Daptomycin Use in Patients With Cancer and Neutropenia: Data From a Retrospective Registry

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Abstract: Clinical data for daptomycin in the treatment of neutropenic cancer patients with documented gram-positive infections are limited. For this study, neutropenic patients were identified from an ongoing retrospective registry (Cubicin Outcome Registry and Experience [CORE]; 2006 program year). Clinical outcomes included cure, improved, failed, and nonevaluable response, and were assessed at the end of daptomycin therapy. Patients who had a nonevaluable clinical response were only included in the safety analysis. Eighty-four patients were identified, of which 72 (86%) were clinically evaluable. Thirty-four (47%) evaluable patients had severe neutropenia (<100 cells/mm^3). Hematologic malignancies were most common (82%). Bacteremia was the most common infection (76%), and vancomycin-resistant enterococci (50%), coagulase-negative staphylococci (24%), and *Staphylococcus aureus* (11%) were the most common pathogens isolated. Sixty-three patients (88%) received prior antibiotics, including vancomycin (83%), cefepime (17%), and linezolid (16%). The overall success rate (cure + improved) was 90%. Success rates stratified by degree of neutropenia were 85% for patients with less than 100 cells/mm^3, 93% for those with 100–499 cells/mm^3, and 100% for those with 500–1,000 cells/mm^3. The median final daptomycin dose was 6 mg/kg (range, 3–8) and the median duration of therapy was 13 days (range, 1–86). Of the 84 patients analyzed for safety, 24 (29%) developed 44 adverse events; only 5 (6%) patients had adverse events possibly related to daptomycin. The results suggest that daptomycin may be useful for specific cases involving neutropenic patients, and comparative clinical trials are feasible.

Introduction

Infection is still the most common complication in cancer patients who develop neutropenia.[1] The frequency and severity of infection is inversely proportional to the neutrophil count, and bacterial infections predominate during the initial phases of a neutropenic episode.[2] Bacteremia occurs in approximately 20% of patients with febrile neutropenia with gram-positive organisms causing

the majority of these infections.[3-6] Many gram-positive pathogens (eg, coagulase-negative staphylococci [CoNS], *Corynebacterium* spp., methicillin-resistant *Staphylococcus aureus* [MRSA], vancomycin-resistant enterococci [VRE], and viridans group streptococci [VGS]) are resistant to antimicrobial agents frequently used for prophylaxis and empiric therapy in such patients.[7-9] Infections caused by these organisms are difficult to treat and may be associated with substantial morbidity and mortality unless anticipated and dealt with promptly.[10]

Vancomycin has been the mainstay of therapy for infections caused by resistant gram-positive pathogens such as MRSA for several decades.[11] Vancomycin has also been used frequently in empiric regimens in patients with febrile neutropenia when such pathogens are anticipated.[9] Empiric vancomycin usage, however, has not been shown to improve overall response rates compared with regimens that do not initially contain vancomycin.[12-14] Increased vancomycin use has also been associated with the selection of resistant organisms such as VRE.[15] Recent reports have also focused on declining vancomycin susceptibilities among gram-positive organisms (minimum inhibitory concentration [MIC] creep) and declining bactericidal activity due to tolerance or polymorphism at the accessory gene regulator locus, which have resulted in clinical failures.[16-19] One recent study reported response rates to vancomycin of 9.5% for isolates with MIC values of 1–2 μg/mL compared with 55.6% if the MIC was 0.5 μg/mL or less.[17] Declining bactericidal activity is concerning, particularly for patients with neutropenia in whom the use of bactericidal agents is preferable.[20] Data such as these have led the Clinical Laboratory Standards Institute to lower the susceptibility break points of vancomycin.[21]

Daptomycin is a lipopeptide antibiotic with rapid bactericidal activity against most clinically relevant gram-positive pathogens, including many antibiotic-resistant strains.[22-25] It has been approved for the treatment of complicated skin and skin-structure infections caused by susceptible pathogens, including MRSA, and for the treatment of *S. aureus* bacteremia and right-sided endocarditis.[26,27] Daptomycin has not been formally evaluated in patients with neutropenia, but several case reports and abstracts have been published documenting its potential in this setting.[28-32] The goal of this study was to retrospectively evaluate the efficacy and safety of daptomycin for the treatment of documented infections in cancer patients with neutropenia.

Patients and Methods

The Cubicin Outcome Registry and Experience (CORE) program is an ongoing, multicenter, retrospective observational study.[33] Standardized case report forms and protocols were used to collect demographic and clinical information about patients treated with daptomycin from January 2006 through December 2006 at 55 institutions in the United States. After institutional review board approval, information was collected from medical records by trained study investigators at each site. For this study, the records of patients with a history of cancer who were neutropenic during daptomycin therapy were reviewed for safety and efficacy according to predetermined criteria. The Infectious Diseases Society of America's (IDSA) definition of neutropenia (absolute neutrophil count [ANC] of <500 cells/mm^3 or an ANC of <1,000 cells/mm^3 if a decrease to <500 cells/mm^3 is expected) was used and patients were stratified into 3 categories based on the level of neutropenia (<100 cells/mm^3; 100–499 cells/mm^3; and 500–1,000 cells/mm^3). Information for each patient included basic demographic data (eg, age, gender, underlying malignancy), renal function, and factors related to the infection and treatment, such as type of infection, microbial data, therapy prior to and concurrent with daptomycin, and daptomycin dose and administration setting.

Clinical outcomes at the end of daptomycin therapy were categorized as 1 of 4 responses: cure, improvement, failure, and nonevaluable. Cure was defined as resolution of clinical signs and symptoms, no indication for additional antibiotic therapy, and/or negative culture reported at the end of therapy. Improvement was defined as partial resolution of clinical signs and symptoms and/or indication for additional antibiotic therapy at the end of therapy. Failure was defined as inadequate response to therapy because of worsening, new/recurrent signs and symptoms, need for a change in antibiotic therapy, or positive culture reported at the end of therapy. Nonevaluable was defined as insufficient information to determine end of treatment response. The success rate was defined as the sum of patients cured and patients who showed improvement at the end of daptomycin therapy. For those who had successful treatment with daptomycin, available data on time to infection clearance—based on signs, symptoms, or culture results—were collected.

Statistical comparisons of interest were performed to analyze data using the appropriate parametric or nonparametric test. Statistical significance was defined as $P<.05$. The chi square or Fisher exact test, where appropriate, was used to assess differences between evaluable and nonevaluable patients and the effect of patient characteristics and primary pathogen on daptomycin outcomes. Chi square for trend was used to assess the effect of the degree of neutropenia on outcomes, and the Wilcoxon rank-sum test was used for comparisons of median dose by pathogen and infection type.

Table 1. Baseline Demographics and Characteristics

	Absolute Neutrophil Count, neutrophils/mm³			
	<100 (n=34)	**100–499 (n=28)**	**500–1,000 (n=10)**	**All (n=72)**
Sex				
Male	18 (53)	17 (61)	7 (70)	42 (58)
Age range, years				
≤50	12 (35)	10 (36)	3 (30)	25 (35)
51–65	15 (44)	11 (39)	5 (50)	31 (43)
≥66	7 (21)	7 (25)	2 (20)	16 (22)
Underlying diseases* (>10%)				
Cancer (hematologic)	31 (91)	21 (75)	7 (70)	59 (82)
Immunosuppressed host†	20 (59)	12 (43)	3 (30)	35 (49)
Hypertension	8 (24)	8 (29)	5 (50)	21 (29)
Cancer (solid organ)	4 (12)	9 (32)	3 (30)	16 (22)
Transplant	6 (18)	4 (14)	2 (20)	12 (17)
Diabetes mellitus	4 (12)	4 (14)	3 (30)	11 (15)
Anemia/all hematologic disorders	5 (15)	2 (7)	2 (20)	9 (13)
Daptomycin administration setting				
Inpatient only	30 (88)	21 (75)	7 (70)	58 (81)
Both inpatient and outpatient	4 (12)	7 (25)	3 (30)	14 (19)
Intensive care unit stay during daptomycin therapy	7 (21)	4 (14)	2 (20)	13 (18)
Creatine clearance <30 mL/min at start of daptomycin	2 (6)	1 (4)	2 (20)	5 (7)
Dialysis at start of daptomycin	0	1 (4)	2 (20)	3 (4)

Note: Patients were categorized by their lowest absolute neutrophil count. Data are number of patients and (%) unless otherwise indicated.

*Patients may have more than one underlying disease reported.

†As defined by the investigator.

Logistic regression analysis was used to assess risk factors for failure. All statistical analyses were performed with JMP version 7.0 or SAS version 9.1.3 (SAS Institute, Cary, NC).

Results

Patient Demographics and Characteristics

Patients from the CORE 2006 registry who met the criteria for having neutropenia during daptomycin therapy and a history of cancer were included in the safety assessment (N=84). Of those patients, 86% (72/84) were evaluable for outcomes from daptomycin therapy.

Approximately half of the patients (47%, 34/72) had severe neutropenia with neutrophil counts of less than 100/mm³. The remainder of patients had neutrophil counts of 100–499/mm³ (39%, 28/72) or 500–1,000/mm³ (14%, 10/72; Table 1). Overall, 58% of the patients were men, 35% were 50 years of age or younger, 43% were 51–65 years of age, and 22% were 66 years or older. Although the most common underlying diseases (more than 1 disease could be reported) were hematologic cancer (82%) and immunosuppression (49%), a notable proportion of patients had undergone transplantation (17%). The 12 patients excluded from the efficacy analysis did not differ from the patients analyzed, except for a higher rate of first-line use of daptomycin (42% vs 13%; *P*=.012).

Infection Types and Microbiology

Most patients (62/72; 86%) had documented culture-positive infections. The most common infections were catheter-related bacteremia (38; 53%) and noncatheter–related bacteremia (17; 24%; Table 2). Other infections included skin and skin-structure infections (9; 13%), urinary tract infections/pyelonephritis (7; 10%), and osteomyelitis (2; 3%). Five (7%) suspected infections were not microbiologically defined.

The most common pathogen was VRE, identified in 36 (50%) patients, followed by CoNS, identified in 17 (24%) patients (Table 2). *S. aureus* was present in 8 patients (11%), 5 of whom had MRSA (63%).

Table 2. Infection Types and Microbiology

	Absolute Neutrophil Count, neutrophils/mm^3			
	<100 (n=34)	**100–499 (n=28)**	**500–1000 (n=10)**	**All (n=72)**
Infection types				
Bacteremia, catheter-related	20 (59)*	12 (43)†	6 (60)	38 (53)
Bacteremia, non–catheter-related	6 (18)	10 (36)	1 (10)	17 (24)
Skin and skin-structure	4 (12)	3 (11)	2 (20)	9 (13)
Urinary tract/pyelonephritis	5 (15)	1 (4)	1 (10)	7 (10)
Osteomyelitis	0	2 (7)	0	2 (3)
Undefined	3 (9)	1 (4)	1 (10)	5 (7)
Microbiology‡				
Enterococcus faecium, VR	18 (53)	10 (36)	5 (50)	33 (46)
E. faecium	0	0	2 (20)	2 (3)
E faecalis	1 (3)	1 (4)	0	2 (3)
Enterococcus spp., VR	3 (9)	0	0	3 (4)
Enterococcus spp., VS	0	1 (4)	0	1(1)
CoNS	9 (26)	8 (29)	0	17 (24)
MRSA	1 (3)	3 (11)	1 (10)	5 (7)
MSSA	1 (3)	2 (7)	0	3 (4)
Viridans group streptococci	1 (3)	2 (7)	0	3 (4)
Streptococcus spp.	0	1 (4)	1 (10)	2 (3)
Gram-positive bacilli	0	1 (4)	1 (10)	2 (3)

CoNS=coagulase-negative staphylococci (includes one vancomycin-resistant); MRSA=methicillin-resistant Staphylococcus aureus; MSSA=methicillin-susceptible S aureus (includes those with unreported methicillin susceptibility); VR=vancomycin resistant; VS=vancomycin susceptible.

Patients may have more than one infection reported. Patients were categorized by their lowest absolute neutrophil count. Data are number of patients and (%) unless otherwise indicated.

*Includes 2 concomitant foreign body, intravascular infections.

†Includes 1 concomitant foreign body, intravascular infection.

‡Sum of total percentages are greater than 100%; calculated as the percentage of patients with gram-positive pathogens.

Daptomycin Dose Regimens

The median dose of daptomycin was 6 mg/kg (range, 3–8 mg/kg), and did not differ according to the infecting organism (enterococci, CoNS, or *S. aureus*, *P*=.72) or infection type (bacteremia, osteomyelitis, and all others; *P*=.36). Daptomycin was administered every 24 hours in 66 (92%) patients and every 48 hours in 6 (8%) patients, 5 of whom had a creatinine clearance of less than 30 mL/min. Median duration of daptomycin therapy was 13 days (range, 1–86 days); the median duration of therapy was 14 days for enterococci, 11 days for CoNS, and 13.5 days for *S. aureus*.

Prior and Concomitant Antibiotic Therapy

Sixty-three patients (88%) received antibiotic therapy prior to daptomycin treatment. The most common prior antibiotic therapies were vancomycin (83%), cefepime (17%), and linezolid (16%). Over one-third of patients (37%) were switched to daptomycin from a previous antibiotic because of resistant pathogens, and prior antibiotic therapy was unsuccessful in 21% of patients. Therapy was unsuccessful in 25% (4/16) of patients who were previously treated with vancomycin for staphylococcal or streptococcal pathogens, and they were switched to daptomycin. The majority of patients (85%, 61/72) treated with daptomycin received concomitant antibiotics; the most commonly prescribed were cefepime (16%), imipenem (10%), and meropenem (9%).

Treatment Outcomes

Overall, the treatment success rate was high, with 90% (65/72) of patients reported as cured or improved at the end of daptomycin therapy (Figure 1). Outcomes were not significantly different when analyzed by degree of neutropenia (*P*=.13). The success rate was 85% (29/34) for patients with severe neutropenia (neutrophil counts

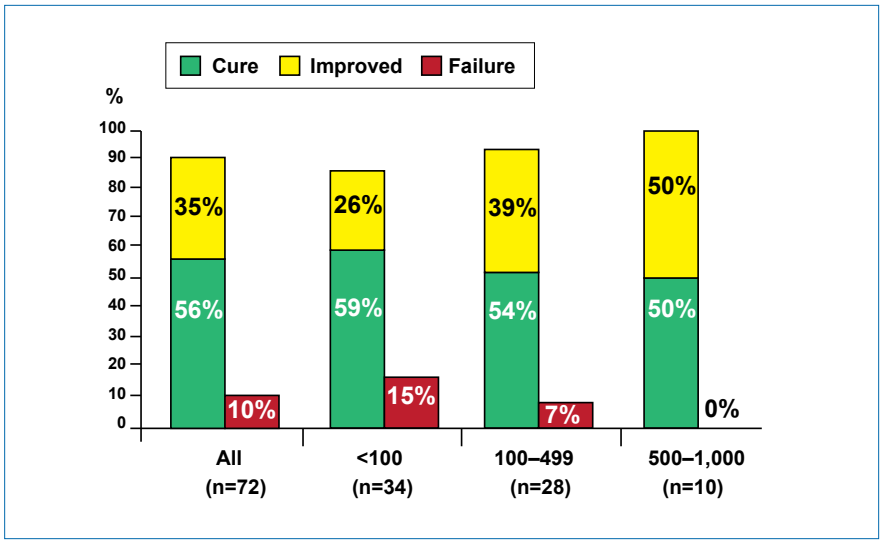

Figure 1. Clinical outcomes by degree of neutropenia (neutrophils/mm^3) for patients with cancer and neutropenia who were treated with daptomycin.

Note: Percentage may equal more than 100% because of rounding.

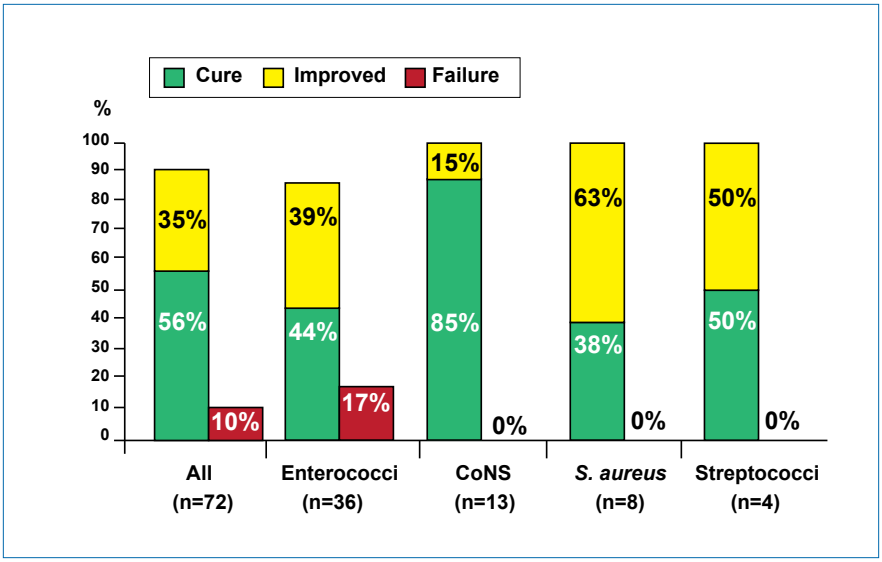

Figure 2. Clinical outcomes by primary pathogen for patients with cancer and neutropenia who were treated with daptomycin.

Note: Percentage may equal more than 100% because of rounding. The primary pathogen was assigned by investigator when multiple pathogens were present.

CoNS=coagulase-negative staphylococci.

of <100/mm^3) and increased to 93% (26/28) and 100% (10/10) for those with neutrophil counts of 100–499/mm^3 and of 500–1,000/mm^3, respectively (Figure 1).

If patients had more than 1 pathogen, the investigator indicated which pathogen was primary. When analyzed by primary pathogen, no significant differences in treatment outcomes were observed (P=.20). Of patients whose primary pathogen was enterococci, 83% (30/36) achieved clinical success and were cured or improved at the end of daptomycin therapy (Figure 2). All patients whose primary pathogens were CoNS (13/13), *S. aureus* (8/8), or streptococci (4/4) achieved clinical success at the end of daptomycin therapy.

The success rate was 89% (8/9) for patients treated with daptomycin as first-line therapy, compared with a success rate of 90% (57/63) for patients treated with daptomycin subsequent to prior antibiotic therapy (P=1.0, Fisher's exact test). The success rate was 100% (13/13) for patients who had evidence of antibiotic therapy failure prior to daptomycin; 9 of these patients had prior vancomycin therapy failure.

Patients who had enterococcal bacteremia had a success rate of 87% (27/31), and 55% of them had severe neutropenia (neutrophil counts of <100/mm^3). The treatment success rate was 100% (15/15) for patients with CoNS in blood cultures. Of these patients, 3 also

Table 3. Adverse Events Possibly Related to Daptomycin Use*

	n (%)	Serious	Severity	Outcome
Clostridium difficile colitis	1 (1)	Yes	Mild	Resolved
Rash	1 (1)	No	Severe	Unknown
Blood CPK increased	1 (1)	No	Mild	Unknown
Diarrhea	1 (1)	No	Mild	Resolved
Chromaturia	1 (1)	No	Mild	Unknown

CPK=creatine phosphokinase.

*No patients discontinued daptomycin because of a treatment-related adverse event.

had vancomycin-resistant *Enterococcus faecium* and 1 had viridans group streptococci in their blood cultures.

In univariate analyses, unsuccessful outcomes with daptomycin were not significantly associated with any patient variable, including demographics, type of pathogen, prior antibiotic use, or daptomycin dose. In a logistic regression model including 9 variables, no factors were associated with failure. All patients who received at least part of their daptomycin therapy as outpatients (14/14) were successfully treated. Among 47 patients who had treatment success and time to clearance data based on signs, symptoms, or culture results, the median time to response to daptomycin was 4 days (range, 1–21 days).

Safety

Twenty-four of 84 (29%) patients available for safety assessment reported a total of 44 adverse events (AEs). The most frequently reported AEs were cardio-respiratory arrest (3.6%), hypotension (3.6%), back pain (2.4%), congestive cardiac failure (2.4%), febrile neutropenia (2.4%), mental status changes (2.4%), and respiratory failure (2.4%). Five patients (6%) had AEs that were classified as possibly related to daptomycin therapy (Table 3). Eleven (13%) deaths were reported; 8 in the evaluable population and 5 in the nonevaluable population. No deaths were classified as possibly related to daptomycin therapy. Eight (10%) deaths were reported as having occurred during daptomycin therapy; 1 patient was assessed as a daptomycin failure, 2 patients were nonevaluable for daptomycin outcome, and the remaining patients had infections that were at least improving at the time of the patient's death. Overall, 3 of the patients who died had daptomycin therapy failure. Compared with patients who survived, a significantly higher percentage of patients who died received daptomycin in the intensive care unit (63% [7/11] vs 14% [10/73]; P=.0009) and were infected with enterococci (91% [10/11] vs 48% [35/73]; P=.009). One occurrence of *Clostridium difficile* colitis met regulatory criteria for a serious AE; however, severity of the colitis was mild and resolved upon treatment with metronidazole while the patient continued daptomycin therapy. The rates of AEs (serious or nonserious) possibly related or not related to daptomycin use were not different between the group of patients evaluated for efficacy (n=72) and the 12 patients excluded from those analyses. No patient discontinued daptomycin therapy because of a treatment-related AE.

This patient population of neutropenic cancer patients appeared to have a different array of AEs and to be at a greater risk for adverse events than the entire 2006 registry population. In 2006, there were 1,483 patients, of which 248 (17%) had at least 1 AE. The most frequently reported AEs in the registry were blood creatinine phosphokinase increased (2.0%), diarrhea (1.5%), nausea (1.3%), and hypotension (1.1%). Of all patients, 102 patients (7%) had an adverse event possibly related to daptomycin, 52 (3.5%) patients discontinued daptomycin due to an AE, and the mortality rate was 4.4% (n=65).

Discussion

Evaluation of the role of individual agents in the treatment of infections in cancer patients, particularly those that are neutropenic, has always been challenging.[34] Most studies of empiric therapy in patients with febrile neutropenia evaluate the response rates associated with the various regimens used in this setting.[9] Because only a small proportion of patients (20–30%) develop microbiologically-documented infections, it is often difficult to evaluate the specific role of individual agents when combination therapy is used. This is particularly true of narrow-spectrum agents with activity primarily against gram-positive organisms, because most broad-spectrum agents used in this setting (eg, cephalosporins, carbapenems) have overlapping activity against many gram-positive pathogens. Several studies have shown that the empiric use of agents such as vancomycin was not associated with better outcomes when compared with initiation of specific gram-positive therapy based on microbiologic data.[12-14] Additionally, because empiric therapy is commonplace in cancer patients suspected of harboring an infection, they frequently receive potentially effective therapy prior to microbiologic data becoming available. This aspect further confounds the interpretation of the responses achieved.

This analysis of the clinical outcomes in neutropenic cancer patients treated with daptomycin from the CORE registry is different in several aspects. The proportion of

patients in this study who had microbiologically documented gram-positive infections (86%) is much higher than typical reports in this patient population.[35] The high percentage of patients with bacteremia (76%) and of failure of previous antimicrobial therapy, including vancomycin (21%), also indicates possible selection of patients with more invasive or severe infections. Nearly half of the patients studied (47%) had severe neutropenia (≤100 cells/mm^3) and a substantial proportion (17%) had undergone transplantation, further highlighting the compromised nature of the patients treated.

In the current CORE registry analysis, the success rate associated with daptomycin was high (90%), with a median time to improvement of 4 days. Although most patients in this study had been previously treated (vancomycin, 83%; cefepime, 17%; linezolid, 16%), more than half had failed to respond to their prior regimen or had pathogens isolated that were resistant to treatment (eg, VRE). The success rate with daptomycin was 100% for patients who had previous therapy failure. High success rates were also seen in patients with (85%) and without (93%) severe neutropenia.

Although data are sparse, case studies have shown that daptomycin is effective in treating patients with neutropenia with infections caused by *Enterococcus* spp. In a report by Barber and colleagues,[28] the success of daptomycin plus gentamicin was documented in a patient with febrile neutropenia with bacteremia/sepsis caused by a glycopeptide-resistant strain of *E. gallinarum*. Additionally, in a small open-label, emergency-use trial, Poutsiaka and coworkers[30] reported success in 4 of 9 (44%) patients who had VRE bacteremia during episodes of fever and neutropenia. Most enterococci isolated in this study were vancomycin resistant (36/41; 89%). Thirty-one patients had enterococcal bacteremia; the success rate with daptomycin in this patient population was 87%. These results are encouraging because overall mortality rates of 37–67% have previously been reported in patients with VRE bacteremia, with 26–36% of deaths being directly attributed to the infection.[36,37] Another case report documents the successful use of daptomycin in the treatment of a patient with left-sided endocarditis associated with MRSA and vancomycin-induced neutropenia.[29] A pharmacokinetic study of daptomycin 6 mg/kg in 29 patients with febrile neutropenia reported a median time to defervescence of 3 days (range, 1–11 days); 28 of 29, including 15 of 16 patients with bacteremia, were successfully treated.[38] Collectively, these reports, along with the data from this study, suggest that daptomycin is a potentially effective agent for the treatment of serious gram-positive infections in patients with neutropenia.

Other common treatments for serious gram-positive infections, such as vancomycin and linezolid, have been studied in febrile neutropenic patients. One trial compared these 2 medications in this population and found similar clinical success rates: 87.3% and 85.2% for linezolid and vancomycin, respectively.[39] No difference was seen between patients in either population based on their underlying condition or type of infection. Outcomes were similar regardless of pathogen, with the exception of infections caused by *E. faecium*, for which the number of successes was significantly lower with vancomycin than linezolid (29% [2/7] vs 100% [4/4], respectively; P=.02). Importantly, both drugs had higher drug-related adverse event rates (linezolid: 17.2%, vancomycin: 24%) than seen with daptomycin in the current analysis.[39]

Both vancomycin and linezolid have limitations with respect to their use in patients with neutropenia. The current analysis and previous reports have documented the frequency of VRE infections in such patients.[40] Recent reports have also detailed increasing MICs for vancomycin (MIC creep) against MRSA and other gram-positive pathogens.[25,41,42] Several investigators have demonstrated the declining bactericidal activity of vancomycin (an important feature of agents used in neutropenic patients) against isolates with an MIC of 1.0 μg/mL or higher.[17,43] Linezolid is active against VRE and other resistant gram-positive pathogens. However, it is not bactericidal and may not be as effective as daptomycin in eradicating catheter-related MRSA embedded in biofilm (linezolid package insert).[44,45] Linezolid use has also been associated with myelosuppression, particularly thrombocytopenia.[46] This limits its use in patients who have chemotherapy-induced pancytopenia, and in hematopoietic stem cell transplant recipients awaiting engraftment. Other uncommon but serious adverse effects associated with linezolid include lactic acidosis, serotonin syndrome, and peripheral/optic neuropathy.[47] In contrast, daptomycin was found to be well tolerated in the current analysis. Only 6% of patients experienced AEs possibly related to daptomycin, and none required discontinuation of daptomycin therapy.

Some patients with febrile neutropenia are considered low risk and candidates for outpatient antibiotic therapy.[48] Daptomycin appears to be well suited for outpatient therapy because of its once daily administration, short infusion time (30 minutes), and easy tolerability. In this study, 19% of patients successfully received at least part of their therapy on an outpatient basis.

One potential drawback of daptomycin is inhibition of its antibacterial activity through sequestration by pulmonary surfactant.[49] Up to 40% of patients with neutropenia with a clinically documented site of infection have pneumonia, and some with bacteremia or another site of infection also have a pulmonary infiltrate.[50] Daptomycin is not indicated in such patients, and alternative agents should be used.

This study has several limitations, including its retrospective nature. The noncomparative design of the study most likely resulted in some selection bias. In addition, data on underlying cancer types (hematologic malignancies/solid tumors), duration of neutropenia, and recovery from or persistence of neutropenia were not collected. No long-term follow-up was conducted to assess the occurrence of relapses or delayed adverse effects. The small number of patients studied also makes it difficult to make definitive conclusions about the efficacy and safety of daptomycin in this patient population. Despite these limitations, our data indicate that daptomycin may be useful in specific cases of gram-positive infections in cancer patients with neutropenia. These data are promising, and comparative clinical trials are feasible.

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References

1. Bodey GP. Infection in cancer patients. A continuing association. *Am J Med.* 1986;81:11-26.
2. Bodey GP, Buckley M, Sathe YS, Freireich EJ. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Ann Intern Med.* 1966;64:328-340.
3. Klastersky J, Ameye L, Maertens J, et al. Bacteraemia in febrile neutropenic cancer patients. *Int J Antimicrob Agents.* 2007;30(Suppl 1):S51-S59.
4. Wisplinghoff H, Seifert H, Wenzel RP, Edmond MB. Current trends in the epidemiology of nosocomial bloodstream infections in patients with hematological malignancies and solid neoplasms in hospitals in the United States. *Clin Infect Dis.* 2003;36:1103-1110.
5. Yadegarynia D, Tarrand J, Raad I, Rolston K. Current spectrum of bacterial infections in patients with cancer. *Clin Infect Dis.* 2003;37:1144-1145.
6. Zinner SH. Changing epidemiology of infections in patients with neutropenia and cancer: emphasis on gram-positive and resistant bacteria. *Clin Infect Dis.* 1999;29:490-494.
7. Rolston KV, Yadegarynia D, Kontoyiannis DP, Raad II, Ho DH. The spectrum of Gram-positive bloodstream infections in patients with hematologic malignancies, and the in vitro activity of various quinolones against Gram-positive bacteria isolated from cancer patients. *Int J Infect Dis.* 2006;10:223-230.
8. Diekema DJ, Coffman SL, Marshall SA, Beach ML, Rolston KV, Jones RN. Comparison of activities of broad-spectrum beta-lactam compounds against 1,128 gram-positive cocci recently isolated in cancer treatment centers. *Antimicrob Agents Chemother.* 1999;43:940-943.
9. Hughes WT, Armstrong D, Bodey GP, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis.* 2002;34:730-751.
10. Rolston KV. Challenges in the treatment of infections caused by gram-positive and gram-negative bacteria in patients with cancer and neutropenia. *Clin Infect Dis.* 2005;40(Suppl 4):S246-S252.
11. Moellering RC Jr. Vancomycin: a 50-year reassessment. *Clin Infect Dis.* 2006;42(Suppl 1):S3-S4.
12. Rubin M, Hathorn JW, Marshall D, Gress J, Steinberg SM, Pizzo PA. Gram-positive infections and the use of vancomycin in 550 episodes of fever and neutropenia. *Ann Intern Med.* 1988;108:30-35.
13. Cometta A, Kern WV, de Bock R, et al. Vancomycin versus placebo for treating persistent fever in patients with neutropenic cancer receiving piperacillin-tazobactam monotherapy. *Clin Infect Dis.* 2003;37:382-389.
14. Feld R. Vancomycin as part of initial empirical antibiotic therapy for febrile neutropenia in patients with cancer: pros and cons. *Clin Infect Dis.* 1999;29:503-507.
15. Edmond MB, Ober JF, Weinbaum DL, et al. Vancomycin-resistant *Enterococcus faecium* bacteremia: risk factors for infection. *Clin Infect Dis.* 1995;20:1126-1133.
16. Safdar A, Rolston KV. Vancomycin tolerance, a potential mechanism for refractory gram-positive bacteremia observational study in patients with cancer. *Cancer.* 2006;106:1815-1820.
17. Sakoulas G, Moise-Broder PA, Schentag J, Forrest A, Moellering RC Jr, Eliopoulos GM. Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *J Clin Microbiol.* 2004;42:2398-2402.
18. Moise-Broder PA, Sakoulas G, Eliopoulos GM, Schentag JJ, Forrest A, Moellering RC Jr. Accessory gene regulator group II polymorphism in methicillin-resistant *Staphylococcus aureus* is predictive of failure of vancomycin therapy. *Clin Infect Dis.* 2004;38:1700-1705.
19. Soriano A, Marco F, Martinez JA, et al. Influence of vancomycin minimum inhibitory concentration on the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *Clin Infect Dis.* 2008;46:193-200.
20. Finberg RW, Moellering RC, Tally FP, et al. The importance of bactericidal drugs: future directions in infectious disease. *Clin Infect Dis.* 2004;39:1314-1320.
21. Tenover FC, Moellering RC Jr. The rationale for revising the Clinical and Laboratory Standards Institute vancomycin minimal inhibitory concentration interpretive criteria for *Staphylococcus aureus*. *Clin Infect Dis.* 2007;44:1208-1215.
22. Cilli F, Aydemir S, Tunger A. In vitro activity of daptomycin alone and in combination with various antimicrobials against Gram-positive cocci. *J Chemother.* 2006;18:27-32.
23. Mortin LI, Li T, Van Praagh AD, Zhang S, Zhang XX, Alder JD. Rapid bactericidal activity of daptomycin against methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* peritonitis in mice as measured with bioluminescent bacteria. *Antimicrob Agents Chemother.* 2007;51:1787-1794.
24. Steenbergen JN, Alder J, Thorne GM, Tally FP. Daptomycin: a lipopeptide antibiotic for the treatment of serious Gram-positive infections. *J Antimicrob Chemother.* 2005;55:283-288.
25. Kapadia M, Coyle E, Prince R, Rolston K. Declining *in vitro* activity of vancomycin against *Staphylococcus aureus* isolates from cancer patients. Presented at: 45th Annual Meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); December 16–19, 2005; Washington, DC. Abst E-807.
26. Arbeit RD, Maki D, Tally FP, Campanaro E, Eisenstein BI. The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. *Clin Infect Dis.* 2004;38:1673-1681.
27. Fowler VG Jr, Boucher HW, Corey R, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. *N Engl J Med.* 2006;355:653-665.
28. Barber GR, Lauretta J, Saez R. A febrile neutropenic patient with *Enterococcus gallinarum* sepsis treated with daptomycin and gentamicin. *Pharmacotherapy.* 2007;27:927-932.
29. Mergenhagen KA, Pasko MT. Daptomycin use after vancomycin-induced neutropenia in a patient with left-sided endocarditis. *Ann Pharmacother.* 2007;41:1531-1535.
30. Poutsiaka DD, Skiffington S, Miller KB, Hadley S, Snydman DR. Daptomycin in the treatment of vancomycin-resistant *Enterococcus faecium* bacteremia in neutropenic patients. *J Infect.* 2007;54:567-571.
31. Hogan HL, Adachi JA, Coyle EA, Rolston KVI. Daptomycin therapy of gram-positive infections (GPI) in pediatric cancer patients. Presented at: 14th International Symposia on Infections in the Immunocompromised Host; June 2007; Thessaloniki, Greece.
32. Hogan H, Raad I, Rolston K. Daptomycin therapy for gram-positive infections in cancer patients. Presented at: 17th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) and 25th International Congress of Chemotherapy; March 31-April 3, 2007; Munich, Germany. Abstract P-1666.
33. Rolston KV, Segreti J, Lamp KC, Friedrich LV. Cubicin Outcomes Registry and Experience (CORE) methodology. *Am J Med.* 2007;120:S4-S5.

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34. Hughes WT, Pizzo PA, Wade JC, Armstrong D, Webb CD, Young LS. Evaluation of new anti-infective drugs for the treatment of febrile episodes in neutropenic patients. *Clin Infect Dis.* 1992;15(Suppl 1):S206-S215.
35. Cometta A, Zinner S, de Bock R, et al. Piperacillin-tazobactam plus amikacin versus ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. *Antimicrob Agents Chemother.* 1995;39:445-452.
36. Edmond MB, Ober JF, Dawson JD, Weinbaum DL, Wenzel RP. Vancomycin-resistant enterococcal bacteremia: natural history and attributable mortality. *Clin Infect Dis.* 1996;23:1234-1239.
37. Erlandson KM, Sun J, Iwen PC, Rupp ME. Impact of the more-potent antibiotics quinupristin-dalfopristin and linezolid on outcome measure of patients with vancomycin-resistant *Enterococcus bacteremia*. *Clin Infect Dis.* 2008;46:30-36.
38. Bubalo JS, Munar MY, Cherala G, Hayes-Lattin B, Maziarz R. Daptomycin pharmacokinetics in adult oncology patients with neutropenic fever. *Antimicrob Agents Chemother.* 2009;53:428-434.
39. Jaksic B, Martinelli G, Perez-Oteyza J, Hartman CS, Leonard LB, Tack KJ. Efficacy and safety of linezolid compared with vancomycin in a randomized, double-blind study of febrile neutropenic patients with cancer. *Clin Infect Dis.* 2006;42:597-607.
40. Matar MJ, Tarrand J, Raad I, Rolston KV. Colonization and infection with vancomycin-resistant *Enterococcus* among patients with cancer. *Am J Infect Control.* 2006;34:534-536.
41. Rhee KY, Gardiner DF, Charles M. Decreasing in vitro susceptibility of clinical *Staphylococcus aureus* isolates to vancomycin at the New York Hospital: quantitative testing redux. *Clin Infect Dis.* 2005;40:1705-1706.
42. Wang G, Hindler JF, Ward KW, Bruckner DA. Increased vancomycin MICs for *Staphylococcus aureus* clinical isolates from a university hospital during a 5-year period. *J Clin Microbiol.* 2006;44:3883-3886.
43. Rolston KV. Review: Daptomycin for the treatment of gram-positive infections in neutropenic cancer patients. *Clin Adv Hematol Oncol.* 2008;6:815-817.
44. Raad I, Hanna H, Jiang Y, et al. Comparative activities of daptomycin, linezolid, and tigecycline against catheter-related methicillin-resistant *Staphylococcus* bacteremic isolates embedded in biofilm. *Antimicrob Agents Chemother.* 2007;51:1656-1660.
45. ZYVOX® (linezolid) [package insert]. New York, NY: Pharmacia & Upjohn: Division of Pfizer, Inc; 2008.
46. Falagas ME, Siempos II, Vardakas KZ. Linezolid versus glycopeptide or beta-lactam for treatment of Gram-positive bacterial infections: meta-analysis of randomised controlled trials. *Lancet Infect Dis.* 2008;8:53-66.
47. Narita M, Tsuji BT, Yu VL. Linezolid-associated peripheral and optic neuropathy, lactic acidosis, and serotonin syndrome. *Pharmacotherapy.* 2007;27:1189-1197.
48. Klastersky J, Paesmans M, Rubenstein EB, et al. The Multinational Association for Supportive Care in Cancer risk index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol.* 2000;18:3038-3051.
49. Silverman JA, Mortin LI, Vanpraagh AD, Li T, Alder J. Inhibition of daptomycin by pulmonary surfactant: in vitro modeling and clinical impact. *J Infect Dis.* 2005;191:2149-2152.
50. Rolston KVI, Bodey GP. Infections in patients with cancer. In: Kufe DW, Frei EI, Holland JF, et al, eds. *Cancer Medicine*. 7th ed. Hamilton, Ontario, Canada: BC Decker, Inc., 2006:2222-2245.