

Evolving Infection Prevention in HSCT and Cellular Therapies

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Allogeneic haematopoietic stem cell transplantation (HSCT) and other cellular therapies present a unique immunological landscape, rendering recipients highly susceptible to severe infections. The persistent clinical dilemma lies in balancing effective immunosuppression to prevent graft-versus-host disease (GVHD) with robust infection prophylaxis and treatment. Emerging data from EHA 2026 highlight a shift towards more targeted and personalised infection prevention strategies, moving beyond broad-spectrum approaches.

KEY TAKEAWAYS

- **The Pivot:** Infection prevention is moving from broad-spectrum prophylaxis to targeted, risk-stratified, and pre-emptive strategies.
- **The Data:** While specific HR or p-values are not yet available for all emerging strategies, the focus is on reducing pathogen-specific infection rates and associated mortality.
- **The Action:** Clinicians should consider incorporating pathogen-specific surveillance, personalised antimicrobial stewardship, and novel immunotherapeutic approaches into their practice for HSCT and cellular therapy recipients.

Recipients of allogeneic HSCT and cellular therapies, such as CAR T-cell therapy, experience profound and prolonged immunosuppression, making them highly vulnerable to bacterial, viral, fungal, and parasitic infections.¹ This susceptibility is multifactorial, stemming from myeloablative conditioning regimens, T-cell depletion, GVHD, and the immunosuppressive medications used to manage GVHD.¹ Historically, infection prevention has relied on broad-spectrum antimicrobial prophylaxis, environmental controls, and vaccination. However, the increasing prevalence of multidrug-resistant organisms (MDROs), the emergence of novel viral pathogens, and the specific immune dysregulation associated with different cellular therapies necessitate a re-evaluation of these conventional strategies.² The clinical imperative is to reduce infection-related morbidity and mortality without contributing to antimicrobial resistance or increasing toxicity.

Evolving Strategies in Infection Prevention

Current discussions at EHA 2026 underscore a move towards more refined and individualised infection prevention protocols. One key area of evolution is the application of advanced diagnostic techniques for early pathogen detection. Molecular assays, including multiplex PCR panels for respiratory viruses and gastrointestinal pathogens, allow for rapid identification and targeted pre-emptive therapy, potentially reducing the reliance on empiric broad-spectrum antibiotics.³ For example, pre-emptive ganciclovir based on CMV PCR positivity has significantly reduced CMV disease incidence

compared to universal prophylaxis.⁴ Similarly, surveillance cultures for MDROs, particularly vancomycin-resistant enterococci (VRE) and carbapenem-resistant Enterobacteriaceae (CRE), are guiding targeted decolonisation strategies and informing empiric antibiotic choices in febrile neutropenic patients.⁵

Antifungal prophylaxis remains a cornerstone, with agents like posaconazole and voriconazole demonstrating efficacy against invasive mould infections in high-risk patients.⁶ However, concerns regarding drug-drug interactions, toxicity, and the emergence of azole-resistant fungi are driving research into novel antifungal agents and risk-stratified prophylaxis.⁷ Data presented at EHA 2026 suggest a growing interest in biomarkers, such as galactomannan and beta-D-glucan, to guide the duration and intensity of antifungal prophylaxis, potentially reducing unnecessary exposure.⁸

Vaccination strategies are also undergoing refinement. While standard vaccinations are critical, the timing and efficacy in immunocompromised patients are complex. Novel approaches include vaccination of donors prior to HSCT and the use of adjuvanted vaccines or higher-dose formulations to enhance immunogenicity in recipients.⁹ For instance, the use of a recombinant zoster vaccine has shown promising results in preventing herpes zoster reactivation in HSCT recipients, a common and debilitating complication.¹⁰

Beyond antimicrobial agents, immunotherapeutic approaches are gaining traction. Adoptive transfer of pathogen-specific T-cells, particularly for viruses like CMV, EBV, and adenovirus, represents a highly targeted strategy to restore antiviral immunity.¹¹ Early phase trials have demonstrated the feasibility and safety of these approaches, with some studies reporting reductions in viral load and disease progression.¹² Furthermore, strategies to enhance innate immunity, such as granulocyte colony-stimulating factor (G-CSF) administration or the use of immunomodulatory agents, are being explored to bolster host defences during periods of profound neutropenia.¹³

The integration of antimicrobial stewardship principles is paramount. This involves optimising antimicrobial selection, dosing, and duration based on local epidemiology, patient-specific risk factors, and real-time diagnostic results.¹⁴ The goal is to preserve the efficacy of existing antimicrobials and mitigate the development of resistance. Environmental infection control measures, including HEPA filtration and strict hand hygiene protocols, remain foundational, though their specific impact on infection rates is difficult to quantify in isolation.¹⁵

Limitations in current evidence include the heterogeneity of patient populations, conditioning regimens, and GVHD prophylaxis, which complicate direct comparisons between studies. Many emerging strategies are still in early phase trials, lacking large-scale, randomised controlled data demonstrating a definitive reduction in overall mortality or long-term outcomes. The cost-effectiveness of highly specialised diagnostics and immunotherapies also requires further evaluation. Future research needs to focus on developing predictive models to identify patients at highest risk for specific infections, allowing for truly personalised prevention strategies. Furthermore, the impact of the gut microbiome on infection susceptibility and GVHD is an active area of investigation, with potential for microbiome-modulating interventions to reduce infection risk.¹⁶

CLINICAL IMPLICATIONS

The shift in infection prevention for HSCT and cellular therapy recipients from broad-brush approaches to precision medicine is a welcome, if overdue, development. Clinicians must now navigate a more complex landscape of diagnostics and targeted interventions. The days of simply prescribing universal broad-spectrum

prophylaxis for extended periods are, rightly, drawing to a close. The increasing sophistication of molecular diagnostics means that a 'wait and see' approach to infection is becoming less defensible, particularly for viral pathogens where pre-emptive therapy has demonstrated clear benefits. The challenge will be integrating these advanced diagnostics into routine clinical workflows without overwhelming laboratory capacity or incurring prohibitive costs, especially in settings with limited resources.

For the pharmaceutical industry, this evolution presents both opportunities and demands. The market for novel, targeted antimicrobial agents, immunomodulators, and pathogen-specific cellular therapies will expand. However, the commercial viability of highly specific agents for smaller patient populations, particularly those with rare or resistant infections, will require innovative development and pricing models. Furthermore, the industry must invest in robust clinical trials that demonstrate not just efficacy against a pathogen, but a tangible reduction in patient morbidity and mortality, alongside a favourable safety profile in this highly vulnerable population. The regulatory pathway for these complex biologicals and diagnostics will also need to adapt. Patients undergoing these intensive therapies stand to benefit significantly from more personalised infection prevention. Reduced exposure to broad-spectrum antimicrobials may mitigate side effects, preserve the gut microbiome, and decrease the risk of antimicrobial resistance. The prospect of fewer severe infections and hospitalisations translates directly into improved quality of life and potentially better long-term outcomes. However, the complexity of these new strategies means patients will require clear, concise communication regarding their individualised prevention plan, the rationale behind specific diagnostics, and the potential benefits and risks of novel therapies. Ensuring equitable access to these advanced strategies across different healthcare systems will be a critical ethical consideration.

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