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Febrile neutropenia in children treated for malignancy

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Summary Febrile neutropenia (FN) in children treated for malignancy is a common and direct sequela of chemotherapy. Episodes of FN can be life-threatening, and demand prompt recognition, assessment and treatment with broad spectrum antibiotics. While in the majority of episodes no causal infection is identified, 10—20% are secondary to a bloodstream infection (BSI). A reduction in episodes of BSI could be achieved through robust infection prevention strategies, such as CVL care bundles. Alongside good antimicrobial stewardship, these strategies could reduce the risk of emergent, multi-drug resistant (MDR) infections.

Emerging bacterial pathogens in BSI include Viridans Group Streptococci (VGS) and Enterobacteriaceae such as *Klebsiella* spp. which are known for their ability to carry MDR genes. There is also increased recognition of the role of invasive fungal infection (IFI) in FN, in particular with *Aspergillus* spp. Novel diagnostics, including multiplex blood and respiratory polymerase chain reaction assays can identify infections early in FN, facilitating targeted therapy, and reducing unnecessary antimicrobial exposure. Given appropriate, and sensitive rapid diagnostics, potential also exists to safely inform the risk assessment of patients with FN, identifying those at low risk of complication, who could be treated in the out-patient setting.

Several clinical decision rules (CDR) have now been developed and validated in defined populations, for the risk assessment of children being treated for cancer. Future research is needed to develop a universal CDR to improve the management of children with FN.

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Introduction

Children with cancer receiving cytotoxic chemotherapy and other antineoplastic therapy experience significant neutropaenia as a direct consequence of their treatment. The presence of an indwelling central line, with often concurrent loss of the mucosal integrity of the gastrointestinal tract, further predisposes these patients to bacteraemia and sepsis. Febrile episodes are observed in 34% of neutropenic periods in children treated for cancer, with bacteraemia identified in 10—20% of cases whereas an unknown aetiology is the most likely outcome (up to 79% of the cases).[1]

Definition and immediate management in children with febrile neutropenia

The National Institute for Health and Care Excellence (NICE) defines febrile neutropenia (FN) or "neutropenic sepsis" as a patient with an absolute neutrophil count (ANC) $<$ 500 cells/μl **and** temperature above 38 °C or signs and symptoms of sepsis.[2] FN is a recognised and avoidable cause of death in children receiving treatment for cancer. Patient and parent education around understanding stages of treatment where low ANC are likely, recognising early signs of sepsis and pyrexia, and seeking urgent medical attention is essential. Further to this, education of both nurses and doctors in primary and shared care oncology centres is necessary to ensure the timely evaluation and treatment of children admitted with episodes of FN.

The aggressive, protocol driven management of FN with prompt nursing and medical assessment of patients, and empiric, intravenous, antimicrobial therapy has seen mortality rates reduced from approximately 30% to less than 1% toward the end of the last century.[3] Monotherapy with a broad spectrum intravenous agent, either piperacillin/tazobactam or meropenem, is recommended. Following initial treatment and stabilisation of the patient, antibiotic therapy should be tailored to individual patient, guided by previous infective episodes, surveillance cultures (where available), allergies, and identified focal infection.

Data on the efficacy of monotherapy vs combined agents for empirical therapy in FN has shown similar clinical outcomes and, in view of increased risk of adverse effects from combination therapy (i.e. nephrotoxicity associated with the use of aminoglycosides), monotherapy is now recommended by all international guidelines.[2,4,5] An audit comparing FN practice in UK PTC demonstrated an increase in the use of piperacillin/aminoglycoside combination (7 increased to 17) and piptazobactam monotherapy (0 increased to 4) between 2005 and 2012, with a general decrease in other antibiotic therapies.[6]

Prevention

Strategies for the prevention of FN secondary to bacteraemia and sepsis include effective hand hygiene, adherence to infection control policies, the incorporation of aseptic procedures such as Aseptic Non-Touch Techniques (ANTT) into routine practice, and patient and family education. Many chemotherapy protocols include guidance and strategies to facilitate ANC recovery between the administration of subsequent course to avoid prolonged episodes of neutropaenia.

Within the paediatric setting, including paediatric intensive care but also on medical and surgical wards, CVL care bundle implementations have demonstrated effectiveness in reducing the incidence of Central Lines Associated Bloodstream Infections (CLABSI).[7,8] There is also recently published evidence on central venous lines (CVL) care bundle strategies being effective, albeit to a lesser extent, in paediatric oncology patients.[9] The difficulty in reducing CLABSI in oncology patients may be related to factors such as the underlying immunosuppression and the loss of mucosal integrity leading to the translocation of microorganisms in the bloodstream.[7,10] The 2014 CDC CLABSI definition now takes this factor into account and has added a definition for Mucosal Barrier Injury Laboratory-Confirmed Bloodstream Infection (MBI-LCBI) for oncology patients in this latest guidance.[11] Further work is needed to develop strategies to further reduce CLABSI's in paediatric oncology patients.

Risk assessment

Clinical risk assessment

Risk assessment involves the assessment and consideration of a child's risk of actually developing an infection, given their underlying diagnosis and treatment. Examples of high risk patients include children with Down's Syndrome, children receiving high dose chemotherapy as first line treatment (e.g. osteosarcoma, AML), relapse therapy (e.g. fludarabine in relapse ALL), and patients at risk of prolonged episodes of neutropaenia (e.g. patients undergoing HSTC).

While there is a small proportion of patients at increased risk of sepsis, approximately 79% of episodes of febrile neutropaenia are not associated with serious infection.[1] Identification of low risk patients, and out-patient management with oral antibiotics would reduce the risk of hospital acquired infection, reduce the cost of clinical care as well as the potential for development of multi-drug antibiotic resistance while having a positive impact on quality of life for patients and their families.

Risk assessment using biomarkers

Research exploring biomarkers such as serum cytokines (e.g. interleukins IL-6, IL-8, IL-10), C-reactive protein and pro-calcitonin have demonstrated potential utility for risk stratification of FN.[12—15] In particular, the strategies looking at combination of several of these biomarkers have shown high sensitivity and negative predictive value (>90%) for the presence of a culture positive bacterial infection.[14] However, the paucity of data on the value of these biomarkers in children, and their unavailability in most clinical laboratories means that further work is needed before they can be integrated into routine clinical practice.[16]