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ORIGINAL ARTICLE

Management of febrile neutropenia in solid tumours and lymphomas using the Multinational Association for Supportive Care in Cancer (MASCC) risk index: feasibility and safety in routine clinical practice

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Abstract
Goals of work Febrile neutropenia (FN) represents a spectrum of severity in which low-risk patients can be defined using the Multinational Association for Supportive Care in Cancer (MASCC) risk index. However, despite publication in 2000, there remains limited published literature to date to support the use of MASCC risk assessment in routine clinical practice and eligibility for early hospital discharge. In this study, we present our experience with the routine use of the MASCC risk index to determine the management of FN in our institution.
Patients and methods Patients treated for solid tumours or lymphomas with low-risk FN (MASCC score ≥21) were eligible for oral antibiotics (ciprofloxacin plus either co-amoxiclav or doxycycline) and for early hospital discharge irrespective of first or subsequent episode. The primary outcome was rate of resolution of FN without serious medical complications (SMC). Secondary outcomes were the "success" of antibiotic therapy without treatment modifications, duration of hospitalisation and rate of readmissions.
Results A total of 100 FN episodes occurring in 83 patients were treated over a 6-month period. Ninety of these episodes were low-risk (90%), of which 75 received oral antibiotics (83.3%) and 3 (3.3%) experienced SMC, and the success rate was 94.5% [95% confidence interval (CI) 89.6–99.3%] in low-risk episodes. The median duration of hospitalisation was 2.5 days (25th centile: 1.0 day; 75th centile: 5.0 days) in low-risk compared to 6.5 days (25th centile: 5.3 days; 75th centile: 9.3 days) in high-risk episodes (p=0.003); 2 days for low-risk episodes treated with oral antibiotics compared to 4 days for low-risk receiving intravenous antibiotics (p=0.015). Positive predictive value for the MASCC index was 96.7% (95% CI 95.0–98.6%).
Conclusion The MASCC risk index is both feasible and safe when used in standard clinical practice to guide the management of FN in patients with solid tumours and lymphomas. Patients predicted to have low risk can be managed safely with oral antibiotics and early hospital discharge.

Keywords MASCC risk index · Low-risk febrile neutropenia · Oral antibiotics

Introduction

Over recent years, there has been a re-assessment of the management of febrile neutropenia (FN), with increasing realisation that the previous "gold-standard" management of in-patient treatment with intravenous broad-spectrum antibiotics until resolution is neither necessary nor appropriate for all patients. This has resulted from the recognition that FN represents a spectrum of severity, with the large majority of patients with FN being at "low-risk" of developing significant medical complications. In turn, it has been demonstrated that, for such patients, alternative treatment strategies including the use of oral antibiotics [2, 4] and early hospital discharge [3] are appropriate.

Implementation of these newer treatment strategies into general clinical usage has been hampered by the lack of an

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agreed definition of low-risk; different investigators use different sets of criteria, some of which may be difficult to assess in clinical settings [1, 9–11, 13]. In 2000, the Multinational Association for Supportive Care in Cancer (MASCC) [5] published a risk index (Table 1) based on more than one thousand patients with FN in 15 participating countries. This index is a weighted scoring system of seven clinical characteristics assessed at presentation with fever and neutropenia. A score of ≥21 was recommended as the threshold for definition of low risk, 7% developing serious medical complications compared to 49% of those scoring <21. The value of this scoring system in the prediction of the development of serious complications has subsequently been validated in both the single-centre [12] and multi-centre settings [8]. However, these publications do not yet support the role of MASCC risk assessment in routine clinical practice and its role in defining patients for oral antibiotics and early hospital discharge. Recently, Klastersky et al. [6] published their single-centre experience of combining a policy of early hospital discharge in low-risk patients receiving oral antibiotics after the first episode of neutropenia. The findings support the feasibility and safety of such a policy, although the eligible group only represented 20.6% of the low-risk febrile episodes analysed.

Here, we present our experience with the routine use of the MASCC risk index to determine patient management in a large UK cancer centre treating solid tumours and lymphomas but not leukaemias. The centre deals with approximately seven thousand new cancer referrals per year. Patients defined by the MASCC score as having low-risk FN (≥21 points) were eligible for treatment with oral antibiotics and for early hospital discharge as previously described [3] and irrespective of first or subsequent episode.

Table 1 MASCC risk-index score

Characteristic	Score
Burden of illness	
No or mild symptoms[a]	5
Moderate symptoms[a]	3
Severe symptoms[a]	0
No hypotension (systolic BP >90 mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumour/lymphoma with no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Outpatient status at onset of fever	3
Age <60 years	2

[a] Points attributed to the variable "burden of illness" are not cumulative. The maximum theoretical score is 26. Patients with a MASCC score index ≥21 are regarded as low-risk and <21 as high-risk

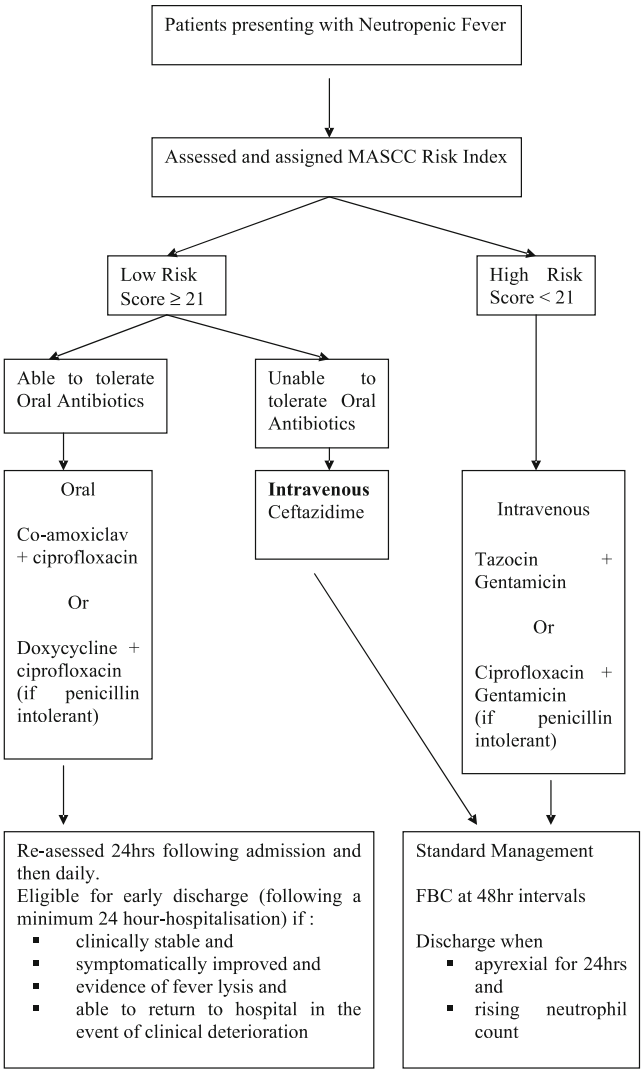

Fig. 1 Flow diagram for the management of neutropenic fever

Patients and methods

In February 2003, we implemented a protocol for the management of all patients presenting with FN, illustrated in Fig. 1. Data on all patients were collected and documented prospectively. FN was defined as a temperature of ≥38.0°C on at least two occasions (or 38.5°C on one occasion), one of which could include the patient's own reading, together with a neutrophil count of $<0.5\times10^9$/L (or $<1.0\times10^9$/L and expected to fall below 0.5×10^9/L within 24 to 48 h). All patients were initially assessed with a history and full physical examination, and whilst they remained in hospital, they were re-assessed at least daily by the consultant-led ward round and as necessary. Standard screening investigations consisted of a full blood count and differential, a biochemical screen and a minimum of one set of peripheral blood cultures in addition to cultures via a central venous catheter if present. Chest radiographs and

other microbiological cultures were performed only where clinically indicated. Patients were assigned "low-risk" or "high-risk" status by the assessing doctor, according to the MASCC scoring system, using a score of ≥21 as the definition of low risk. On the basis of this risk status, the protocol recommended the appropriate first-line antibiotic therapy. However, individual treating clinicians were urged to use their discretion in implementing the protocol in borderline cases, thus maintaining a low threshold for broad-spectrum intravenous antibiotics.

Low-risk patients

Low-risk patients (scoring ≥21) received oral antibiotics with ciprofloxacin plus either co-amoxiclav or doxycycline (in penicillin-allergic/intolerant patients). Those low-risk patients who were unable to tolerate oral medication (e.g. severe mucositis or vomiting) or were already receiving oral antibiotics (including prophylactic antibiotic regimens) were commenced on intravenous ceftazidime according to our previous experience [7]. The addition of vancomycin was recommended for both high- and low-risk patients with suspected central venous line tunnel infections.

All low-risk patients were hospitalised for a minimum of 24 h. Those patients receiving oral antibiotics, who were clinically stable, symptomatically improved and, with evidence of fever lysis, were eligible for discharge, providing they had evidence of good social support and were able to return to the hospital in the event of any clinical deterioration. Such patients were given a supply of antibiotics to complete a 5-day course and oral and written instructions with a 24-h-contact telephone number, emphasising the need for regular monitoring of temperature (three times a day) and early reporting of any deterioration in symptoms. Patients were not required to routinely attend the centre for further assessment unless clinically indicated. Any patients requiring readmission had their antibiotic regimen altered at the discretion of the treating clinician depending on the indication for readmission. Those low-risk patients receiving oral antibiotics who were not discharged at 24 h were re-assessed daily including their eligibility for discharge as described above.

Low-risk patients receiving intravenous antibiotics were clinically reassessed daily with repeat full blood count and differential at 48-h intervals. Such patients were eligible for discharge when afebrile for 24 h with a rising neutrophil count (irrespective of the absolute value). In all cases, indications for changes in the treatment regimen included persistent fever (temperature ≥38°C for more than 72 h), positive culture results with resistant organisms, or clinical deterioration at the discretion of the treating clinician.

High-risk patients

High-risk patients received combination intravenous antibiotics, either gentamicin plus Tazocin (piperacillin + tazobactam) or gentamicin plus ciprofloxacin for those who were penicillin-allergic/intolerant.

Outcomes

The primary outcome measure was success, defined as fever resolution for seven consecutive days in the absence of serious medical complications and irrespective of antibiotic modifications. Serious medical complications were defined as the development of one or more of the following: death, hypotension, respiratory/renal failure, intensive care admission, confusion or altered mental status, congestive cardiac failure, bleeding requiring transfusions, ECG changes, arrhythmia requiring treatment, development of a fungal infection or an allergic reaction (readmission per se was not considered a serious medical complication). Secondary outcome measures were "success" without antibiotic modification, total duration of hospital admission (including any readmission) and frequency of readmission.

Statistical methods

Descriptive statistics were used to express proportions together with 95% confidence intervals (CI). Statistical significance of the difference between median durations of hospital stay were calculated using two-sample t tests. All reported p values were two-sided and values of less than 0.05 were deemed to be significant. Analyses were done with SPSS version 14.0.

Results

Between February and September 2003, 100 episodes of FN were treated. These occurred in 83 patients (71 patients had 1, 7 had 2 and 5 had 3 episodes of FN). Overall, 90% of episodes were assessed as low-risk and 10% high-risk. Of the 83 first-FN episodes, 89% were low-risk and 11% were high-risk. Of the 17 second or third episodes, 16 were identified as low-risk and only 1 episode was considered high-risk.

Characteristics of patient episodes including underlying diagnoses, patient demographics and risk score are summarised in Table 2. The median age was 54 years (range 19 to 77) with a higher median age in high-risk episodes, 58 compared to 53 years. The majority were females receiving treatment for early or advanced breast cancer. There was a full range of possible risk index scores, although these were unevenly distributed (see Fig. 2). The median neutrophil

Table 2 Characteristics of patient episodes

	Low risk (n=90)	High risk (n=10)
Median age, years (range)	53 (19–77)	58 (33–75)
Gender		
Male, number (%)	20 (22.2%)	2 (20%)
Female, number (%)	70 (77.8%)	8 (80%)
Median ANC at hospital admission $\times 10^9$/l (range)	0.10 (0.00–0.90)	0.07 (0.00–0.60)
Median MASCC score index (range)	24 (21–26)	18 (16–20)
Tumour types, number (%)		
Solid tumours	85 (94%)	9 (90%)
Breast carcinoma	44 (49%)	4 (40%)
Lung carcinoma	11 (12%)	1 (10%)
Sarcomas	8 (9%)	1 (10%)
Testicular cancer	6 (7%)	1 (10%)
Endometrial carcinoma	4 (4%)	0 (0%)
Colorectal carcinoma	2 (2%)	0 (0%)
Ovarian carcinoma	2 (2%)	0 (0%)
Pancreatic carcinoma	2 (2%)	0 (0%)
Other	6 (7%)	2 (20%)
Haematologic malignancies	5 (6%)	1 (10%)
Non-Hodgkin's lymphoma	5 (6%)	1 (10%)

count on admission was 0.1×10^9/l (range 0.0 to 0.9×10^9/l; 25th centile, 0.04×10^9/l; 75th centile, 0.33×10^9/l).

Low-risk episodes

The clinical outcomes (complications, success rates of empirical antibiotics therapy, duration of hospital admission and re-admission rates) are summarised in Table 3. In 83.3% (95% CI 75.5–91.2%) of low-risk episodes (75 of 90 episodes), patients were commenced on oral antibiotics. Ten of the 75 episodes occurred in patients with a history of penicillin intolerance or allergy, who received doxycycline and ciprofloxacin. In 15 of 90 episodes, patients received intravenous antibiotics from the outset, as a consequence of nausea and/or vomiting (4 cases), oral mucositis (4 cases), pre-admission antibiotic history (3 cases) and central venous line infection (1 case). Three patients received intravenous antibiotics at the assessing doctor's discretion, of these, two had borderline scores of 21 and the third had a severe cellulitis. The intravenous antibiotic regimens were as follows: ceftazidime, 10 episodes; tazocin plus gentamicin, 2 episodes; ceftazidime plus vancomycin, 1 episode; levofloxacin plus gentamicin, 1 episode, and teicoplanin plus ciprofloxacin, 1 episode.

Overall, 85 episodes resolved without complication or need for readmission, resulting in a success rate in low-risk patients of 94.5% (95% CI 89.6–99.3%). Eighty-seven (96.6%, 95% CI 93.0–100.0%) of low-risk episodes resolved without any serious medical complications. Two patients developed serious medical complications before the episode resolved and one patient died during readmission from progressive malignancy. One of these patients (MASCC score 24) developed an episode of atrial fibrillation with a rapid ventricular response rate within 24 h of admission. The patient was treated with digoxin and spontaneously cardioverted 1 day later. The episode of neutropenia resolved on oral antibiotics without further complication. The second patient was admitted after two previous episodes of FN that occurred despite granulocyte-colony stimulating factor prophylaxis. The admission MASCC score was 21 and the patient received intravenous ceftazidime because of vomiting. Within 48 h of admission, the patient's condition deteriorated rapidly, with development of acute abdominal pain and peritonism. The patient subsequently underwent subtotal colectomy for a perforation of the colon secondary to pseudomembranous colitis. After a protracted in-patient stay, the patient made a full recovery.

The success rate without modification of the empirical therapy in patients with low-risk FN was 77% (95% CI 68.0%–86.0%), 75% for those initially receiving co-amoxiclav plus ciprofloxacin, 80% for those receiving ciprofloxacin and doxycycline and 80% for those receiving intravenous antibiotics. Three low-risk patients (3.3%) required re-admission to hospital. One patient was re-admitted 5 days after discharge with hepatorenal failure secondary to progressive metastatic breast cancer despite resolution of the FN episode. The patient died on the sixth day after re-admission. The other two patients required re-admission due to recurrent fever within 7 days of discharge. The first patient with a MASCC score of 22 at initial admission failed first-line oral co-amoxiclav and ciprofloxacin as a result of persistent fever. The second patient (MASCC score 26) was discharged on a course of oral antibiotics 24 h after admission and had been afebrile for 12 h. Both patients were re-admitted within 48 h after discharge with recurrent fever. On both occasions, the patients were clinically stable and the episodes resolved on antibiotics treatments without further complications.

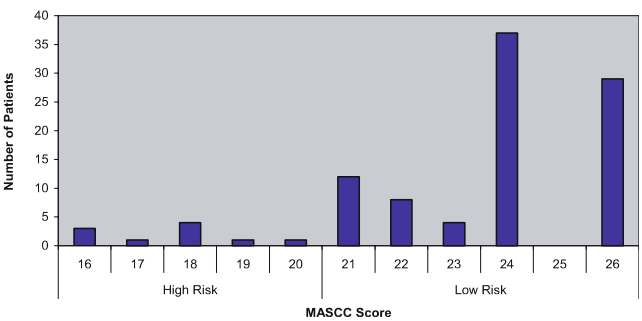

Fig. 2 Distribution of MASCC score. A MASCC score of ≥21 is regarded as low-risk and <21 as high-risk

High-risk episodes

The success rate without antibiotic modification was 60%. Of the 10 high-risk episodes, 2 (20%) developed significant medical complications (Table 3). One patient with MASCC score 16 died on day 1 of overwhelming sepsis. The second patient (MASCC score 16) developed hypotension and acute renal failure. The patient made a full recovery after a protracted in-patient stay.

MASCC score prediction and stay length

Overall, the sensitivity of the MASCC score in predicting patient outcome was 91.6% (95% CI 90.0–93.4%), with specificity of 40.0% (95% CI 12.2–75.2%), positive predictive value 96.7% (95% CI 95.0–98.6%) and negative predictive value 20.0% (95% CI 6.1–37.6%). The median stay length for patients with low-risk FN was 2.5 days (25th centile, 1.0 day; 75th centile, 5.0 days) compared to 6.5 days (25th centile, 5.3 days; 75th centile, 9.3 days) for patients with high-risk FN ($p=0.003$). For patients with low-risk FN initially treated with oral antibiotics, the median duration of fever and median stay was 36 h and 2 days (25th centile, 1.0 day; 75th centile, 4.0 days), respectively (2 days for those receiving oral co-amoxiclav plus ciprofloxacin and 2.5 days for ciprofloxacin plus doxycycline) compared to 4.0 days (25th centile, 2.3 days; 75th centile, 5.0 days) for those initially receiving intravenous antibiotics ($p=0.015$).

Of the 90 patients with low-risk episodes, 44 (48.9%) were discharged at ≤48 h; 3 of the 15 (20.0%) episodes commenced on intravenous antibiotics and 41 of the 75 (54.7%) episodes commenced on oral antibiotics. The reasons for hospital stay beyond 48 h in the 75 low-risk episodes commenced on oral antibiotics were as follows: 18 required treatment change due to persistent fever or becoming unable to tolerate oral antibiotics, 12 with persistent fever not requiring treatment modifications, blood transfusion delaying discharge in 1 episode, subjective reluctance of the clinician in 2 episodes and 1 episode of serious medical complication with atrial fibrillation with full recovery as discussed earlier.

Table 3 Clinical course and outcome of low- and high-risk episodes

	Low risk ($n=90$)	High risk ($n=10$)
Resolution		
Without serious medical complications	87 (96.6%)	8 (80%)
With serious medical complications	3[a] (3.3%)	1 (10%)
Death before resolution	0 (0%)	1 (10%)
Number of readmissions	3[a] (3.3%)	0 (0%)
Response to empiric antibiotic (without modification)		
Success	69 (76.7%)	6 (60%)
Failure	21	
Co-amoxiclav/ciprofloxacin ($n=65$)		
Success	49 (75.4%)	
Failure	16	
Doxycycline/ciprofloxacin ($n=10$)		
Success	8 (80%)	
Failure	2	
Intravenous antibiotics ($n=15$)		
Success	12 (80%)	
Failure	3	
Median duration of hospital admission, days (range)	2.5 (0.5–12)	6.5 (0.3–11)
Oral antibiotics		
Co-amoxiclav/ciprofloxacin	2 (0.5–10)	
Doxycycline/ciprofloxacin	2.5 (0.5–8)	
Intravenous antibiotics	4.5 (1.5–12)	

[a] One patient was readmitted with serious medical complications

Second and third FN episodes

A total of 17 episodes of FN occurred as second or third events. Sixteen of these episodes were considered low-risk, and the serious complication rate was 6% (1/16 cases). This patient is described above with an episode of pseudomembranous colitis occurring during the third FN episode. Of the 16 low-risk patients, 14 were managed with oral antibiotics with a success of 85.7% without antibiotic modification (12 of 14 episodes). Two patients received initial intravenous antibiotics with a success of 50% without modification. No low-risk patients were readmitted for complications or persistent fever.

Discussion

In this study we present our experience from a large UK cancer centre of using the MASCC risk-index to determine the management of FN in patients with solid tumours and lymphomas. Patients with low-risk FN were routinely treated with oral antibiotics and were eligible for an early discharge policy after a minimum of 24 h of hospitalisation. We found 90% of all febrile neutropenic episodes in this study to be low-risk. This was somewhat higher than in other studies [5, 6]. This is mainly due to the patient population, because only patients with solid tumours and lymphomas were treated in this centre. It is also possible that some patients who were very unwell with FN may have presented to their local hospitals instead of the cancer centre.

We have found the MASCC index to be highly suitable for initial patient assessment in the routine clinical setting. In particular, its reliance on basic clinical parameters at

initial assessment of a patient with FN allows accurate evaluation by less experienced junior medical staff without a detailed knowledge of specific chemotherapy regimens or predicted neutrophil nadir timing or expected duration of neutropenia. In many clinical settings this is essential, as the initial attending physician may not be familiar with either the patient or the expert management of FN.

We have used the MASCC index to determine not only the primary antibiotic regimen but also potential eligibility for early discharge for those deemed low-risk. Consequently, the most important measure of the value of the MASCC score is its positive predictive value. In this regard it performed excellently with a positive predictive value of 96.7% (i.e. very low likelihood of a patient with a score ≥21 developing serious complications). This is somewhat better than the 91% reported in the validation set of the initial study by Klastersky et al. [5] and reflects the relatively small number of patients developing serious medical complications in the current study. This, in turn, is likely to result from the inclusion of only patients with solid tumours and lymphomas in this study and is consistent with the finding of a better positive predictive value for the MASCC index for solid tumour patients in a recent multi-centre prospective validation of the MASCC index by Paesmans et al. [8].

Our study findings in low-risk episodes are supported by a larger prospective review from the Institut Jules Bordet in Belgium [6] in which low-risk patients were safely discharged on oral antibiotics (median time to discharge of 26 h). The response rate to oral antibiotics was similar in the two studies (80 and 77%). In contrast to our own findings, the proportion of low-risk patients in the Klastersky study who were eligible for oral antibiotics was lower (46.5 vs 83.3%). The difference is mainly due to the higher percentage of patients who had had prior exposure to prophylactic antibiotics in the Klastersky study, which included haematological malignancies. However, the proportion of patients commenced on oral antibiotics who were discharged at ≤48 h was similar in the two studies (44.4 and 54.7%).

Low-risk patients receiving oral therapy had hospital stay length approximately 50% of those receiving initial intravenous antibiotics (median 2.5 vs 4 days). This is consistent with our previous experience [3] and, in part, reflects the additional supportive care needs of patients who are unable to tolerate oral medication, as well as a more stringent discharge eligibility policy that incorporates neutrophil recovery. Overall, of 75 low-risk episodes managed with oral antibiotics, 41 (55%) were discharged at ≤48 h and 16 (21%) were discharged between days 3 and 5.

In contrast to Klastersky's findings [6], success without modification was similar in both oral and intravenous antibiotic low-risk groups, which, once again, reflects the variation in patient population and prophylactic antibiotic usage across the two centres. Only two patients developed serious medical complications directly related to the febrile episode, and in both cases, this occurred in the initial hospitalisation phase. One patient died of progressive malignancy following the successful management of the febrile episode. No patient subsequently deteriorated due to progressive or recurrent sepsis following initial discharge. Thus, the policy of early discharge, when guided by MASCC, appears safe, although caution is required, given the limited patient numbers. The lower serious medical complication rate compared to Klastersky's findings [6] (3.3 vs 5%) can in part be explained by the inclusion of readmission as a definition of complication in the latter publication.

Of interest, 10 of 75 episodes occurred in patients with a history of penicillin intolerance or allergy. Conventionally, such patients have been treated with intravenous antibiotics and, therefore, typically have hospital stay lengths double those of oral antibiotic patients. Guided by local microbiological advice, we have now instituted a policy of oral antibiotics with ciprofloxacin and doxycycline in otherwise low-risk patients. Although largely anecdotal, it is perhaps noteworthy that all patients responded favourably and were successfully managed by our low-risk policy in a manner analogous to that of non-penicillin-allergic patients.

In contrast to Klastersky et al. [6], we present data on all episodes of FN which included 17 episodes of second or third admission. Although the MASCC index has not yet been validated on more than one episode of FN per patient, our preliminary experience suggests that similar risk-directed policies using oral antibiotics and early discharge may be relevant to any episode of FN.

In summary, we have demonstrated that the MASCC score is both feasible and safe when used in standard clinical practice and can inform management strategies in FN. MASCC index-defined low-risk patients can be managed safely with oral antibiotics, and such a strategy can be combined with a policy of early hospital discharge, thus minimising hospital stays and risks of hospital-acquired infection. Taken together, our results and those of Klastersky et al. demonstrate the feasibility of the MASCC index to determine patient management and early hospital discharge within specialist centres and despite different patient populations. However, caution is required in the generalisability of this management strategy to other centres, and consequently, we aim to further evaluate the strategy of MASCC index-driven management and hospital discharge in a forthcoming Cancer Research UK-funded UK national multi-centre randomised prospective clinical trial (the ORANGE trial).

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