Emergency Department Management of Patients With Febrile Neutropenia: Guideline Concordant or Overly Aggressive?

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Scholarly Report submitted in partial fulfillment of the MD Degree at Harvard Medical School

Date: 5 February 2018

Student Name: Thomas Wang, B.A. in Biology

Scholarly Report Title: Emergency Department Management of Patients with Febrile Neutropenia: Guideline Concordant or Overly Aggressive?

Mentor Name(s) and Affiliations: Christopher W. Baugh, MD, MBA, Medical Director, Department of Emergency Medicine, Brigham and Women’s Hospital

Collaborators, with Affiliations:

Daniel J. Pallin MD, MPH, Co-mentor, Research Director, Department of Emergency Medicine, Brigham and Women’s Hospital

Oleksa N. Baker PhD, Statistician, Division of Health Policy Translation, Brigham and Women’s Hospital
**Title:** Emergency Department Management of Patients with Febrile Neutropenia: Guideline Concordant or Overly Aggressive?

Christopher W. Baugh MD, MBA, Thomas J. Wang BS, Jeffrey M. Caterino MD, MPH, Olesya N. Baker PhD, Gabriel A. Brooks MD, Audrey C. Reust PA-C, Daniel J. Pallin MD, MPH

**Objectives**
The Infectious Diseases Society of America (IDSA) and the American Society of Clinical Oncology (ASCO) recommend risk stratification of patients with febrile neutropenia (FN) and discharge with oral antibiotics for low-risk patients. We studied guideline concordance and clinical outcomes of FN management in our emergency department (ED).

**Methods**
Our urban, tertiary care teaching hospital provides all emergency and inpatient services to a large comprehensive cancer center. We performed a structured chart review of all FN patients seen in our ED from January 2010 to December 2014. Using electronic medical records, we identified all visits by patients with fever and an absolute neutrophil count of <1,000 cells/mm$^3$ and then included only patients without a clear source of infection. Following national guidelines, we classified patients as low or high risk and assessed guideline concordance in disposition and parenteral versus oral antibiotic therapy by risk category as our main outcome measure.

**Results**
Of 173 qualifying visits, we classified 44 (25%) as low risk and 129 (75%) as high risk. Management was guideline concordant in 121 (70%, 95% confidence interval [CI] = 63% to 77%). Management was guideline discordant in 43 (98%, 95% CI = 88% to 100%) of low-risk patients versus 9 (7%, 95% CI = 3% to 13%) of high-risk patients (relative risk [RR] = 14, 95% CI = 7.5 to 26). Of 52 guideline-discordant cases, 36 (83%, 95% CI = 72% to 93%) involved low-risk cases with treatment that was more aggressive than recommended.

**Conclusions**
Guideline concordance was low among low-risk patients, with management tending to be more aggressive than recommended. Unless data emerge that undermine the guidelines, we believe that many of these hospitalizations and parenteral antibiotic regimens can be avoided, decreasing the risks associated with hospitalization, while improving antibiotic stewardship and patient comfort.
**Intellectual contribution:**

When I first reached out to Dr. Christopher Baugh on possibly working together on this project, he had already identified the febrile neutropenia population as a research topic of interest and had framed the broader questions and key factors to explore (e.g., percentage of admissions, antibiotics use, primary outcomes, etc.). I played a significant role in designing study details and efficiently perform the chart review process, as I was responsible for the vast majority of the chart review. A large part of my early work was identifying patients who met all study inclusion criteria. I was aided significantly on this effort by Drs. Baugh and Pallin, who have a strong background in clinical epidemiology, statistics, and population health. After carefully thinking through our inclusion and exclusion criteria and multiple attempts at finding the right cohort through the Research Patient Data Registry, we identified 930 candidate patients.

I led the initial screening process. This was my first time performing a chart review on the Partners LMR system, and I spent a large part of my time closely working with Dr. Baugh on the initial 100 cases to design a method to more efficiently go through the process while making sure we identified all the eligible study patients. Once I was happy with the process, I completed the rest of the screening and narrowed the cohort down to 326 patients. I then performed a secondary, more detailed review of the records for these patients, and with the first 50 again worked closely with Dr. Baugh to determine what type of data we wanted to capture, how best to capture/display this data, and how to interpret certain criteria (i.e., Who would be considered to have mild, moderate, or severe burden of symptoms?), which was difficult for me to do alone given my lack of clinical training at the time. I went through multiple iterations of the chart review process before arriving at a satisfactory version and consistently applied it to the 326 cases. Out of these, only 173 were included in the final study, as the other half of the patient cohort had documentation of at least one exclusion criterion.

Once all data were collected, I performed an initial analysis and discussed these results with Drs. Baugh and Pallin. We then went over the data in detail and performed additional analyses together. Dr. Baugh then brought in Oleysa Baker, a statistician fellow at the Brigham and Women’s Hospital, who helped us perform the statistical analysis.

Afterwards, I played a major role in the manuscript writing over the fall and winter period. My major contributions were writing the first drafts of the methods and results section and making the initial tables and figures. I also helped write the abstract, edited the introduction and discussion sections, and compiled the references section. I then aided in the revision process of the entire manuscript, along with the other authors of the study.

**Detailed Description of Project:**

Cancer patients are frequently immunocompromised due to the state of their cancer or the chemotherapy used to treat it. Often, these patients develop FN, or fever in conjunction with low neutrophil count, which can result in more severe complications such as sepsis or even death. FN is one of the most common oncologic emergencies, and occurs in 10-50% of patients with solid tumors and >80% of those with hematologic malignancies. FN patients are typically sent to the ED, where they are immediately treated with antibiotics due to risk of severe bacterial infection and are often hospitalized, though fewer than 30% are found to actually have clinically identified bacterial infections. Thus, the majority of patients may not need parenteral antibiotics and hospitalizations, and could possibly benefit more from taking oral antibiotics and being closely monitored at home given their vulnerability to severe complications (i.e., adverse medication reactions, *Clostridium difficile* colitis, drug-resistant organisms).

Currently, clinical guidelines recommend use of the Multinational Association for Supportive Care in Cancer (MASCC) score to identify FN patients who may be safe for outpatient care. The MASCC score consist of a series of clinical criteria (see table below) totaling to a score of 26, and patients with a score of ≥21 are defined as low risk and are recommended for outpatient management and oral antibiotics.

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<th>CHARACTERISTIC</th>
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<tr>
<td>Burden of febrile neutropenia with no or mild Symptoms¹</td>
<td>5</td>
</tr>
<tr>
<td>No hypotension (systolic BP &gt; 90 mm Hg)</td>
<td>5</td>
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<tr>
<td>No chronic obstructive pulmonary disease²</td>
<td>4</td>
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<tr>
<td>Solid tumor or hematological malignancy with no previous fungal infection²</td>
<td>4</td>
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<tr>
<td>No dehydration requiring parenteral fluids</td>
<td>3</td>
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<tr>
<td>Burden of febrile neutropenia with moderate Symptoms⁴</td>
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<td>Outpatient status</td>
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<td>Age &lt; 60 years</td>
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The IDSA and ASCO have additional clinical criteria that can aid clinicians in deciding which patients would benefit from inpatient care. Despite the presence of these guidelines, it was observed anecdotally that, given the high risk of FN patients in general, the vast majority of patients with FN of unknown etiology when presenting to the ED were being hospitalized and continued to be given intravenous antibiotics. This observation however has never been formally studied. Therefore, we wished to study this phenomenon more systematically to determine if there is indeed a discordance between guidelines and routine clinical care, and if so, set the foundation in bridging this disparity to provide better quality care for our patients. To do this, my mentors and I designed this retrospective chart review study to see how patients with FN were treated in the ED over the past few years, analyze the level of concordance with established guidelines, and evaluate 30-day outcomes (e.g., bacteremia, sepsis, death) that may provide insight on the appropriateness of the hospitalizations.

Our results show that despite existing guidelines, the vast majority of low risk patients were hospitalized as inpatients and treated with IV antibiotics, and those who are deemed low-risk by the MASCC score and the ASCO and IDSA guidelines had a low rate of adverse outcomes. This has significant clinical implications. One, as mentioned above, hospitalizing low-risk patients may unnecessarily place them at risk for iatrogenic complications while in the hospital. In addition, with more aggressive interventions, we place a higher burden on the healthcare system by increasing costs and utilizing limited resources. Our study is limited in scope given its retrospective nature; for example, we cannot make any conclusions on causation, that whether more aggressive inpatient management could have reduced the likelihood of adverse outcomes that patients may have otherwise received as an outpatient. Therefore, a follow-up prospective study, ideally conducted at multiple centers, would be helpful in determining whether strictly following the existing guidelines are effective in preventing adverse outcomes for low-risk patients. On the policy level, this knowledge can help improve the standard practices at the Emergency Department at the Brigham and Women’s Hospital in managing patients with FN, and possibly at other hospitals across the country as well, as they may use this study’s results to re-evaluate their own clinical practices.

**Link and Citation:**
