



# RISK STRATIFICATION AND FEBRILE NEUTROPENIA

## The Ottawa experience

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### A complex care challenge

Febrile neutropenia is a common occurrence in cancer patients receiving chemotherapy. Clinical management of these patients is highly variable among different institutions and clinicians. Increasingly, selected patients considered to be at lower risk of life-threatening outcomes are being treated for febrile neutropenia as outpatients, which is beneficial to their quality of life and often offers overall cost savings. At The Ottawa Hospital, an interdisciplinary group has developed a series of patient assessment and management tools to guide the optimal management of cancer patients with febrile neutropenia, including standardized admission orders, an inpatient clinical pathway and outpatient care protocols.

Despite many resources developed over the past several years, the care of the patient with febrile neutropenia remains largely based on subjective clinician choice. The scenario described in the case study opposite is very familiar to those who care for medical oncology patients. This paper outlines the evolution of a model of care developed for patients diagnosed with febrile neutropenia at The Ottawa Hospital, a multicampus 1000-bed teaching hospital.

#### STANDARDIZED ADMISSION ORDERS

In 2003, an interdisciplinary group at The Ottawa Hospital reviewed the antimicrobial management of medical oncology patients presenting with febrile neutropenia. This was prompted by the wide variations in practice observed both within the hospital and at the regional oncology satellite clinics. In an effort to provide standardized, evidence-based care for patients with febrile neutropenia, an interdisciplinary group consisting of nurses, physicians and pharmacists developed a treatment protocol. The protocol was drafted following a review of the literature including recently published guidelines, and took into consideration the institution's drug formulary and local bacterial resistance patterns. The final protocol included risk-stratification criteria for the febrile neutropenic patient to direct choice of antibiotics (Table 1, page 45), a treatment algorithm for the initial antibiotic selection (Figure 1, page 46) and an algorithm outlining when to alter therapy and treatment duration. Finally, these treatment recommendations were incorporated into a preprinted standardized admission order form (available from the authors) to ensure consistent care for patients admitted to the medical oncology unit.

#### MEDICAL ONCOLOGY INPATIENTS

In an effort to build on the initial care outlined above, a clinical pathway for patients with febrile neutropenia was

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then developed and implemented in our medical oncology inpatient unit (available from the authors). The impetus arose from the need for timely procurement of blood work, prompt initiation of antibiotic therapy and the streamlining of care for this patient population. It was felt that medical oncology patients were better suited to a standardized care plan than the higher-risk hematology-oncology population.

A clinical pathway specifies the care that will be given and the outcomes expected within a specified time frame for the usual client within a given diagnosis. Clinical pathways identify and describe clinical standards implemented to provide high-quality patient care. At The Ottawa Hospital, clinical pathways are interdisciplinary and describe all routine interventions for the client. Because they are an integral part of the clinical record, documentation made on the pathway does not need to be repeated elsewhere in the patient chart. Problems or deviations from the standard, known as variances, are documented in the interdisciplinary progress notes. Clinical pathways generally contain the clinical pathway, a preprinted physician order sheet and a patient education booklet.

The key to success in the implementation of any clinical pathway is interdisciplinary input and collaboration. Although this may slow the process of creating the pathway, it ensures acceptance by all groups and facilitates implementation of the project. The febrile neutropenia pathway development team included a medical oncologist, a general practitioner in oncology (GPO) with a specialty in infectious disease, a pharmacist, clinical nurses, the medical oncology liaison nurse, a nurse educator, an Advanced Practice Nurse (APN), the inpatient unit manager, the corporate clinical pathways coordinator and a representative from the health records department. Further, the Head of Medical Oncology supported the project. Members of the pathway team kept all stakeholders up to date on project development.

Much time and effort was required to develop this pathway and the team faced many challenges including human resource issues, project leadership transitions, minimal experience in the development of complex medical pathways (although the institution has implemented many surgical pathways) and education. The entire process spanned 2 full years. Completion was facilitated by the guidance of a corporate coordinator for clinical pathways, the assistance of a dedicated oncology nurse in the Late Career Initiative program funded by the Ministry of Health and Long-Term Care, and the new unit manager's decision to make the pathway a clinical priority. Implementation and evaluation was assigned to the oncology nurse in the Late Career Initiative program. Interdisciplinary education occurred either in group settings or individually, on the inpatient unit and in the emergency department. In addition, a febrile neutropenia poster was available on the inpatient unit for reference. Feedback and recommendations were incorporated throughout this process. The education and implementation process took approximately 3 months during the summer of 2006.

## OUTPATIENT TREATMENT

Although many guidelines have been developed to assist care providers to risk-stratify their patients and select initial

## Case study

Mrs. A, a 48-year-old female, was diagnosed with node-positive breast cancer in the spring of 2006. Since then, she has received 3 cycles of AC (doxorubicin and cyclophosphamide) chemotherapy, with the last cycle initiated 13 days ago. She has tolerated therapy very well with only a few minor complications. On day 13 she presented for blood work and assessment with a 1-day history of high fever (40° C), clear respiratory secretions, mucositis and chills with rigours. A family member at home was experiencing similar respiratory symptoms. Her physical exam was unremarkable except for heart rate of 120 beats per minute and blood pressure of 100/75 mm Hg. No localizing symptoms of infection were identified. Her central line was intact. Blood work on admission revealed a white blood count of  $0.1 \times 10^9/L$ , hemoglobin 94 g/L, platelets  $10 \times 10^9/L$ , sodium 129 mmol/L and potassium 2.9 mmol/L. Indices of liver function and renal function were normal.

### Course in hospital

Blood cultures drawn on the day of admission grew viridans group streptococcus in 3/3 bottles. Mrs. A was treated empirically with intravenous (IV) combined piperacillin + tazobactam 3.375 g q 6 h, vancomycin 1 g q 12 h, and normal saline at 100 cc/h. She responded well to this therapy and her condition improved gradually over the course of 3–4 days. Her chest x-ray was normal and an influenza swab was negative. She experienced some diarrhea (negative for *Clostridium difficile* toxin) that resolved prior to discharge. Subsequent blood cultures were negative for growth. An echocardiogram was negative for valvular vegetations. Mrs. A experienced some renal wasting (loss) of potassium and phosphate, and slight fluid overload. She had an exacerbation of asthma, which was managed with oxygen and salbutamol inhalations with good results.

therapies, it has become obvious that patients experiencing febrile neutropenia induced by chemotherapy do not constitute a homogeneous group.<sup>1</sup>

One of the limitations of existing tools is that they are heavily weighted toward patients being treated for solid tumours, a group in which the proportion of low-risk patients is greater. In hematologic malignancies, a substantial number of patients fall into a higher-risk group. Leukemia and Stage III–IV lymphoma patients, patients receiving

escalated doses of chemotherapy, and patients undergoing hematopoietic stem cell transplantation are all at a higher risk for complications.<sup>2,3</sup> National guidelines illustrate the issues and controversies associated with the management of fever: each institution resolves these based on identification of the most probable pathogen given the underlying malignancy, the nature of the treatment, the degree and duration of immunosuppression, the type of immune deficit and the clinician's knowledge of the predominant pathogens at the hospital where the patient receives care.<sup>4,5</sup>

Historically, gram-negative bacilli arising from the gastrointestinal tract have been the prominent pathogens in neutropenic hosts. *Escherichia coli*, *Klebsiella* species and *Pseudomonas aeruginosa* accounted for the majority of microbiologically documented infections. Gram-negative bacteremia is associated with high mortality rates if left untreated or treated inappropriately. Mortality rates greater than 50% within 48 hours have been reported. The pattern has changed over the years, however, with the proportion of gram-positive organisms increasing from 62% in 1995 to 76% in 2000.<sup>6</sup> The majority of these infections are coagulase-negative staphylococci, which have limited virulence. The reasons for this shift are debatable, but identifiable causes include the routine use of central venous access devices, widespread fluoroquinolone prophylaxis, and the administration of high-dose cytarabine-containing chemotherapeutic regimens in patients with hematologic malignancies.<sup>7</sup> Fewer virulent pathogens combined with advances in antibiotic therapies has made the outpatient treatment of patients with febrile neutropenia a viable option.

In the majority of patients classified as low-risk, outpatient treatment also affords opportunities to reduce the cost of care by avoiding hospitalizations or decreasing the length of hospital stays.<sup>8</sup> Success in this patient population, combined with ever-increasing pressure on inpatient bed utilization, has increased the temptation to administer outpatient therapy to a larger group that may be assessed by clinicians as having "clinically stable" febrile neutropenia — where strategies have been developed to maximize patient safety, deliver appropriate antibiotic care and reduce inpatient stays. Careful selection of patients with low probability of developing complications is required. Selection criteria include:

- ability to receive appropriate therapy
- feasibility of daily monitoring
- clinical stability, i.e. normotensive; controlled nausea, pain and diarrhea; adequate oral intake
- access to prompt medical attention
- duration of neutropenia < 10 days
- presence of a caregiver 24/7
- no significant comorbidities

Institutional attributes considered necessary to ensure safe delivery of outpatient antimicrobial therapy include:

- ability to perform full clinical evaluation, e.g. 24-hour availability of appropriate medical, nursing, pharmacy and laboratory staff
- rapid turnaround time for laboratory and diagnostic tests
- capacity to admit patients
- availability of a clinical team to monitor therapy response and react quickly and appropriately

**TABLE 1. Patient risk stratification criteria**

**Inclusion criteria for oral antibiotic therapy**

Patients with the following characteristics have been identified as being at low risk of complications and mortality, and may qualify for initial treatment with oral antibiotic therapy:

- outpatient presentation
- no clinical evidence of any specific infection (e.g. normal CXR, no catheter site infection/inflammation)
- no signs or symptoms of systemic infection (e.g. hypotension, rigours, respiratory insufficiency, dehydration) other than fever
- no significant comorbid illness (e.g. COPD, liver or renal dysfunction, diabetes)
- absolute neutrophil count (ANC) > 100 cells/mm<sup>3</sup>
- recovery of neutrophils is expected within 7–10 days
- peak temperature < 39°C
- no neurologic or mental status changes
- respiratory rate < 24/minute
- no nausea, vomiting, diarrhea or severe mucositis
- ECOG performance status of 0 or 1

**Exclusion criteria for oral antibiotic therapy**

In addition, patients with the following characteristics are excluded from consideration of treatment with oral antibiotics:

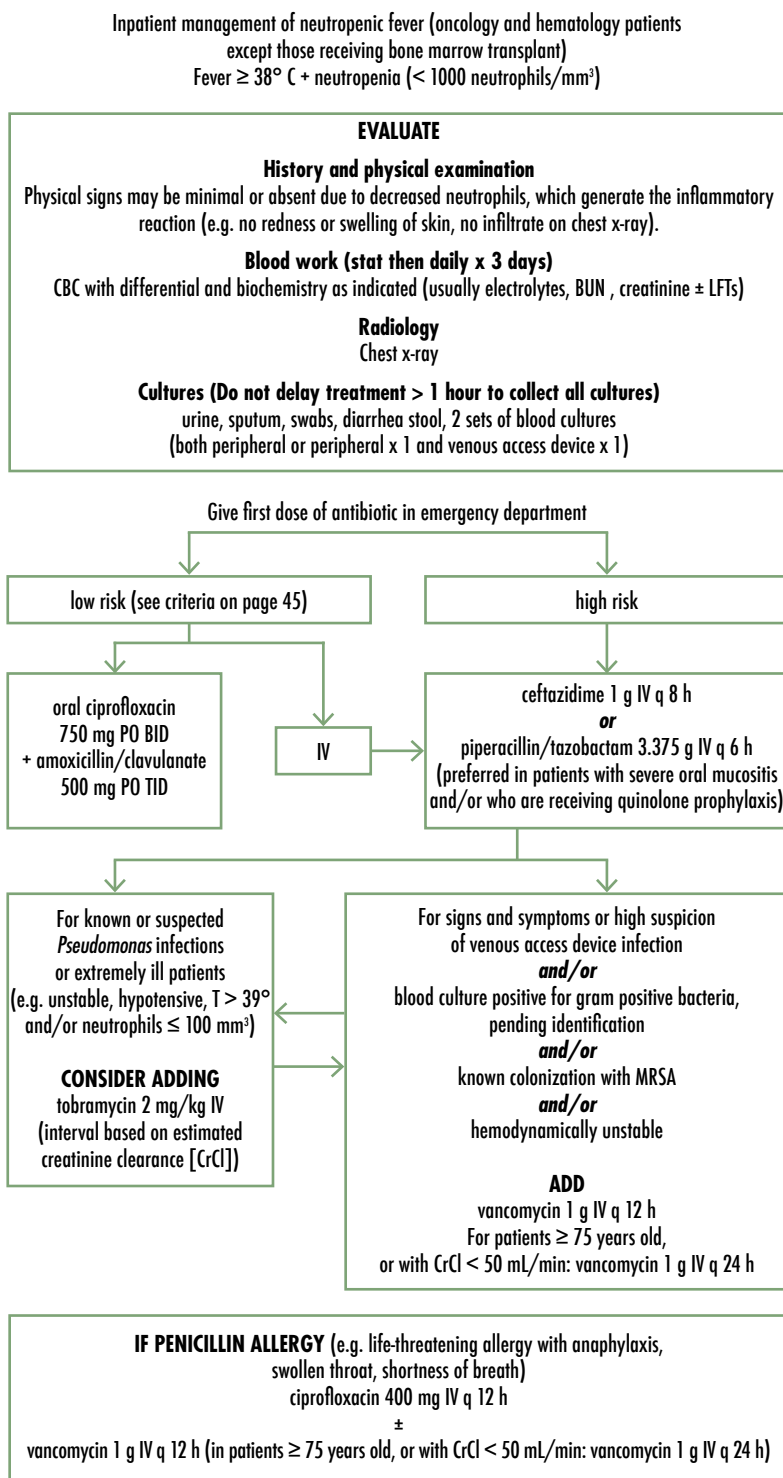
- malignancy "uncontrolled"
- receiving allogeneic bone marrow transplant
- requiring acute hospital care for reasons other than fever/neutropenia, e.g. pain control, dehydration
- have received antibiotics (IV or PO) within the past 7 days
- allergic to penicillins or fluoroquinolones
- receiving concomitant therapy with agents likely to complicate oral antibiotic therapy, e.g. antacids, sucralfate, iron, theophylline, allopurinol

**Additional criteria for outpatient oral therapy**

The following additional criteria determine eligibility for outpatient treatment with oral antibiotics, although the safety of oral therapy to treat febrile neutropenic patients on an outpatient basis has not been validated or confirmed by a large randomized study:

- solid tumour (i.e. not hematologic)
- patient is considered to be reliable and capable of understanding and following the requirements of outpatient treatment
- patient has prompt access to medical care
- 24-hour observation by a reliable caregiver is possible

**FIGURE 1. Febrile neutropenia treatment algorithm**




All of these antibiotics need a dose and/or interval adjustment in patients with impaired renal function. CrCl must be calculated.

- availability of clearly-written patient education materials with self-monitoring instructions, healthcare provider contact information, and followup instructions reviewed with and given to patients prior to the initiation of outpatient antimicrobial administration.<sup>9</sup>

## Antimicrobial therapy

While debate continues over the use of antibiotic prophylaxis, the combination of antibiotics to be administered and the route of administration, it is widely agreed that prompt initiation of adequate antimicrobial therapy is the gold standard. Although 85% to 90% of all documented infections that develop in febrile neutropenic hosts are bacterial, in 30% to 40% of patients no source of infection is identified, despite the fact that 95% respond and defervesce with antibiotic therapy. Monotherapy with the newer broad-spectrum antimicrobials has tended to replace classic combination therapies. When the use of oral fluoroquinolones is not appropriate or clinically indicated, outpatient IV administration of antimicrobial agents has been successful.<sup>2</sup> The ideal antibiotic for outpatient administration should be efficacious, well tolerated, easy to administer and inexpensive. The development of antibiotics with prolonged half-lives, allowing once-daily administration, has been useful. Ceftriaxone, a third-generation cephalosporin, has extended spectrum and bactericidal activity against many gram-negative bacteria as well as significant gram-positive coverage. In adults with non-central nervous system infections, a 1-gram dose given IV once daily is recommended.

## FUTURE DIRECTIONS

Despite what we know about the care of patients with febrile neutropenia, many questions remain unanswered. Cancer Care Ontario's Advanced Practice Nursing Community of Practice is initiating preliminary exploration towards developing an interdisciplinary Clinical Practice Guideline to address some of the key questions identified in Table 2. Provincial interdisciplinary collaborations facilitate access to evidence-based guidelines and standards of practice for all cancer care providers. 

**TABLE 2. Research questions for proposed febrile neutropenia clinical practice guideline\***

General topics	Specific issues
What patients are at risk for developing febrile neutropenia?	<ul style="list-style-type: none"> <li>• risk stratification criteria</li> </ul>
What measures can be implemented to modify patient risk?	<ul style="list-style-type: none"> <li>• pharmacologic modification, e.g. role of prophylactic growth factors</li> <li>• nonpharmacologic modification, e.g. diet, environmental</li> </ul>
Models of care: how and where should patients with febrile neutropenia be cared for?	<ul style="list-style-type: none"> <li>• who should provide care, e.g. oncologist, GPO, APN, etc.</li> <li>• how care should be provided, e.g. standing orders, clinical pathways etc.</li> <li>• where should care be provided, e.g. inpatient setting, outpatient setting</li> </ul>
What are the criteria for patient education?	<ul style="list-style-type: none"> <li>• minimizing risk and prevention</li> <li>• what to do and when to do it</li> <li>• where to go</li> </ul>

\* Interested readers with comments or suggestions are invited to respond directly to Gail Macartney (see address for correspondence on page 43) or to Esther Green, Provincial Head Nursing and Psychosocial Oncology, Cancer Care Ontario, 620 University Avenue, Toronto, ON M5G 2L7; Tel: 416-217-1278; Fax: 416-217-1281; Email: esther.green@cancercare.on.ca

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