

HEALTH CARE REFORM

Deviations From Guideline-Based Therapy for Febrile Neutropenia in Cancer Patients and Their Effect on Outcomes

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Importance: Although febrile neutropenia (FN) is a major source of morbidity and mortality for patients with solid tumors, little is known about the use of guideline-based care.

Objectives: To examine compliance with guideline-based recommendations for FN treatment, explore the factors that influence adherence to consensus guidelines, and analyze how the use of guideline-based care affects the outcomes.

Design: The Perspective database was used to examine the treatment of cancer patients with FN from January 1, 2000, through March 31, 2010. To capture initial decision making, we examined treatment within 48 hours of hospital admission. We determined use of guideline-based antibiotics and nonguideline-based treatments, vancomycin, and granulocyte colony-stimulating factors (G-CSF). Hierarchical models were developed to examine the factors associated with treatment. Patients were stratified into low- and high-risk groups, and the effect of the initial treatment on outcome (nonroutine hospital discharge and death) was examined.

Setting and Participants: Twenty-five thousand two hundred thirty-one patients with solid tumors hospitalized for neutropenia.

Main Outcome Measure: Use of guideline-based antibiotics, vancomycin, and G-CSF and their affect on outcome.

Results: Among 25 231 patients admitted with FN, guideline-based antibiotics were administered to 79%, vancomycin to 37%, and G-CSF to 63%. Patients treated at high FN-volume hospitals (odds ratio [OR], 1.56; 95% CI, 1.34-1.81) by high FN-volume physicians (OR, 1.19; 95% CI, 1.03-1.38) and patients managed by hospitalists (OR, 1.49; 95% CI, 1.18-1.88) were more likely to receive guideline-based antibiotics ($P < .05$). Vancomycin use increased from 17% in 2000 to 55% in 2010, while G-CSF use only decreased from 73% to 55%. Among low-risk patients with FN, prompt initiation of guideline-based antibiotics decreased discharge to a nursing facility (OR, 0.77; 95% CI, 0.65-0.92) and death (OR, 0.63; 95% CI, 0.42-0.95).

Conclusions and Relevance: While use of guideline-based antibiotics is high, use of the nonguideline-based treatments, vancomycin, and G-CSF is also high. Physician and hospital factors are the strongest predictors of both guideline- and nonguideline-based treatment.

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FEBRILE NEUTROPENIA (FN) from myelosuppressive chemotherapy results in substantial morbidity, typically requires hospitalization, results in high medical costs, and is associated with significant mortality.¹⁻⁵ A review of data from 115 centers in the United States noted that the inpatient mortality rate for FN was 9.5%. The same study noted that the median cost per episode of FN was more than \$19 000, and the mean hospital stay was 11.5 days.² In addition to the direct consequences of FN, FN often results in reductions in the chemotherapy dose intensity that may affect oncologic outcomes.²

A better understanding of the etiology, natural history, and prevention of FN has led to reductions in morbidity for patients with FN during the past 2 decades.⁵⁻⁷ Much of the improved outcome for FN has been the result of the recognition of the importance of early administration of empiric

See Invited Commentary at end of article

broad-spectrum antibiotics.⁵⁻⁷ A large body of literature has emerged evaluating new antibiotics, alternate treatment regimens, and strategies for the use of granulocyte colony-stimulating factors (G-CSF) to pro-

Table 1. Risk of Death Based on Selected Complications in Cancer Patients With Febrile Neutropenia

| Complication | Risk of Death ^a |
|----------------------------------------------------------------|----------------------------|
| Univariate models (models included individual parameters only) | |
| Pneumonia | 3.77 (3.19-4.45) |
| Hypotension | 4.79 (2.66-8.64) |
| Sepsis | 6.90 (5.99-7.96) |
| ICU use | 10.74 (9.23-12.49) |
| Mechanical ventilatory assistance | 50.64 (40.82-62.84) |
| Multivariate models (model including all the parameters) | |
| Pneumonia | 1.80 (1.47-2.21) |
| Hypotension | 3.16 (1.57-6.35) |
| Sepsis | 3.66 (3.09-4.33) |
| ICU use | 2.69 (2.19-3.31) |

Abbreviation: ICU, intensive care unit.

^a $P < .05$.

mote neutrophil production. These data have not only increased the number of treatment options available to clinicians but also dramatically increased the complexity and costs of therapy.⁶⁻⁹

To guide management, many professional societies have developed practice guidelines for the treatment of FN.⁶⁻⁹ In addition to recommendations for empiric antibiotic therapy, these guidelines address more controversial and costly treatments, such as the use of therapeutic G-CSF, antifungal and antiviral agents, and empiric vancomycin.⁶⁻⁹ While therapeutic G-CSF for patients with FN may minimally reduce the length of hospitalization, randomized clinical trials have reported that its use does not affect mortality, and these agents are not recommended.⁶⁻¹⁷ Likewise, there seems to be little benefit to the use of empiric vancomycin treatment outside of specific clinical scenarios.^{6,7,18}

Despite the fact that consensus guidelines for FN have been in place for longer than a decade, little is known about adherence to these recommendations by clinicians. Small institutional series and surveys have suggested that there are wide variations in practice patterns among oncologists.¹⁹⁻²¹ This is problematic because underuse of beneficial treatments and overuse of ineffective treatments may not only result in adverse outcomes but also have a substantial effect on cost and resource use. The objectives of our study were to examine compliance with guideline-based recommendations for FN treatment, explore the factors that influence adherence to consensus guidelines, and analyze how the use of guideline-based care affects outcomes.

METHODS

DATA SOURCE

Data from the Perspective database (Premier) was used. Perspective is a voluntary, fee-supported database that captures data from more than 600 acute care hospitals throughout the United States. In addition to patient demographics, disease characteristics, and procedures, the database collects information about all billed services rendered during a patient's hospital stay. Data in Perspective undergo a rigorous quality control process, and this data set

has been used in several outcomes studies.²²⁻²⁵ In 2006, almost 5.5 million hospital discharges (representing approximately 15% of all hospitalizations) were captured in Perspective.²²

PATIENT SELECTION

We analyzed patients with neutropenia treated from January 1, 2000, through March 31, 2010. Only patients with an admitting or primary diagnosis of neutropenia (*International Classification of Diseases, Ninth Revision [ICD-9]* code 288.0) in combination with an ICD-9 code for a solid tumor were included in this study. Prior studies have captured hospital admissions for neutropenia using a variety of methods, often classifying patients with a primary diagnosis of fever or infection as having FN.^{1-3,26} To capture initial decision making and treatment, we focused our analysis on only hospitalized patients with a primary or admitting diagnosis of neutropenia. Primary tumor sites were classified into the following groups: colorectal, other gastrointestinal, head and neck, lung, breast, skin, soft tissue, genitourinary, gynecologic, lymphoma, or brain.

While numerous risk stratification systems for FN have attempted to use clinical scenarios associated with high-risk neutropenia, no consensus exists and there is no objective system to stratify risk using population-based administrative data.^{6,7} We performed a series of sensitivity analyses to develop a risk stratification schema using administrative data. We first developed univariate regression models to examine the risk of in-hospital death associated with each of the clinical, demographic, and disease characteristics of our cohort (**Table 1**). On the basis of data from these analyses, we then developed a series of models sequentially incorporating combinations of the variables associated with death. A final model incorporating the characteristics that remained associated with death was developed. In the model, sepsis, pneumonia, hypotension, intensive care unit admission, and mechanical ventilatory assistance remained independently associated with death. We classified patients as high risk if they had any of the aforementioned 5 clinical characteristics.

CLINICAL AND DEMOGRAPHIC CHARACTERISTICS

Clinical data analyzed included age (<60 and ≥60 years), date of admission (2000-2003, 2004-2006, or 2007-2010), race (white, black, or other [including Hispanic, Asian and patients with undefined race]), marital status, and insurance status (Medicare, Medicaid, commercial, self-pay, and unknown). Each patient's admitting physician was noted and his or her specialty classified as follows: medical oncology (including hematology), internal medicine (other than medical oncology), family practice, hospitalist, other, or unknown. Hospitals in which patients were treated were characterized based on location (metropolitan or nonmetropolitan), region of the country (northeast, midwest, west, or south), size (<400, 400-600, and >600 beds), and teaching status (teaching or non-teaching).

Risk adjustment for comorbid conditions was performed using the Charlson Comorbidity Index.^{27,28} Each physician's and hospital's annual FN volume was estimated by dividing the number of subjects admitted with FN by the number of years an individual hospital or physician contributed at least one patient with FN to the cohort. The distribution of annual FN volume was analyzed and cut points selected to create 3 tertiles of physician (low, <1.4 cases per year; intermediate, 1.4-2.7 cases per year; or high, >2.7 cases per year) and hospital FN volumes (low, <8.375 cases per year; intermediate, 8.375-14.59 cases per year; or high, ≥14.6 cases per year) as previously described.^{29,30}

Table 2. Univariate and Multivariate Analysis of Factors Associated With Use of Guideline-Based Antibiotics

| Variable | No. (%) ^a | Odds Ratio | |
|---------------------|----------------------|-------------------------------|-------------------------------|
| | | Univariate | Multivariate |
| Total No. | 19 897 (78.9) | | |
| Age, y | | | |
| <60 | 9111 (81.3) | 1 [Reference] | 1 [Reference] |
| ≥60 | 10 786 (77.0) | 0.77 (0.72-0.82) ^b | 0.89 (0.81-0.98) ^b |
| Sex | | | |
| Male | 8057 (80.8) | 1 [Reference] | 1 [Reference] |
| Female | 11 840 (77.6) | 0.82 (0.77-0.88) ^b | 0.82 (0.75-0.90) ^b |
| Year of diagnosis | | | |
| 2000-2003 | 5563 (75.1) | 1 [Reference] | 1 [Reference] |
| 2004-2006 | 5807 (78.9) | 1.24 (1.15-1.34) ^b | 1.17 (1.06-1.28) ^b |
| 2007-2010 | 8527 (81.5) | 1.46 (1.36-1.57) ^b | 1.40 (1.27-1.53) ^b |
| Race | | | |
| White | 14 541 (79.4) | 1 [Reference] | 1 [Reference] |
| Black | 1934 (81.3) | 1.13 (1.01-1.26) ^b | 1.12 (0.98-1.27) |
| Other | 3422 (75.5) | 0.80 (0.74-0.87) ^b | 0.96 (0.87-1.07) |
| Marital status | | | |
| Married | 11 293 (79.4) | 1 [Reference] | 1 [Reference] |
| Single | 2974 (81.5) | 1.14 (1.04-1.25) ^b | 0.98 (0.87-1.09) |
| Unknown | 5630 (76.5) | 0.84 (0.79-0.90) ^b | 0.91 (0.84-0.99) ^b |
| Insurance status | | | |
| Medicare | 8251 (76.4) | 1 [Reference] | 1 [Reference] |
| Medicaid | 1746 (81.9) | 1.39 (1.24-1.57) ^b | 1.25 (1.07-1.46) ^b |
| Commercial | 8928 (80.5) | 1.27 (1.19-1.36) ^b | 1.19 (1.08-1.30) ^b |
| Uninsured | 484 (83.0) | 1.51 (1.21-1.88) ^b | 1.39 (1.07-1.80) ^b |
| Unknown | 488 (78.0) | 1.09 (0.90-1.32) | 1.03 (0.82-1.30) |
| Location | | | |
| Metropolitan | 17 312 (79.0) | 1 [Reference] | 1 [Reference] |
| Nonmetropolitan | 2585 (78.2) | 0.95 (0.87-1.04) | 1.05 (0.91-1.21) |
| Teaching status | | | |
| Nonteaching | 10 697 (76.0) | 1 [Reference] | 1 [Reference] |
| Teaching | 9200 (82.5) | 1.49 (1.40-1.59) ^b | 1.32 (1.18-1.48) ^b |
| Hospital size, beds | | | |
| <400 | 8804 (76.7) | 1 [Reference] | 1 [Reference] |
| 400-600 | 5799 (78.7) | 1.12 (1.04-1.20) ^b | 0.94 (0.84-1.07) |
| >600 | 5294 (82.9) | 1.47 (1.36-1.59) ^b | 0.97 (0.82-1.13) |
| Hospital location | | | |
| Eastern | 2706 (82.9) | 1 [Reference] | 1 [Reference] |
| Midwest | 4076 (81.0) | 0.88 (0.79-0.99) ^b | 0.90 (0.76-1.06) |
| Southern | 10 535 (78.2) | 0.74 (0.67-0.81) ^b | 0.74 (0.64-0.86) ^b |
| West | 2580 (74.6) | 0.60 (0.54-0.68) ^b | 0.77 (0.64-0.92) ^b |

(continued)

MAIN OUTCOME MEASURES

The following 3 primary end points were analyzed: use of guideline-based antibiotics, use of vancomycin, and use of GCSF. These outcomes were based on a review of published treatment guidelines for FN.^{6-12,31} We chose a permissive definition of guideline-based antibiotics that included all antibiotics that have been recommended by consensus groups in guidelines during the last decade.^{6,10,32} Administration of 1 dose of any of the following antibiotics within 48 hours of hospital admission was considered guideline-based antibiotic therapy: cefepime hydrochloride, ceftazidime, imipenem hydrochloride, meropenem, piperacillin sodium/tazobactam sodium, and an aminoglycoside (any) in combination with any of the aforementioned agents or ciprofloxacin hydrochloride or ticarcillin/clavulanate potassium.^{6,10} Use of vancomycin was defined as at least 1 dose of vancomycin during the first 48 hours of hospitalization.^{6,10} Use of GCSF was defined as at least 1 dose of either filgrastim or pegfilgrastim during the hospitalization.^{6,8,9,11,12,31} For patients who received filgrastim,

we calculated the total number of days in which the drug was given.

We examined how the use of guideline-based therapy influenced nonroutine discharge (discharge to a nursing home, skilled nursing facility, or acute or subacute rehabilitation center), in-hospital mortality, and cost. Among patients who received GCSF, we examined the number of days in which filgrastim was administered. Cost estimates for the total number of doses administered to low- and high-risk patients were then calculated using published 2010 Medicare reimbursement schedules (filgrastim, 300 µg/d, at \$233.43 per dose).

STATISTICAL ANALYSIS

Frequency distributions between categorical variables were compared using the χ^2 test. We used hierarchical logistic regression analysis to determine the factors associated with guideline-based antibiotics, vancomycin and GCSF use, nonroutine hospital discharge, and death. These models included all patient, physician, and hospital characteristics as well as

Table 2. Univariate and Multivariate Analysis of Factors Associated With Use of Guideline-Based Antibiotics (continued)

| Variable | No. (%) ^a | Odds Ratio | |
|-----------------------------------|----------------------|-------------------------------|-------------------------------|
| | | Univariate | Multivariate |
| Comorbidity | | | |
| <2 | 2662 (79.6) | 1 [Reference] | 1 [Reference] |
| 2 | 3267 (79.2) | 0.98 (0.87-1.09) | 0.94 (0.82-1.07) |
| >2 | 13 968 (78.6) | 0.94 (0.86-1.03) | 0.89 (0.79-0.99) ^b |
| Physician specialty | | | |
| Medical oncology | 12 741 (79.5) | 1 [Reference] | 1 [Reference] |
| Internal medicine | 3916 (79.1) | 0.98 (0.91-1.06) | 1.12 (0.99-1.26) |
| Family practice | 1084 (76.0) | 0.82 (0.72-0.93) ^b | 0.98 (0.83-1.17) |
| Hospitalist | 715 (82.8) | 1.24 (1.04-1.49) ^b | 1.49 (1.18-1.88) ^b |
| Other | 863 (72.1) | 0.67 (0.59-0.76) ^b | 0.76 (0.63-0.93) ^b |
| Unknown | 578 (76.4) | 0.84 (0.70-0.99) ^b | 1.02 (0.74-1.40) |
| Physician volume | | | |
| Low | 6417 (77.2) | 1 [Reference] | 1 [Reference] |
| Intermediate | 6664 (78.6) | 1.09 (1.01-1.17) ^b | 1.10 (0.98-1.23) |
| High | 6816 (80.8) | 1.24 (1.15-1.34) ^b | 1.19 (1.03-1.38) ^b |
| Hospital volume | | | |
| Low | 6256 (74.8) | 1 [Reference] | 1 [Reference] |
| Intermediate | 6527 (78.4) | 1.23 (1.14-1.32) ^b | 1.22 (1.08-1.37) ^b |
| High | 7114 (83.3) | 1.68 (1.55-1.81) ^b | 1.56 (1.34-1.81) ^b |
| Primary tumor site | | | |
| Colorectal | 1647 (76.9) | 0.88 (0.80-0.98) ^b | 0.87 (0.65-1.16) |
| Other gastrointestinal | 1513 (78.8) | 1.00 (0.89-1.12) | 0.87 (0.65-1.17) |
| Head and neck | 922 (82.2) | 1.25 (1.07-1.46) ^b | 1.06 (0.78-1.44) |
| Lung | 4800 (77.0) | 0.86 (0.81-0.93) ^b | 0.83 (0.63-1.10) |
| Breast | 5257 (78.5) | 0.97 (0.91-1.04) | 0.99 (0.75-1.30) |
| Skin | 180 (84.5) | 1.47 (1.01-2.13) ^b | 1.46 (0.91-2.34) |
| Soft tissue | 894 (88.3) | 2.08 (1.71-2.53) ^b | 1.74 (1.24-2.44) ^b |
| Genitourinary | 1104 (77.3) | 0.91 (0.80-1.03) | 0.77 (0.58-1.03) |
| Gynecologic | 1056 (72.4) | 0.69 (0.61-0.77) | 0.75 (0.55-1.01) |
| Lymphoma | 2582 (84.1) | 1.48 (1.34-1.64) ^b | 1.25 (0.94-1.66) ^b |
| Brain | 169 (74.1) | 0.77 (0.57-1.03) | 0.60 (0.39-0.93) ^b |
| Disease characteristics | | | |
| Sepsis | 2572 (83.3) | 1.39 (1.25-1.53) ^b | 1.32 (1.17-1.48) ^b |
| Pneumonia | 1698 (83.2) | 1.36 (1.21-1.54) ^b | 1.40 (1.22-1.61) ^b |
| Intensive care use | 227 (14.0) | 1.70 (1.48-1.97) ^b | 1.62 (1.36-1.93) ^b |
| Hypotension | 78 (83.0) | 1.31 (0.76-2.24) | 1.28 (0.70-2.33) |
| Mechanical ventilatory assistance | 336 (86.4) | 1.71 (1.28-2.29) ^b | 1.17 (0.83-1.65) |

^a Reflects the percentage of patients who received guideline-concordant care.

^b $P < .05$.

physician- and hospital-specific random effects. Separate models were developed for low- and high-risk patients. A priori with our sample size of approximately 25 000 patients, we estimated that with an α of .05 and power of 80% that the minimum detectable odds ratio (OR) for the detection of an outcome of interest even for a relatively uncommon characteristic (20%) was 1.11. All analyses were performed using SAS, version 9.2 (SAS Institute, Inc).

RESULTS

A total of 25 231 patients with FN were identified. Guideline-based antibiotics were administered to 19 897 patients (78.9%) (Table 2). The use of guideline-based antibiotics increased minimally over time from 73.4% in 2000 to 80.3% in 2010 ($P < .001$) (Figure 1A). Guideline-based antibiotics were used in 77.8% of low-risk patients and 82.7% ($P < .001$) of high-risk patients.

Patients treated more recently (OR, 1.40; 95% CI, 1.27-1.53), black patients (1.12; 0.98-1.27), those at teaching hospitals (1.32; 1.18-1.48), patients treated at high-volume hospitals (1.56; 1.34-1.81) and by high FN-volume physicians (1.19; 1.03-1.38), those cared for by hospitalists (1.49; 1.18-1.88), and patients treated in the intensive care unit or those with sepsis or pneumonia were more likely to receive guideline-based antibiotics (Table 2). Likewise, compared with those who have Medicare, Medicaid recipients and patients with commercial insurance were more likely to receive guideline-based antibiotics. In contrast, older patients (OR, 0.89; 95% CI, 0.81-0.98) and women (0.82; 0.75-0.90) were less likely to receive guideline-based antibiotics.

Up-front vancomycin was administered to 9311 patients (36.9%) and increased with time from 17.2% in 2000 to 54.9% in 2010 ($P < .001$) (Figure 1B). Vancomycin was used in 33.1% of low-risk patients and in 50.8%

of high-risk patients. Patients with more severe disease (ie, sepsis, pneumonia, and those in the intensive care unit) more often received vancomycin (**Table 3**). Black patients (OR, 1.21; 95% CI, 1.08-1.35), patients with more than 2 comorbidities (1.12; 1.02-1.24), and those treated at large hospitals (1.30; 1.13-1.50) were more likely to receive vancomycin. Nonmetropolitan residents (0.71; 0.62-0.81) were less likely to receive vancomycin. Use of vancomycin was inversely associated with physician case volume. Compared with medical oncologists, other internists (OR, 1.38; 95% CI, 1.23-1.54) and hospitalists (1.61; 1.32-1.96) more often used vancomycin.

Despite recommendations against empiric use, GCSF were given to 15 880 patients (62.9%) and only decreased with time from 72.5% in 2000 to 55.0% in 2010 ($P < .001$) (Figure 1C). Granulocyte colony-stimulating factors were used in 62.1% of low-risk patients and in 65.9% of high-risk patients. Among patients who received filgrastim, 15.2% received 1 day of treatment and 22.2% received 2 days, while 13.0% received the agent for longer than 5 days (**Figure 2A**). In the cohort that received 1 to 2 days of filgrastim, 33.8% had a hospital stay of shorter than 3 days while 27.4% were hospitalized for longer than 5 days. Among patients who received filgrastim, 14.8% received the drug for less than 25% of the days of their hospitalization, 33.0% for 25% to 50% of their hospitalization, and 30.1% for 51% to 75% of their hospitalization. Those who received GCSF (22.2%) received them for longer than 75% of the days in which they were hospitalized (Figure 2B). Patients treated at teaching hospitals (OR, 0.71; 95% CI, 0.63-0.80) and those at large hospitals (0.80; 0.67-0.95) were less likely to receive GCSF (Table 3). Use of GCSF was higher in patients with pneumonia and those admitted to the intensive care unit. Among the 12 184 low-risk patients who received filgrastim, a total of 40 080 daily doses were administered at a cost of \$9 355 874. The 3570 high-risk patients who received filgrastim received a total of 14 351 daily doses at a cost of \$3 349 954.

The effect of adherence to guideline-based treatment recommendations on adverse outcomes was examined (**Table 4**). Among low-risk patients, use of guideline-based antibiotics reduced the risk of nonroutine hospital discharge by 23% (OR, 0.77; 95% CI, 0.65-0.92) and reduced in-hospital mortality by 37% (0.65; 0.42-0.95). In contrast, use of empiric vancomycin and GCSF did not improve outcomes. In general, among low-risk patients with FN, adverse outcomes were more common in older patients, Medicare beneficiaries, and those with more comorbid diseases. For high-risk patients with FN, no association was noted between use of guideline-based antibiotics and improved outcomes. Likewise, use of vancomycin and GCSF did not positively influence outcomes.

COMMENT

We noted substantial variability in the allocation of guideline-based care for cancer patients with FN. The use of appropriate empiric antibiotic therapy is high and increasing, with more than 80% of patients admitted with FN receiving guideline-concordant antibiotics in 2010. How-

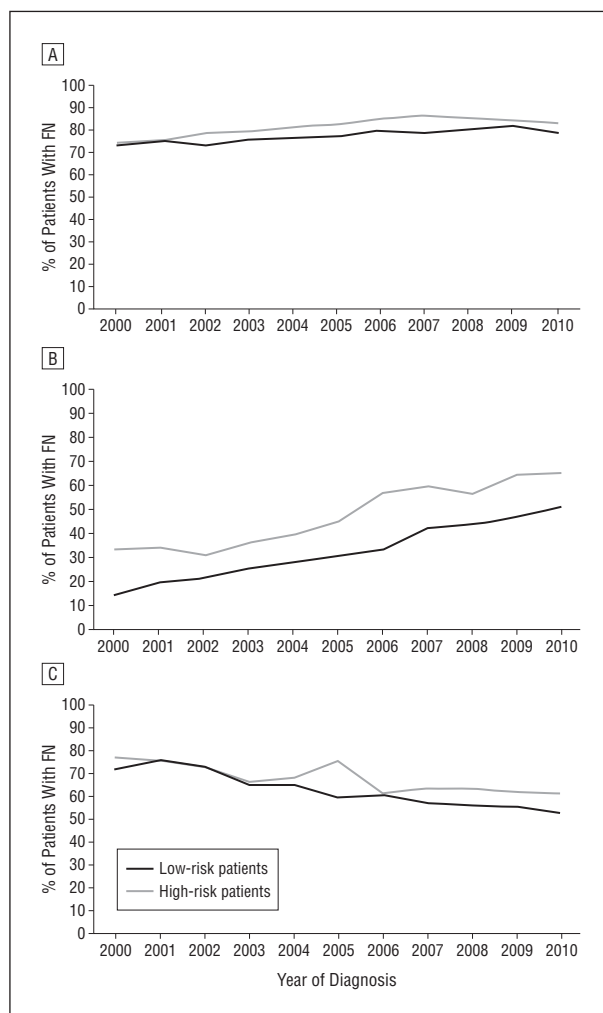


Figure 1. Use of guideline- and nonguideline-based treatment for cancer patients with febrile neutropenia (FN) stratified into low- and high-risk groups. A, Guideline-based antibiotics. B, Vancomycin treatment. C, Granulocyte colony-stimulating factors use.

ever, use of vancomycin and GCSF also remains common despite guideline recommendations against routine use.

Prior studies of practice patterns for the treatment and prevention of FN have suggested that recommendations by clinicians are often poorly aligned with guideline-based care.¹⁹⁻²¹ In a survey of more than 1200 members of the American Society of Clinical Oncology addressing the management of low-risk patients with FN, Freifeld et al²¹ noted that most respondents recommended nonguideline-concordant antibiotics and that 48% adjunctively used GCSF for low-risk patients.²¹ While guideline-based antibiotics were correctly given to almost three-quarters of the patients in our cohort, we identified widespread overuse of empiric vancomycin and GCSF.

The use of therapeutic GCSF for high-risk patients with established FN remains an area of controversy. Randomized clinical trials and meta-analyses have suggested that therapeutic GCSF use is associated with small (1 day), but statistically significant, reductions in length of stay and time to neutrophil recovery but has no effect on mortality.¹³⁻¹⁷ Despite the lack of convincing data, some consensus guidelines suggest that GCSF can be “considered” in higher-risk

Table 3. Univariate and Multivariate Analysis of Factors Associated With Use of Nonguideline-Based Care, With Vancomycin and Granulocyte Colony-Stimulating Factors

| Variable | Vancomycin Treatment | | | Granulocyte Colony-Stimulating Factors Treatment | | |
|---------------------|----------------------|-------------------------------|-------------------------------|--------------------------------------------------|-------------------------------|-------------------------------|
| | No. (%) ^a | Odds Ratio | | No. (%) ^a | Odds Ratio | |
| | | Univariate | Multivariate | | Univariate | Multivariate |
| Total No. | 9311 (36.9) | | | 15 880 (62.9) | | |
| Age, y | | | | | | |
| <60 | 4484 (40.0) | 1 [Reference] | 1 [Reference] | 6775 (60.5) | 1 [Reference] | 1 [Reference] |
| ≥60 | 4827 (34.4) | 0.77 (0.72-0.84) ^b | 0.77 (0.71-0.84) ^b | 9105 (64.9) | 1.22 (1.15-1.28) ^b | 1.10 (1.01-1.20) ^b |
| Sex | | | | | | |
| Male | 3824 (38.3) | 1 [Reference] | 1 [Reference] | 6442 (64.6) | 1 [Reference] | 1 [Reference] |
| Female | 5487 (36.0) | 0.90 (0.86-0.95) ^b | 1.00 (0.93-1.09) | 9438 (61.9) | 0.89 (0.84-0.94) ^b | 1.03 (0.94-1.12) |
| Year of diagnosis | | | | | | |
| 2000-2003 | 1691 (22.8) | 1 [Reference] | 1 [Reference] | 5261 (71.0) | 1 [Reference] | 1 [Reference] |
| 2004-2006 | 2526 (34.3) | 1.56 (1.44-1.70) ^b | 1.73 (1.58-1.89) ^b | 4613 (62.7) | 0.69 (0.64-0.74) ^b | 0.58 (0.53-0.63) ^b |
| 2007-2010 | 5094 (48.7) | 2.97 (2.73-3.22) ^b | 3.40 (3.11-3.71) ^b | 6006 (57.4) | 0.55 (0.52-0.59) ^b | 0.42 (0.38-0.46) ^b |
| Race | | | | | | |
| White | 6705 (36.6) | 1 [Reference] | 1 [Reference] | 11 257 (61.5) | 1 [Reference] | 1 [Reference] |
| Black | 1064 (44.7) | 1.12 (1.01-1.25) ^b | 1.21 (1.08-1.35) ^b | 1524 (64.1) | 1.12 (1.02-1.22) ^b | 1.17 (1.04-1.32) ^b |
| Other | 1542 (34.0) | 0.94 (0.85-1.03) | 0.92 (0.84-1.01) | 3099 (68.4) | 1.36 (1.27-1.45) ^b | 1.22 (1.10-1.35) ^b |
| Marital status | | | | | | |
| Married | 5198 (36.6) | 1 [Reference] | 1 [Reference] | 8983 (63.2) | 1 [Reference] | 1 [Reference] |
| Single | 1592 (43.6) | 1.06 (0.97-1.16) | 1.10 (1.00-1.22) ^b | 2275 (62.3) | 0.96 (0.89-1.04) | 1.03 (0.93-1.14) |
| Unknown | 2521 (34.2) | 0.98 (0.91-1.06) | 0.96 (0.89-1.04) | 4622 (62.8) | 0.98 (0.93-1.04) | 0.96 (0.88-1.04) |
| Insurance status | | | | | | |
| Medicare | 3761 (34.4) | 1 [Reference] | 1 [Reference] | 7048 (65.3) | 1 [Reference] | 1 [Reference] |
| Medicaid | 818 (38.4) | 0.96 (0.85-1.09) | 0.94 (0.83-1.08) | 1341 (62.9) | 0.90 (0.82-0.99) ^b | 1.05 (0.91-1.20) |
| Commercial | 4275 (38.5) | 1.04 (0.96-1.12) | 1.05 (0.97-1.15) | 6729 (60.7) | 0.82 (0.78-0.87) ^b | 0.93 (0.85-1.01) |
| Uninsured | 219 (37.6) | 0.87 (0.70-1.06) | 0.84 (0.67-1.05) | 384 (65.9) | 1.03 (0.86-1.22) | 1.04 (0.82-1.31) |
| Unknown | 238 (38.0) | 1.09 (0.90-1.33) | 1.07 (0.86-1.32) | 378 (60.4) | 0.81 (0.69-0.96) ^b | 0.87 (0.70-1.09) |
| Location | | | | | | |
| Metropolitan | 8319 (37.9) | 1 [Reference] | 1 [Reference] | 13 815 (63.0) | 1 [Reference] | 1 [Reference] |
| Nonmetropolitan | 992 (30.0) | 0.75 (0.61-0.92) ^b | 0.71 (0.62-0.81) | 2065 (62.4) | 0.98 (0.90-1.05) | 0.90 (0.77-1.06) |
| Teaching status | | | | | | |
| Nonteaching | 4828 (34.3) | 1 [Reference] | 1 [Reference] | 9212 (65.4) | 1 [Reference] | 1 [Reference] |
| Teaching | 4483 (40.2) | 1.16 (0.96-1.39) | 1.10 (0.99-1.22) | 6668 (59.8) | 0.79 (0.75-0.83) ^b | 0.71 (0.63-0.80) ^b |
| Hospital size, beds | | | | | | |
| <400 | 3867 (33.7) | 1 [Reference] | 1 [Reference] | 7308 (63.7) | 1 [Reference] | 1 [Reference] |
| 400-600 | 2560 (34.7) | 1.06 (0.87-1.29) | 0.97 (0.87-1.09) | 4871 (66.1) | 1.11 (1.05-1.18) ^b | 1.22 (1.07-1.40) ^b |
| >600 | 2884 (45.2) | 1.34 (1.01-1.78) ^b | 1.30 (1.13-1.50) ^b | 3701 (58.0) | 0.79 (0.74-0.84) ^b | 0.80 (0.67-0.95) ^b |
| Hospital location | | | | | | |
| Eastern | 1344 (41.2) | 1 [Reference] | 1 [Reference] | 2073 (63.5) | 1 [Reference] | 1 [Reference] |
| Midwest | 2020 (40.2) | 1.09 (0.85-1.40) | 1.06 (0.92-1.22) | 3055 (60.7) | 0.89 (0.81-0.97) ^b | 0.72 (0.61-0.86) ^b |
| Southern | 4765 (35.4) | 1.03 (0.81-1.31) | 0.97 (0.85-1.11) | 8396 (62.3) | 0.95 (0.88-1.03) | 0.96 (0.82-1.12) |
| West | 1182 (34.2) | 0.89 (0.67-1.18) | 0.84 (0.71-0.99) ^b | 2356 (68.1) | 1.23 (1.11-1.36) ^b | 1.10 (0.91-1.34) |
| Comorbidity | | | | | | |
| <2 | 1162 (34.8) | 1 [Reference] | 1 [Reference] | 2058 (61.5) | 1 [Reference] | 1 [Reference] |
| 2 | 1468 (35.6) | 0.99 (0.89-1.11) | 0.98 (0.88-1.10) | 2505 (60.7) | 0.97 (0.88-1.06) | 0.95 (0.85-1.08) |
| >2 | 6681 (37.6) | 1.13 (1.03-1.23) ^b | 1.12 (1.02-1.24) ^b | 11 317 (63.7) | 1.10 (1.02-1.18) ^b | 1.04 (0.94-1.16) |
| Physician specialty | | | | | | |
| Medical oncology | 5674 (35.4) | 1 [Reference] | 1 [Reference] | 9899 (61.7) | 1 [Reference] | 1 [Reference] |
| Internal medicine | 2163 (43.7) | 1.28 (1.16-1.41) ^b | 1.38 (1.23-1.54) ^b | 3306 (66.8) | 1.25 (1.17-1.33) ^b | 1.23 (1.08-1.40) ^b |
| Family practice | 498 (34.9) | 0.94 (0.81-1.09) | 0.93 (0.79-1.10) | 870 (61.0) | 0.97 (0.87-1.08) | 0.97 (0.80-1.16) |
| Hospitalist | 438 (50.7) | 1.62 (1.36-1.93) ^b | 1.61 (1.32-1.96) ^b | 533 (61.7) | 1.00 (0.87-1.15) | 0.99 (0.79-1.25) |
| Other | 381 (31.8) | 0.78 (0.67-0.92) ^b | 0.75 (0.62-0.91) ^b | 757 (63.2) | 1.07 (0.94-1.20) | 1.03 (0.83-1.28) |
| Unknown | 157 (20.7) | 1.03 (0.79-1.35) | 1.10 (0.80-1.52) | 515 (68.0) | 1.32 (1.13-1.54) ^b | 0.68 (0.47-0.98) ^b |
| Physician volume | | | | | | |
| Low | 3343 (40.2) | 1 [Reference] | 1 [Reference] | 5350 (64.3) | 1 [Reference] | 1 [Reference] |
| Intermediate | 3107 (36.6) | 0.99 (0.91-1.07) | 0.94 (0.85-1.04) | 5407 (63.8) | 0.98 (0.92-1.04) | 1.02 (0.90-1.15) |
| High | 2861 (33.9) | 0.88 (0.80-0.97) ^b | 0.77 (0.67-0.88) ^b | 5123 (60.7) | 0.86 (0.80-0.91) ^b | 0.88 (0.74-1.04) |
| Hospital volume | | | | | | |
| Low | 2742 (32.8) | 1 [Reference] | 1 [Reference] | 5492 (65.7) | 1 [Reference] | 1 [Reference] |
| Intermediate | 2979 (35.8) | 1.03 (0.85-1.24) | 1.25 (1.12-1.39) ^b | 5276 (63.4) | 0.91 (0.85-0.97) ^b | 0.95 (0.83-1.08) |
| High | 3590 (42.0) | 1.21 (0.92-1.57) | 1.45 (1.27-1.65) ^b | 5112 (59.8) | 0.78 (0.73-0.83) ^b | 1.04 (0.89-1.23) |

(continued)

Table 3. Univariate and Multivariate Analysis of Factors Associated With Use of Nonguideline-Based Care, With Vancomycin and Granulocyte Colony-Stimulating Factors (continued)

| Variable | Vancomycin Treatment | | | Granulocyte Colony-Stimulating Factors Treatment | | |
|-----------------------------------|----------------------|-------------------------------|-------------------------------|--------------------------------------------------|-------------------------------|-------------------------------|
| | No. (%) ^a | Odds Ratio | | No. (%) ^a | Odds Ratio | |
| | | Univariate | Multivariate | | Univariate | Multivariate |
| Primary tumor site | | | | | | |
| Colorectal | 793 (37.0) | 1.17 (0.92-1.48) | 1.21 (0.94-1.56) | 1476 (68.9) | 1.34 (1.22-1.47) ^b | 1.29 (0.98-1.70) |
| Other gastrointestinal | 743 (38.7) | 1.24 (0.98-1.58) | 1.31 (1.01-1.69) ^b | 1257 (65.5) | 1.13 (1.02-1.24) ^b | 1.18 (0.89-1.56) |
| Head and neck | 475 (42.3) | 1.38 (1.08-1.77) ^b | 1.42 (1.09-1.86) ^b | 753 (67.1) | 1.21 (1.07-1.38) ^b | 1.24 (0.92-1.65) |
| Lung | 1998 (32.1) | 0.90 (0.72-1.13) ^b | 0.91 (0.72-1.17) | 4069 (65.3) | 1.14 (1.08-1.21) ^b | 1.05 (0.81-1.36) |
| Breast | 2331 (34.8) | 1.15 (0.91-1.45) ^b | 1.17 (0.92-1.50) | 3922 (58.6) | 0.78 (0.74-0.82) ^b | 0.74 (0.56-0.96) ^b |
| Skin | 98 (46.0) | 1.68 (1.18-2.40) ^b | 1.85 (1.26-2.72) ^b | 141 (66.2) | 1.15 (0.87-1.54) | 1.02 (0.66-1.56) |
| Soft tissue | 455 (45.0) | 1.49 (1.15-1.92) ^b | 1.66 (1.25-2.19) ^b | 519 (51.3) | 0.61 (0.54-0.69) ^b | 0.64 (0.47-0.86) ^b |
| Genitourinary | 523 (36.6) | 1.08 (0.86-1.39) | 1.13 (0.87-1.46) | 948 (66.3) | 1.17 (1.05-1.31) ^b | 1.10 (0.83-1.46) |
| Gynecologic | 478 (32.8) | 0.99 (0.77-1.28) | 1.11 (0.84-1.46) | 967 (66.3) | 1.17 (1.05-1.31) ^b | 1.10 (0.82-1.48) |
| Lymphoma | 1445 (47.1) | 1.76 (1.39-2.22) ^b | 1.85 (1.44-2.39) ^b | 1856 (60.5) | 0.89 (0.82-0.96) ^b | 0.85 (0.65-1.12) |
| Brain | 100 (43.9) | 1.46 (1.02-2.10) ^b | 1.40 (0.93-2.09) | 158 (69.3) | 1.33 (1.00-1.77) ^b | 1.57 (1.00-2.46) ^b |
| Disease characteristics | | | | | | |
| Sepsis | 1668 (54.0) | 1.80 (1.64-1.97) ^b | 1.86 (1.69-2.05) ^b | 2006 (65.0) | 1.11 (1.02-1.20) ^b | 1.02 (0.92-1.14) |
| Pneumonia | 998 (48.9) | 1.61 (1.44-1.79) ^b | 1.65 (1.47-1.85) ^b | 1371 (67.2) | 1.23 (1.11-1.35) ^b | 1.24 (1.09-1.40) ^b |
| Intensive care use | 1059 (65.1) | 2.38 (2.09-2.71) ^b | 2.63 (2.29-3.03) ^b | 1171 (72.0) | 1.55 (1.39-1.74) ^b | 1.64 (1.40-1.92) ^b |
| Hypotension | 38 (40.4) | 0.89 (0.56-1.42) | 0.98 (0.59-1.6) | 66 (70.2) | 1.39 (0.89-2.16) | 1.41 (0.81-2.47) |
| Mechanical ventilatory assistance | 271 (69.7) | 1.78 (1.37-2.31) ^b | 1.81 (1.37-2.40) ^b | 276 (71.0) | 1.45 (1.16-1.80) ^b | 1.04 (0.77-1.41) |

^a Reflects the percentage of patients who received guideline-concordant care.

^b $P < .05$.

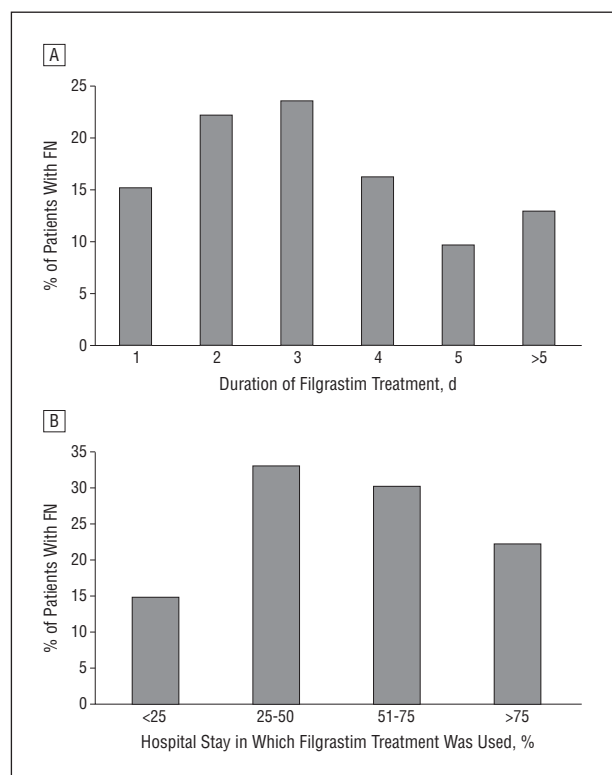


Figure 2. Use of filgrastim treatment in cancer patients with febrile neutropenia (FN). A. Number of days of filgrastim use. B. Percentage of hospital days in which filgrastim was used in patients who received the drug.

patients with profound or prolonged FN or FN associated with severe infectious complications (ie, sepsis, pneumonia, or hypotension).^{9,12} However, the most recent rendition of the

Infectious Disease Society of America guidelines for FN continue to recommend against therapeutic GCSF for all patients with FN given the cost and adverse effects of the drugs.⁶ We noted that use of GCSF remains common, but perhaps more concerning was the pattern of use of GCSF in patients who received the drug. More than one-third of patients received only 1 or 2 days of filgrastim, a dose unlikely to lead to any meaningful clinical benefit.⁹ We previously noted similar findings in patients receiving erythropoiesis-stimulating agents; misuse was common, with almost one-quarter of patients receiving only 1 week of therapy.³²

While patient characteristics, such as age, race, and insurance status, influenced patterns of care for FN, we noted that physician and hospital factors also impacted treatment choices. Overall, FN case volume had the strongest association with guideline adherence. Patients treated at high FN-volume hospitals were more likely to receive guideline-based antibiotics and vancomycin treatment and less likely to receive GCSF treatment, while patients managed by high FN-volume physicians were more likely to receive appropriate antibiotics and less likely to receive vancomycin treatment. While the association among volume, treatment, and outcome has received the most attention for surgical procedures, there is growing recognition that volume affects care for common medical conditions as well.^{33,34} Physician specialty was also associated with treatment choice; hospitalists were more likely to use guideline-based antibiotics and more likely to treat cancer patients with FN with vancomycin. Prior work has suggested that care by hospitalists is associated with reduced cost for common medical conditions.³⁵

Among lower-risk patients with FN, prompt administration of guideline-based antibiotics was associated with reduced in-hospital mortality. The demonstration that

Table 4. Effect of Treatment Patterns on Outcome for Low- and High-Risk Cancer Patients With Febrile Neutropenia

| Variable | Low-Risk Patients | | High-Risk Patients | |
|---------------------|-----------------------------------|-------------------------------|-----------------------------------|-------------------------------|
| | Nonroutine Discharge (n = 882) | Death (n = 273) | Nonroutine Discharge (n = 619) | Death (n = 555) |
| Age, y | | | | |
| <60 | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| ≥60 | 2.16 (0.88-1.27) | 2.71 (1.62-4.54) ^a | 1.53 (1.17-2.00) ^a | 1.61 (1.15-2.25) ^a |
| Sex | | | | |
| Male | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| Female | 1.05 (0.88-1.27) | 0.98 (0.66-1.47) | 1.22 (0.99-1.51) | 0.98 (0.74-1.28) |
| Year of diagnosis | | | | |
| 2000-2003 | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| 2004-2006 | 1.07 (0.87-1.31) | 0.73 (0.46-1.16) | 1.01 (0.78-1.31) | 0.70 (0.50-0.97) ^a |
| 2007-2010 | 0.95 (0.78-1.17) | 0.61 (0.37-1.01) | 0.96 (0.74-1.23) | 0.66 (0.48-0.90) ^a |
| Race | | | | |
| White | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| Black | 1.25 (0.96-1.63) | 1.32 (0.70-2.52) | 1.01 (0.75-1.38) | 1.16 (0.77-1.74) |
| Other | 0.92 (0.74-1.14) | 1.08 (0.59-1.98) | 0.72 (0.55-0.95) ^a | 0.99 (0.70-1.39) |
| Marital status | | | | |
| Married | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| Single | 2.31 (1.83-2.92) ^a | 0.86 (0.45-1.62) | 1.60 (1.20-2.13) ^a | 1.17 (0.81-1.70) |
| Unknown | 1.84 (1.54-2.20) ^a | 0.84 (0.55-1.28) | 1.58 (1.29-1.94) ^a | 0.94 (0.72-1.24) |
| Insurance status | | | | |
| Medicare | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| Medicaid | 0.57 (0.40-0.80) ^a | 1.47 (0.71-3.07) | 0.54 (0.36-0.82) ^a | 0.65 (0.38-1.11) |
| Commercial | 0.50 (0.40-0.61) ^a | 0.65 (0.41-1.03) | 0.56 (0.44-0.71) ^a | 0.73 (0.54-0.99) ^a |
| Uninsured | 0.34 (0.16-0.71) ^a | 1.82 (0.59-5.61) | 0.07 (0.01-0.51) ^a | 0.85 (0.35-2.11) |
| Unknown | 0.48 (0.25-0.92) ^a | 1.22 (0.36-4.21) | 0.37 (0.16-0.87) ^a | 0.95 (0.41-2.20) |
| Location | | | | |
| Metropolitan | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| Nonmetropolitan | 0.87 (0.66-1.15) | 0.89 (0.30-2.66) | 1.01 (0.76-1.34) | 1.07 (0.72-1.60) |
| Teaching status | | | | |
| Nonteaching | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| Teaching | 0.96 (0.78-1.19) | 0.94 (0.40-2.20) | 0.98 (0.78-1.23) | 0.91 (0.67-1.25) |
| Hospital size, beds | | | | |
| <400 | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| 400-600 | 1.13 (0.90-1.41) | 1.22 (0.50-3.01) | 1.07 (0.84-1.36) | 0.80 (0.57-1.13) |
| >600 | 0.99 (0.73-1.33) | 1.21 (0.37-3.93) | 1.01 (0.73-1.38) | 0.88 (0.57-1.34) |
| Hospital location | | | | |
| Eastern | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| Midwest | 0.82 (0.62-1.08) | 0.64 (0.19-2.20) | 1.24 (0.91-1.70) | 0.57 (0.36-0.88) ^a |
| Southern | 0.61 (0.47-0.80) ^a | 0.83 (0.28-2.46) | 0.95 (0.70-1.27) | 0.73 (0.49-1.10) |
| West | 0.69 (0.50-0.96) ^a | 0.92 (0.23-3.63) | 0.95 (0.65-1.37) | 0.70 (0.43-1.14) |
| Comorbidity | | | | |
| <2 | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| 2 | 1.50 (1.07-2.10) ^a | 1.90 (0.84-4.27) | 1.47 (0.92-2.34) | 1.50 (0.85-2.66) |
| >2 | 1.89 (1.42-2.52) ^a | 2.26 (1.11-4.60) ^a | 1.81 (1.20-2.73) ^a | 1.49 (0.90-2.45) |
| Physician specialty | | | | |
| Medical oncology | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| Internal medicine | 1.81 (1.43-2.28) ^a | 1.18 (0.46-3.03) | 1.80 (1.40-2.32) ^a | 0.98 (0.70-1.37) |
| Family practice | 1.74 (1.24-2.43) ^a | 1.15 (0.28-4.75) | 1.91 (1.31-2.79) ^a | 1.07 (0.64-1.80) |
| Hospitalist | 2.31 (1.55-3.45) ^a | 0.54 (0.05-6.40) | 1.40 (0.88-2.22) | 0.77 (0.40-1.46) |
| Other | 1.30 (0.87-1.96) | 1.11 (0.24-5.26) | 1.41 (0.88-2.27) | 1.00 (0.52-1.92) |
| Unknown | 1.33 (0.75-2.37) | 2.53 (0.42-15.11) | 1.81 (0.99-3.30) ^a | 0.91 (0.35-2.35) |

(continued)

guideline adherence improves outcomes is not only important for clinical care but also suggests that antibiotic choice can be used as a quality metric for FN. For many diseases, it has been difficult to correlate adherence to a process measure with outcome. The results of a large study examining the well-accepted practice of perioperative antibiotic use indicated that adherence to individual measures had no association with infection and adherence to an all-or-none composite measure had only a modest

association with infection rates.³⁶ We were unable to demonstrate an association between guideline-based antibiotic use and outcomes for higher-risk patients; however, 82.7% of high-risk patients received guideline-based antibiotics and 50.8% received treatment with vancomycin. Although patients who received vancomycin and GCSF may have had more severe underlying disease, we noted that both interventions were associated with increased cost, but neither was associated with

Table 4. Effect of Treatment Patterns on Outcome for Low- and High-Risk Cancer Patients With Febrile Neutropenia (continued)

| Variable | Low-Risk Patients | | High-Risk Patients | |
|---------------------------------------|-----------------------------------|--------------------------------|-----------------------------------|----------------------------------|
| | Nonroutine Discharge (n = 882) | Death (n = 273) | Nonroutine Discharge (n = 619) | Death (n = 555) |
| Physician volume | | | | |
| Low | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| Intermediate | 0.95 (0.77-1.18) | 0.78 (0.32-1.90) | 1.07 (0.85-1.35) | 0.86 (0.62-1.18) |
| High | 1.06 (0.80-1.40) | 0.76 (0.25-2.26) | 1.10 (0.82-1.49) | 0.74 (0.49-1.11) |
| Hospital volume | | | | |
| Low | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| Intermediate | 0.86 (0.69-1.07) | 0.78 (0.43-2.48) | 0.79 (0.63-1.00) | 1.20 (0.87-1.66) |
| High | 0.59 (0.45-0.79) ^a | 0.68 (0.22-2.15) | 0.74 (0.55-1.00) ^a | 1.14 (0.76-1.72) |
| Primary tumor site | | | | |
| Colorectal | 0.78 (0.44-1.39) | 2.83 (0.86-9.34) | 1.25 (0.61-2.55) | 1.48 (0.61-3.58) |
| Other gastrointestinal | 0.66 (0.36-1.20) | 2.47 (0.72-8.45) | 1.12 (0.54-2.32) | 1.14 (0.47-2.78) |
| Head and neck | 0.88 (0.47-1.63) | 0.84 (0.21-3.29) | 0.77 (0.35-1.68) | 0.85 (0.34-2.12) |
| Lung | 0.61 (0.35-1.07) | 3.76 (1.17-12.06) ^a | 1.03 (0.52-2.04) | 1.82 (0.78-4.24) |
| Breast | 0.34 (0.19-0.61) ^a | 0.56 (0.16-1.90) | 0.73 (0.35-1.49) | 0.89 (0.37-2.18) |
| Skin | 1.07 (0.47-2.47) | 0.49 (0.04-6.65) | 1.73 (0.52-5.74) | 1.69 (0.38-7.59) |
| Soft tissue | 0.36 (0.17-0.78) ^a | 0.74 (0.13-4.21) | 1.34 (0.57-3.14) | 1.55 (0.53-4.54) |
| Genitourinary | 0.79 (0.44-1.43) | 0.58 (0.15-2.30) | 1.21 (0.59-2.48) | 0.97 (0.39-2.43) |
| Gynecologic | 0.73 (0.39-1.35) | 2.55 (0.69-9.50) | 0.89 (0.40-1.95) | 1.58 (0.59-4.23) |
| Lymphoma | 0.75 (0.42-1.35) | 0.35 (0.09-1.36) | 0.82 (0.40-1.68) | 0.72 (0.29-1.75) |
| Brain | 3.70 (1.74-7.90) ^a | 1.82 (0.20-16.32) | 3.77 (1.44-9.86) ^a | 0.78 (0.16-3.70) |
| Treatment | | | | |
| Guideline-based antibiotics | 0.77 (0.65-0.92) ^a | 0.63 (0.42-0.95) ^a | 1.02 (0.80-1.31) | 0.80 (0.59-1.09) |
| Vancomycin | 1.39 (1.17-1.65) ^a | 1.70 (1.12-2.59) ^a | 1.69 (1.38-2.08) ^a | 0.98 (0.76-1.27) |
| Granulocyte colony-stimulating factor | 1.15 (0.97-1.35) | 1.64 (1.08-2.50) ^a | 1.09 (0.90-1.34) | 0.89 (0.69-1.16) |
| Disease characteristics | | | | |
| Sepsis | | | 0.94 (0.76-1.16) | 3.15 (2.30-4.30) ^a |
| Pneumonia | | | 1.15 (0.92-1.43) | 1.46 (1.10-1.95) ^a |
| Intensive care use | | | 1.59 (1.29-1.96) ^a | 2.76 (2.06-3.70) ^a |
| Hypotension | | | 1.02 (0.50-2.08) | 3.11 (1.32-7.31) ^a |
| Mechanical ventilatory assistance | | | 1.14 (0.82-1.57) | 27.38 (13.35-56.16) ^a |

^a *P* < .05.

improved outcome in any of the subsets of patients we analyzed. However, without these interventions, it is always possible that these patients may have done worse.

While our study benefits from the inclusion of a large cohort of cancer patients with FN, we recognize several important limitations. Current ICD-9 coding lacks a specific code for FN. Prior studies have used a variety of classification schema, including selecting patients with neutropenia, or fever, or infection, or various combinations. Although these selection criteria demonstrated good validity, a priori we chose a restrictive definition to include only cancer patients specifically admitted with a primary diagnosis of FN. Although this may have limited our sample, we believe it allowed us to accurately capture those patients whose primary diagnosis was FN and to measure initial decision making.^{1-3,26} Likewise, using administrative data, it is difficult to use previously developed risk stratification schema for FN. We analyzed a series of factors that predicted poor outcome (death) that were reliably identifiable from administrative data and that have been used as components in other risk stratification schema and used the presence of these factors as a surrogate for high-risk FN. Using administrative data, we were unable to capture several confounding factors, most notably the tumor characteristics and absolute neutrophil count, which influence both prognosis and treatment.⁵⁻⁷ Because these factors were most likely to influ-

ence use of vancomycin and GCSF, we performed sensitivity analyses and noted that even among the lowest-risk patients (younger, with little comorbidity, and short lengths of hospital stay), use of vancomycin and GCSF was substantial. As with any study of administrative data, we can report associations but defining causality requires further randomized controlled trials. Finally, while we examined a large sample of hospitals from across the United States, patterns of care may differ at other facilities.

The variability in practice patterns for FN suggests that initiatives to improve outcomes and reduce medical expenditures are urgently needed. For many inpatient conditions, formalized order-writing protocols have led to improved outcomes.^{37,38} The American College of Chest Physicians guidelines for the prevention of venous thromboembolic disease specifically call on hospitals to establish formalized guidelines to guide physicians.³⁹ Similarly, computerized alerts to guide best practice have been shown to increase use of evidence-based treatments in some settings.⁴⁰ There has also been an increase in public reporting and pay-for-performance initiatives to improve quality.⁴¹ The American Society of Clinical Oncology Quality Oncology Practice Initiative has gained increased interest and includes some measures of symptom and toxicity measurements.⁴² These initiatives provide further opportunities to promote more effective and less costly care for cancer patients with FN.

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