirus disease after autologous marrow transplantation. J Infect Dis 172(4):939–943

185. Winston DJ et al (2008) Maribavir prophylaxis for prevention of cytomegalovirus infection in allogeneic stem cell transplant recipients: a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. Blood 111(11):5403–5410

186. Avery RK et al (2010) Oral maribavir for treatment of refractory or resistant cytomegalovirus infections in transplant recipients. Transplant Infect Dis 12(6):489–496

187. Marty FM et al (2011) Maribavir prophylaxis for prevention of cytomegalovirus disease in recipients of allogeneic stem-cell transplants: a phase 3, double-blind, placebo-controlled, randomised trial. Lancet Infect Dis 11(4):284–292

188. Marty FM et al (2013) CMX001 to prevent cytomegalovirus disease in hematopoietic-cell transplantation. N Engl J Med 369(13):1227–1236
221. Cortez K et al (2002) Immune-globulin prophylaxis of respiratory syncytial virus infection in patients undergoing stem-cell transplantation. J Infect Dis 186(6):834–838
222. Robinson P et al (2007) Evidence-based guidelines on the use of intravenous immune globulin for hematologic and neurologic conditions. Transfus Med Rev 21(2 Suppl 1):S3–S8
223. Sullivan KM et al (1990) Immunomodulatory and antimicrobial efficacy of intravenous immunoglobulin in bone marrow transplantation. N Engl J Med 323(11):705–712
224. Winston DJ et al (1987) Intravenous immune globulin for prevention of cytomegalovirus infection and interstitial pneumonia after bone marrow transplantation. Ann Intern Med 106(1):12–18
225. Raanani P et al (2008) Immunoglobulin prophylaxis in hematopoietic stem cell transplantation: systematic review and meta-analysis. J Clin Oncol : Off J Am Soc Clin Oncol 27(5):770–781
226. Cordonnier C et al (2003) Should immunoglobulin therapy be used in allogeneic stem-cell transplantation? A randomized, double-blind, dose effect, placebo-controlled, multicenter trial. Ann Intern Med 139(1):8–18
227. Schmidt-Hieber M et al (2009) Prophylactic i.v. lgs in patients with a high risk for CMV after allo-SCT. Bone Marrow Transplant 44(3):185–192
228. Norlin AC et al (2008) Allogeneic stem cell transplantation: low immunoglobulin levels associated with decreased survival. Bone Marrow Transplant 41(3):267–273
229. Smoller MC et al (1993) NIH conference. New insights into common variable immunodeficiency. Ann Intern Med 118(9):720–730
230. Kerr JP et al (2003) The use of stimulated granulocyte transfusions to prevent recurrence of past severe infections after allogeneic stem cell transplantation. Br J Haematol 123(1):114–118
231. Oza A et al (2006) Granulocyte-colony-stimulating factor-mobilized prophylactic granulocyte transfusions given after allogeneic peripheral blood progenitor cell transplantation result in a modest reduction of febrile days and intravenous antibiotic usage. Transfusion 46(1):14–23
232. EMA (2006) E.M.A., guideline on clinical evaluation of new vaccines. EMEA/CHMP/VWP/164653/2005
233. Dignani MC et al (2002) Valacyclovir prophylaxis for the prevention of Herpes simplex virus reactivation in recipients of progenitor cells transplantation. Bone Marrow Transplant 29(3):263–267
234. Kim DH et al (2008) Clinical efficacy of prophylactic strategy of long-term low-dose acyclovir for Varicella-Zoster virus infection after allogeneic peripheral blood stem cell transplantation. Clin Transplant 22(6):770–779
235. Erard V et al (2007) One-year acyclovir prophylaxis for preventing varicella-zoster virus disease after hematopoietic cell transplantation: no evidence of rebound varicella-zoster virus disease after drug discontinuation. Blood 110(8):3071–3077
236. Oshima K, et al. (2010) One-year low-dose valacyclovir prophylaxis for varicella-zoster virus disease after allogeneic hematopoietic stem cell transplantation. A prospective study of the Japan Hematology and Oncology Clinical Study Group. Transpl Infect Dis 12(5):421–427
237. Asano-Mori Y et al (2008) Long-term ultra-low-dose acyclovir against varicella-zoster virus reactivation after allogeneic hematopoietic stem cell transplantation. Am J Hematol 83(6):472–476
238. Einsele H et al (1995) Polymerase chain reaction monitoring reduces the incidence of cytomegalovirus disease and the duration and side effects of antiviral therapy after bone marrow transplantation. Blood 86(7):2815–2820
239. Reusser P et al (2002) Randomized multicenter trial of foscarnet versus ganciclovir for preemptive therapy of cytomegalovirus infection after allogeneic stem cell transplantation. Blood 99(4):1159–1164
240. Einsele H et al (2006) Oral valganciclovir leads to higher exposure to ganciclovir than intravenous ganciclovir in patients following allogeneic stem cell transplantation. Blood 107(7):3002–3008
241. Ayala E et al (2006) Valganciclovir is safe and effective as preemptive therapy for CMV infection in allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 37(9):851–856
242. Burns LJ et al (2002) Randomized clinical trial of ganciclovir vs acyclovir for prevention of cytomegalovirus antigenemia after allogeneic transplantation. Bone Marrow Transplant 30(12):945–951
243. Verdonck LF et al (1997) A risk-adapted approach with a short course of ganciclovir to prevent cytomegalovirus (CMV) pneumonia in CMV-seropositive recipients of allogeneic bone marrow transplants. Clin Infect Dis 24(5):901–907
244. Micklethwaitie K et al (2007) Ex vivo expansion and prophylactic infusion of CMV-pp 65 peptide-specific cytotoxic T-lymphocytes following allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 13(6):707–714
245. Lau GK et al (2002) Preemptive use of lamivudine reduces hepatitis B exacerbation after allogeneic hematopoietic cell transplantation. Hepatology 36(3):702–709
246. Loomba R et al (2008) Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. Ann Intern Med 148(7):519–528
247. Chang TT et al (2006) A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. N Eng J Med 354(10):1001–1010
248. Tamori A et al (2014) Prospective long-term study of hepatitis B virus reactivation in patients with hematologic malignancy. J Gastroenterol Hepatol 29(9):1715–1721
249. Shang J et al (2016) A comparison of lamivudine vs entecavir for prophylaxis of hepatitis B virus reactivation in allogeneic hematopoietic stem cell transplantation recipients: a single-institutional experience. Bone Marrow Transplant 51(4):581–586
250. Koskinas JS et al (2014) The role of tenofovir in preventing and treating hepatitis B virus (HBV) reactivation in immunosuppressed patients. A real life experience from a tertiary center. Eur J Intern Med 25(8):768–771
251. Leong J et al (2014) Lamivudine resistance leading to de novo hepatitis B infection in recipients of hepatitis B core antibody positive liver allografts. Hepatol Res 44(12):1248–1252
252. Chiba T et al (2003) Successful clearance of hepatitis B virus after allogeneic stem cell transplantation: beneficial combination of adoptive immunity transfer and lamivudine. Eur J Haematol 71(3):220–223
253. Matsue K et al (2009) High risk of hepatitis B-virus reactivation after hematopoietic cell transplantation in hepatitis B core antibody-positive patients. Eur J Haematol 83(4):357–364
254. Foppa CU et al (1991) A retrospective study of primary and maintenance therapy of toxoplasmic encephalitis with oral clindamycin and pyrimethamine. Eur J Clin Microbiol Infect Dis 10(3):187–189
255. Katlama C (1991) Evaluation of the efficacy and safety of clindamycin plus pyrimethamine for induction and maintenance therapy of toxoplasmic encephalitis in AIDS. Eur J Clin Microbiol Infect Dis 10(3):189–191
256. Leport C et al (1989) An open study of the pyrimethamine-clindamycin combination in AIDS patients with brain toxoplasmosis. J Infect Dis 160(3):557–558
257. Cordonnier C et al (2009) Randomized study of early versus late immunization with pneumococcal conjugate vaccine after allogeneic stem cell transplantation. Clin Infect Dis 48(10):1392–1401
259. Seggewiss R, Einsele H (2010) Immune reconstitution after allo-
geneic transplantation and expanding options for immunomodulation: an update. Blood 115(19):3861–3868

260. Eisenberg RA et al (2013) Rituximab-treated patients have a poor response to influenza vaccination. J Clin Immunol 33(2):388–396

261. Bedognetti D et al (2011) Impaired response to influenza vaccine associated with persistent memory B cell depletion in non-
Hodgkin’s lymphoma patients treated with rituximab-containing regimens. J Immunol 186(10):6044–6055

262. Berglund A et al (2014) The response to vaccination against in-
fluenza A (H1N1) 2009, seasonal influenza and Streptococcus pneumoniae in adult outpatient with ongoing treatment for cancer
with and without rituximab. Acta Oncol 53(9):1212–1220

263. Juergens C et al. (2014) Safety and immunogenicity of 13-valent pneumococcal conjugate vaccine formulations with and without
aluminum phosphate and comparison of the formulation of choice with 23-valent pneumococcal polysaccharide vaccine in elderly
adults: A randomized open-label trial. Hum Vaccin Immunother 10(5)

264. Hata A et al (2002) Use of an inactivated varicella vaccine in
recipients of hematopoietic-colony-stimulating factors. J Infect Dis 185(1):26–34

265. Burrows SR et al (1997) Cross-reactive memory T cells for
Epstein-Barr virus augment the alloresponse to common human leukocyte antigens: degenerate recognition of major histocompat-
ibility complex-bound peptide by T cells and its role in alloreactivity. Eur J Immunol 27(7):1726–1736

266. Dhedin N et al (2014) Comparable humoral response after two
doses of adjuvanted influenza A/H1N1pdm2009 vaccine or natu-
ral infection in allogeneic stem cell transplant recipients. Vaccine 32(5):585–591

267. Olikoivu H et al (2012) Immunity after (re) vaccination of pedi-
atriatric patients following haematopoietic stem cell transplantation.
Acta Paediatr 101(8):e373–e377

268. Hilgendorf I et al (2011) Vaccination of allogeneic hematopoietic
stem cell transplant recipients: report from the international con-
sensus conference on clinical practice in chronic GVHD. Vaccine 29(16):2825–2833

269. Pao M et al (2008) Response to pneumococcal (PCNCRM7) and
haemophilus influenzae conjugate vaccines (HIB) in pediatric and
adult recipients of an allogeneic hematopoietic cell transplantation
(alloHCT). Biol Blood Marrow Transplant 14(9):1022–1030

270. Cordonnier C et al (2010) Immune response to the 23-valent polysaccharide pneumococcal vaccine after the 7-valent conjugate vac-
cine in allogeneic stem cell transplant recipients: results from the
EBMT IDWP01 trial. Vaccine 28(15):2730–2734

271. Avetsyan G et al (2008) Evaluation of immune responses to se-
asonal influenza vaccination in healthy volunteers and in patients
after stem cell transplantation. Transplantation 86(2):257–263

272. Ljungman P, Avetsyan G (2008) Influenza vaccination in hemato-
poietic SCT recipients. Bone Marrow Transplant 42(10):637–
641

273. Engelhard D et al (1993) Antibody response to a two-dose regi-
men of influenza vaccine in allogeneic T cell-depleted and autol-
ogous BMT recipients. Bone Marrow Transplant 11(1):1–5

274. Gueller S et al (2011) Enhanced immune response after a second
dose of an AS03-adjuvanted H1N1 influenza A vaccine in patients
after hematopoietic stem cell transplantation. Biol Blood Marrow
Transplant 17(10):1546–1550

275. de Lavallade H et al (2011) Repeated vaccination is required to
optimize seroprotection against H1N1 in the immunocompro-
mised host. Haematologica 96(2):307–314

276. Inaba H et al (2012) Longitudinal analysis of antibody response
to immunization in paediatric survivors after allogeneic haematopoietic stem cell transplantation. Br J Haematol 156(1):
109–117

277. Lambert LC (2014) Pertussis vaccine trials in the 1990s. J Infect
Dis 209(Suppl 1):S4–S9

278. Edwards KM, Berbers GA (2014) Immune responses to pertussis
vaccines and disease. J Infect Dis 209(Suppl 1):S10–S15

279. Parkkali T et al (1997) A randomized comparison between early
and late vaccination with tetanus toxoid vaccine after allogeneic
BMT. Bone Marrow Transplant 19(9):933–938

280. Ljungman P et al (1990) Response to tetanus toxoid immunization
after allogeneic bone marrow transplantation. J Infect Dis 162(2):
496–500

281. Li Volti S et al (1994) Immune status and immune response to
diphtheria-tetanus and polio vaccines in allogeneic bone marrow-
transplanted thalassemic patients. Bone Marrow Transplant 14(2):
225–227

282. Dengler TJ et al (1999) Vaccination against tick-borne encephalitis
under therapeutic immunosuppression. Reduced efficacy in heart
transplant recipients. Vaccine 17(7–8):867–874

283. Ljungman P, Duraz V, Magnus L (1991) Response to immuniza-
tion against polio after allogeneic marrow transplantation. Bone
Marrow Transplant 7(2):89–93

284. Barra A et al (1992) Immunogenicity of Haemophilus influenzae
type b conjugate vaccine in allogeneic bone marrow recipients. J
Infect Dis 166(5):1021–1028

285. Guinan EC et al (1994) Polysaccharide conjugate vaccine re-
sponses in bone marrow transplant patients. Transplantation 57(5):677–684

286. Parkkali T et al (1996) Loss of protective immunity to polio, diph-
theria and Haemophilus influenzae type b after allogeneic bone
marrow transplantation. APMIS 104(5):383–388

287. Engelhard D et al (1991) Immune response to polio vaccination in
bone marrow transplant recipients. Bone Marrow Transplant 8(4):
295–300

288. Barra A et al (1992) Immunogenicity of Haemophilus influenzae
type b conjugate vaccine in allogeneic bone marrow recipients. J
Infect Dis 166(5):1021–1028

289. Vance E et al (2007) A randomized study on donor immuniza-
tion with tetanus-diphtheria, Haemophilus influenzae type b and
inactivated poliovirus vaccines to improve the recipient responses
to the same vaccines after allogeneic bone marrow transplantation.
Bone Marrow Transplant 39(3):179–186

290. Guinan EC et al (1994) Polysaccharide conjugate vaccine re-
sponses in bone marrow transplant patients. Transplantation 57(5):677–684

291. Parkkali T et al (1996) A comparison of early and late vaccination
with Haemophilus influenzae type b conjugate and pneumococcal
polysaccharide vaccines after allogeneic BMT. Bone Marrow
Transplant 18(5):961–967

292. Vance E et al (1998) Comparison of multiple immunization sched-
ules for Haemophilus influenzae type b-conjugate and tetanus tox-
oid vaccines following bone marrow transplantation. Bone
Marrow Transplant 22(8):735–741

293. van Wessel K et al (2011) Nontypeable Haemophilus influenzae
invasive disease in The Netherlands: a retrospective surveillance
study 2001–2008. Clin Infect Dis 53(1):e1–e7

294. Kalies H et al (2009) Invasive Haemophilus influenzae infections
in Germany: impact of non-type b serotypes in the post-vaccine
era. BMC Infect Dis 9:45

295. Patel SR et al (2007) Revaccination with measles, tetanus, polio-
virus, Haemophilus influenzae type B, meningococcus C, and
pneumococcus vaccines in children after hematopoietic stem cell
transplantation. Clin Infect Dis 44(5):625–634

296. Jacobsson S et al (2008) Characteristics of Neisseria meningitidis
isolates causing fatal disease. Scand J Infect Dis 40(9):734–744

297. Poolman JT et al (1986) Meningococcal serotypes and serogroup
B disease in north-west Europe. Lancet 2(8506):555–558
298. Onozawa M et al (2008) HB vaccination in the prevention of viral reactivation in allogeneic hematopoietic stem cell transplantation recipients with previous HBV infection. Biol Blood Marrow Transplant 14(11):1226–1230
299. Jaffe D et al (2006) Immunogenicity of recombinant hepatitis B vaccine (rHBV) in recipients of unrelated or related allogeneic hematopoietic cell (HC) transplants. Blood 108(7):2470–2475
300. Idilman R et al (2003) Hepatitis B virus vaccination of recipients and donors of allogeneic peripheral blood stem cell transplantation. Clin Transplant 17(5):438–443
301. Ljungman P et al (1989) Efficacy and safety of vaccination of marrow transplant recipients with a live attenuated measles, mumps, and rubella vaccine. J Infect Dis 159(4):610–615
302. Spoulou V et al (2004) Long-term immunity to measles, mumps and rubella after MMR vaccination among children with bone marrow transplants. Bone Marrow Transplant 33(12):1187–1190
303. King SM et al (1996) Response to measles, mumps and rubella vaccine in paediatric bone marrow transplant recipients. Bone Marrow Transplant 17(4):633–636
304. Sauerbrei A et al (1997) Varicella vaccination in children after bone marrow transplantation. Bone Marrow Transplant 20(5):381–383
305. Issa NC et al (2014) Live attenuated varicella-zoster vaccine in hematopoietic stem cell transplantation recipients. Biol Blood Marrow Transplant 20(2):285–287
306. Kussmaul SC et al (2010) Safety of the live, attenuated varicella vaccine in pediatric recipients of hematopoietic SCTs. Bone Marrow Transplant 45(11):1602–1606
307. Aoki T et al (2016) Safety of live attenuated high-titer varicella-zoster virus vaccine in pediatric allogeneic hematopoietic stem cell transplantation recipients. Bio Blood Marrow Transplant 22(4):771–775
308. Cordonnier C et al (2015) Immunogenicity, safety, and tolerability of 13-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal polysaccharide vaccine in recipients of allogeneic hematopoietic stem cell transplant aged >=2 years: an open-label study. Clin Infect Dis 61(3):313–323
309. Begue PC et al (1998) Comparative reactogenicity and immunogenicity of booster doses of diphtheria-tetanus-acellular pertussis-inactivated poliovirus vaccine and diphtheria-tetanus-inactivated poliovirus vaccine in preadolescents. Pediatr Infect Dis J 17(9):804–809
310. Meerveld-Eggink A et al (2009) Antibody response to polysaccharide conjugate vaccines after nonmyeloablative allogeneic stem cell transplantation. Biol Blood Marrow Transplant 15(12):1523–1530
311. Townsend K et al. (2014) Evaluation and validation of a serum bactericidal antibody assay for Haemophilus influenzae type b and the threshold of protection. Vaccine 32(43):5650–5656
312. Pinson JB, Weart CW (1992) New considerations for Haemophilus influenzae type b vaccination. Clin Pharm 11(4):332–336
313. Centers for Disease, C. and Prevention (2011) License of a meningococcal conjugate vaccine for children aged 2 through 10 years and updated booster dose guidance for adolescents and other persons at increased risk for meningococcal disease–Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 60(30):1018–1019
314. Toneatto D et al (2011) Early clinical experience with a candidate meningococcal B recombinant vaccine (rMenB) in healthy adults. Hum Vaccin 7(7):781–791
315. Mahler MB et al (2012) Safety and immunogenicity of the tetravalent protein-conjugated meningococcal vaccine (MCSV4) in recipients of related and unrelated allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 18(1):145–149
316. Beran J, Xie F, Zent O (2014) Five year follow-up after a first booster vaccination against tick-borne encephalitis following different primary vaccination schedules demonstrates long-term antibody persistence and safety. Vaccine 32(34):4275–4280
317. McMahon BJ et al (2009) Antibody levels and protection after hepatitis B vaccine: results of a 22-year follow-up study and response to a booster dose. J Infect Dis 200(9):1390–1396
318. Tung J et al (2010) A randomized clinical trial of immunization with combined hepatitis A and B versus hepatitis B alone for hepatitis B seroprotection in hemodialysis patients. Am J Kidney Dis 56(4):713–719
319. Kim HN et al (2009) Hepatitis B vaccination in HIV-infected adults: current evidence, recommendations and practical considerations. Int J STD AIDS 20(9):595–600
320. Li Volti S et al (1997) Immune status and the immune response to hepatitis B vaccine: results of a 22-year follow-up study and response to a booster dose. J Infect Dis 200(9):1390–1396
321. Fahlgren K (1988) Two doses of MMR vaccine–sufficient to eradicate measles, mumps and rubella? Scand J Soc Med 16(3):129–135
322. American Academy of Pediatrics Committee on Infectious Diseases (1997) Immunization of adolescents: recommendations of the advisory committee on immunization practices, the american academy of pediatrics, the american academy of family physicians, and the american medical association. Pediatrics 99(3):479–488
323. Nader S et al (1995) Age-related differences in cell-mediated immunity to varicella-zoster virus among children and adults immunized with live attenuated varicella vaccine. J Infect Dis 171(1):13–17