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REVIEW ARTICLE

# The Multinational Association for Supportive Care in Cancer (MASCC) risk index score: 10 years of use for identifying low-risk febrile neutropenic cancer patients

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**Abstract** The Multinational Association for Supportive Care in Cancer risk index score developed, through a multinational collaboration, was published in 2000 with the aim to identify patients with chemotherapy-induced febrile neutropenia at low risk of serious medical complication development. It has been endorsed as a reliable tool since 2002 by Infectious Diseases Society of America. Ten years after, we thought worth to review its use, its characteristics in the external validations that occurred after the initial publication and also to review how the recognition of a group of patients at low risk has changed the management of febrile neutropenia. We also raise the issue of identification of high-risk patients that remains a challenge today.

**Keywords** Febrile neutropenia · MASCC score · Low-risk identification

## Febrile neutropenia: the historical perspectives

The importance of infection, as a major cause of morbidity and mortality in chemotherapy-treated neutropenic cancer patients, has been recognized in the early 1960s by Bodey et al. [1]. In many of such patients, fever is actually the only manifestation of an ongoing infection and this observation led to the concept of "febrile neutropenia" (FN). The course of bacterial infection may be fulminant in patients with FN that led to the wide acceptance of "empirical therapy," as proposed by Schimpff et al. [2]. At the same time, Klastersky [3] showed that synergistic combinations of antibiotics were superior to single-drug therapies or non-synergistic regimens in patients with FN.

These observations served as a basis for a paradigm of the management of FN in the 1970s and 1980s: FN in a chemotherapy-treated cancer patient required the prompt in-hospital intravenous administration of a potentially synergistic combination of antibiotics, most often a beta-lactam plus an aminoglycoside [4].

It should be stressed that, at that time, the majority of patients with FN were suffering from acute leukemia and were receiving very aggressive chemotherapy, often responsible for prolonged episodes of severe neutropenia. The development of chemotherapy for solid tumor patients resulted in less severe and prolonged neutropenic episodes and, as a consequence, the clinical picture and the prognosis of FN changed. It was recognized that FN was becoming a heterogeneous syndrome with different outcomes in terms of vital prognosis and severity of various complications which are seen in patients with FN and often require an admission to the intensive care unit (ICU).

Talcott et al. [5] proposed a model to predict individual patients' risk of complications and death during a FN episode. Briefly, patients were considered at low risk if they were outpatients at presentation, exhibit no indication for hospitalization other than FN, and have adequately controlled cancer. Unfortunately, that model, although being reliable for predicting FN patients at low risk of complications, was not effective, in a pilot study published early after validation of the model, for safely selecting low-risk patients for home therapy [6] as 9 patients out of 30 (30 %) needed readmission, five for observation and four for development, at home of a serious medical complication.

Subsequently, various other attempts have been made to predict a low risk of complications in patients with FN, as indicated in Table 1 [7, 8] without generating a consensus.

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**Table 1** Pragmatic exclusion criteria for prediction of a low risk of complications

| Kern et al. [7] | Freifeld et al. [8] |
|---|---|
| Allogeneic transplantation | Hemodynamic instability |
| Renal failure | Abdominal pain |
| Shock | Nausea and/or vomiting |
| Respiratory insufficiency | Diarrhea |
| IV supportive therapy | Neurological or mental changes |
| HIV | Catheter-related infection |
| Catheter-related infection | New pulmonary infiltrates |
| CNS infections | Renal failure |
| Risk of death within 48 h | Liver insufficiency |

In a multinational, multicenter study of more than 1,100 patients with FN, the study section on infection of the Multinational Association for Supportive Care in Cancer (MASCC) demonstrated that certain characteristics, easily identifiable at the onset of FN, could safely predict a low risk of serious medical complications. Using these factors, a simple and easy-to-use MASCC risk index score has been developed (Table 2) and its clinical prediction rule for identification of low-risk patients has been validated [9]. The event "occurrence of a serious medical complication" was precisely defined in the study protocol and can be found in [9]. The MASCC score has been, since 2002, accepted as a standard technique to evaluate the risk of complications in patients with FN by the European Society of Medical Oncology [10] and by Infectious Diseases Society of America (IDSA) [11, 12].

## Recent validations of the MASCC score

In our original study to establish the so-called MASCC score [9], we used a derivation set (756 patients) to identify the predictive factors of complications and a validation set in which a MASCC score value ≥21 identified low-risk patients with a positive predictive value of 91 %, a specificity of 68 %, and a sensitivity of 71 %.

To our knowledge, the first study attempting to externally validate the MASCC score was published by Uys [13]. In that study, the MASCC score had a positive predictive value of 98 % and a negative predictive value of 86 % with both sensitivity and specificity of 95 %. It was concluded that the MASCC score correctly identified patients at low and high risk of complications at presentation with FN.

Subsequently, several validation studies were also published (Table 3). For all the studies, the positive predictive value was above 83 %; when few patients with hematological malignancies were present in the patients population, it was largely above 90 %. This suggests more caution when using the MASCC score in patients suffering from a hematological malignancy. Sensitivity ranges from 59 to 95 % and, in all studies but one, is greater than 75 %. Again, the worst sensitivity is observed in a series with all patients with a hematological malignancy as underlying disease.

Our model clearly represents an improvement over the Talcott's classification since it has a lower misclassification rate (30 vs. 59 %) and a better sensitivity (71 vs. 30 %), with a substantial increase in the rate of patients predicted at low risk of complications (63 vs. 26 %). Another advantage of our model was that we replaced the "uncontrolled cancer" variable, not selected in our multivariate analysis, with measures more specifically associated with the clinical severity of the FN episode rather than with the underlying cancer, such as the burden of illness, hypotension, and dehydration, and the general comorbidity variable was replaced with specific conditions (e.g., obstructive pulmonary disease or age). Comorbidities such as diabetes, cardiac disease, mental confusion, and others, which are relatively uncommon in our series, were not included in our final model; they are probably replaced by the variable "burden of illness." The inclusion of this covariate should be considered as a weakness of the model; indeed, its assessment is certainly associated to some subjectivity. Nevertheless, no other set of covariates could satisfactorily be substituted to it, and it represents, although not completely objective, a strong prognostic factor as performance index is a strong and reproducible prognostic factor of cancer outcome.

One covariate that we expected to predict development of serious complications, i.e., the underlying disease (hematologic malignancy vs. solid tumor) was not included in our model. Nevertheless, the role of the underlying disease probably appears in our model as the interaction between prior fungal infection and underlying cancer; it may be a surrogate marker for refractory or relapsed leukemia and/or prolonged prior episodes of neutropenia.

Although not included in our model, the severity and further duration of neutropenia (duration of neutropenia

**Table 2** MASCC Scoring System

| Characteristic | Weight |
|---|---|
| Burden of illness: no or mild symptoms | 5 |
| No hypotension | 5 |
| No chronic obstructive pulmonary disease | 4 |
| Solid tumor or no previous fungal infection | 4 |
| No dehydration | 3 |
| Burden of illness: moderate symptoms | 3 |
| Outpatient status | 3 |
| Age <60 years | 2 |

Points attributed to the variable "burden of illness" are not cumulative. The maximum theoretical score is therefore 26

**Table 3** Validation studies

| Reference | *N* of episodes | Patients with hematological malignancy (%) | Predicted at low risk (%) | Se (%) | Sp (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| Paesmans [30] | 1,003 | 55 | 72 | 79 | 56 | 88 | 40 |
| Stratum of hematological tumors | 549 | 100 | 70 | 77 | 51 | 84 | 40 |
| Stratum of solid tumor patients | 454 | 0 | 74 | 81 | 64 | 93 | 38 |
| Uys [13] | 80 | 30 | 73 | 95 | 95 | 98 | 86 |
| Cherif [14] | 279 | 100 | 38 | 59 | 87 | 85 | 64 |
| Klastersky [30] | 611 | 43 | 72 | 78 | 54 | 88 | 36 |
| Innes [29] | 100 | 6 | 90 | 92 | 40 | 97 | 20 |
| Baskaran [15] | 116 | 100 | 71 | 93 | 67 | 83 | 85 |
| Hui [16] | 227 | 20 | 70 | 81 | 60 | 86 | 52 |
| Carmona-Bayonas [17][a] | 169 | 0 | ? | 94 | 36 | NA | NA |

The characteristics were calculated for a test aiming to identify low-risk patients and may then differ from the original publications

[a]Selected patients population ("apparently" stable patients). Due to the case–control design of the study, the rate of patients predicted at low risk as well as the negative and positive predictive values is meaningless

which is however unpredictable at onset of FN) might be an important issue, especially for patients with hematological malignancies; actually, there has been some concern about the value of MASCC predictive score in patients with hematological malignancies. However, Cherif et al. found that the MASCC score was a valuable tool for identifying FN patients with hematological malignancies at low risk of complications [14]. This was confirmed [15] in a study showing that the MASCC score was indeed a useful predictor of outcome in patients with FN with underlying hematological malignancies; in that study, other predictors of a favorable outcome were low serum albumin, underlying neoplastic disease (lymphoma vs. leukemia), and duration of neutropenia (≥7 days)—this late factor can however not be part of a predictive model as unknown at the time a patients presents with FN. That study, conducted in a Malaysian patient population, showed that the use of the MASCC score was widely applicable: it predicted the outcome of FN episodes with a positive predictive value of 83 %, a sensitivity of 93 %, and a specificity of 67 %.

Another study from Asia also validated the MASCC score more recently [16] that investigation enrolled prospectively 227 consecutive patients, 20 % of whom had hematological malignancies, and who were classified according to the MASCC score and the Talcott model. The sensitivity, specificity, positive predictive value, and negative predictive value were, respectively 81, 60, 86, and 52 % for MASCC score value ≥21 and 50, 72, 84, and 33 % for the Talcott model. In the low-risk group identified by MASCC score ≥21 (70 % of all patients), 12 % developed complications and 2 % died compared with 43 and 9 %, respectively, in the Talcott model. It was concluded that the MASCC score demonstrated a better overall performance than the Talcott model.

A study from Spain [17], in a review of 861 episodes of FN in outpatients with solid tumors with apparent clinical stability, attempted to study the value of the MASCC score to predict complications (and not low risk, i.e., absence of complications) in this selected patients population. They concluded that the MASCC score was inefficient for that purpose. This is not surprising at all as it was not the objective of the prediction rule using a threshold of 21. If one might try to predict complications, other thresholds need to be considered and prospectively validated. In that series, sensitivity to predict low risk of serious complication development and specificity were in the range of observations from other validation studies (respectively, 94 % for sensitivity and 36 % for specificity). We come back to the problem of high-risk identification later in this review. In that Spanish study, they suggest using a case–control design (matching the patients with complications to two patients without complications + some additional patients due to expected missing data) that ECOG performance status ≥2, chronic bronchitis, chronic heart failure, stomatitis, monocyte count, and stress hyperglycemia are factors associated to complications. However, it is likely that these variables will be difficult to integrate in a predictive model as their prevalence is low and not taken into account due to the case–control design.

Other attempts to improve the MASCC score by incorporating biological variables, namely measurement of various interleukins TNF, procalcitonin, and CRP have not proven to be useful so far, although the use of IL-6, IL-8, and procalcitonin probably warrant further studies [18].

Similarly, the incorporation to the MASCC score of a prediction of bacteremia—provided such a prediction would be reliably possible—does not appear to improve its performance [19].

## Antimicrobial empiric therapy for FN

The optimal antibiotic regimens for empirical management of FN change over time, as resistance of pathogens develops and new drugs enter our therapeutic armamentarium.

Initially, synergistic combinations were recommended; more recently, monotherapy with broad-spectrum agents appears to be as effective [20], although it is still unclear whether some patients, at very high risk of complications, would still not benefit from combination therapy. Moreover, the use of combinations of antibiotics extends the antimicrobial spectrum of empirical therapy, which might be important in the context of emerging widespread resistance in nosocomial pathogens.

A series of recent papers focused on the paradigms for empirical antimicrobial therapy in patients with FN. Interestingly enough, all refer to the MASCC score to stratify empirical therapy according to the risk of complications. As an example, the approach proposed by Kridel et al. [21] selects low-risk and high-risk patients on the basis of the MASCC score and propose oral amoxicillin plus clavulanic acid with ciprofloxacin in the former patients and imipenem, meropenem, piperacillin-ticarcillin, or cefepime for the others; glycopeptide or aminoglycoside addition is considered only on the basis of specific clinical manifestations. This approach has been recommended in several more recent reviews [22–24]. For the low-risk patients however, it has been shown subsequently that oral moxifloxacin was as effective as the combination therapy, making once daily oral therapy feasible in this subset of selected patients [25].

The introduction of a reliable scoring technique, such as the MASC score, to identify low-risk patients who can be treated with simpler (and less expensive) antimicrobial regimens allows the implementation of a critical pathway for the management of FN, which has been shown to decrease all-cause mortality and reduce the length of use of antibiotics [26].

## Early hospital discharge in low-risk FN patients

Outpatient treatment of FN is attractive for many reasons among which potential savings in resources, reduction of the risk of nosocomial infections, and improved quality of life. Outpatient treatment of FN necessarily requires acceptance by reliable patients and their physicians, as well as appropriate and easy surveillance by the medical team. It also requires that the expected risk of complications would be low and, usually, necessitates a brief baseline assessment, with or without hospitalization, to watch for clinical stability and tolerance to the antimicrobial regimen. The antimicrobial coverage can consist of orally administered antibiotics, as already discussed, but may also consist of intravenously administered regimens. This latter option makes home therapy more cumbersome and is probably not necessary, as oral moxifloxacin has been found as active as ceftriaxone for the treatment of low-risk FN patients suitable for early hospital discharge [27].

Innes et al. published a first randomized study comparing a standard inpatient intravenous management with oral antibiotics and early discharge [28]. The latter approach was not inferior in terms of clinical efficacy and resulted in an estimated 50 % cost saving. In that trial, the definition of "low risk" was based on the Talcott definition with additional criteria because of safety concerns, resulting in a stringent definition of "low-risk", thus limiting the eligible patient population. The same group published, afterwards, an open study in 100 patients with solid tumors (94 %) or lymphomas, selected on the basis of the MASCC scoring index [29]. The median duration of hospitalization was 2.5 days and 94 % of these patients treated with oral antibiotics as outpatients had resolution of FN without any complications. More recently, Klastersky et al. examined a similar strategy using the MASCC score to define low risk in 611 consecutive FN patients, seen over 3 years at the Institut Jules Bordet [30]. Patients suitable for oral therapy with combination of amoxicillin–clavulanate plus ciprofloxacin were eligible for discharge after a minimum 24 h observation period. Among 178 such eligible patients, 44 % (79) were discharged within 2 days; no severe complications were observed and only three (4 %) patients required readmission. The main reason for not administering oral antibiotics to otherwise low-risk patients was the concomitant use of antibacterial prophylaxis (71 %); the main reason for prolonged hospitalization in patients eligible for early discharge was persistent fever, need for treatment change, or other medical complications, during the 24-h observation period. In those patients, the rate of severe medical complication was 9 %.

In a similar study, Cherif et al. confirmed the value of the MASCC score for identifying low-risk patients with hematological malignancies, as already mentioned [14]. In that series, all patients were started on intravenous antibiotics as inpatients and were transferred to oral therapy if they remained clinically stable and defervesced. There were only three (5 %) readmissions; the mean hospital stay was 6 days, clearly longer than in the two preceding studies, that included mostly patients with solid tumors. A similar strategy of a prompt step down from intravenous to oral therapy was found not inferior to full inpatient management with intravenous antibiotics in children with FN [31].

A meta-analysis of ten studies comparing inpatient vs. outpatient therapy of FN, by Carstensen and Sorensen [32], did not find any significant difference in mortality or response rate. The readmission rate for the outpatient was 14 % overall, primarily for persistent fever rather than life-threatening complications. That meta-analysis provides a strong evidence that outpatient management of FN, in carefully selected patients, is as safe and effective as standard inpatient therapy.

More recently, Teuffel et al. published another systematic review and meta-analysis of 14 randomized studies about outpatient management of cancer patients with FN [33]. They concluded that outpatient treatment of FN was a safe and efficacious alternative to inpatient management. The same group analyzed the cost-effectiveness of outpatient treatment for FN in adult cancer patients [34]; they concluded that, for such patients, treatment in hospital is more expensive than outpatient strategies. A retrospective study by Elting et al. also concluded that outpatient management of low-risk patients with FN was as safe and effective as in patient management and significantly less costly [35].

Recently, Talcott et al. published the final results of a multicenter randomized controlled trial of the safety of early discharge of predicted low-risk patients with FN (Talcott model) that was initiated 17 years ago and was stopped due to poor accrual more than a decade ago [36, 37]. The study was initially designed to detect an increase from 4 to 8 % in medical complication rate and then revised to detect an increase from 4 to 10 % with a planned sample size of 448 episodes; fairly cumbersome intravenous regimens were used at home. The study was published with 66 episodes randomized in the hospital care arm and 47 episodes in the early discharge arm. Although the study is underpowered, the authors concluded to no evidence of adverse medical consequences of the home arm (9 % complications rate vs. 8 % and a 95 % confidence interval for the difference from −10 to 13 %) and to reduced costs for home therapy. The prediction rule can be considered today as lacking from sensitivity and we also can wonder why the study hypothesis was the inferiority of the experimental arm.

Quite surprising also was the observation that the quality-of-life indices measured in that trial were only marginally in favor of home-based therapy. Actually, the quality-of-life issue of home-based therapy for FN has not been adequately evaluated so far, perhaps because less demanding oral therapy with less hospitalization would be intuitively felt as providing quality-of-life benefits. On the other hand, it is possible that outpatients, undergoing anticancer therapy and having just experienced fever (and perhaps other symptoms related to infection), feel unsafe and neglected when a comprehensive medical surveillance is not provided around-the-clock.

Actually, the preference for the type of treatment (outpatient vs. inpatient) has been evaluated in both adults [38] and children [39]. It was found that a majority of adult patients (75 %) would prefer an outpatient strategy while 55 % of parents preferred hospital-based treatment for children presenting FN, although the outpatient management with oral antibiotics has been found safe in adequately selected children, without infection-related mortality [40]. It is likely that programs for FN management should be designed differently for adults and children, as the attitude of self-respondents and parents respondents can differ considerably [41].

Another important issue is the acceptance of home therapy of FN by the oncologists; a recent review shows that many (80 %) American oncologists are willing to prescribe outpatient oral antibiotics treatment for low-risk FN in a substantial proportion of their patients, but their practice varies considerably and is based on favorable clinical factors [42].

These considerations regarding the subjective perception of home therapy for FN by both the patient and the oncologist may explain why some patients, otherwise eligible for oral therapy as outpatients, are not discharged actually. In our study, among 178 such patients eligible for early discharge from the hospital, 38 (21 %) were kept hospitalized due to subjective reluctance of the responsible physician, the patient's family, or patients refusal [30]; the rate of complete resolution was 96 % in those patients while it was only 79 % in those who were kept hospitalized for persistent fever or a change of therapy.

It can be concluded that—although the outpatient management of low-risk FN patients has been used for many years, namely at the MD Anderson Cancer Center [43]—it is the availability of a reliable tool for predicting safely to those patients with an acceptably low risk of severe complications that allowed such a strategy to be proposed as a new paradigm. In that respect, the MASCC score did play a major role and its use has been widely accepted by institutions different from those who developed it.

Prediction of a low risk of complications and safe discharge on oral antibiotics of patients with FN are different but nonetheless interconnected issues. Instruments like the MASCC score allow the selection of patients at low risk of complications which is a prerequisite for a simplified treatment. Further, some of these patients will benefit from a more simple and less expensive approach, such as outpatient therapy with oral antibiotics, provided a series of prerequisites are fulfilled, such as acceptance by patients and physicians, adequate monitoring, compliance with instructions, and tolerance to the oral regimen.

It is likely that a series of other issues still need to be answered and will require further research (Table 4).

## Prediction and management of the non-low-risk patients

The MASCC score was initially developed to predict FN patients who have a low risk of serious complications; another important issue is to identify patients with very high risk of complications and/or death who might also benefit from therapies adapted to risk. Looking at patients with MASCC score <21 is certainly not a satisfactory solution. In the study of Klastersky et al., the resolution rate was 88 %

**Table 4** Remaining issues about the acceptance of orally administered antibiotics and early discharge for low-risk cancer patients with FN

| |
|---|
| •Predictive factors for discharge |
| •Standardized surveillance system |
| •Education of physician and patient anxiety about safety |
| •Demonstration of a quality-of-life benefit |
| •Applicability to low income countries and rural areas |
| •Definition of the cost-effectiveness |

in 441 patients with a MASCC score ≥21 and was 64 % in 170 patients with a score <21 [30]. In Innes's study, also using the MASCC score to predict the risk of complications during FN, the success rate without antibiotic modification was 60 % in high-risk patients vs. 77 % in low-risk [29]. Therefore, prediction rules using the same threshold at 21 would obviously lack from sensitivity.

In a large study, combining the data from two sequential observational studies carried out by MASCC [44], the authors looked at the possible importance for the MASCC score at the beginning of FN in relation to bacteremia. If the score was <21, the rates of severe medical complications and death were 49 and 19 %, respectively, while the corresponding figures were 18 and 3 % in patients with a MASCC score ≥21. If the score was <15, overall complications (79 %) and mortality (36 %) were much higher, with 15–20 being intermediate in risk (40 and 14 %, respectively). These data suggest that patients with a low MASCC score and bacteremia have a poor prognosis and may require a different therapeutic approach. The prediction of bacteremia itself is notoriously difficult in those FN patients, and, as already mentioned, it would probably not add to the performance of the MASCC score alone [19].

The use of the MASCC score was also recognized by Blot and Nitenberg to predict patients with FN at a high risk of complications; they suggested to improve its performance by repeated calculation of the severity score and by inclusion of number of organ dysfunction, although no practical model was proposed [45].

FN should probably be treated as a medical emergency and the patients should receive antimicrobial therapy promptly if the MASCC score is low; however, this is not always the case. In a recent study, it was found that the compliance with optimum standards of care was poor, as only 9 % of the patients were getting antibiotics within 1 h of presenting to hospital and 53 % only within 1 h of being assessed by a clinician [46]. This was confirmed in a French study, reporting that in cancer patients with FN, the management was often inadequate and that the severity was often under-evaluated especially in the critically ill [47]. Nevertheless, in that study, the MASCC score was helpful for the administration of a predefined "adequate management," which was given to 26/38 (68 %) of high-risk patients. On the other hand, signs of severe infection (severe sepsis or septic shock) were not associated with predefined adequate management; thus, when based on clinical observations only, the severity of the situation was under-evaluated.

As a matter of fact, if most international recommendations insist on the necessity of empiric antimicrobial therapy for FN to be "swiftly" or "prompt" (which would probably mean within 1 h after admission to emergency unit), it is obvious that, in many instances, therapy for FN is much delayed. Sammut et al. reported a median time to initial antibiotic therapy of 157 min and found that there was a strong correlation between the delay of starting therapy and the length of stay [47].

A recent paper stresses the use of an electronic clinical practice guideline which use allowed a decrease in time from triage to first antibiotic by 1 h (3.9 vs. 4.9 h) [48]. Unfortunately, both studies were small; it remains that the time to initiation of effective antimicrobial therapy was recognized as the strongest predictor of outcome in patients with sepsis, pneumonia, and meningitis; these conclusions can probably be extrapolated to FN patients, especially those with a poor prognostic feature. Therefore, it might be essential, for non-low-risk FN patients, selected on the basis of a reliable predictive instrument, like the MASCC score, not to lose a "golden hour" for initiating empirical antimicrobial therapy [49]. Other possibly effective approaches might consist of early admission to ICU, use of broad-spectrum potentially synergistic combinations of antibiotics, administration of G-CSF or granulocytes transfusions, and taking advantage of the novel technologies to prevent and/or treat septic shock.

In a recent study, Ahn et al. confirmed the value of the MASCC score to predict poor outcome in patients with FN [50]; in addition, they found that thrombocytopenia and increased CRP were strongly associated with a poor outcome. Various laboratory markers such as mannose-binding lectin, IL-6, IL-8, and procalcitonin have been used and are probably superior to CRP [51]. However, Uys et al. found that in cancer patients who present with FN, the MASCC score was indeed a useful predictor of outcome, while measurement of procalcitonin, CRP, IL-13, IL-6, IL-8, and IL-10 was of little value [52].

It was also suggested that measurement of serum lactate in FN patients might be a significant prognostic information about the risk of developing septic shock [53, 54]; similarly, electrolytes abnormalities (hypokalemia, hyponatremia, hypomagnesemia) may have a negative impact on the outcome of patients with FN [55].

## Alternatives to the MASCC scoring system

Because the MASCC score was developed in patients, two of three of whom with solid tumors, other systems have been

proposed for patients with hematological malignancies who are often considered to present more serious complications during FN, although this is not confirmed in recent studies [44]. Several such models combining clinical and biological parameters have been proposed [56, 57], but none has been validated so far in prospective studies and no attempts to compare them to the MASCC score have been made.

Even for patients with a low risk of complications, modified MASCC score or different predictive models have been proposed. In one of such attempts [58] adjustment of the MASCC score was made by introducing the notion of "complex infection." In another proposal [59], a new scoring system used clinical factors predictive of bacteremia, although such approaches might benefit from recently developed technological improvements to detect bacteremia, such as the multiplex blood PCR [60] or the detection of a new biomarker for bacteremia, such as pentraxin 3 [61], the issue of predicting bacteremia, as an addition to the predictive value of the MASCC score, remains uncertain, as it has been already said [19].

Recently, a model for prediction of individual risk of neutropenic complications has been proposed by Lyman et al. [62]. The study population consisted of 3,760 patients with solid tumors or lymphoma who were beginning a new chemotherapy at 115 sites throughout USA. A regression model was developed and then validated by using a random split-sample selection process. The model itself is rather cumbersome, as it amalgamates clinical and biological parameters, as well as characteristics of the received chemotherapy, making it difficult to use in a busy emergency department environment. It is unlikely that such complicated models will achieve a wide acceptance by clinicians.

## The risk of FN and the role of G-CSF's

The risk of developing severe neutropenia is clearly related to the type of chemotherapy which the patient has received. This has been recognized in international recommendations for the prediction of the risk of FN [10]. Nonetheless, the prediction of the severity and of the duration of neutropenia, on the basis of the type of chemotherapy received by the patient, remains difficult [62–64]. In spite of these problems, the type of chemotherapy is usually used to primarily assess the risk for developing FN. It is currently recommended to give primary prophylaxis with G-CSF's to patients with a ≥20 % risk of developing FN after chemotherapy [65]. Age is probably an important co-factor to be taken into consideration when deciding which patients should receive G-CSF's and other comorbidities might be important as well, but need further prospective studies.

The use of G-CSF's has dramatically changed our approach to the management of neutropenia and consequently that of FN [66]. Indeed, as shown in a recent meta-analysis, primary prophylaxis with G-CSF's significantly reduces FN incidence in adults undergoing chemotherapy for solid tumors or lymphoma [67]; overall, the relative risk of FN for any G-CSF's prophylaxis versus non-prophylaxis was 0.51 in that study, and, in terms of comparison between G-CSF's, the incidence of FN was significantly lower for pegfilgrastim.

However, the recommendations for the use of G-CSF's are based on economical factors taking into account the balance between the cost of G-CSF's and the expenses related to the treatment of FN; it is usually accepted that a 20 % risk of development of FN (which is not easy to predict, as already mentioned) justifies the administration of primary prophylaxis with G-CSF's. However, most of patients receiving chemotherapy for solid tumors today have a risk of FN <20 %. Nonetheless, when FN strikes, their morbidity and mortality is not different from patients at a higher initial risk of FN [68]. Therefore, it may be asked whether indications for the use of G-CSF's should not be extended [69], with the availability of less expensive biosimilars and the possibility to use of simplified G-CSF's regimens [70]. The broadening of the indications might avoid significant morbidity and mortality from FN, in considerable number of patients.

## Conclusions

The MASCC score has been published in 2000 and has been endorsed by IDSA for use in clinical practice since 10 years. It has been shown as a reliable tool for identifying low-risk patients in several validation studies and to be part of the selection process of patients who can safely be treated at home. However, it is not perfect: especially specificity could be improved in all patients as well as positive predictive value, mainly in patients with hematological tumor. We are still waiting for an improvement of the model and progress might come from the development of models dedicated to patients with hematological tumors or from the integration of biological markers.

Also, careful monitoring of the predictive characteristics of the prediction rule needs to be an ongoing process as patients characteristics, tumor characteristics, anticancer treatments, and management of febrile neutropenia are evolving over time.

As MASCC score specificity is weak at the recommended threshold of 21, a prediction rule targeting high-risk patients remains to be developed and is a challenge for further research in this area.

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