Clinical Practice Statement

Can risk stratification tools be utilized to safely discharge low-risk febrile neutropenic patients from the emergency department? **(11/10/2021)**

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Summary Recommendation:

1. Febrile Neutropenia risk stratifications tools, such as the Multinational Association of Supportive Care in Cancer (MASCC) and Clinical Index of Stable Febrile Neutropenia (CISNE) scores, are supported by the existing literature and may be included as part of the decision-making process when considering adult patient disposition. There is no widely accepted risk stratification tool for use in the pediatric population.

2. Further research is needed before biomarkers can be included in febrile neutropenia risk stratification decisions.

Introduction:

Chemotherapy-induced febrile neutropenia (FN) is considered a potentially serious condition that often prompts an extensive infectious workup and broad-spectrum antibiotics. Despite mounting evidence in the oncology literature suggesting that simple, low-risk cases of FN can be safely managed at home, the vast majority of FN cases presenting to the emergency department (ED) are admitted to the hospital[1]. Existing literature has demonstrated that managing low-risk FN at home has several benefits including decreased cost, decreased nosocomial infections, and improved patient and physician satisfaction[1-3]. Within the past 5 years, there has been a growing body of literature evaluating FN risk stratification methods for use in the ED. These have generally included clinical decision tools that were initially validated in the outpatient clinic setting, as well as biomarkers. This guideline seeks to address whether the existing body of literature is adequate to support the use of these methods when evaluating and treating patients with FN in the ED.

Executive Summary:

We searched PubMed from January 1, 2016 to March 19, 2021 using the following search strategy: ("febrile neutropenia" OR (fever AND neutropenia)) AND (emerg* OR outpatient) AND (admit OR admission OR hospitalization). This was intended to focus on only the most recent data. The search yielded 371 articles, which were independently screened for relevance by two authors, with 23 articles selected for inclusion because they directly addressed the study question. Each of the selected articles was subjected to detailed

review by the authors and assigned a grade of evidence based on focus, research design, and methodology (Table).

We identified 1 meta-analysis, 7 prospective observational trials, and 15 retrospective analyses that directly addressed our research question. Most of these articles utilized previously validated risk stratification tools to identify low-risk candidates for ED discharge. The most common decision support tool was the Multinational Association of Supportive Care in Cancer (MASCC) Risk Index score, followed by the Clinical Index of Stable Febrile Neutropenia (CISNE) score.

The MASCC score was developed in 2002 and incorporates a variety of historical and clinical characteristics to produce a weighted score, with 21 or greater being considered low risk for poor outcome[4]. The CISNE score was developed in 2011 and was derived for use in patients with solid tumors, with a score of 0 being low risk for complications, 1-2 being moderate risk, and $\geq$3 being high risk[5].

The MASCC score was utilized in 10 of the identified studies, of which 8 specifically evaluated the discriminative ability of the MASCC score in identifying a low-risk cohort of ED patients with FN[6-13]. Each of these studies concluded that the score was useful in the ED setting for this purpose. The 2 additional studies evaluated adherence to national oncology guidelines, which utilize the MASCC score, and found that the vast majority of "low-risk" patients were being admitted to the hospital (non-adherent to the guidelines)[14,15].

There were 4 studies that compared the MASCC and CISNE scores and their relative abilities to identify low-risk FN patients[16-19]. A majority of these studies, including a meta-analysis, demonstrated that the CISNE score had a higher sensitivity than the MASCC score (96.7% vs 32.9% respectively) though with a lower specificity (22.2% vs 89.5%)[19]. Of note, the CISNE index was originally validated for use in solid tumor patients, while these studies applied the tool to all cancer types. Therefore, the utility of the CISNE score for patients with leukemia/lymphoma remains unclear.

There were 5 studies that specifically evaluated risk stratification tools for use in the pediatric FN cohort[20-24]. Among these studies there was no consensus as to which score was most appropriate for use in the pediatric emergency population.

We identified 4 studies that evaluated the use of biomarkers in FN risk stratification[7,25-27]. The most common biomarker tested among these studies was procalcitonin, which was found to be superior to other lab values (Neutrophil-to-Lymphocyte Ratio, C-Reactive Protein, lipopolysaccharide binding protein, pancreatic stone protein, and soluble receptor of interleukin 2). One study compared procalcitonin to MASCC in its ability to predict downstream complications and found similar test characteristics (AUC 0.83 (95% CI: 0.74 - 0.89), 0.85 (95% CI: 0.77 - 0.91) respectively)[7].

Conclusion:

Emerging literature supports the use of risk stratifications tools such as the MASCC and CISNE scores for adult FN risk stratification in the emergency department. However, given the lack of large, multi-center, clinical trials these scores should be used cautiously, and only as part of the decision-making process. Biomarkers, while promising, lack sufficient evidence to warrant their routine use in FN risk stratification at this time.