TECHNICAL REPORT FOR THE DRUG SAFETY AND EFFECTIVENESS NETWORK:

INTERVENTIONS FOR THE PROPHYLAXIS AND TREATMENT OF VIRAL, FUNGAL, AND BACTERIAL INFECTIONS IN PATIENTS UNDERGOING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

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EXECUTIVE SUMMARY

Overview

While hematologic stem cell transplant (HSCT) has become a vital therapy in treating patients with a variety of malignant and non-malignant disorders, a challenge that remains is the sizeable risk of mortality related to infection. Although advances in antimicrobial therapies in HSCT have occurred in recent years, infection still accounts for 16–19% of deaths after allogeneic HSCT. Considerable variability exists between treatment facilities regarding the care of HSCT patients with respect to infection prevention and treatment. This systematic review was performed to provide evidence to guide best practice development around this area of HSCT patient care.

Objectives Addressed in this Review

1) *To compare the benefits and harms of competing preventive (includes pre-emptive strategies) and treatment (includes pre-emptive/treatment) agents for viral infections in patients undergoing HSCT to establish a hierarchy of intervention strategies based on their efficacy and safety.*
2) *To compare the benefits and harms of competing preventive (includes pre-emptive strategies) and treatment (includes pre-emptive/treatment) agents for fungal infections in patients undergoing HSCT to establish a hierarchy of intervention strategies based on their efficacy and safety.*
3) *To compare the benefits and harms of competing preventive (includes pre-emptive strategies) and treatment (includes pre-emptive/empiric treatment) agents for bacterial infections in patients undergoing HSCT to establish a hierarchy of intervention strategies based on their efficacy and safety.*

METHODS

The databases Medline, PubMed, Embase, and the Cochrane Register of Controlled Trials were searched for RCTs of patients undergoing HSCT. Studies were included if patients underwent allogeneic HSCT in the treatment of hematologic neoplasias or benign disease, and were randomly allocated to receive a pharmacological intervention for the prophylaxis or treatment of viral, fungal, or bacterial infections. Outcomes of interest included risk of disease (prophylaxis objectives), risk of infection (prophylaxis and pre-emptive treatment objectives), treatment success (treatment objectives), risk of drug-related neutropenia (viral prophylaxis), overall mortality, and non-relapse mortality. Within each objective (i.e., viral, fungal, and bacterial), we conducted separate analyses for prophylaxis, pre-emptive treatment, and treatment, using Bayesian network meta-analysis to compare interventions for outcomes of interest, where feasible. Where necessary, analyses were further subdivided by infectious organism (e.g., cytomegalovirus (CMV), herpes simplex virus (HSV), and varicella zoster virus (VZV) within the viral prophylaxis objective). All outcomes were analysed as binary endpoints, with summary comparisons between regimens reported as odds ratios with 95% credible intervals. For outcomes for which network meta-analyses were not possible, detailed narrative summaries have been provided.

RESULTS

1. RESULTS

Thirty-three trials assessed viral, fungal, and bacterial prophylaxis and treatment in a total of 7,712 patients. The interventions studied, numbers of trials, and numbers of patients have been summarized by review objective in **Table 1**. Overall, there was substantial variability in patient populations with respect to age, underlying hematologic disease, graft source, HLA matching of donor, and presence of graft-versus-host disease (GVHD). Trial publication dates ranged from 1985–2015.

Table 1: Interventions compared in included trials of viral, fungal, and bacterial prophylaxis and treatment					
Viral prophylaxis	**Viral pre-emptive treatment**	**Fungal prophylaxis**	**Fungal treatment**	**Bacterial prophylaxis**	**Bacterial empiric treatment**
13 trials (n = 2,682)	**2 trials (n = 285)**	**12 trials (n = 3,758)**	**2 trials (n = 153)**	**1 trial (n = 155)**	**3 trials (n = 679)**
• Acyclovir • Brincidofovir • Ganciclovir • Letermovir • Maribavir • Valaciclovir • Placebo	• Foscarnet • Ganciclovir • Placebo	• Amphotericin B • Fluconazole • Itraconazole • Ketoconazole • Micafungin • Nystatin • Posaconazole • Voriconazole	• Amphotericin B • Voriconazole • Voriconazole + anidulafungin	• Vancomycin-added prophylaxis • No-vancomycin-added prophylaxis	• Cefepime • Ceftazidime • Meropenem • Netilmicin + imipenemin-cilastatin • Netilmicin + ceftazidime • Piperacillin + tazobactam

1.1. Objective 1: Comparing interventions for viral prophylaxis and pre-emptive treatment

The included viral prophylaxis studies evaluated prevention of CMV (prophylaxis starting at engraftment: 9 trials; prophylaxis of late CMV in high-CMV-risk patients: 1 trial; pre-emptive treatment: 2 trials), HSV (prophylaxis: 2 trials), and VZV (prophylaxis: 1 trial).

Network meta-analysis was only possible for outcomes reported in trials of CMV prophylaxis starting at engraftment. The ideal outcome to assess CMV prophylaxis (i.e., risk of confirmed CMV disease at 100 days post-transplant) was unavailable for many trials. Although most trials reported confirmed CMV disease during extended follow-up, after discontinuation of study drugs, these follow-up times varied substantially. In all networks, most comparisons were informed only by indirect evidence (i.e. head-to-head trials were not available), and many of the direct comparisons were based on single studies with small numbers of patients. This sparse evidence base reduced the robustness of NMAs. Viral prophylaxis objectives that could not undergo NMA were summarized narratively. Clinical interpretation of findings from NMAs and narrative summaries are as follows:

- **Prevention of CMV disease using CMV prophylaxis starting at time of initial hematopoietic engraftment**: Two NMAs were performed on endpoints measuring confirmed CMV disease during study treatment and over extended follow-up. Six interventions were included in the networks: ganciclovir, valaciclovir, acyclovir, brincidofovir, maribavir, and placebo. Few significant differences in prophylactics were found due to sparse evidence. Ganciclovir consistently trended to be the highest ranked intervention in both networks; however, ganciclovir was not significantly more efficacious than valaciclovir, acyclovir, or brincidofovir. Ganciclovir was significantly more efficacious than maribavir and placebo.

- **Impact on overall mortality using CMV prophylaxis starting at time of initial engraftment**: Two NMAs measuring overall mortality at 100 and 180 days post-transplant were performed, including seven different interventions: ganciclovir (both networks), valaciclovir (180 days), acyclovir (180 days), maribavir (both networks), letermovir (100 days), brincidofovir (100 days), and placebo (both networks). No significant differences in prophylactics were found in either NMA. Only one small trial reported overall mortality at both 100 and 180 days post-transplant, highlighting the lack of consistency on reporting of outcomes in CMV prevention studies.

- **Drug-related neutropenia in comparisons of CMV prophylaxis starting at engraftment**: While ganciclovir may be most beneficial in the prevention of CMV disease, it was associated with a significantly higher risk of drug-related neutropenia than all other CMV prophylactic drugs in our NMA, which included valaciclovir, acyclovir, maribavir, and placebo.

- **Prevention of late CMV disease or infection (>100 days post-transplant) in high-CMV-risk patients:** A single study compared valganciclovir with placebo in the prevention of late CMV disease beyond 100 days post-transplant in high-CMV-risk patients. The study design allowed comparison of prophylactic valganciclovir with PCR-guided pre-emptive treatment after 100 days post-transplant. No significant differences were found between prophylactic and pre-emptive treatment, with respect to confirmed CMV disease, mortality, or neutropenia. However, prophylactic valganciclovir was associated with a lower risk of CMV viremia while patients were on the study drug. No other drugs have been tested in RCTs.

- **Pre-emptive treatment of CMV infection:** Two trials evaluating pre-emptive treatment of CMV were identified and summarized narratively. Ganciclovir was found to significantly reduce the risk of confirmed CMV disease, CMV pneumonia, and overall mortality at 180 days post-transplant compared to placebo, but not compared to foscarnet. At 100 days post-transplant, there was no difference in overall mortality between ganciclovir and placebo; however, non-relapse mortality was significantly reduced by ganciclovir.

- **Prevention of confirmed HSV disease:** A pairwise meta-analysis was possible for two older studies published in 1987 and 1989 that compared acyclovir to placebo in the prophylaxis of HSV infection. When pooled, acyclovir was associated with a significantly reduced risk of HSV infection.

- **Prevention of confirmed VZV disease:** A single study published in 1989 compared acyclovir to placebo in the prevention of VZV disease. While on study drugs to one year post-transplant, there was a significant reduction in the risk of confirmed VZV disease in acyclovir patients; however, the difference was not significant once study drugs were discontinued.

- ***Key clinical messages regarding interventions for viral prophylaxis were as follows***:

    - Based on limited evidence, ganciclovir trends to be the most effective antiviral agent to prevent confirmed CMV disease and CMV infection; however, it is associated with significant drug-related neutropenia. It is unclear if other antiviral agents (e.g., valaciclovir, acyclovir, and brincidofovir) may be equally efficacious and yet be associated with lower drug-related neutropenia.

    - When used pre-emptively to treat CMV infection, ganciclovir performed significantly better than placebo in one study; however, it is unclear if other antiviral agents (e.g., foscarnet) may be equally efficacious.

    - All studies evaluating antivirals for HSV and VZV prophylaxis were published >25 years ago. In those studies, acyclovir significantly reduced the risk of both HSV and VZV infection, while patients were on medication.

1.2. Objective 2: Comparing interventions for fungal prophylaxis and treatment

Network meta-analysis was only possible for outcomes reported in trials evaluating fungal prophylaxis. Where NMAs were conducted, most comparisons were informed only by indirect evidence (i.e. head-to-

head trials were not available), and many of the direct comparisons were based on single studies with small numbers of patients. This sparse evidence base reduced the robustness of NMAs. Trials evaluating treatment of fungal infections were summarized narratively. Primary findings from included studies were as follows:

- **Prevention of invasive fungal infections at any follow-up time**: Three NMAs were conducted for (1) proven invasive fungal infections (IFIs), (2) proven or probable IFIs, and (3) any IFI (proven, probable, or possible). Five interventions were included: fluconazole (networks 1, 2, and 3), itraconazole (networks 1, 2, and 3), voriconazole (networks 1, 2, and 3), amphotericin B (networks 1 and 2), and micafungin (network 3 only). No significant differences were demonstrated between any of the fungal prophylaxis agents in networks evaluating proven IFIs or any IFI. Voriconazole was significantly more efficacious than fluconazole in the prevention of proven or probable IFIs; however, this finding should be interpreted cautiously due to limited evidence in the network.

- **Effects of fungal prophylaxis on overall and non-relapse mortality**: One NMA was conducted evaluating overall mortality at 180 days and no significant differences were found amongst the three fungal prophylactics included (voriconazole, fluconazole, itraconazole). However, in a single-study narrative summary, ketoconazole demonstrated significantly reduced overall mortality compared to nystatin within 1 month of engraftment. Similarly, in narrative summaries, itraconazole and fluconazole were not significantly different with respect to non-relapse mortality at 180 or 250 days post-transplant.

- **Prevention of invasive fungal infections in GVHD patients**: Two studies examined fungal prophylaxis starting at the time of GVHD diagnosis. Posaconazole was associated with significantly fewer proven or probable IFIs than fluconazole while patients were on study medication and up to 168 days after the diagnosis of GVHD. Voriconazole and itraconazole appeared equally efficacious at preventing proven and probable IFIs. No significant differences were demonstrated, however, between any of the antifungals with respect to overall mortality in patients with GVHD.

- **Treatment of aspergillosis**: One study demonstrated that voriconazole was significantly more efficacious than amphotericin B in the treatment of aspergillosis, and that voriconazole reduced overall mortality at 12 weeks. Another study demonstrated that there were no significant differences between voriconazole alone and in combination with anidulafungin in either efficacy or overall mortality.

- ***Key clinical messages regarding interventions for fungal prophylaxis and treatment***:

    - Based on limited evidence, voriconazole trends to be more efficacious than itraconazole, amphotericin B, and fluconazole in preventing IFIs after HSCT; however, these findings should be interpreted cautiously. No study evaluated posaconazole immediately after transplant and only three studies compared micafungin with triazole agents. None of these three trials reported data for the preferred more specific outcomes ("proven" and "proven or probable" IFIs).

    - Based on one study, posaconazole appears to be significantly more efficacious than fluconazole in preventing IFIs at the time HSCT patients are diagnosed with GVHD.

    - Based on one study, voriconazole appears more efficacious than amphotericin B in the treatment of aspergillosis in HSCT recipients.

1.3. Objective 3: Comparing interventions for bacterial prophylaxis and treatment

Network meta-analyses were not possible and narrative summaries were performed for bacterial prophylaxis and empiric treatment.

- **Bacterial prophylaxis**: One study assessed the inclusion of vancomycin or not in bacterial prophylaxis regimens. Regimens that included vancomycin were not demonstrated to have significantly improved efficacy for preventing documented Gram-positive cocci infections, septicemia, or fever of unknown origin compared to regimens that did not include vancomycin.

- **Empiric treatment of febrile neutropenia**: Febrile neutropenia was considered a proxy for bacterial infection. Three studies evaluated the treatment of febrile neutropenia in immunocompromised patients, including HSCT recipients, comparing (1) netilmicin + imipenem-cilastatin with netilmicin + ceftazidime, (2) meropenem with ceftazidime, and (3) piperacillin-tazobactam with cefepime. No significant differences were demonstrated between the netilmicin regimens in the improvement of febrile neutropenia. Meropenem was associated with significantly higher clinical success at the end of therapy than ceftazidime. Piperacillin-tazobactam was associated with significantly greater treatment success at 72 hours after the start of therapy compared to cefepime; however, this difference was not significant at later follow-up times. There were no differences in overall mortality between any of the interventions.

- ***Key clinical messages regarding interventions for bacterial prophylaxis and empiric treatment***:

    - There is a significant lack of data regarding antibacterial prophylaxis and empiric treatment of febrile neutropenia in HSCT recipients.

    - Studies evaluating the treatment of febrile neutropenia focused on antipseudomonal agents such as ceftazidime, cefepime, piperacillin-tazobactam, and meropenem. A trend toward better outcomes was suggested in the beta-lactam/beta-lactamase or carbapenem over antipseudomonal cephalosporins.

2. RECOMMENDATIONS AND FUTURE STUDIES

Hematopoietic stem cell transplant recipients are at high risk of life-threatening viral, fungal, and bacterial infections post-transplant due to being severely immune-compromised. Numerous prophylactic, pre-emptive, and empiric treatments are available to reduce the risk of infection, disease, and death; however, some of these agents are associated with significant side-effects. This systematic review of the evidence, incorporating network meta-analyses where possible, was conducted to compare the benefits and harms associated with infectious disease interventions for HSCT recipients. Overall, thirty-three trials were included in the review, encompassing viral, fungal, and bacterial prophylaxis, pre-emptive, and empiric treatment.

We saw consistently across infection domains that there was limited evidence evaluating anti-infection agents in the HSCT population. As well, our NMAs consistently were unable to identify statistically significant differences between interventions for all types of infection prophylaxis and treatment, likely due to this paucity of evidence. We speculate that HSCT clinicians borrow evidence from other populations in their development of clinical strategies for infection control in HSCT patients.

The following key points for clinical practice were identified in this review:

- Ganciclovir is currently the most efficacious antiviral for CMV prophylaxis; however, it is associated with significant neutropenia compared to other anti-CMV agents. Newer yet equally

efficacious antiviral medications or other novel approaches such as CMV vaccination or host-directed immune therapy are needed.

- Voriconazole appears to be better than itraconazole, amphotericin B, and fluconazole in preventing IFI; however, studies evaluating posaconazole and echinocandins were lacking. Clear recommendations regarding fungal prophylaxis in HSCT recipients cannot be made.

- There is a significant lack of data regarding bacterial prophylaxis and empiric treatment of febrile neutropenia in the HSCT setting. Clear recommendations in these areas cannot be made.

At the design stage, future studies of infectious disease interventions for HSCT recipients should carefully consider the comparator of interest, the patient population, and assessment of the economics of the interventions. For example, pre-emptive treatment with ganciclovir remains the standard to which other antiviral strategies should be compared in the future. Similarly, voriconazole should be considered for comparison of other antifungals. The use of antifungal agents in HSCT recipients continues to be extrapolated from other immunocompromised populations and more transplant-focussed studies are recommended. Cost effectiveness should be assessed, given the significant cost of these drugs.

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ACRONYMS AND ABBREVIATIONS

AA = aplastic anemia
aGVHD = acute graft-versus-host disease
ALL = acute lymphoblastic leukemia
AML = acute myeloid leukemia
ATG = antithymocyte globulin
AZA = alemtuzumab
BM = bone marrow
cGVHD = chronic graft-versus-host disease
CI = confidence interval
CML = chronic myelogenous leukemia
CMV = cytomegalovirus
CrI = credible interval
DIC = deviance information criteria
DNA = deoxyribonucleic acid
FE = fixed effects
GVHD = graft-versus-host disease
HCQ = hydroxychloroquine
HSCT = hematopoietic stem cell transplant
HSV=herpes simplex virus
IFI=invasive fungal infection
ITT = intention to treat
K-M = Kaplan-Meier
MDR=multi-drug resistant
MDS = myelodysplastic syndromes
MM = multiple myeloma
MMF = mycophenolate mofetil
MRSA= methicillin-resistant Staphylococcus aureus
MSCs = mesenchymal stem cells
mTOR = mammalian target of rapamycin
MTX = methotrexate
NHL = non-Hodgkins Lymphoma
NMA = network meta-analysis
NR = not reported
OR = odds ratio
PB = peripheral blood
PCR = polymerase chain reaction
PLB = placebo
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT = randomized controlled trial
RE = random effects
SUCRA = surface under the cumulative ranking curve
TNF = tissue necrosis factor
UC = umbilical cord
UDCA = ursodeoxycholic acid
VOD = veno-occlusive disease
VZV=varicella zoster virus

3. INTRODUCTION

While HSCT has become a vital therapy in treating patients with a variety of malignant and non-malignant disorders, a challenge that remains is the sizeable risk of mortality related to infection. Although advances in antimicrobial therapies in HSCT have occurred in recent years, infection still accounts for 16–19% of deaths after allogeneic HSCT.[1] Great variability exists between treatment facilities regarding the care of HSCT patients with respect to infection prevention and treatment. This systematic review will aim to provide evidence to guide best practice development around this area of HSCT patient care.

Ninety percent of infections in HSCT recipients are bacterial in origin.[2] Conditioning regimens prior to stem cell transplant induce cytotoxic effects on epithelial surfaces as well as profound neutropenia. Damage to epithelial barriers, especially the oral and gastrointestinal mucosae, leads to a series of effects, including the initiation of an inflammatory cascade, mucositis, increased mucosal permeability, and translocation of commensal microorganisms across normally impermeable surfaces.[3] Systemically, profound neutropenia caused by the conditioning regimen prevents a normal immune response to invading commensals, increasing the risk of infection. If antimicrobial prophylaxis is not instituted, a potentially life-threatening infection may occur.

Invasion of commensal micro-organisms can occur at any site of reduced epithelial integrity, including the upper and lower respiratory tracts, upper and lower gastrointestinal tracts, and the skin.[3] Injured oral mucosa may allow invasive infections caused by viridans streptococci and/or other oral anaerobes such as *Veillonella* spp., or *Fusobacterium* spp., while invaders of gastrointestinal mucosae may include *Escherichia coli, Klebsiella pneumoniae*, gut anaerobes such as *Clostridium* spp. or *Bacteroides* spp., and opportunistic fungal organisms such as *Candida* spp.[3]

From the gastrointestinal system, microorganisms translocate into the blood stream through damaged mucosae and are extracted from the portal circulation by the liver, where they are phagocytized by Kupffer cells (tissue macrophages), stimulating the production of inflammatory cytokines including interleukin-1 (IL-1).[4] IL-1 acts as an endogenous pyrogen, causing fever and the production of acute phase proteins such as fibrinogen. When the capacity of the Kupffer cells to remove the invading bacteria is overwhelmed, sepsis will occur without therapeutic intervention; however, preventive antimicrobial therapy may temper or prevent the systemic inflammatory response to the bacteremia. Despite antimicrobial therapy, pyrexia may persist due to the ongoing production of IL-1 by the Kupffer cells. Fever in the presence of reduced circulating neutrophils is termed febrile neutropenia.

Typically, febrile neutropenia occurs 10–14 days after the first day of the conditioning regimen.[3] This coincides with the timing of the nadir of the circulating absolute neutrophil count, as well as the time of maximal oral and gastrointestinal mucositis, leading to commensal translocation. The timing of occurrence of febrile neutropenia after reduced-intensity conditioning regimens remains the same despite the induction of less profound neutropenia and mucositis.[3] Febrile neutropenia may or may not be associated with a clinical focus of infection; however, pyrexia may be the earliest and only sign of infection in the neutropenic cancer patient, thus warranting rapid workup and empiric systemic antimicrobial therapy.[3]

Infection prevention in HSCT patients is comprised of both non-pharmacological and pharmacological measures. Non-pharmacological measures include hand hygiene, environmental cleaning/disinfection, isolation, and surveillance for colonization of patients by resistant bacterial organisms (e.g., vancomycin-resistant *Enterococcus* (VRE)).[5, 6] In large hospitals, exposure to antibiotics and host factors rather than a breakdown in infection control have been associated with colonization with VRE in HSCT patients.[5] Thus, antimicrobial stewardship programs with dedicated staff are recommended for HSCT units to reduce the use of broad-spectrum antimicrobials and the acquisition of multi-drug resistant (MDR) organisms.[5] Other pharmacological measures for infection prevention include interventions to modify gastrointestinal flora,

antimicrobial prophylaxis, and empiric and targeted pharmacotherapy. Selective digestive decontamination has been used by some clinicians to reduce the intestinal load of Gram-negative commensal organisms that may subsequently invade the blood stream after HSCT.[5] However, a lack of robust evidence of positive long-term outcomes and a concern over promotion of Gram-negative resistance have reduced the perceived utility and widespread use of selective digestive decontamination.[5] Similarly, modifying gastrointestinal flora after antibiotic therapy to reduce the density of MDR organisms through the use of probiotics or fecal microbiota transplantation have been considered; however, the risk of blood stream infections from the probiotic or transplanted organisms is high in HSCT patients. Further clinical research in these areas is needed.[5]

Antibiotic prophylaxis following HSCT usually comprises the use of an anti-pseudomonal antibiotic such as a fluoroquinolone (e.g., levofloxacin or ciprofloxacin), a third- or fourth-generation cephalosporin (e.g., cefepime), or a macrolide (e.g., azithromycin).[5, 6] See the description of interventions below for more detail. Reductions in febrile neutropenia events, bacteremia, hospitalization, and mortality have been demonstrated with the use of fluoroquinolone prophylaxis[5]; however, fluoroquinolone resistance prevalence can be high and breakthrough bacteremias associated with methicillin-resistant *Staphylococcus aureus* (MRSA), MDR *Escherichia coli*, and *Pseudomonas aeruginosa* have been associated with fluoroquinolone prophylaxis.[5] Because of breakthrough infections, antibiotic prophylaxis may result in increased use of carbapenems, a group of "last-resort" antibiotics that currently are associated with minimal resistance, ultimately promoting resistance to this reserve group of antimicrobials as well. Due to the cost of antibacterial prophylaxis and the potential to promote resistance, some recent HSCT patient management guidelines recommend against the routine use of antimicrobial prophylaxis for Gram-negative bacteremia.[5]

In patients that develop febrile neutropenia, initial antimicrobial selection is empiric, based on the suspected source of infection, the microbial agents known to cause local nosocomial infections and their antimicrobial resistance patterns, and patient factors such as clinical complications and risk factors for complications of severe infections and for MDR organisms.[6-9] Broad-spectrum antimicrobials are often used. Two competing strategies for empiric therapy of febrile neutropenia have been proposed—escalation and de-escalation therapy. Escalation therapy is defined as the use of a standard monotherapy initially, then the addition of other drugs (i.e., combination therapy) if the patient's condition worsens or resistant organisms are detected.[2, 9] Generally, this approach is adopted in centres where resistant pathogens are not common and in patients without risk factors predisposing to resistant infections.[9] De-escalation therapy is defined as the use of a combination therapy active against the MDR organism expected in the treatment centre, with discontinuation of the anti-MDR antimicrobial if the resistant microbe is not isolated.[9] This approach is adopted in centres where antimicrobial resistance is common and in patients with risk factors for MDR infections.[9] Guidelines are conflicted regarding the implementation of escalation and de-escalation strategies, with the escalation approach thought to reduce the pressure for carbapenem resistance, toxicity, and treatment costs, and the de-escalation approach thought to provide potentially broader bacterial coverage in the first 48 hours of treatment, before pathogen confirmation.[7] A recent review of guidelines for the empiric treatment of febrile neutropenia suggests that a monotherapy should be considered as the initial empiric treatment, given the risk of nephrotoxicity in combination therapies.[7] These monotherapies may include carbapenems, a third- or fourth-generation cephalosporin with anti-pseudomonal activity), or piperacillin-tazobactam. The review suggested combination therapy be limited to cases with antimicrobial resistance or clinical complications.[7] In these cases, addition of an aminoglycoside, beta-lactamase inhibitor (e.g., tazobactam), or fluoroquinolone was recommended in adults, and addition of a second Gram-negative agent or glycopeptide was recommended in children.[7]

Any antibiotic therapy can reduce the load of protective commensal bacteria, leading to the overgrowth of opportunistic organisms, including fungal organisms. Thus, antifungal prophylaxis or empiric therapy may be required in combination with antibiotic medications in patients considered at high risk of fungal infection (i.e., those with persistent or recurrent fever after 4–7 days of antibiotics, whose overall duration of

neutropenia is expected to be >7 days).[8] Routine antifungal prophylaxis in patients without risk factors is not recommended.[8] Recommended antifungals for high-risk HSCT patients include fluconazole, itraconazole, voriconazole, posaconazole, micafungin, and caspofungin.[6, 8]

Viral infections may also cause severe morbidity following HSCT. Cytomegalovirus (CMV) is a human Herpesvirus, with a wide spectrum of disease severity, depending on the immune status of the host. Like all Herpesviruses, CMV can lie latent, deep in body tissues, through immunosuppressive mechanisms of its own,[10] until a time when host immunity is weak and it can reactivate to cause disease. In the immunocompromised HSCT recipient, CMV can cause significant morbidity and mortality, with the natural history of the disease being dependent upon the relationship of the infection status of both donor and recipient.[10] To prevent primary infections and recrudescence of latent CMV infection, prophylactic antiviral drugs (e.g., acyclovir, ganciclovir, valaciclovir) are provided to seronegative recipients with seropositive donors and to all CMV-seropositive recipients.[10]

CMV-negative patients lack acquired immunity to CMV and are especially at risk of developing highly pathogenic primary infections, if they receive stem cells from a CMV-positive donor.[11] While prophylaxis may effectively suppress primary CMV infection in these patients, it also prevents development of acquired immunity. When prophylaxis is removed, CMV viral rebound can be expected, and without acquired immunity, severe disease may occur, including pneumonia, hepatitis, and effects throughout the entire gastrointestinal tract.[10] Because of its broad range of severe effects, primary CMV infection post-HSCT may be confused with widespread GVHD. CMV-negative recipients of CMV-positive stem cells may also experience higher mortality due to bacterial and fungal infections than those receiving CMV-negative stem cells, possibly due to the innate immunosuppressive effects of CMV or its therapy.[10]

Compared to CMV-negative HSCT recipients, CMV-positive recipients are at a lower risk of developing severe CMV-related disease when transplanted with CMV-positive stem cells because pre-existing acquired immunity aids in the prevention of primary CMV infection once viral prophylaxis is discontinued. While the immunosuppressive effects of conditioning regimens may cause latent CMV infection to reactivate, the disease associated with reactivated CMV infections is usually less severe than that associated with primary CMV infections. Reactivation is often treated pre-emptively using ganciclovir or valganciclovir, based on increasing viral load identified by quantitative PCR surveillance.[10] In the literature, it is suggested that patients with reactivated CMV may be less likely to develop GVHD, potentially due to immunosuppressive effects of the virus itself.

3.1. Natural history of infections in HSCT recipients

During the pre-engraftment phase (0–45 days after transplant), prolonged, profound neutropenia and inevitable breaks in mucocutaneous barriers heighten the risk for primary viral, fungal, and bacterial infections, as well as reactivation of latent viral infections. Although lower, infection risk continues to be high in the early post-engraftment phase (30–100 days after transplant), when cell-mediated immunity may be impaired due to GVHD and concomitant immunosuppressive therapy. During this time, patients continue to be at risk of invasive bacterial infections and viral infections such as CMV, Epstein-Barr virus (EBV), and varicella zoster virus (VZV). During late post-engraftment (>100 days post-transplant), the presence of chronic GVHD can cause continued susceptibility to infections caused by viruses and encapsulated bacteria such as *Streptococcus pneumoniae*. As well during this period, removal of antiviral drugs may result in rebound CMV disease that may mimic GVHD.

Time since transplantation and the presence of GVHD are the primary risk factors for infection occurring in HSCT recipients; however, other influencing factors include donor/host histocompatibility (HLA mismatched vs. matched; allogeneic vs. autologous/syngeneic), underlying disease severity at the time of transplant, graft type (umbilical cord vs. bone marrow vs. peripheral blood stem cells), graft contents (T-

cell depletion vs. no T-cell depletion), conditioning regimen intensity, and occurrence of successful neutrophil engraftment.[6, 12]

3.2. Interventions available for use in the prophylaxis and treatment of viral, fungal, and bacterial infections

A variety of pharmacologic agents are used for the prevention and treatment of different types of infections in patients undergoing HSCT. They include the following:

For viral infections:

- ***Nucleoside analogue antivirals (e.g., acyclovir, valaciclovir, famciclovir)***: The nucleoside analogue antivirals act to competitively inhibit viral DNA synthesis in infected host cells. They selectively inhibit herpes simplex virus types (HSV) 1 and 2 and varicella-zoster virus (VZV), with modest activity against cytomegalovirus (CMV).[13] Valaciclovir and famciclovir are later generation agents.

- ***Acyclic analogues of nucleoside guanosine (e.g., ganciclovir, valganciclovir)***: Ganciclovir and its prodrug valganciclovir are antivirals that act to inhibit viral DNA synthesis in infected host cells.[14] These drugs are used primarily for the treatment of CMV infections.

- ***Letermovir***: Letermovir is an investigational antiviral drug for the treatment of CMV infections. It is currently under testing and has been granted fast-track status by the FDA. Letermovir is derived from the quinazolines and acts to inhibit human CMV viral terminase.[15]

- ***Brincidofovir (CMX001):*** Brincidofovir is also an investigational antiviral drug for the treatment of CMV, HSV, and VZV. Like letermovir, brincidofovir has also been granted fast-track status by the FDA and is being studied in phase III clinical trials. This agent is a prodrug of cidofovir, converted intracellularly, which reduces its relative toxicity. It inhibits viral DNA polymerase, with a broad spectrum of activity against double-stranded DNA viruses.[16]

For bacterial infections:

- ***Trimethoprim/Sulfamethoxazole***: Trimethoprim/sulphamethoxazole is a combination antibiotic that inhibits folate biosynthesis and metabolism within bacterial cells.[17] It is considered to be bactericidal and is the mainstay for prevention of *Pneumocystis* pneumonia in HSCT patients.[12]

- ***Fluoroquinolones (e.g., levofloxacin, ciprofloxacin)***: The fluoroquinolones are bacterial DNA-gyrase inhibitors and act by preventing the unwinding of DNA for replication.[18] Fluoroquinolones are commonly used to prevent infection 0–100 days after adult HSCT.[12] Their use in children is limited due to associated musculoskeletal adverse effects but can be used in high-risk groups, such as allogeneic HSCT or during induction therapy for acute leukemia. Resistance due to frequent prophylactic use may limit their utility.[12]

- ***Beta-lactam antibiotics*:** Beta-lactam antibiotics inhibit bacterial cell wall formation, having a bactericidal action against Gram-negative and, for some beta-lactams, Gram-positive organisms.[19] Penicillins (e.g., amoxicillin, dicloxacillin, piperacillin), cephalosporins (e.g., cefepime, ceftazidime), and carbapenems are all beta-lactam antibiotics. Some beta-lactams have activity against *Pseudomonas* infections (e.g., ceftazidime, cefepime, imipenem, meropenem). Carbapenems are generally considered to be reserve antibiotics, to be used only after other treatment options have failed; however, some guidelines recommend them as an option for initial

monotherapy for HSCT patients with febrile neutropenia[7]. Widespread resistance to penicillin and cephalosporin beta-lactams, and increasingly identified resistance to carbapenems, has raised concern and resulted in increased interest in combination therapies of beta-lactam antibiotics (e.g., cefepime or piperacillin) with beta-lactamase inhibitors (e.g., tazobactam or clavulanate).[7, 20]

- ***Glycopeptide antibiotics*** (***e.g. vancomycin***): Glycopeptide antibiotics inhibit peptidoglycan synthesis, halting bacterial cell-wall synthesis in Gram-positive organisms only.[19] They are often used in severely ill patients who have been diagnosed with a Gram-positive infection or a beta-lactam-resistant infection, and in patients who have a hypersensitivity to beta-lactams. Increasing isolation of vancomycin-resistant organisms and a possible increase in mortality in patients in which resistant organisms are found has discouraged the routine empirical use of vancomycin in HSCT patients.[5, 12]

- ***Linezolid:*** Linezolid is a relatively recently developed synthetic oxazolidinone antibiotic that interrupts the production of bacterial intracellular proteins but not DNA or RNA, resulting in a bacteriostatic activity in Gram-positive organisms.[21] Linezolid is generally used to treat vancomycin-resistant enterococcus (VRE) infections and infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA).[5, 9] Resistance to linezolid remains rare[22]; however, its superiority to vancomycin remains debatable and its cost is a limitation.[22]

For fungal infections:

- ***Triazole antifungals (e.g., fluconazole, itraconazole, voriconazole, posaconazole)***: The triazole antifungals are antifungal medications that interfere with fungal cell membrane synthesis.[23] Posaconazole has a broader spectrum activity than itraconazole, which is broader than fluconazole. The triazoles have fewer nephrotoxic effects than amphotericin B but many drug interactions.

- ***Amphotericin B***: Amphotericin B is a polyene antifungal agent that disrupts fungal cell wall synthesis.[24] It has a broad spectrum of activity, is considered fungicidal, and is often the standard treatment for severe, invasive fungal infections. Due to its high toxicity, it is usually reserved for life-threatening conditions but is less toxic in its liposomal formulation.

- ***Echinocandin antifungals (e.g., caspofungin, micafungin)***: The echinocandin antifungals target the fungal cell wall, resulting in a fungicidal activity.[25] They are especially active against *Candida* spp. that may be resistant to triazole antifungals, and have low nephro- and hepatotoxicity. Micafungin has been approved by the FDA as a prophylactic agent for *Candida* infections in adults undergoing HSCT.

3.3. Why this review is important

Numerous agents are used for the prophylaxis and treatment of viral, bacterial, and fungal infections at various phases of the HSCT process. Additionally, considerable practice variation exists between institutions given the lack of comparative evidence to support these interventions, with head-to-head data lacking for many comparisons of possible treatments. A systematic review of the evidence, incorporating network meta-analyses to compare these agents and their impact on key outcomes, will help to explore the relative benefits and harms of competing interventions in this area. Network meta-analysis is an increasingly used methodology used to address evidence synthesis situations wherein there exists multiple clinically relevant comparators of interest and there is both direct and indirect evidence available; given the varied treatments available under the current treatment scenario, this provided the ideal framework to address the current research questions of interest.

3.4. Objectives of this systematic review

1) To compare the benefits and harms of competing preventive (includes pre-emptive strategies) and treatment (includes pre-emptive/empiric treatment) agents for viral infections in patients undergoing HSCT to establish a hierarchy of intervention strategies based on their efficacy and safety.

2) To compare the benefits and harms of competing preventive (includes pre-emptive strategies) and treatment (includes pre-emptive/empiric treatment) agents for fungal infections in patients undergoing HSCT to establish a hierarchy of intervention strategies based on their efficacy and safety.

3) To compare the benefits and harms of competing preventive (includes pre-emptive strategies) and treatment (includes pre-emptive/empiric treatment) agents for bacterial infections in patients undergoing HSCT to establish a hierarchy of intervention strategies based on their efficacy and safety.

4. REVIEW METHODS

The checklist from the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Extension Statement for Network Meta-analyses was used to guide preparation of this report.[26] A completed checklist is provided in the appendices to this report. This report also adheres to the recent CADTH Guidance Document on Reporting Indirect Comparisons: https://www.cadth.ca/guidance-document-on-reporting-indirect-comparisons.

4.1. Protocol and Registration

The protocol for the review was developed using an integrative framework amongst researchers from the Ottawa Hospital Research Institute, the Canadian Bone Marrow Transplant Group, and the pan-Canadian Oncology Drug Review. The protocol for the review was subsequently made openly available online in the University of Ottawa Library's online repository, and can be found at the following link: https://www.ruor.uottawa.ca (search the term 'DSEN stem cell transplantation'). The protocol was also registered in PROSPERO (CRD42015026738).

4.2. Study Eligibility Criteria

Table 1 provides a detailed summary of the eligibility criteria set out for this review using the Population-Interventions-Comparators-Outcomes-Study design (PICOS) framework.

Table 1: Overview of study eligibility criteria for prophylaxis and pre-emptive/empiric treatment of viral, fungal, and bacterial infections

PICOS Element	Description
Population	Patients undergoing allogeneic HSCT for the treatment of Acute Lymphoblastic Leukemia (ALL), Non-Hodgkin Lymphoma (NHL), Chronic Myelogenous Leukemia (CML), Myelodysplastic Syndromes (MDS), Acute Myeloid Leukemia (AML), Multiple Myeloma (MM), Aplastic Anemia (AA), or other cancers. Population criteria for empiric treatment studies were expanded to include studies that included allogeneic HSCT recipients and any other immunocompromised patient group, regardless if allogeneic HSCT subgroup data were reported.

Table 1: Overview of study eligibility criteria for prophylaxis and pre-emptive/empiric treatment of viral, fungal, and bacterial infections	
PICOS Element	**Description**
Interventions/Comparators	For all agents, no restrictions on treatment dosage will be used. Both intravenous and oral formats of all agents will be eligible. Comparisons of dose or administration within a single agent will be excluded. **Viral agents** • Nucleoside analogue antivirals, acyclic analogues of nucleoside guanosine, letermovir, brincidofovir, foscarnet, placebo/no treatment **Fungal agents** • Triazoles except posaconazole (fluconazole, itraconazole, voriconazole), posaconazole, echinocandin anti-fungals, amphotericin B, placebo/no treatment **Bacterial agents** • Fluoroquinolones, penicillin and derivatives, cephalosporins, carbapenems, trimethoprim/sulfamethoxazole, glycopeptide antibiotics (vancomycin as well as others), linezolid, placebo/no treatment
Outcomes	• Efficacy of prophylaxis/treatment • All-cause mortality • Transplant-related mortality • Relapse of underlying disease • % of patients with febrile neutropenia • Incidence of acyclovir-resistant HSV; incidence of ganciclovir/valganciclovir-resistant CMV pneumonia
Study Design	Randomized controlled trials

- ***Dealing with duplicate publications and other characteristics.*** For studies that are associated with multiple publications (e.g., updates of different follow-up durations), we will retain the most up-to-date reports and make note of all related manuscripts. Only studies published in English will be retained for inclusion.[27]

4.3. Search strategies to identify relevant literature

In June 2013, requestors of this DSEN query conducted preliminary work with members of the MAGIC team based at The Ottawa Hospital to explore some of the literature available for developing clinical guidance related to allogeneic HSCT. This was conducted in the form of a scoping review of published RCTs, and involved a systematic search for studies for various aspects of care in the realm of HSCT. The search was developed and conducted with the input of an information specialist and covered the following databases: Medline, PubMed, Embase, and the Cochrane Register of Controlled Trials. The search was also peer reviewed by a second information specialist using PRESS criteria.[28] The search strategy is provided in **Appendix 1**, along with a flow diagram summarizing results from screening.

Following screening of abstracts and then potentially relevant full text reports by two independent researchers, approximately 700 RCTs were identified in relation to the following aspects of care: 1) donor selection and source of cells, 2) conditioning regimens, 3) prevention and treatment of GVHD, 4) transfusion-related interventions, 5) prevention and treatment of infections, 6) prevention and treatment of hepatic sinusoidal obstruction syndrome, 7) prevention and/or treatment of bronchiolitis obliterans, and 8) others that were not otherwise classifiable. There were approximately 50 RCTs that were identified as relevant to the comparison of conditioning regimens. We updated the search to identify new studies published since June 2013 for inclusion in the proposed review in August 2015, producing a total of approximately 2,000 additional citations for review. These were combined with those from the initial search to establish our evidence base.

4.4. Process of study selection

For new citations obtained from the updated search, review of citations based on title, keywords, and abstract (Level 1 screening) and full text articles (Level 2 screening) were carried out independently by two reviewers. Level 1 citations deemed potentially relevant or lacking sufficient information to make a decision were carried forward to Level 2. Study selection was conducted using Distiller Systematic Review Software (DSR) (Evidence Partners, Inc; Ottawa, Canada). Where consensus was not achieved following discussion, a third independent party was consulted to settle disagreements. At both stages of screening, a pilot exercise of a number of abstracts/full texts was performed to establish a baseline amongst the reviewers. The process of literature selection has been reported using a flow diagram as recommended by the PRISMA statement[29], and encompasses both the 2013 and 2015 searches performed. Studies were not screened on outcome; however, studies included at the full-text stage that did not have an outcome of interest to the review did not move forward for data extraction.

4.5. Data collection from included studies

Primary data collection of included studies was performed independently by two reviewers using a standardized electronic data collection form in Distiller®. Collected data was compared for accuracy and agreement, with disagreements settled by discussion. The following elements were collected for each included study:

- study characteristics (e.g., authors, year of publication, journal, countries of performance);
- patient characteristics (e.g., eligibility criteria; number per group; key demographics, including age, gender, primary disease diagnosis, disease duration, comorbidities, HLA matching, CMV status of donors and recipients);
- Intervention data (e.g., drug name, dosage, frequency);
- Outcome data (e.g., number of events and number of patients randomized for binary endpoints, and means with standard deviations for continuous endpoints).

All study characteristics were summarized in tabular form to facilitate inspection and discussion with clinical experts in terms of study heterogeneity, grouping of interventions, and other such topics required to inform analysis.

All relevant RCTs were evaluated using the revised Cochrane risk-of bias (RoB) tool.[30] The Cochrane RoB tool evaluates seven domains including sequence generation, allocation concealment, blinding, missing outcome data, selective outcome reporting, attrition, and "other sources of bias." Other sources of bias evaluated for this review included dissimilarities between treatment groups, with respect to demographics, comorbidities, co-interventions, and other factors. An overall assessment of the RoB for each study was determined for each general outcome category (i.e., efficacy, mortality). Any disagreements were resolved through discussion. Results from these appraisals have been summarized in the appendices of the report.

4.5.1. Outcomes of interest

4.5.1.1. Efficacy outcomes

Efficacy outcomes of interest varied by objective (e.g., viral, fungal, or bacterial prophylaxis or treatment) and were guided by the available evidence, with respect to testing methods and follow-up time.

Viral prophylaxis and pre-emptive treatment efficacy outcomes included confirmed CMV disease, CMV disease or infection, confirmed CMV pneumonia, localized Varicella Zoster Virus (VZV) infection, and localized Herpes Simplex Virus (HSV) infection. Patients with confirmed CMV disease must have been exhibiting clinical signs or symptoms of disease, with at least one positive confirmatory test (e.g., PCR,

culture, histopathology, or cytology). To be included in the "CMV disease or infection" outcome, patients must have exhibited clinical signs or symptoms of disease or have a positive laboratory test, with one of the tests used for infection detection being PCR. CMV PCR was identified by our clinical experts as being the most sensitive test available for detection of active CMV viremia, thus, the "CMV disease or infection" outcome was considered the most sensitive CMV outcome definition in this review.

Fungal prophylaxis efficacy outcomes of interest included "proven" invasive fungal infections (IFIs), and "proven or probable" IFIs. Most studies used the same consensus criteria to define "proven," "probable," and "possible" IFIs;[31] however, there was minor heterogeneity in fungal testing methods used in the application of the criteria.

We anticipated variation in the follow-up times reported in the included studies for all outcomes given potential variation in the duration of the treatments evaluated. Ultimately, the duration of treatment for most of the studied viral prophylactics was until 100 days post-transplant. Thus, follow-up times of 100 and 180 days post-transplant were selected for CMV efficacy network meta-analyses in order to capture disease occurring during study therapy and late CMV disease occurring after discontinuation of study drugs. Duration of fungal prophylaxis was variable between studies as were follow-up times, and ultimately, sufficient evidence was only available for network meta-analysis at a follow-up of 180 days post-transplant.

For all other objectives (i.e., fungal treatment, and bacterial prophylaxis and treatment), there was a paucity of studies and outcomes were summarized narratively, guided by the outcomes reported in the included studies. Empiric fungal treatment efficacy outcomes reported included "complete response" (i.e., resolution of all signs and symptoms, and more than 90% radiographic improvement compared with baseline), "partial response" (i.e., clinical improvement and more than 50% radiographic improvement compared with baseline), and "overall success" (i.e., complete or partial response).

Bacterial prophylaxis efficacy outcomes included documented Gram-positive cocci infection, documented septicemia (including Gram-positive infection), and episodes of fever of unknown origin.

Empiric treatment of febrile neutropenia was considered a proxy for empiric treatment of bacterial infections. In one study of empiric treatment of febrile neutropenia, efficacy was reported as "improvement" of microbiologically or clinically documented episodes or episodes of fever of unknown origin, with "improvement" defined as lasting defervescence and complete disappearance of cultural signs of infection without modification of therapy, except addition of antifungal, within 72 hours of start of study drug. In another study of empiric treatment of febrile neutropenia, efficacy was reported as "clinical success" in microbiologically or clinically defined infections or episodes of fever of unknown origin, with "clinical success" defined as cure, cure with modification (i.e., new fever after initial defervescence, requiring a change in antimicrobial agent or addition of antifungal or antiviral), or improvement. A third study evaluating empiric treatment of febrile neutropenia reported efficacy as "treatment success" at various time points, with "treatment success" defined as resolution of all signs/symptoms of infection without modification of the initial antibacterial regimen.

4.5.1.2. Mortality outcomes

Mortality outcomes of interest for all objectives included overall mortality at 100 and 180 days post-transplant. Other time points have been summarized narratively, where they have been reported.

For objectives where it was reported, non-relapse mortality has been summarized narratively as the competing risk of disease relapse prevented network meta-analysis, without a time-to-event framework.

4.5.1.3. Specific harms

Neutropenia is a recognized adverse event associated with the toxicity of some antiviral medications (e.g., ganciclovir). Neutropenia is commonly defined by a cutoff of the absolute neutrophil count (ANC), with cutoffs of ≤1000, ≤750, and ≤500 cells/µl commonly used to define mild, moderate, and severe neutropenia, respectively. For this review, we were interested in neutropenic events observed while on study drugs (i.e., drug-related neutropenia). Sufficient data for network meta-analysis were only available for drug-related neutropenia at an ANC cutoff of ≤750 cells/µl in CMV prophylaxis studies. The data available at other ANC cutoffs, including both drug-related and overall neutropenia episodes, have been summarized narratively.

4.6. Classification of interventions for network meta-analysis

Input from clinical experts deemed that analyses for this review should be focused at the drug level, with no additional reflection of drug dosage when establishing treatment groups for meta-analyses. Thus, all interventions of the same drug were grouped into the same node in the network, regardless of dosage or route of administration. Studies evaluating 2 or more different dosages of the same drug or different routes of administration of the same drug, without another control arm, were not included in the review. In studies where multiple dosages of a drug were compared to another drug or placebo, we used the study drug dosage deemed to have the most clinical effectiveness by the study authors (i.e., a balance of high efficacy and low harms) in our network meta-analyses.

4.7. Methods for meta-analysis and network meta-analysis

A priori, there was interest to explore the feasibility of network meta-analysis for all clinical endpoints given the presence of multiple interventions of interest. For each outcome, we first assessed whether a connected treatment network of interventions was present (a necessary criterion for NMA). When this was present, we next explored the extent of homogeneity/similarity of patient populations and study methods across included studies, as the performance of valid network meta-analyses requires a similar distribution of effect modifiers across studies; where more than one study was present for pairwise comparisons within the treatment network, we also assessed statistical heterogeneity of corresponding treatment effects using the I^2 statistic. If homogeneity within pairwise comparisons and across comparisons within the network were judged sufficient, network meta-analyses were performed. Where studies could not be included in a network due to poor reporting of specific interventions or extensive between-study heterogeneity, a narrative summary of the study was undertaken. Similarly, where networks could not be generated due to fragmentation and low numbers of studies, pairwise ORs were calculated to identify regimen comparisons with significant associations with the various outcomes, and narrative summaries for each outcome were written.

Traditional pairwise frequentist meta-analyses were also conducted using the statistical software Comprehensive Meta-analysis© (Biostat, Inc., Englewood, NJ: https://www.meta-analysis.com/). Both fixed and random effects models were fit and assessments of heterogeneity were made using the I^2 statistic. The results of the traditional pairwise meta-analyses were useful in the evaluation of heterogeneity and inconsistency in the network meta-analyses discussed below.

Bayesian network meta-analyses were conducted using well established methods described by the National Institute for Clinical Excellence.[30, 32] All analyses were conducted using WinBUGS software and the algorithms presented in technical guidance documents published by NICE. Both fixed and random effects models were fit to arm-level data. All models were fit using 10,000 or more burn-in iterations and 10,000 sampling iterations. Model convergence was assessed by inspection of trace plots and Monte Carlo standard error of the estimated parameters.

Model fit was evaluated by posterior residual deviance values for both FE and RE models, with the model fit assumed to be adequate if the posterior residual deviance was similar to the number of data points in the model. DIC values were used to compare the relative fit of the models—a model was identified as having a relatively better fit if its DIC value was 5 points or lower than the DIC of another model. However, if the network contained many single-study connections between interventions, results from the FE model were preferred. All of the networks analysed for this report were comprised mainly of single-study connections; thus, results from FE models have been summarized with findings from random effects models provided in the report's appendices. This approach has previously been seen in applications in other clinical realms and avoids misleading summary estimates which can be a consequence of the presence of a poorly estimated between-study variance parameter.[33]

4.8. Summarizing measures of effect

4.8.1. Summary measures and reference interventions

All outcomes of interest were assessed as binary endpoints, allowing pairwise comparisons (whether from individual studies or from meta-analysis) to be summarized using odds ratios (ORs) and corresponding 95% credible intervals (CrIs). Odds ratios obtained through traditional pairwise meta-analyses were compared to ORs obtained from network meta-analyses to aid in evaluation of consistency between the direct and indirect evidence of the network.

For each outcome of interest, forest plots were generated to provide a visual display of efficacy of each regimen in the network compared to placebo or the current treatment standard, when a placebo node was not included in the network. A placebo node was not present in networks of the fungal prophylaxis studies, and consequently, fluconazole was selected as the referent for forest plot representations, given its widespread use in the HSCT community. All ORs <1 in analyses presented in this report suggest the comparator regimen had greater efficacy than placebo, while ORs >1 indicated the comparison regimen had lower efficacy than placebo. For all analyses, 95% credible intervals which included the value of 1 were considered to indicate that there was no statistically significant difference between the comparison regimen and placebo.

4.8.2. Graphical presentations of findings

Forest plots of summary comparisons versus placebo or the treatment standard have been presented for all endpoints where network meta-analyses were performed. Additionally, *league tables* presenting all pairwise comparisons estimated from network meta-analysis were prepared; in these tables, interventions in the upper/left-most region of the league table have potentially greater efficacy than interventions appearing lower and further right in the table. For each league table, interventions are ordered from left to right in terms of decreasing SUCRA value, meaning preferred interventions are those presented on the left of the table (as SUCRA values nearer 1 suggest preferred interventions). The SUCRA value[34] for each intervention has also been presented above the intervention, allowing evaluation of relative rankings of interventions. One intervention may appear above another in the league table; however, their SUCRA values may show little difference, indicating inferences regarding relative ranking should be made with caution. ORs and 95% CrIs should be considered the primary means of assessing the importance of differences between interventions.

League tables can be complex to interpret in the presence of many interventions. Furthermore, when evidence networks consist of many interventions and the comparisons made within trials are broad, there may be varying degrees of faith in pairwise comparisons dependent upon the number of intermediate treatments between therapies; those with just one intermediate therapy are often called *simple indirect comparisons*, while those with more intermediate therapies are called *compound indirect evidence.* Comparisons of treatments involving direct evidence (i.e., where at least one head-head trial informs the

comparison of two therapies) are commonly considered of greatest validity, while comparisons informed by simple indirect evidence are typically considered of greater validity than comparisons informed by compound indirect evidence. We have color-coded league tables of summary findings in this report to demonstrate key sources of evidence for each comparison as follows:

- Red squares denote pairwise comparisons with at least one head-to-head trial available;
- Orange squares denote pairwise comparisons with simple indirect evidence available;
- Yellow squares denote pairwise comparisons with compound indirect evidence available.

4.9. Assessment of heterogeneity and inconsistency for network meta-analyses

An important step in the practice of systematic reviews that incorporate network meta-analyses is the validation of the assumption that patients in the included trials are 'jointly randomizable,' or in other words, that they are sufficiently homogeneous clinically that a patient in any one of the studies could have been a patient in any of the other included trials.[35] We empirically evaluated this assumption by review of the patient eligibility criteria and pertinent patient demographics, in collaboration with our participating clinical experts (DA, JC).

To ensure homogeneity and similarity across pairwise comparisons in the treatment network, we compared the descriptive statistics of key measures across the different pairwise comparisons in the network to verify they were similar. To identify covariates necessary for review, we consulted our clinical expert team members and grouped traits that were identified in past studies of prognostic risk factors. The following characteristics were considered most important to the establishment of transitivity within and across pairwise comparisons:

- Patient age and gender distribution;
- Distribution of primary diseases (e.g., AML, ALL, CML);
- Year of study publication (for consideration of changes in co-interventions such as newer conditioning regimens and more effective GVHD prophylaxis, the availability of PCR testing, and changes in antimicrobial resistance patterns);
- % of patients receiving an unrelated donor transplant;
- % of patients with full HLA-matched donor;
- source of donor cells (bone marrow, peripheral blood stem cells, umbilical cord blood);
- % of patients with GVHD;
- For viral studies, the serostatus of recipients and donors with respect to the viral pathogen of interest.

Homogeneity in the timing of the start of viral and fungal prophylactic therapies with respect to transplant as well as the duration of treatment were also considered. Only studies evaluating CMV prophylaxis starting at engraftment were included in network meta-analyses. Studies evaluating CMV prophylaxis starting prior to or at the time of transplant, with some treatment arms changing therapy at engraftment were excluded. One study evaluating CMV prophylaxis in the late post-transplant period (i.e., ~100 days post-transplant) was summarized separately. Studies evaluating pre-emptive viral therapeutics were analysed separately from prophylaxis studies. All fungal prophylaxis studies began study drugs either at the start of the conditioning regimen or at the time of transplant. The duration of treatment varied across viral and fungal prophylaxis studies and this source of heterogeneity has been considered in the interpretation of results.

The duration of follow-up was considered a potential issue in both viral and fungal prophylaxis analyses. In consultation with our clinical experts, viral prophylaxis analyses were conducted using data from two follow-up times: (1) at ≤100 days post-transplant and (2) at extended follow-up >100 days post-transplant. The risk of CMV infection varies over time, with the highest risk occurring under 100 days post-transplant.

For fungal prophylaxis studies, it was unclear whether fungal infection risk varied over time post-transplant and, therefore, it was unclear how the duration of follow-up may impact event rates. We decided to include all studies in analyses, regardless of the duration of follow-up to explore the potential impact of this heterogeneity.

Heterogeneity in efficacy outcome testing methods and outcome definitions was expected across both viral and fungal prophylaxis studies. To account for this, CMV prophylaxis analyses were conducted for two different outcome definitions—"confirmed CMV disease" and "CMV disease or infection"—with disease confirmation required by culture or histopathology and infection detection methods required to include PCR testing to maximise sensitivity. Fungal prophylaxis analyses were conducted for three different outcome definitions that increased in potential definition heterogeneity: (1) proven invasive fungal infections (IFIs), (2) proven or probable IFIs, and (3) proven, probable, or possible IFIs. The sensitivity of IFI detection could be increased with the use of galactomannan surveillance testing and this potential source of heterogeneity has been considered in the interpretation of results.

We discussed the heterogeneity of antiviral therapies used between transplant and engraftment (i.e., prior to the start of study drugs) in CMV prophylaxis studies with our clinical experts, who determined that this heterogeneity should not affect the reported clinical outcomes. Minimal CMV disease occurs in the pre-engraftment period as CMV relies on replication within leukocytes, which are found in low numbers pre-engraftment. Other sources of heterogeneity in CMV prophylaxis studies that were discussed but not considered significant enough to exclude studies from analysis were the inclusion of actively viremic patients at randomization and the use of CMV IVIG. These factors were considered as potential sources of heterogeneity in the interpretation of results.

In fungal prophylaxis analyses, studies conducted strictly in GVHD patients were analysed separately from studies conducted in general HSCT populations. Patients suffering from GVHD are treated with highly immunosuppressive medications that increase their risk of infection. A table summarizing the potential sources of heterogeneity in fungal prophylaxis studies has been included in the Results section to improve interpretation of analysis results. This table reports the durations of follow-up for each study in relation to the respective timing of the start and discontinuation of study drugs, as well as the use of galactomannan surveillance testing.

Another key assumption underlying NMA is that of *consistency*. That is, there is no conflict between direct and indirect evidence[32] that could result from heterogeneity in effect modifiers in the studies contributing to the direct and indirect evidence. To assess consistency, one commonly compares DIC statistics in fitted consistency and inconsistency models. As well, the posterior mean deviance of the individual data points in inconsistency models may be plotted against the posterior mean deviance in consistency models to identify any loops in the network where inconsistency was present. Additionally, NMA estimates may be qualitatively compared with direct frequentist pairwise estimates.

Although planned in the review's protocol to further establish the robustness of findings from primary analyses, subgroup analyses and meta-regression analyses were not feasible due to the presence of many single-study connections in most evidence networks, as well as a failure of studies to report outcomes in patient subgroups of relevance.

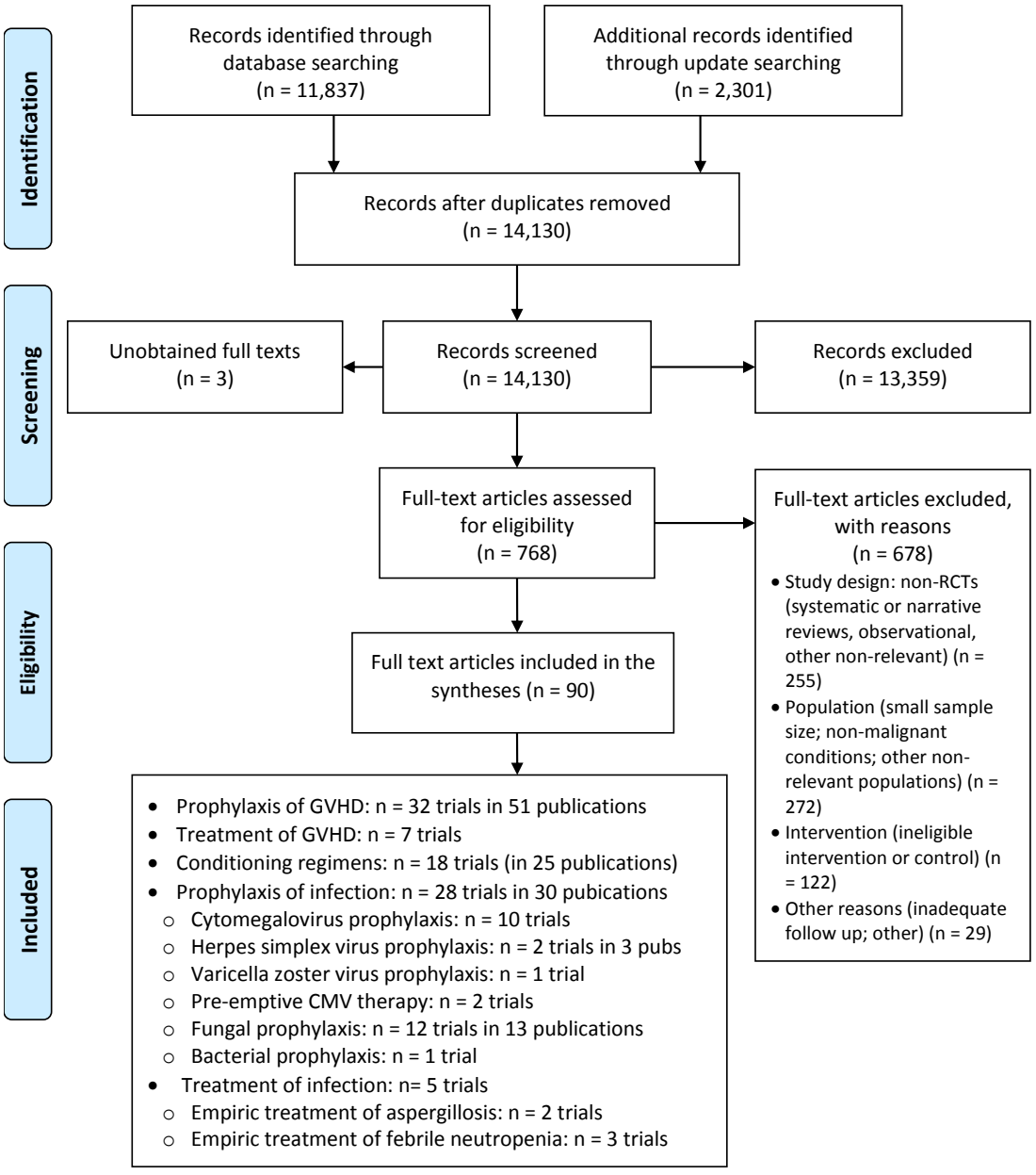
5. REVIEW FINDINGS

5.1. Availability of relevant literature

Figure 1 presents a summary of the process of study selection. The electronic literature search identified a total of 14,136 citations for review following removal of duplicates. Stage 1 screening identified a total of 768 citations that were potentially eligible, and which were subsequently retrieved in full text for Stage 2

screening. Following screening of full text articles, a total of 35 publications describing 33 unique studies were retained. In the following sections, for the two included studies that were published in more than one publication, only the primary paper has been cited in the text, while both primary and secondary publications for these two studies have been cited in tables.

Figure 1: PRISMA flow diagram of study selection



5.2. Overview of study characteristics

Thirty-three trials[40-72] were reported in 35 publications, covering 10 different infection objectives: CMV prophylaxis post-engraftment (9 studies[43, 44, 46, 54, 58, 59, 68, 70, 71]), late CMV prophylaxis in high-risk patients (1 study[41]), HSV prophylaxis (2 studies[61, 62]), VZV prophylaxis (1 study[40]), pre-emptive CMV therapy (2

studies[47, 60]), fungal prophylaxis (10 studies[50-52, 55, 56, 63, 66, 67, 69, 72]), fungal prophylaxis in GVHD patients (2 studies[48, 65]), empiric treatment of aspergillosis (2 studies[49, 57]), bacterial prophylaxis (1 study[64]) and treatment of febrile neutropenia (a proxy for bacterial treatment; 3 studies[42, 45, 53]). A total of 7,712 patients were included in all trials. Median year (range) of publication was 2004 (1985–2015). Totals of 3 (9.1%), 6 (18.2%), 16 (48.5%), and 8 (24.2%) trials were initially published between 1980–1990, 1991–2000, 2001–2010, and after 2010, respectively. Twenty studies (61%) were conducted in multiple-site settings, eight (24%) in a single-site setting, while this information was not reported for the remaining 5 studies (15%). Funding for the included trials was received from industry only, both industry and non-industry (government/not for profit), or by non-industry only in 17 (52%), 5 (15%), and 2 (6%), respectively. No information regarding the financial support was reported in the remaining 9 studies (27%). Study characteristics have been summarized in **Tables 2**, **3**, and **4**.

5.3. Overview of patient characteristics

Fifteen studies (45%) enrolled patients 12 years of age or younger (overall age range for these studies: 6 months–79 years). Eleven studies (33%) included adolescents >12 but under 18 years, as well as adults (age range: 13–85 years). Seven studies (23%) included only adult patients (age range: 18–77). The median proportion of female patients was 43.8% (range 22–58%) in 29 studies (88%) reporting this information. Information regarding graft source was reported in 26/33 studies. Graft source was 100% bone marrow in 13 studies (50% of studies reporting data). Five studies (19%) included patients receiving either bone marrow or peripheral blood transplants. Eight studies included patients receiving umbilical cord stem cell transplants, as well as patients receiving bone marrow and peripheral blood stem cells. Umbilical cord HSCT recipients comprised <10% of the sample size in seven of these eight studies (range <1–8.1%), with the remaining study[50] recruiting 21% umbilical cord stem cell recipients. The extent of HLA matching was only reported in 17 studies (52%), with full HLA matching for all included patients in 3 studies[44, 66, 72] (18% of studies reporting data). The proportion of patients receiving fully matched stem cells in the remaining 13 studies that reported data ranged from 48–96%. Nineteen studies (58%) reported the proportion of related donors, with a median of 58% of all patients receiving a related donor transplant (range 45–95%). Sex matching of donor and recipient was not reported in any of the included studies.

All studies reported the distribution of patients' underlying hematologic diseases, however limitations in reporting were identified. Many studies[40, 46, 50, 55, 58, 69-71] reported the proportion of patients with "lymphoma," without reporting the distribution of Hodgkin and non-Hodgkin lymphoma. Similarly, many studies[40, 43, 58, 62, 69-71] reported the proportion of patients with "acute leukemia," without reporting the distribution between acute lymphoblastic and acute myelogenous leukemia. Many early studies included patients with CML, however CML is no longer treated with HSCT. The review inclusion criteria for empiric treatment studies, were expanded to encompass any study that recruited allogeneic HSCT, with or without results reported for the allogeneic HSCT subgroup (i.e., studies were included that recruited at least some allogeneic HSCT patients, but the overall sample in empiric treatment studies could include any immunocompromised patient, regardless of cause). As a result, patients in these studies included HSCT recipients (both allogeneic and autologous), patients with hematologic malignancies that did not undergo HSCT, patients receiving solid organ transplants, and patients with several non-malignant conditions (e.g., AIDS, corticosteroid treatment). Underlying disease distributions for viral, fungal, and bacterial prophylaxis studies have been summarized in the appendices to the report.

Table 2: Summary of characteristics of studies included in the systematic review of infection control agents: viral, fungal, and bacterial prophylaxis and pre-emptive treatments

Author (year)	Funding source	Sample size	Interventions compared	Patient age range median (years)	Graft source (%BM/ PB/ UC)	% related donor	% full HLA match	% with GVHD	% given systemic steroids during study period	Endpoints reported
CMV prophylaxis starting at engraftment (n = 2,288)										
Goodrich (1993)[46]	Not for profit	64	Ganciclovir vs Placebo	34 (4–57)	100/0/0%	64%	NR	Unclear if reported GVHD occurring at baseline or during study: Acute grades II-IV: 48%	NR	α^a, §^{a}, ∞^a, π^a, χ^b
Winston (1993)[68]	Mixed	85	Ganciclovir vs Placebo	33 (14–50)	100/0/0%	82%	88%	Assumed to be GVHD occurring during study: Acute: 61%	NR	α^a, §^{a}, ∞^a, π^b, χ^b
Burns (2002)[43]	NR	91	Ganciclovir vs Acyclovir	37 (1–55)	71/26/2%	58%	82%	NR	NR	α^a, §^{a}, ∞^b, π^{ab}
Ljungman (2002)[54]	For profit	727	Valaciclovir vs Acyclovir	37 (13–59)	100/0/0%	72%	92%	During study: Acute grades III-IV: 4% Chronic extensive: 4%	NR	α^a, β^b, ∞^a
Winston (2003)[70]	NR	168	Ganciclovir vs. Valaciclovir	42 (13–66)	100/0/0%	76%	92%	Assumed to be GVHD occurring during study: Acute grades II-IV: 36% Chronic: 18%	NR	α^a, §^{a}, ∞^a, π^{ab}, χ^b
Winston (2008)[71]	For profit	111	Maribavir vs Placebo	47 (19–64)	12/80/8%	53%	NR	During study: Acute grades II-IV: 28%	NR	α^a, β^a, ∞^a, π^{ab}, χ^b
Marty (2011)[58]	For profit	681	Maribavir vs Placebo	52 (18–77)	10/84/6%	50%	48%	At baseline: Acute grades II-IV: 11% During study: Acute grades II-IV: 35%	NR	α^a, β^{ab}, ∞^a, π^b
Marty (2013)[59]	For profit	230	Brincidofovir vs Placebo	>18	12/81/7%	45%	90%	At baseline: Acute grades NR: 7% During study: 46%	NR	α^a, β^a, ∞^a, π^b
Chemaly (2014)[44]	For profit	131	Letermovir vs Placebo	54 (22–71)	3/97/0%	55%	100%	Prior to randomization: Acute grade II: 5% Acute grades >II: 0% At baseline: Acute grades II: 1% Acute grades >II: 0% During study: Acute in skin: 12%	NR	β^a, ∞^a, π^b, χ^b

								Acute in intestine: 9%		
Late[c] CMV prophylaxis in high-CMV-risk patients[d]										
Boechk (2015)[41]	Mixed	184	Valganciclovir vs Placebo	50 (16–70)	15/84/1%	49%	NR	All had a history of GVHD or CMV disease requiring treatment between engraftment and randomization	NR	ψ[b], α[b], ∞[b], π[b]
HSV prophylaxis (n = 133)										
Shepp (1987)[62]	For profit	51	Acyclovir vs Placebo	29 (3–49)	100/0/0%	NR	NR	NR	53%	λ[b]
Selby (1989)[61, 73]	NR	82	Acyclovir vs Placebo	Mean ~25 (NR)	100/0/0%	NR	84%	NR	NR	λ[b]
VZV prophylaxis (n=77)										
Boeckh (2006)[40]	Mixed	77	Acyclovir vs Placebo	31 (10–65)	100/0/0%	95%	84%	At baseline: Acute grades II-IV: 36%	NR	ρ[b], ∞[b], π[b]
Pre-emptive CMV therapy (n = 285)										
Goodrich (1991)[47]	Mixed	72	Ganciclovir vs Placebo	32 (3–56)	100/0/0%	67%	82%	At baseline: Acute grades NR: 68%	NR	α[b], §[b], ∞[b], χ[b], π[b]
Reusser (2002)[60]	For profit	213	Ganciclovir vs Foscarnet	39 (12–61)	62/38/0.4%	70%	NR	NR	NR	α[b], §[b], ∞[b], χ[b], π[b]
Fungal prophylaxis (n = 3,092)										
Shepp (1985)[63]	Not for profit	56	Nystatin vs Ketoconazole	23 (4–50)	100/0/0%	NR	89%	NR	20%	ε[b], ∞[b]
Koh (2002)[52]	NR	140	Amphotericin B vs Fluconazole	29 (4–63)	BM and PB only (% unclear)	NR	NR	During study (assumed): Acute grades II-IV: 67%	54%	Ω[a], φ[a]
Winston (2003)[69]	For profit	140	Fluconazole vs Itraconazole	40 (14–63)	84/16/0%	65%	89%	During study: Acute grades II-IV: 34% Chronic GVHD: 15% **GVHD occurrence was significantly different between treatment groups (46% vs 23%; p = 0.004)**	~85%	Ω[a], ∞[a], χ[b]
Marr (2004)[56]	Mixed	299	Fluconazole vs Itraconazole	98% >20 years	NR	MRD: 54%	At least 54%	During study (assumed): Acute grades II-IV: 79%	NR	Ω[a], ε[a], φ[a], ∞[b], χ[b]
van Burik (2004)[66]	For profit	882 (total) 476 (allogeneic HSCT)	Fluconazole vs Micafungin	Overall 42 (<1–73)	28/69/3% (includes autologous)	NR	100%	During study (includes autologous recipients): 22%	NR	φ[a]
Wolff (2000)[72]	NR	103	Amphotericin B vs Fluconazole	40 (18–58)	100/0/0%	83%	100%	Within 1 month before entry: 16% received steroids	NR	Ω[a], ∞[b]

Hiramatsu (2008)[50]	NR	100	Fluconazole vs Micafungin	Mean = 47 (16–67)	58/21/21%	NR	NR	During study: GVHD (not defined): 52%	46%	φ[a]
Wingard (2010)[67]	For profit	600	Fluconazole vs Voriconazole	43 (2–65)	36/64/<1%	57%	96%	To 1 year post-transplant: Acute grades II-IV: 41% Chronic (not defined): 46%	NR	Ω[a], ε[a], φ[a], ∝[a]
Marks (2011)[55, 74]	For profit	489	Itraconazole vs Voriconazole	Mean = 43 (11–70)	NR	MRD: 57%	At least 57%	During study: GVHD (not defined): 46%	NR	Ω[a], ε[a], ∝[ab]
Huang (2012)[51]	For profit	283	Itraconazole vs Micafungin	Mean = 33 (18–58)	NR	NR	NR	NR	NR	φ[a], ∝[b]
Fungal prophylaxis in GVHD patients (n = 666)										
Ullmann (2007)[65]	For profit	600	Fluconazole vs Posaconazole	Mean = 41 (13–65)	NR	NR	NR	At baseline: Acute grades II-IV: 66% Chronic extensive: 33%	100%	ε[b], ∝[b]
Hayashi (2014)[48]	NR	66	Itraconazole vs Voriconazole	Adults (ages NR)	NR	NR	NR	At baseline: Acute grades II-IV or chronic GVHD requiring steroid treatment: 100%	NR	Ω[b], ε[b], ∝[b]
Bacterial prophylaxis (n=155)										
Teinturier (1995)[64]	NR	155	Vancomycin-added vs No vancomycin added to prophylaxis	Children and adults	100/0/0%	NR	NR	NR	NR	Gram+ cocci infection[b], septicemia[b], fever of unknown origin[b]

Endpoints reported by each study are denoted using symbols in the final column, where α = confirmed CMV disease; β = signs of CMV disease or infection (tested with PCR); § = CMV pneumonia; ∝ = overall mortality; π = neutropenia during treatment; χ = non-relapse mortality; ψ = CMV disease, invasive bacterial or fungal infection, or death (whichever occurred first); λ = HSV infection; ρ = confirmed VZV disease; Ω = proven IFI; ε = proven or probable IFI; φ = any IFI (proven, probable, or possible)

[a]Endpoint analysed with NMA

[b]Endpoint summarized narratively

[c]Median time of randomization post-transplant of 97 days

[d]"High-risk CMV patients" included seropositive recipients who had either CMV infection with appropriate treatment before random assignment; a history of GVHD requiring treatment with corticosteroids at doses >0.5 mg/kg before enrolment; chronic, clinically extensive GVHD requiring treatment with corticosteroids; or received of ganciclovir, valganciclovir, foscarnet, or cidofovir prophylaxis between engraftment and random assignment.

BM = bone marrow; GVHD = graft-versus-host-disease; HLA = human leukocyte antigen; HSCT = hematologic stem cell transplant; IFI = invasive fungal infection; MRD = matched related donor; NR = not reported; PB = peripheral blood; UC = umbilical cord

Table 3: Summary of characteristics of studies included in the systematic review of infection control agents: empiric treatment of aspergillosis (fungal infection) (n = 153)

Author (year)	Funding source	Sample size	Interventions compared	Patient age range (years)	Patient inclusion criteria	Underlying conditions	% with GVHD	% with neutropenia	Endpoints reported
Herbrecht (2002)[49]	For profit	67	Amphotericin B vs Voriconazole	Mean = 50 (12–79)	Any immune-compromised patient	**Allogeneic HSCT: 24%** Autologous HSCT: 4% Acute leukemia, without HSCT: 43% Other hematologic cancer, without HSCT: 13% Solid-organ transplant: 5% AIDS: 5% Corticosteroid treatment: 6% Other: 1%	At baseline (assumed): GVHD not defined: 17%	45% ANC <500/µl at baseline or during previous 2 weeks	α, β, ε, ∞
Marr 2015)[57]	For profit	86	Voriconazole vs Voriconazole + Anidulafungin	≥16	Hematologic malignancy or HSCT	**Allogeneic HSCT: 31%** Autologous HSCT: 3% Acute leukemia, without HSCT: 45% Other hematologic cancer, without HSCT: 21%	Before randomization: 5% of total (17% of allogeneic HSCT recipients) had GVHD treated with high-dose corticosteroids	60% ANC <500 cells/µl at baseline	α, β, ε, ∞

Endpoints reported by each study are denoted using symbols in the final column, where α = overall treatment success (complete or partial response); β = complete response to treatment; ε = partial response to treatment; ∞ = overall mortality
All endpoints were summarized narratively.
AIDS = acquired immunodeficiency syndrome; ANC = absolute neutrophil count; GVHD = graft-versus-host-disease; HSCT = hematologic stem cell transplant

Table 4: Summary of characteristics of studies included in the systematic review of infection control agents: empiric treatment of febrile neutropenia (empiric bacterial treatment) (n = 679)							
Author (year)	**Funding source**	**Sample size**	**Interventions compared**	**Patient age median and range (years)**	**Patient inclusion criteria**	**Underlying conditions**	**Endpoints reported (all summarized narratively)**
Laszlo (1997)[53]	NR	66	(Netilmicin + Imipenemin-cilastatin) vs (Netilmicin + Ceftazidime)	32 (9–57)	HSCT, ANC <500/µl, Fever >38 °C	**Allogeneic HSCT: 45%** Autologous HSCT: 55%	Improvement of infection episode
Feld (2000)[45]	For profit	85	Meropenem vs Ceftazidime	48 (17–85)	Malignancy, ANC <500/µl Fever >38.3 °C single oral temperature or >38 °C on two oral temperatures within a 12-h period	**Allogeneic HSCT: 5%** Autologous HSCT: 16% Hematologic malignancy without HSCT: 70% Solid organ tumours: 9%	Clinical success, overall mortality
Bow (2006)[42]	For profit	528	(Piperacillin + Tazobactam) vs Cefepime	52 (17–83)	Cytotoxic therapy for HSCT or hematologic malignancy, ANC <500/µl, Fever	**Allogeneic HSCT: 15%** Autologous HSCT: 34% Unspecified peripheral blood HSCT: 4% Hematologic malignancy without HSCT: 47%	Treatment success, overall mortality
ANC = absolute neutrophil count; HSCT = hematologic stem cell transplant							

5.4. Overview of intervention characteristics

Tables 5 and **6** below present the interventions evaluated in the included trials sorted by the date of study publication (from most to least recent) for the two review objectives with the greatest number of included studies: CMV prophylaxis and fungal prophylaxis. Similar tables for the remaining review objectives with multiple studies included have been provided in the appendices to the report. Three of the four most recent placebo-controlled CMV prophylaxis studies were Phase 2 dose-ranging clinical trials of newer anti-CMV drugs.[44, 59, 71] Fluconazole was the most common control arm in fungal prophylaxis studies; however, the three most recent studies either compared later-generation triazole antifungals to each other or to echinocandin antifungals.[51, 55, 57]

Table 5: Interventions evaluated in trials of CMV prophylaxis, ordered by year of publication

Author	Year	Placebo	Ganciclovir	Acyclovir	Valaciclovir	Foscarnet	Maribavir	Brincidofovir	Letermovir
Goodrich[46]	1993	X	X						
Winston[68]	1993	X	X						
Burns [43]	2002		X	X					
Ljungman [54]	2002			X	X				
Reusser [60]	2002		X			X			
Winston [70]	2003		X		X				
Winston [71]	2008	X					X		
Marty [58]	2011	X					X		
Marty[59]	2013	X						X	
Chemaly [44]	2014	X							X

Table 6: Interventions evaluated in trials of fungal prophylaxis, ordered by year of publication

Author	Year	Nystatin	Ketoconazole	Fluconazole	Amphotericin B	Itraconazole	Micafungin	Voriconazole	Voriconazole + Anidulafungin
Shepp [63]	1985	X	X						
Koh [52]	2002			X	X				
Winston [69]	2003			X		X			
Marr[56]	2004			X		X			
van Burik[66]	2004				X		X		
Wolff [72]	2005			X	X				
Hiramatsu [50]	2008			X			X		
Wingard [67]	2010			X				X	
Marks[55, 74]	2011					X		X	
Huang [51]	2012					X	X		
Marr[57]	2015							X	X

5.5. Structure of the presentation of results

In the following sections, we present the results of both NMAs (where synthesis was feasible based upon data availability) and narrative summaries of studies for situations where synthesis was not possible. The findings are presented by review objective and sub-objective, with the following framework:

- **Viral prophylaxis**
    - CMV prophylaxis post-engraftment—NMAs and narrative summaries
    - Late CMV prophylaxis—narrative summary
    - HSV and VZV prophylaxis—NMA and narrative summaries
- **Pre-emptive CMV therapy**
    - narrative summaries
- **Fungal prophylaxis**
    - Fungal prophylaxis beginning pre-/post-transplant—NMAs and narrative summaries
    - Fungal prophylaxis beginning at time of GVHD diagnosis—narrative summaries
- **Fungal treatment**
    - narrative summaries
- **Bacterial prophylaxis**
    - narrative summary
- **Treatment of febrile neutropenia (treatment of suspected bacterial infection)**
    - narrative summaries

5.6. Objective 1: Viral prophylaxis/treatment—CMV prophylaxis starting at engraftment

5.6.1. Findings: Confirmed CMV disease at 100 days post-transplant

Five[43, 46, 58, 68, 71] CMV prophylaxis studies reported confirmed CMV disease data at approximately 100 days post-transplant in 976 patients and were included in an NMA (**Figure 2**). Four studies began CMV prophylaxis at engraftment and one study[68] randomized patients to study drugs at the start of the conditioning regimen, stopping treatment at transplant and resuming at engraftment. Two studies[43, 68] included the pre-engraftment period in the follow-up period and also included patients with active viremia at engraftment. Two studies[46, 71] reported zero events for one treatment arm, which required addition of 0.5 to those arms as a continuity correction factor. All studies provided rescue treatment in case of active viremia while on study drugs. Study drugs were discontinued during rescue treatment. Rescue treatments may have differed between studies, which may have affected the risk of CMV disease developing.

Figure 2: Network diagram for NMA of confirmed CMV disease within 100 days post-transplant in the evaluation of CMV prophylaxis

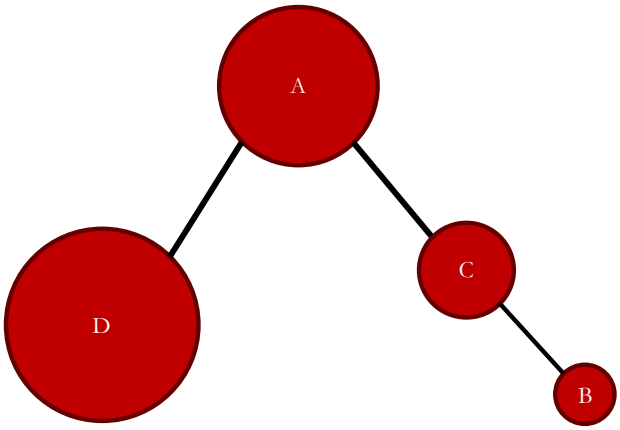


Figure legend
A = Placebo
B = Acyclovir
C = Ganciclovir
D = Maribavir

5.6.1.1. Results from traditional pairwise meta-analyses

Table 7 presents summaries of pairwise estimates that were derived from direct evidence (i.e., the head-to-head trials), summarized alongside the numbers of available trials and patients for each direct comparison, as well as the related summary estimate derived from the network meta-analysis.

One of the three direct comparisons was a single-study comparison, with the other two encompassing 2 studies each. The two-study direct comparison between ganciclovir and placebo demonstrated significant differences between the two treatments, with ganciclovir significantly reducing the risk of confirmed CMV disease within 100 days of transplant. There was moderate heterogeneity between the two studies[46, 68] informing this direct estimate, potentially due to differences in the start of study drug (e.g., at the start of conditioning regimen vs at engraftment), inclusion of the pre-engraftment period in the follow-up period, and duration of study treatment and follow-up (100 days vs 120 days post-transplant). Both studies were conducted in 1993 and had similar event rates in their placebo arms (29% vs 24%), suggesting that there was minimal heterogeneity in the underlying risk of viral infection. Estimates from traditional pairwise meta-analyses compared well with estimates derived from network meta-analysis.

Table 7: Summary of results from pairwise meta-analysis and NMA, confirmed CMV disease within 100 days post-transplant in the evaluation of CMV prophylaxis

Comparison		# of Trials (patients)	Heterogeneity (I^2)	Direct Estimate OR (95% CI)	FE NMA Estimate OR (95% CrI)
				**Values <1 favor comparator*	
Comparator	**Reference**				
Ganciclovir	Acyclovir	1 (91)	NA	0.59 (0.13–2.61)	0.57 (0.10–2.60)
Ganciclovir	Placebo	2 (149)	50.140	**0.24 (0.08–0.75)**	**0.17 (0.05–0.49)**
Maribavir	Placebo	2 (736)	29.667	0.75 (0.29–1.96)	0.71 (0.29–1.85)

5.6.1.2. Results from network meta-analysis

Half of the comparisons (i.e., 3 of 6) were informed only by indirect evidence and one of the three comparisons with direct evidence was informed only by a single study with a limited numbers of patients.

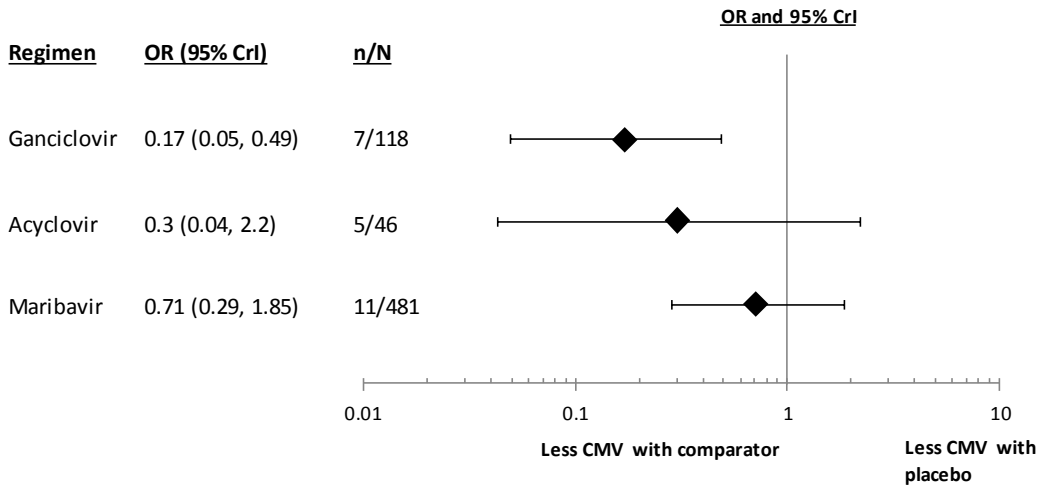
Model fit statistics for the NMA indicated that both the fixed-effects (FE) and random-effects (RE) models had an adequate fit. Posterior residual deviance values for the FE and RE models of 12.52 and 10.33, respectively, were obtained, the latter of which was a more desirable fit, given the 10 data points in the model. DIC values (51.246 and 50.167) did not suggest difference in fit between the FE and RE models. A FE model was preferred due to the number of single-study connections in the network, though RE model findings are presented in the appendices.

Comparisons versus placebo

Figure 3 presents a forest plot summarizing comparisons of all treatments in the evidence network to the placebo reference. One study treatment—ganciclovir—was found to have statistically significantly reduced the risk of confirmed CMV disease relative to placebo (OR = 0.17; 95% CrI = 0.05–0.49). Both acyclovir and maribavir were associated with credible intervals that included 1 and, thus, were not significantly different from placebo in preventing confirmed CMV disease before day 100 post-transplant.

Figure 3: Forest plot of comparisons versus placebo, Confirmed CMV disease at 100 days post-transplant in studies evaluating CMV prophylaxis

100-day overall mortality



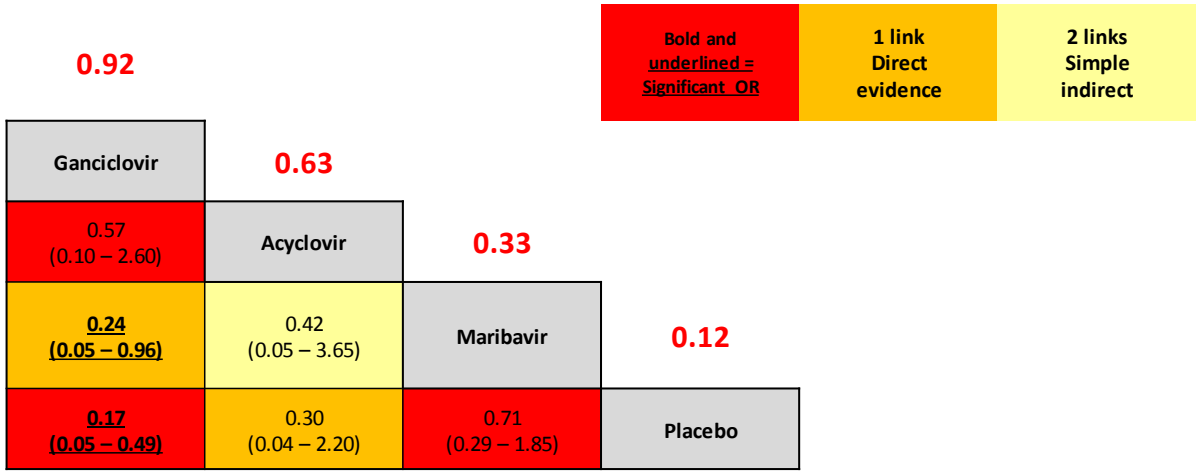
Odds ratios from network meta-analysis comparing each regimen to the reference placebo treatment are presented along with the number of events and patients per regimen. Odds ratios <1 suggest more risk of CMV disease with placebo while odds ratios >1 suggest less risk of CMV disease with placebo.

Comparisons between all conditioning regimens

Figure 4 presents a league table of the estimates for all pairwise comparisons generated from the network meta-analysis. Some of the comparisons included in the league table should be interpreted carefully, specifically those which are not informed by head to head trials or where the comparison was based on compound indirect evidence (i.e., comparisons in which there are 2 or more intermediate treatments between the interventions of interest).

Ganciclovir demonstrated improved efficacy to reduce the risk of confirmed CMV disease compared to placebo, while the same result was not found for acyclovir or marivavir. Ganciclovir was significantly more efficacious than the newer drug, maribavir, while all other pairwise comparisons between active therapies were inconclusive. Ganciclovir was associated with the largest SUCRA value (0.92). Results of pairwise comparisons from the corresponding RE model were associated with notably wider credible intervals, and all were inconclusive.

Figure 4: League table summary of pairwise comparisons from NMA (Odds Ratios with 95% CrI), Confirmed CMV disease within 100 days post-transplant in studies evaluating CMV prophylaxis



Interventions are sorted from left to right in order of decreasing SUCRA value (i.e., preferred treatments appear first). For each comparison shown, the upper/left-most regimen is the comparator group while the lower/right-most treatment is the reference treatment; a value <1 suggests fewer cases of confirmed CMV disease with the comparator than with the reference group. Statistically significant differences (i.e., estimates with a 95% credible interval excluding 1) are bolded and underlined. Comparisons with direct evidence, simple indirect evidence, and compound indirect evidence have been highlighted in red, orange, and yellow, respectively.

5.6.2. Findings: Confirmed CMV disease during extended follow-up

Six CMV prophylaxis studies[43, 46, 54, 58, 59, 70] reported confirmed CMV disease data over follow-up periods that extended beyond discontinuation of the study drugs in 1,840 patients and were included in an NMA (**Figure 5**). If multiple extended follow-up data were reported in a study, the earliest data were used in the NMA. The extended follow-up periods in the 6 included studies ranged from 147 to 365 days post-transplant. Where multiple doses of drugs were compared to placebo in a single study, the dose identified within the study as the best for clinical use (e.g., most efficacious with fewest adverse events) was included in the NMA.

All studies began CMV prophylaxis at engraftment; however, three studies[43, 54, 70] included the pre-engraftment period in the follow-up period. Three studies also included patients with active viremia at engraftment[43, 54, 59] and one was unclear with respect to viremia status of patients at engraftment[70]. The risk of confirmed CMV disease or positive PCR is significantly greater in patients with active viremia at engraftment: in Marty et al.[59], 31/50 (62%) DNA-positive patients and 23/180 (13%) DNA-positive patients developed confirmed CMV disease, for a relative risk of 4.85 ($p < 0.0001$). Thus, the prophylaxes evaluated in studies that include DNA-positive patients at engraftment may appear to fare worse than those interventions in studies that exclude DNA-positive patients.

Figure 5: Network diagram for the NMA of the outcome of confirmed CMV disease over extended follow-up in the evaluation of CMV prophylaxis

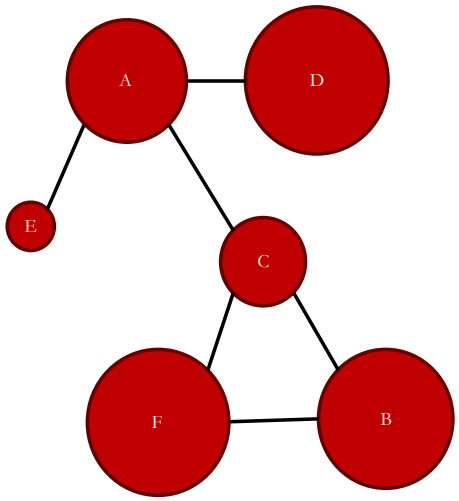


Figure legend
A = Placebo
B = Acyclovir
C = Ganciclovir
D = Maribavir
E = Brincidofovir
F = Valaciclovir

5.6.2.1. Results from traditional pairwise meta-analyses

Table 8 presents summaries of pairwise estimates that were derived from direct evidence (i.e., the head-to-head trials), summarized alongside the numbers of available trials and patients for each direct comparison, as well as the related summary estimate derived from the network meta-analysis.

All six of the direct comparisons were informed by single studies. The single study direct comparison between ganciclovir and placebo demonstrated significant differences between the two treatments, with ganciclovir significantly reducing the risk of confirmed CMV disease during extended follow-up. Generally, estimates from traditional pairwise meta-analyses compared well with estimates derived from network meta-analysis in that there were no changes in significance or in direction of trends between the two methods. Point estimates appeared to vary slightly between the two methods for studies that included DNA+ patients in their samples.

Table 8: Summary of results from pairwise meta-analysis and NMA, confirmed CMV disease within 100 days post-transplant in the evaluation of CMV prophylaxis

Comparison		# of Trials (patients)	Heterogeneity (I^2)	Direct Estimate OR (95% CI)	FE NMA Estimate OR (95% CrI)
				**Values <1 favor comparator*	
Comparator	**Reference**				
Ganciclovir	Acyclovir	1 (91)	NA	0.73 (0.23–2.31)	0.62 (0.21–1.78)
Ganciclovir	Placebo	1 (64)	NA	**0.21 (0.05–0.86)**	**0.19 (0.04–0.74)**
Maribavir	Placebo	1 (681)	NA	0.91 (0.43–1.92)	0.92 (0.44–2.03)
Brincidofovir	Placebo	1 (109)	NA	0.58 (0.05–6.61)	0.48 (0.02–6.55)
Ganciclovir	Valaciclovir	1 (168)	NA	0.48 (0.04–5.42)	0.86 (0.24–2.94)
Valaciclovir	Acyclovir	1 (727)	NA	0.68 (0.29–1.60)	0.72 (0.31–1.65)

5.6.2.2. Results from network meta-analysis

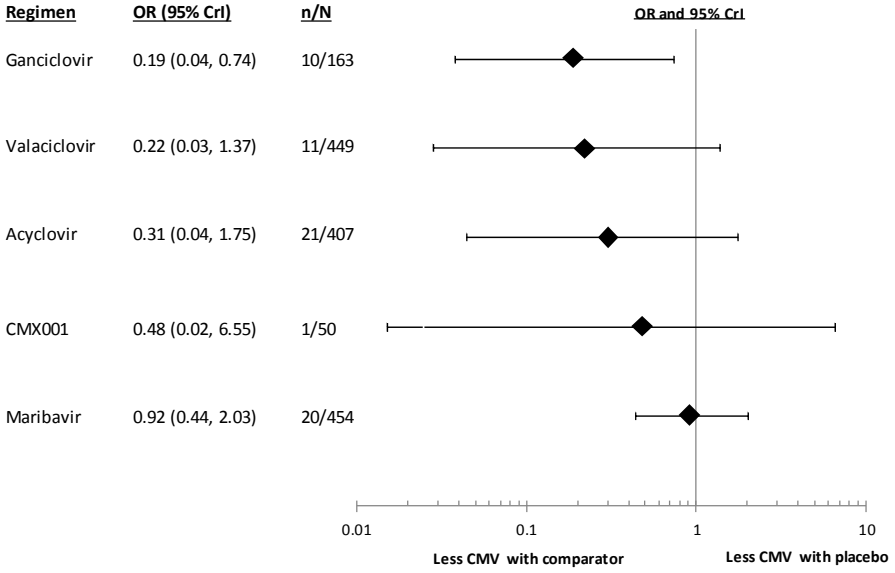
More than half of the comparisons (i.e., 9 of 15) were informed only by indirect evidence, and all of the 6 comparisons with direct evidence were informed by single studies. Model fit statistics for the NMA indicated that both the fixed-effects (FE) and random-effects (RE) models had an adequate fit. Posterior residual deviance values for the FE and RE models of 11.72 and 12.08, respectively, were obtained, demonstrating adequate fit, given the 12 data points in the model. DIC values (62.890 vs 63.777) did not suggest difference in fit between the FE and RE models. A FE model was preferred due to the number of single-study connections in the network.

Comparisons versus placebo

Figure 6 presents a forest plot summarizing comparisons of all treatments in the evidence network to the placebo reference. One prophylactic regimen—ganciclovir—was found to have statistically significantly reduced risk of confirmed CMV disease relative to placebo (OR = 0.19; CrI = 0.04–0.74). All other interventions were associated with a credible interval that included 1 and, thus, were not significantly different from placebo in preventing confirmed CMV disease after extended follow-up.

Figure 6: Forest plot of comparisons versus placebo, Confirmed CMV disease at extended follow-up in studies evaluating CMV prophylaxis

100-day overall mortality

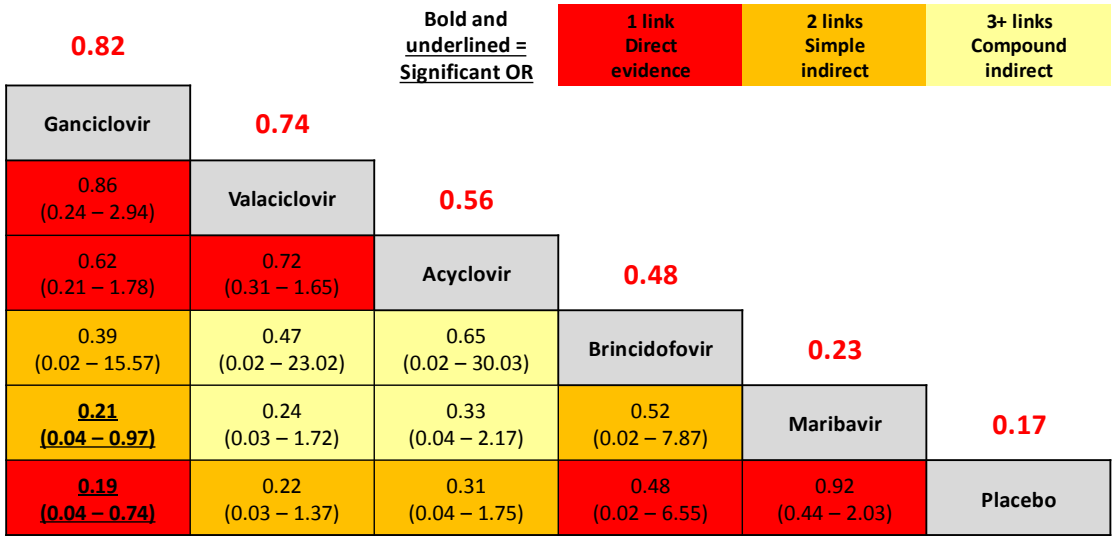


Odds ratios from network meta-analysis comparing each regimen to the reference placebo treatment are presented along with the number of events and patients per regimen. Odds ratios <1 suggest more risk of CMV disease with placebo while odds ratios >1 suggest less risk of CMV disease with placebo.

Comparisons between all conditioning regimens

Figure 7 presents a league table of the estimates for all pairwise comparisons generated from the network meta-analysis. Some of the comparisons included in the league table should be interpreted carefully, specifically those which are not informed by head to head trials or where the comparison was based on compound indirect evidence (i.e., comparisons in which there are 2 or more intermediate treatments between the interventions of interest). Ganciclovir was the highest-ranking prophylactic to reduce the risk of confirmed CMV disease during extended follow-up; however, it was not significantly better than most of the other interventions in the analysis, other than maribavir and placebo. Findings from the RE model are present in the report's supplement; while point estimates were comparable, no pairwise comparisons identified significant differences between interventions.

Figure 7: League table summary of pairwise comparisons from NMA (Odds Ratios with 95% CrI), Confirmed CMV disease during extended follow-up in studies evaluating CMV prophylaxis



Interventions are sorted from left to right in order of decreasing SUCRA value (i.e., preferred treatments appear first). For each comparison shown, the upper/left-most regimen is the comparator group while the lower/right-most treatment is the reference treatment; a value <1 suggests fewer cases of confirmed CMV disease with the comparator than with the reference group. Statistically significant differences (i.e., estimates with a 95% credible interval excluding 1) are bolded and underlined. Comparisons with direct evidence, simple indirect evidence, and compound indirect evidence have been highlighted in red, orange, and yellow, respectively.

5.6.3. Findings: CMV disease or CMV infection diagnosed by PCR or other ancillary tests at 100 days post-transplant

Four CMV prophylaxis studies[44, 58, 59, 71] reported data for patients developing either CMV disease or infection at approximately 100 days post-transplant, in a total of 891 patients. To ensure similarity of outcome definitions and the highest sensitivity for infection detection, included studies must have used PCR as one of the tests for infection detection. If multiple outcomes were reported with multiple different tests, the most sensitive was used in our analysis (i.e., the one with the most tests, including PCR). There remained potential for some heterogeneity in outcome definition as two of the four studies[59, 71] did not include antigenemia as a method of infection detection. The four studies were included in an NMA (**Figure 8**). Where multiple doses of drugs were compared to placebo in a single study, the dose identified within the study as the best for clinical use (e.g., most efficacious with fewest adverse events) was included in the NMA.

All studies began CMV prophylaxis at engraftment and no studies included the pre-engraftment period in the follow-up period. As well, no studies included patients with active viremia at engraftment.

Figure 8: Network diagram for the NMA of the outcome of CMV disease or CMV infection at 100 days post-transplant in the evaluation of CMV prophylaxis

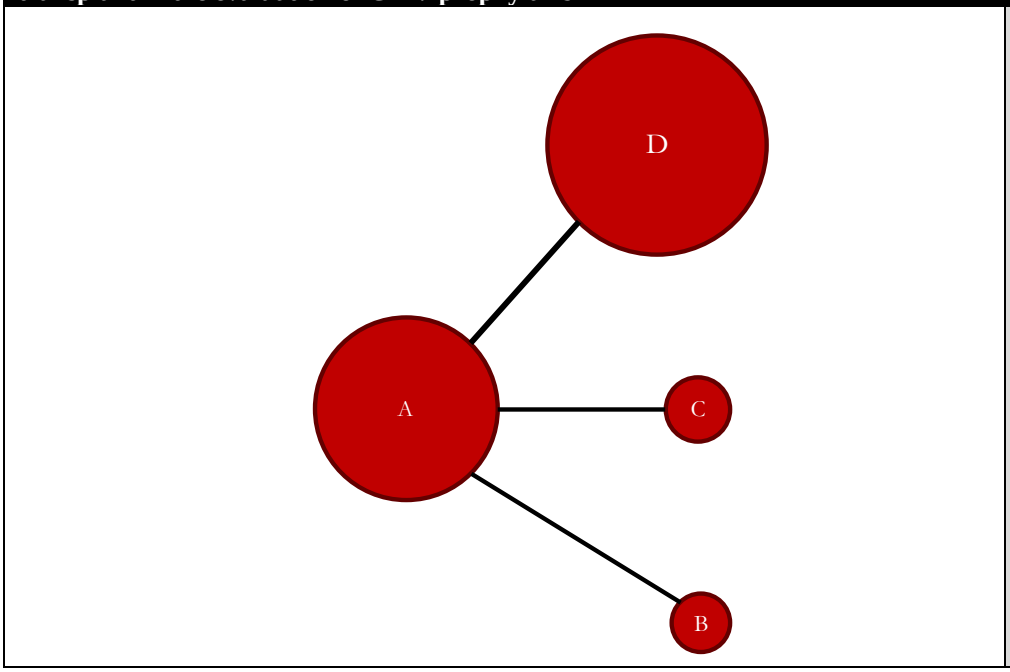


Figure legend
A = Placebo
B = Letermovir
C = Brincidofovir
D = Maribavir

5.6.3.1. Results from traditional pairwise meta-analyses

Table 9 presents summaries of pairwise estimates that were derived from direct evidence (i.e., the head-to-head trials), summarized alongside the numbers of available trials and patients for each direct comparison, as well as the related summary estimate derived from the network meta-analysis.

Two of the three direct comparisons were informed by single studies. Considerable heterogeneity was identified in the pairwise comparison informed by two studies (maribavir vs placebo).[58, 71] This heterogeneity may have been at least partially a result of heterogeneity of the outcome definition as one study[58] included antigenemic patients as outcome positive, while the other study[71] did not. The two single-study direct comparisons demonstrated significant differences between the two treatments; whereas the multi-study direct comparison did not. Generally, point estimates (i.e., the odds ratios) from traditional pairwise meta-analyses compared well with estimates derived from network meta-analysis; however, after inclusion of indirect evidence via NMA, the odds ratio for the letermovir vs placebo comparison was no longer statistically significant.

Table 9: Summary of results from pairwise meta-analysis and NMA, CMV disease or CMV infection at 100 days post-transplant in the evaluation of CMV prophylaxis

Comparison		# of Trials (patients)	Heterogeneity (I^2)	Direct Estimate OR (95% CI)	FE NMA Estimate OR (95% CrI)
				*Values <1 favor comparator	
Comparator	**Reference**				
Brincidofovir	Placebo	1 (88)	NA	**0.03 (0.001–0.44)**	**0.01 (0.00–0.46)**
Letermovir	Placebo	1 (67)	NA	**0.11 (0.02–0.54)**	0.09 (0.00–2.06)
Maribavir	Placebo	2 (736)	84.295	0.31 (0.04–2.46)	0.33 (0.03–2.22)

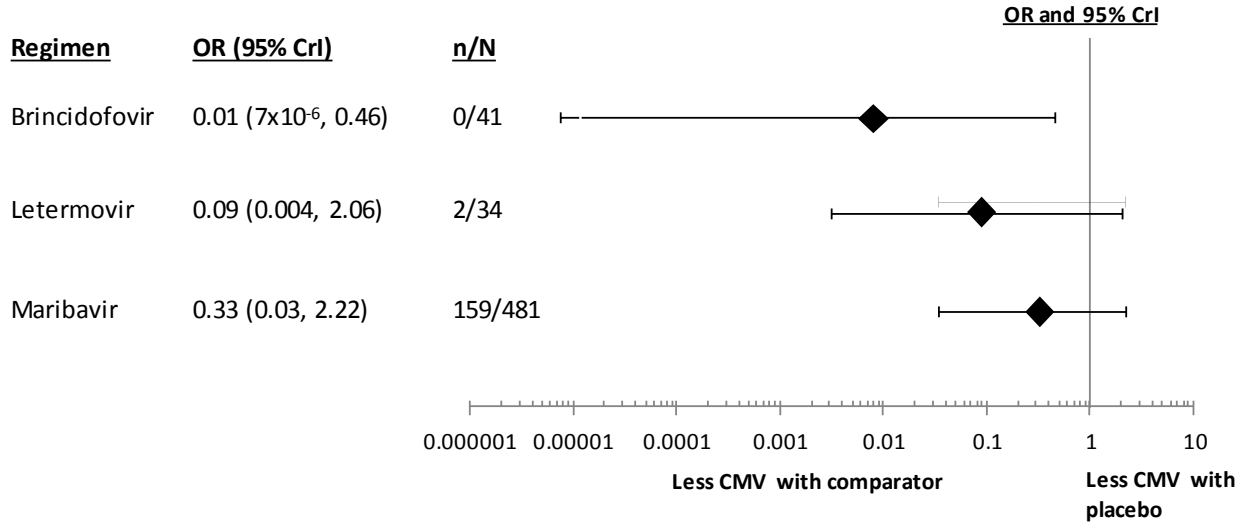
5.6.3.2. Results from network meta-analysis

Three of the 6 possible pairwise comparisons were informed only by indirect evidence, and 2 of the 3 comparisons with direct evidence were informed by single studies. Model fit statistics for the NMA indicated that the random-effects (RE) model had an adequate fit, while the FE model was not. Posterior residual deviance values for the FE and RE models of 15.840 and 8.598, respectively (with 8 unconstrained data points in the analysis). DIC values (53.261 vs 46.959 for FE and RE, respectively) also suggested difference in fit between the FE and RE models, with the RE model favoured. Therefore, results of the RE model have been reported.

Comparisons versus placebo

Figure 9 presents a forest plot summarizing comparisons of all treatments in the evidence network to the placebo reference. One prophylactic intervention—brincidofovir—was found to have statistically significantly reduced the risk of CMV disease or infection relative to placebo (OR = 0.01; CrI = 7×10^{-6}–0.46). Zero CMV disease or infection events were found for this intervention in the single study that evaluated it. All other interventions were associated with a credible interval that included 1 and, thus, were not significantly different from placebo in preventing confirmed CMV disease after extended follow-up.

Figure 9: Forest plot of comparisons versus placebo, CMV disease or infection at 100 days post-transplant in studies evaluating CMV prophylaxis

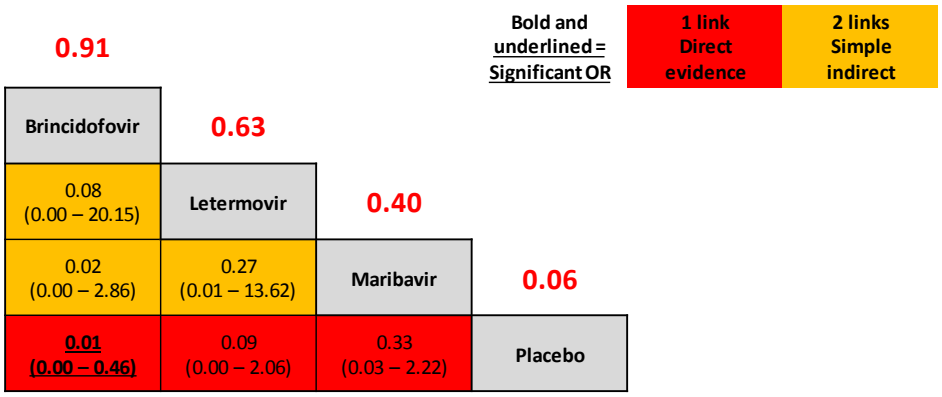


Odds ratios from network meta-analysis comparing each regimen to the reference placebo treatment are presented along with the number of events and patients per regimen. Odds ratios <1 suggest more risk of CMV disease or infection with placebo while odds ratios >1 suggest less risk of CMV disease or infection with placebo.

Comparisons between all conditioning regimens

Figure 10 presents a league table of the estimates for all pairwise comparisons generated from the RE model of the network meta-analysis. Some of the comparisons included in the league table should be interpreted carefully, specifically those which are not informed by head to head trials (i.e., comparisons in which there are 2 intermediate treatments between the interventions of interest). Ganciclovir was the highest ranking prophylactic to reduce the risk of confirmed CMV disease during extended follow-up based upon SUCRA values; however, it was not significantly better than other interventions in the analysis, aside from placebo.

Figure 10: League table summary of pairwise comparisons from NMA (Odds Ratios with 95% CrI), CMV disease or infection at 100 days post-transplant in studies evaluating CMV prophylaxis



Interventions are sorted from left to right in order of decreasing SUCRA value (i.e., preferred treatments appear first). For each comparison shown, the upper/left-most regimen is the comparator group while the lower/right-most treatment is the reference treatment; a value <1 suggests fewer cases of \ CMV disease or infection with the comparator than with the reference group. Statistically significant differences (i.e., estimates with a 95% credible interval excluding 1) are bolded and underlined. Comparisons with direct evidence and simple indirect evidence have been highlighted in red and orange, respectively.

5.6.4. Findings: CMV disease or CMV infection diagnosed by PCR or other ancillary tests during extended follow-up

To ensure similarity of outcome definitions and the highest sensitivity for infection detection, studies included in this outcome must have used PCR as one of the tests for infection detection. If multiple outcomes were reported with multiple different tests, the most sensitive was used in our analysis (i.e., the one with the most tests, including PCR). Two CMV prophylaxis studies[54, 58] reported data for patients developing either CMV disease or infection over extended follow-up beyond the discontinuation of study drugs. The two studies evaluated four different interventions and, thus, could not be analysed with NMA and have been summarized narratively instead.

In the study by Ljungman et al.[54], patients with active CMV viremia at the time of engraftment were included and patients were followed from the time of transplant to 154 days post-transplant (study drug provided from engraftment to 126 days post-transplant). PCR was not used in all study sites for infection detection. Valaciclovir significantly reduced the risk of CMV disease or infection compared to acyclovir over extended follow-up (OR = 0.58; CI = 0.43–0.79).

Marty et al.[58] compared maribavir to placebo in patients without active viremia at engraftment. Patients were followed from engraftment to 180 days post-transplant, with study drugs provided from engraftment to 100 days post-transplant. No significant difference was found between maribavir and placebo in the risk of CMV disease or infection after extended follow-up.

Table 10: Summary of results: CMV disease or infection over extended follow-up in the evaluation of CMV prophylaxis

Study	Outcome definition	Follow-up	Intervention	Group risk	OR (95% CI)
Ljungman (2002)[54]	Signs of CMV disease OR antigenemia, culture, or PCR. PCR used in some but not all study sites.	From transplant to 154 days PT (study drugs given to 126 days PT)	Valaciclovir	102/366 (28%)	**0.58 (0.43–0.79)**
			Acyclovir	144/361 (40%)*	

Table 10: Summary of results: CMV disease or infection over extended follow-up in the evaluation of CMV prophylaxis					
Study	**Outcome definition**	**Follow-up**	**Intervention**	**Group risk**	**OR (95% CI)**
Marty (2011)[58]	Signs of CMV disease OR antigenemia (≥1 cell/100,000 WBC) OR PCR-positive (>≥1000 copies/ml)	From engraftment to 180 days PT (study drugs given to 100 days PT)	Maribavir	183/454 (40%)	0.84 (0.61–1.16)
			Placebo	101/227 (44%)*	
*denotes the reference group for each pairwise comparison BAL = bronchoalveolar lavage; CMV = cytomegalovirus; OR = odds ratio; PCR = polymerase chain reaction; PT = post-transplant; WBC = white blood cells					

5.6.5. Findings: CMV pneumonia within 100–120 days post-transplant

Three CMV prophylaxis studies[43, 46, 68] reported data for CMV pneumonia within 100–120 days post-transplant in 241 patients (**Figure 11**). Data were reported up to the discontinuation of study drugs in all three studies, which was 100 days post-transplant in 2 studies[43, 46] and 120 days post-transplant in 1 study[68].

Two studies began CMV prophylaxis at engraftment and one study[68] began study drugs at the start of the conditioning regimen, stopped at transplant, then resumed study drugs at engraftment. Two of the studies[43, 68] included the pre-engraftment period in the follow-up period. One study also included patients with active viremia at engraftment[43], and one was unclear with respect to viremia status of patients[68]. The risk of CMV disease, including pneumonia, is significantly greater in patients with active viremia at engraftment. Thus, the prophylaxes evaluated in studies that include DNA-positive patients at engraftment may appear to fare worse than those interventions in studies that exclude DNA-positive patients.

Figure 11: Network diagram for the NMA of the outcome of CMV pneumonia at 100–120 days post-transplant in the evaluation of CMV prophylaxis

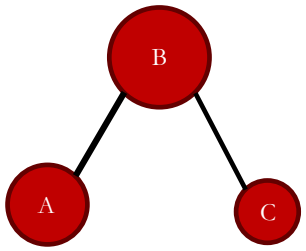


Figure legend
A = Placebo
B = Ganciclovir
C = Acyclovir

5.6.5.1. Results from traditional pairwise meta-analyses

Table 11 presents summaries of pairwise estimates that were derived from direct evidence (i.e., the head-to-head trials), summarized alongside the numbers of available trials and patients for each direct comparison, as well as the related summary estimate derived from the network meta-analysis. One of the two direct comparisons was informed by a single study. No significant differences were demonstrated in any of the pairwise direct comparisons; however, from the corresponding NMA, ganciclovir was demonstrated to be significantly different from placebo. The latter is a result from a narrowing of the credible interval of the NMA compared to the confidence interval of the pairwise meta-analysis. Inclusion of indirect evidence in the NMA may account for this narrowing. One of the studies in the ganciclovir vs placebo comparison had zero events in the ganciclovir arm.

Table 21: Summary of results from pairwise meta-analysis and NMA, confirmed CMV disease within 100 days post-transplant in the evaluation of CMV prophylaxis					
Comparison		**# of Trials (patients)**	**Heterogeneity (I^2)**	**Direct Estimate OR (95% CI)**	**NMA Estimate OR (95% CrI)**
				**Values <1 favor comparator*	
Comparator	**Reference**				
Ganciclovir	Acyclovir	1 (91)	NA	0.67 (0.11–4.19)	0.63 (0.07–4.43)
Ganciclovir	Placebo	2 (150)	0.000	0.33 (0.09–1.18)	**0.28 (0.07–0.93)**

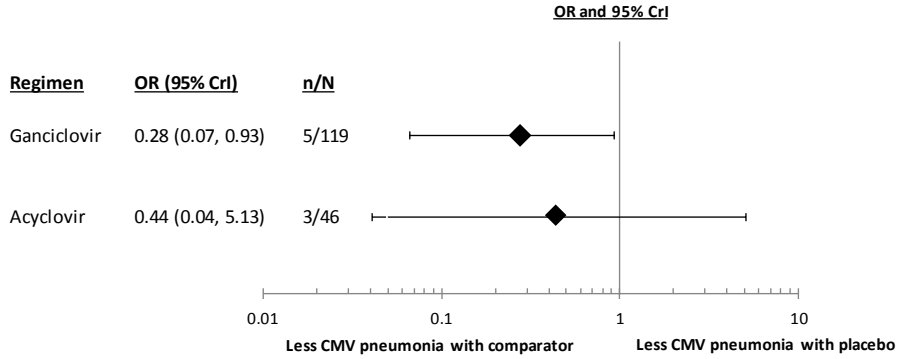
5.6.5.2. Results from network meta-analysis

One of the three possible comparisons was informed only by indirect evidence, while one of the two comparisons with direct evidence was informed by a single study. Model fit statistics for the NMA indicated that both the fixed-effects (FE) and random-effects (RE) models had an adequate fit. Posterior residual deviance values for the FE and RE models of 6.159 and 6.039, respectively, were obtained, demonstrating adequate fit, given the 6 data points in the model. DIC values (27.673 and 27.975) did not suggest difference in fit between the FE and RE models. A FE model was preferred due to the number of single-study connections in the network, while results from the RE model are provided in the report appendices.

Comparisons versus placebo

Figure 12 presents a forest plot summarizing comparisons of all treatments in the evidence network to the placebo reference. Ganciclovir was associated with a significant reduction in the risk of CMV pneumonia compared to placebo (OR = 0.28; 95% CrI = 0.07–0.93). Acyclovir was associated with a credible interval that included 1 and, thus, was not significantly different from placebo in preventing CMV pneumonia within 100–120 days post-transplant.

Figure 22: Forest plot of comparisons versus placebo, CMV pneumonia within 100–120 days post-transplant in studies evaluating CMV prophylaxis

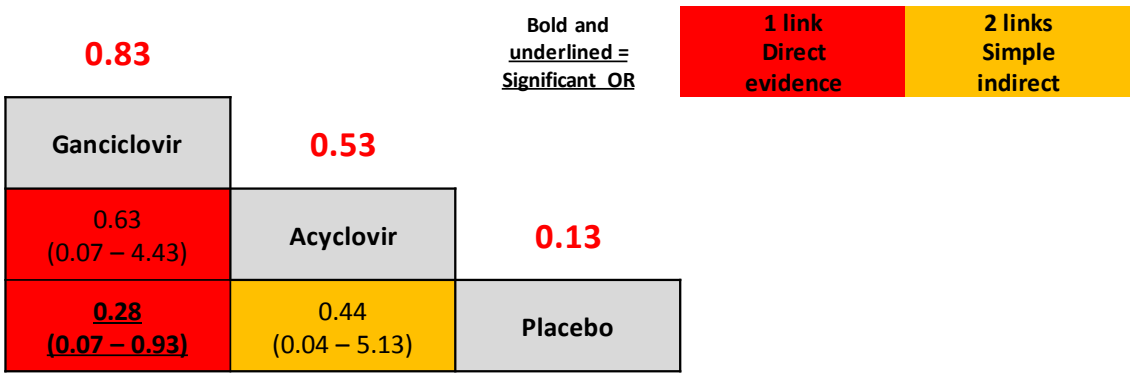


Odds ratios from network meta-analysis comparing each regimen to the reference placebo treatment are presented along with the number of events and patients per regimen. Odds ratios <1 suggest more risk of CMV pneumonia with placebo while odds ratios >1 suggest less risk of CMV pneumonia with placebo.

Comparisons between all conditioning regimens

Figure 13 presents a league table of the estimates for all pairwise comparisons generated from the network meta-analysis. The comparison between acyclovir and placebo should be interpreted more carefully than the others because it was not informed by head-to-head trials (i.e., there is an intermediate treatment between the interventions of interest). Ganciclovir was the highest-ranking prophylactic to reduce the risk of CMV pneumonia while on study treatment (100–120 days post-transplant). Ganciclovir was significantly more efficacious than placebo but not when compared to acyclovir.

Figure 33: League table summary of pairwise comparisons from NMA (Odds Ratios with 95% CrI), CMV pneumonia during within 100–120 days post-transplant in studies evaluating CMV prophylaxis



Interventions are sorted from left to right in order of decreasing SUCRA value (i.e., preferred treatments appear first). For each comparison shown, the upper/left-most regimen is the comparator group while the lower/right-most treatment is the reference treatment; a value <1 suggests fewer cases of CMV pneumonia with the comparator than with the reference group. Statistically significant differences (i.e., estimates with a 95% credible interval excluding 1) are bolded and underlined. Comparisons with direct evidence and simple indirect evidence have been highlighted in red and orange, respectively.

5.6.6. Findings: CMV pneumonia over extended follow-up

Three CMV prophylaxis studies[43, 46, 70] reported data for CMV pneumonia at extended follow-up in 323 patients (**Figure 14**). Data were reported beyond the discontinuation of study drugs in all three studies, ranging from 180 days (2 studies[46, 70]) to 365 days post-transplant (1 study[43]).

All three studies began CMV prophylaxis at engraftment; however, two of the studies[43, 70] included the pre-engraftment period in the follow-up period. One study also included patients with active viremia at engraftment[43] and one was unclear with respect to viremia status of patients at engraftment[70]. The risk of CMV disease, including pneumonia, is significantly greater in patients with active viremia at engraftment. Thus, the prophylaxes evaluated in studies that include DNA-positive patients at engraftment may appear to fare worse than those interventions in studies that exclude DNA-positive patients.

Figure 44: Network diagram for the NMA of the outcome of CMV pneumonia over extended follow-up in the evaluation of CMV prophylaxis

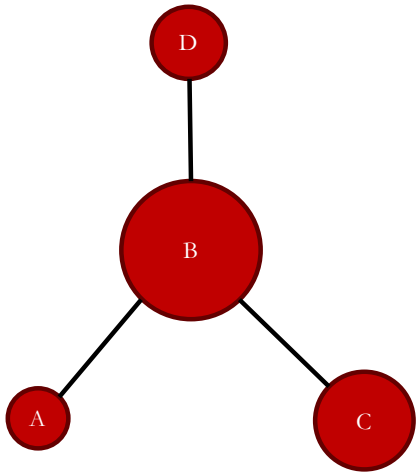


Figure legend
A = Placebo
B = Ganciclovir
C = Valaciclovir
D = Acyclovir

5.6.6.1. Results from traditional pairwise meta-analyses

Table 12 presents summaries of pairwise estimates that were derived from direct evidence (i.e., the head-to-head trials), summarized alongside the numbers of available trials and patients for each direct comparison, as well as the related summary estimate derived from the network meta-analysis.

All three direct comparisons were informed by single studies. No significant differences were demonstrated in any of the pairwise direct comparisons. The pairwise OR for ganciclovir compared to valaciclovir was not estimable due to zero events in both treatment arms. Generally, estimates from traditional pairwise meta-analyses compared well with estimates derived from network meta-analysis.

Table 32: Summary of results from pairwise meta-analysis and NMA, confirmed CMV disease within 100 days post-transplant in the evaluation of CMV prophylaxis

Comparison		# of Trials (patients)	Heterogeneity (I^2)	Direct Estimate OR (95% CI)	NMA Estimate OR (95% CrI)
				**Values <1 favor comparator*	
Comparator	**Reference**				
Ganciclovir	Acyclovir	1 (91)	NA	0.65 (0.17–2.48)	0.62 (0.14–2.42)
Ganciclovir	Placebo	1 (64)	NA	0.27 (0.05–1.45)	0.24 (0.03–1.23)
Ganciclovir	Valaciclovir	1 (168)	NA	Not estimable	0.99 (0.02–41.34)

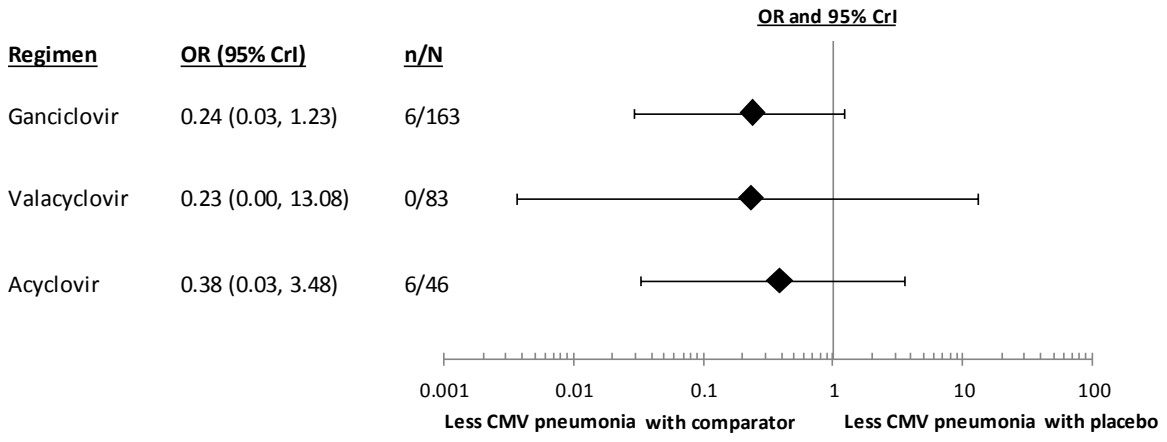
5.6.6.2. Results from network meta-analysis

Three of the six possible comparisons were informed only by indirect evidence, and all 3 comparisons with direct evidence were informed by single studies. Model fit statistics for the NMA indicated that both the fixed-effects (FE) and random-effects (RE) models had an adequate fit. Posterior residual deviance values for the FE and RE models of 6.496 and 6.451, respectively, were obtained, demonstrating adequate fit, given the 6 data points in the model. DIC values (28.903 and 28.831) did not suggest difference in fit between the FE and RE models. A FE model was preferred due to the number of single-study connections in the network, while RE model findings are presented in the report's appendices.

Comparisons versus placebo

Figure 15 presents a forest plot summarizing comparisons of all treatments in the evidence network to the placebo reference. All interventions were associated with a credible interval that included 1 and, thus, were not significantly different from placebo in preventing confirmed CMV pneumonia after extended follow-up.

Figure 55: Forest plot of comparisons versus placebo, CMV pneumonia over extended follow-up in studies evaluating CMV prophylaxis



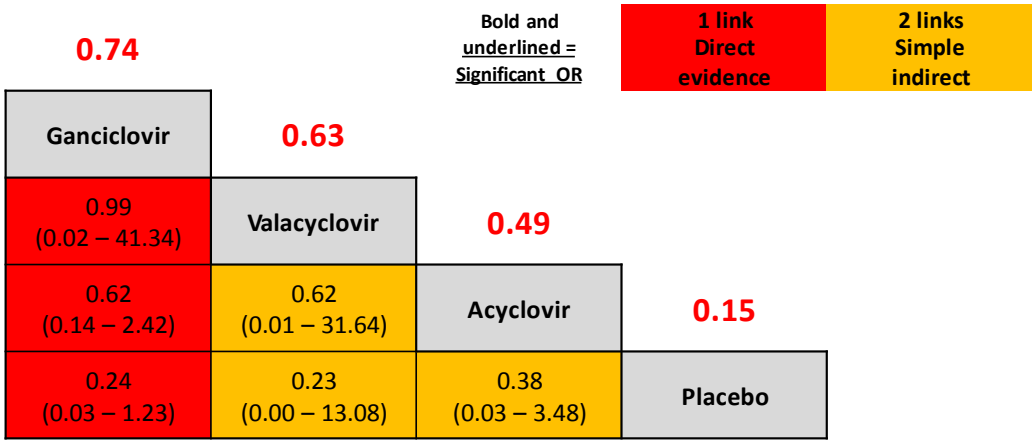
Odds ratios from network meta-analysis comparing each regimen to the reference placebo treatment are presented along with the number of events and patients per regimen. Odds ratios <1 suggest more risk of CMV pneumonia with placebo while odds ratios >1 suggest less risk of CMV pneumonia with placebo.

Comparisons between all conditioning regimens

Figure 16 presents a league table of the estimates for all pairwise comparisons generated from the network meta-analysis. Some of the comparisons included in the league table should be interpreted carefully, specifically those which are not informed by head to head trials (i.e., comparisons in which there are 2 intermediate treatments between the interventions of interest).

Ganciclovir was the highest-ranking prophylactic to reduce the risk of CMV pneumonia during extended follow-up; however, it was not significantly better than any of the other interventions in the network, including placebo. No intervention was significantly different than any of the others in the network in the prevention of CMV pneumonia. The same was observed in results estimated from the corresponding RE analysis which is provided in the appendices to the report.

Figure 16: League table summary of pairwise comparisons from NMA (Odds Ratios with 95% CrI), CMV pneumonia during extended follow-up in studies evaluating CMV prophylaxis



Interventions are sorted from left to right in order of decreasing SUCRA value (i.e., preferred treatments appear first). For each comparison shown, the upper/left-most regimen is the comparator group while the lower/right-most treatment is the reference treatment; a value <1 suggests fewer cases of CMV pneumonia with the comparator than with the reference group. Statistically significant differences (i.e., estimates with a 95% credible interval excluding 1) are bolded and underlined. Comparisons with direct evidence and simple indirect evidence have been highlighted in red and orange, respectively.

5.6.7. Findings: Overall mortality at 100–120 days post-transplant

Five CMV prophylaxis studies[44, 46, 58, 59, 68] reported overall mortality data at 100–120 days post-transplant in 999 patients and were included in an NMA (**Figure 17**). Where multiple doses of drugs were compared to placebo in a single study, the dose identified within the study as the best for clinical use (e.g., most efficacious with fewest adverse events) was included in the NMA.

Four of five studies began CMV prophylaxis at engraftment, with the fifth[68] beginning study drugs at the start of the conditioning regimen, stopping at transplant, then resuming at engraftment. This study also was the only of the five to include the pre-engraftment period in the follow-up period. One study[59] included patients with active viremia at engraftment, although the impact of this patient heterogeneity on overall mortality is unclear.

Figure 17: Network diagram for the NMA of the outcome of overall mortality within 100–120 days post-transplant in studies evaluating CMV prophylaxis

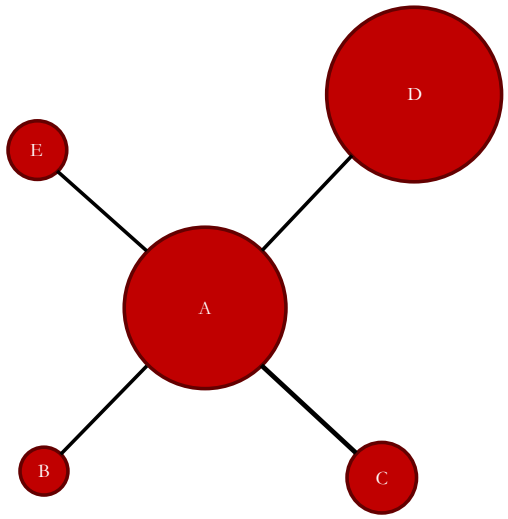


Figure legend
A = Placebo
B = Letermovir
C = Ganciclovir
D = Maribavir
E = Brincidofovir

5.6.7.1. Results from traditional pairwise meta-analyses

Table 13 presents summaries of pairwise estimates that were derived from direct evidence (i.e., the head-to-head trials), summarized alongside the numbers of available trials and patients for each direct comparison, as well as the related summary estimate derived from the network meta-analysis.

Three of the four direct comparisons were informed by single studies and none demonstrated significant differences in the risk of overall mortality between interventions. Estimates from traditional pairwise meta-analyses compared well with estimates derived from network meta-analysis in that there were no changes in significance or in direction of trends between the two methods. The 95% credible interval was wider than the 95% confidence interval for the comparison evaluating letermovir vs placebo, possibly due to the low number of mortality events in the single available study relative to the other studies in the network.

Table 43: Summary of results from pairwise meta-analysis and NMA, Overall mortality within 100–120 days post-transplant in studies evaluating CMV prophylaxis

Comparison		# of Trials (patients)	Heterogeneity (I^2)	Direct Estimate OR (95% CI)	FE NMA Estimate OR (95% CrI)
				**Values <1 favor comparator*	
Comparator	**Reference**				
Placebo	Brincidofovir	1 (109)	NA	0.83 (0.23–3.06)	0.83 (0.21–3.28)
Letermovir	Placebo	1 (67)	NA	0.97 (0.06–16.17)	0.94 (0.03–35.64)
Maribavir	Placebo	1 (674)	NA	0.77 (0.42–1.39)	0.77 (0.43–1.42)
Ganciclovir	Placebo	2 (149)	0.000	0.71 (0.31–1.93)	0.71 (0.32–1.49)

5.6.7.2. Results from network meta-analysis

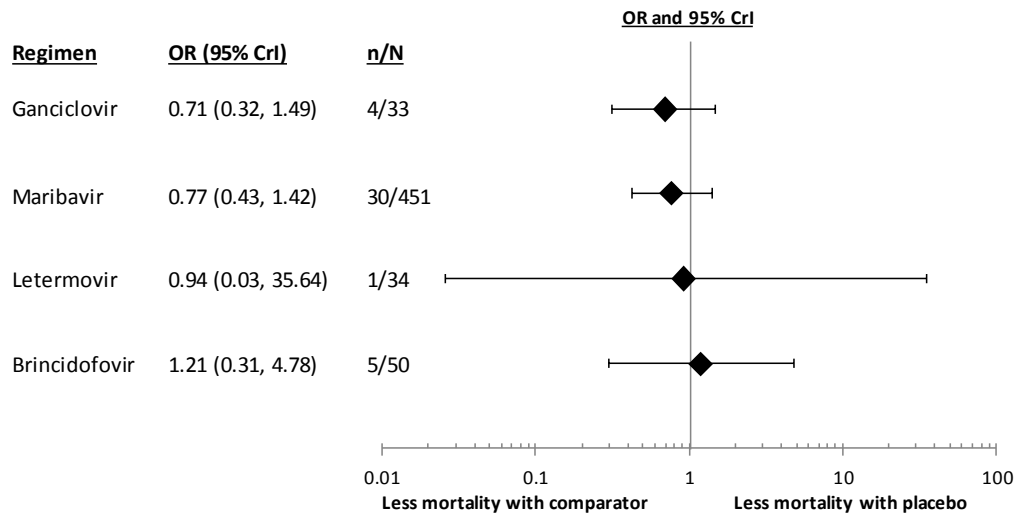
More than half of the comparisons (i.e., 6 of 10) were informed only by indirect evidence, and 3 of the 4 comparisons with direct evidence were informed by single studies. Model fit statistics for the NMA indicated that both the fixed-effects (FE) and random-effects (RE) models had an adequate fit. Posterior

residual deviance values for the FE and RE models of 9.534 and 10.110, respectively, were obtained, demonstrating adequate fit, given the 8 data points in the model. DIC values (53.645 and 54.835) did not suggest difference in fit between the FE and RE models. A FE model was preferred due to the number of single-study connections in the network, while findings from RE analyses are provided in the report's appendices.

Comparisons versus placebo

Figure 18 presents a forest plot summarizing comparisons of all treatments in the evidence network to the placebo reference. All interventions were associated with a credible interval that included 1 and, thus, were not significantly different from placebo in reducing overall mortality within 100–120 days post-transplant.

Figure 18: Forest plot of comparisons versus placebo, Overall mortality within 100–120 days post-transplant in studies evaluating CMV prophylaxis



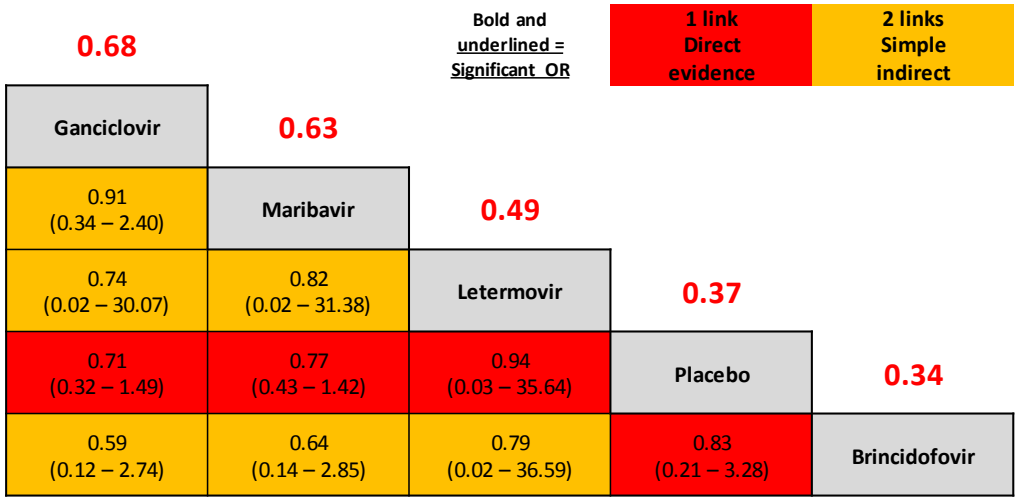
Odds ratios from network meta-analysis comparing each regimen to the reference placebo treatment are presented along with the number of events and patients per regimen. Odds ratios <1 suggest more risk of mortality with placebo while odds ratios >1 suggest less risk of mortality with placebo.

Comparisons between all conditioning regimens

Figure 19 presents a league table of the estimates for all pairwise comparisons generated from the network meta-analysis. Some of the comparisons included in the league table should be interpreted carefully, specifically those which are not informed by head to head trials (i.e., comparisons in which there are 1 or more intermediate treatments between the interventions of interest).

Ganciclovir was the highest-ranking prophylactic with respect to lowest risk of overall mortality within 100–120 days post-transplant; however, it was not significantly better than any of the other interventions in the network, including placebo. No intervention was significantly different than any of the others in the network in reducing overall mortality within 100 days post-transplant. Findings were analogous in findings from the RE analysis.

Figure 19: League table summary of pairwise comparisons from NMA (Odds Ratios with 95% CrI), Overall mortality within 100 days post-transplant in studies evaluating CMV prophylaxis



Interventions are sorted from left to right in order of decreasing SUCRA value (i.e., preferred treatments appear first). For each comparison shown, the upper/left-most regimen is the comparator group while the lower/right-most treatment is the reference treatment; a value <1 suggests fewer cases of death with the comparator than with the reference group. Statistically significant differences (i.e., estimates with a 95% credible interval excluding 1) are bolded and underlined. Comparisons with direct evidence and simple indirect evidence have been highlighted in red and orange, respectively.

5.6.8. Findings: Overall mortality at 180 days post-transplant

Four CMV prophylaxis studies[46, 54, 70, 71] reported overall mortality data at 180 days post-transplant in 893 patients and were included in an NMA (**Figure 20**). Where multiple doses of drugs were compared to placebo in a single study, the dose identified within the study as the best for clinical use (e.g., most efficacious with fewest adverse events) was included in the NMA.

All studies began CMV prophylaxis at engraftment; however, two studies included the pre-engraftment period in the follow-up period, which may have inflated the number of deaths relative to the other studies. One study[54] included patients with active viremia at engraftment and one study was unclear regarding this[70], although the impact of this patient heterogeneity on overall mortality is unclear.

Figure 20: Network diagram for the NMA of the outcome of overall mortality within 180 days post-transplant in studies evaluating CMV prophylaxis

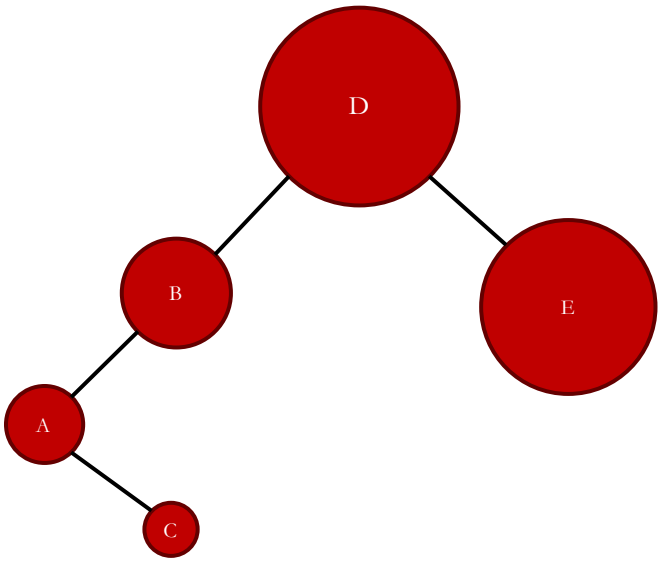


Figure legend
A = Placebo
B = Ganciclovir
C = Maribavir
D = Valaciclovir
E = Acyclovir

5.6.8.1. Results from traditional pairwise meta-analyses

Table 14 presents summaries of pairwise estimates that were derived from direct evidence (i.e., the head-to-head trials), summarized alongside the numbers of available trials and patients for each direct comparison, as well as the related summary estimate derived from the network meta-analysis.

All four direct comparisons were informed by single studies and none demonstrated significant differences in the risk of overall mortality between interventions within 180 days post-transplant. Estimates from traditional pairwise meta-analyses compared well with estimates derived from network meta-analysis.

Table 54: Summary of results from pairwise meta-analysis and NMA, Overall mortality within 100 days post-transplant in studies evaluating CMV prophylaxis

Comparison		# of Trials (patients)	Heterogeneity (I^2)	Direct Estimate OR (95% CI)	NMA Estimate OR (95% CrI)
				**Values <1 favor comparator*	
Comparator	**Reference**				
Ganciclovir	Valaciclovir	1 (168)	NA	0.65 (0.35–1.20)	0.65 (0.35–1.20)
Maribavir	Placebo	1 (56)	NA	0.61 (0.15–2.46)	0.59 (0.13–2.43)
Placebo	Ganciclovir	1 (64)	NA	0.80 (0.27–2.39)	0.81 (0.25–2.48)
Valaciclovir	Acyclovir	1 (605)	NA	0.79 (0.51–1.22)	0.79 (0.51–1.22)

5.6.8.2. Results from network meta-analysis

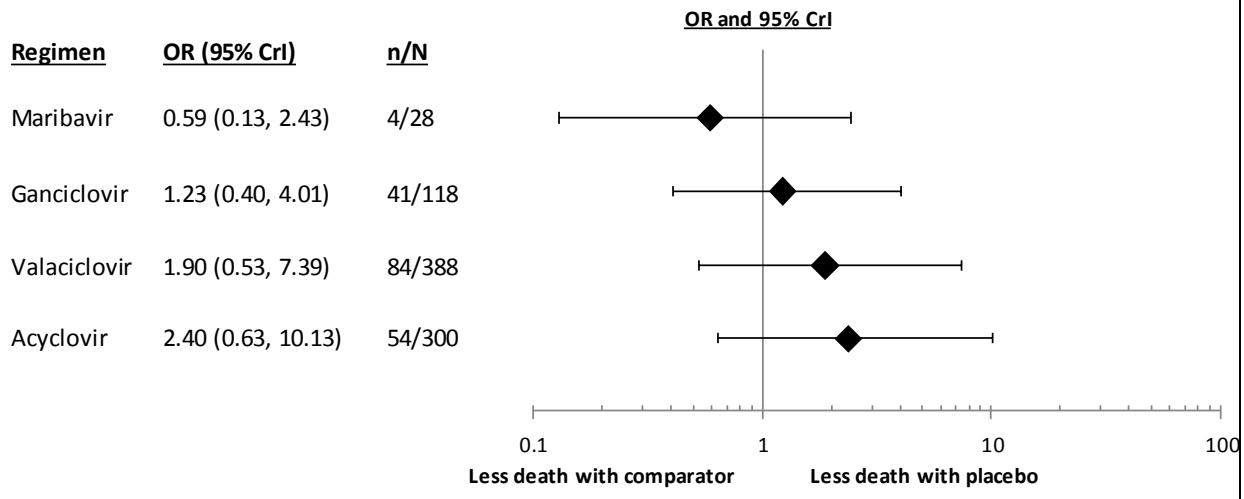
More than half of the comparisons (i.e., 6 of 10) were informed only by indirect evidence, and all 4 comparisons with direct evidence were informed by single studies. Model fit statistics for the NMA indicated that both the fixed-effects (FE) and random-effects (RE) models had an adequate fit. Posterior residual deviance values for the FE and RE models of 8.207 and 8.192, respectively, were obtained, demonstrating adequate fit, given the 8 data points in the model. DIC values (51.121 and 51.086) did not

suggest difference in fit between the FE and RE models. A FE model was preferred due to the number of single-study connections in the network, while RE findings are presented in the report's appendices.

Comparisons versus placebo

Figure 21 presents a forest plot summarizing comparisons of all treatments in the evidence network to the placebo reference. All other interventions were associated with a credible interval that included 1 and, thus, were not significantly different from placebo in reducing overall mortality within 180 days post-transplant.

Figure 21: Forest plot of comparisons versus placebo, Overall mortality within 180 days post-transplant in studies evaluating CMV prophylaxis



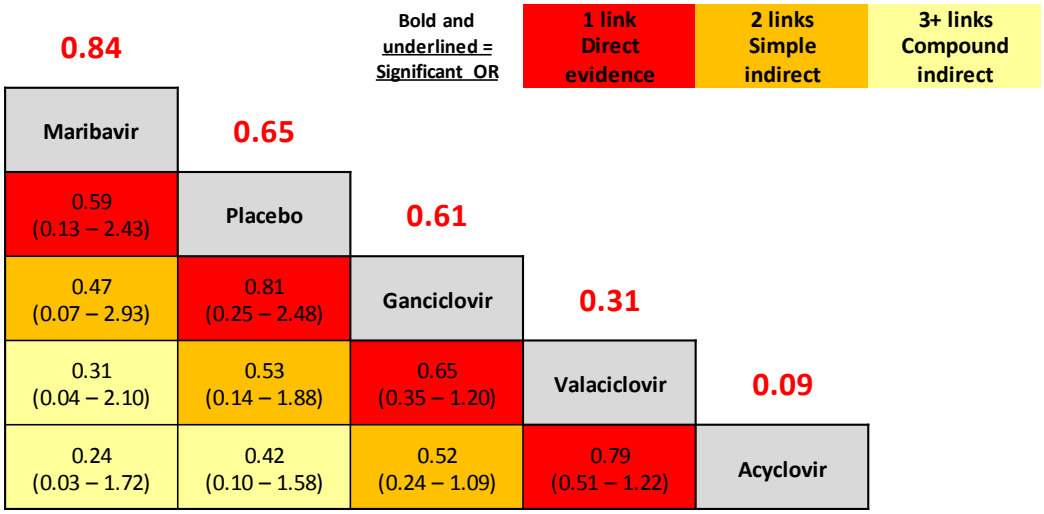
Odds ratios from network meta-analysis comparing each regimen to the reference placebo treatment are presented along with the number of events and patients per regimen. Odds ratios <1 suggest more risk of mortality with placebo while odds ratios >1 suggest less risk of mortality with placebo.

Comparisons between all conditioning regimens

Figure 22 presents a league table of the estimates for all pairwise comparisons generated from the network meta-analysis. Some of the comparisons included in the league table should be interpreted carefully, specifically those which are not informed by head to head trials (i.e., comparisons in which there are 2 or more intermediate treatments between the interventions of interest).

Maribavir was the highest-ranking prophylactic with respect to lowest risk of overall mortality within 180 days post-transplant; however, it was not significantly better than any of the other interventions in the network, including placebo. No intervention was significantly different than any of the others in the network in reducing overall mortality within 180 days post-transplant. The same was found to be true in the corresponding RE NMA analysis presented in the appendices.

Figure 62: League table summary of pairwise comparisons from NMA (Odds Ratios with 95% CrI), Overall mortality within 180 days post-transplant in studies evaluating CMV prophylaxis



Interventions are sorted from left to right in order of decreasing SUCRA value (i.e., preferred treatments appear first). For each comparison shown, the upper/left-most regimen is the comparator group while the lower/right-most treatment is the reference treatment; a value <1 suggests fewer cases of death with the comparator than with the reference group. Statistically significant differences (i.e., estimates with a 95% credible interval excluding 1) are bolded and underlined. Comparisons with direct evidence and simple indirect evidence have been highlighted in red and orange, respectively.

5.6.9. Findings: Overall mortality at 365 days post-transplant

One CMV prophylaxis study[43] reported overall mortality at 365 days post-transplant in the assessment of acyclovir vs ganciclovir. Forty-six percent of patients had died by 365 days post-transplant in the acyclovir group (21 of 46) compared to 36% in the ganciclovir group (16 of 45); however, the difference was not statistically significant (OR = 1.52; 95% CI = 0.66–3.53).

5.6.10. Findings: Neutropenia (ANC ≤ 750/µl) while on study drug

Four CMV prophylaxis studies[43, 46, 70, 71] reported drug-related neutropenia data, defined as an absolute neutrophil count ≤ 750/µl while the patient was taking the study drug, in 348 patients and these studies were included in an NMA (**Figure 23**). The duration of study treatment and consequently the follow-up period in the 4 included studies were consistent at 100 days post-transplant. Where multiple doses of drugs were compared to placebo in a single study, the dose identified within the study as the best for clinical use (e.g., most efficacious with fewest adverse events) was included in the NMA.

One study included patients with active viremia at engraftment[43] and one was unclear with respect to viremia status of patients at engraftment[70]; however, it is not clear if viremia status would impact the drug-related neutropenia outcome.

Figure 73: Network diagram for the NMA of the outcome of drug-related neutropenia (ANC ≤ 750/µl) in studies evaluating CMV prophylaxis

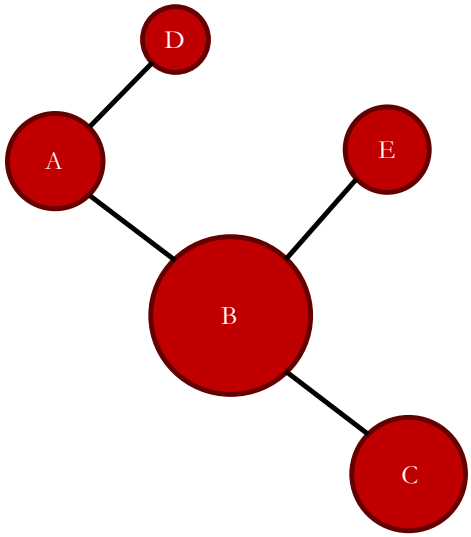


Figure legend
A = Placebo
B = Ganciclovir
C = Valaciclovir
D = Maribavir
E = Acyclovir

5.6.10.1. Results from traditional pairwise meta-analyses

Table 15 presents summaries of pairwise estimates that were derived from direct evidence (i.e., the head-to-head trials), summarized alongside the numbers of available trials and patients for each direct comparison, as well as the related summary estimate derived from the network meta-analysis.

All four direct comparisons were informed by single studies. Ganciclovir treatment was found to be associated with a significantly higher risk of drug-related neutropenia than valaciclovir, acyclovir, and placebo. Maribavir treatment did not alter the risk of drug-induced neutropenia compared to placebo. Estimates from traditional pairwise meta-analyses compared well with estimates derived from network meta-analysis.

Table 65: Summary of results from pairwise meta-analysis and NMA, Drug-related neutropenia (ANC ≤ 750/µl) in studies evaluating CMV prophylaxis

Comparison		# of Trials (patients)	Heterogeneity (I^2)	Direct Estimate OR (95% CI)	NMA Estimate OR (95% CrI)
				**Values <1 favor comparator*	
Comparator	**Reference**				
Valaciclovir	Ganciclovir	1 (137)	NA	**0.31 (0.13–0.74)**	**0.30 (0.12–0.71)**
Acyclovir	Ganciclovir	1 (91)	NA	**0.13 (0.05–0.36)**	**0.12 (0.04–0.32)**
Placebo	Ganciclovir	1 (64)	NA	**0.04 (0.002–0.64)**	**0.02 (0.00–0.25)**
Placebo	Maribavir	1 (56)	NA	1.00 (0.22–4.47)	1.00 (0.21–5.07)

5.6.10.2. Results from network meta-analysis

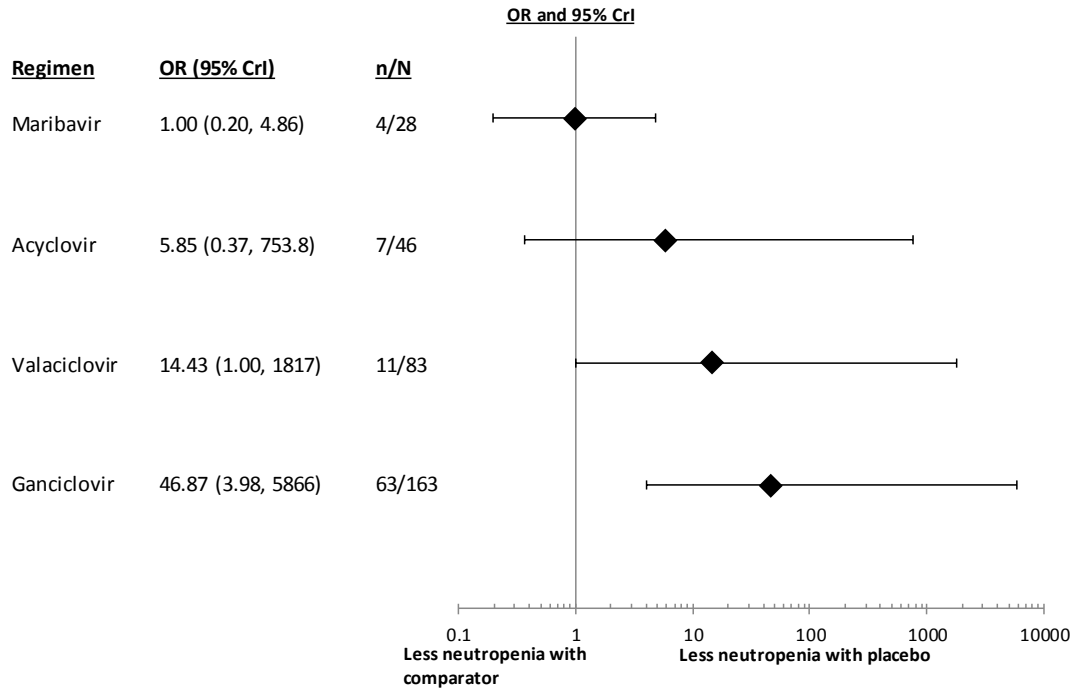
More than half of the comparisons (i.e., 6 of 10) were informed only by indirect evidence, and all 4 comparisons with direct evidence were informed by single studies. Model fit statistics for the NMA indicated that both the fixed-effects (FE) and random-effects (RE) models had an adequate fit. Posterior

residual deviance values for the FE and RE models of 8.232 and 8.766, respectively, were obtained, demonstrating adequate fit, given the 8 data points in the model. DIC values (43.807 and 44.327) did not suggest difference in fit between the FE and RE models. A FE model was preferred due to the number of single-study connections in the network, while results from the corresponding RE analysis are provided in the appendices.

Comparisons versus placebo

Figure 24 presents a forest plot summarizing comparisons of all treatments in the evidence network to the placebo reference. One prophylactic—ganciclovir—was found to statistically significantly increase the risk of neutropenia relative to placebo (OR = 46.87; 95% CrI = 3.98–5,866.0), while valaciclovir had a significantly higher risk of neutropenia compared to placebo (OR = 14.43; 95% CrI = 1.003–1,817). All other interventions were associated with a credible interval that included 1 and, thus, were not significantly different from placebo in their association with drug-related neutropenia.

Figure 84: Forest plot of comparisons versus placebo, Drug-related neutropenia (ANC ≤ 750/µl) in studies evaluating CMV prophylaxis



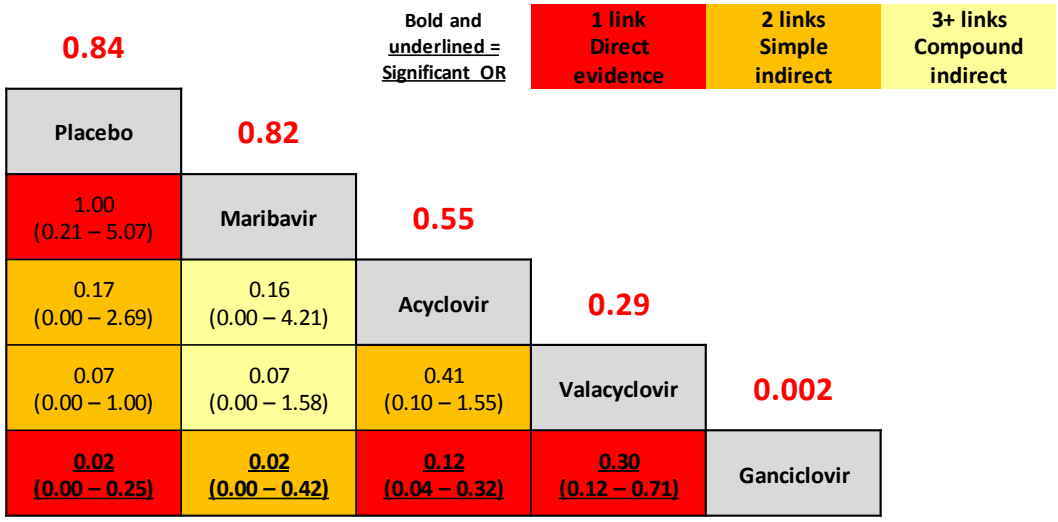
Odds ratios from network meta-analysis comparing each regimen to the reference placebo treatment are presented along with the number of events and patients per regimen. Odds ratios <1 suggest more risk of neutropenia with placebo while odds ratios >1 suggest less risk of neutropenia with placebo.

Comparisons between all conditioning regimens

Figure 25 presents a league table of the estimates for all pairwise comparisons generated from the network meta-analysis. Some of the comparisons included in the league table should be interpreted carefully, specifically those which are not informed by head to head trials or where the comparison was based on compound indirect evidence (i.e., comparisons in which there are 2 or more intermediate treatments between the interventions of interest).

Ganciclovir was the lowest-ranking prophylactic, indicating that it was associated with a greater risk of drug-related neutropenia. This association was statistically significant when compared to all interventions in the network. No other prophylactics demonstrated a significantly greater risk of drug-related neutropenia compared to placebo or the non-ganciclovir treatments.

Figure 95: League table summary of pairwise comparisons from NMA (Odds Ratios with 95% CrI), Drug-related neutropenia (ANC ≤ 750/µl) in studies evaluating CMV prophylaxis



Interventions are sorted from left to right in order of decreasing SUCRA value (i.e., preferred treatments appear first). For each comparison shown, the upper/left-most regimen is the comparator group while the lower/right-most treatment is the reference treatment; a value <1 suggests fewer cases of neutropenia with the comparator than with the reference group. Statistically significant differences (i.e., estimates with a 95% credible interval excluding 1) are bolded and underlined. Comparisons with direct evidence, simple indirect evidence, and compound indirect evidence have been highlighted in red, orange, and yellow, respectively.

5.6.11. Findings: Neutropenia—definitions other than ANC ≤ 750/µl, while on study drug

Seven CMV prophylaxis studies[43, 44, 58, 59, 68, 70, 71] assessed neutropenia using a definition other than ANC ≤ 750 µl, while on study drug. The findings for these varied outcomes have been summarized in **Table 16**. For the majority of comparisons, no statistically significant differences were demonstrated. However, at 100 days post-transplant, ganciclovir was associated with a significantly higher risk of any moderate neutropenia (ANC < 750/µl), not necessarily drug-related than acyclovir (OR = 3.83; 95% CI = 1.60–9.19). Ganciclovir was also associated with a significantly higher risk of mild drug-related neutropenia (ANC < 1000/µl) than placebo (OR = 3.63; 95% CI = 1.51–8.76). As well, at 91 days post-transplant, brincidofovir was associated with a significantly higher risk of mild drug-related neutropenia (ANC < 1000/µl) (OR = 3.10; 95% CI = 1.08–8.91). At 98–114 days post-transplant, maribavir appeared to have a protective effect compared to placebo against the development of moderate neutropenia, but not mild or severe neutropenia. This was likely a spurious result.

Table 76: Summary of results: Findings for neutropenia other than ANC ≤ 750/µl, while on study drug, in studies evaluating CMV prophylaxis

Study	Outcome definition	Duration of study treatment	Follow-up	Intervention	Group risk	OR (95% CI)
Chemaly (2014)[44]	Unclear ANC; all cases	84 days post-engraftment	~100–125 days PT	Letermovir	3/34 (9%)	1.50 (0.23–9.61)
				Placebo	2/33 (6%)*	

Table 76: Summary of results: Findings for neutropenia other than ANC ≤ 750/µl, while on study drug, in studies evaluating CMV prophylaxis						
Study	**Outcome definition**	**Duration of study treatment**	**Follow-up**	**Intervention**	**Group risk**	**OR (95% CI)**
		(~100–125 days PT)				
Chemaly (2014)[44]	Unclear ANC; cases "at least possibly related to study drug"	84 days post-engraftment (~100–125 days PT)	~100–125 days PT	Letermovir	0/34 (0%)	NE
				Placebo	0/33 (0%)*	
Burns (2002)[43]	ANC < 750/µl; all cases	100 days PT	100 days PT	Acyclovir	18/46 (39%)*	**3.83 (1.60–9.19)**
				Ganciclovir	32/45 (71%)	
Marty (2011)[58]	ANC < 1000/µl; all cases	100 days PT	100 days PT	Maribavir	175/450 (39%)	0.88 (0.64–1.22)
				Placebo	93/222 (42%)*	
Marty (2011)[58]	ANC < 750/µl; all cases	100 days PT	100 days PT	Maribavir	127/450 (28%)	0.80 (0.57–1.14)
				Placebo	73/222 (33%)*	
Marty (2011)[58]	ANC < 500/µl; all cases	100 days PT	100 days PT	Maribavir	87/450 (19%)	0.92 (0.61–1.37)
				Placebo	46/222 (21%)*	
Winston (1993)[68]	ANC < 1000/µl; drug-related	120 days PT	120 days PT	Ganciclovir	25/43 (58%)	**3.63 (1.51–8.76)**
				Placebo	13/47 (28%)	
Winston (2008)[71]	ANC < 1000/µl; drug-related	98–114 days PT	98–114 days PT	Maribavir	6/28 (21%)	1.64 (0.41–6.58)
				Placebo	4/28 (14%)*	
Winston (2008)[71]	ANC < 500/µl; drug-related	98–114 days PT	98–114 days PT	Maribavir	3/28 (11%)	1.56 (0.24–10.14)
				Placebo	2/28 (7%)*	
Winston (2008)[71]	ANC < 1000/µl; all cases	98–114 days PT	98–114 days PT	Maribavir	7/28 (25%)	0.52 (0.16–1.62)
				Placebo	11/28 (39%)*	
Winston (2008)[71]	ANC < 750/µl; all cases	98–114 days PT	98–114 days PT	Maribavir	4/28 (14%)	**0.26 (0.07–0.95)**
				Placebo	11/28 (39%)*	
Winston (2008)[71]	ANC < 500/µl; all cases	98–114 days PT	98–114 days PT	Maribavir	3/28 (11%)	0.44 (0.10–1.97)
				Placebo	6/28 (21%)*	
Marty (2013)[59]	ANC < 1000/µl; drug related	91 days PT	91 days PT	Brincidofovir	13/50 (26%)	**3.10 (1.08–8.91)**
				Placebo	6/59 (10%)*	
Winston (2003)[70]	ANC < 750/µl; all cases	100 days PT	180 days PT	Ganciclovir	22/85 (26%)	0.72 (0.37–1.41)
				Valaciclovir	27/83 (33%)*	
Winston (2003)[70]	ANC < 500/µl; all cases	100 days PT	180 days PT	Ganciclovir	16/85 (19%)	1.37 (0.61–3.11)
				Valaciclovir	12/83 (14%)*	
Winston (2003)[70]	ANC < 250/µl; all cases	100 days PT	180 days PT	Ganciclovir	6/85 (7%)	0.82 (0.27–2.57)
				Valaciclovir	7/83 (8%)*	
*denotes the reference group for each pairwise comparison ANC = absolute neutrophil count; NE = not estimable; OR = odds ratio; PT = post-transplant						

5.6.12. Findings: Non-relapse mortality

Five studies[44, 46, 68, 70, 71] reported data related to non-relapse mortality. Because of the competing risk of relapse, these data could not be analysed by NMA and instead have been summarized in **Table 17**. No study identified a significantly different risk of non-relapse mortality between treatment groups.

Table 87: Summary of results: CMV prophylaxis—non-relapse mortality				
Study	**Follow-up**	**Intervention**	**Group risk**	**OR (95% CI)**
Chemaly (2014)[44]	100–125 days PT	Letermovir	1/34 (3%)	0.97 (0.06–16.17)
		Placebo	1/33 (3%)	
Goodrich (1993)[46]	180 days PT	Ganciclovir	7/33 (21%)	1.12 (0.33–3.80)
		Placebo	6/31 (19%)	
Winston (1993)[68]	120 days PT	Ganciclovir	12/40 (30%)	0.95 (0.38–2.39)
		Placebo	14/45 (31%)	
Winston (2008)[71]	154–170 days PT	Maribavir	3/28 (11%)	1.00 (0.18–5.44)
		Placebo	3/28 (11%)	
Winston (2003)[70]	180 days PT	Valaciclovir	33/83 (40%)	1.21 (0.65–2.26)
		Ganciclovir	30/85 (35%)	
*denotes the reference group for each pairwise comparison CMV = cytomegalovirus; OR = odds ratio; PT = post-transplant				

5.7. Objective 1: Viral prophylaxis/treatment—Late CMV prophylaxis

A single placebo-controlled trial (Boeckh, 2015)[41] evaluated the use of valganciclovir as prophylaxis against CMV infection late in the post-transplantation recovery period, after withdrawal of prophylactic or pre-emptive treatments begun in the early post-engraftment period. Randomization occurred at a median time post-transplant of 97 days and patients received study drug to 270 days post-transplant or until a CMV DNA level >1000 copies/ml. When CMV DNA levels crossed threshold, open-label ganciclovir or valganciclovir pre-emptive treatment was begun. The placebo-controlled design effectively compared the use of late post-engraftment valganciclovir prophylaxis to PCR-guided pre-emptive therapy with ganciclovir or valganciclovir. The results of this trial have been summarized narratively below.

Prophylactic valganciclovir therapy significantly reduced the risk of viremia identified by PCR, compared to patients receiving no prophylactic therapy. However, no significant differences were found between the two treatment groups with respect to the composite outcome (CMV disease or invasive bacterial/fungal infections or death), or these three main outcomes analysed separately. The risk of drug-related neutropenia was not significantly increased in patients receiving valganciclovir.

Table 98: Summary of results: Findings for all outcomes in the evaluation of prophylaxis against CMV disease late in the post-engraftment period (from Boeckh, 2015)[41]				
Outcome definition	**Follow-up**	**Intervention**	**Group risk**	**OR (95% CI)**
Composite outcome[a]	From randomization (~day 97 PT) to day 270 PT	Valganciclovir	18/95 (19%)	0.94 (0.46–1.91)
		Placebo	18/89 (20%)*	
Composite outcome[a]	From randomization (~day 97 PT) to day 640 PT	Valganciclovir	32/95 (34%)	0.88 (0.50–1.55)
		Placebo	34/89 (38%)*	
Confirmed CMV disease	From randomization (~day 97 PT) to day 270 PT	Valganciclovir	2/95 (2%)	0.94 (0.13–6.79)
		Placebo	2/89 (2%)*	
Confirmed CMV disease	From randomization (~day 97 PT) to day 640 PT	Valganciclovir	5/95 (5%)	0.94 (0.26–3.35)
		Placebo	5/89 (6%)*	
Mortality	From randomization (~day 97 PT) to day 270 PT	Valganciclovir	6/95 (6%)	0.94 (0.29–3.01)
		Placebo	6/89 (7%)*	
Mortality	From randomization (~day 97 PT) to day 640 PT	Valganciclovir	17/95 (18%)	1.00 (0.47–2.09)
		Placebo	16/89 (18%)*	
		Valganciclovir	17/95 (18%)	1.06

Table 98: Summary of results: Findings for all outcomes in the evaluation of prophylaxis against CMV disease late in the post-engraftment period (from Boeckh, 2015)[41]				
Outcome definition	**Follow-up**	**Intervention**	**Group risk**	**OR (95% CI)**
Invasive bacterial or fungal infection	From randomization (~day 97 PT) to day 270 PT	Placebo	15/89 (17%)*	(0.50–2.25)
Invasive bacterial or fungal infection	From randomization (~day 97 PT) to day 640 PT	Valganciclovir	21/95 (22%)	0.82 (0.43–1.58)
		Placebo	24/89 (27%)*	
CMV DNAemia[b]	From randomization (~day 97 PT) to day 270 PT	Valganciclovir	10/95 (11%)	**0.32 (0.14–0.65)**
		Placebo	31/89 (35%)*	
Neutropenia while receiving study drug[c]	While on medication (180 days) to ~270 days PT	Valganciclovir	5/95 (7%)	0.78 (0.23–2.65)
		Placebo	6/89 (10%)*	
*denotes the reference group for each pairwise comparison [a]CMV disease, invasive bacterial or fungal infections, or death (whichever occurred first) [b]>1000 copies/ml or 5-fold increase over baseline [c]ANC < 500/µl CMV = cytomegalovirus; OR = odds ratio; PT = post-transplant				

5.8. Objective 1: Viral prophylaxis/treatment—HSV prophylaxis

Two studies evaluated the use of prophylaxis for HSV.[61, 62] Both compared acyclovir to placebo and their data have been analysed in pairwise meta-analyses below. No outcomes of interest were reported other than confirmed HSV infection.

Both studies evaluated culture-positive HSV infection (**Table 19**). At 100 days follow-up, no significant difference in the risk of HSV infection was found by Shepp et al.[62]; however, by 180 days, acyclovir significantly reduced the risk of HSV infection compared to placebo. When these data were meta-analysed, prophylactic acyclovir was found to significantly reduce the risk of HSV compared to placebo after HSCT.

In a subgroup analysis, Shepp et al.[62] found that amongst the ~70% of patients who completed therapy, those who took acyclovir were significantly less likely to develop HSV infection than those who took placebo (OR = 0.20; 95% CI = 0.05–0.85). However, patients who did not complete acyclovir therapy were not significantly more likely to develop HSV infection than patients who did not complete placebo therapy (OR = 1.40; 95% CI = 0.14–13.57). The sample size was very small for the latter subgroup analysis (n = 7 and 9 patients, respectively), making the power to detect a significant difference low.

Table 19: Summary of results of pairwise meta-analysis of data for the HSV infection outcome for studies evaluating HSV prophylaxis							
Study	**Outcome definition**	**Follow-up**	**Intervention**	**Group risk**	**Study OR**	**Pairwise meta-analysis OR (95% CI)**	**I^2**
Shepp (1987)[62]	Culture positive	100 days PT	Acyclovir	9/25 (36%)	0.41 (0.13–1.27)	**0.27 (0.12–0.61)**	0.236
			Placebo	15/26 (58%)*			
Selby (1989)[61, 73]	Culture positive	180 days PT	Acyclovir	5/42 (12%)	**0.18 (0.06–0.56)**		
			Placebo	17/40 (43%)*			
*denotes the reference group for each pairwise comparison HSV = Herpes simplex virus; I^2 = statistical heterogeneity between studies; OR = odds ratio; PT = post-transplant							

5.9. Objective 1: Viral prophylaxis/treatment—VZV prophylaxis

A single placebo-controlled trial (Boeckh, 2006)[40] evaluated the use of acyclovir as prophylaxis against VZV infection post-engraftment. The study drugs were started at a median of 63 days post-transplant and continued to 1 year post-transplant. The placebo-controlled design effectively compared the use of acyclovir prophylaxis to empiric therapy with acyclovir. The results of this trial have been summarized narratively below.

Prophylactic acyclovir therapy significantly reduced the risk of VZV disease at 1 year post-transplant, the duration of treatment, compared to patients receiving no prophylactic therapy. The authors report that all cases of VZV during the treatment period occurred in patients who were unable to take acyclovir (these patients were not rechallenged). At later follow-up times, after discontinuation of study treatment, no significant differences were found between the two treatment groups with respect to VZV disease (i.e., when acyclovir was discontinued, rebound cases of VZV occurred, but overall patient health may have been more stable at this time to fight infection). Neither the risk of death nor the risk of neutropenia at 1 year post-transplant were significantly different between the two treatment groups. No significant hazard ratios were reported for univariate survival analyses at 1, 2, 3, and 5 years post-transplant reported in the original paper (results not shown). No significant difference in adverse events were reported between the two study groups.

Table 100: Summary of results: Findings for all outcomes in the evaluation of post-engraftment prophylaxis against VZV disease (from Boeckh, 2006)[40]

Outcome definition	Follow-up	Intervention	Group risk	RD or OR (95% CI)
Confirmed VZV disease[a]	1 year PT	Acyclovir	2/38 (5%)	**OR = 0.16 (0.03–0.79)**
		Placebo	10/39 (26%)*	
Confirmed VZV disease[a]	2 year PT	Acyclovir	8/38 (21%)	OR = 0.60 (0.21–1.69)
		Placebo	12/39 (31%)*	
Confirmed VZV disease[a]	3 year PT	Acyclovir	11/38 (29%)	OR = 0.81 (0.31–2.14)
		Placebo	13/39 (33%)*	
Confirmed VZV disease[a]	5 year PT	Acyclovir	14/38 (37%)	OR = 1.04 (0.41–2.64)
		Placebo	14/39 (36%)*	
Confirmed VZV disease[a]	10 year PT	Acyclovir	15/38 (39%)	OR = 1.04 (0.42–2.61)
		Placebo	15/39 (38%)*	
Overall mortality	1 year PT	Acyclovir	6/38 (16%)	OR = 0.38 (0.13–1.12)
		Placebo	13/39 (33%)*	
Overall neutropenia, ANC cutoff not reported	1 year	Acyclovir	0/38 (0%)	RD = -0.03 (-0.08–0.02)
		Placebo	1/39 (3%)	

*denotes the reference group for each pairwise comparison
[a]typical clinical symptoms confirmed by culture or histopathology
ANC = absolute neutrophil count; OR = odds ratio; PT = post-transplant; VZV = varicella zoster virus

5.10. Objective 1: Viral prophylaxis/treatment—Pre-emptive CMV therapy

Two studies evaluated pre-emptive CMV therapies.[47, 60] Relatively small samples sizes in the two studies and anticipated high heterogeneity due to an 11-year difference in publication date and differences in treatment duration reduced the potential robustness of network meta-analysis, favouring narrative summary. The findings of the studies are summarized below.

5.10.1. Findings: Confirmed CMV disease

Both studies assessed confirmed CMV disease, with Goodrich et al.[47] demonstrating a significant reduction in the risk of CMV disease in patients treated pre-emptively with ganciclovir compared to those treated with placebo. This significant reduction occurred while patients were on study drugs (to 100 days post-transplant) and beyond to 180 days post-transplant. No significant difference in confirmed CMV disease was found between ganciclovir and foscarnet at 180 days post-transplant.

Table 111: Summary of results: Findings for confirmed CMV disease in the evaluation of pre-emptive CMV treatment

Study	Outcome definition	Duration of study treatment	Follow-up	Intervention	Group risk	OR (95% CI)
Goodrich (1991)[47]	Signs of disease confirmed by biopsy or culture	To 100 days PT	100 days PT	Ganciclovir	1/37 (3%)	**0.04 (0.004–0.30)**
				Placebo	15/35 (53%)*	
Goodrich (1991)[47]	Signs of disease confirmed by biopsy or culture	To 100 days PT	180 days PT	Ganciclovir	6/37 (16%)	**0.26 (0.09–0.78)**
				Placebo	15/35 (43%)*	
Reusser (2002)[60]	Signs of disease confirmed by biopsy or BAL	14–28 days	180 days PT	Ganciclovir	5/110 (5%)	0.93 (0.26–3.32)
				Foscarnet	5/103 (5%)*	

*denotes the reference group for each pairwise comparison
OR = odds ratio; PT = post-transplant

5.10.2. Findings: Confirmed CMV pneumonia

Both studies[47, 60] reported confirmed CMV pneumonia as a subset of CMV disease. A significant reduction in risk for ganciclovir patients compared to placebo patients was identified while on study drug (to 100 days post-transplant) and beyond to 180 days post-transplant. No significant difference in confirmed CMV pneumonia was found between ganciclovir and foscarnet at 180 days post-transplant.

Table 122: Summary of results: Findings for confirmed CMV pneumonia in the evaluation of pre-emptive CMV treatment

Study	Outcome definition	Duration of study treatment	Follow-up	Intervention	Group risk	OR (95% CI)
Goodrich (1991)[47]	Signs of pneumonia confirmed by biopsy or culture	To 100 days PT	100 days PT	Ganciclovir	1/37 (3%)	**0.07 (0.008–0.58)**
				Placebo	10/35 (29%)*	
Goodrich (1991)[47]	Signs of pneumonia confirmed by biopsy or culture	To 100 days PT	180 days PT	Ganciclovir	2/37 (5%)	**0.14 (0.03–0.71)**
				Placebo	10/35 (29%)*	
Reusser (2002)[60]	Signs of pneumonia confirmed by biopsy or BAL	14–28 days	180 days PT	Ganciclovir	3/110 (3%)	1.42 (0.23–8.65)
				Foscarnet	2/103 (2%)*	

*denotes the reference group for each pairwise comparison
OR = odds ratio; PT = post-transplant

5.10.3. Findings: Overall mortality

Both studies[47, 60] reported overall mortality data. Overall mortality was not significantly different between ganciclovir and placebo groups while patients were on study treatment (to 100 days post-transplant); however, by 180 days post-transplant, there was a significant reduction in overall mortality in the

ganciclovir group (OR = 0.26; 95% CI = 0.08–0.93). No significant difference in overall mortality was found between ganciclovir and foscarnet at 180 days post-transplant.

Table 133: Summary of results: Findings for overall mortality in the evaluation of pre-emptive CMV treatment

Study	Duration of study treatment	Follow-up	Intervention	Group risk	OR (95% CI)
Goodrich (1991)[47]	To 100 days PT	100 days PT	Ganciclovir	1/37 (3%)	0.13 (0.02–1.18)
			Placebo	6/35 (17%)*	
Goodrich (1991)[47]	To 100 days PT	180 days PT	Ganciclovir	4/37 (11%)	**0.26 (0.08–0.93)**
			Placebo	11/35 (31%)*	
Reusser (2002)[60]	14–28 days	180 days PT	Ganciclovir	29/110 (26%)	1.25 (0.66–2.33)
			Foscarnet	23/103 (22%)*	

*denotes the reference group for each pairwise comparison
OR = odds ratio; PT = post-transplant

5.10.4. Findings: Non-relapse mortality

Only Goodrich et al.[47] evaluated non-relapse mortality. These data have been summarized narratively in **Table 24**. At 100 days post-transplant, ganciclovir therapy was associated with a 17% reduction in the risk of non-relapse mortality compared to placebo, and this difference was significant at the 95% level. However, at 180 days post-transplant, there was no significant difference in the risk of non-relapse mortality between ganciclovir and placebo.

Table 144: Summary of results: Pre-emptive CMV therapy—Non-relapse mortality (from Goodrich et al. (1991)[47])

Follow-up	Intervention	Group risk	RD or OR (95% CI)
100 days PT	Ganciclovir	0/37 (0%)	**Risk difference: -0.17 (-0.30– -0.05)**
	Placebo	6/35 (17%)*	
180 days PT	Ganciclovir	3/37 (3%)	Odds ratio: 0.30 (0.07–1.23)
	Placebo	8/35 (23%)*	

*denotes the reference group for each pairwise comparison
CMV = cytomegalovirus; OR = odds ratio; RD = risk difference; PT = post-transplant

5.10.5. Findings: Drug-related neutropenia

The two studies[47, 60] evaluating pre-emptive CMV therapies did not report the same outcome definition for neutropenia, thus, their findings have been summarized narratively in **Table 25**. Goodrich et al.[47] reported cases of ANC < 750/µl, while Reusser et al.[60] reported cases of ANC < 500/µl.

Compared to placebo, ganciclovir was associated with a significantly higher risk of moderate neutropenia (ANC <750/µl) after 180 days post-transplant. However, foscarnet and ganciclovir demonstrated no significant differences in the development of severe neutropenia (ANC < 500/µl) at 180 days post-transplant.

Table 25: Summary of results: Findings drug-related neutropenia

Study	Outcome definition	Follow-up	Intervention	Group risk	OR (95% CI)
Goodrich (1991)[47]	ANC <750/µl	180 days PT	Ganciclovir	11/37 (30%)	**4.51**

Table 25: Summary of results: Findings drug-related neutropenia					
Study	**Outcome definition**	**Follow-up**	**Intervention**	**Group risk**	**OR (95% CI)**
			Placebo	3/35 (9%)*	**(1.14–17.89)**
Reusser (2002)[60]	ANC <500/µl	180 days PT	Ganciclovir	4/110 (4%)	0.32 (0.10–1.03)
			Foscarnet	11/103 (11%)*	
*denotes the reference group for each pairwise comparison ANC = absolute neutrophil count; OR = odds ratio; PT = post-transplant					

5.11. Objective 2: Fungal prophylaxis/treatment—Fungal prophylaxis beginning pre-/post-transplant

Nine studies[50-52, 55, 56, 63, 67, 69, 72] assessed fungal prophylaxis in allogeneic HSCT recipients beginning around the time of transplant. One of these studies[63] was published much earlier than the other eight studies (1985 compared to 2002 and onward) and compared treatments that are no longer of clinical relevance. These two treatments were also not included in any of the other 8 studies, preventing inclusion of the older study in any NMAs. Data from this study (Shepp et al.[63]) have been summarized narratively following the other fungal prophylaxis analyses.

5.11.1. Findings: Proven invasive fungal infection at any follow-up time

Six fungal prophylaxis studies[52, 55, 56, 67, 69, 72] reported data for proven invasive fungal infections (IFIs) at any follow-up time in 1,769 patients and these studies were included in an NMA (**Figure 26**). The duration of follow-up ranged from ~40 days (median time of discharge from hospital) to 180 days post-transplant. The definition of proven IFI was consistent across studies, with studies published after 2002 citing consensus criteria from Ascioglu et al..[31] Two studies[52, 72] published prior to 2002 defined proven IFI in lesser detail than the definition of Ascioglu et al. One study[67] used galactomannan EIA surveillance to trigger further testing, which may have increased the sensitivity to detect some IFIs.

All but two studies began fungal prophylaxis within 1 day of transplant. The other two studies[52, 56] began fungal prophylaxis at the start of the conditioning regimen. Three studies[55, 67, 69] discontinued treatment at 100 days post-transplant, although two of those studies[55, 67] allowed treatment to continue to 180 days post-transplant in patients at high risk of IFI (e.g., ongoing treatment with high-dose corticosteroids for GVHD). The third 100-day study[69] did not extend treatment in high-risk patients and reported that 85% of included patients received systemic steroids for the prevention of GVHD, and these patients were unevenly distributed between the two treatment arms, which may have contributed to the high incidence of IFIs in the fluconazole arm of that study. Two earlier studies[52, 72] only provided fungal prophylaxis until engraftment (<20 days treatment duration). The final study[56] provided fungal prophylaxis for a total of 120 days after the start of conditioning regimen, or up to 180 days for patients on corticosteroids for GVHD. The heterogeneity of duration of treatment and follow-up times in the included studies is summarized in **Table 26** below.

Table 26: Summary of heterogeneity of galactomannan surveillance, and durations of study treatment and follow-up in the studies included in the NMA of proven invasive fungal infections at any follow-up time						
Study	**Fungal prophylaxes evaluated**	**Use of galactomannan in IFI detection**	**Start of fungal prophylaxis**	**End of fungal prophylaxis**	**Actual duration of fungal prophylaxis (days)**	**Follow-up period**
Wolff (2000)[72]	Fluconazole Amphotericin B	NR	Day before transplant	**To engraftment**	**Median (range)** **FLU: 13 (4–46)** **AB: 15 (2–41**	**Until hospital discharge (~40 days; range 18–126)**
Koh (2002)[52]	Fluconazole Amphotericin B	NR	Day before conditioning regimen	**To engraftment**	**Mean (range)** **FLU: 20 (4–37)** **AB: 20 (5–44)**	**To 100 days PT**
Winston (2003)[69]	Fluconazole Itraconazole	Weekly surveillance but did not trigger further testing	Day after transplant	**To 100 days PT** **(not extended for high-risk patients, although 85% were on systemic corticosteroids for GVHD prevention)**	Mean (range). IV drug was scheduled for 14 days followed by PO drug, or when tolerated. Total duration of therapy not reported. FLU IV: 26 (1–95) followed by FLU PO: 52 (1–94) ITRA IV: 22 (3–65) followed by ITRA PO: 63 (2–91)	To 180 days PT
Marr (2004)[56]	Fluconazole Itraconazole	NR	Day of start of conditioning regimen	For 120 days total (180 days if on steroids for GVHD)	Median (range) **FLU: 120 (1–183)** **ITRA: 89 (1–189)** **(p = 0.001)**	To 180 days from start of conditioning regimen
Wingard (2010)[67]	Fluconazole Voriconazole	**Surveillance twice weekly, which, if positive, triggered further testing**	Day of transplant	To 100 days PT (up to 180 days in high-risk patients)	Median (IQR) FLU: 91 (27,100) VORI: 96 (34, 101)	To 180 days PT
Marks (2011)[55, 74]	Itraconazole Voriconazole	NR	Day of transplant	To 100 days PT (up to 180 days in high-risk patients)	Median **VORI: 96** **ITRA: 68** **(p < 0.01)**	To 180 days PT

AB = amphotericin B; FLU = fluconazole; GVHD = graft-versus-host disease; IFI = invasive fungal infection; ITRA = itraconazole; IV = intravenous; VORI = voriconazole; NR = not reported; PO = per os (orally); PT = post-transplant;

Figure 26: Network diagram for the NMA of the outcome of proven invasive fungal infections at any follow-up time in studies evaluating fungal prophylaxis

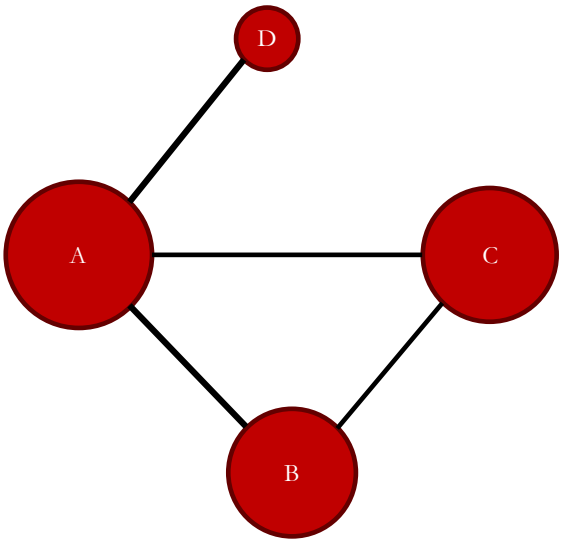


Figure legend
A = Fluconazole
B = Itraconazole
C = Voriconazole
D = Amphotericin B

5.11.1.1. Proven IFIs: Results from traditional pairwise meta-analyses

Table 27 presents summaries of pairwise estimates that were derived from direct evidence (i.e., the head-to-head trials), summarized alongside the numbers of available trials and patients for each direct comparison, as well as the related summary estimate derived from the network meta-analysis.

Two of the four direct comparisons were informed by single studies. No statistically significant differences were identified in the direct pairwise comparisons. Generally, estimates from traditional pairwise meta-analyses compared well with estimates derived from network meta-analysis. Very low event rates (<1%) and modest sample sizes in the single study informing the comparison between voricanazole and itraconazole caused wide confidence intervals for the pairwise comparison. When indirect data were included in the NMA, the credible interval narrowed and the point estimate changed from being >1 to being <1, suggesting that voriconazole may trend toward reducing the risk of proven IFIs compared to itraconazole (although this association remained non-significant).

The two studies[56, 69] informing the comparison of fluconazole vs. itraconazole demonstrated substantial heterogeneity (I^2 = 68.4%). While both studies used similar study drug doses and followed patients to 180 days post-transplant, Winston et al.[69] did not extend antifungal prophylaxis for the duration of follow-up for patients with GVHD that are considered at high risk of developing fungal infections. The proportion of patients with GVHD was significantly higher in the fluconazole arm than the itraconazole arm of this study (46% vs. 23%; p = 0.004), which may have led to an increased IFI event rate in the fluconazole arm. Event rates in the fluconazole arm of this study were significantly higher than in the fluconazole arm of the study by Marr et al. (28% vs. 9%, respectively; χ^2 test p-value < 0.001); however, itraconazole event rates did not differ between the two studies (13% vs. 10%, respectively; p = 0.539).

Table 27: Summary of results from pairwise meta-analysis and NMA, Proven IFIs at any follow-up time in studies evaluating fungal prophylaxis

Comparison		# of Trials (patients)	Heterogeneity (I^2)	Direct Estimate OR (95% CI)	NMA Estimate OR (95% CrI)
				*Values <1 favor comparator	
Comparator	**Reference**				
Voriconazole	Fluconazole	1 (600)	NA	0.53	0.54

				(0.18–1.60)	(0.18–1.49)
Voriconazole	Itraconazole	1 (489)	NA	1.09 (0.07–17.53)	0.83 (0.24—2.58)
Itraconazole	Fluconazole	2 (437)	68.369	0.67 (0.38–1.19)	0.64 (0.36–1.13)
Amphotericin B	Fluconazole	2 (243)	0.000	1.04 (0.47–2.32)	1.03 (0.45–2.35)

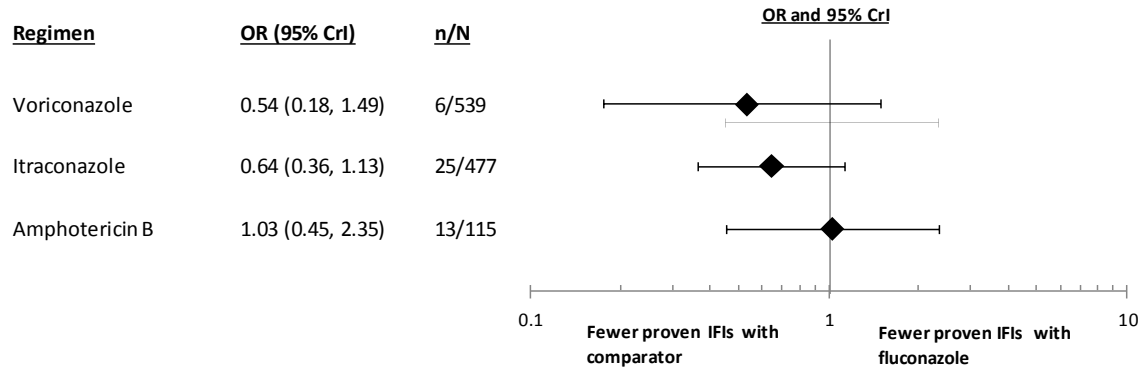
5.11.1.2. Proven IFIs: Results from network meta-analysis

Two of the six possible pairwise comparisons were informed only by indirect evidence, and two of the four pairwise comparisons with direct evidence were informed by single studies. Model fit statistics for the NMA indicated that both the fixed-effects (FE) and random-effects (RE) models had an adequate fit. Posterior residual deviance values for the FE and RE models of 12.79 and 11.52, respectively, were obtained, demonstrating adequate fit, given the 12 data points in the model. DIC values (64.919 and 65.209) did not suggest difference in fit between the FE and RE models. A FE model was preferred due to the number of single-study connections in the network. Findings from the corresponding RE model are presented in the appendices to the report.

Proven IFIs: Comparisons versus fluconazole

Figure 27 presents a forest plot summarizing comparisons of all treatments in the evidence network to the reference treatment fluconazole. All interventions were associated with a credible interval that included 1 and, thus, were not significantly different from fluconazole in their risk of proven IFIs.

Figure 27: Forest plot of comparisons versus fluconazole, Proven IFIs at any follow-up time in studies evaluating fungal prophylaxis



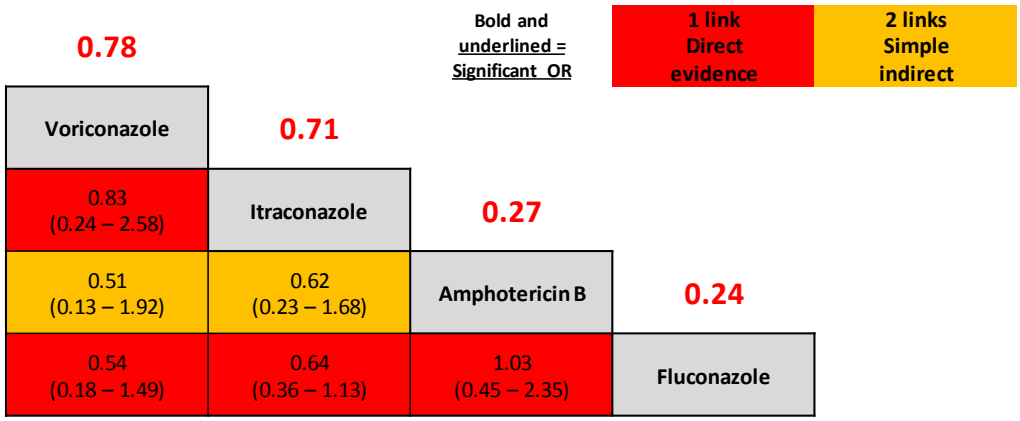
Odds ratios from network meta-analysis comparing each regimen to the reference placebo treatment are presented along with the number of events and patients per regimen. Odds ratios <1 suggest less risk of proven IFI with the comparator while odds ratios >1 suggest less risk of proven IFI with fluconazole.

Proven IFIs: Comparisons between all conditioning regimens

Figure 28 presents a league table of the estimates for all pairwise comparisons generated from the network meta-analysis. Some of the comparisons included in the league table should be interpreted carefully, specifically those which are not informed by head to head trials or where the comparison was based on compound indirect evidence (i.e., comparisons in which there are 2 intermediate treatments between the interventions of interest).

Voriconazole was the highest-ranking prophylactic, indicating that it was associated with a lower risk of proven IFI than the other interventions in the network; however, none of the associations in the network were statistically significant. The same was true amongst findings from the corresponding RE analysis.

Figure 28: League table summary of pairwise comparisons from NMA (Odds Ratios with 95% CrI), Proven IFIs at any follow-up time in studies evaluating fungal prophylaxis



Interventions are sorted from left to right in order of decreasing SUCRA value (i.e., preferred treatments appear first). For each comparison shown, the upper/left-most regimen is the comparator group while the lower/right-most treatment is the reference treatment; a value <1 suggests fewer cases of proven IFI with the comparator than with the reference group. Statistically significant differences (i.e., estimates with a 95% credible interval excluding 1) are bolded and underlined. Comparisons with direct evidence and simple indirect evidence have been highlighted in red and orange, respectively.

5.11.2. Findings: Proven or probable invasive fungal infection at any follow-up

Three fungal prophylaxis studies[55, 56, 67] reported data for proven or probable IFIs at any follow-up time in 1,388 patients and these studies were included in an NMA (Figure X). The duration of follow-up was relatively consistent across studies at either 180 days after the start of conditioning regimen (1 study)[56] or 180 days post-transplant (2 studies). The outcome definition was generally consistent across studies, with all three studies citing the consensus criteria of Ascioglu et al..[31] One study[67] used galactomannan EIA surveillance to trigger further testing, which may have increased the sensitivity to detect proven IFIs.

Figure 29: Network diagram for the NMA of the outcome of proven or probable invasive fungal infections at any follow-up time in studies evaluating fungal prophylaxis

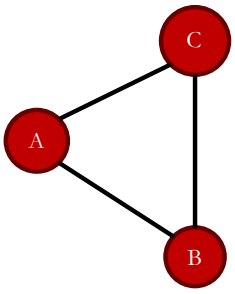


Figure legend
A = Fluconazole
B = Itraconazole
C = Voriconazole

5.11.2.1. Proven/probable IFIs: Results from traditional pairwise meta-analyses

Table X presents summaries of pairwise estimates that were derived from direct evidence (i.e., the head-to-head trials), summarized alongside the numbers of available trials and patients for each direct comparison, as well as the related summary estimate derived from the network meta-analysis.

All three direct comparisons were informed by single studies. No statistically significant differences were identified in the direct pairwise comparisons. Generally, estimates from traditional pairwise meta-analyses compared well with estimates derived from network meta-analysis. When indirect data were added in the NMA for the comparison of voriconazole with fluconazole, the credible interval narrowed causing the association to become significant.

Table 15: Summary of results from pairwise meta-analysis and NMA, Proven or probable IFIs at any follow-up time in studies evaluating fungal prophylaxis

Comparison		# of Trials (patients)	Heterogeneity (I^2)	Direct Estimate OR (95% CI)	NMA Estimate OR (95% CrI)
				**Values <1 favor comparator*	
Comparator	**Reference**				
Voriconazole	Fluconazole	1 (600)	NA	0.54 (0.28–1.07)	**0.53 (0.27–0.97)**
Voriconazole	Itraconazole	1 (489)	NA	0.65 (0.15–2.75)	0.69 (0.31–1.50)
Itraconazole	Fluconazole	1 (299)	NA	0.75 (0.40–1.42)	0.76 (0.42–1.37)

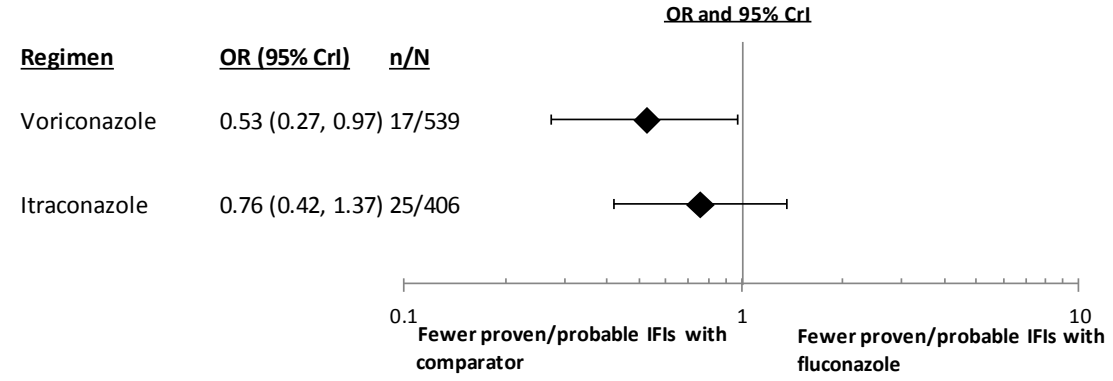
5.11.2.2. Proven/probable IFIs: Results from network meta-analysis

All three possible pairwise comparisons were informed by direct evidence; however, they were each informed by only single studies. Model fit statistics for the NMA indicated that both the fixed-effects (FE) and random-effects (RE) models had an adequate fit. Posterior residual deviance values for the FE and RE models of 5.078 and 5.640, respectively, were obtained, demonstrating adequate fit, given the 12 data points in the model. DIC values (35.459 and 36.554) did not suggest difference in fit between the FE and RE models. A FE model was preferred due to the number of single-study connections in the network.

Proven/probable IFIs: Comparisons versus fluconazole

Figure 30 presents a forest plot summarizing comparisons of all treatments in the evidence network to the reference treatment fluconazole. All interventions were associated with a credible interval that included 1 and, thus, were not significantly different from fluconazole in their risk of proven IFIs.

Figure 30: Forest plot of comparisons versus fluconazole, Proven or probable IFIs at any follow-up time in studies evaluating fungal prophylaxis



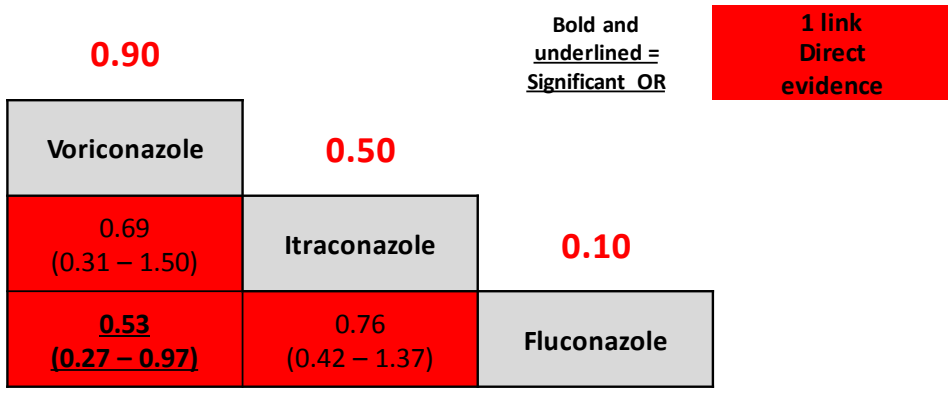
Odds ratios from network meta-analysis comparing each regimen to the reference placebo treatment are presented along with the number of events and patients per regimen. Odds ratios <1 suggest less risk of proven IFI with the comparator while odds ratios >1 suggest less risk of proven IFI with fluconazole.

Proven/probable IFIs: Comparisons between all interventions

Figure 31 presents a league table of the estimates for all pairwise comparisons generated from the network meta-analysis. All comparisons included in the league table were informed by both direct and indirect evidence.

Voriconazole was the highest-ranking prophylactic, indicating that it was associated with a lower risk of proven IFI than the other interventions in the network; however, it was only significantly more efficacious than fluconazole.

Figure 31: League table summary of pairwise comparisons from NMA (Odds Ratios with 95% CrI), Proven or probable IFIs at any follow-up time in studies evaluating fungal prophylaxis



Interventions are sorted from left to right in order of decreasing SUCRA value (i.e., preferred treatments appear first). For each comparison shown, the upper/left-most regimen is the comparator group while the lower/right-most treatment is the reference treatment; a value <1 suggests fewer cases of proven or probable IFI with the comparator than with the reference group. Statistically significant differences (i.e., estimates with a 95% credible interval excluding 1) are bolded and underlined. All comparisons were informed by direct evidence and have been highlighted in red.

5.11.3. Findings: Any proven, probable, or possible/suspected invasive fungal infection at any follow-up

Six fungal prophylaxis studies[50-52, 56, 66, 67] reported data for any proven, probable, or possible invasive fungal infection (IFIs) at any follow-up time in 1,794 patients and these studies were included in an NMA (**Figure 32**). The duration of follow-up ranged from a maximum of 70 days post-transplant[50, 51] to 180 days from the start of conditioning regimens. The definitions of proven, probable, and possible IFI were somewhat heterogenous as "possible" IFI could be defined in different ways. The definitions of proven and probable IFI were consistent across studies, with all studies citing consensus criteria from Ascioglu et al.[31]

Figure 32: Network diagram for the NMA of the outcome of any proven, probable, or possible invasive fungal infections at any follow-up time in studies evaluating fungal prophylaxis

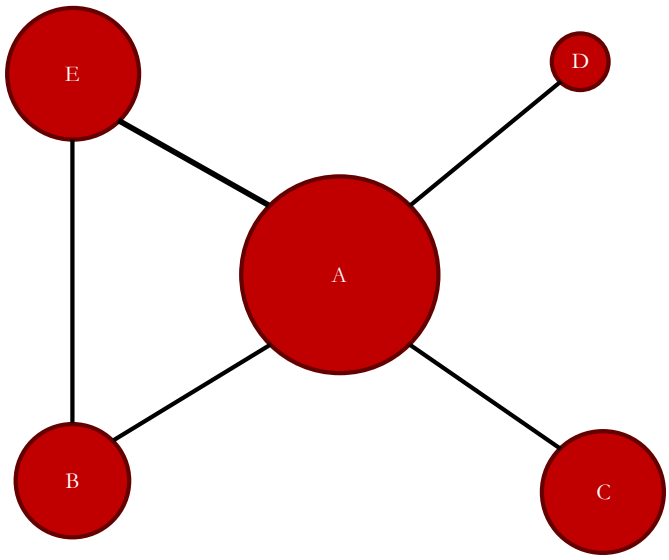


Figure legend
A = Fluconazole
B = Itraconazole
C = Voriconazole
D = Amphotericin B
E = Micafungin

5.11.3.1. Any IFI: Results from traditional pairwise meta-analyses

Table 28 presents summaries of pairwise estimates that were derived from direct evidence (i.e., the head-to-head trials), shown alongside the numbers of available trials and patients for each direct comparison, as well as the related summary estimates derived from the network meta-analysis.

Four of the five direct comparisons were informed by single studies. No statistically significant differences were identified in the direct pairwise comparisons. Estimates from traditional pairwise meta-analyses compared well with estimates derived from network meta-analysis. Indirect evidence in the NMA caused micafungin to trend toward being less protective than itraconazole, where it trended to being more protective in the pairwise comparison. However, both point estimates were close to 1 and non-significant, indicating there was no definitive difference in the two treatments.

Table 28: Summary of results from pairwise meta-analysis and NMA, Any proven, probable, or possible IFIs at any follow-up time in studies evaluating fungal prophylaxis

Comparison		# of Trials (patients)	Heterogeneity (I^2)	Direct Estimate OR (95% CI)	FE NMA Estimate OR (95% CrI)
				**Values <1 favor comparator*	
Comparator	**Reference**				
Voriconazole	Fluconazole	1 (600)	NA	0.62 (0.35–1.09)	0.61 (0.34–1.07)
Itraconazole	Fluconazole	1 (299)	NA	0.93 (0.52–1.68)	0.90 (0.54–1.52)
Amphotericin B	Fluconazole	1 (140)	NA	0.74 (0.29–1.87)	0.73 (0.28–1.88)
Micafungin	Fluconazole	2 (528)	0.000	0.84 (0.58–1.24)	0.85 (0.59–1.23)
Micafungin	Itraconazole	1 (227)	NA	1.03 (0.37–2.84)	0.94 (0.52–1.67)

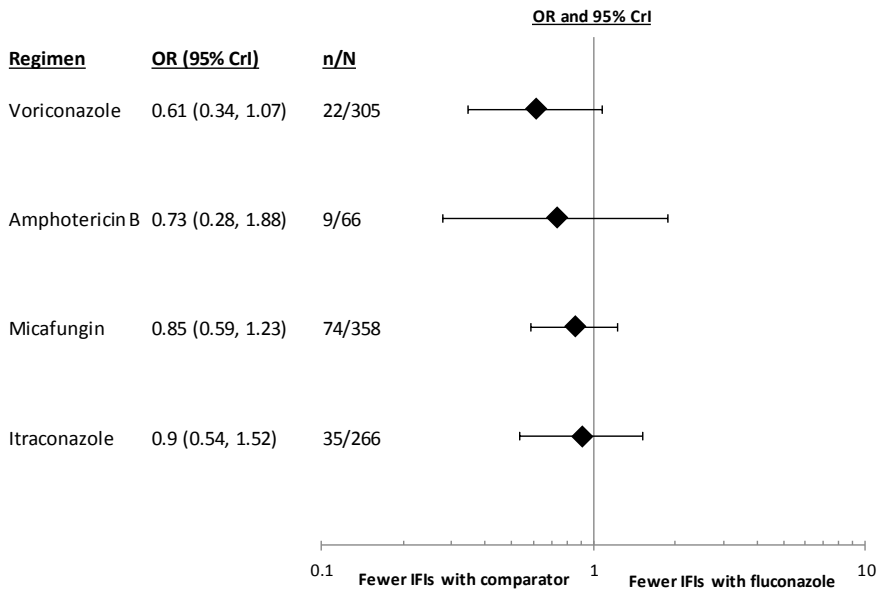
5.11.3.2. Any IFI: Results from network meta-analysis

Five of the 10 possible pairwise comparisons were informed only by indirect evidence, and four of the five pairwise comparisons with direct evidence were informed by single studies. Model fit statistics for the NMA indicated that both the fixed-effects (FE) and random-effects (RE) models had an adequate fit. Posterior residual deviance values for the FE and RE models of 10.47 and 11.12, respectively, were obtained, demonstrating adequate fit, given the 12 data points in the model. DIC values (73.969 and 75.472) did not suggest difference in fit between the FE and RE models. A FE model was preferred due to the number of single-study connections in the network, while RE findings are shown in the report's appendices.

Any IFI: Comparisons versus fluconazole

Figure 33 presents a forest plot summarizing comparisons of all treatments in the evidence network to the reference treatment fluconazole. All interventions were associated with a credible interval that included 1 and, thus, were not significantly different from fluconazole in their risk of any proven, probable, or possible IFI.

Figure 33: Forest plot of comparisons versus fluconazole, Any proven, probable, or possible IFIs at any follow-up time in studies evaluating fungal prophylaxis

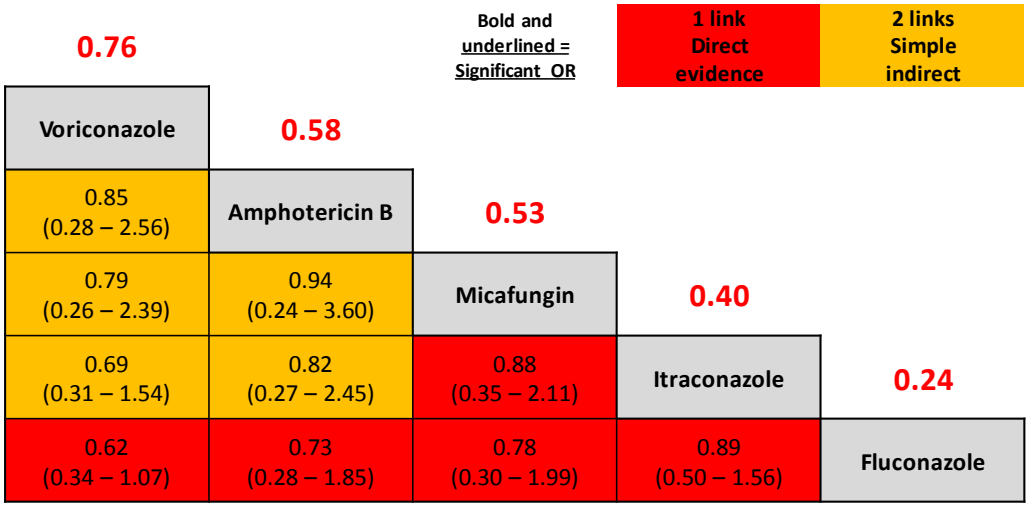


Odds ratios from network meta-analysis comparing each regimen to the reference placebo treatment are presented along with the number of events and patients per regimen. Odds ratios <1 suggest less risk of any IFI with the comparator while odds ratios >1 suggest less risk of any IFI with fluconazole.

Any IFI: Comparisons between all interventions

Figure 34 presents a league table of the estimates for all pairwise comparisons generated from the network meta-analysis. Some of the comparisons included in the league table should be interpreted carefully, specifically those which are not informed by head to head trials (i.e., simple indirect comparisons in which there is an intermediate treatment between the interventions of interest). Voriconazole was the highest-ranking prophylactic, indicating that it was associated with a lower risk of any proven, probable, or possible IFI than the other interventions in the network; however, none of the associations in the network were statistically significant. Clinical interpretations from the RE mode were analogous.

Figure 34 League table summary of pairwise comparisons from NMA (Odds Ratios with 95% CrI), Any proven, probable, or possible IFIs at any follow-up time in studies evaluating fungal prophylaxis



Interventions are sorted from left to right in order of decreasing SUCRA value (i.e., preferred treatments appear first). For each comparison shown, the upper/left-most regimen is the comparator group while the lower/right-most treatment is the reference treatment; a value <1 suggests fewer cases of any proven, probable, or possible IFI with the comparator than with the reference group. Statistically significant differences (i.e., estimates with a 95% credible interval excluding 1) are bolded and underlined. Comparisons with direct evidence and simple indirect evidence have been highlighted in red and orange, respectively.

5.11.4. Findings: Overall mortality at 180 days post-transplant in fungal prophylaxis studies

Three fungal prophylaxis studies[55, 67, 69] reported data for overall mortality at 180 days post-transplant in 1,227 patients and these studies were included in an NMA (**Figure 35**). All studies began fungal prophylaxis on either the day of transplant or 1 day after transplant, and all studies discontinued treatment at 100 days post-transplant, although two studies[55, 67] allowed treatment to continue to 180 days post-transplant in patients with high risk of IFI (e.g., ongoing treatment with high-dose corticosteroids for GVHD). The third study reported that 85% of included patients received systemic steroids for the prevention of GVHD, which probably contributed to the high incidence of IFIs in that study.

Figure 35: Network diagram for the NMA, Overall mortality within 180 days post-transplant in studies evaluating fungal prophylaxis

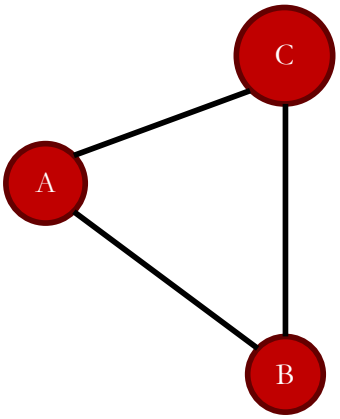


Figure legend
A = Fluconazole
B = Itraconazole
C = Voriconazole

5.11.4.1. 180-day overall mortality, fungal prophylaxis: Results from traditional pairwise meta-analyses

Table 29 presents summaries of pairwise estimates that were derived from direct evidence (i.e., the head-to-head trials), summarized alongside the numbers of available trials and patients for each direct comparison, as well as the related summary estimate derived from the network meta-analysis.

All three direct comparisons were informed by single studies. No statistically significant differences were identified in the direct pairwise comparisons. Estimates from traditional pairwise meta-analyses compared well with estimates derived from network meta-analysis.

Table 29: Summary of results from pairwise meta-analysis and NMA, Overall mortality within 180 days post-transplant in studies evaluating fungal prophylaxis

Comparison		# of Trials (patients)	Heterogeneity (I^2)	Direct Estimate OR (95% CI)	FE NMA Estimate OR (95% CrI)
				**Values <1 favor comparator*	
Comparator	**Reference**				
Voriconazole	Fluconazole	1 (600)	NA	0.92 (0.61–1.38)	0.94 (0.65–1.35)
Voriconazole	Itraconazole	1 (489)	NA	0.79 (0.50–1.25)	0.89 (0.60–1.33)
Fluconazole	Itraconazole	1 (138)	NA	0.88 (0.45–1.72)	0.94 (0.60–1.49)

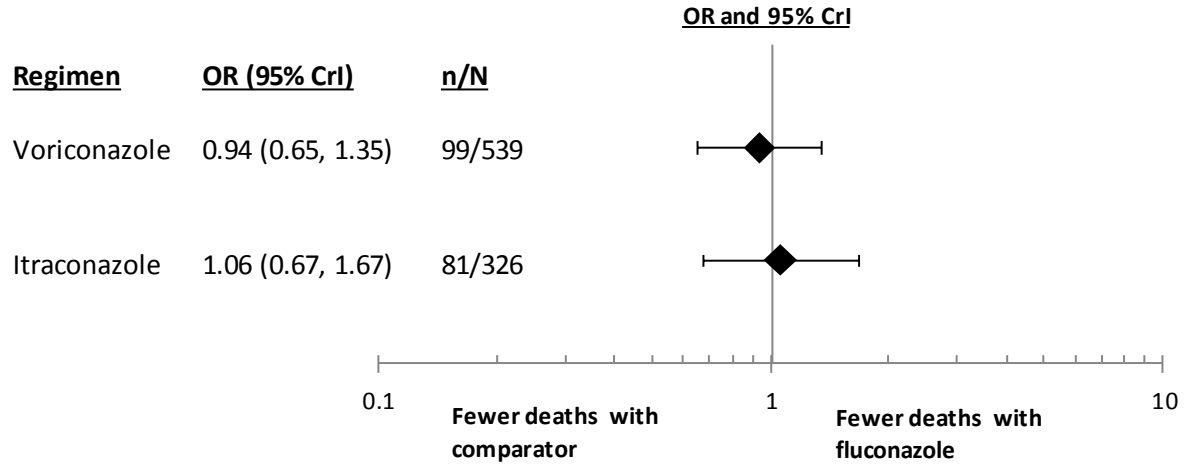
5.11.4.2. 180-day overall mortality, fungal prophylaxis: Results from network meta-analysis

All three possible pairwise comparisons were informed by both direct and indirect evidence; however, all direct pairwise comparisons were informed only by single studies each. Model fit statistics for the NMA indicated that both the fixed-effects (FE) and random-effects (RE) models had an adequate fit. Posterior residual deviance values for the FE and RE models of 5.118 and 5.663, respectively, were obtained, demonstrating adequate fit, given the 6 data points in the model. DIC values (41.767 and 42.928) did not suggest difference in fit between the FE and RE models. A FE model was preferred due to the number of single-study connections in the network, while corresponding RE results are provided in the appendices.

180-day overall mortality, fungal prophylaxis: Comparisons versus fluconazole

Figure 36 presents a forest plot summarizing comparisons of all treatments in the evidence network to the reference treatment fluconazole. All interventions were associated with a credible interval that included 1 and, thus, were not significantly different from fluconazole in their risk of death over 180 days post-transplant.

Figure 36: Forest plot of comparisons versus fluconazole, Overall mortality within 180 days post-transplant in studies evaluating fungal prophylaxis



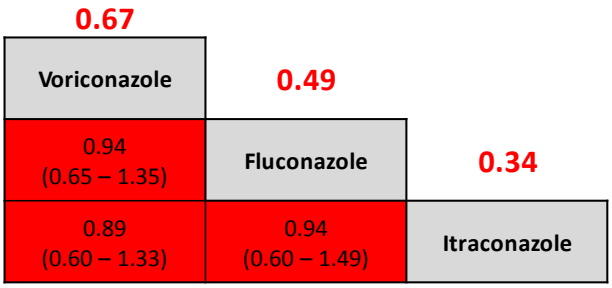
Odds ratios from network meta-analysis comparing each regimen to the reference placebo treatment are presented along with the number of events and patients per regimen. Odds ratios <1 suggest less risk of death with the comparator while odds ratios >1 suggest less risk of death with fluconazole.

180-day overall mortality, fungal prophylaxis: Comparisons between all conditioning regimens

Figure 37 presents a league table of the estimates for all pairwise comparisons generated from the network meta-analysis. All comparisons were informed by both direct and indirect evidence; however, there were few treatments in the network and only single studies informed each direct comparison.

Voriconazole was the highest-ranking prophylactic, however, none of the pairwise comparisons between treatments in the network were statistically significant, indicating no significant differences could be found between the treatments for this outcome. Interpretations from the RE model were analogous.

Figure 37: League table summary of pairwise comparisons from NMA (Odds Ratios with 95% CrI), Overall mortality within 180 days post-transplant in studies evaluating fungal prophylaxis



Interventions are sorted from left to right in order of decreasing SUCRA value (i.e., preferred treatments appear first). For each comparison shown, the upper/left-most regimen is the comparator group while the lower/right-most treatment is the reference treatment; a value <1 suggests fewer deaths with the comparator than with the reference group. Statistically significant differences (i.e., estimates with a 95% credible interval excluding 1) are bolded and underlined. All comparisons were informed by direct evidence and have been highlighted in red.

5.11.5. Findings: Overall mortality at other follow-up times in fungal prophylaxis studies

Five studies[51, 55, 56, 63, 72] evaluated overall mortality at follow-up times other than 180 days post-transplant. The findings of these studies have been summarized narrative in **Table 30**. No significant differences were found between any of the interventions compared except for nystatin and ketoconazole. Until engraftment, there had been no mortality events in either treatment arm. However, within 1 month of engraftment, nystatin was associated with a significantly higher risk of death than ketoconazole (RD = 0.17; 0.03–0.31).

Table 30: Summary of results: Fungal prophylaxis—Overall mortality at follow-up other than 180 days post-transplant

Study	Follow-up	Intervention	Group risk	RD or OR (95% CI)
Shepp (1985)[63]	To engraftment (11–54 days PT)	Nystatin	0/29 (0%)	RD = 0 (0–0)
		Ketoconazole	0/27 (0%)	
Shepp (1985)[63]	Within 1 month of engraftment (11–54 days + 1 month PT)	Nystatin	5/29 (17%)	**RD = 0.17 (0.03–0.31)**
		Ketoconazole	0/27 (0%)	
Marr (2004)[56]	250 days PT	Fluconazole	44/148 (30%)	OR = 0.74 (0.46–1.20)
		Itraconazole	55/151 (36%)	
Wolff (2000)[72]	Until hospital discharge (median = 40 days; range 18–126)	Fluconazole	16/54 (30%)	OR = 1.17 (0.49–2.76)
		Amphotericin B	13/49 (27%)	
Marks (2011)[55, 74]	100 days PT	Voriconazole	19/234 (8%)	OR = 1.04 (0.54–2.00)
		Itraconazole	20/255 (8%)	
Marks (2011)[55, 74]	365 days PT	Voriconazole	62/234 (26%)	OR = 0.73 (0.50–1.08)
		Itraconazole	84/255 (33%)	
Huang (2012)[51]	70 days from the start of conditioning regimen	Micafungin	0/136 (0%)	RD = -0.007 (-0.02–0.006)
		Itraconazole	1/147 (1%)	

*denotes the reference group for each pairwise comparison
OR = odds ratio; PT = post-transplant; RD = risk difference

5.11.6. Findings: Non-relapse mortality in fungal prophylaxis studies

Two studies reported non-relapse mortality in the evaluation of fungal prophylaxis. Their data have been summarized in **Table 31**. Neither study identified a significant difference in the risk of non-relapse mortality between itraconazole and fluconazole.

Table 31: Summary of results: Fungal prophylaxis—Non-relapse mortality

Study	Follow-up	Intervention	Group risk	OR (95% CI)
Winston (2003)[69]	180 days PT	Itraconazole	28/71 (39%)	1.03 (0.52–2.04)
		Fluconazole	26/67 (39%)*	
Marr (2004)[56]	250 days PT	Itraconazole	49/151 (32%)	1.55 (0.93–2.58)
		Fluconazole	35/148 (24%)*	

*denotes the reference group for each pairwise comparison
OR = odds ratio; PT = post-transplant

5.11.7. Narrative summary of findings of Shepp et al. 1985

Shepp et al.[63], compared nystatin and ketoconazole as fungal prophylaxis in a study published 17 years prior to any of the other included studies. This study was disjoint from the treatment network formed by the other studies and compares interventions that are of low clinical relevance currently. The data from this study have been summarized in **Table 32**. Although there was no significant difference between nystatin and ketoconazole with respect to prevention of invasive fungal infections during or after discontinuation of study drugs, there was a significant difference in overall mortality within 1 month of engraftment or discontinuation of protective environment due to critical illness, with nystatin being associated with a 17% increase in risk of death compared to ketoconazole (95% CI: 3–31%).

Table 32: Summary of results: Findings for all outcomes in Shepp et al. (1985)[63] (fungal prophylaxis)

Outcome definition	Follow-up	Intervention	Group risk	RD (95% CI)
Invasive fungal infection[a] while on study treatment	To engraftment or discontinuation of protective environment[b] (11–54 days after the start of conditioning regimen)	Nystatin	0/29 (0%)	Not estimable
		Ketoconazole	0/27 (0%)*	
Invasive fungal infection[a] after study drug administration	39–82 days after the start of conditioning regimen	Nystatin	2/29 (7%)	0.07 (-0.02–0.16)
		Ketoconazole	0/27 (0%)*	
Overall mortality	To engraftment or discontinuation of protective environment[b] (11–54 days after the start of conditioning regimen)	Nystatin	0/29 (0%)	Not estimable
		Ketoconazole	0/27 (0%)*	
Overall mortality	Within 1 month of engraftment or discontinuation of protective environment[b]	Nystatin	5/29 (17%)	**0.17 (0.03–0.31)**
		Ketoconazole	0/27 (0%)*	

*denotes the reference group for each pairwise comparison
[a]Fungi recovered from cultures of blood or histologic evidence of invasive fungi on biopsy or autopsy tissues
[b]Patients were removed from the protective environment following engraftment or due to critical illness
RD = risk difference

5.12. Objective 2: Fungal prophylaxis/treatment—Fungal prophylaxis beginning at diagnosis of GVHD

Two studies[48, 65] evaluated fungal prophylaxis in patients who developed GVHD after HSCT. The interventions evaluated did not overlap between studies, precluding analysis by NMA. The outcomes reported have been summarized narratively below.

5.12.1. Findings: Proven invasive fungal infection in studies of fungal prophylaxis in GVHD patients

Only Hayashi et al.[48] reported data for proven invasive fungal infections. At 60 days after diagnosis of GVHD, no cases of proven IFI had been identified in either the voriconazole group (n = 33) or the itraconazole group (n = 33).

5.12.2. Findings: Proven or probable invasive fungal infection in studies of fungal prophylaxis in GVHD patients

Both studies[48, 65] reported data for proven or probable IFIs. Follow-up times were 60 and 112 days after diagnosis of GVHD for Hayashi et al.[48] and Ullman et al.[65], respectively. The duration of follow-up corresponded to the duration of treatment in both studies. The data have been summarized narratively in **Table 33**. No significant difference in the risk of proven or probable IFI was found when voriconazole was compared to itraconazole at 60 days post-diagnosis of GVHD. When posaconazole was compared to fluconazole, there was no significant difference in the intention-to-treat (ITT) sample at 112 days post-diagnosis of GVHD (the fixed treatment period). However, at 168 days post-diagnosis of GVHD in the ITT sample, the risk of proven or probable IFIs was significantly reduced in the posaconazole group compared to the fluconazole group. When only patients who received treatment were followed to 7 days after discontinuation of study drug, the risk of proven or probable IFIs was significantly reduced in the posaconazole group compared to the fluconazole group.

Table 33: Summary of results: Fungal prophylaxis in GVHD patients—Proven or probable invasive fungal infection

Study	Follow-up	Intervention	Group risk	RD or OR (95% CI)
Hayashi (2014)[48]	60 days post-diagnosis of GVHD	Voriconazole	0/33 (0%)	Risk difference: -0.03 (-0.09–0.03)
		Itraconazole	1/33 (3%)*	
Ullmann (2007)[65]	During the fixed 112-day treatment period[a]	Posaconazole	16/301 (5%)	Odds ratio: 0.57 (0.30–1.07)
		Fluconazole	27/299 (9%)*	
Ullmann (2007)[65]	During the 168-day observation period[b]	Posaconazole	20/301 (7%)	**Odds ratio: 0.44 (0.25–0.76)**
		Fluconazole	42/299 (14%)*	
Ullmann (2007)[65]	During the exposure period[c]	Posaconazole	7/291 (2%)	**Odds ratio: 0.30 (0.13–0.71)**
		Fluconazole	22/288 (8%)*	

*denotes the reference group for each pairwise comparison
[a]all surviving patients were followed for 112 days after diagnosis of GVHD, even if study treatment was discontinued
[b]all surviving patients were followed for 168 days after diagnosis of GVHD
[c]the "exposure period" encompassed the time on treatment plus 7 days after discontinuation and varied by patient according to their duration of treatment. The mean exposure period was 80 days. Patients that did not start treatment were not exposed and, therefore, not included in these data
GVHD = graft-versus-host-disease; OR = odds ratio; RD = risk difference

5.12.3. Findings: Overall mortality in studies of fungal prophylaxis in GVHD patients

Both studies reported overall mortality data at varying follow-up times. The data have been summarized narratively in **Table 34**. Neither study demonstrated a significant difference in overall mortality between the interventions compared during any of the follow-up periods reported.

Table 34: Summary of results: Fungal prophylaxis in GVHD patients—Overall mortality

Study	Follow-up	Intervention	Group risk	OR (95% CI)
Hayashi (2014)[48]	3 years PT	Voriconazole	22/33 (67%)	1.88 (0.70–5.09)
		Itraconazole	17/33 (52%)	
Ullmann (2007)[65]	During the fixed 112-day treatment period[a]	Posaconazole	58/301 (19%)	0.97 (0.65–1.45)
		Fluconazole	59/299 (20%)	
Ullmann (2007)[65]	During the 168-day observation period[b]	Posaconazole	76/301 (25%)	0.86 (0.60–1.24)
		Fluconazole	84/299 (28%)	
Ullmann (2007)[65]	During the exposure period[c]	Posaconazole	22/291 (8%)	0.90 (0.49–1.64)
		Fluconazole	24/288 (8%)	

*denotes the reference group for each pairwise comparison
[a]all surviving patients were followed for 112 days after diagnosis of GVHD, even if study treatment was discontinued
[b]all surviving patients were followed for 168 days after diagnosis of GVHD
[c]the "exposure period" encompassed the time on treatment plus 7 days after discontinuation and varied by patient according to their duration of treatment. The mean exposure period was 80 days. Patients that did not start treatment were not exposed and, therefore, not included in these data
GVHD = graft-versus-host-disease; OR = odds ratio; PT = post-transplant

5.13. Objective 2: Fungal prophylaxis/treatment—Empiric treatment of aspergillosis

Two studies[49, 57] evaluated empiric treatment of aspergillosis in patients, some of whom received allogeneic HSCT. One early study (Herbrecht et al., 2002)[49] included any immunocompromised patient, regardless of underlying cause (e.g., HSCT, acute leukemia, other hematologic cancer, solid organ transplant, AIDS, corticosteroid treatment, etc.), while the other later study (Marr et al., 2015)[57] included only HSCT recipients (both allogeneic and autologous). Herbrecht et al.[49] compared intravenous voriconazole with intravenous amphotericin B, while Marr et al. (2015)[57] compared monotherapy of oral voriconazole with combined therapy of oral voriconazole plus anidulafungin. Because of heterogeneity of patient populations and heterogeneity of route of administration of voriconazole, a narrative summary was prepared. The included studies have been summarized in **Tables 35** and **36**.

There were no differences in overall treatment success when voriconazole monotherapy was compared with combination therapy. However, voriconazole was associated with significantly higher overall treatment success compared to amphotericin B (OR = 2.42; 95% CI = 1.48–3.96). This association was mainly driven by a significant difference in the odds of a partial response (OR = 2.65; 95% CI = 1.47–4.79). When voriconazole and amphotericin B were compared only in allogeneic HSCT recipients, there was no significant difference between the treatments with respect to overall treatment success (data not reported below: OR = 3.12; 95% CI = 0.89–10.97).

Table 165: Summary of results: Empiric treatment of aspergillosis—treatment success					
Study	**Outcome**	**Follow-up**	**Intervention**	**Group risk**	**OR (95% CI)**
Marr (2015)[57]	Overall success[a]	6 weeks	Voriconazole	61/142 (43%)	1.56 (0.95–2.54)
			Voriconazole + anidulafungin	44/135 (32%)*	
Marr (2015)[57]	Complete response[b]	6 weeks	Voriconazole	17/142 (12%)	2.16 (0.90–5.18)
			Voriconazole + anidulafungin	8/135 (5%)*	
Marr (2015)[57]	Partial response[c]	6 weeks	Voriconazole	44/142 (31%)	1.23 (0.73–2.08)
			Voriconazole + anidulafungin	36/135 (26%)*	
Herbrecht (2002)[49]	Overall success[a]	12 weeks	Voriconazole	76/144 (53%)	**2.42 (1.48–3.96)**
			Amphotericin B	42/133 (32%)*	
Herbrecht (2002)[49]	Complete response[b]	12 weeks	Voriconazole	30/144 (21%)	1.33 (0.72–2.44)
			Amphotericin B	22/133 (17%)*	
Herbrecht (2002)[49]	Partial response[c]	12 weeks	Voriconazole	46/144 (32%)	**2.65 (1.47–4.79)**
			Amphotericin B	20/133 (15%)*	

*denotes the reference group for each pairwise comparison
[a]Overall success = complete or partial response
[b]Complete response = resolution of all signs and symptoms, and more than 90% radiographic improvement compared with baseline
[c]Partial response = clinical improvement and more than 50% radiographic improvement compared with baseline
CI = confidence interval; OR = odds ratio

There were no differences in overall mortality when voriconazole monotherapy was compared with combination therapy, when all HSCT patients were included. When only allogeneic HSCT patients were evaluated, the association remained not statistically significant (data not reported below: OR = 1.36; 95% CI = 0.51–3.60). However, voriconazole significantly reduced overall mortality at 12 weeks compared to amphotericin B (OR = 0.38; 95% CI = 0.23–0.63).

Table 36: Summary of results: Empiric treatment of aspergillosis—overall mortality				
Study	**Follow-up**	**Intervention**	**Group risk**	**OR (95% CI)**
Marr (2015)[57]	6 weeks	Voriconazole	39/142 (28%)	1.59 (0.90–2.79)
		Voriconazole + anidulafungin	26/135 (19%)*	
Marr (2015)[57]	12 weeks	Voriconazole	55/142 (39%)	1.56 (0.94–2.57)
		Voriconazole + anidulafungin	39/135 (29%)*	
Herbrecht (2002)[49]	12 weeks	Voriconazole	42/144 (29%)	**0.38 (0.23–0.63)**
		Amphotericin B	69/133 (52%)*	

*denotes the reference group for each pairwise comparison
CI = confidence interval; OR = odds ratio

5.14. Objective 3: Bacterial prophylaxis/treatment—Bacterial prophylaxis

One study (Teinturier 1994)[64] was found that compared bacterial prophylactic regimens in HSCT patients. This study was conducted between 1986 and 1988, and patients were randomized to either receive intravenous vancomycin or not from day -5 to day +1 before and after transplant. The study found no vancomycin-resistant Gram-positive cocci, which calls into question its current clinical relevancy. Since its publication, the prevalence of vancomycin-resistant *Enterococci* (VRE) pre-transplant has risen significantly to approximately 28%[75] and the presence of VRE is associated with substantial mortality in the peri-transplant period (9% case-fatality rate).[75] We report the findings of Tenturier et al.[64] in **Table 36**

for historical interest. Prophylaxis with vancomycin from day -5 to +1 peri-transplant was not associated with a significant difference in risk of infections or fever of unknown origin.

An earlier paper[76], published in 1991, was not included in our review due to small sample size of HSCT patients. This study identified a significant decrease in the risk of Gram-positive infections in HSCT patients receiving vancomycin from day -2 to engraftment compared to patients that did not receive vancomycin; however once again, this study would have been conducted prior to significant vancomycin resistance being present. Other studies evaluating the use of bacterial prophylaxis in immunocompromised or neutropenic patients due to HSCT as well as other causes (e.g., chemotherapy, AIDS, etc.) have been published; however, they did not meet the inclusion criteria for this review due to a lack of HSCT patients or a lack of reporting for the HSCT patient subgroup.

Table 36: Summary of results: Findings for all outcomes in the evaluation of bacterial prophylaxis with vancomycin (from Tenturier et al., 1994)[64]

Outcome definition	Follow-up	Intervention	Group risk	OR (95% CI)
Documented Gram-positive cocci infection	During aplasia (to day 23 PT)	Vancomycin	19/75 (25%)	0.88 (0.43–1.80)
		No vancomycin	22/79 (28%)*	
Documented septicemia (including Gram-positive infection)	During aplasia (to day 23 PT)	Vancomycin	28/75 (37%)	1.03 (0.54–1.98)
		No vancomycin	29/79 (37%)*	
Fever of unknown origin	During hospitalization	Vancomycin	47/75 (63%)	1.08 (0.57–2.08)
		No vancomycin	48/79 (61%)*	

*denotes the reference group for each pairwise comparison
OR = odds ratio; PT = post-transplant

5.15. Objective 3: Bacterial prophylaxis/treatment—Empiric treatment of febrile neutropenia

Three studies[42, 45, 53] evaluated antibiotic regimens for the empiric treatment of febrile neutropenia, whether confirmed to be of bacterial origin or not. The patient populations of these three studies were not strictly HSCT recipients; however, HSCT patient subgroup data were reported in each. For the review of treatment interventions (vs prophylactic interventions), we did not differentiate between autologous and allogeneic graft sources as the patient response to empiric treatment would not differ. There was no overlap in the interventions evaluated by the three studies; thus, their findings have been summarized narratively. Because outcome definitions varied substantially across studies, the summaries are presented by study rather than by endpoint.

Laszlo et al.[53] evaluated netilmicin + imipenem-cilastatin versus netilmicin + ceftazidime for empiric treatment of febrile neutropenia in bone marrow transplant recipients (45% allogeneic, 55% autologous). No significant differences were found between the two treatment regimens with respect to improvement of any type of episode (microbiologically confirmed infection, clinically confirmed infection, or fever or unknown origin) individually or overall. No infection-related deaths were reported in the study.

Feld et al.[45] evaluated meropenem versus ceftazidime in the treatment of febrile neutropenia in patients with malignancy (hematologic or solid organ) that did or did not receive a bone marrow transplant (5% allogeneic BMT, 16% autologous BMT, 70% hematologic malignancy without BMT, 9% solid organ tumour). Clinical success was significantly increased by the end of therapy (median 7 days) in all patients receiving meropenem compared to ceftazidime; however, the magnitude of effect was greater for BMT recipients compared to the entire patient sample (OR = 7.27 (2.79–18.95) vs 1.53 (1.03–2.25), respectively). Patients that had received antibiotic prophylaxis were significantly more likely to experience clinical success than patients that did not receive antibiotic prophylaxis (OR = 2.27 (1.14–4.50) vs 1.3 (0.83–2.10), respectively). Episodes of fever of unknown origin were potentially more likely to have clinical success

than episodes of microbiologically confirmed or clinically confirmed infections (OR = 1.87 (1.13–3.10) vs 2.99 (0.31–28.94) vs 1.11 (0.42–2.95)); however, the subgroup sizes for microbiologically and clinically confirmed infections were relatively small, reducing the power to detect a significant effect. Overall mortality did not significantly differ between the two treatment groups.

Bow et al.[42] evaluated piperacillin + tazobactam versus cefepime in the treatment of febrile neutropenia in patients with hematologic malignancy the did or did not receive an HSCT (15% allogeneic HSCT, 34% autologous HSCT, 4% unspecified peripheral blood HSCT, 47% hematologic malignancy without HSCT). At the test-of-cure time point (7 days after the end of study drug), there was no significant difference in treatment success between treatment groups for allogeneic HSCT recipients, any HSCT recipients, or all patients. At 72 hours after the start of study therapy, there was a significant increase in treatment success for patients receiving piperacillin + tazobactam versus those receiving cefepime; however, the difference between the groups became non-significant by the end of therapy (~8 days) and at the test-of-cure time point. Overall mortality did not significantly differ between the two treatment groups at the end of therapy.

Table 37: Summary of results: Findings for all outcomes in the evaluation of empiric antibiotic treatment of febrile neutropenia (from Laszlo et al. (1997)[53])

Outcome definition	Follow-up	Intervention	Group risk	RD or OR (95% CI)
Improvement[a] of microbiologically documented episode[b]	72 hours	Netilmicin + Imipenem-cilastatin	7/10 (70%)	Odds ratio: 3.11 (0.41 to 23.39)
		Netilmicin + Ceftazidime	3/7 (43%)*	
Improvement[a] of clinically documented episode[c]	72 hours	Netilmicin + Imipenem-cilastatin	1/1 (100%)	Risk difference: 0.5 (-0.19 to 0.87)
		Netilmicin + Ceftazidime	1/2 (50%)*	
Improvement[a] of fever of unknown origin[d]	72 hours	Netilmicin + Imipenem-cilastatin	17/20 (85%)	Odds ratio: 1.18 (0.25 to 5.62)
		Netilmicin + Ceftazidime	24/29 (83%)*	
Improvement[a] of any episode (total of above)	72 hours	Netilmicin + Imipenem-cilastatin	25/31 (80%)	Odds ratio: 1.49 (0.47 to 4.68)
		Netilmicin + Ceftazidime	28/38 (73%)*	

*denotes the reference group for each pairwise comparison
[a]Improvement = lasting defervescence and complete disappearance of cultural signs of infection without modification of therapy, except addition of antifungal, within 72 hours of start of study drug
[b]Microbiologically documented episode = isolation of etiologic agents in cultured specimens during an episode of febrile neutropenia (ANC <500/µl and fever >38 °C)
[c]Clinically documented episode = definite signs and symptoms with an identifiable site of infection, in the absence of microbiological proof of an etiologic agent, during an episode of febrile neutropenia (ANC <500/µl and fever >38 °C)
[d]Fever of unknown origin = possible infection without an identifiable site and with negative microbiological data
OR = odds ratio; RD = risk difference

Table 38: Summary of results: Findings for all outcomes in the evaluation of empiric antibiotic treatment of febrile neutropenia (from Feld et al. (2000)[45])

Outcome definition	Follow-up	Intervention	Group risk	OR (95% CI)
Clinical success[a] in bone marrow transplant recipients	End of therapy (median 7 days; IQR: 5–11 days)	Meropenem	30/41 (73%)	**7.27 (2.79–18.95)**
		Ceftazidime	12/44 (27%)*	
Clinical success[a] in all patients	End of therapy (median 7 days; IQR: 5–11 days)	Meropenem	112/206 (54%)	**1.53 (1.03–2.25)**
		Ceftazidime	89/203 (44%)*	
Clinical success[a] in all patients with antibiotic prophylaxis	End of therapy (median 7 days; IQR: 5–11 days)	Meropenem	49/69 (71%)	**2.27 (1.14–4.50)**
		Ceftazidime	40/77 (52%)*	

Clinical success[a] in all patients with no antibiotic prophylaxis	End of therapy (median 7 days; IQR: 5–11 days)	Meropenem	63/137 (46%)	1.34 (0.82–2.19)
		Ceftazidime	49/126 (39%)*	
Clinical success[a] in all clinically defined infections[b]	End of therapy (median 7 days; IQR: 5–11 days)	Meropenem	19/46 (41%)	1.79 (0.72–4.46)
		Ceftazidime	11/39 (28%)*	
Clinical success[a] in all microbiologically defined infections[c]	End of therapy (median 7 days; IQR: 5–11 days)	Meropenem	14/31 (45%)	0.79 (0.31–1.98)
		Ceftazidime	22/43 (51%)*	
Clinical success[a] in all episodes of fever of unknown origin[d]	End of therapy (median 7 days; IQR: 5–11 days)	Meropenem	79/128 (62%)	**1.87 (1.13–3.10)**
		Ceftazidime	56/121 (46%)*	
Overall mortality during treatment for all patients	End of therapy (median 7 days; IQR: 5–11 days)	Meropenem	3/206 (1%)	2.99 (0.31–28.94)
		Ceftazidime	1/203 (0.5%)*	
Overall mortality during full follow-up for all patients	7 days beyond the end of therapy (~14 days total)	Meropenem	9/206 (4%)	1.11 (0.42–2.95)
		Ceftazidime	8/203 (4%)*	

*denotes the reference group for each pairwise comparison
[a]Clinical success = cure, cure with modification (i.e., new fever after initial defervescence, requiring a change in antimicrobial agent or addition of antifungal or antiviral), or improvement
[b]Clinical signs/symptoms of infection but no pathogen isolated from infection site
[c]Pathogen isolated from a blood sample, infection site, or both
[d]Fever was the only clinical sign of infection
IQR = interquartile range; OR = odds ratio

Table 39: Summary of results: Findings for all outcomes in the evaluation of empiric antibiotic treatment of febrile neutropenia (from Bow et al. (2006)[42])

Outcome definition	Follow-up	Intervention	Group risk	OR (95% CI)
Treatment success[a] (all HSCT patients)	Test-of-cure time point[b]	Piperacillin-tazobactam	33/134 (25%)	1.27 (0.73–2.23)
		Cefepime	30/147 (20%)*	
Treatment success[a] (allogeneic HSCT patients)	Test-of-cure time point[b]	Piperacillin-tazobactam	7/43 (16%)	2.27 (0.54–9.48)
		Cefepime	3/38 (8%)*	
Treatment success[a] (all patients)	Test-of-cure time point[b]	Piperacillin-tazobactam	71/265 (27%)	1.42 (0.95–2.12)
		Cefepime	54/263 (21%)*	
Treatment success[a] (all patients)	72 hours after start of therapy	Piperacillin-tazobactam	153/265 (58%)	**1.46 (1.04–2.06)**
		Cefepime	127/263 (48%)*	
Treatment success[a] (all patients)	End of treatment[c]	Piperacillin-tazobactam	105/265 (40%)	1.42 (0.99–2.04)
		Cefepime	83/263 (32%)*	
Overall mortality (all patients)	End of treatment[c]	Piperacillin-tazobactam	8/265 (3%)	0.51 (0.21–1.24)
		Cefepime	15/263 (6%)*	

*denotes the reference group for each pairwise comparison
[a]Treatment success = resolution of all signs/symptoms of infection without modification of the initial antibacterial regimen
[b]Test-of-cure time point = at least 7 days beyond the duration of treatment. See [c] below.
[c]Duration of treatment was significantly different between treatment groups ($p < 0.001$; For piperacillin-tazobactam vs cefepime, mean (± SD) = 9.9 ± 5.3 vs 8.1 ± 4.4 and median (range) days of treatment = 8 (1–23) vs 7 (1–26), respectively.
OR = odds ratio

5.16. Assessment of between-study heterogeneity

The need for sensitivity and subgroup analyses accounting for the effect of patient-related factors (e.g., patient age, primary disease, related donor, HLA-matched donor, donor cell source, GVHD status) was considered by inspection of patient eligibility criteria and summary measures of patient demographics across the included trials (summary tables were provided in the preceding questions). Generally, CMV prophylaxis studies that were published from 2008 onward tended to include older patients, a higher proportion of stem cells derived from umbilical cord sources, and a lower proportion of related donor

transplants. These patient-level factors may result in greater need for immunosuppression and thus a higher risk of CMV infection and disease. However, earlier studies were more likely to include patients with active CMV viremia, who would also have an increased risk of CMV disease. Event rates of confirmed CMV disease at 100 days follow-up in the placebo arms of two studies published in 1993[46, 68] appeared to be considerably higher than those in the placebo arms of two studies published in 2008 and 2011[58, 71] (29 and 24% vs 11 and 3%, respectively); however, patients with active CMV viremia may have only been included in one of these earlier studies (reporting was unclear in this study).[68] The lower event rates in the later studies may have resulted from changes in HSCT clinical methods that had occurred in the 25-year interim, including newer conditioning regimens and more effective GVHD prophylaxis that could have reduced infection risk. Heterogeneity in the inclusion of patients with active viremia and study-level factors such as differences in pre-engraftment antiviral therapies and the administration of CMV IVIG have been summarized in **Table 40** for CMV prophylaxis studies. Studies published from 2008 onward did not administer CMV prophylaxis pre-engraftment (before the start of study drugs), whereas earlier studies did, and CMV IVIG administration was often not reported. While there appears to be potential heterogeneity in both patient- and study-level characteristics that could affect infection risk, sparse networks in our NMAs with small sample sizes and primarily single-study connections precluded meta-regression to account for these sources of heterogeneity. Some of the study-level sources of heterogeneity in CMV prophylaxis studies (e.g., differences in follow-up duration, differences in testing methods, differences in outcome definitions) have been accounted for by analysis of multiple efficacy outcomes at multiple follow-up times in the main body of this report.

Poor reporting of patient characteristics in the included fungal prophylaxis studies limited our ability to identify potential sources of between-study heterogeneity. The proportion of patients with GVHD during the study period was potentially heterogenous; however, differences in the definition of GVHD between studies (i.e., acute, chronic, all GVHD, various grades, etc.) prevented comparison. Other sources of heterogeneity included the use of galactomannan surveillance testing, and differences in the timing of study treatment and the durations of treatment and follow-up. One study[67] used galactomannan surveillance testing to detect IFIs, which may have resulted in greater sensitivity of detection of probable or possible IFIs compared to the other studies (but not proven IFIs as galactomannan testing was not a part of that outcome definition). This study was removed from the NMAs for proven/probable IFIs and any IFI and the results of these sensitivity analyses are presented below. Similarly, two studies[52, 72] that had short follow-up durations were removed from the NMA of proven IFIs to determine if duration of follow-up impacted the results, and the results of this sensitivity analysis are also presented below.

Table 40: Summary of some sources of heterogeneity in the studies evaluating CMV prophylaxis				
Study	**Interventions**	**Pre-engraftment antiviral therapy**	**Exclusion of patients with active viremia**	**CMV IVIG administered**
Goodrich (1993)[46]	Ganciclovir vs Placebo	High-dose acyclovir from conditioning to engraftment	Yes	NR
Winston (1993)	Ganciclovir vs Placebo	Ganciclovir (2.5 mg/kg q8h) from conditioning (day -7) to day -1. No antivirals between transplant and engraftment.	Unclear. Included patients were seropositive for CMV antibody and were required to have no evidence of pneumonia or other CMV clinical syndrome. CMV viremia status not reported.	Not administered
Burns (2002)[43]	Ganciclovir vs Acyclovir	Ganciclovir (5 mg/kg q12h) from day -7 to -2 then acyclovir (10 mg/kg IV q8h) from day -1 to engraftment	No.	Yes, all patients received
Ljungman (2002)[54]	Valaciclovir vs Acyclovir	Acyclovir 500 mg/m2 IV q8h starting as early as day -5 to engraftment	No.	Allowed but unclear how many received
Winston (2003)[77]	Ganciclovir vs Valaciclovir	All patients received acyclovir 500 mg/m2 q8h from day 0 to engraftment	Unclear. Surveillance tests for CMV antigen or DNA were not routinely performed at study sites, but culture was performed prior to entry into study. The range of dates for onset of CMV infection was 2–121 days post-transplant, so it appears that CMV infected patients were not excluded.	Excluded if received IVIG
Winston (2008)[71]	Maribavir vs Placebo	No anti-CMV drug prior to study drug. Low dose acyclovir, valacyclovir, or famciclovir could be administered for prophylaxis of HSV or VZV.	Yes	NR
Marty (2011)[58]	Maribavir vs Placebo	No anti-CMV drug prior to study drug, but acyclovir, valacyclovir, or famciclovir could be administered for prophylaxis of HSV or VZV	Yes	NR
Marty (2013)[59]	Brincidofovir vs Placebo	No anti-CMV drug prior to study drug (excluded if given)	No. Patients were eligible to participate if they had no or low levels of CMV DNA in plasma that did not require treatment according to site investigator's criteria. Secondary outcomes were reported for patients that were CMV DNA-negative at baseline but "confirmed dz" outcome was only presented for all patients.	NR
Chemaly (2014)[44]	Letermovir vs Placebo	No anti-CMV prophylaxis (excluded if given pre-transplant), but low-dose acyclovir, valacyclovir or famciclovir could be administered for prophylaxis of HSV or VZV	Yes	NR

5.16.1. Sensitivity analyses related to study characteristics

Sensitivity analyses were conducted to determine if galactomannan surveillance testing impacted the findings of NMAs of (1) proven/probable IFIs and (2) any IFIs. One study[67] was removed from both of these networks and the NMAs reanalysed. In the reduced network of proven/probable IFI studies, only 2 studies remained, evaluating 3 interventions, and a connection was lost that had previously formed a closed loop. When this sparse network was analysed by NMA, no significant differences were detected between interventions, where there had been a significant difference between voriconazole and fluconazole in the full network (**Table 41**). The widening of the credible interval for this comparison suggests the change in significance was simply due to a loss of power to detect a difference and not likely a real effect of removing the galactomannan surveillance testing. The relative rankings of the 3 interventions remained unchanged.

Table 41: Summary of results of a sensitivity analysis to determine impact of galactomannan surveillance testing on proven/probable IFIs

Comparison		# of Trials (patients)	Full network: galactomannan surveillance included OR (95% CrI)	Reduced network: galactomannan surveillance removed OR (95% CrI)
			**Values <1 favor comparator*	
Comparator	**Reference**			
Voriconazole	Fluconazole	Full: 1 (600) Reduced: 0 (0)	**0.53 (0.27–0.97)**	0.46 (0.08–2.32)
Voriconazole	Itraconazole	1 (489)	0.69 (0.31–1.50)	0.61 (0.12–2.68)
Itraconazole	Fluconazole	1 (299)	0.76 (0.42–1.37)	0.75 (0.39–1.41)

When the study using galactomannan surveillance testing was removed from the network evaluating any IFI, the voriconazole node was lost. The findings of NMA of the reduced network were similar to those of the full network and the relative rankings of interventions remained unchanged **(Table 42)**.

Table 42: Summary of results of a sensitivity analysis to determine impact of galactomannan surveillance testing on the detection of any IFI

Comparison		# of Trials (patients)	Full network: galactomannan surveillance included OR (95% CrI)	Reduced network: galactomannan surveillance removed OR (95% CrI)
			**Values <1 favor comparator*	
Comparator	**Reference**			
Itraconazole	Fluconazole	1 (299)	0.90 (0.54–1.52)	0.90 (0.53–1.51)
Amphotericin B	Fluconazole	1 (140)	0.73 (0.28–1.88)	0.73 (0.28–1.83)
Micafungin	Fluconazole	2 (528)	0.85 (0.59–1.23)	0.85 (0.59–1.23)
Micafungin	Itraconazole	1 (227)	0.94 (0.52–1.67)	0.94 (0.53–1.69)
Voriconazole	Fluconazole	Full: 1 (600) Reduced: 0 (0)	0.61 (0.34–1.07)	Not in network

A sensitivity analysis was conducted to determine the effect of differences in follow-up duration across fungal prophylaxis studies evaluating proven IFIs. Four studies following patients to 180 days post-transplant were included in a NMA[55, 56, 67, 69], and two studies that followed patients to 100 days or less post-transplant were excluded.[52, 72] Both of these studies compared fluconazole to amphotericin B and this node was dropped from the network. The findings of the NMA conducted at 180 days post-transplant were not different from those of the NMA conducted at all follow-up times (**Table 43**) and the relative ranking of the remaining three treatments was unchanged.

Table 43: Summary of results of a sensitivity analysis to determine impact of follow-up duration on proven IFIs

Comparison		# of Trials (patients)	Full network: all follow-up times OR (95% CrI)	Reduced network: 180 days post-transplant OR (95% CrI)
			**Values <1 favor comparator*	
Comparator	**Reference**			
Voriconazole	Fluconazole	1 (600)	0.54 (0.18–1.49)	0.54 (0.18–1.50)
Voriconazole	Itraconazole	1 (489)	0.83 (0.24—2.58)	0.83 (0.25–2.60)
Itraconazole	Fluconazole	2 (437)	0.64 (0.36–1.13)	0.65 (0.37–1.13)
Amphotericin B	Fluconazole	Full: 2 (243) Reduced: 0 (0)	1.03 (0.45–2.35)	Not in network

5.16.2. Assessing the assumption of inconsistency for network meta-analyses

The majority of evidence networks formulated in the current review were of a star-shaped structure, and the corresponding lack of closed loops precluded the fitting of inconsistency models to the data. In comparing the DIC from the consistency and inconsistency models for endpoints where one or more closed loops were present, none presented clear indications of inconsistency: confirmed CMV infection (consistency model 62.9 versus inconsistency model 64.7); proven invasive fungal infection (64.9 vs 66.9); any proven, probable or possible invasive fungal infection (74.0 vs 75.9); 180-day mortality fungal prophylaxis (41.8 vs 43.8) .

5.17. DISCUSSION

This systematic review incorporating network meta-analyses was conducted to address gaps in knowledge in the prevention and treatment of infections in HSCT recipients. Network meta-analysis is an increasingly used methodology in the context of systematic reviews and technology assessment to address situations involving multiple comparators as well as comparisons with both direct and indirect information available, and was a valuable method for the current review. This systematic review of the evidence, incorporating network meta-analyses where possible, was conducted to compare the benefits and harms associated with infectious disease interventions for HSCT recipients. Overall, thirty-three trials were included in the review, encompassing viral, fungal, and bacterial prophylaxis, pre-emptive, and empiric treatment. We saw consistently across infection domains that there was limited evidence evaluating anti-infection agents in the HSCT population. As well, our NMAs consistently were unable to identify statistically significant differences between interventions for all types of infection prophylaxis and treatment, likely due to this paucity of evidence. We speculate that HSCT clinicians borrow evidence from other populations in their development of clinical strategies for infection control in HSCT patients. Most comparisons between treatments in our analyses were based on indirect evidence only. Further discussion of findings from the completed work follows below. *It should be emphasized that findings from network meta-analyses described in the report should be interpreted with caution given the high degree of heterogeneity present between studies which could not be well addressed based upon the evidence structure as well as the mixed reporting and eligibility criteria of studies.*

The current review considered several outcomes related to the prophylaxis and management of infections. The available evidence was sparse in most cases, as was evident from the networks of evidence studied. Regarding viral infections, data assessed in the current review found ganciclovir to be the most beneficial antiviral for CMV prophylaxis, though it was also found to be associated with a greater risk of neutropenia compared to other anti-CMV agents. There is a need for additional efficacious antiviral medications or other novel approaches such as CMV vaccination or host-directed immune therapy. Notable differences for mortality effects were not identified in the included data. Regarding fungal infections, the included data suggests that voriconazole offers more benefits than itraconazole, amphotericin B, and fluconazole, however, studies evaluating posaconazole and echinocandins were lacking. Definitive messaging for recommendations related to fungal prophylaxis in HSCT recipients thus could not be established. Lastly, based upon the minimal information identified from the current review's search of the literature, the review found that there currently exists a sizable lack of data regarding bacterial prophylaxis and empiric treatment of febrile neutropenia in the HSCT setting. Potential recommendations in these areas were thus also unclear.

We identified one systematic review and NMA by Zhao et al published in the domain of infection prevention or treatment in HSCT recipients[78]. This publication focused on fungal prophylaxis using triazole antifungals and was not limited to allogeneic HSCT patients, including patients undergoing chemotherapy for underlying hematopoietic disorders as well as recipients of autologous hematopoietic stem cell transplants. In an effort to determine if the effects of the antifungal prophylaxes were the same in these three different patient subgroups, the authors conducted a network meta-regression, a statistical technique in which variables can be added to a statistical model to determine if they influence the results. The authors did not identify any differences in the patient subgroups; however, the amount of data available for analysis (n = 21 studies) may have provided limited statistical power. In comparing the studies included by Zhao et al. to those included in the current review, all studies comparing a triazole antifungal to another triazole antifungal were included in both studies. However, literature searches in the current review were not limited strictly to triazole antifungals, and we identified several other studies comparing a triazole antifungal to a drug in another antifungal class (e.g., echinocandins). This allowed for a more comprehensive assessment of the antifungal literature within the very specific patient population of allogeneic HSCT recipients. The findings of the NMA by Zhao et al. are difficult to compare to those discussed in the current review given the differences in inclusion criteria of studies as well as the differences in interventions included in the

respective networks. In our review, voriconazole significantly reduced the incidence of proven or probable IFIs, while in the Zhao review, a difference was identified but it was not statistically significant. In the Zhao review, significant prophylactic effects were found with posaconazole compared to fluconazole and itraconazole. However, none of the studies evaluating posaconazole were conducted strictly with allogeneic HSCT recipients and, thus, they were not included in our review. Posaconazole was not included in NMAs in the current review. Generally, the broader patient inclusion criteria of the Zhao review allowed for a greater number of studies to be included evaluating triazole antifungals; however, the broader inclusion criteria also resulted in higher patient heterogeneity, which may possibly limit the validity of the results.

5.18. Limitations

While the current review represents a vast effort to compile all of the relevant several limitations of the current review should be noted. First of all, we found that across domains there were limited studies evaluating anti-infection agents in HSCT recipients, meaning clinical practice is likely guided by research in other patient populations. NMA was not possible for bacterial prophylaxis and treatment for infections as well as other areas due to a paucity of studies; thus, the ability to identify important differences between interventions for the indications studied was limited given the size of the evidence base. Second, generalizability of findings from the analyses and findings presented is difficult to assess, as the majority of included studies were conducted in mixed populations of patients with an assortment of malignancies; this complicates the application of summary findings to the task of treatment selection for any single patient. From the perspective of meta-analyses presented in the current report, the ability to address the presence of between-study heterogeneity of populations was highly limited; this was a consequence of both the geometry of evidence networks (primarily single study connections, which precludes the ability to perform meta-regression analyses) as well as the failure of most trials to provide subgroup data for the outcomes of interest. Rapidly changing supportive care over time (i.e., co-interventions including antibiotic use, prophylactic regimens for GVHD and other endpoints), changes over time in matching ability (e.g. earlier studies tended to use a higher proportion of related donors because typing methods were by serology, which is less specific than current typing approaches) and between-study variability in definitions of endpoints such as IFIs also limited the homogeneity amongst the set of identified trials.

5.19. Conclusions

The current systematic review found that comparative evidence from RCTs is lacking for comparisons of interventions currently used for prophylaxis and treatment of infections in the HSCT population. This review was performed in an effort to address some of these gaps. ***The following key points for clinical practice were identified in this review***:

- Ganciclovir is currently the most efficacious antiviral for CMV prophylaxis; however, it is associated with significant neutropenia compared to other anti-CMV agents. Newer yet equally efficacious antiviral medications or other novel approaches such as CMV vaccination or host-directed immune therapy are needed.
- Voriconazole appears to be better than itraconazole, amphotericin B, and fluconazole in preventing IFI; however, studies evaluating posaconazole and echinocandins were lacking. Clear recommendations regarding fungal prophylaxis in HSCT recipients could not be made.
- There is a significant lack of data regarding bacterial prophylaxis and empiric treatment of febrile neutropenia in the HSCT setting. Clear recommendations in these areas cannot be made.

Future studies of infectious disease interventions for HSCT recipients should carefully consider the comparator of interest, the patient population, and assessment of the economics of the interventions. For example, pre-emptive treatment with ganciclovir remains the standard to which other antiviral strategies should be compared in the future. Similarly, voriconazole should be considered for comparison of other antifungals. The use of antifungal agents in HSCT recipients continues to be extrapolated from other

immunocompromised populations and more transplant-focussed studies are recommended. Cost effectiveness should be assessed, given the significant cost of these drugs.

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6. REPORT APPENDICES

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Appendix 1. Literature Search Strategies

Appendix 2. Additional Characteristics of Included Studies.

Appendix 3. Risk of Bias Assessments of Included Studies.

Appendix 4. Findings from Random Effects Analyses.

Appendix 5. PRISMA NMA Checklist

6.1. Appendix 1: Literature search strategies

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> **June 12, 2013; updated June 2015**

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1 Hematopoietic Stem Cell Transplantation/
2 ((h?ematopoietic adj3 transplant$) or hsct$).tw.
3 peripheral blood cell transplant$.tw.
4 peripheral blood stem cell transplant$.tw.
5 Bone Marrow Transplantation/
6 bone marrow transplant$.tw.
7 STEM CELL TRANSPLANTATION/
8 stem cell transplant$.tw.
9 stem cell therap$.tw.
10 PERIPHERAL BLOOD STEM CELL TRANSPLANTATION/
11 peripheral stem cell transplant$.tw.
12 H?ematopoietic peripheral blood stem cell transplant$.tw.
13 or/1-12
14 randomized controlled trial.pt.
15 controlled clinical trial.pt.
16 randomized.ab.
17 placebo.ab.
18 clinical trials as topic.sh.
19 randomly.ab.
20 trial.ti.
21 or/14-20
22 exp animals/ not humans.sh.
23 21 not 22
24 13 and 23

6.2. Appendix 2: Additional characteristics of included viral, fungal, and bacterial prophylaxis studies

Table 17: Distribution of underlying disease across studies of viral, fungal, and bacterial prophylaxis

Underlying disease	# of studies that included any patients with the underlying disease (28 studies overall)	Number of patients with the underlying disease (6,880 patients overall)
ALL	12	560
AML	12	1,366
CML	18	1,058
Non-Hodgkin lymphoma	8	225
Myelodysplastic syndrome	13	508
Multiple myeloma	13	292
Other malignant disease[a]	19	449
Any acute leukemia[b]	20	2,503
Any lymphoma[c]	19	739
Aplastic anemia	13	112
Other non-malignant disease[d]	10	30

[a] includes Hodgkin's lymphoma, chronic lymphocytic leukemia, and other unspecified malignancies
[b] includes the sum of ALL and AML patients listed separately in table as well as patients reported as "acute leukemia"
[c] includes non-Hodgkin lymphoma patients listed separately in table as well as patients reported as "lymphoma"
[d] includes attenuated severe combined immune deficiency, myeloproliferative disorders, and others not specified

Table 18: Interventions evaluated in trials of HSV and VZV prophylaxis, ordered by year of publication

Author	Year	Placebo	Acyclovir
Shepp[a 62]	1987	X	X
Selby[a 61, 73]	1989	X	X
Boeckh[b 40]	2006	X	X

[a]HSV prophylaxis study
[b]VZV prophylaxis study

Table 19: Interventions evaluated in trials of fungal prophylaxis in GVHD patients, ordered by year of publication

Author	Year	Fluconazole	Posaconazole	Itraconazole	Voriconazole
Ullmann[65]	2007	X	X		
Hayashi[48]	2014			X	X

Table 20: Interventions evaluated in trials of fungal treatment, ordered by year of publication

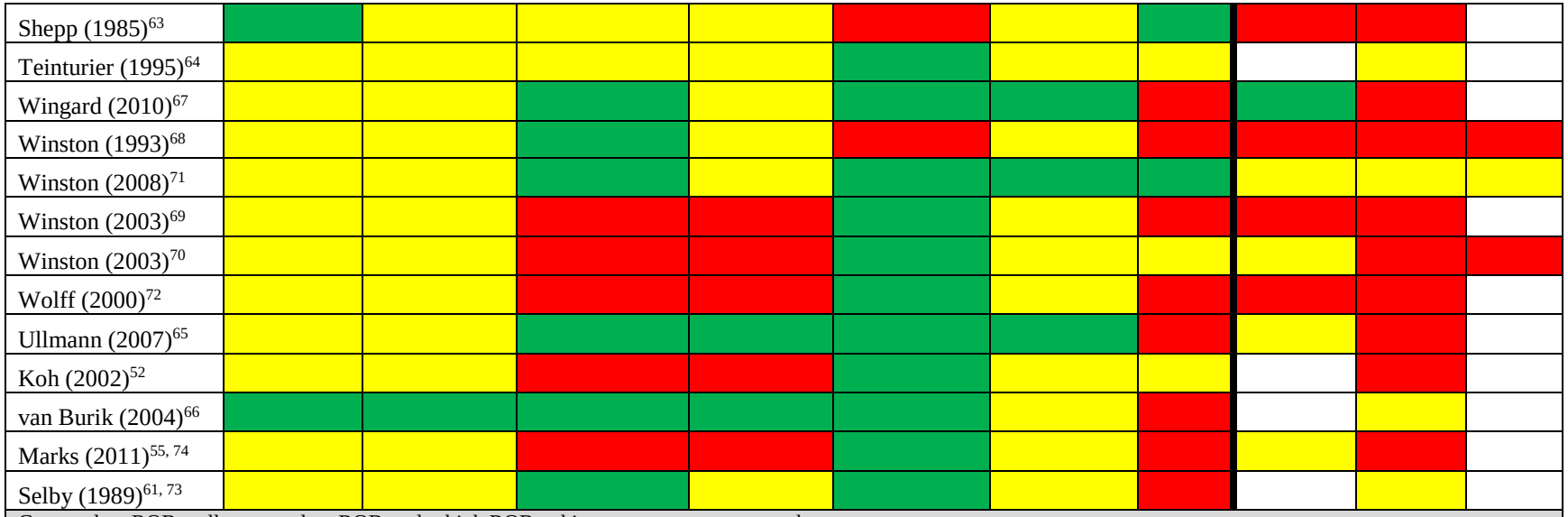
Author	Year	Amphotericin B	Voriconazole	Fluconazole	Itraconazole
Herbrecht[49]	2002	X	X		
Marr[56]	2004			X	X

Table 21: Interventions evaluated in trials of empiric treatment of febrile neutropenia (empiric bacterial treatment), ordered by year of publication							
Author	**Year**	**Netilmicin + Imipenem + Cilastatin**	**Netilmicin + Ceftazidime**	**Meropenem**	**Ceftazidime**	**Piperacillin + Tazobactam**	**Cefepime**
Laszlo[53]	1997	X	X				
Feld[45]	2000			X	X		
Bow[42]	2006					X	X

6.3. Appendix 3: Risk of bias assessments of included studies

Table 22: Risk of bias assessments of included studies

Study	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Summary assessment of bias by outcome[b]		
	Random sequence generation	Allocation concealment	Blinding of patients and personnel	Blinding of outcome assessor	Incomplete outcome data	Selective outcome reporting	Other bias[a]	Mortality	Efficacy	Harms
Boechk (2015)[41]										
Chemaly (2014)[44]										
Marty (2013)[59]										
Marr (2015)[57]										
Hayashi (2014)[48]										
Boeckh (2006)[40]										
Bow (2006)[42]										
Burns (2002)[43]										
Feld (2000)[45]										
Goodrich (1993)[46]										
Goodrich (1991)[47]										
Herberecht (2002)[49]										
Hiramatsu (2008)[50]										
Huang (2012)[51]										
Laszlo (1997)[53]										
Ljungman (2002)[54]										
Marr (2004)[56]										
Marty (2011)[58]										
Reusser (2002)[60]										
Shepp (1987)[62]										



Shepp (1985)[63]										
Teinturier (1995)[64]										
Wingard (2010)[67]										
Winston (1993)[68]										
Winston (2008)[71]										
Winston (2003)[69]										
Winston (2003)[70]										
Wolff (2000)[72]										
Ullmann (2007)[65]										
Koh (2002)[52]										
van Burik (2004)[66]										
Marks (2011)[55, 74]										
Selby (1989)[61, 73]										

Green = low ROB; yellow = unclear ROB; red = high ROB; white = outcome not reported

[a]Studies that were funded by industry in whole or in part were considered to have a high risk of "other" bias. Studies with treatment groups that were unbalanced with respect to patient demographics were considered to have a high risk of "other" bias.

[b]Summary assessments were based on the highest risk identified in any of the key domains for each outcome group. If all key domains demonstrated low risk, the summary assessment was low ROB. If one or more of the key domains demonstrated unclear risk and the rest were low risk, the summary assessment was unclear ROB. If one or more of the key domains demonstrated high risk, the summary assessment was high risk. For mortality outcomes, which were considered objective, performance bias, detection bias, and industry funding not considered to be key domains and were excluded from the summary assessments. For the subjective outcomes of efficacy and harms, all domains were considered key.

6.4. Appendix 4: Findings from Random Effects Analyses

RE Model, Confirmed CMV Disease at 100 days

Ganciclovir			
0.55 (0.03 – 9.93)	**Acyclovir**		
0.25 (0.01 – 5.79)	0.44 (0.01 – 37.16)	**Maribavir**	
0.14 (0.01 – 1.01)	0.24 (0.01 – 8.48)	0.55 (0.05 – 3.74)	**Placebo**

RE Model, Confirmed CMV Disease During Extended Follow-up

Ganciclovir					
0.74 (0.05 – 6.91)	**Valaciclovir**				
0.57 (0.06 – 4.83)	0.77 (0.10 – 7.39)	**Acyclovir**			
0.41 (0.01 – 75.19)	0.57 (0.00 – 174.50)	0.74 (0.01 – 213.45)	**CMX001 100 mg 2x/wk**		
0.21 (0.01 – 7.18)	0.28 (0.00 – 26.31)	0.37 (0.01 – 25.85)	0.50 (0.00 – 30.72)	**Maribavir**	
0.19 (0.01 – 2.57)	0.26 (0.01 – 11.33)	0.33 (0.01 – 10.90)	0.46 (0.01 – 13.88)	0.91 (0.08 – 10.24)	**Placebo**

RE Model, CMV Pneumonia within 100-120 Days

Ganciclovir		
0.61 (0.03 – 12.62)	**Acyclovir**	
0.23 (0.02 – 1.71)	0.37 (0.01 – 14.03)	**Placebo**

RE Model, CMV Pneumonia During Extended Follow-up

Ganciclovir			
1.03 (0.01 – 77.82)	**Valaciclovir**		
0.63 (0.04 – 11.07)	0.62 (0.00 – 98.52)	**Acyclovir**	
0.23 (0.01 – 4.26)	0.22 (0.00 – 37.14)	0.36 (0.01 – 19.47)	**Placebo**

RE Model, CMV Prophylaxis – Mortality at 100-120 days

Ganciclovir				
0.89 (0.05 – 12.55)	**Maribavir**			
0.68 (0.01 – 62.43)	0.79 (0.01 – 89.17)	**Letermovir**		
0.68 (0.12 – 3.45)	0.77 (0.09 – 7.04)	0.97 (0.01 – 80.42)	**Placebo**	
0.55 (0.03 – 10.32)	0.64 (0.02 – 17.02)	0.81 (0.01 – 125.39)	0.82 (0.07 – 9.73)	**Brincidofovir**

RE Model, CMV 180 day mortality

Maribavir 200 mg				
0.57 (0.03 – 9.62)	**Placebo**			
0.45 (0.01 – 21.07)	0.80 (0.05 – 11.06)	**Ganciclovir**		
0.29 (0.00 – 27.82)	0.51 (0.01 – 20.17)	0.64 (0.05 – 8.59)	**Valaciclovir**	
0.23 (0.00 – 42.50)	0.41 (0.00 – 35.11)	0.51 (0.01 – 20.09)	0.79 (0.06 – 10.21)	**Acyclovir**

RE Model, Neutropenia (ANC ≤ 750/µl) while on study drug

Maribavir				
0.83 (0.17 – 4.53)	Placebo			
0.10 (0.00 – 7.70)	0.12 (0.00 – 6.77)	Acyclovir		
0.04 (0.00 – 3.16)	0.05 (0.00 – 2.72)	0.41 (0.02 – 10.91)	Valacyclovir	
0.01 (0.00 – 0.52)	0.02 (0.00 – 0.43)	0.12 (0.01 – 1.25)	0.30 (0.03 – 2.81)	Ganciclovir

RE Model, Fungal: Proven Invasive Fungal Infections (any follow-up time)

Voriconazole			
0.86 (0.11 – 6.28)	Itraconazole		
0.51 (0.05 – 5.03)	0.60 (0.08 – 3.76)	Amphotericin B	
0.53 (0.09 – 3.15)	0.63 (0.17 – 2.17)	1.05 (0.25 – 4.77)	Fluconazole

RE Model, Fungal: Any Invasive Fungal Infection

Voriconazole				
0.83 (0.07 – 10.07)	Amphotericin B			
0.75 (0.11 – 6.33)	0.90 (0.11 – 8.33)	Micafungin		
0.71 (0.09 – 6.47)	0.85 (0.09 – 8.36)	0.95 (0.23 – 3.66)	Itraconazole	
0.62 (0.11 – 3.40)	0.73 (0.12 – 4.31)	0.82 (0.24 – 2.32)	0.87 (0.22 – 3.15)	Fluconazole

RE Model, Fungal: 180-day Mortality

Voriconazole		
0.96 (0.20 – 4.83)	**Fluconazole**	
0.89 (0.18 – 4.47)	0.93 (0.19 – 4.62)	**Itraconazole**

6.5. Appendix 5: PRISMA NMA checklist

PRISMA NMA Checklist of Items to Include When Reporting a Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, *including mention of why a network meta-analysis has been conducted.*	15
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	16

METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	16
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	16-17
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	17
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	18
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	18-20
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	18-20
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	20
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	18
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings*	21

		and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.	
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	20-23
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	23
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	22
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	23-24

Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	Throughout results section
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	Throughout results section
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	26, 64, Appendix 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Appendix 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	Throughout results section
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	26-86
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	86
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	NA
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, *alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	85
DISCUSSION			

Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	87
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	88
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	88
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	89

PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.