

Management of the febrile neutropenic cancer patient: lessons from 40 years of study

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ABSTRACT

Almost forty years ago the relationship between the circulating neutrophil count and the risk of pyogenic infection was established. Since that time, through the vehicle of clinical trials, much has been learnt about the etiologies, risk factors, pathogenesis, and natural history of first and subsequent febrile neutropenic episodes. Refinements to the empirical antibacterial management has reduced infection-related mortality to less than 10 percent. Algorithmic approaches to persistent fever in the setting of severe neutropenia have been developed. Circumstances wherein preventative strategies are most efficacious have been defined. Clinicians have learned that neutropenic patients comprise a heterogeneous population that does not encounter the same risks for infection-related morbidity and mortality. Tailored stratified approaches to management of the febrile neutropenic patient have been developed that are safe and cost-effective.

Keywords: cancer, febrile neutropenic episodes, natural history, neutropenia, pathogenesis, prophylaxis, review, risk factors

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INTRODUCTION

The standard of practice for the management of febrile neutropenic cancer patients includes a rapid clinical evaluation to identify a clinical focus of infection and a pathogen, in-hospital intravenous administration of broad-spectrum antibacterial therapy, and a strategy to monitor the patient for medical complications [1–4]. This approach has been based upon the recognition that such patients with invasive Gram-negative bacillary infection have a very high mortality rate unless treated without delay [5]. However, it is recognised that not all neutropenic patients have the same risks for fever and infection, and not all febrile neutropenic episodes have the same mortality and morbidity. A better understanding of the pathogenesis of infection in neutropenic patients has permitted investigators to develop more rational approaches to this heterogeneous problem.

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A SHORT HISTORY OF FEVER IN NEUTROPENIA

Over the last 40 years, much has been learned about infections in neutropenic cancer patients and the management thereof. The seminal work of Bodey *et al.* initially described the relationship between the absolute neutrophil count and the risk for pyogenic infection [6,7]. The importance of prompt initiation of broad-spectrum combination antibacterial therapy with carbenicillin and gentamicin for preventing resistance, broadening the spectrum of antimicrobial activity and potential synergy was described by Schimpff *et al.* in 1971 [8]. These same investigators went on to describe the relationship between mucosal colonisation by nosocomially-acquired bacterial pathogens and invasive infection in patients with acute myeloid leukaemia [9]. The question of the duration of broad-spectrum antibacterial therapy was addressed in a study from the National Cancer Institute, wherein persistently neutropenic recipients initially responsive to empirical antibacterial therapy had a 41% rate of recrudescence unless the antibacterial regimen was continued until

neutrophil recovery [10]. Those same investigators also defined the role for empirical antifungal therapy among persistently febrile neutropenic patients unresponsive to broad-spectrum antibacterial therapy [11]. The value of broad-spectrum aminoglycoside-based combination empirical antibacterial therapy has been recently questioned [12,13]. While the value of neutrophil transfusion therapy has been controversial [14,15], it has shown promise under specified conditions [16]. Haematopoietic growth factors have not been shown to be beneficial in the management of febrile neutropenic patients [17] and are not recommended for this use [18]. Prevention of pyogenic bacterial infections in high-risk patients by the administration of prophylactic oral antimicrobial agents has been widely studied with mixed success, largely related to the changing epidemiology of bacterial infections towards Gram-positive infections and the prevalence of resistance of pathogens targeted by the chemoprophylaxis strategy [19–22]. There has been an increased focus on strategies of prevention [23–25] and management [26,27] of invasive fungal infections based upon standardized definitions [28] in defined groups of high-risk patients. Finally, the ability to stratify febrile neutropenic patients by risk for significant medical complications has allowed for the identification of groups of patients for whom outpatient management strategies are safe and effective [29–31].

PATHOGENESIS OF FEBRILE NEUTROPENIC EPISODES

The timing of the first febrile neutropenic episode in patients receiving a given cycle of cytotoxic therapy is correlated with the nadir of the neutrophil count and with the integumental damage due to the effects of the cytotoxic regimen on the intestinal mucosal epithelium. The median time for onset of the febrile neutropenic episode is day 12 from the first day of the current cycle of cytotoxic therapy [32].

Cytotoxic therapy-induced intestinal epithelial damage is an important component in the pathogenesis of first and subsequent fevers in neutropenic patients [33]. Microorganisms colonising damaged mucosal surface may then undergo translocation and subsequent tissue invasion [9]. Investigators have reported relationships between the administration of cytotoxic agents such as high-dose cytarabine and oral mucositis and

subsequent bloodstream infections due to resident periodontal microflora such as the viridans group streptococci [34]. Sonis *et al.* reported the relationship between the severity of oropharyngeal mucositis, as measured on a standardised scale, and the incidence of febrile events, documented infections, days of hospitalisation and costs in haematopoietic stem cell transplant recipients [35]. The timing of maximal mucositis scores correlates independently with the neutrophil nadir [36–38].

The infections reported in febrile neutropenic patients have been classified as ‘unexplained fevers’ if neither a pathogen nor a focus of infection has been identified, as ‘clinically documented’ if only a clinical focus is identified, and as ‘microbiologically documented’ if both a pathogen and a site of infection are identified [39]. The gastrointestinal tract, in particular the oropharynx and periodontium, is now the most common source of infection identified in febrile neutropenic patients [40]. The bloodstream is the next most common site wherein Gram-positive microorganisms are the pathogens isolated in almost two-thirds of cases [40]. The use of fluoroquinolone-based antibacterial chemoprophylaxis strategies has reduced the risk of Gram-negative infection under the epidemiological circumstances wherein the prevalence of fluoroquinolone resistance among aerobic Gram-negative bacilli is less than 3–5% [19–22]. In decreasing order, the skin (predominantly the indwelling central venous catheter site), lower respiratory tree and urinary tract are the next most common sites of infection.

Cytotoxic therapy-induced myelosuppression and the associated risk of infection vary with the dose-intensity of the chemotherapeutic regimen [41]. Regimens based upon cytarabine plus an anthracycline or high-dose cytarabine administered for remission-induction therapy for acute myeloid leukaemia are typically associated with periods of severe neutropenia (absolute neutrophil count $< 0.5 \times 10^9/L$) lasting 10–14 days or more before recovery of the absolute neutrophil count to $> 0.5 \times 10^9/L$. The risk of opportunistic infection is directly related to the duration of severe neutropenia [42]. In contrast, the expected duration of severe neutropenia among patients receiving cyclophosphamide, doxorubicin, vincristine and prednisone for non-Hodgkin’s lymphoma is only 3–5 days [43]. Seventy to 90 per

cent of patients undergoing remission-induction chemotherapy for acute myeloid leukaemia will experience one or more febrile episodes during the neutropenic period. Up to 98% of patients undergoing high-dose chemotherapy with hematopoietic stem-cell rescue experience febrile neutropenic episodes during the pre-engraftment neutropenic phase [44]. In contrast, in specific circumstances associated with intensive cytotoxic therapy such as non-myeloablative allogeneic haematopoietic stem-cell transplants or administration of cyclophosphamide, doxorubicin, vincristine and prednisone in elderly patients for diffuse large cell lymphoma, the duration of severe neutropenia may be shorter; however, the incidence of febrile neutropenic episodes has remained relatively high, ranging from 35% (Hagen CID 2003) to 45% [44]. In general, the incidence of febrile neutropenic episodes among patients with non-Hodgkin's lymphoma is lower, with reported ranges of 10–20% [41,47–48] and with the greatest risk occurring within the first two cycles of chemotherapy (47). Other factors including age ≥ 65 years, tumour burden, receipt of average relative dose-intensity of chemotherapy of $\geq 85\%$, absolute neutrophil count of $\leq 1.5 \times 10^9/L$ at diagnosis, baseline serum albumin of ≤ 35 grams/L at diagnosis, and the presence of additional medical co-morbidities at baseline have been associated with increased risk for febrile neutropenic episodes among patients receiving cyclophosphamide, doxorubicin, vincristine and prednisone for large B-cell lymphoma [48,49] despite the relatively short duration of severe neutropenia.

STRATIFICATION OF FEBRILE NEUTROPENIC PATIENTS BY RISK

Febrile neutropenic cancer patients form a very heterogeneous population with respect to the risks for complications that require prolonged hospitalisation [50]. Such complications involve the requirement for critical care services, to cope with haemodynamic instability, hypotension, and respiratory insufficiency; symptom control of pain, nausea, vomiting, and diarrhoea; altered mental status and delirium; reduced performance status; haemorrhage requiring blood product transfusion; cardiac dysrhythmia requiring monitoring and treatment; and changes in renal function requiring intervention and treatment

modifications. Factors present at the onset of the febrile neutropenic episode can be identified to assign patients a high- or low-risk probability for these complications [51–55]. Such approaches have been used to identify patients appropriate for oral antibacterial therapy [56–59] administered on an outpatient basis [30,59–66].

The expectation for response, defined by defervescence, varies with the risk group. The median time-to-defervescence for high-risk patients treated with appropriate empirical antibacterial regimens is of the order of 5 days [32,40,67–69]. In contrast, the expected time-to-defervescence among low-risk patients has been of the order of 2–3 days [57,58]. Febrile neutropenic patients who do not promptly defervesce are often targets for inappropriate early regimen modification [70], particularly with glycopeptide antibiotics, the value of which has been recently disputed [71]. The major indications for empirical antibiotic regimen modification before the median expected time-to-defervescence include documented progression of signs and symptoms of infection, the pathogen resistant to the initial empirical regimen, and regimen-related toxicity. Premature modification of the empirical regimen adds potential toxicity and cost to the management plan.

IMPACT OF ANTIBACTERIAL CHEMOPROPHYLAXIS STRATEGIES IN NEUTROPENIC CANCER PATIENTS

Effective antibacterial chemoprophylaxis strategies should reduce the incidence of febrile episodes, reduce the incidence of documented Gram-positive and Gram-negative infections, reduce infection-related mortality, be tolerable, and result in a significant modification of physician prescribing behaviour.

Patients receiving fluoroquinolone-based antibacterial prophylaxis are more likely to develop invasive infection due to Gram-positive bacteria, including coagulase-negative staphylococci and viridans group streptococci [72], unless supplemented by augmented Gram-positive coverage [22,73]. Even without the use of fluoroquinolone-based prophylaxis, the incidence of invasive Gram-positive infections has demonstrably increased [74]. Accordingly, empirical therapy with agents such as piperacillin-tazobactam or

meropenem, which are active against the viridans group streptococci, is appropriate. Addition of glycopeptides should be reserved for patients in whom coagulase-negative staphylococcal bloodstream infections are demonstrated [3,71,75]. Such an approach has not been associated with excess patient morbidity or mortality [71,75].

Arguments against the use of fluoroquinolone-based chemoprophylaxis include selection for Gram-positive infections, the inability in clinical trials to demonstrate clinically significant reductions in the overall incidence of fever or reductions in overall mortality, the risk of selecting for resistant pathogens, the potential for masking documented infections, and promotion of fungal colonisation with possible increase in the risk for invasive fungal infections. In contrast, the arguments favouring prophylaxis include statistically significant reductions in the incidence of fever [20,21], reductions in the incidence of Gram-negative infections [19–21], and the potential for both reducing the need for broad Gram-negative coverage in febrile neutropenic episodes and changing physician prescribing behaviour [32,76,77]. Overall, clinical trials have demonstrated that fluoroquinolone-based antibacterial prophylaxis does consistently reduce the risk of Gram-negative and Gram-positive infections, if supplemented in the latter case. Fluoroquinolone-based prophylaxis does not eliminate fever or the need for empirical antibacterial therapy, nor does it reduce episode-related mortality or modify physician prescribing behaviour, as related to empirical therapy.

The initial treatment of febrile neutropenic episodes in patients receiving fluoroquinolone prophylaxis in an environment with a low prevalence of Gram-negative fluoroquinolone resistance should be according to the current published guidelines [1–4]; however, such patients who continue the fluoroquinolone prophylaxis may be candidates for early discontinuance of Gram-negative coverage in favour of antimicrobial therapy targeting Gram-positive pathogens [33]. This remains an area for further clinical trial-based research.

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