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REVIEW

Bloodstream infections in haematology: Risks and new challenges for prevention

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SUMMARY

Bloodstream infections are an important cause of morbidity and mortality in the haematology population, and may contribute to delayed administration of chemotherapy, increased length of hospitalisation, and increased healthcare expenditure. For gram-positive, gram-negative, anaerobic and fungal infections, specific risk factors are recognised. Unique host and environmental factors contributing to pathogenesis are acknowledged in this population. Trends in spectrum and antimicrobial susceptibility of pathogens are examined, and potential contributing factors are discussed. These include the widespread use of empiric antimicrobial therapy, increasingly intensive chemotherapeutic regimens, frequent use of central venous catheters, and local infection control practices. In addition, the risks and benefits of prophylaxis, and spectrum of endemic flora are identified as relevant factors within individual centres. Finally, challenges are presented regarding prevention, early detection, surveillance and prophylaxis. To reduce the rate and impact of bloodstream infections multifaceted and customised strategies are required within individual haematology units.

Introduction

Bloodstream infections are an important cause of morbidity and mortality in immunocompromised populations.[1] In patients with haematological disorders, infection may lead to delayed administration of chemotherapy, prolonged hospitalisation, and additional costs associated with directed antimicrobial therapy.

The risks and causes of bloodstream infection are often quite different within the haematology population, when compared to immunocompetent hosts. New and more intensive immune-modulating therapies may contribute to development of opportunistic infection,[2] and chronic underlying immune compromise related to indolent malignant disorders[3] or graft-versus-host disease (GVHD)[4] may give rise to prolonged at-risk periods for opportunistic infection.

Over the last three decades, a changing spectrum and antimicrobial susceptibility has been observed in this population. We review the relevant contributory factors, and provide recommendations regarding screening, surveillance and prophylaxis to minimise the impact of bloodstream infection in the haematology population. Beyond the scope of this review is in-depth discussion regarding antimicrobial treatment regimens, and the reader is referred elsewhere for this information.[5–9]

Risk stratification in haematology

Within the haematology population, risks for bloodstream infection are not uniform. Specific defects in humoral (e.g. hypogammaglobulinaemia secondary to CLL[10]) and cellular (e.g. lymphopaenia due to alemtuzumab therapy[3]) immunity may be related to underlying malignancy or therapy, and each confers risk for infection. Throughout this review, we refer to the haematology population, inclusive of patients receiving chemotherapy for underlying haematologic lymphoreticular malignancy and patients requiring autologous stem cell or allogeneic bone marrow transplantation. Where possible, specific or predominant risk factors are outlined for individual disease or treatment groups. Patients may be classified according to the presence of risk factors for infection – neutropenia, mucositis, corticosteroid administration, donor mismatch, GVHD and hyposplenism all contribute to increased risk for bacterial and fungal bloodstream infections,[11] and one or more of these factors may contribute to risk in a single patient.[12] Risk stratification allows informed decisions regarding empiric antimicrobial therapy,[13] and this is discussed further below.

Gram-positive bloodstream infections

Staphylococcus aureus bacteraemia is not uncommon in patients with haematological malignancy. One 10-year study estimated that 7% of all bacteraemic episodes in neutropenic patients with malignancy were caused by this organism.[14] As with non-neutropenic patients, *S. aureus* bacteraemia is associated with skin and

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soft-tissue infections, or with intravascular devices. The former group includes patients with cutaneous T-cell lymphoma, who are frequently colonised with *S. aureus*, prior to development of bloodstream infection.[15] It is not clear if complicated (septic emboli, abscesses) or endovascular infections (endocarditis, septic thrombophlebitis) are more frequently observed in association with *S. aureus* bloodstream infections in patients with haematologic malignancy, as these have been reported as endpoints in retrospective series only.[16,17] Observational data suggest that catheter-related *S. aureus* bacteraemia in the haematology population is more frequently associated with extra-vascular complications (e.g. septic arthritis, deep tissue abscess, osteomyelitis) when compared to patients with solid tumours, when intravascular complications (infective endocarditis, septic thrombosis) are more frequent.[18] Device removal is required in the presence of catheter-related bloodstream infection.[19] Attributable mortality has been estimated at 4.5–44% in this population,[14,17,20] depending on age,[17] underlying haematologic disease[17,21] and primary site of infection.[17]

Coagulase-negative staphylococci are frequently identified as skin commensals in this population, and are often regarded as a contaminant when isolated in blood cultures.[22] However, these organisms may also be responsible for clinically significant nosocomial bacteraemia, especially in relation to intravascular devices[23] and underlying immunocompromised states.[24] This group of organisms is the single largest cause of bloodstream[25,26] and central venous catheter (CVC)-related bloodstream infections,[23] where biofilm production plays a role in pathogenesis.[27] While often considered to be of low-virulence,[28,29] there is also evidence for an association with increased mortality, associated with particular strains[30] or underlying immunocompromise. In hospitalised populations, coagulase-negative staphylococci are often methicillin-resistant[31,32] and emerging resistance to linezolid[31] and teicoplanin[29,33] is reported in the haematology population.

Streptococcus pneumoniae bacteraemia may be associated with pneumonia or CVC-related infection, but it is not clear if clinical spectrum of disease or outcomes are unique for the haematology population. A large retrospective review of consecutive bloodstream infections at the M.D. Anderson Cancer Centre demonstrated a 36% prevalence of penicillin resistance, although initially inappropriate antibiotic therapy of penicillin non-susceptible strains was not associated with increased mortality rates in these high-risk patients with cancer.[34] Risk factors for pneumococcal bloodstream infection include autologous transplantation with total body irradiation conditioning, allogeneic bone marrow transplantation (BMT), and chronic GVHD, with significant mortality (approximately 20%) in both early and late transplant periods.[35,36]

The viridans streptococci are bacteria that frequently colonise the gastrointestinal tract (including the oral cavity), as well as the female genital and respiratory tracts. Bloodstream infections in patients with haematologic malignancy or neutropenia have been associated with intensive chemotherapy with cytarabine,[37,38] receipt of antacids or H2-blockers,[39] and antimicrobial prophylaxis with either a fluoroquinolone or trimethoprim-sulfamethoxazole.[40] The association with intensive chemotherapeutic regimens is likely to be confounded by the presence of intercurrent mucositis. Indeed, other risk factors for mucosal damage have been identified as risk factors for viridans streptococci bloodstream infections, including oral cavity irradiation[41] and lack of prophylaxis against herpes simplex virus infections.[42]

Enterococcus species also colonise the intestinal tract and may cause bacteraemia in the haematology population. Although considered to have low intrinsic pathogenicity, this group is significant in terms of multidrug resistance, predominantly glycopeptide resistance. In a retrospective case series, vancomycin use, gastrointestinal procedures, acute renal failure, and diabetes were identified as risk factors for vancomycin-resistant (VRE) bloodstream infection in colonised haematology and oncology patients,[43] while a case-control study of haematology and oncology patients with VRE bloodstream infection (controls with colonisation) identified mucositis as a significant risk factor.[44] Another case-control study has identified receipt of vancomycin therapy and an underlying diagnosis of acute myeloid leukaemia as significant associations with VRE infection.[45]

Bacillus species (*licheniformis* and *cereus*) are identified as causes of bacteraemia in the haematology population, and should not be considered as skin contaminants. Infection may be associated with significant mortality.[46] The pathogenesis includes toxin production,[47] and focal infection (e.g. brain abscess)[48] has also been reported. One outbreak was associated with contamination of cotton wool used for skin disinfection.[49]

In the haematology population, bloodstream infection due to *Corynebacterium jeikeium* has been associated with the presence of CVCs[50] and environmental contamination.[51,52] Other risk factors include neutropenia and previous exposure to antibiotics.[53] Mortality rates of 5–34% have been reported, with prognosis related to neutrophil recovery.[53]

Impaired cell-mediated immunity due to underlying disease or treatment may predispose haematology patients to specific infections. Fludarabine therapy for chronic lymphocytic leukaemia has been associated with CD4 lymphopaenia[54] and increased incidence of *Listeria* bloodstream infection.[55] Bloodstream infections with non-tuberculous mycobacteria have also been reported in immunocompromised patient populations, including patients with haematological malignancy.[56] Frequently, infection is associated with an indwelling CVC (especially with *Mycobacterium fortuitum* and *Mycobacterium chelonae*),[57,58] and catheter removal plays an important role in management.[59]

Gram-negative bloodstream infections

Gram-negative rods are a heterogenous group of organisms, found predominantly in the gastrointestinal tract. In the haematology population, bacteraemia is often associated with breaches in mucosal integrity, such as during periods of severe mucositis. A number of case-control studies have investigated potential risk factors for gram-negative bacteraemia, largely where multi-resistant organisms or nosocomial outbreaks have been observed. Whilst Enterobacteriacae (e.g. *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterobacter cloacae*, *Serratia marcescens*) are the commonest cause of gram-negative bloodstream infection, other less common organisms are emerging as significant pathogens in the haematology population.

Outbreaks of *Pseudomonas* spp. bacteraemia have been reported in relation to contaminated water taps, shower heads and disinfectant fluids.[60–62] In multidrug resistant cases (e.g. metallo-beta-lactamase producing),[63] combination therapy including polymyxin B may be required.[64,65] Adjuvant serial granulocyte transfusions have also been successfully used.[66] Bacteraemia may be seen in association with ecthyma gangrenosum,[67] although the incidence of these skin lesions is decreasing (<5%), possibly related to early therapy with anti-pseudomonal agents.[68] Pseudomonal bloodstream infections may be associated with high mortality,[69,70] and combination drug therapy (e.g. aminoglycoside plus beta-lactam agent with anti-pseudomonal activity)[71] may be used to prevent development of antibiotic resistance.[72]

Bloodstream infections due to multi-resistant gram-negative bacteria have been associated with recent antibiotic exposure, administration of prophylactic antibiotics, and duration of hospitalisation. Significant risk factors for bacteraemia due to multi-resistant gram-negative bacilli in adult haematology and oncology patients include previous fluoroquinolone prophylaxis and prior