

A multicentre evaluation of the effectiveness and safety of high-dose daptomycin for the treatment of infective endocarditis

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Objectives: Despite significant medical advances, infective endocarditis (IE) remains an infection associated with high morbidity and mortality. The objective was to assess the safety and efficacy of high-dose daptomycin, defined as ≥ 8 mg/kg/day, in patients with confirmed or suspected staphylococcal and/or enterococcal IE.

Methods: This was a multicentre, retrospective observational study (2005–11). Adult patients, not undergoing haemodialysis, with blood cultures positive for staphylococci or enterococci and a definitive or possible diagnosis of IE, who received daptomycin ≥ 8 mg/kg/day (based on total body weight) for ≥ 72 h were included.

Results: Seventy patients met the inclusion criteria and comprised 33 (47.1%) with right-sided IE (RIE), 35 (50%) with left-sided IE (LIE) and 2 with both RIE and LIE. Several patients had concomitant sites of infection, with bone/joint infection being most prevalent (12.9%). Sixty-five patients received daptomycin as salvage therapy. Pathogens were isolated from 64 patients, with methicillin-resistant *Staphylococcus aureus* as the most common organism (84.4%), followed by vancomycin-resistant *Enterococcus faecium* (7.8%). The median (IQR) daptomycin dose was 9.8 mg/kg/day (8.2–10.0 mg/kg/day), and was similar in RIE and LIE patients (9.8 and 9.3 mg/kg/day, respectively). A total of 24 (34.3%) received combination therapy. For those patients with pathogens isolated ($n=64$), the organism was eradicated in 57 (89.1%) patients. Among 64 clinically evaluable patients, 55 (85.9%) achieved clinical success. No patients required discontinuation of high-dose daptomycin due to creatine phosphokinase elevations.

Conclusions: Patients with both RIE and LIE had successful outcomes with high-dose daptomycin therapy. Additional clinical trials evaluating high daptomycin dosages in patients with IE are warranted.

Keywords: MRSA, infections, patient outcomes

Introduction

Infective endocarditis (IE) is a serious infection, which, despite important medical advances, remains associated with high morbidity and mortality.^{1,2} Complicating matters, drug resistance in pathogens that commonly cause IE, particularly methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE), have steadily increased during the past decade, severely hindering

the choice of effective antimicrobial treatment.^{3,4} In fact, Fowler *et al.*⁵ revealed that *S. aureus* was the most common pathogen among a cohort of 1779 patients with IE, with MRSA isolated in $>25\%$ of these cases.

Vancomycin, a glycopeptide that has been available for >50 years, has been the primary treatment for invasive MRSA infections, including IE.⁶ However, the utilization of this antimicrobial has been questioned due to increasing reports of failure and

decreased susceptibility.⁷⁻⁹ It is evident that there is a need for novel strategies in treating multidrug-resistant Gram-positive organisms in patients with serious infections such as IE. Daptomycin is an alternative to vancomycin for the treatment of serious infections, including IE,^{6,10,11} and is approved by the US FDA at 4 mg/kg/day for the treatment of complicated skin and skin structure infections and 6 mg/kg/day for the treatment of *S. aureus* bacteraemia, including right-sided endocarditis.^{12,13} However, based on its concentration-dependent activity, higher dosages may increase the rate of bacterial killing and reduce the emergence of resistance.¹⁴⁻¹⁶

The potential clinical response of higher doses is supported further both by *in vitro* pharmacokinetic/pharmacodynamic models utilizing high inocula of *S. aureus* and enterococci and in an animal model of IE against strains with reduced daptomycin susceptibility.¹⁷⁻¹⁹ Several case reports and post-marketing surveillance data have suggested that higher dosages may be safe and efficacious.²⁰⁻²³ A recent guideline recommends that, for patients with persistent MRSA bacteraemia and vancomycin failure, treatment with daptomycin at 10 mg/kg/day should be utilized;²⁴ however, there are few clinical studies that have supported these recommendations.^{23,25,26} Although daptomycin is generally well tolerated, concerns about potential clinical or biochemical myositis as an adverse reaction warrant creatine phosphokinase (CPK) measurements weekly during therapy.²⁷ Therefore, our objective was to assess the safety of high-dose daptomycin therapy, defined as ≥ 8 mg/kg/day, and the clinical response in patients with confirmed or suspected staphylococci and/or enterococcal IE in a multicentre evaluation.

Methods

Study design

From 2005 to 2011, a retrospective evaluation of high-dose daptomycin treatment was conducted at five medical centres in the USA.²⁵ Participating institutions included: Detroit Medical Center, Detroit, MI, USA; Henry Ford Hospital, Detroit, MI, USA; Rush University Medical Center, Chicago, IL, USA; Sharp Memorial Hospital, San Diego, CA, USA; and Johns Hopkins Hospital, Baltimore, MD, USA. This study was approved by the Human Investigation Committee at each study site. Eligible subjects were all consecutive patients ≥ 18 years of age with positive blood cultures for staphylococcal or enterococcal species, who received daptomycin at ≥ 8 mg/kg/day (based on total body weight) for ≥ 72 h. Patients receiving any form of dialysis or renal replacement were excluded. The physicians caring for the patient at the time of initiation of therapy determined the treatment course. The IE subset included patients with a definite or possible diagnosis of IE as documented by the treating physician according to the modified Duke criteria.²⁸

Clinical and demographic data collected included patient characteristics at the initiation of high-dose daptomycin therapy (e.g. age, gender, weight), presence of comorbid conditions (e.g. diabetes mellitus, renal disease, cerebral vascular accident), adverse events and the dose, frequency and duration of high-dose daptomycin therapy.

Clinical and microbiological outcomes

The primary outcomes were based on clinical and microbiological assessments of the primary diagnosis, IE, and were performed at the end of inpatient high-dose daptomycin therapy by the unblinded site investigator according to pre-defined clinical criteria. Clinical success included cure or

improvement, defined as: (i) cure: signs and symptoms resolved and no additional antibiotic therapy was required and bacteraemia was cleared with negative cultures reported at the end of daptomycin therapy; and (ii) improvement: partial resolution of signs and symptoms and/or antibiotics were continued after inpatient high-dose daptomycin. Clinical failure was defined as an inadequate response to daptomycin therapy characterized by persistent, worsening or new/recurrent signs and symptoms or a positive culture reported at the end of daptomycin therapy. All patients meeting the inclusion criteria were evaluated for safety; clinical success was evaluated in the clinically evaluable population, which excluded patients for whom medical records did not contain all necessary information to determine response at the end of inpatient daptomycin therapy.

Pathogen information for Gram-positive isolates, site of infection and systemic Gram-positive therapy received before or during high-dose daptomycin were recorded for each patient. Organism identification and local susceptibility data were assessed for all positive blood cultures. Microbiological response was defined as organism eradication, organism persistence or no follow-up culture data available.

Additional clinical assessments included the presence and duration of fever (temperature $\geq 38.3^{\circ}\text{C}$), leucocytosis ($\geq 10 \times 10^3$ cells/mm³), intensive care unit (ICU) admission, mechanical ventilation and positive blood culture (time from first positive blood culture to first day of 48 h of negative cultures). Patients' length of hospital stay and antibiotic therapy during hospitalization, discharge disposition and status 30 days post-discharge were also evaluated.

Safety assessments

Safety evaluations were recorded for all patients and included adverse events documented in the medical record by a treating physician as being suspected to be associated with daptomycin. Serum CPK levels, when available, were recorded as the baseline level, the level at the end of therapy and the highest level observed during therapy. CPK level elevations were defined as values >1000 IU/L [$\sim 5 \times$ upper limit of normal (ULN)] in patients with unexplained signs and symptoms of myopathy and CPK levels >2000 IU/L ($\geq 10 \times$ ULN) in patients without reported symptoms²⁷ while on high-dose daptomycin therapy.

Statistical analysis

The primary analysis to evaluate drug utilization and outcomes was descriptive, with median (IQR), and proportions for categorical data. Additionally, characteristics potentially associated with clinical or microbiological outcome were compared using the χ^2 test for categorical variables, and continuous variables were compared by Student's *t*-test or the Mann-Whitney *U*-test. A *P* value of <0.05 was considered significant. All calculations were computed using SPSS, version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Patients

A total of 70 patients with definitive or possible IE received high-dose daptomycin during the study period. Fifty-nine patients (84.3%) received vancomycin prior to high-dose daptomycin for a median (IQR) of 4 days (2-8 days). Eight patients (11.4%) received <8 mg/kg/day of daptomycin for a median of 4 days prior to being switched to high-dose daptomycin. Of the 70 patients, 33 (47.1%) had right-sided IE (RIE), 35 (50%) had left-sided IE (LIE), and 2 had both RIE and LIE; these two patients were analysed as part of the LIE group. Patient characteristics of the entire cohort and comparison of RIE versus LIE are displayed

Table 1. Demographic and baseline clinical characteristics of patients

Clinical characteristic	RIE (n=33), median (IQR) or n (%)	LIE (n=37), median (IQR) or n (%)	Total (n=70), median (IQR) or n (%)
Age (years) ^a	49 (40–58)	56 (50–68)	53 (44–63)
Gender			
female	17 (51.5)	14 (37.8)	31 (44.3)
male	16 (48.5)	23 (62.2)	39 (55.7)
Race			
white	11 (33.3)	14 (37.8)	25 (35.7)
black	21 (63.6)	22 (59.5)	43 (61.4)
other	1 (3.0)	1 (2.7)	2 (2.8)
APACHE II score	6 (4–9)	8 (5–11)	7 (5–10)
Weight (kg)	66.7 (58.9–79.2)	75 (62.9–86.1)	71.5 (59.9–86.0)
Creatinine clearance (mL/min)	71.7 (57.8–97.8)	65.7 (40.8–91.6)	69.7 (53.3–95.3)
Prior hospitalization ≤1 year	18 (54.5)	20 (54.1)	38 (54.3)
Prior MRSA infection ≤1 year	10 (30.3)	5 (13.5)	15 (21.4)
Prior vancomycin ≤30 days of indexed hospitalization	5 (15.2)	4 (10.8)	9 (12.9)
Prosthetic device/hardware	2 (6.1)	6 (16.2)	8 (11.4)
Renal disease (ARF or CKD)	7 (21.2)	10 (27)	17 (24.3)
Injection drug user ^a	25 (75.8)	17 (45.9)	42 (60)
Liver disease (hepatitis or cirrhosis) ^a	16 (48.5)	9 (24.3)	25 (35.7)
Diabetes	6 (18.2)	9 (24.3)	15 (21.4)

APACHE II, Acute Physiology and Chronic Health Evaluation II; ARF, acute renal failure; CKD, chronic kidney disease.

^aP<0.05 between patients with RIE and LIE.

in Table 1. Compared with the LIE group, the RIE group were significantly younger, had a higher percentage of patients with liver disease and had a higher percentage of injection drug users. Several patients had concomitant sites of infection, with bone/joint infections being the most prevalent (12.9%), followed by skin/wound (11.4%) and hardware-related (8.6%) infections. Sixty-five of the 70 (92.9%) patients received daptomycin as salvage therapy; these patients failed to clear blood cultures while receiving another antimicrobial therapy directed at Gram-positive organisms prior to high-dose daptomycin.

A pathogen was isolated in 64 patients (91.4%), with MRSA as the most common organism [54 patients (84.4%)], followed by vancomycin-resistant *Enterococcus faecium* [5 patients (7.8%)]. One patient had vancomycin-susceptible *Enterococcus faecalis* isolated, one patient had methicillin-resistant *S. epidermidis* isolated, one patient had methicillin-susceptible *S. aureus* (MSSA) isolated and two patients had both MRSA and *Streptococcus viridans* isolated. The distribution of organisms between the RIE and LIE groups was similar.

Overall, the median (IQR) daptomycin dose was 9.8 mg/kg/day (8.2–10.0 mg/kg/day), and was similar in RIE and LIE patients (9.8 and 9.3 mg/kg/day, respectively). Eleven patients (33.3%) with RIE received combination therapy compared with 13 (35.1%) in the LIE group. Antimicrobial agents co-administered with daptomycin included gentamicin (25.7%), gentamicin and rifampicin (20%), trimethoprim/sulfamethoxazole (7.1%), clindamycin (5.7%) and linezolid (5.7%). The primary pathogen isolated in these patients receiving combination therapy was MRSA. Patients with RIE received combination therapy for a median (IQR) of 3 days (1–7 days) versus

5 days (3–11 days) for those with LIE. There were no differences in outcomes in patients that received combination therapy compared with those that did not.

Clinical outcomes

The clinical courses of patients with RIE and LIE are displayed in Figure 1. Sixty-four (91.4%) patients were clinically evaluable, with 55/64 (85.9%) patients deemed clinical success. Nine (14.1%) patients were assessed as clinical failures and six (8.6%) patients were non-evaluable. Among the patients with RIE, 26 (86.7%) were assessed as clinical success, four (13.3%) failed therapy and three had indeterminate outcomes due to underlying conditions. Success and failure rates were similar in the LIE group, with 29 (85.3%) patients deemed clinical success, 5 (14.7%) assessed as clinical failure and 3 considered non-evaluable. MRSA was isolated from eight (88.9%) of the nine patients that were deemed clinical failures. No patients who failed therapy had any other concomitant sites of infection. Discharge dispositions were as follows: 29 (41.4%) were discharged home; 11 (15.7%) were discharged to skilled nursing facilities; 11 (15.7%) were discharged to rehabilitation facilities; 9 (12.9%) patients died during hospitalization; 3 (4.3%) patients were transferred to another hospital; and 7 (10%) patients had other dispositions. Thirty-day follow-up was available for 52/70 patients, with 44 (84.6%) alive and 8 (15.4%) died (either during hospitalization or within 30 days after discharge). Two of the nine patients that died had their death attributed to the infection. The first patient that died had MRSA LIE that required an aortic valve replacement, as well as MRSA meningitis with a haemorrhagic embolic

cerebrovascular accident and subarachnoid haemorrhage. The second patient that died had *E. faecalis* aortic and mitral valve IE with concomitant multidrug-resistant *Acinetobacter baumannii* pneumonia.

Microbiological outcomes and organism characteristics

For those patients with pathogens isolated (n=64), the organism was eradicated in 57 (89.1%) patients, persisted at end of daptomycin therapy in 6 (9.4%) patients [median (IQR) days of persistent bacteraemia: 21 days (7–30 days)] and 1 (1.6%) patient had no follow-up culture available. Each of the six patients who had persistent bacteraemia was infected with MRSA; data on subsequent antimicrobial therapy were available for three. Two of the six patients with persistent bacteraemia received combination therapy. One patient cleared his bacteraemia after receiving concomitant high-dose daptomycin (10 mg/kg), trimethoprim/sulfamethoxazole and rifampicin. Bacteraemia cleared in the second patient when he was switched from daptomycin to trimethoprim/sulfamethoxazole, and the last patient cleared on vancomycin (15 mg/kg) post-daptomycin therapy. Patients with RIE and LIE had similar microbiological outcomes.

The MIC₅₀ and MIC₉₀ values of daptomycin for baseline *S. aureus* isolates (n=45) were 0.5 and 1 mg/L, respectively (range 0.38–2 mg/L). The MIC₅₀ and MIC₉₀ values for baseline *S. aureus* isolates for vancomycin were 1.5 (Etest) and 2 mg/L (broth microdilution) (range ≤0.5–2 mg/L). The daptomycin MIC₅₀ and MIC₉₀ for

baseline enterococcal isolates were both 2 mg/L (range 1 to >4 mg/L). For vancomycin the MIC₅₀ and MIC₉₀ for baseline enterococcal isolates were both ≥64 mg/L (range 0.5 to ≥64 mg/L). Six (8.6%) patients developed non-susceptibility to daptomycin (Table 2); each had MRSA IE and had prior vancomycin exposure. Daptomycin non-susceptibility was identified after a median of 11 days of receiving high-dose daptomycin. Of note, five patients from the cohort of 70 patients received high-dose daptomycin as first-line therapy; none developed non-susceptibility to daptomycin.

Safety

Two (2.9%) patients experienced mild or moderate adverse events attributed to high-dose daptomycin therapy. One patient experienced hyperkalaemia on day 7 of therapy and was switched to an alternative agent. The second patient developed thrombocytosis 5 days into therapy and remained on high-dose daptomycin, with the platelet count resolving. Median (IQR) values for baseline (n=58), observed peak level (n=51) and end-of-therapy (n=37) available CPK levels were as follows: 45 (27–103), 74 (45–271) and 38 IU/L (26–97 IU/L), respectively. No patients developed an elevated CPK level that reached an abnormal value. There were 10 (14.3%) patients taking concomitant 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors and none discontinued daptomycin therapy due to myopathy or myositis. Five (7.1%) patients with normal baseline CPK levels experienced an elevation in CPK (median 272 IU/L); however, all remained asymptomatic and none required discontinuation of high-dose daptomycin.

Discussion

We evaluated 70 patients with RIE or LIE who were treated with ≥8 mg/kg/day of daptomycin and found a success rate of 85.9% at the end of high-dose daptomycin therapy and 84.6% survival at 30 days. High-dose daptomycin was well tolerated, with only one patient requiring discontinuation of therapy due to an adverse event of hyperkalaemia, a previously unreported adverse event that may also have arisen from underlying conditions.

There are currently few data on the safety and clinical effectiveness of high-dose daptomycin in patients with IE, particularly with MRSA as the primary pathogen. Cunha et al.^{29,30} described two case reports of patients who had *E. faecalis* vancomycin-susceptible enterococcal bacteraemia and MRSA mitral valve acute bacterial endocarditis, both treated successfully with high-dose daptomycin, defined as 12 mg/kg/day. Durante-Mangoni

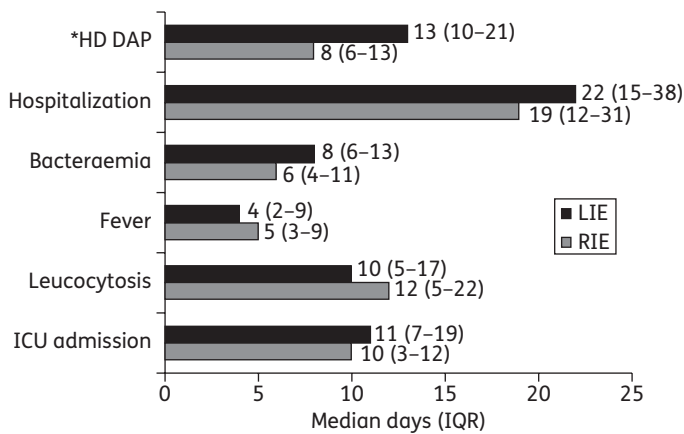


Figure 1. Clinical course of patients with RIE and LIE. *High-dose daptomycin treatment while in hospital.

Table 2. Patients with MRSA IE developing non-susceptibility to daptomycin

IE	DAP MIC (mg/L)	DAP MIC change	VAN MIC (mg/L)	VAN exposure (days)	Outcome
RIE	0.38→4	day 7 HD DAP	1.5→2	17	cleared on SXT
RIE	1→4	day 1 HD DAP	2→2	5	cleared on SXT
RIE	0.5→4	day 21 HD DAP	1→2	≤30 days prior to admission	organism persisted
LIE	1→4	day 8 HD DAP	2→2	2	cleared on HD DAP
RIE/LIE	0.5→4	day 11 HD DAP	hVISA 2→4	prior to admission VAN x6 weeks	cleared on HD DAP
RIE/LIE	1→2	day 18 HD DAP	1.5→2	20	cleared on HD VAN

DAP, daptomycin; VAN, vancomycin; HD, high-dose; hVISA, heterogeneous vancomycin-intermediate *S. aureus*; SXT, trimethoprim/sulfamethoxazole.

*et al.*²⁶ recently evaluated the efficacy and safety of high-dose daptomycin (defined as >6 mg/kg/day) in 25 patients with cardiac implantable electronic device-related IE due to staphylococci. The investigators noted an overall clinical success rate of 80% and microbiological eradication of 92%, with 20% of patients experiencing a significant CPK elevation; however, no patients required discontinuation of daptomycin due to adverse events or myopathy. Most studies describe the use of lower doses of daptomycin, the largest being that recorded in the Cubicin Outcomes Registry and Experience (CORE) database, where 49 patients with IE were evaluated.³¹ The median (range) dose of daptomycin was 6 mg/kg/day (4–7 mg/kg/day), with 55% patients receiving ≥ 6 mg/kg/day. Clinical outcomes were favourable, with 63% of patients assessed as clinical success. In a randomized registration trial¹³ 6 mg/kg/day of daptomycin was compared with combination therapy with either a semi-synthetic penicillin or vancomycin plus initial gentamicin in patients with *S. aureus* bacteraemia and endocarditis. Among patients with RIE or bacteraemia, the clinical success rates of 70.0% for those who received daptomycin monotherapy and 68.7% among those who received the comparator combinations were similar to our results. However, in that study there were very few patients with LIE. Only a few of these patients received the full course of therapy and none of the patients with LIE due to MRSA were adjudicated as clinical successes. Additionally, the ascertainment of clinical success was based on a different definition compared with our study. The difference in outcomes may also be attributed to the high proportion of injection drug user (IDU)-related cases in our cohort. These patients tend to be younger with fewer comorbidities and often have better outcomes than non-IDUs.

Of note, the utilization of high-dose daptomycin has been shown to be beneficial in *in vitro* studies, in which there was enhanced killing and decreased emergence of resistance in simulated *S. aureus* and enterococci endocarditis vegetations in an *in vitro* pharmacokinetic/pharmacodynamic model treated with 8–12 mg/kg of daptomycin compared with dosages of 6 mg/kg.^{15,18,19,32,33} Additionally, since *Enterococcus* species typically have higher MICs of daptomycin than other Gram-positive organisms (0.5–4 versus 0.25–1 mg/L), patients with these serious infections may require higher dosages of daptomycin for optimal treatment.^{10,18,24,34}

All the *S. aureus* and enterococci isolates were susceptible to daptomycin at onset of therapy. Six (8.6%) patients with MRSA IE developed non-susceptibility to daptomycin; all had prolonged prior vancomycin exposure, consistent with prior observations.³⁵ From the patients with follow-up data available, all cleared their infection when switched to an alternative agent or on high-dose daptomycin.

We observed a low incidence of toxicity associated with high-dose daptomycin in this population, with only two patients experiencing either mild or moderate adverse reactions. The median end-of-therapy CPK level was 38 IU/L (26–97 IU/L). In a previous report, which included these cases, we described 250 patients with complicated Gram-positive infections receiving ≥ 8 mg/kg/day of daptomycin.²⁵ High-dose daptomycin was well tolerated in the larger study cohort, with 10 (8.5%) patients with end-of-therapy CPK levels >200 IU/L (normal CPK levels are <200 IU/L) and no patients with values >604 IU/L at the end of therapy. Additionally, there was no significant correlation found between daptomycin dose and highest observed CPK level. Similarly, Figueroa *et al.*²²

assessed the safety of ≥ 6 mg/kg of daptomycin in 61 patients. The mean dose that patients received was 8 mg/kg for a median of 25 days. The authors found that 3/61 (4.9%) patients experienced grade 3 CPK level elevations (levels >1000 IU/L), with all cases reversible by the discontinuation of daptomycin therapy.

There are several limitations of this study that should be noted. First, this was a subset analysis of a prior study²⁵ that was not designed to collect specific information about the nature, diagnosis and management of IE, including surgical interventions, which are often indicated in patients at high risk of complications. However, the results of this study are still valuable since these patient cases were predominantly treatment-experienced and had serious comorbid conditions. Additionally, the retrospective observational nature of the study design did not allow for a matched cohort of patients who received standard dosages of daptomycin; however, since a majority of patients received daptomycin as salvage therapy, obtaining a comparable group would be difficult. Further, as a majority of our patients were placed on vancomycin prior to daptomycin, additional information regarding dosage and trough levels may have been beneficial. However, patients were placed on vancomycin for a short period of time (median 4 days) and our primary objective in this study was to evaluate the effectiveness of high-dose daptomycin. Lastly, retrospective, observational studies, such as our study, to assess toxicity are suboptimal for non-laboratory-based events.

In conclusion, high-dose daptomycin, defined as ≥ 8 mg/kg/day, may be an effective and safe antimicrobial for patients with either RIE or LIE. In addition, as noted above, it is important that our study revealed that patients with both RIE and LIE had successful outcomes with high-dose daptomycin therapy. Additional clinical trials evaluating high dosages of daptomycin in patients with IE are warranted.

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Transparency declarations

At the time of writing, R. K. had received speaking honoraria from Cubist Pharmaceuticals and Forest Laboratories, and served on the Advisory Board of Optimer Pharmaceuticals. R. K. is now employed by Cubist Pharmaceuticals and owns Cubist Pharmaceuticals stock. A. M. C. has received grant support from Cubist Pharmaceuticals, Forest Laboratories and the Michigan Department of Community Health. S. L. D. has served on the Advisory Board of Forest Laboratories. D. P. L. has received grant support from AstraZeneca, Cubist Pharmaceuticals and Cerexa, received speaking honoraria from AstraZeneca, Merck, Novartis, Forest and Cubist Pharmaceuticals, and served on the Advisory Board of Cerexa, Forest, RibX, Theravance and Cubist Pharmaceuticals. G. S. has received grant support from Forest Laboratories and speaking honoraria from Cubist Pharmaceuticals and Forest Laboratories. S. E. C. has received grant support from Cubist Pharmaceuticals and has consulted for Novartis. M. J. R. has received grant support from, consulted for or provided lectures for Cubist Pharmaceuticals, Forest Laboratories, Durata, Cepheid and Novartis. J. J. Z., C. W. C. and J. S.: none to declare.

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