DSEN ABSTRACT

A Systematic Review Comparing Interventions for the Prophylaxis and Treatment of Viral, Fungal and Bacterial Infections in Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

Summary

- **Limited evidence was found.** Evidence from randomized trials evaluating anti-infection agents in the HSCT population is lacking or of limited size. NMAs were largely unable to identify differences between interventions for all types of infection prophylaxis and treatment. Clinicians may look to evidence from other immunosuppressed patient populations in their development of clinical strategies for infection control.
- **Findings.** (1) Gancyclovir is currently the most efficacious antiviral for CMV prophylaxis, but it may be associated with more neutropenia compared to other anti-CMV agents. Newer yet equally efficacious antiviral medications or other novel approaches such as CMV vaccination are needed. (2) Voricanazole appears better than itracanazole, amphotericin B and fluconazole in preventing invasive fungal infections, although studies evaluating posaconazole and echinocandins were lacking. (3) There is a lack of data regarding bacterial prophylaxis and empiric treatment of febrile neutropenia. (4) The between-study diversity in patient populations and study methods requires careful interpretation of findings presented.

What is the issue?

- While allogeneic hematopoietic stem cell transplant (HSCT) has become a vital therapy in the treatment of a variety of malignant and non-malignant disorders, mortality related to infection remains a sizeable risk. 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.

What was the aim of the study?

The following objectives were addressed:

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.

How was the study conducted?

- Medline, Embase and the Cochrane Trials Register were searched in 2013 to identify randomized trials of regimens for prophylaxis or treatment of viral, fungal and bacterial infections in patients undergoing HSCT for treatment of hematologic neoplasias or benign disease. Searches were updated in 2015 and 2017. Outcomes of interest included mortality and confirmed infections after prophylaxis (cytomegalovirus (CMV), invasive fungal infections, bacterial infections). We conducted Bayesian network meta-analyses (NMA) to compare interventions. For outcomes where NMA was not possible, narrative summaries were prepared.

What did the study find?

- 33 trials studied assorted prophylactic and treatment regimens for viral, fungal and bacterial infections in 7,712 patients. Evidence networks of prophylactic and treatment regimens were typically small (range 3–6 interventions). There was variability between study populations with respect to age, underlying disease, risk of relapse/mortality, donor status and endpoint definition (in some cases). Publication dates ranged from 1985–2015. Prophylaxis and treatment regimens varied by infection type, and included acyclovir (ACY), brincidofovir (BRI), ganciclovir (GAN), letermovir (LET), maribavir (MAR), valaciclovir (VAL), foscarnet (FOS), amphotericin B (AMP), fluconazole (FLU), itraconazole (ITR), posaconazole (POS), voriconazole (VOR), ketoconazole (KET), nystatin (NYS), vancomycin (VAN), cefepime (CEF), ceftazidime (CEFT), meropenem (MER), and netilmicin (NET). When formulating networks of studies for outcomes, connections between treatments were often informed by single trials, and the majority of included studies were of small sample size. NMA was not feasible for all endpoints.

- **Future research.** Future studies should carefully consider the comparator of interest, the patient population, and assessment of the economics of the interventions. Use of antifungal agents in HSCT recipients continues to be extrapolated from other populations and more transplant-focused studies are recommended.

Research Question 1: Viral Infections

- NMA was only possible for outcomes reported in trials of CMV prophylaxis starting at engraftment. Although most trials reported confirmed CMV disease during extended follow-up, after discontinuation of study drugs, follow-up times varied substantially.
- Two NMAs were performed on endpoints measuring confirmed CMV disease during treatment and over extended follow-up. Few differences in prophylactics were found due to sparse evidence. GAN consistently trended to be the highest ranked intervention in both networks, though significant differences versus other treatments were limited to MAR. An NMA of the incidence of drug-related neutropenia found GAN to be associated with higher risk compared to VAL, ACY and MAR.
- No significant differences in overall mortality were identified in NMAs evaluating CMV prophylaxis regimens.
- In a single study comparing pre-emptive treatments, no differences in effects on CMV disease, CMV pneumonia or 180-day mortality were noted between GAN and FOS.
- Small studies from >20 years ago found ACY to be better than placebo for prevention of herpes simplex virus and varicella zoster virus.

Research Question 2: Fungal Infections

- NMA was only possible for outcomes reported in trials evaluating fungal prophylaxis. NMAs were conducted for proven invasive fungal infections (IFIs), proven or probable IFIs, and any IFI (proven, probable, or possible). No significant differences were demonstrated between any of the fungal prophylaxis agents in networks evaluating proven IFIs or any IFI. VOR was significantly more efficacious than FLU in the prevention of proven or probable IFIs.
- An NMA found no relevant differences in 180-day mortality between VOR, FLU and ITR. One trial showed significantly reduced overall mortality with KET was compared to NYS within one month of engraftment.
- In patients with graft versus host disease, POS may offer benefits for the prevention of invasive infections over FLU. One study found VOR was more efficacious than AMP in treatment of aspergillosis and related mortality after 12 weeks.

Research Question 3: Bacterial Infections

- NMAs were not possible and narrative summaries of study findings were prepared.
- One study assessed inclusion of VAN (vs no inclusion) in prophylaxis regimens. Regimens including VAN did not improve efficacy for the prevention of Gram-positive cocci infections, septicemia, or fever compared to those without VAN.
- Febrile neutropenia (FN) was considered a proxy for bacterial infection. Three studies evaluated treatment of FN in immune-compromised patients, including HSCT recipients. No differences were demonstrated between the NET regimens in the improvement of FN. MER was associated with significantly higher clinical success at the end of therapy than CEFT. Piperacillin-tazobactam was associated with significantly greater treatment success at 72 hours after the start of therapy compared to CEF; however, the difference was reduced over time. There were no differences in overall mortality between interventions.

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