

Ambulatory Outpatient Management of patients with low risk febrile neutropaenia

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Abstract

Patients with febrile neutropenia are a heterogeneous group with only a minority developing significant medical complications. Scoring systems, such as the Multinational Association for Supportive Care in Cancer (MASCC) score, have been developed and validated to identify low risk patients.

Caring for patients with low risk febrile neutropenia in an ambulatory setting is proven to be safe and effective. Benefits include admission avoidance, cost savings and reduced risk of nosocomial infections, as well as improved patient experience and satisfaction.

Implementation of an ambulatory pathway for low risk febrile neutropenia provides an excellent opportunity for Acute Physicians and Oncologists to collaborate in delivering care for this group of patients.

Keywords

Neutropenia, fever, sepsis, low risk, ambulatory care, cancer, chemotherapy.

Key points

- Febrile neutropenia is a medical emergency requiring immediate assessment and treatment in a hospital setting
- Patients with febrile neutropenia should be assessed using a validated risk scoring system such as the Multinational Association for Supportive Care in Cancer (MASCC) score
- Patients who are identified as low risk may be suitable for management in an ambulatory setting
- Ambulatory management of patients with febrile neutropaenia requires close collaboration between Acute Physicians, Oncologists and patients, along with systems to ensure immediate access to further medical assessment, when required

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Introduction

Fever in a neutropenic patient is an acute medical emergency. Neutropenic sepsis is a potentially fatal complication of cancer therapies, particularly chemotherapy, and requires immediate evaluation and treatment.¹⁻³

Empirical antibiotic therapy has been the key tenet of management for patients with neutropenia and fever for the last 40 years.⁴ Traditionally, the standard of care for this cohort of patients has been inpatient management until both fever and neutropenia resolved.^{5,6}

Patients with febrile neutropenia are a heterogeneous group with only a minority developing significant medical complications.^{7,8} Scoring systems, such as the Multinational Association for Supportive Care in Cancer (MASCC) score, have been developed and validated to identify low risk patients.⁹ Ambulatory, outpatient management of patients with low risk febrile neutropenia has been shown to be safe and cost-effective.¹⁰ The expansion of ambulatory care in the United Kingdom (UK) driven by Acute Medicine might allow an increase in the number of patients managed in this way.

Case vignette

A 54 year old lady with right breast carcinoma being treated with neoadjuvant AC (Doxorubicin and

Cyclophosphamide) presents to the AMU. She is one week post cycle 2 of her chemotherapy regime. She complains of a productive cough and an episode of fever (38.5°C). She has no other systemic symptoms.

She has no other significant previous medical history. She has never smoked. Her WHO performance status is 1 (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature).

On examination she is comfortable. She is afebrile (36.9°C). Her blood pressure is 120/70 mmHg with a pulse of 80bpm in sinus rhythm. Her respiratory rate is 16, with oxygen saturations of 98% on air. There are no added sounds. The rest of her examination is unremarkable.

She is treated with an empirical dose of intravenous tazocin and intravenous fluids. She receives other standard supportive measures.

Investigations show a WCC (White Cell Count) of $0.7 \times 10^9/L$, with a neutrophil count of $0.3 \times 10^9/L$. Her U&Es are normal. Her chest x-ray shows no focal consolidation.

Defining risk amongst patients with febrile neutropaenia

Assessing and identifying patients who are at high or low risk for the development of severe infection and significant medical complications is important when managing patients with febrile neutropenia. The

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assessment helps inform the decision regarding the route and duration of antibiotic therapy as well as the need for inpatient admission.^{2,4,7,11}

Factors used to discriminate between high and low risk groups include the presenting clinical condition, the underlying malignancy and pre-existing medical co-morbidities.^{2,7,11} Patients are considered to be high-risk if they have significant neutropenia which is predicted to last for more than one week. Patients should also be categorized as high risk, necessitating admission for intravenous antimicrobial therapy, if they have any of the following:

- Haemodynamic instability
- Gastrointestinal disturbances, such as abdominal pain, diarrhoea or vomiting
- Acute neurological symptoms such as delirium
- Respiratory compromise either due to chronic lung disease or acute hypoxia
- Evidence of renal or hepatic insufficiency.

The MASCC Score

The MASCC score (see table 1) is a formal scoring system for assessing and identifying patients at high and low risk of severe infection and complications.^{9,11} The score is calculated using seven criteria associated with improved outcome. Points are accrued for each predictor. The maximum score is 26. High risk patients have a score less than 21 and require inpatient care. Patients with a score of 21 or more have a low risk of significant complications with low rates of bacteraemia.^{7,9,11,12}

In the MASCC validation study 6% of low risk patients developed complications compared with 39% in high risk patients.⁹ A number of subsequent prospective studies have confirmed the score to have high levels of positive predictive value, sensitivity and specificity.^{11,13-17} It is recommended by NICE (The National Institute for health and Care Excellence) and is an excellent tool to help in risk stratifying patients who may be suitable for outpatient ambulatory management.¹⁷ Other scores, such as CISNE (Clinical Index of febrile Stable Neutropenia)¹⁸ and Talcott⁶, have also been designed to risk stratify patients but are not as well validated as the MASCC score whilst also appearing to be weaker predictors.

Outpatient management of patients with low risk febrile neutropenia

Ambulatory care delivers traditional hospital care including treatment and diagnostics. The key feature of ambulatory care is that patients are not admitted and spend the vast majority of time away from hospital. Ambulatory care differs from outpatient care because of its focus on caring for acutely unwell medical patients and facilitating discharge from

Table 1. Multinational Association for Supportive Care in Cancer (MASCC) Risk Score.

Characteristic	Score
Burden of illness (febrile neutropenia)	
No or mild symptoms	5
Moderate symptoms	3
Severe symptoms or moribund	0
No hypotension (Systolic blood pressure >90mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumour or haematological malignancy with no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Outpatient status	3
Age <60 years	2

hospital for patients who would ordinarily stay in hospital. To function successfully, ambulatory care units are staffed by a multidisciplinary team with close links to other acute services, especially the acute medical unit (AMU).

The benefits of ambulatory care are well known to Acute Physicians. They include admission avoidance, cost savings, reduced risk of nosocomial infections as well as improved patient experience and satisfaction.

Caring for patients with low risk febrile neutropenia in an ambulatory setting is proven to be safe and effective.⁹⁻¹² Two meta-analyses have been performed demonstrating the utility of this approach. Cartensen et al., examining 10 studies comparing inpatient and outpatient therapy of febrile neutropenia, did not find any significant difference in mortality or outcome.¹⁹ A further meta-analysis of 14 randomized studies examining outpatient management of low risk febrile neutropenia patients concluded that it was a safe and efficacious strategy in the treatment of this cohort of patients.²⁰

The choice of antibiotics for ambulatory treatment

Intravenous and oral antibiotic regimens have been shown to be equally effective in patients with low risk febrile neutropenia.^{11,12,21} Fluoroquinolones have high oral bioavailability and broad spectrum of activity against gram negative pathogens. A recent multicentre study showed that outpatient fluoroquinolone therapy is safe in low risk patients with equivalence between oral moxifloxacin and combined oral co-amoxiclav and ciprofloxacin.²² Moxifloxacin is currently not suggested in most UK and international guidelines. It is also important to consider local sensitivity and resistance patterns in determining the most appropriate regimen.^{17,23}

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Case Vignette - continued

The patient is diagnosed with neutropenic fever and a lower respiratory tract infection. Her MASCC score is calculated as 26, indicating that she falls into a 'low risk' group. She is observed in hospital for a further 12 hours, during which she remains afebrile; in the absence of any adverse risk factors she is deemed suitable for outpatient management.

She is discharged with oral levofloxacin. Prior to discharge it was confirmed with the patient that she has appropriate Oncology follow up, had the local chemotherapy helpline telephone number and knew the symptoms that should prompt her to seek further medical attention.

Advantages, costs and barriers to Implementation

Ambulatory management of patients with low risk febrile neutropenia has been shown to deliver cost savings.^{10,24} It is essential to ensure that ambulatory outpatient management continues to be safe and does not worsen medical outcomes.

There has been a reticence among Oncologists in the UK to develop ambulatory management pathways for patients with low risk neutropenia.^{25,26} When surveyed, the majority of Oncologists did not risk stratify patients and did not routinely discharge them until the fever and neutropenia had resolved. In part, inpatient care was favoured because the infrastructure to facilitate early discharge was not in place.²⁶

A key component of providing outpatient ambulatory care for low risk neutropenic patients is a clear follow up plan and access to a 24 hour

specialist oncology telephone helpline.^{2,11,17} It is also important that patients feel supported, know the signs and symptoms that should trigger them to seek medical assessment and know when they should return to the hospital.

Improved patient experience is a key driver for the development of ambulatory emergency care in the UK. An Australian survey showed that 75% of cancer patients preferred outpatient antibiotic therapy.²⁷ However, Talcott et al did not demonstrate significantly improved quality of life measures among patients when treated as outpatients.⁶ This may reflect that a proportion of their cohort were on intravenous antibiotics at home, with its inherent constraints, or that the quality of life measures used were not sensitive in the population studied. It may represent the fact that some cancer patients feel safer in hospital with full multi-disciplinary support immediately available.^{6,28}

The challenges of delivering ambulatory care for patients with low risk febrile neutropenia are significant. In one study, only 30% of patients suitable for ambulatory management received it due to logistical challenges such as care packages, transport issues and, in a small number of cases, patient preference.²² With the increased growth of ambulatory care in the UK it is likely that the infrastructure will develop to reduce these barriers.

Conflicts of Interest

None

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References

1. Pizzo PA. Management of fever in patients with cancer and treatment-induced neutropenia. *N Engl J Med* 1993; **328**: 1323-32
2. Cooksley T, Holland M. The febrile patient with neutropenia. *Acute Med* 2012; **11**: 246-50.
3. Kuderer N, Dale D, Crawford J, Cosler L, Lyman G. Mortality, morbidity and cost associated with febrile neutropenia in adult cancer patients. *Cancer* 2006; **106**: 2258-66.
4. Friefeld A, Bow E, Sepkowitz K *et al*. Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2011; **52**: e56-e93.
5. Klastersky J, Paesmans M, Georgala A *et al*. Outpatient oral antibiotics for febrile neutropenic cancer patients using a score predictive for complications. *J Clin Oncol* 2006; **24**: 4129-34.
6. Talcott J, Yeap B, Clark J *et al*. Safety of early discharge for low-risk patients with febrile neutropenia: a multicentre randomized controlled trial. *J Clin Oncol* 2011; **29**: 3977-3988.
7. Paesmans M, Klastersky J, Maertens J *et al*. Predicting febrile neutropenic patients at low risk using the MASCC score: does bacteremia matter? *Support Care Cancer* 2011; **19**: 1001-1008.
8. Lynn J, Chen K, Weng Y, Chiu T. Risk factors associated with complications in patients with chemotherapy-induced febrile neutropenia in emergency department. *Hematol Oncol* 2013; **31**: 189-96.
9. Klastersky J, Paesmans M, Rubenstein E *et al*. The Multinational Association for Supportive Care in Cancer Risk Index: A Multinational Scoring System for Identifying Low-Risk Febrile Neutropenic Cancer Patients. *J Clin Oncol* 2000; **18**: 3038-51.
10. Elting L, Lu C, Escalante C *et al*. Outcomes and cost of outpatient or inpatient management of 712 patients with febrile neutropenia. *J Clin Oncol* 2008; **26**: 606-11.
11. Klastersky J, Paesmans M. The Multinational Association for Supportive Care in Cancer (MASCC) risk score: 10 years of use for identifying low risk neutropenic cancer patients. *Support Care Cancer* 2013; **21**: 1487-95.
12. Klastersky J, Paesmans M, Georgala A *et al*. Outpatient oral antibiotics for febrile neutropenic cancer patients using a score predictive for complications. *J Clin Oncol* 2006; **24**: 4129-34.
13. Uys A, Rapoport B, Anderson R. Febrile neutropenia: a prospective study to validate the Multinational Association of Supportive Care of Cancer (MASCC) risk index score. *Support Care Cancer* 2004; **12**: 555-560.
14. Pun Hui E, Leung K, Poon T *et al*. Prediction of outcome in cancer patients with febrile neutropenia: a prospective validation of the Multinational Association for Supportive Care in Cancer risk index in a Chinese population and comparison with the Talcott model and artificial neural network. *Support Care Cancer* 2011; **19**: 1625-35.
15. Baskaran N, Gan G, Adeeba K. Applying the Multinational Association for Supportive Care in Cancer risk scoring in predicting outcome of febrile neutropenia patients in a cohort of patients. *Ann Hematol* 2008; **87**: 563-9.
16. Cherif H, Johannsson E, Bjorkholm M *et al*. The feasibility of early hospital discharge with oral antimicrobial therapy in low risk patients with febrile neutropenia following chemotherapy for hematologic malignancies. *Haematologica* 2006; **91**: 215-222.
17. NICE Guideline. Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients. September 2012.
18. Carmona-Bayonas A, Jiménez-Fonseca P, Virizuela Echaburu J *et al*. Prediction of serious complications in patients with seemingly stable febrile neutropenia: validation of the Clinical Index of Stable Febrile Neutropenia in a prospective cohort of patients from the FINITE study. *J Clin Oncol* 2015; **33**: 465-71.
19. Carstensen M, Sorensen J. Outpatient management of febrile neutropenia: time to revise present treatment strategy. *J Support Oncol* 2008; **6**: 199-208.
20. Teuffel O, Ethier M, Alibhai S *et al*. Outpatient management of cancer patients with febrile neutropenia: a systematic review and meta-analysis. *Ann Oncol* 2011; **22**: 2358-65.
21. Friefeld A, Marchigiani D, Walsh T *et al*. A double-blind comparison of empirical oral and intravenous antibiotic therapy for low-risk febrile patients with neutropenia during cancer with chemotherapy. *N Engl J Med* 1999; **341**: 305-11.
22. Kern W, Marchetti O, Drgona L *et al*. Oral antibiotics for fever in low-risk neutropenic patients with cancer: A double-blind, randomized, multicentre trial comparing single daily moxifloxacin with twice daily ciprofloxacin plus amoxicillin/clavulanic acid combination therapy – EORTC Infectious Diseases Group trial XV. *J Clin Oncol* 2013; **31**: 1149-56.
23. Lingaratnam S, Thursky K, Slavin M. Fluoroquinolone prophylaxis: a word of caution. *Leuk Lymphoma* 2011; **52**: 5-6.
24. Teuffel O, Amir E, Alibhai S *et al*. Cost-effectiveness of outpatient treatment for febrile neutropenia in adult cancer patients. *Br J Cancer* 2011; **104**: 1377-83.
25. Innes H, Billingham L, Gaunt C *et al*. Management of febrile neutropenia in the United Kingdom: Time for a national trial? *Br J Cancer* 2005; **93**: 1324-28.
26. Ziglam H, Gelly K, Olver W. A survey of the management of neutropenic fever in oncology units in the UK. *Int J Antimicrob Agents* 2007; **29**: 430-33.
27. Teuffel O, Cheng S, Ethier M *et al*. Health-related quality of life anticipated with different management strategies for febrile neutropenia in adult cancer patients. *Support Care Cancer* 2012; **20**: 2755-64.
28. Friefeld A, Sepkowitz K. No Place Like Home? Outpatient management of patients with febrile neutropenia and low risk. *J Clin Oncol* 2011; **29**: 3952-4.