Can Neutropenic Fever Ever Be Low Risk?

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0196-0644/$-see front matter

http://dx.doi.org/10.1016/j.annemergmed.2017.03.068

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[Ann Emerg Med. 2017;69:765-767.]

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ANNALS CASE

While on a typical, busy shift in the emergency department (ED), you are notified by a nurse about a febrile patient. She is currently receiving chemotherapy and has an absolute neutrophil count less than 500 $\times$ $10^3/\mu L$. Finally, a case with an unequivocal plan! We are obviously confident of the traditional management: broad-spectrum antibiotics, source identification, and admission.[1,2]

But what if we told you there was some subtlety in the evaluation of neutropenic fever, some gray area, some evidence that there might be another way? It turns out that these well-appearing patients without signs of end-organ dysfunction may be at low risk for serious complications.[2-4] In fact, in the ambulatory hematology-oncology setting, these low-risk patients, identified by risk-stratification indices such as the Multinational Association for Supportive Care in Cancer (MASCC) and Clinical Index of Stable Febrile Neutropenia (CISNE) scores, are sent home with oral antibiotics.[3,4] These risk-stratification tools, however, have yet to be applied to the ED…until now.

In this article by Coyne et al,[2] the authors retrospectively apply these risk-stratification scores to a cohort of febrile, neutropenic ED patients and review adverse outcome rates across the various risk groups.

But how does this apply to the patient sitting in front of you?

THE CASE

A 54-year-old woman with breast cancer who is currently undergoing chemotherapy with docetaxel presents to the ED, reporting subjective fever and generalized malaise for 6 hours. Review of systems reveals nausea with decreased oral intake since her last chemotherapy 1 week ago. In the ED, she is febrile to 38.3°C (101°F) and has pulse rate 108, blood pressure 110/65 mm Hg, respiratory rate 18 breaths/min, and oxygen saturation 99% on room air. Her physical examination result demonstrates dry oral mucosa, painful mouth ulcerations, and mild tachycardia, without any other significant findings. Chest radiography and urinalysis results are negative for pneumonia or urinary tract infection. After ibuprofen, antiemetics, intravenous fluids, and a delicious tray of hospital food (including at least one mystery meat), she is no longer febrile or tachycardic and is asking to be discharged.

Is she at low risk for adverse outcomes? Can we discharge her?

RISK STRATIFICATION: THE CASE

Using MASCC

The MASCC risk-stratification tool has been previously validated in the ambulatory hematology-oncology setting. The score is calculated according to severity of presenting symptoms (none, mild, moderate, or severe), hypotension, the presence of chronic obstructive pulmonary disease, tumor type, dehydration, and age (Figure).[5] The higher the MASCC score, the lower the risk for serious medical complications, with scores greater than 21 considered to represent low risk.[5]

In this case—no other comorbidities, younger than 60 years, moderate systemic presenting symptoms, clinical and laboratory evidence of dehydration requiring intravenous fluids, and ambulatory setting when neutropenia occurred—the MASCC score is 21. In the ambulatory setting, this patient may be considered low risk for the development of serious complications, and could be considered for outpatient management.[2,5] Of concern, in the study by Coyne et al,[2] 27 of 169 (16%) ED patients classified as low risk by MASCC score had adverse events. The MASCC score in this study was 83%

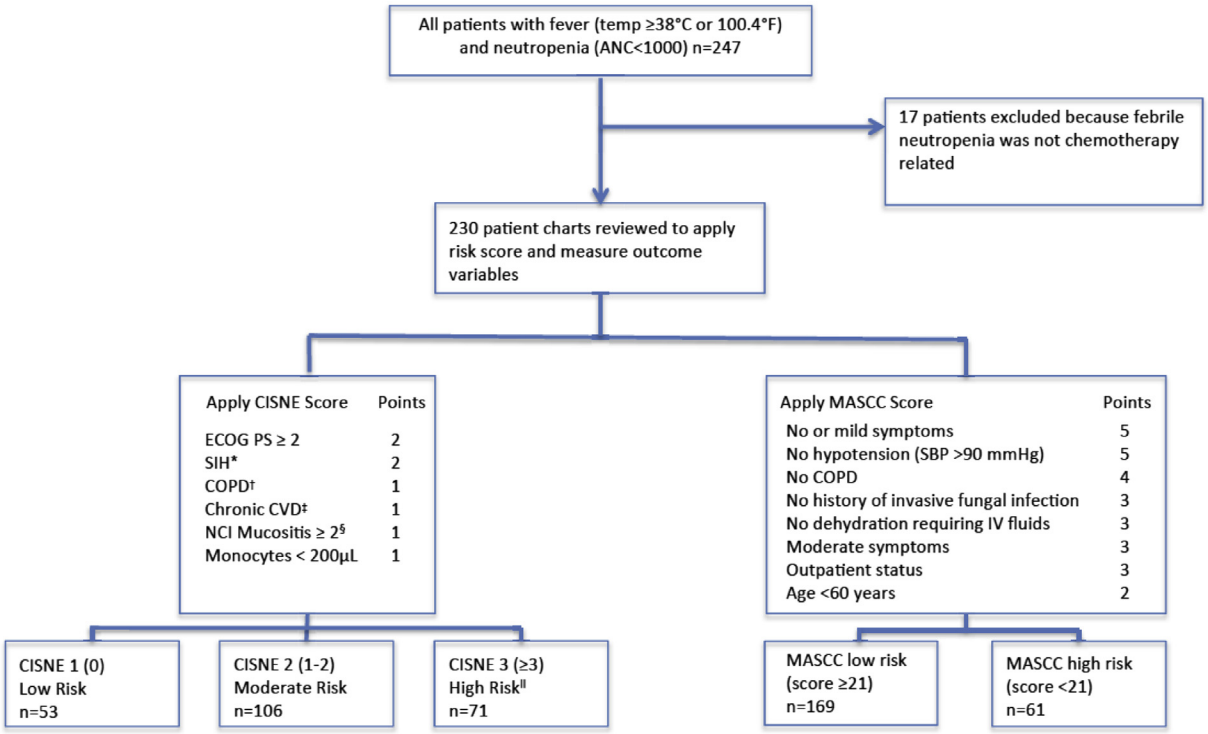

Figure. CISNE and MASCC score application to an ED cohort from Coyne et al[2]. *ECOG PS*, Eastern Cooperative Oncology Group performance score; *SIH*, stress-induced hyperglycemia; *COPD*, chronic obstructive pulmonary disease; *CVD*, chronic cardiovascular disease; *NCI*, National Cancer Institute.

sensitive and 54% specific for identifying low-risk patients. Those might be good odds in Vegas but not in the ED.

Using CISNE

The newer CISNE score was first validated in the ambulatory setting in 2015. It requires more historical information than the MASCC score and relies less on acute patient symptoms.[2,6] It lacks the subjective assessment of symptom severity included in the MASCC score. The CISNE score includes the presence of chronic obstructive pulmonary disease, hyperglycemia, chronic cardiovascular disease, presence and severity of chemotherapy-induced mucositis, and the Eastern Cooperative Oncology Group functional performance score, which assesses activities of daily living and overall well-being (Figure).

For the CISNE score, 0 is considered low risk for serious complications (1.5%), 1 to 2 is intermediate risk (4%), and greater than 3 is high risk (34% up to 95% when all factors are present).[6,7] As if intentionally included in our case, the presence of mucositis increases our patient's CISNE score from low to moderate risk; hence, typical care and admission. Perhaps mucositis identifies a subgroup of patients at higher risk of adverse outcomes who would otherwise be missed by the MASCC score. When the CISNE score was retrospectively applied in the study cohort of Coyne et al,[2] the specificity was greater for identifying low-risk patients than that of the MASCC score, 98% compared with 54% (positive predictive value 98% and positive likelihood ratio 18).

The same patient is considered to be at low risk by MASCC score and moderate risk by CISNE score. Whew! This is a tough one!

DISCUSSION

As you may have heard, certain chemotherapy patients are immunosuppressed. In fact, despite the advancements in targeted antineoplastic therapies that may not otherwise be immunosuppressive, a 2014 study demonstrated a 17% incidence of febrile neutropenia during a chemotherapy regimen.[8] Thus, these patients are more prone to infections with serious complications, including sepsis and multisystem organ dysfunction.[1,2,4,6] Furthermore, immunosuppression makes assessing and diagnosing infection more challenging, which confounds attempts at risk stratification.[1,2,4,6] Hence, the traditional disposition is admission. Admission, though, is not without risks itself, such as hospital-acquired infection and cost.[2]

Before we compare these risk scores, we should first ask whether these tools are appropriate to use in the ED.

Unlike their counterparts in the ambulatory clinic, emergency providers are not familiar with the patient's baseline status and overall well-being, and some providers see this complaint infrequently. Thus, these tools may be difficult to apply accurately in the ED.

Our example patient falls right into that gray zone, where subtle features change the risk stratification and management. She is at low risk by MASCC score and moderate risk by CISNE score. This may highlight the higher specificity of the CISNE score in identifying patients at low risk for negative outcomes. In this retrospective study, the MASCC score classified many patients as low risk who ended up having negative outcomes.

Another important question is whether liquid tumors (cancers of the blood or bone marrow) and solid tumors should be considered separately. Liquid-tumor patients are often considered at higher risk because they can be neutropenic longer and often receive immunosuppressive agents.[1,2,5-7] As such, they have previously been considered too high risk for outpatient management and have been excluded from other studies.[1,2,5-7] Sixty-five percent of the study population in the study by Coyne et al[2] had liquid tumors. If looking specifically at liquid-tumor patients, this study would not have been sufficiently powered to detect specificity. So the question remains about whether these scores can be applied.

WHERE DO WE GO FROM HERE?

Although this study is a great conversation icebreaker with your local hematologist-oncologist, prospective data in the ED are needed. This is the first study to assess risk of febrile neutropenic patients in the ED and provide hints for identifying low-risk patients who can potentially be spared from the risks of hospitalization.

Perhaps in collaboration with patients and their oncologist, a plan for discharge of low-risk patients, close outpatient follow-up, and strict return precautions may be reasonable. Often, this involves interdepartmental communication with agreed-on protocols for safe and expedited patient care.

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