Management of Neutropenic Fever During a Transition from Traditional Hematology/Oncology Service to Hospitalist Care

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ABSTRACT

Objectives: Increasingly, hospitalists across the United States provide primary inpatient care for almost all subspecialty patients, including hematology and medical oncology. Febrile neutropenia (FN) is a serious condition often seen as a complication of cytotoxic chemotherapy or in patients with underlying bone marrow defects. The purpose of this study was to document the change of inpatient management of a common admission diagnosis during a transition of providers from hematologists/oncologists to the use of hospitalists in a tertiary care medical center, and to compare the appropriateness of treatment and outcomes over a period of 5.5 years of this transition.

Methods: The medical records of all patients with neutropenia at a community-based teaching hospital during a period of conversion from hematologist/oncologist to hospitalist coverage were retrospectively reviewed. Patients with fever and absolute neutrophil counts of less than 500/μL (.5 x 10^9/L) on admission were included. Study cases were divided into 3 groups by admission date, roughly demarcating the nascent hospitalist era, the era of transition to hospitalist, and the mature hospitalist era. Management of FN during these eras was compared.

Results: Three hundred ninety-nine inpatients were identified as neutropenic. Of these, 184 did not meet case-inclusion criteria. The remaining 215 cases were included in the study. The internal medicine hospitalist service admitted less than 10% of this population in 2003, but by 2007-2008 it admitted over 90%. The use of 4th-generation cephalosporins and carbapenems increased over time ($P = .027$), and the infectious disease service was consulted more frequently over time ($P = .007$). Outcomes varied due to changes in underlying disease states, use of hospice services, and changes in the types of patients hospitalized with FN. Morbidity decreased due to the change in the type and nonantibiotic therapy of cases, but inappropriate antimicrobial treatment was unusual, and septic morbidity or mortality related to inappropriate therapy was too rare to compare through these eras.

Conclusion: Over the 3 eras compared, care of most neutropenic fever patients was transferred from specialists to hospitalists. Care became more uniform, guideline based, and used more infectious disease consultation, and mortality decreased. Complex changes in the types and treatments of cancer, neutropenia therapy, and in the types of patients hospitalized with FN prevent any conclusion of added value for this change in the type of primary provider management.

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INTRODUCTION

In patients receiving cytotoxic chemotherapy with significant myelosuppressive effects, febrile neutropenia (FN) is a common but serious occurrence that, if unrecognized, can result in significant morbidity and mortality. FN is usually defined as a body temperature of >38.3°C in a patient with an absolute neutrophil count (ANC) <500/μL (.5 x 10^9/L). FN often mandates hospitalization and treatment with intravenous antibiotics. This not only has a detrimental effect on the patient's quality of life but could also result in inferior treatment outcomes, such as decreased overall survival due to subsequent reduction in the dose of chemotherapy.[1-3] In most institutions, neutropenic fever is treated in accordance with the guidelines of the Infectious Diseases Society of America (IDSA) and the American Society of Clinical Oncology (ASCO). In addition, treatment should always be guided by local resistance patterns. Depending on many clinical factors (ie, patient wishes, type and location of infection if known, degree of neutropenia, type of cancer, and chemotherapy administered), treatment can range from outpatient treatment with oral antibiotics to broad-spectrum intravenous antibacterials and antifungals.

In the last 2 decades, hospitalists have emerged as a new physician group in the United States. Transition of inpatient care to hospitalists has been bolstered by several studies showing that hospitalist programs decrease length of stay and cost, as well as improve quality of care.[3-5] These studies have compared hospitalists with primary care physicians, that is, physicians who see both in- and outpatients. The disease groups in the studies have generally been internal medicine diagnoses.

A secondary effect of this evolution has been a broadening of the clinical scope of the hospitalists. As hospitalists are caring for an increasing number of general medicine patients, they are also increasingly managing patients with subspecialty internal medicine and noninternal medicine illness and are now increasingly taking a primary role in the care of patients who, in the past, were not considered within the scope of internal medicine.[3] It is unknown to what degree hematology and oncology patients are managed by hospitalists in the United States, but there is little doubt that this number is growing steadily.

Our institution underwent a transition from subspecialty primary teams to hospitalist teams for management of hospitalized hematology and medical oncology patients from 2004 to 2006. Since FN is a common occurrence in this particular patient population, we decided to retrospectively compare the outcomes of patients with FN over these specific time periods in order to determine whether any difference in outcomes existed between the 2 practice groups. To our knowledge, our study is the first to compare outcomes of FN and to compare outcomes between subspecialists and hospitalists in the management of FN.

METHODS

Setting

Gundersen Health System is centered around a 325-bed community-based, tertiary-care, teaching hospital in La Crosse, Wisconsin. In 2002, the first hospitalist service was implemented and, since then, 5 more hospitalist services have been added. These services are staffed by full-time hospitalists and by primary care internists doing 7-day blocks of hospitalist medicine.

Since 2003, the hospitalist services have admitted an increasingly large percentage of our hospitalized patients. When one disregards same-day admissions, that is, admissions for transfusions or invasive studies, most internal medicine subspecialty departments have stopped admitting patients altogether. The cardiology and pulmonary services continue to be primary providers for approximately 50% of admitted patients with heart or lung conditions, but hematology, oncology, gastroenterology, endocrinology, infectious disease, and neurology now function as consultation services only.

The incidence of neutropenic patients with fever is relatively high for a medium-sized tertiary-care hospital due to an active Center for Cancer and Blood Disorders that treats most solid tumors, lymphoma, and leukemia. Patients are transferred to larger centers only for autologous and allogeneic hematopoietic cell transplants, where immediate complications of these transplant procedures are treated.

After obtaining Institutional Review Board approval, we retrospectively reviewed the medical records of FN patients hospitalized from January 2003 through July 2008. The following data were extracted from the records of patients who fit the case definition: presence of fever >38.3°C, admitting service, length of stay, type of malignancy, intent of chemotherapy (palliative vs curative), ANC on admission and discharge, primary antibiotics (those used within 24 hours of admission), secondary antibiotics (those added >24 hours after admission), type and outcome of infections, outcome of hospitalization (death/hospice vs discharge), and use of the infectious disease consult service. Cases without both fever and neutropenia were excluded from further study. We also excluded patients admitted solely for chemotherapy administration even if they developed fever during their hospitalization because most of these patients were already on prophylactic antibiotics at the time they developed neutropenic fever.

We then divided the study period into 3 eras: *Prehospitalist,* during which hematologists and medical oncologists admitted and managed patients with FN (January 2003 through June 2004); *Transitional,* during which the hospitalist service admitted some of these patients (July 2004 through May 2007); and *Hospitalist,* during which the hospitalist services admitted all of these patients (June 2007 through July 2008).

We analyzed whether length of stay, use of antibiotics, and use of the infectious disease consult service had changed over the 3 eras and determined appropriateness of the antibiotic regimen by comparing national guideline recommendations for neutropenic fever, septicemia, and/or an infectious focus.

Infectious focus on admission was determined by reviewing the admission note and any note (by the admitting service or consulting service) in the first 24 hours after admission. If a blood stream infection and another focus were noted, the case was considered a blood stream infection. Similarly, we determined the focus of infection at discharge by review of the discharge summary, as well as the discharge billing codes. Here again, if a blood stream infection and another focus were noted, the case was included as a blood stream infection. If a patient had a positive culture result prior to admission, treatment aimed at this specific infection was deemed appropriate based on the susceptibility of the organism(s). Neither infiltrate on chest radiograph nor signs and symptoms suggestive of soft-tissue infection in the absence of a culture positive for growth were deemed sufficient to narrow the antibiotic spectrum.

Whenever it was unclear whether the antibiotic regimen met national guidelines, the senior author, an infectious disease specialist, reviewed the medical record and determined appropriateness of other antibiotics based on characteristics of the pathogen. Because single-agent antibiotic therapy with a 4th-generation cephalosporin or meropenem meets guidelines, more medical records were examined from the first 2 eras than from the latter. Other regimens deemed to meet national guidelines included regimens with broad-spectrum antibiotics with antipseudomonas coverage. When appropriate for site and by susceptibility testing, such regimens included piperacillin-tazobactam, ciprofloxa-

cin, and an antipseudomonal beta lactam and gentamicin. A few cases with multiple allergies received unconventional antibiotic regimens; these patients were categorized as appropriately treated only after review by the infectious disease specialist.

Statistical analyses included descriptive statistics, analysis of variance (ANOVA) for comparison of continuous variables, and the Mantel-Haenszel test for linear trend for comparison of discrete variables. The statistical analysis was completed using SAS version 9.3 (SAS Institute, Cary, North Carolina), and *P* values <.05 were considered significant.

RESULTS

Three hundred ninety-nine hospitalized patient records were reviewed, of which 184 were excluded (Table 1), most commonly for transient neutropenia, that is, only 1 measurement of ANC <500/μL (.5 × 10^9/L) or lack of neutropenia on admission (36%), lack of fever on admission (30%), admission for chemotherapy only (18%), drug induced (4%), and other causes (12%). The remaining 215 cases were included in the study.

Median age was 69 years. Median length of stay was 4 days. ANC on admission ranged from 0/μL to 490/μL (0–.49 × 10^9/L), with a median ANC of 70/μL (.07 × 10^9/L). ANC on discharge ranged from 0/μL to 192 000/μL (0–192 × 10^9/L), with a median of 1220/μL.

Over the 3 eras, solid tumor patients comprised most of the frequent FN cases (34%). Underlying causes of neutropenia over the 3 eras are listed in Table 2. Patients had received recent (within 1 month) chemotherapy in 60% of all included cases, most frequently in patients with solid tumors (89%) and non-Hodgkin lymphomas (80%). Eight cases had drug-induced neutropenia (not including myelosuppresive chemotherapy). The drugs responsible were methotrexate (2 cases), rituximab, sulfasalazine, vancomycin, trazodone, azathioprine, and amiodarone.

In the Prehospitalist, Transitional, and Hospitalist eras, hospitalists admitted <10%, approximately 65%, and >90% of patients with FN, respectively. A few patients in the Prehospitalist era were admitted by primary care internal medicine. In all 3 eras, and with very few exceptions, patients with neutropenic fever who were not admitted by hospitalists were admitted by either the hematology or oncology service.

The infectious focus identified on admission and discharge over the 3 eras is listed in Table 3. Although respiratory source was identified as the most common source of infection in all 3 eras, no identifiable focus of infection was more common at discharge during the Prehospitalist era compared with the Hospitalist era (*P*=.003).

Antibiotic regimens were defined as *primary antibiotics* (antibiotics instituted within 24 hours of admission) or *secondary antibiotics* (antibiotics added after 24 hours). We examined the use of an antipseudomonas 4th-generation cephalosporin and/or carbapenems, compared with other regimens, usually based on fluoroquinolones or broad-spectrum penicillins/1st- to 3rd-generation cephalosporins. Over time, regimens containing 4th-generation cephalosporins and/or carbapenems were used more frequently. The percentages of patients treated appropriately in the 3 eras were 84.9, 85.5, and 98.2, respectively (*P*=.019), including 4th-generation cephalosporins and/or carbapenems (Figure 1).

During the study period, there was no significant change in the La Crosse area antibiotic susceptibility patterns. For instance, the susceptibility ranges of the major pathogens—*Staphylococcus aureus,* 65% to 68% to oxacillin, *Klebsiella sp*, 96% to 100% to ceftriaxone, *Pseudomonas aeruginosa* 82% to 85% to quinolones, and 98% to 99% to piperacillin—were remarkably stable.

The infectious disease service was consulted in 33% of cases overall. Over the 3 eras, the service was consulted in 20%, 34.6%, and 45.1% of cases, respectively. This trend over time was statistically significant (*P*=.005).

Median length of stay was 4 days (range 1–44 days). The median ANC on admission was 70/μL, range 0–490/μL, (.07 × 109/L, range 0–.49 × 10^9/L) and 1200/μL, range 0–192,000/μL (1.2 × 10^9/L, range 0–192 × 10^9/L) at discharge. Mean length of stay declined slightly over the 3 eras (6.7, 5.9, and 5.7 days, respectively), although this was not statistically significant (*P*=.724).

Table 1. Reasons for Exclusion of Patients from a Study of Comparison of Treatment of Neutropenic Fever by Hospitalists and Hematologists/Oncologists (N=184)

Reason for Exclusion	No. of Patients Excluded (%)
Transient neutropenia	66 (36)
No fever	55 (30)
Admitted for chemotherapy only	33 (18)
Drug-induced	8 (4)
Other[a]	22 (12)

[a]Other includes neutropenia secondary to severe, nonhematologic illness (n=13); patient on hospice care (n=3); autoimmune diseases (n=3); human immunodeficiency virus infection (n=1); infectious mononucleosis (n=1); and transfer from rehabilitation unit, that is, admission analyzed previously (n=1).

Table 2. Underlying Cause of Neutropenic Fever in Study Patients Admitted to Hospital by Era[a]

Underlying cause	Prehospitalist n=60	Transitional n=104	Hospitalist n=51	Total N=215
Solid tumors	23 (38.3)	36 (34.6)	15 (29.4)	74 (34.4)
Leukemia	13 (21.7)	31 (29.8)	19 (37.3)	63 (29.3)
Lymphoma	21 (35.0)	22 (21.2)	2 (3.9)	45 (20.9)
Myelodysplastic syndrome	3 (5.0)	12 (11.5)	9 (17.7)	24 (11.2)
Other[b]	0 (0.0)	3 (2.9)	6 (11.8)	9 (4.2)

[a] All data are presented as number of patients (%).
[b] Other includes aplastic anemia (n = 3), multiple myeloma (n = 4), and Waldenström (n = 2).

Table 3. Infectious Focus of Inpatients with Neutropenic Fever upon Admission and at Discharge by Era[a]

	Prehospitalist n=60		Transitional n=104		Hospitalist n=51	
Infectious focus	**Admission**	**Discharge**	**Admission**	**Discharge**	**Admission**	**Discharge**
Respiratory	16.7	25.0	18.3	23.1	11.8	33.3
Skin, nose, mouth	15.0	13.3	9.6	6.7	7.8	15.7
Abdominal	3.3	10.0	12.5	8.7	7.8	11.8
Blood stream[b]	1.7	16.7	3.8	25.0	2.0	15.7
Urologic	1.7	0.0	2.9	6.7	0.0	9.8
Other	3.3	1.7	1.0	1.0	0.0	2.0
No focus	61.7	45.0	56.7	36.5	70.6	17.6

[a]Some patients had more than 1 infectious focus noted, so totals do not equal 100%.
[b]Including intravenous catheters.

Figure 1. Percentage of Antibiotic Regimens Deemed Appropriate for the Treatment of Neutropenic Fever by Era

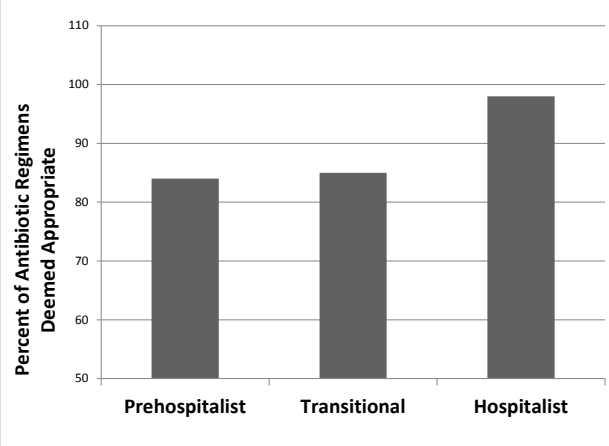
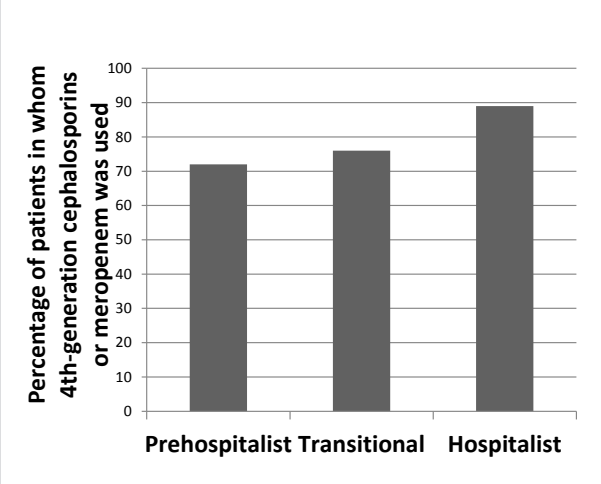


Figure 2. Use of 4th-generation Cephalosporins or Meropenem in Percentage of Patients by Era ($P<.027$).



Overall, 15.3% of study patients either died in hospital or were discharged to hospice. Analysis by era demonstrated that 26.7% of patients died or were discharged to hospice in the Prehospitalist era, compared with 7.8% in the Hospitalist era ($P=.05$). Both inpatient and overall 30-day mortality fell significantly from the Prehospitalist (17% and 35%, respectively), to the Transitional (8% and 17%, respectively), and to the Hospitalist eras (2% and 12%, respectively) ($P=.006$ and $P=.002$). Additionally, in-hospital death from inappropriately treated sepsis occurred in only a few cases during the entire study, precluding statistical analysis.

In the Prehospitalist era, 81.9% of patients received chemotherapy with curative (vs palliative) intent, compared with 72.5% in the Hospitalist era, although this difference was not significant ($P=.248$). The percentage of patients receiving chemotherapy with curative intent for solid tumors in the Prehospitalist and Hospitalist eras was similar (34% and 37.9%, respectively), but there was a shift in diagnosis pattern of cases receiving chemotherapy with curative intent only. Whereas in the Prehospitalist era 24% of cases had leukemia and 42% had lymphoma, in the Hospitalist era 55% had leukemia and 6.9% had lymphoma ($P=.007$).

DISCUSSION

Although it appears that hospitalists will eventually replace primary care internists in most large hospitals, the degree to which hospitalists will admit patients with subspecialty diagnoses remains to be determined. In recent times, hospitalist as a subspecialty is an evolving practice group.[6] The medical center examined in this study has been at the forefront of the hospitalist movement. By 2010, not only were all patients with general medical illnesses admitted to hospitalist services, but also virtually all patients with subspecialty illnesses were cared for by hospitalists, with the exception of some with cardiology or pulmonology diagnoses. Over the 5 1/2 years this study reviewed, the internal medicine hospitalist service essentially assumed care of all patients with neutropenic fever (from <10% in 2003 to >90% in 2007 and 2008). No study that we could identify has documented such a transfer of care from specialists to hospitalists.

Our study shows that over the period of 5 1/2 years analyzed, the transfer of care from hematologists and oncologists to internal medicine–trained hospitalists resulted in significant management changes. Hospitalists were more likely to pursue aggressive antibacterial treatment (more often starting with a 4th-generation cephalosporin, typically cefepime), whereas specialists, despite knowledge of the national guidelines, more frequently used alter-

native regimens. Several factors could explain this. For instance, although the 2002 IDSA guidelines approve the use of cefepime or an antipseudomonal carbapenem in high-risk patients with neutropenic fever, we found that such a unitherapy beta lactam recommendation was not uniformly used in the Prehospitalist era, when 76.1% patients received only a 4th-generation cephalosporin or carbapenem, compared with the Hospitalist era, in which 94.1% of patients received such approved treatments, although the difference was not statistically significant ($P = .101$). Familiarity of the hematologists/oncologists with their patients prior to admission, including their past morbidities and prior response to different antibiotics, appeared to explain this difference because they were more likely to "aim" for a relapse of a prior infectious focus. Conversely, hospitalists often meet patients for the first time on the day of admission and were more likely to opt for single broad-spectrum beta-lactam antibiotic until more information becomes available.

The hospitalists in our study knew the national guidelines for the treatment of neutropenic fever. However, the treatment of patients with FN offered in the most recent era, managed primarily by hospitalists, was deemed "appropriate" more frequently than was treatment offered in the earliest era, in which their treatment was managed by hematology/oncology specialists. Whether this finding is true in other hospital settings is unknown.

The same pattern was true for infectious disease consults. The frequency of infectious disease consultation nearly doubled in the 5 1/2 year period we examined. It is perhaps not surprising that hospitalists, who are generalists by training, seek more advice in treating this very sick patient population.

The observed change in treatment patterns is at least partly unrelated to the hospitalist movement. The study period spanned 5 1/2 years. In this time, myelosuppresive chemotherapeutics and national (but not local) microbial resistance patterns had changed.[7] Arguably, these changes led to a sicker patient population and/or to physicians' belief in the need for broader-spectrum antibiotics and more frequent infectious disease consultation. While data support the use of available guidelines for treatment of patients hospitalized with FN, non–guideline-based therapy has also been increasingly used, as we saw in the Prehospitalist era, in this high-risk population.[8]

It is interesting to note that the number of patients receiving chemotherapy for curative intent admitted for neutropenic fever fell over the course of years, from 50 in the Prehospitalist era to 29 in the Hospitalist era. This is likely due to the change in pattern of chemotherapy regimens over time and, possibly, to the use of granulocyte colony–stimulating factor (G-CSF) support in patients receiving aggressive high-dose chemotherapy with curative intent.

A marked change in the admission diagnoses was noted over the 3 eras. Although lymphoma represented 26.9% of admissions in the Prehospitalist era, it represented only 6.9% in the Hospitalist era, with leukemia constituting 55.2% of admissions in this era. This is likely due to adherence to National Comprehensive Cancer Network (NCCN) guidelines in our facility for recommended use of G-CSF in high-risk patients with lymphoma and, thus, a trend toward lower rate and shorter duration of neutropenic fever.[9]

Overall, the 30-day case mortality rate fell drastically, from nearly a third of patients in the Prehospitalist era to approximately 10% of patients in the Hospitalist era (26.7% vs 7.8%, $P = .005$). Changes in antibiotic treatment alone cannot account for this shift. A low septic death rate did not change through these years; rather, the majority of the shift in mortality can be explained by the fact that more terminal patients were treated at home in the Hospitalist era. In addition, inpatients treated by our palliative care service, which expanded significantly from 2003 to 2008, usually did not have blood tests done. Thus, they did not meet inclusion criteria for this study, artificially lowering the case mortality in the Transitional and Hospitalist eras.

To determine whether intention of treatment could attribute to change in pattern of mortality, we compared patients receiving curative and palliative intent chemotherapy. In this subgroup analysis, patients receiving chemotherapy with curative intent did not demonstrate change in 30-day mortality pattern or discharge to hospice rate over the 3 eras ($P = .151$). Involvement of our palliative care team with most patients with incurable malignancies at the outset was done in the outpatient setting, and when these patients with incurable malignancies required hospitalization, they often opted for nonaggressive measures of therapy and comfort-based options. Furthermore, a more active involvement of our palliative care team in the inpatient setting developed, thus accounting for more discharges to hospice.

There are limitations to our study. Although we conducted a retrospective analysis of a unique period of transition from subspecialists to hospitalists, the outcomes listed are likely more reflective of case mix or changes in practice that occurred over time, rather than to the treatments provided by particular groups of physicians. A prospective study with a larger patient population would be ideal to assess whether the difference in outcome was, in fact, due to the transition to another type of physician service. Secondly, we do not have specific microbiology on every patient. However, a review of the documented infections did not show a change in the pattern of infection or a significant resistant pattern that could be attributed to application of broader-spectrum antibiotics in the Hospitalist era.

This is the first study to examine the treatment of neutropenic fever by hospitalists in the United States. It is one of few studies comparing treatment and outcomes of hospitalists with those of medical subspecialists, despite the fact that hospitalists in the United States admit increasing numbers of subspecialty

patients. This is remarkable when one considers the number of studies dedicated to the comparison of primary care physicians with hospitalists.

In conclusion, this study focused on a finite and unusual period in health care in America. It shows that as the care of neutropenic fevers transitioned to hospitalist providers, therapy became more guideline-based and used infectious disease consultation more frequently; however, it was not possible to prove a higher value for this change. Equal or better outcomes due to the rapidly changing therapies and approaches to neutropenia/cancer were apparent, even in this single medical center over a short 5 1/2 year period. But as the landscape of inpatient medicine continues to change, careful studies should be dedicated to the transfer of care from specialists to hospitalists, and possibly to subspecialty hospitalists, if this transition is to justify claims of lower resource utilization or better outcomes. More likely this change will continue, driven by other medical system needs, without true value of care measurements.

Funding/Support: None declared.

Financial Disclosures: None declared.

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