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REVIEW

Optimising Antimicrobial Selection and Duration in the Treatment of Febrile Neutropenia in Children

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Abstract: Febrile neutropenia (FN) is a frequent complication of cancer treatment in children. Owing to the potential for overwhelming bacterial sepsis, the recognition and management of FN requires rapid implementation of evidenced-based management protocols. Treatment paradigms have progressed from hospitalisation with broad spectrum antibiotics for all patients, through to risk adapted approaches to management. Such risk adapted approaches aim to provide safe care through incorporating antimicrobial stewardship (AMS) principles such as implementation of comprehensive clinical pathways incorporating de-escalation strategies with the imperative to reduce hospital stay and antibiotic exposure where possible in order to improve patient experience, reduce costs and diminish the risk of nosocomial infection. This review summarises the principles of risk stratification in FN, the current key considerations for optimising empiric antimicrobial selection including knowledge of antimicrobial resistance patterns and emerging technologies for rapid diagnosis of specific infections and summarises existing evidence on time to treatment, investigations required and duration of treatment. To aid treating physicians we suggest the key features based on current evidence that should be part of any FN management guideline and highlight areas for future research. The focus is on treatment of bacterial infections although fungal and viral infections are also important in this patient group.

Keywords: paediatric, febrile neutropenia, antimicrobials

Plain Language Summary

Children undergoing treatment for cancer are at risk of serious infections which may be seen as a fever with a low white blood cell count (neutropenia). This condition is called febrile neutropenia (FN). The treatment of FN has changed over time. In the past all patients were treated in hospital with antibiotics that cover a range of infections. Now, treatment depends on the chance that an individual child has a serious infection. This means for some children we can reduce the time spent in hospital and use fewer antibiotics. This article describes the research behind current best practice in the treatment of FN in children. We focus on:

- Recognising FN quickly.
- Starting treatment rapidly.
- Which antibiotics to use.
- How long to give them for.

We suggest the things that all health care workers should think about when treating children with FN and what further research is needed to improve care in the future.

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Introduction

Fever with neutropenia (febrile neutropenia; FN) is one of the commonest complications in the treatment of childhood cancer and is a significant cause of hospitalisation with attendant disruption to the child and family, risks of nosocomial infection and associated healthcare costs. Bacteraemia is identified in 11–24% of children with FN and intensive care admission is reported in up to 11% of episodes with mortality rates of up to 3%.[1] Overall gram positive organisms tend to be identified in blood cultures slightly more commonly than gram negative organisms, however this ratio is influenced by the timing of blood cultures (i.e pre or post antibiotic), presence of central lines and concurrent antibacterial prophylaxis.[2,3] In a large series of FN episodes in children with cancer, 59% of children had no documented clinical or microbiological evidence of infection, 24% had bacteraemia, 2% had a microbiologically documented infection without bacteraemia, 6% had a clinically documented infection and 9% had a fungal infection.[4]

Owing to the risk of bacteraemia, FN is traditionally managed by urgent hospital attendance and empirical broad spectrum intravenous antibiotics until resolution of fever with average inpatient stay reported as 5 days across many UK and Australian paediatric oncology settings.[5–8] However, it has become apparent in recent years that FN episodes are heterogenous; the risk of significant infection varies among different patients and episodes and the approach of hospitalising all patients until resolution of fever and recovery of neutrophil count overtreats a significant group of lower risk patients, increasing hospital stay and costs and risking evolution of antimicrobial resistance. Current international guidance now recommends a risk-stratified approach to treatment of paediatric FN with the aim of improving patient experience and practising responsible antimicrobial stewardship (AMS) by limiting unnecessary or prolonged antibiotics in carefully selected patients.[9]

This article is focused on improving detection and optimising antibacterial management of FN and highlights recent literature in this area. An updated paediatric specific FN guideline is available elsewhere.[9,10] Fungal and viral infections and their treatment will not be considered in detail and non-neutropenic fever is reviewed elsewhere.[11,12] We will discuss optimising antimicrobial selection, reducing hospital stay, the role of biomarkers to predict infection risk and the role of new rapid diagnostic techniques. Many of the recommendations we discuss are informed by data from studies in high-income countries. Clinicians working in low and middle-income countries may need to consider other factors such as the prevalence of other specific infections (including malaria and other parasites), the availability of diagnostic testing, patient access to healthcare (including transport options), nutritional status of the population, the intensity of chemotherapy regimes delivered (with their associated infection risks), antibiotic resistance patterns and availability of specific antimicrobial medicines when planning effective FN management pathways.[13]

Diagnosis and Initial Investigation of FN

Optimal management of FN requires consistent, evidence-based, definitions of the condition. No international consensus exists on the definitions of fever and neutropenia although common definitions of fever include >38 °C, >38.3 °C, or >38.5 °C, and for neutropenia are <0.5 $x10^9$/L or <1.0 $x10^9$/L and expected to fall to <0.5 $x10^9$/L within 48 h.[14] Within the UK, the National Institute for Health and Care Excellence (NICE) guidelines advise the use of a neutrophil count of ≤0.5 $x10^9$/L and either a fever >38 °C or other signs or symptoms consistent with clinically significant sepsis.[15] However, only 64% of UK centres used this definition in a 2017 audit.[16] Furthermore, a recent trial conducted in Switzerland has suggested that a limit of 39 °C ear temperature is non-inferior to 38.5 °C.[17] Further work is needed to clarify the most appropriate definitions of FN, and to facilitate consistency of use across the clinical and research community.

Blood cultures remain the gold standard test for diagnosis of blood stream infections in FN. While early studies found up to 22% of children with FN had a bacteraemia, more recent observational data indicate that bacteraemia rates may be lower than this and likely explained by the exclusion of common commensals unless cultured more than once.[3] Not surprisingly, the diagnostic yield is highest when two or more blood cultures are taken prior to the first dose of antibiotics and, in the absence of a new fever or clinical instability, blood cultures beyond 48 hours of persistent fever have limited diagnostic utility.[3] Data from a prospective, observational paediatric FN study found that almost 75% of blood cultures were positive within the first 24 hours of collection. Observational paediatric data also show as many as 17% of true blood

stream infections in patients with a central venous catheter (CVC) are detected in cultures taken from a peripheral vein only, suggesting both CVC and peripheral vein cultures should be collected to optimise diagnosis.[18] The quality of collection, including number of sets (aerobic and anaerobic) taken pre antibiotics and volume of blood have also been shown to impact the diagnostic yield of blood cultures in the general paediatric population, highlighting the importance of specific blood culture collection guidelines in FN.[19]

Rapid diagnostic technologies that expedite pathogen identification are, in theory, an important way to improve antibiotic use in FN. Despite the availability and use of these technologies for infection diagnosis in other areas of medicine, few studies have explored the clinical impact of these in the FN population.[20] Concerns about polymerase chain reaction (PCR) based systems include that the panels used may not cover all of the organisms seen in this population, the sensitivity of the PCR means tiny amounts of bacterial nucleic acids or contamination create noisy results and not all antimicrobial resistance can be spotted in the circulating DNA.[21]

There is emerging evidence that PCR based tests for respiratory viruses can increase diagnostic accuracy in children with FN. In a study of nasopharyngeal samples obtained in 1044 episodes of FN in 525 children, multiplex PCR testing for 17 respiratory viruses revealed at least 1 respiratory virus in 46% of cases and respiratory virus as the sole pathogen(s) detected in 34% of episodes.[22] The most common viruses detected were rhinovirus, respiratory syncytial virus, parainfluenza, influenza viruses, adenovirus and human metapneumovirus. The same researchers randomised 176 patients with FN, negative bacterial cultures and favourable clinical evolution of their illness at 48 h between continuing antibiotics and stopping antibiotics in hospital, with no differences in duration of fever, days of hospitalisation and bacterial infections, no deaths and only one case of sepsis requiring intensive care admission in a patient continuing antibiotics.[23] With further data on safety and efficacy, such approaches may make an important contribution to AMR in the future.

Data on the role of PCR for detecting blood stream infections are more limited. In adult patients with FN, multiplex PCR systems reduced time to appropriate antibiotics but had limited impact on duration in two studies.[24] In contrast, a randomised trial of BioFire Filmarray coupled with a comprehensive AMS program in adult patients, including 40% who were immunocompromised, did show reductions in both areas.[25] While the data for rapid, molecular based diagnostics in paediatric FN are scant so far, these results highlight the importance of both diagnostic and AMS interventions to ensure appropriate use of these, often costly, tests.

Biomarkers to predict infection or severity of illness have been extensively explored in paediatric FN.[1,26,27] However, while over 40 studies have investigated a range of biomarkers, most commonly procalcitonin, C-reactive protein and IL-6 and IL-8, very few clinical decision rules or risk stratification strategies incorporate these. The lack of validation and impact studies, combined with cost and availability, may in part explain this.

The role of diagnostic imaging, specifically fluorodeoxyglucose positron emission tomography (FDG-PET) combined with computed tomography (CT) or magnetic resonance imaging (MRI), for investigation of prolonged FN is also emerging as a potentially useful tool.[28,29] A retrospective study of children with cancer and prolonged or recurrent FN found that, compared to conventional imaging, FDG-PET/CT identified additional sites of clinically significant infection/inflammation compared to conventional imaging. The study also showed that the FDG-PET results had a clinical impact in 80%, leading to de-escalation or stopping of antibiotics in many patients.[30] Routine use of FDG-PET has also been proposed as an adjunct to guiding treatment duration of invasive fungal infection in immunocompromised patients and has been shown to be cost-effective in this situation.[31,32] The potential benefits of FDG-PET for prolonged or unexplained FN in children, in particular the identification of occult infection, needs to be balanced with availability and requirement for sedation in some patients.

Principles/Concept of Risk Stratification in Paediatric FN

Many groups have generated systems to stratify FN episodes at presentation, and during treatment, into low- or high-risk of infection-related adverse outcomes.[33] The systems are intended to allow clinicians to alter the intensity, duration and consequently location of empiric therapy, in particular to select patients who are suitable for reduced intensity, often home-based, care. The systems tend to combine factors derived from the likely depth and duration of immunosuppression, episode-related elements of clinical presentation such as shock or hypoxia,

and in the case of those choosing patients for out-of-hospital programmes, the patient's social situation.[34,35] These are integrated to mean those who have received conditioning chemotherapy for a hematopoietic stem cell transplant, or live far from medical facilities without their own transport, or have arrived in hospital in septic shock would not be treated as out-patients. Although many risk-stratification approaches have been proposed, few of them have proven effective in isolation.[8] This may be overcome by embedding them into FN care pathways and taking a systems approach to implementation and evaluation. To be useful in practice, clinical decision rules should define at least 20% of patients as low risk;[8] one study embedding clinical risk stratification into FN care pathways identified 27% of patients as "low risk".[36] Other groups are conducting trials to determine if a biomarker-led approach may be even more effective than the clinically based stratification.[37]

Optimising Antimicrobial Selection

Empiric Antibiotics

The choice of empirical antibacterial agents is derived from a knowledge of the expected incidence of particular bacteria, in part driven by risk stratification, the consequence of infection, and their likely antibacterial resistance.[38] Gram positive organisms are identified in blood cultures more commonly than gram negative organisms (58% vs 42%): the commonest pathogens identified are coagulase negative staphylococci (23%), Enterobacteriaceae (23%), viridans streptococci (13%) and *Pseudomonas aeruginosa* (9%).[39] In most countries, there has been a historical evolution through intravenous dual-therapy (with an aminoglycoside) to stratified single-agent treatment with an intravenous anti-pseudomonal agent in those at higher risk of serious infection, and oral therapy with an antipseudomonal fluoroquinolone with or without a penicillin in those at lower risk of infection. This has been guided by many randomised clinical trials as agents have been introduced to the market, mostly in adult and all-age populations, and trials driven by the development of stratification systems which promote reduced intensity therapy in the low-risk groups.[9,15,40]

The "best guess" antibacterial therapies are then modified in the light of the developing clinical picture. Such changes have historically included planned progressive therapy; such as the addition of a glycopeptide if fever continues beyond 2–3 days. Clinical trials have demonstrated the lack of value of this,[41–43] but the practice continues and highlights the need for robust AMS interventions such as pre-authorisations and implementation of clinical pathways encompassing the entire FN journey coupled with clinical audit and feedback.[41–43] These interventions are critical as the increase in antimicrobial resistance (AMR) worldwide threatens the success of traditional empiric FN antibiotic choices. An international study across 15 paediatric cancer centres in eight countries found high rates of piperacillin-tazobactam resistance among some important Gram-negative pathogens including, *Escherichia coli, Klebsiella pneumoniae* and *P. aeruginosa*.[44] As the incidence of AMR will vary between hospitals and even individual departments, empiric FN choices should be informed by local antibiograms in consultation with microbiology and infectious diseases specialists. In studies of children with cancer, independent risk factors for AMR include prior antibiotic exposure and hospitalisation and AMR infections are associated with adverse outcomes including ICU admission, prolonged hospitalisation and death.[45,46] For patients travelling from overseas for treatment, the incidence of AMR at the sending centre may be unknown and the potential for AMR may be a particular consideration. To combat these concerns, diagnostic and AMS principles should be embedded within FN guidelines to ensure the right investigations are done and interpretation of these inform the right antibiotic choice and duration.[47,48] Comprehensive and collaborative AMS interventions have been shown to reduce antibiotic exposure in immunocompromised patients without compromising patient safety and are vital to limiting the impact of AMR.[47,49–51]

Timing of Antibiotics

As well as choice of antibiotics, the time to administration (TTA) of empirical antibiotics is expected to influence the outcome for patients with bacteraemia or sepsis. Within existing research, TTA is most commonly defined as time from arrival in hospital to administration of antibiotics although in some studies is defined as onset of fever to antibiotic administration.[52] Adult FN guidelines in Europe and America advocate a TTA of <1 hour; most paediatric guidelines are not specific on this point but a time of <1 hour is generally considered as good practice among treating physicians.[53,54] A systematic review of TTA in adult and paediatric FN episodes was suggestive of an increased risk of death, intensive care admission and sepsis with a longer TTA but triage bias (in which patients

who are more unwell receive faster treatment) was noted.[52] Despite this lack of precise evidence, TTA is considered a measure of quality of care in paediatric FN and a number of different, successful approaches to reduce TTA have been described.[55] These include staff training interventions, guidelines, checklists and treatment algorithms.[56]

Viral and Fungal Infections

As in many instances of paediatric fever, viral infections are common within the paediatric oncology population, although, due to underlying immunosuppression, may present atypically.[57] Obtaining a history of contact with infectious individuals and consideration of risk factors for viral reactivation (ie allogeneic HSCT) is important and will guide diagnostics, preferably molecular based. Empirical anti-viral therapy, eg oseltamivir, may be considered in children with an influenza-like illness, during periods of high population prevalence. Where viral infections are suspected, local or international guidelines for management should be followed.[58–63]

The paediatric oncology patients who are most at risk of invasive fungal infections (IFI) are those with severe and prolonged neutropenia, often those with acute leukaemias or receiving HSCT. Additional factors associated with IFI include high-dose steroid exposure, acute and chronic GvHD and increasing age.[64] Particular attention should be paid to the clinical history, in particular symptoms such as haemoptysis, chest pain, sinus pain, dental pain, or skin lesions. Diagnostic markers such as aspergillus antigen, candida antigen, and beta-D-glucan have variable performances and tissue or fluid culture or histopathology remains the gold standard.[9] Imaging with CT chest ± sinuses, ultrasound of the abdomen to exclude hepatosplenic lesions and fundoscopy are recommended. Empirical treatment with anti-fungal agents is usually considered in patients at higher risk of IFI between days 3 and 5 when there has been inadequate response to initial antibiotic therapies. However, this may be indicated early in very high-risk individuals (eg post-allogeneic HSCT, induction therapy for acute leukaemia) or in those with symptoms or signs of invasive fungal disease. A review of international antifungal treatment guidelines has shown that these are varied in quality and recommendations; thus, no single national or international guideline can be recommended.[65] Preemptive antifungal therapy in the face of evidence of IFI can be considered as a strategy in place of empirical antifungal therapy for children with FN at risk of IFI but this approach is currently not widely practised and is dependent on rapid access to pulmonary CT imaging, galactomannan test results and, ideally, the ability to undertake bronchoscopies with bronchoalveolar lavage.[66]

Impact of Prophylaxis

Antimicrobial selection for FN should also take into consideration concurrent prophylaxis. A systematic review of RCTs, including 13 paediatric studies, found fluoroquinolone prophylaxis with levofloxacin reduced episodes of bacteraemia, fever and FN.[67] However there was no difference in overall mortality and not surprisingly, an increase in fluoroquinolone resistance. Prophylaxis guidelines for prevention of viral, *Pneumocystis jirovecii* pneumonia, and invasive fungal infections are available and beyond the scope of this review.[58,65,68–71]

Duration of Treatment

The duration of empirical antibiotic therapy remains contentious. An early trial, looking at discontinuation after a negative blood culture result compared with continuing to count recovery, showed an increased risk of death in the early stopping arm.[72] This understandably unsettled the oncology world, and led to a standard being set of continuing therapy until the patient was afebrile, free of documented infection, and had a neutrophil count above a specified threshold (often 0.5 $x10^9$/L).

While there are robust paediatric data for reduced intensity therapy such as oral antibiotics or home-based treatments for children with low-risk FN, the specific evidence for antibiotic duration in either low- or high-risk groups is scant.[73] For children with unexplained fever, there are generally two approaches to duration namely (i) continue until clear signs of marrow recovery or (ii) continue until patient is stable and afebrile, irrespective of neutrophil count or expected duration of neutropenia.[15,74,75] Despite the frequency with which FN occurs in both adult and paediatric cancer patients, as few as eight RCTs have specifically compared these two approaches, with only one focusing on high-risk patients.[76] While children are well represented in these studies, there is marked heterogeneity in underlying risk status, type of malignancy, definition of clinical failure and time of randomisation of included participants and most studies were conducted before the year 2000. Acknowledging these limitations, a Cochrane review found no significant differences in rates of mortality or

clinical failures between short or long-course empiric antibiotic therapy arms and fewer antibiotic days (by 3–7 days) in the former.[76] Well conducted, prospective trials that address antibiotic duration in paediatric patients with high-risk FN and that challenge the dogma of continuing antibiotics until count recovery are urgently required to inform guidelines and clinical practice internationally.

The lack of solid data on when to stop empiric treatment mirrors the lack of data supporting the duration of focused treatment in identified infections, and the lack of attention to this topic in paediatrics generally. Traditional approaches have tended to the decimal or the lunar - with treatments being a multiple of 7 days, or occasionally 10. For central line associated blood stream infections (CLABSIs), the duration of therapy may depend on the organism identified and whether or not the line remains in situ, guided by local policies. More individualised approaches, where the duration of antimicrobials is guided by inflammatory or infectious markers, are currently under investigation in large trials of immunocompetent children, such as the Batch study in the UK.[77]

When considering the duration of therapy in FN, both the duration of antimicrobials and the duration of hospitalisation should be considered. Over the years, various regimes have been evaluated, including multiple combinations of locations (hospital vs home) and route of antibiotic administration (IV vs oral). A 2016 systematic review of these approaches in paediatric patients with low-risk FN found that reduced intensity therapies were safe with low rates of treatment failure.[73] An implementation study from Australia similarly showed a significant reduction in hospital length (from 4.0 to 1.5 days) with low readmission rates (13%) and no adverse outcomes in patients managed on a formal low-risk FN program.[78] This program is being scaled nationwide and has been adapted for use in the UK. Beyond safety, home-based FN care has been shown to improve quality of life, and reduce healthcare costs, which have been estimated at between US $5600 and $11,700 per episode of FN, depending on the regimes used for comparison and the country in which the research was performed.[79–81]

Current Best Practice and Future Directions in FN

Whilst the above evidence review shows that there are still acceptable variations in practice owing to a number of unanswered questions about FN management, there is broad agreement on the key considerations in FN care. Local centres should have policies and care pathways for FN management that cover the features included in Box 1 and Figure 1. Box 2 shows areas for further research in paediatric FN.

Implementing the findings of research in this area has met challenges in terms of effecting change in healthcare provision. Within the UK, repeated national audits of paediatric FN management have found slow changes in practice, despite clear national guidelines. Some of these issues may relate to previous healthcare professional experiences and approaches to risk stratification.[82] However, our experiences of the recent COVID-19 pandemic have highlighted the ability to effect rapid implementation of new practices within FN management, based on previous research.[83] Thus, future research may focus also on the key aspects of implementation science in this area.

Conclusion

Although the importance of recognition and careful management of FN has long been known, modern best practice demands prompt recognition, early treatment according to risk stratified pathways and attention to the choice of empiric antibiotics, role of oral as well as intravenous

Box 1 Key Features of FN Policies and Guidelines

- Definitions of FN
- Early recognition of FN
- Routine investigations for suspected FN including peripheral blood cultures even if central venous access device present
- Rapid administration of broad-spectrum antibiotics
- Recommended empirical antibiotic regimes
- Risk stratification with defined management pathways for
  - Low-risk episodes of care
  - High-risk episodes of care
- Guidelines on treatment modification including investigation and initiation of antifungal therapy
- Guidelines on duration of treatment by risk group

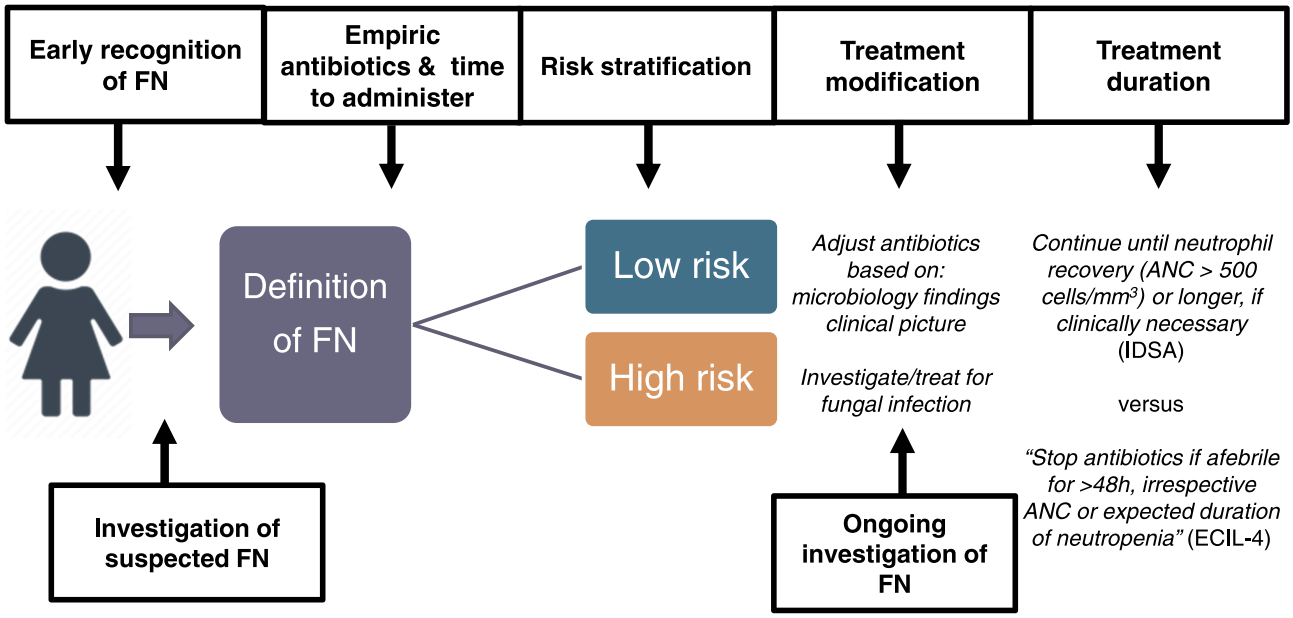

Figure 1 Paediatric FN patient pathway and opportunities for intervention and optimisation.[74,75]

antibiotics, place of care and duration of treatment in order to give optimal treatment to high-risk patients whilst reducing hospital stay where possible and exercising good AMS for all patients. Future research will be important to close current gaps in knowledge to further refine current treatment protocols and optimise ways of effecting

Box 2 Research Gaps in Paediatric FN[9,10]

- **Optimal definition of fever and neutropenia**
- **Routine investigations for suspected FN**
  - Incremental value of a peripheral blood culture in addition to CVC cultures of adequate volume in children with FN
  - Utility of new serum biomarkers in children with FN
  - Impact of novel biomarkers or point of care tests on antimicrobial selection and duration, including role of PCR for respiratory viruses
- **Rapid administration of broad-spectrum antibiotics**, including optimal TTA
  - Which patients with FN will benefit from antibiotic administration within 1 hr
- **Recommended empirical antibiotic regimes**
  - Optimal empirical antibiotics in low-risk FN
- **Risk stratification and care pathways**
  - Developing a validated high-risk stratification schema for paediatric FN
  - Implementation and impact (clinical, economic and QoL) of risk stratification pathways
  - Optimal type and frequency of re-evaluation for paediatric outpatients with low-risk FN
- **Treatment modification**
  - Optimal frequency of blood culture sampling in persistently febrile paediatric patients with neutropenia who are either clinically stable or unstable
  - Optimal investigation and treatment for viral and fungal infections in children with FN
  - Safety and efficacy of short course antibiotics in children with high-risk FN
  - Safety and efficacy of targeted therapy for documented clinical infection
  - Should diagnostic and therapeutic approaches differ for prolonged continuous fever vs recurrent fever during FN

Optimal duration of antibiotic therapy
- Optimal treatment duration for microbiologically documented sterile site infections during FN
- Guidelines on duration of treatment by risk group
- Cost-effectiveness of different approaches to managing paediatric FN

adoption of such improvements. It remains to be seen whether rapid diagnostic PCR-based techniques will be able to revolutionise pathogen detection, antibiotic selection and antimicrobial stewardship.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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