Empiric Antibiotic Prescribing Practice in Febrile Neutropenia: Compliance with IDSA Guidelines

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ABSTRACT

Objective: To assess compliance with recommendations for empiric antibiotic therapy for febrile neutropenia, as outlined in the 1997 guidelines of the Infectious Diseases Society of America (IDSA), and to compare selected outcomes of episodes for which treatment was or was not in compliance with these guidelines.

Methods: A concurrent, noninterventional chart review was conducted for 50 consecutive episodes of febrile neutropenia that occurred in 44 patients between January and May 1999 at a university-affiliated, tertiary care referral oncology centre. Empiric antibiotic therapy was assessed for compliance with IDSA guidelines. Episodes treated with compliant and noncompliant treatment regimens were compared for defervescence at 72 h and other selected clinical outcomes. Infection and response to therapy were assessed according to previously published criteria.

Results: An empiric antibiotic regimen that was in compliance with the guidelines was prescribed in 28 (56%) of the 50 episodes. Patients who received such therapy were more likely than those receiving noncompliant therapy to be male (71% and 41%, $p = 0.03$) and to have a hematological malignancy (75% and 50%, $p = 0.07$). There were no significant differences between groups with respect to defervescence at 72 h, overall response to therapy, number of modifications to the antibiotic regimen, duration of empiric and total antibiotic therapy, adverse drug reactions, consultation to the infectious disease service, admission to the intensive care unit, or mortality rate.

Conclusion: Because outcomes were similar in patients receiving compliant and noncompliant therapy, it appears unnecessary to implement a prescriptive policy enforcing compliance for all episodes of febrile neutropenia at this oncology centre.

Key words: febrile neutropenia, guidelines

RÉSUMÉ

Objectif : Évaluer la conformité aux recommandations en matière d'antibiothérapie empirique pour le traitement de la neutropénie fébrile, telles que décrites dans les lignes directrices de 1997 de l'Infectious Diseases Society of America (IDSA), et comparer des résultats thérapeutiques choisis pour les épisodes pour lesquels les lignes directrices avaient ou n'avaient pas été observées.

Méthodes : Une analyse simultanée non expérimentale a été menée sur les données de 50 épisodes consécutifs de neutropénie fébrile qui sont survenus chez 44 patients, entre janvier et mai 1999 à un centre de références de soins tertiaires oncologiques affilié à une université. L'antibiothérapie empirique a été évaluée pour observer le résultat de la conformité aux lignes directrices de l'IDSA. Les épisodes pour lesquels le schéma thérapeutique était ou non conforme avec les lignes directrices ont été comparés, à la recherche de signes de défervescence 72 heures après le traitement et d'autres résultats cliniques choisis. L'infection et la réaction au traitement ont aussi été évaluées conformément à des critères déjà publiés.

Résultats : L'antibiothérapie empirique conforme aux lignes directrices a été prescrite dans 28 (56 %) des 50 épisodes. Les patients qui ont reçu cette antibiothérapie étaient pour la plupart, contrairement à ceux qui ont reçu une antibiothérapie non conforme aux lignes directrices, des hommes (71 % vs 41 %, $p = 0{,}03$) et présentaient une affection hématologique (75 % vs 50 %, $p = 0{,}07$). Aucune différence notable entre les deux groupes n'a été observée au chapitre de la défervescence à 72 heures, de la réponse globale au traitement, du nombre de modifications de schéma thérapeutique, de la durée du traitement antibiotique empirique et généralisé, des réactions médicamenteuses indésirables, des consultations au service des maladies infectieuses, des admissions à l'unité des soins intensifs, ou de la mortalité.

Conclusion : Étant donné que les résultats étaient semblables pour les patients qui recevaient ou non l'antibiothérapie conformément aux lignes directrices, il semble donc inutile de mettre en oeuvre une politique normative obligeant l'observance des lignes directrices pour tous les épisodes de neutropénie fébrile dans ce centre de soins oncologiques.

Mots clés : neutropénie fébrile, lignes directrices

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INTRODUCTION

Patients undergoing cytotoxic chemotherapy and bone marrow transplantation for treatment of malignant disease are at high risk for hematological toxicities, including neutropenia. Neutropenia and other immunological impairments increase susceptibility to infection in these patients.[1,2]

The rate and degree of neutrophil decline, as well as the duration of neutropenia, have been shown to influence the risk of infection in patients with acute leukemia.[3] The risk of infection is most significant for patients who have an absolute neutrophil count of less than 0.5×10^9/L.[3] The incidence of bacteremia and death is greatest among patients with a granulocyte count of less than 0.1×10^9/L.[4] Infection remains a leading cause of morbidity and mortality for patients undergoing cancer chemotherapy and bone marrow transplantation.[4] Infection in a neutropenic patient is difficult to evaluate because the normal inflammatory response to the infecting microorganism is blunted.[2] Fever may be the only presenting sign of infection, and it is considered to be of infectious origin unless proven otherwise.[1] The onset of fever in a neutropenic patient is an indication for empiric initiation of high-dose, parenteral, broad-spectrum antibiotic therapy to reduce illness and death due to infection.

The possible causes of infectious fever in a neutropenic patient are varied, making the choice of an empiric antimicrobial regimen difficult. The most common pathogens associated with febrile neutropenia are aerobic gram-positive cocci and gram-negative bacilli.[2] Therefore, antibiotic regimens used as empiric therapy for febrile neutropenic patients should possess bactericidal activity against these pathogens.

Many single- and multiple-agent regimens for treating febrile neutropenia have been studied, and this research has recently been evaluated and summarized.[5] The Infectious Diseases Society of America (IDSA) has published evidence-based, peer-reviewed guidelines for the treatment of unexplained fever in neutropenic patients.[5] The guidelines are concerned primarily with the choice and duration of empiric antibiotic therapy in patients with neutropenia secondary to cancer chemotherapy in the hospital setting. A review of the MEDLINE, International Pharmaceutical Abstracts, EMBASE, and CancerLit databases did not retrieve any studies assessing compliance of antimicrobial prescribing practices with the IDSA guidelines or describing the outcomes associated with compliant prescribing.

The primary objective of this study was to determine if the empiric antibiotic regimens for febrile neutropenia prescribed in the oncology unit of a university-affiliated teaching hospital were in compliance with the IDSA guidelines. The secondary objective was to determine if differences exist with respect to defervescence at 72 h and other selected outcomes between patients whose empiric antibiotic therapy was compliant with these guidelines and those whose therapy was noncompliant.

METHODS

The study was designed as a concurrent, noninterventional chart review of a cohort of adult inpatients with febrile neutropenia on the oncology unit of a university-affiliated teaching hospital and tertiary care referral centre.

The eligibility criteria were based on the definition of febrile neutropenia in the IDSA guidelines.[5] According to the guidelines, fever is defined as a single oral temperature reading of greater than 38.3°C or a temperature of at least 38.0°C lasting at least 1 h. Neutropenia is defined as an absolute neutrophil count of less than 0.5×10^9/L or less than 1.0×10^9/L with predicted decline to 0.5×10^9/L or less. Eligible patients were identified by a single clinical pharmacist on the oncology unit (who was not involved in the data collection) using computerized laboratory reports of absolute neutrophil counts, antibiotic prescription orders, and a chart review for the presence of fever. Other pharmacy staff, patients, and medical, nursing, and clerical staff were unaware of the study. The first 50 consecutive episodes of febrile neutropenia that met these criteria were included in the study. An episode of febrile neutropenia was defined as the period from the onset of fever up to and including the seventh day after discontinuation of antibiotic therapy. Multiple episodes from a single patient were permitted.

Demographic data about the patients, including age, sex, use of granulocyte colony-stimulating factor (G-CSF), type of malignant disease, and type of presenting infection (microbiologically defined, clinically defined, or fever of unexplained origin), were collected.

The empiric antibiotic regimen was defined as the antibiotic or antibiotics prescribed at first presentation of the episode of febrile neutropenia. This empiric regimen was assessed for compliance with the IDSA guidelines. The following regimens were considered to be compliant with the guidelines: ceftazidime or imipenem-cilastin (referred to here as imipenem) monotherapy or duotherapy involving an aminoglycoside and an

antipseudomonal penicillin. The guidelines also outline criteria for the empiric addition of vancomycin. The IDSA-specified criteria for adding vancomycin empirically are as follows: the presence of clinically obvious, serious catheter-related infections; substantial mucosal damage; quinolone antibiotic prophylaxis before the febrile episode; known colonization with methicillin-resistant *Staphylococcus aureus* or penicillin-resistant *Streptococcus pneumoniae*; blood culture positive for gram-positive bacteria before final identification and susceptibility testing; and hypotension or other evidence of cardiovascular impairment. For the purpose of this study, infection-related hypotension at time of presentation with fever was prospectively defined as systolic blood pressure less than 90 mm Hg or a reduction in blood pressure of at least 40 mm Hg from baseline, in the absence of any other causes.[6] Mucositis is a common problem for patients undergoing chemotherapy, but systemic infection is more likely to occur in severe cases. Mucositis was considered severe if the following clinical criteria were met: documentation of poor nutritional intake secondary to mucositis or use of total parental nutrition for this reason, use of systemic narcotic analgesics for relief of symptoms related to mucositis, or documentation in the patient record of "severe mucositis".[7]

Selected patient outcomes were prospectively followed and recorded. The primary outcome of interest was defervescence at 72 h. Additional outcomes included number of modifications to the antibiotic regimen per episode; duration of empiric and total antibiotic regimen (in days); overall response to therapy; adverse reactions, grouped by organ system (renal, hepatic, hematological, central nervous system, gastrointestinal, and dermatological), that led to a change in or discontinuation of antibiotic therapy; consultation to the infectious disease service; admission to the intensive care unit; and death. Patients were monitored for these outcomes up to and including 7 days after discontinuation of antibiotic therapy. Inpatient and outpatient chart review allowed monitoring of patient outcomes related to the episode of febrile neutropenia during the hospital stay and after discharge, where necessary.

The overall response to therapy was assessed by means of the criteria presented in a consensus statement published by the Immunocompromised Host Society.[8] That statement recommends that evaluation of clinical response to an empiric antibiotic regimen should depend on whether the initial febrile episode was defined microbiologically or clinically, or if it was fever of unexplained origin (Appendix 1). On the basis of these definitions, response to empiric therapy was classified as a success, an initial response with modification, or a failure (Appendix 2).

Statistical analysis included the unpaired Student's *t*-test for all parametric data. Fisher's exact and chi-squared tests were used for proportional data, as appropriate. Significance was defined as $p < 0.01$. Data are presented as mean ± standard deviation unless stated otherwise.

RESULTS

Compliance with the IDSA guidelines and patient outcomes were assessed for 50 consecutive episodes of febrile neutropenia identified in a total of 44 patients between January 11 and May 18, 1999. Six patients were enrolled for 2 episodes each, with a minimum of 14 days separating each episode. The choice of empiric regimen during the second admission did not appear to be affected by the patient response or regimen prescribed during the first admission.

Mean age was similar between the groups receiving compliant and noncompliant therapy (52 and 51 years, respectively) (Table 1). Sex distribution was different between the groups, with proportionately more men in the group receiving compliant therapy (71% and 41%, $p = 0.03$) (Table 1).

Use of G-CSF, type of presenting infection, and presence of bacteremia with the primary infection were not statistically different between the groups (Table 1). The presence of hematological malignancy was more common in the group receiving compliant therapy, but this difference was not statistically significant (75% and 50%, $p = 0.07$).

Empiric antibiotic therapy was in compliance with the IDSA guidelines for 28 (56%) of the 50 episodes of febrile neutropenia. The prescribed empiric regimens are summarized in Table 2. For most of the episodes for which therapy was in compliance with the guidelines, the antibiotic prescribed was imipenem (20/28 [71%]). Empiric vancomycin therapy was used for 2 episodes (8%) that received compliant therapy.

For most episodes of febrile neutropenia treated with a noncompliant regimen, cefazolin and an aminoglycoside, usually gentamicin, were prescribed (15/22 [68%]). Two episodes (9%) were treated with ciprofloxacin and vancomycin, presumably because of reported ß-lactam allergies, and imipenem and ciprofloxacin were prescribed for one episode (5%). In 4 (18%) of the 22 episodes, imipenem monotherapy was deemed noncompliant because vancomycin was

Table 1. Characteristics of 50 Consecutive Episodes of Febrile Neutropenia in 44 Patients between January 11 and May 18, 1999

Characteristic	No. (and %) of Episodes*				*p*
	Regimen in Compliance with IDSA Guidelines[5] (*n* = 28)		Regimen Not in Compliance with IDSA Guidelines[5] (*n* = 22)		
Mean age ± SD (years)	52 ± 15		51 ±16		0.92
Sex					
Men	20	(71)	9	(41)	0.03
Women	8	(29)	13	(59)	
Type of malignancy					
Hematological	21	(75)	11	(50)	0.07
Nonhematological	7	(25)	11	(50)	
G-CSF received	6	(21)	6	(27)	0.63
Primary infection[8]					
Microbiologically defined	9	(32)	10	(46)	0.61
Clinically defined	7	(25)	4	(18)	
Fever of unexplained origin	12	(43)	8	(36)	
Bacteremia with presenting infection	9	(32)	8	(36)	0.75

IDSA = Infectious Diseases Society of America, SD = standard deviation, G-CSF = granulocyte colony-stimulating factor.
*Except where indicated otherwise.

Table 2. Empiric Antibiotic Regimens

Regimen	No. (and %) of Episodes	
In compliance with IDSA guidelines[5] (*n* = 28)		
Imipenem	20	(71)
Ceftazidime	6	(21)
Imipenem + vancomycin	1	(4)
Ceftazidime + vancomycin	1	(4)
Not in compliance with IDSA guidelines[5] (n = 22)		
Cefazolin + aminoglycoside	15	(68)
Imipenem*	4	(18)
Ciprofloxacin + vancomycin	2	(9)
Imipenem + ciprofloxacin	1	(5)

IDSA = Infectious Diseases Society of America.
*Imipenem monotherapy not in compliance with guidelines because vancomycin was indicated but not prescribed.

Table 3. Causative Organisms for Microbiologically Defined Primary Infections

Organism	Site	No. of Episodes
Gram-negative		
Escherichia coli	Blood	5
Klebsiella pneumoniae	Urine	1
Klebsiella oxytoca	Blood	1
Pseudomonas aeruginosa	Blood	1
Moraxella sp.	Blood	2
Gram-positive		
Staphylococcus aureus	Blood	2
*Enterococcus faecalis**	Blood	1
*Staphylococcus epidermidis**	Blood	2
α-Hemolytic *Streptococcus**	Blood	1
Staphylococcus hominis	Blood	1
Streptococcus mitis	Blood	1
Streptococcus pneumoniae	Blood	1
Anaerobes		
Clostridium difficile	Stool	1
Clostridium subterminale	Blood	1

*Two organisms identified from a single blood culture.

indicated (according to the predefined criteria) but not prescribed. In 3 of these cases, defervescence had not occurred at 72 h.

A total of 19 episodes involved a microbiologically defined infection (9 and 10 episodes in the groups with compliant and noncompliant therapy, respectively). Table 3 identifies the organisms isolated as the presenting cause of infection. For two episodes, two organisms were identified on blood culture, whereas for all other episodes, a single organism was identified. Subsequent or secondary infections are not represented in Table 3.

Gram-negative organisms were isolated in 48% (10 of 21) of cultures, whereas gram-positive organisms and anaerobes were identified in 43% (9 of 21) and 10% (2 of 21) of cultures, respectively. The most common presenting organism was *Escherichia coli*, isolated in 5 of the 19 microbiologically defined infections.

At 72 h after initiation of antibiotic therapy there was no significant difference between the groups in the rate of defervescence (Table 4). There was also no significant difference in this outcome parameter when subcategories of the 2 groups (fever of unexplained origin and microbiologically or clinically defined infections) were compared (data not shown, $p = 0.69$). The total duration of antibiotic therapy was longer for the group receiving compliant therapy than the group receiving noncompliant therapy (18 and 12 days, respectively), although this difference was

Table 4. Patient Outcomes

Outcome	No. (and %) of Episodes*				*p*
	Regimen in Compliance with IDSA Guidelines[5] (*n* = 28)		Regimen Not in Compliance with IDSA Guidelines[5] (*n* = 22)		
Response to therapy					
Defervescence at 72 h	13	(46)	13	(59)	0.20
Success[8]	10	(36)	10	(46)	
Initial response with modification[8]	7	(25)	5	(23)	0.78
Failure[8]	11	(39)	7	(32)	
Features of therapy					
Modifications to antibiotic regimen (mean ± SD per episode)	0.6 ± 0.8		0.6 ± 0.9		0.74
Mean duration ± SD of empiric antibiotic regimen (days)	8 ± 5		6 ± 4		0.31
Mean total duration ± SD of antibiotic therapy	18 ± 13		12 ± 6		0.03
ADR leading to change or discontinuation of therapy	2	(7)	1	(5)	0.70
Overall outcomes					
Consultation with infectious disease service	10	(36)	4	(18)	0.17
Admission to ICU	1	(4)	0	(0)	0.38
Deaths	1	(4)	1	(5)	0.86

IDSA = Infectious Diseases Society of America, SD = standard deviation, ADR = adverse drug reaction, ICU = intensive care unit.
*Except where indicated otherwise.

not statistically significant ($p = 0.03$). Overall response to therapy, number of modifications to the antibiotic regimen, and duration of empiric antibiotic regimen were similar between the 2 groups.

There were no significant differences between the groups in the frequency of adverse drug reactions. Three adverse reactions that prompted a change or discontinuation in antibiotic regimen occurred during the study. One patient who received noncompliant therapy experienced a deterioration in renal function while receiving gentamicin and cefazolin. Serum creatinine increased from a baseline of 168 µmol/L to 304 µmol/L after 48 h (4 doses) of gentamicin therapy and peaked at 476 µmol/L by day 6, which suggested nephrotoxicity.[9] However, peak and trough blood levels were within laboratory reference ranges, and renal ultrasonography performed at that time identified an obstructive bladder tumour. After placement of a stent, the serum creatinine level decreased to within 25% of baseline over 2 weeks. Two patients in the group receiving compliant therapy had dermatological reactions (rashes) while receiving imipenem that resulted in therapy changes. For both patients the rash resolved within 48 hours of the change in antibiotics, and there were no related complications.

One episode in each group ended in death. One patient died in the intensive care unit while receiving compliant antibiotic therapy. There were no statistically significant differences between groups in terms of infectious disease consultation, transfer to the intensive care unit, or mortality rate. Infectious disease recommendations did not affect selection of the drug regimen, as all such consultations occurred after the empiric antibiotic regimen had been chosen.

DISCUSSION

Compliance with the IDSA guidelines for the treatment of febrile neutropenia has not been reported previously. This study determined the frequency of compliance with the IDSA guidelines for empiric antibiotic regimens and compared the outcomes of patients receiving compliant and noncompliant therapy.

Therapy was in compliance with the IDSA guidelines in 28 (56%) of 50 consecutive episodes of febrile neutropenia that presented during the study period. For episodes treated with compliant therapy, patients received either imipenem (75%) or ceftazidime (25%). Duotherapy with an antipseudomonal penicillin and an aminoglycoside was not prescribed for any episode. The predominant use of imipenem likely reflects a recent decision by hematology and oncology physicians at this institution to adopt this antibiotic as first-line therapy for febrile neutropenia associated with hematological malignancies and bone marrow transplantation.

For most episodes treated with noncompliant therapy (15/22 [68%]), cefazolin with an aminoglycoside was prescribed, and patients receiving such therapy were more likely to have a nonhematological malignancy. The

combination of cefazolin and gentamicin is not discussed or recommended by the current IDSA guidelines.[5] In the present study this combination would have provided empiric coverage for many of the organisms listed in Table 3, with the exception of *Clostridium subterminale*, *Staphylococcus epidermidis* (1 of 2 isolates), *Enterococcus faecalis*, and *Clostridium difficile*. A review of the literature identified 2 published trials that examined the use of cephalothin (another first-generation cephalosporin) in combination with an aminoglycoside.[9,10] Palmblad and Lonnqvist[10] evaluated the combination of amikacin with either ampicillin or cephalothin as empiric therapy in 30 patients with hematological malignancies. In this small, randomized study, patients improved more often when amikacin was combined with ampicillin than with cephalothin (74% and 55%, $p < 0.05$).[10] The European Organization for Research and Treatment of Cancer (EORTC) group found that the combination of cephalothin plus gentamicin was just as effective as carbenicillin plus cephalothin or carbenicillin plus gentamicin; more than 70% of patients responded to this combination, with less frequent response in patients with bacteremia.[9] However, the EORTC observed that the combination of cephalothin and gentamicin was substantially more nephrotoxic than the other regimens studied.

In this study, imipenem monotherapy administered in 4 cases was deemed noncompliant, because vancomycin was indicated, according to the IDSA-defined criteria for severe mucositis, but was not administered. Although the guidelines themselves do not define "severe mucositis", a prospective definition was set by the investigators in this study. Application of this definition was limited by the noninterventional nature of the study, relying as it did on thorough documentation in the patient record.

The practice of including vancomycin in the empiric regimen for febrile neutropenia has been questioned by the EORTC. A trial of 747 patients comparing ceftazidime and amikacin with and without concomitant empiric vancomycin found no difference in the number of febrile patients each day or the duration of fever.[11] The authors also observed no deaths in patients with gram-positive infections who did not receive empiric vancomycin during the time required for microbiological identification of presenting organisms. However, the study did identify a higher incidence of nephrotoxicity in the group that received vancomycin. The investigators concluded that empiric inclusion of vancomycin was not necessary and might lead to a greater incidence of adverse reactions.

In consideration of these issues, statistical analysis for the present study was repeated excluding an assessment of the appropriateness of empiric vancomycin. In this analysis, the 4 patients with mucositis who were not given empiric vancomycin were considered to have received compliant therapy. In this analysis, the duration of total antibiotic therapy was significantly longer for patients receiving therapy in compliance with the guidelines (18 and 10 days, $p = 0.004$); this result was likely due to the significantly greater percentage of episodes with hematological malignancy (78% and 39%, $p = 0.006$). Compliance of therapy with guidelines, defervescence at 72 h, and all other outcomes were statistically unchanged from the previous analysis. Therefore, the group in which these 4 patients were included did not significantly affect the primary outcomes of the study.

The combination of ciprofloxacin and vancomycin, used for 2 episodes, is not compliant with the guidelines. Presumably, this regimen was prescribed because of reported ß-lactam allergies, although this reason was not specifically documented in the charts. One of these patients had 2 episodes of febrile neutropenia, of which one was treated with a noncompliant regimen and the other with a compliant (ß-lactam-based) regimen; no adverse events were experienced with either regimen. A significant limitation of the IDSA guidelines is that they do not provide alternative empiric regimens for patients with ß-lactam allergies. Nonetheless, for the purpose of this study, any prescribed regimen that was inconsistent with the guidelines, regardless of the reason, was considered noncompliant.

In this study, no significant difference was found in defervescence at 72 h between episodes treated with empiric antibiotic regimens that were compliant and noncompliant with the IDSA guidelines. Additional outcomes, including overall response to therapy, number of modifications to the antibiotic regimen, duration of empiric and total antibiotic regimens, adverse drug reactions, consultation to the infectious disease service, admission to the intensive care unit, and death, were not significantly different between the 2 groups.

These outcome results should be assessed in light of the baseline characteristics of the study population. No differences existed between the groups with respect to use of G-CSF or type of infection (microbiologically defined, clinically defined, or fever of unexplained origin). The types of infections found in this study reflect literature estimates. From a summary of 1290

cases of febrile neutropenia from trials VIII and IX of the EORTC, Klatersky[1] estimated that fever of unexplained origin accounted for 38.0% of episodes, with microbiologically and clinically defined infections accounting for 32.5% and 26.0% of episodes, respectively. In contrast, in the current study, episodes treated with compliant and noncompliant therapy, respectively, accounted for 43% and 36% of cases of fever of unexplained origin, 32% and 46% of cases of microbiologically defined infection, and 25% and 18% of cases of clinically defined infection.

The episodes in the group receiving compliant therapy were more likely to involve male patients (p = 0.03) and to be associated with an underlying hematological malignancy (p = 0.07). Although sex distribution would not be expected to affect patient outcome, the presence of hematological malignancy certainly might. Underlying hematological malignancy or bone marrow transplantation has been used as a surrogate indicator for the expected duration and degree of neutropenia, as these patients often experience more profound and prolonged neutropenia than patients with solid tumours or lymphoma.[5,12] Despite a longer total duration of antibiotic therapy and more frequent infectious disease consultation in the group receiving compliant therapy, defervescence at 72 h and the overall response to therapy (classified as success, initial response with modification, or failure) were similar between groups.

The organisms identified by culture in this study are not consistent with recent reports that gram-positive infections predominate over gram-negative infections (69% and 31%, respectively).[13] This difference may be related to the small sample size of this study or to institution-specific variability (or both). The impact of these findings on the outcomes reported is not known.

Estimates of the mortality rate for patients with febrile neutropenia vary with the populations studied, but a recent review reported rates between 5% and 12%.[1] The overall mortality rate of the current study, 4% (one death in each group), falls below this range.

No previously published trial has compared therapeutic outcomes on the basis of compliance of therapy with the IDSA guidelines. Outcomes-based studies on clinical prescribing guidelines are necessary to delineate the applicability of guidelines to specific patient populations.

Although the IDSA guidelines may be applied to "febrile neutropenic patients with other neoplastic diseases", the authors stated that the guidelines were "derived predominantly from the knowledge of and experience with the hematopoietic and lymphoproliferative malignancies".[5] First-line empiric therapies may differ for patients who are being treated for underlying hematological and nonhematological malignancies.[4] In recent studies, attempts have been made to treat patients according to the heterogeneity of the febrile neutropenic population with respect to prognostic risk factors.[14-16] Indeed, the results of this study may reflect differences in risk and response between febrile neutropenic patients with and without hematological malignancies. The use of broad-spectrum regimens, such as imipenem, may not be necessary for all febrile neutropenic patients. The results of future trials distinguishing between these patient populations may have an important impact on the choice and cost of empiric antibiotic regimens.

Although the combination of cefazolin and gentamicin is not endorsed by the IDSA guidelines, a large, prospective, randomized trial would help to assess the appropriateness of this type of duotherapy at this institution. At present, however, it is reasonable to state that widespread changes in policy regarding empiric antibiotic prescribing for febrile neutropenia at this institution are not necessary, particularly for patients with nonhematological malignancies.

CONCLUSION

Compliance with IDSA guidelines for empiric antibiotic therapy of febrile neutropenia at a university-affiliated, tertiary referral centre for oncology and bone marrow transplantation was 56%. Noncompliance with guidelines was most often due to the use of cefazolin and an aminoglycoside. Defervescence at 72 h after initiation of the empiric regimen, overall response to therapy, number of antibiotic changes, duration of empiric and total antibiotic therapy, adverse drug reactions, consultation to the infectious disease service, transfer to the intensive care unit, and mortality rate were not significantly different between the groups receiving compliant and noncompliant therapy. A large, prospective, randomized trial is needed to assess patient outcomes with the regimens currently employed at this institution.

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Appendix 1. Definitions of Infection (Immunocompromised Host Society[8])

Microbiologically defined bacterial infection
- Bacteremia of single or polymicrobial infection without a definable nonhematogenous locus
- Microbiologically defined site of infection (pneumonia, cellulitis) with or without concomitant bacteremia

Clinically defined infection
- A site of infection is diagnosed (pneumonia, cellulitis), but microbiologic pathogenesis cannot be proven or the site is inaccessible to examination

Fever of unexplained origin
- New fever in a neutropenic patient that is not accompanied by either clinical or microbiologic evidence of infection

Appendix 2. Responses to Therapy (Immunocompromised Host Society[8])

Type of Infection	Response to Therapy		
	Success	**Initial Response but Regimen Modified**	**Failure**
Microbiologically defined infection	All signs, symptoms, and microbiologic evidence of infection are eradicated on primary therapy alone; no recurrence of the infection for at least 1 week after the initial antibacterial regimen is discontinued	Initial infection eradicated with empiric therapy, but a second infection arises that falls outside the empiric spectrum and requires addition of another antimicrobial agent	Addition to, modification of, or change in the initial antibacterial regimen in order to eradicate the primary infection; death due to infection
Clinically defined infection	All signs and symptoms of infection are eradicated on primary therapy; no recurrence of signs or symptoms at 1 week after completion of antibiotics	Initial infection eradicated with empiric therapy, but a second infection arises that falls outside the empiric spectrum and requires addition of another antimicrobial agent	Addition of any antibiotic or change in the initial regimen in order to eradicate the primary infection; death due to infection
Fever of unexplained origin	Defervescence on the initial antibiotic regimen, as well as recovery from the neutropenia, without any modification of therapy; no recurrence of fever or signs of infection during the study or for at least 7 days after completion of antibiotics	A new fever developing after defervescence requires addition of an antimicrobial agent that falls outside the spectrum of the initial antibacterial therapy	Addition of any antibacterial agent because of persistent fever; death due to infection