Incidence, Cost, and Mortality of Neutropenia Hospitalization Associated with Chemotherapy

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BACKGROUND. Neutropenia is a common side effect of chemotherapy, often requiring hospitalization for treatment of severe cases. Neutropenia hospitalization (NH) rates have been reported in individual studies, but national estimates are needed.

METHODS. Chemotherapy-induced NHs were identified in the 1999 hospital discharge data bases from 7 states. Cancer and chemotherapy prevalence data from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program and the National Cancer Data Base were used to calculate national NH rates for 13 cancer types. NH cost was estimated by multiplying charges by institution-specific, cost-to-charge ratios from the 1999 Centers for Medicare and Medicaid Services Hospital Cost Report. NH incidence was projected to national levels using population data from the United States Census and the Centers for Disease Control and Prevention.

RESULTS. There were 20,780 discharges with documentation of cancer, chemotherapy, and neutropenia identified. Projecting to national levels, NH incidence was estimated at 60,294 cases (7.83 cases per 1000 cancer patients). The mean NH cost was $13,372. The mortality rate among patients with NH was estimated at 6.8% or 1 death for every 14 hospitalized patients. Among 13 selected cancer types, the NH rate was 34.20 cases per 1000 patients receiving chemotherapy (1 in 29 patients). NH was particularly common in patients with hematologic tumors, with an incidence of 43.3 cases per 1000 patients with such tumors (1 in 23 patients). The average NH cost for hematologic malignancies was $20,400, more than double the cost of NH for solid tumors.

CONCLUSIONS. According to the current study, NH affects > 60,000 patients with cancer each year in the United States, with an average cost of $13,372 per hospitalization and an associated inpatient mortality rate of 6.8%. ***Cancer* 2005;103: 1916–24.** © *2005 American Cancer Society.*

KEYWORDS: chemotherapy, toxicity, neutropenia, cost.

Neutropenia is a frequent complication of chemotherapy and occurs when myelosuppressive chemotherapeutic treatment reduces absolute neutrophil counts. The condition predisposes cancer patients to potentially life-threatening infection, particularly from Gram-negative bacilli, Gram-positive cocci, and fungi.[1] Risk of infection and mortality increases with the degree and duration of the neutropenic episode and the presence of fever.[2] The duration of neutropenia is typically 7–10 days,[3] with variation a result of the nature and intensity of the chemotherapeutic regimen and patient factors, including bone marrow reserve, cancer type, comorbid conditions, and age.[4] Treatment of neutropenia is variable; empiric antibiotics are often prescribed, and, if it is associated with fever, hospitalization with occasional intensive care isolation may be required.

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Neutropenia can compromise optimal cancer management by causing chemotherapy dose reduction, delay, or even discontinuation.[5–7] These dose modifications often are implemented during the first cycles of chemotherapy, because neutropenic events often occur early during the course of chemotherapy.[8,9] Treatment response frequently depends on the delivery of standard chemotherapy doses, and modifications in dosing may threaten complete response rates and reduce survival.[10–15] Thus, caregivers face a challenge in maintaining adequate chemotherapeutic doses while managing neutropenic complications.

Evaluation of chemotherapy-induced neutropenia is increasing in relevance. Between 1994 and 1998, the overall use of chemotherapy increased by 21.5% among 11 cancer types monitored in the National Cancer Data Base (NCDB).[16] In addition, modest projected increases for various cancer sites have been reported,[17,18] potentially increasing the use of chemotherapy even more. However, despite even greater use of chemotherapeutic agents and the health and treatment implications of reduced neutrophil counts, little is known about the nationwide incidence of chemotherapy-induced neutropenia in clinical practice. Incidence has been reported as a part of various clinical trials but varies greatly based on tumor type, treatment, and patient factors. In an analysis of a larger data base that likely provides more stable estimates, a retrospective study of patients in the Canadian Database Initiative found that 42% of patients with breast carcinoma receiving adjuvant chemotherapy experienced at least 1 neutropenic complication.[19] Although a recent study using the Healthcare Costs and Utilization Project data base and the MarketScan claims data base (MEDSTAT Group, Ann Arbor MI) showed that approximately 5% of hospitalizations for women with breast carcinoma indicated neutropenia, this study also included surgical admissions that were unlikely to be associated with chemotherapy.[20] In addition, an analysis using the Medicare-Surveillance, Epidemiology, and End Results (SEER) data base found that neutropenia hospitalization (NH) occurred in 7.0% of patients within 7 months of diagnosis for those undergoing chemotherapy for breast carcinoma and that chemotherapy-related adverse events were recorded in 3.0% of patients.[21] Information on the prevalence of chemotherapy-induced NH remains limited, however, and additional national estimates are needed.

In 2002, the direct cost associated with treating cancers was estimated at $60.9 billion.[22] The cost associated with NH contributes substantially to this figure.[4,23] In recently reported studies, the mean cost for NH varied from approximately $12,000 to about $38,000 per stay among patients with various malignancies.[24–26] Another analysis of 2 national data bases estimated that the mean charges associated with NH ranged from $17,560 to $22,975 in patients with breast carcinoma.[20] Although these reports have contributed to increased awareness of NH costs, a need exists to develop national NH estimates to effectively evaluate the financial burden of NH in the United States. Therefore, we undertook the current study to estimate the incidence of chemotherapy-related NH in the United States and to investigate the impact of NH in terms of associated cost. We also assessed the inpatient mortality rates associated with NH.

MATERIALS AND METHODS

Study Design and Patient Selection

In this cross-sectional, retrospective analysis, NH cases were identified among the hospitalization discharge records of cancer patients at non-Federal hospitals in seven states. The number of NH cases found in these state data bases was projected to national levels, and NH rates per 1000 patients were estimated. The mean cost per inpatient stay, average length of stay (LOS), and percentage of associated inpatient mortality also were calculated.

To perform the analysis, we constructed a patient data base for the calendar year 1999 from the following state hospital discharge data bases: California,[27] Florida,[28] Massachusetts,[29] New Jersey,[30] New York,[31] Virginia,[32] and Washington.[33] The data set included all medically managed individuals who received care in 1999 in all non-Federal hospitals. From each patient record, we extracted the following data: age, gender, *International Classification of Diseases, ninth revision, clinical modification* (ICD-9-CM) codes for principal discharge diagnosis, up to 25 secondary discharge diagnoses, up to 15 procedures, hospital discharge status as an indicator of mortality, and total charges.[34]

We selected medically managed hospitalization cases that were coded with a diagnosis of cancer, an indication of recent chemotherapy use, and evidence of neutropenia, including fever or infection. We identified as cancer patients all individuals who were hospitalized with a current primary or secondary diagnosis of malignant neoplasm (ICD-9-CM codes between 140.xx and 208.xx) or with a personal history of malignant neoplasm (ICD-9-CM code V10.xx). We were interested primarily in the direct adverse effects of chemotherapy, so we identified patients with chemotherapy-related adverse events through ICD-9-CM codes E933.1 or E930.7. We also estimated whether any chemotherapy took place by identifying patients with either a current encounter or admission for chemotherapy (ICD-9-CM code V58.1) or an examination after chemotherapy (ICD-9-CM code V67.2). Because

no single code for NH exists, we used ICD-9-CM code 288.0 to identify patients who were diagnosed with neutropenia, regardless of chemotherapeutic treatment. Furthermore, it is possible that neutropenia was not coded, whereas infection resulting in hospitalization was coded. Consequently, to identify patients with infection, we used ICD-9-CM codes related to infectious etiology and the presence of underlying comorbidity.[35] We also identified fever of unknown origin by ICD-9-CM code 780.6.

We used the three variables described above (cancer, chemotherapy, neutropenia) to select an analytic cohort. The cohort included individuals who met the following criteria: both cancer and documented receipt of a chemotherapeutic treatment, regardless of adverse events, and either neutropenia, infection, or fever. We chose these criteria because we felt strongly that cancer, neutropenia, and the presence of infectious disease would be documented; we were not confident that chemotherapy-related codes were listed, because they were unlikely to affect reimbursement. Among the hospitalizations, we chose groups of ICD-9-CM codes that let us align hospitalizations with the cancer site reporting categories that were available in national prevalence data.

Study Variables and Calculations

Population data.

We obtained national and state population data from the 1999 United States Census[36] and the Centers for Disease Control and Prevention (CDC) Final Natality Report.[37] The 7-state population in 1999 was 93,400,820 or 34% of the United States population (1999 United States population = 272,690,813). Because the United States Census does not report separately the number of infants age < 1 year, we used the CDC Final Natality Report for 1999 to obtain the number of births by gender for each selected state and for the nation. We subtracted the number of newborns in the CDC report from the number of children age ≤ 4 years in the Census to identify the number of children age < 1 year and the number of children age > 1 year but ≤ 4 years.

Estimated NH cases.

NH data from the seven-state data base were projected to national levels using age-specific and gender-specific multipliers. These multipliers were calculated by dividing the United States population by the 7-state population for each of 38 age and gender groups (ages $<$ 1 year, 1–4 years, 5–9 years, 10–14 years, 15–19 years, 20–24 years, 25–29 years, 30–34 years, 35–39 years, 40–44 years, 45–49 years, 50–54 years, 55–59 years, 60–64 years, 65–69 years, 70–74 years, 75–79 years, 80–84 years, and $\geq$ 85 years, for both males and females). Applying the appropriate age-specific and gender-specific multiplier to each discharge in the sample data base produced a corresponding number of discharges on the national level. For example, the number of males ages 10–14 years was 3,266,136 in the 7-state population and 10,011,707 across the United States, resulting in a multiplier of 3.037 (10,011,707 $\div$ 3,266,136). Therefore, each discharge for a male age 10 years in the study sample correlated to 3.037 discharges at the national level. National estimates were adjusted for differences in population distribution between the seven states and the United States.

NH costs and LOS.

NH costs were estimated by multiplying the reported total charges from each hospital discharge abstract by institution-specific, cost-to-charge ratios from the 1999 Centers for Medicare and Medicate Hospital Cost Report.[34] The average cost was calculated and expressed in 1999 United States dollars. Overall mean LOS also was computed.

Infection, fever of unknown origin, and inpatient mortality.

Incidence of infection, fever of unknown origin, and mortality associated with the NH were calculated.

NH rates overall and by tumor type.

National estimates of NH cases were matched to cancer and chemotherapy prevalence information from SEER and the NCDB, respectively, to calculate the projected national NH rate. The national prevalence of cancer by tumor type was obtained from the SEER Program[38] for the 12 months preceding January 1, 1997. We estimated the chemotherapy prevalence rates for 13 specific tumor types from the NCDB for patients who were diagnosed with cancer in the 1998 calendar year. The estimated prevalence rates for chemotherapy included individuals who were identified as having received chemotherapy alone or in combination with other treatments. Because the NCDB deals with chemotherapy use in initial treatment and not in all patients with a tumor type, we expect that the actual treated prevalence would be much lower and that our NH prevalence rate estimates serve as a lower bound.

The rate of NH was estimated both overall and for the 13 tumor types. NH rates are presented as a function of the total population with the tumor type and by chemotherapeutically treated patients with that tumor type. National NH rates were calculated by dividing the estimated number of NH cases by the cancer prevalence from SEER and multiplying the result by 1000

TABLE 1
Projected Cases, Infection, Fever, Mortality, Length of Stay, and Cost for Neutropenia Hospitalization by Tumor Type: 1999 National Estimates

Tumor type	No.	Age in yrs (mean ± SD)	Gender (% male)	Infection (%)	Fever (%)	Mortality (%)	LOS in days (mean ± SD)	Cost per hospitalization ($1000 US) (mean ± SD)
Overall[a]	60,294	53.8 ± 22.0	46.8	62.8	12.5	6.8	9.2 ± 10.4	13.4 ± 21.0
Hematologic tumors								
NHL	9256	58.1 ± 19.1	55.5	59.1	13.7	5.8	8.2 ± 9.9	11.6 ± 16.7
Hodgkin disease	1086	43.3 ± 20.7	48.8	59.0	13.9	5.1	7.5 ± 9.9	11.1 ± 14.1
Leukemia	11,718	40.5 ± 25.6	53.9	68.3	14.5	8.2	16.9 ± 15.1	28.2 ± 35.6
Subtotal	22,060	48 ± 24.3	54.4	64.0	14.1	7.1	12.8 ± 13.6	20.4 ± 29.5
Solid tumors with high treated prevalence								
Lung and bronchus	6325	65.6 ± 10.7	54.4	65.5	7.1	10.5	7.1 ± 7.4	8.5 ± 9.7
Colon and rectum	3047	65.5 ± 12.5	41.2	58.4	9.0	4.8	7.2 ± 5.7	8.0 ± 9.7
Breast	3792	56.8 ± 12.7	0.2	53.8	11.6	3.4	5.6 ± 5.6	7.1 ± 10.2
Pancreas	587	64.8 ± 10.7	49.1	65.5	14.0	5.5	7.4 ± 6.3	8.4 ± 8.8
Ovary	1591	62.7 ± 14.5	0.0	64.7	9.1	5.5	6.4 ± 5.7	7.6 ± 8.0
Stomach	630	61.0 ± 12.2	61.3	62.7	8.7	7.8	8.2 ± 7.4	10.9 ± 12.2
Subtotal	15,972	63.0 ± 12.6	33.7	61.2	9.0	6.9	6.8 ± 6.5	8.1 ± 9.8
Solid tumors with low treated prevalence								
Urinary bladder	579	69.6 ± 12.5	72.7	74.7	13.6	6.4	7.1 ± 7.8	8.0 ± 8.9
Corpus and uterus, NOS	386	60.3 ± 15.2	0.0	59.3	7.5	5.2	7.1 ± 9.5	8.5 ± 8.2
Cervix	596	49.9 ± 13.8	0.0	73.1	12.8	5.4	5.8 ± 5.6	8.6 ± 10.0
Testis	450	33.4 ± 11.2	100.0	61.0	6.9	3.8	7.0 ± 6.1	9.2 ± 9.3
Subtotal	2011	53.9 ± 18.8	43.3	68.2	10.7	5.3	6.7 ± 7.3	8.6 ± 9.2
Total[b]	40,043	54.3 ± 21.4	45.6	63.1	11.9	6.9	10.1 ± 11.2	14.9 ± 23.6

SD: standard deviation; LOS: length of stay; NHL: non-Hodgkin lymphoma; NOS; not otherwise specified.
[a] Includes all tumor types.
[b] Among 13 tumor types specified.

to obtain the rate per 1000 patients (i.e., United States estimated NH cases ÷ SEER cancer prevalence × 1000 patients). The same formula was used for chemotherapeutically treated rates; however, the denominator was adjusted by multiplying the cancer prevalence by the percentage of chemotherapy use associated with that cancer according to the NCDB (i.e., United States estimated NH cases ÷ [SEER cancer prevalence × NCDB percentage chemotherapy use] × 1000 patients).

RESULTS

Study Population

In total, 11,984,559 hospital discharges were found in the 7 hospital discharge data bases, with 537,606 of these discharges indicating medical management for cancer. Of those patients who were managed medically for cancer, 28,489 had chemotherapy adverse events, and 178,673 had infection or fever of unknown origin. The total number of discharges for cancer patients who received chemotherapy and had neutropenia, infection, or fever was 20,780 discharges. Among these 20,780 patients, the mean age (± standard deviation) was 53.8 ± 22.0 years, and 47.0% of patients were male.

NH Cases

Projecting the 20,780 cases to national levels for 1999, 60,294 cases of NH were estimated (Table 1). Almost two-thirds (62.8%) of these patients will have documented infection, and about 1 in 10 will have fever of unknown origin. We investigated 13 specific cancer sites, which accounted for almost two-thirds of all cases of cancer (4,957,853 cases; 64.4%). NH was most common among the patients with hematologic tumors (22,060 cases), with the highest estimates in patients with leukemia (11,718 cases) and non-Hodgkin lymphoma (9,256 cases).

Mortality

Among patients with NH, estimated inpatient mortality rates ranged from 3.4% to 10.5%, with an overall mortality rate of 6.8% (Table 1). It was projected that the highest mortality rates would be associated with lung and bronchus carcinomas (10.5%), leukemia (8.2%), and gastric carcinomas (7.8%). When it was calculated per chemotherapy-treated patients, the

TABLE 2
Rates of Medically Managed Neutropenia Hospitalizations Across 13 Different Cancer Types: 1999 National Estimates

			Analytic cohort		
Tumor type	Total cancer prevalence[a]	Chemotherapy prevalence (%)[b]	No. of patients	NH rate/1000 with cancer pop cancer pop (95%CI)	Lower bound NH rate/1000 estimated chemotherapy-treated pop (95%CI)
Hematologic tumors					
NHL	275,212	38.0	9256	33.6 (33.0–34.3)	88.6 (86.9–90.3)
Hodgkin disease	95,888	62.0	1086	11.3 (10.7–12.0)	18.3 (17.2–19.3)
Leukemia	138,741	47.5	11,718	84.5 (83.0–85.2)	178.0 (175.1–180.9)
Subtotal	509,841	45.1	22,060	43.3 (42.7–43.8)	96.0 (94.8–97.2)
Solid tumors with high chemotherapy treatment prevalence					
Lung and bronchus	350,121	34.9	6325	18.1 (17.6–18.5)	51.8 (50.5–53.0)
Colon and rectum	958,772	24.9	3047	3.2 (3.1–3.3)	12.8 (12.3–13.2)
Breast	1,771,175	23.8	3792	2.1 (2.1–2.2)	9.0 (8.7–9.3)
Pancreas	23,980	22.0	587	24.5 (22.5–26.4)	111.3 (102.8–119.8)
Ovary	156,836	53.0	1591	10.1 (9.7–10.6)	19.1 (18.2–20.1)
Stomach	62,836	33.6	630	10.0 (9.3–10.8)	29.8 (27.6–32.1)
Subtotal	3,323,720	26.8	15,972	4.8 (4.7–4.9)	17.9 (17.6–18.2)
Solid tumors with low chemotherapy treatment prevalence					
Urinary bladder	449,495	5.1	579	1.3 (1.2–1.4)	25.2 (23.1–27.2)
Corpus and uterus, NOS	419,432	4.0	386	0.9 (0.8–1.0)	22.9 (20.7–25.2)
Cervix	150,849	5.4	596	4.0 (3.6–4.3)	73.7 (68.0–79.4)
Testis	104,517	1.9	450	4.3 (3.9–4.7)	226.5 (208.1–244.9)
Subtotal	1,124,292	4.4	2011	1.8 (1.7–1.9)	40.3 (38.6–42.0)
Total	4,957,853	23.6	40,043	8.1 (8.0–8.2)	34.2 (33.7–34.7)

NH: neutropenia hospitalization; cancer pop: the number of patients with a specified cancer type, regardless of chemotherapy use; chemotherapy-treated cancer pop: the number of patients with a specified cancer type who received chemotherapy; 95%CI: 95% confidence interval; NHL: non-Hodgkin lymphoma; NOS: not otherwise specified;

[a] Based on data from the Surveillance, Epidemiology, and End Results Program.

[b] Based on data from the National Cancer Data Base.

projected mortality rates were highest for leukemia (1 of 69 patients) and ovarian carcinoma (1 of 94 patients).

Hospitalization LOS and Costs

The mean (± standard deviation) hospital LOS was 9.2 ± 10.4 days and the average cost (± standard deviation) of NH was $13,372 ± $21,000 (Table 1). Patients with hematologic tumors were expected to have the highest mean LOS (12.8 days) and the highest mean cost of NH ($20,400), which was nearly 3 times higher among patients with hematologic tumors than among patients with solid tumors. Within the hematologic tumors, estimated NH LOS and cost were highest in patients with leukemia. Average leukemia NH costs were projected to be more than twice the costs of non-Hodgkin lymphoma or Hodgkin disease ($28,200 vs. $11,600 and $11,100, respectively). Among solid tumors, estimated NH LOS and costs were highest in patients with gastric carcinoma. Projected average hospitalization costs among the other solid tumors fell within a close range ($7,100–9,200).

National NH Rates

The national incidence rate of NH was estimated to be 0.22 cases per 1000 individuals in the United States and 7.83 cases per 1,000 patients with cancer. Estimated NH rates and cancer and chemotherapy prevalence data are presented by tumor type in Table 2. The rate of NH across 13 tumor types was projected to be 8.1 cases per 1000 patients with cancer. Hematologic tumors had the highest projected rates of NH, with 43.3 cases per 1000 patients with hematologic malignancies. Among the hematologic malignancies, leukemia and non-Hodgkin lymphoma had the highest population estimates of NH (84.5 and 33.6 cases per 1000 patients with leukemia and non-Hodgkin lymphoma, respectively). In contrast, only 11.3 patients per 1,000 with Hodgkin disease were expected to be hospitalized for neutropenia. Among patients with solid tumors, 4 disease sites had relatively high estimates of NH in the cancer population: the pancreas (24.5 per 1000 patients), lung and bronchus (18.1 per 1000 patients), ovary (10.1 per 1000 patients), and stomach (10.0 per 1000 patients). In the remaining solid tumor sites for which data were considered, the

rate of NH was estimated at < 5 cases per 1000 patients with the specified malignancy.

Table 2 also shows the variation in chemotherapy prevalence by tumor site based on the NCDB data. It was estimated that chemotherapy would be a frequent treatment strategy for the hematologic tumors (38–62% prevalence). Aside from high chemotherapy prevalence for ovarian carcinoma (53%), it was estimated that the solid tumors would be treated with chemotherapy $< 35\%$ of the time. It was expected that 4 of 10 solid tumor sites would be treated chemotherapeutically $\leq 5\%$ of the time: These sites included the urinary bladder, cervix, uterus, and testis.

Calculating the incidence rate for NH only among patients who were receiving chemotherapy and, thus, were at risk for the condition, produced higher estimated incidence rates than the rates obtained for the entire population with the specified tumor type. For patients with leukemia and non-Hodgkin lymphoma, the incidence rates were expected to more than double to 178.0 cases and 88.6 cases per 1000 chemotherapy-treated patients with these malignancies, respectively. Hodgkin disease—the site with the highest chemotherapy treatment prevalence (62%)—increased from 11.3 cases to 18.3 projected NH cases per 1000 chemotherapy-treated patients. Among the patients who had solid tumors with higher chemotherapy prevalence (range, 22–53%), patients with pancreatic tumors had the highest estimated NH incidence rate (111.3 cases per 1000 chemotherapy-treated patients with pancreatic carcinoma), followed by patients with lung and bronchus carcinomas (51.8 per 1000 chemotherapy-treated patients), and patients with gastric malignancies (29.8 per 1000 chemotherapy-treated patients). The chemotherapy-treated population NH incidence estimates for colorectal, breast, and pancreatic malignancies were at least four times greater than their respective overall incidence rates.

The projected NH incidence rates of the four solid tumor sites with the lowest chemotherapy treatment prevalence (urinary bladder, uterus, cervix, and testis) increased the most when comparing population rates with chemotherapy-treated population rates. Among patients who were treated with chemotherapy, the highest NH rate was projected for testicular carcinoma (226.5 per 1000 chemotherapy-treated patients). The other disease sites in this low chemotherapy treatment prevalence group also had sizably increased NH incidence estimates: cervix (73.7 per 1000 chemotherapy-treated patients), urinary bladder (25.2 per 1000 chemotherapy-treated patients), and uterus (22.9 per 1000 chemotherapy-treated patients).

DISCUSSION

We found that NH was common, consumed considerable healthcare resources, and was associated with an inpatient mortality rate of approximately 7%. The estimated national incidence of NH was 60,000 cases per year, yielding a rate of 7.83 cases per 1000 patients with cancer. Considering the rate of NH among 13 selected cancer types, the estimated lower-bound incidence rises to 34.20 cases per 1000 patients receiving chemotherapy, or, dividing both the numerator and the denominator by 34.2, 1 hospitalization for every 29 courses of chemotherapy. The inpatient mortality rate was projected to be 6.8%, or 1 death for every 14 hospitalized patients.

Although the total number of hospitalizations for neutropenia is a simple projection from 34% of the United States to the whole country, estimates of the rate of NH per 1000 individuals undergoing chemotherapy necessarily are conservative lower bounds in our design. The complexity occurs because the hospitalizations are a cross-sectional analysis of a calendar year, and the NCDB treated-prevalence information is from the first year of initial therapy for a tumor type.[16] Because only a fraction of cancer patients receive chemotherapy in any given year, first-year treated-prevalence figures will overestimate the number of patients living with a cancer type who undergo chemotherapy and, thus, will reduce the reported rate of NH; that is, we used a denominator known to be larger than the actual treated prevalence, which yields a smaller incidence rate that we report as a lower bound in Table 2. Although this affects the absolute value of the reported rates, relative rates should be affected less.

NH was particularly common in patients with hematologic tumors, in which it was estimated to affect 1 in 23 patients who were diagnosed with such malignancies and 1 in 10 patients who were treated with chemotherapy. Average hospitalization costs for these NH patients were estimated at $20,300 per inpatient stay, which was more than double the costs of treating NH in patients with solid tumors. Among the hematologic malignancies, chemotherapy-treated leukemia patients had the highest estimates of NH (1 in 6 patients), cost per hospitalization ($28,200), and incidence of inpatient mortality (8.2%). By contrast, only 1 in 55 patients who were treated with chemotherapy for Hodgkin disease were projected to have NH-related codes. In this study, the projected rate of NH in patients with non-Hodgkin lymphoma was 1 in 11 patients, which, for the study design considerations described above, was lower than the rate of 1 in 4 reported recently in a large sample of patients with non-Hodgkin lymphoma who received combination

chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone).[8]

It was estimated that, in the current study sample, several types of solid tumors were treated with chemotherapy at rates similar to hematologic tumors. These tumors included lung and bronchus, colon, breast, pancreas, ovary, and gastric malignancies. Although the estimated chemotherapy prevalence for this group was only slightly lower than that found for hematologic malignancies, the overall rate of NH among patients with these solid tumors was estimated at less than one-fifth of the rate in patients with hematologic tumors (1 in 56 patients vs. 1 in 10 patients). Furthermore, although the hospitalization costs for these patients were expected to be less than half of the costs for patients with hematologic tumors, their estimated inpatient mortality rates were relatively similar. Among the solid tumors with high chemotherapy treatment prevalence, NH was projected to be highest in pancreatic, lung, gastric, and ovarian malignancies and lowest in breast carcinoma. In a previous national estimate of NH prevalence in a sample of hospitalized patients with breast carcinoma, 4.5% of hospital admissions had a neutropenic complication.[20] A recent analysis of linked Medicare and SEER registry data bases[21] reported that $>$ 9% of patients with breast carcinoma who were receiving chemotherapy were hospitalized with neutropenia, fever, thrombocytopenia, or systemic treatment toxicity compared with 0.5% of patients with breast carcinoma who were not receiving chemotherapy. Our analysis projected that 5.9% of patients who were hospitalized for breast carcinoma had neutropenia, an estimate that comports reasonably with the earlier findings.

The results of this study emphasize the magnitude of NH in the United States and underscore the need to prevent its occurrence to optimize patient outcomes. In addition to the potentially life-threatening situation that occurs when neutropenia presents with fever, resulting chemotherapy dose reduction, delay, or discontinuation potentially compromises the effectiveness of chemotherapy among patients who may have demonstrated a response. In a 20-year follow-up study of patients with lymph node-positive breast carcinoma, the patients who received $\geq$ 85% of standard-dose chemotherapy had significantly improved recurrence-free and overall survival rates.[14] Similar findings have been reported from a retrospective analysis of patients with non-Hodgkin lymphoma in which the receipt of $\geq$ 80% of the intended dose was associated significantly with an increase in complete response rates.[39] Furthermore, hospitalization for febrile neutropenia during the first cycle of chemotherapy, when NH often occurs,[8] has been associated with an increased risk of early termination of the chemotherapy,[10] thus preventing patients from receiving the benefit of a full course of treatment.

Several risk models have been developed to estimate the likelihood of a neutropenic event occurring during the course of chemotherapy. Advanced age, comorbid conditions (e.g., heart and hepatic disease), initial patient status (e.g., low albumin, low absolute neutrophil count, elevated lactate dehydrogenase), and planned standard dose intensity have been identified as predictors of severe neutropenia among patients with non-Hodgkin lymphoma receiving chemotherapy.[8,9,40–44] In patients with breast carcinoma, doxorubicin use, first-cycle absolute neutrophil count nadir, and percent decrease in platelet count have been predictive of a severe or febrile neutropenic event.[45–48] These predictive models have important implications for the patient, both in terms of the immediate risk of febrile neutropenia and for the potential impact of chemotherapy dose modification on outcome.

The major limitations of the current study relate to the use of administrative data to define NH. We selected states from the Northeastern, Southern, and Western United States Census regions. Although these regions represent the most heavily populated areas of the United States, we did not have representation from the Midwest, where there were no statewide hospital data bases with an appropriate level of detail and quality. However, when calculating national estimates, we adjusted for differences in population distribution between the seven-state cohort and the entire country, and we do not anticipate that additional data from the Midwest or Southwest would have altered our national estimates substantially. Although we estimated costs using overall institution-specific, cost-to-charge ratios, because that was the only common measure across all of the data bases, it must be emphasized that this is only an estimate of the direct cost to the hospital and does not include indirect costs necessary from a national perspective. This is yet another way in which our estimates constitute a lower bound. We used data from 1999, the last full year for which data were available from all 7 states when we began the study. There have been no significant changes in the management of NH since that time. Cancer and chemotherapy prevalence calculations used data from 1997 and 1998, respectively; as both rates simultaneously increase, their effect on our estimates will be minimal. However, the NCDB reports treatment of first cases, not all cases, and may overestimate chemotherapy prevalence.

We could only identify NH by using available ICD-9-CM codes rather than through clinical and physio-

logic measurements. The NH incidence estimate in our study is probably a lower bound, because there is no diagnostic or reimbursement code for chemotherapy-related neutropenia, and the diagnostic codes that are useful for inferring the presence of the condition (i.e., cancer diagnosis, neutropenia and associated symptoms, and chemotherapeutic treatment) are likely to be omitted or underreported by physicians and hospital staff. For example, Du and coworkers reported that 7.0% of patients with breast carcinoma undergoing chemotherapy had hospitalizations with neutropenia listed, but less than half (3.0%) had an adverse reaction to chemotherapy listed.[22] If rates of reporting are similar across other tumor types, then our estimate of the national burden may be low by more than a factor of two. Furthermore, hospital costs and mortality rates are all-cause estimates and are not the attributable costs or mortality rates of NH. Thus, preventing NH altogether only would diminish and would not extinguish these costs and deaths. Finally, the state data bases were not designed primarily for research; consequently, we did not have the same level of data auditing and quality assurance that would be found in a prospective study.

In conclusion, we found that NH was a common and expensive condition with associated mortality in approximately 1 in 14 hospitalized cancer patients. Our projections showed that NH was most common in patients with hematologic tumors; however, the NH rate in solid tumors with low chemotherapy prevalence was surprisingly high. We believe that the results of this study highlight the value of administrative data bases in understanding the complex relation between comorbid conditions. Furthermore, we identified a variety of epidemiologic and health services research issues that remain poorly addressed, including the need for more reliable and valid coding and measurement of this significant complication of chemotherapeutic treatment.

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