



Clinical Implications of Glycopeptide Use: Pros and Cons

Barbara E. Murray, MD

Professor and Director, Division of Infectious Diseases
University of Texas Medical School, Houston, TX

Introduction

There are many factors that contribute to the success of an antimicrobial treatment regimen for serious gram-positive infections. Factors to consider include the following: the development of resistance, clinical efficacy, predictable pharmacokinetics, convenience, and cost. The presence of resistance in the target species and how frequently it occurs is also an important consideration. In addition, the agent's propensity to select or promote the growth of *C. difficile* and the likelihood that it propagates resistance in other species may influence the physician's choice of antibiotics.

Clinical efficacy may vary and may be influenced by various factors such as whether an agent is bactericidal or bacteriostatic and whether it has activity in biofilms. The amount of free drug at the site of infection (e.g., pulmonary, CSF, urine) will also be important. Evaluation of an antibiotic includes not only its pharmacokinetics but also the potential for toxicity and drug interactions. Convenience and ease of administration are determined by route and frequency of administration and, along with the actual cost of the antimicrobial agent, will affect the ultimate cost of therapy.

Resistance

Resistance among enterococci, particularly *Enterococcus faecium*, to glycopeptides is prevalent and is an ongoing therapeutic challenge. *E. faecium* clinical isolates in the U.S. are often highly resistant to ampicillin, vancomycin and aminoglycosides. Although rare, resistance is also emerging among *Staphylococcus aureus* including the true vancomycin-resistant *S. aureus* (VRSA; minimum inhibitory concentration [MIC] vancomycin is ≥ 32 $\mu\text{g}/\text{mL}$) and vancomycin-intermediate *S. aureus* (VISA; MIC vancomycin is 8-16 $\mu\text{g}/\text{mL}$).¹ However, the phenomenon of "heteroresistance" may be more common. Heteroresistance refers to the variability of vancomycin susceptibilities among subpopulations of a single isolate. A heteroresistant isolate contains a majority population that is susceptible to vancomycin (≤ 4 $\mu\text{g}/\text{mL}$) and a minority population that is resistant.²²

Those strains that produce colonies on vancomycin (4 $\mu\text{g}/\text{mL}$)

containing brain heart infusion (BHI) agar with vancomycin MICs of ≤ 4 $\mu\text{g}/\text{mL}$ are termed heteroresistant VRSA or hetero-VRSA. One large study found that the overall incidence of heteroresistant populations with reduced susceptibilities was 0.2% with only 2 of 630 isolates demonstrating heteroresistance.² The clinical significance of VISA, hetero-VISA, or other staphylococcal isolates with reduced susceptibility to vancomycin has not yet been determined. Anecdotal evidence from reports of individual patients who failed vancomycin therapy or who had prolonged bacteremia without any identifiable reason suggests that heteroresistance is important.

Moore and colleagues tested paired *S. aureus* isolates from a patient with infective endocarditis who had relapsed after vancomycin therapy and was later cured by combination therapy with rifampin and vancomycin.³ The pre-treatment and clinical relapse isolates were typed by pulsed-field gel electrophoresis (PFGE) and determined to be the same strain (MICs ≤ 2 $\mu\text{g}/\text{mL}$) confirming a relapse rather than a new infection in this patient. The presence of a subpopulation that grew on vancomycin-containing agar in the post-therapy clinical relapse isolate but not in the pre-therapy isolate indicated heterogenous resistance to vancomycin. In the rabbit model of endocarditis, vancomycin eradicated the pre-therapy isolate, while the clinical relapse isolate persisted at pre-treatment levels. The data from this animal model showing a poorer outcome with the isolates showing heterogenous resistance to vancomycin strongly suggest that this phenomenon is clinically relevant.

Fridkin et al conducted a nested case-control study of patients in the U.S. who were infected with *S. aureus* with reduced vancomycin susceptibility (4-8 $\mu\text{g}/\text{mL}$).⁴ Bloodstream infections with *S. aureus* were more common among patients infected with *S. aureus* strains with reduced vancomycin susceptibility (68% 13/19; OR 5.4 [1.5-21]) than among control patients (28%; 12/42) without reduced susceptibility (MIC ≤ 2 $\mu\text{g}/\text{mL}$). In a multi-variate analysis, the authors determined that the presence of reduced susceptibility strains was an independent predictor of in-hospital death. Thus, these heterogeneously resistant strains appear to be significant not only in animal models, but this case control study also supports this conclusion.^{3,4}

Efficacy of Vancomycin versus Beta-Lactam Antibiotics

Published in-vitro and animal model data support the concept that vancomycin is not as effective against susceptible *S. aureus* infections as the beta-lactam antibiotics. Small and Chambers performed time-kill studies on 10 isolates of *S. aureus* from intravenous drug users with *S. aureus* endocarditis treated with vancomycin. The mean MICs were comparable for nafcillin and vancomycin (0.5 µg/mL and 1µg/mL, respectively). However, in time-kill curves, the geometric mean CFU at 24 hours for nafcillin and vancomycin was reduced to 2.8 and 1.4 log₁₀ CFU/mL, respectively, showing that vancomycin was less rapidly bactericidal than nafcillin.⁵

Data from experimental infective endocarditis rabbit models (methicillin-susceptible *S. aureus* [MSSA]) suggest that oxacillin is more rapidly bactericidal against staphylococci than vancomycin.^{6,7} Two different studies were conducted in the same laboratory with the same control strains, which were variants of a single strain that differed in their response to thrombin-induced platelet microbicidal protein-1 (tPMP-1). After two days of treatment, the mean log₁₀ concentrations in the ISP479C strain were 6.2-6.8 CFU/g in the control group, 4.9 CFU/g in the vancomycin group, and 2.3 CFU/g in the oxacillin group. Similarly, with the ISP479R strain, mean log₁₀ concentrations were 6.7-6.9 CFU/g, 6.7 CFU/g, and 3.7 CFU/g in the three groups, respectively.

In another study using the experimental infective endocarditis rabbit model, Cantoni and colleagues looked at two different strains of methicillin-susceptible *S. aureus*.⁸ For one of these strains, they found that the percentage of sterile vegetations among vancomycin-treated animals (12/18) was significantly less than that among cloxacillin- or amoxicillin/sulbactam-treated rabbits (25/27; p=0.017). However, with another strain there was no statistical difference in the number of sterile vegetations between the vancomycin (5/6) cloxacillin or amoxicillin/sulbactam (15/18) groups. In a similar experimental model, de Gorgolas et al also found no statistically significant difference between vancomycin (1.6 ±1 CFU/g) and cloxacillin (2.3±1.7 CFU/g).⁹ Strain variability in these reports may contribute to differences in reported results.

The activity of penicillin against a heterogeneously methicillin-resistant clinical isolate of *S. aureus* (MRSA) was compared with that of vancomycin in the rabbit experimental endocarditis model. Penicillin was significantly more effective (4.6 CFU/g versus 7.0 CFU/g; P<0.001) than vancomycin against the non-penicillinase-producing strains in vivo.¹⁰

An extended-spectrum cephalosporin (BAL 9141) with broad in vitro

Table 1

Daily Acquisition Costs

Drug	Frequency of Administration	Cost
Vancomycin	.1 gm Q 12 hr	\$.8
Nafcillin	.1 gm Q 4 hr	\$.12
Linezolid	.600 mg Q 12 hr	\$.132 / 98 (IV / PO)
Daptomycin	.500 mg vial	\$.135
Synercid	.500 mg Q 8 hr	\$.300
Minocycline	.100 mg Q 12 hr	\$.74 / 2 (IV / PO)
Rifampin	.600 mg Q 12 hr	\$.100 / 6 (IV / PO)

Pharmacy acquisition costs in a Houston hospital, 2004.

activity against MRSA was investigated in rats with experimental endocarditis using two strains of penicillinase-producing MRSA. In each strain, only the cephalosporin resulted in 100% sterile vegetations compared with 25% and 50% with vancomycin (P<0.05).¹¹

The clinical, animal, and *in vitro* data described above support the concept that vancomycin is not as effective against MSSA, at least for some *S. aureus* strains and disease states, and that some beta-lactams (with good PBP2a activity) may also be more active than vancomycin against MRSA. It appears that vancomycin, in general, would be more bactericidal than other agents such as linezolid or quinupristin/dalfopristin against strains with constitutive *erm* expression.¹²

Convenience

Factors of convenience are important in considering pros and cons of antibiotic use and include route and frequency of administration, monitoring, drug interactions, and tissue penetration. While vancomycin can be administered orally for a few indications (i.e., the treatment of pseudomembranous colitis due to *C. difficile* or *S. aureus* enterocolitis), administration is via the intravenous route for systemic infections or intraperitoneally in some patients with peritoneal dialysis. Frequency of administration is generally every 12 hours but will be less frequent in patients with impaired renal function. Certain populations of patients (young, very obese, and those with burns or very good renal function) may require more frequent administration (every 6-8 hours). Many clinicians agree that vancomycin has predictable pharmacokinetics such that therapeutic levels do not need to be monitored. Monitoring blood levels may be important, however, in certain clinical situations, especially in complex or atypical patients with high flux membrane dialysis, neonates, and when ascertaining and documenting appropriate CSF concentrations.

Glycopeptides (vancomycin, in particular) lack metabolic interactions that are problematic with some agents. Vancomycin is poorly metabolized and is mainly excreted unchanged in the urine, therefore, interactions with other drugs that are metabolized by hepatic isoenzymes, such as the CYP450 system, are unlikely. However, vancomycin administration may potentiate nephrotoxicity and ototoxicity of concomitantly administered aminoglycosides.



National
Foundation for
Infectious
Diseases
EDUCATION PREVENTION RESEARCH

CLINICAL UPDATES IN
*Infectious
Diseases*

Senior Editor

Susan J. Rehm, M.D.

Managing Editor

Sheena L. Majette

Published by National Foundation
for Infectious Diseases

4733 Bethesda Avenue, Suite 750
Bethesda, MD 20814

301-656-0003 • www.nfid.org

Copyright © 2005. All rights reserved.

Vancomycin penetrates well into many body fluids and highest concentrations are probably found in the urine. However, tissue penetration with vancomycin is relatively poor in the lung epithelial lining fluid and in macrophages. Unless the meninges are inflamed, there is also little penetration in the CSF. While vancomycin levels are thought to be adequate in the CSF of children, penetration is variable in the CSF of adults.¹⁵

Cost

Cost of administration is a necessary consideration in any clinical setting. Daily acquisition costs of various drugs in the hospital setting are listed in **Table 1**. With the exception of oral minocycline or oral rifampin, vancomycin 1gm administered every 12 hours was the least expensive drug to administer at \$8 per day compared to other drugs used to treat MRSA. However, drug acquisition cost is not the only aspect of total drug cost, which must also include direct medical costs such as preparation and administration, monitoring, treatment of adverse events, and therapeutic failure. Using a decision analytic model, Shah et al evaluated the total cost of administering IV vancomycin as primary treatment of MRSA.¹⁴ The authors incorporated the costs of drug acquisition (\$9/dose), set-up, monitoring, and adverse events and estimated the total cost per vancomycin dose at \$29-\$43, for a typical cost/day of \$58-\$86 (twice daily dosing), which is still considerably lower than the costs of administering other IV agents that are being used to treat MRSA.

Adverse Effects

As is true with other therapies, vancomycin therapy has the potential for adverse reactions. The most common adverse reactions associated with vancomycin therapy include the “red man/red neck” syndrome, rashes, neutropenia, nephro- and oto-toxicity, and phlebitis. The red man syndrome results from rapid intravenous infusion or larger than normal dose of vancomycin that causes a histamine-like reaction characterized by flushing and maculopapular rash of the neck, face, trunk, and extremities, hypotension, and rarely, cardiac arrest. Other rashes range in their level of severity (maculo-papular, toxic epidermal necrolysis, Stevens-Johnson, linear IgA bullous disease) and occur in 1-3% of patients. The incidence of neutropenia is 1-2% but may occur in up to 13% of patients on longer-term therapy (e.g., 6 weeks). Ototoxicity and nephrotoxicity are uncommon to rare when vancomycin is used alone, but may be a concern when used in conjunction with aminoglycosides. Phlebitis is reported in about 3-14% of patients.

Hematologic effects of long-term vancomycin use may be a limitation of therapy in the treatment of gram-positive infections. The hematologic effects of long-term vancomycin treatment (mean=42 days of treatment) were compared to those of linezolid in 65 adults with gram-positive bacterial orthopedic infections requiring ≥ 2 weeks of vancomycin or linezolid therapy.¹⁵ A modest reduction in platelets occurred ($<150 \times 10^9$ platelets/L) in 21% of patients while a more marked reduction ($<100 \times 10^9$ platelets/L) occurred in 2% of patients; mean total reduction in platelets was 39%. White blood cells were decreased ($<1500/\text{mL}$) in 12% of patients with a total mean reduction of 41%. The only significant difference in hematologic effects between the two agents was a higher incidence of thrombocytopenia ($<150 \times 10^9$ platelets/L) in the subset of linezolid patients who had received vancomycin within two weeks before starting linezolid therapy ($P=0.02$).

Vancomycin Use and VRE

Because of the large increase in the rate of occurrence of vancomycin-resistant enterococci (VRE) in the U.S. and the United Kingdom, the relationship between vancomycin use and VRE has been the focus of considerable research.¹⁶ Vancomycin is used to a greater extent in the U.S. than in the rest of the world.¹⁷ Ecological data have shown a strong association between higher rates of vancomycin use and increased prevalence of VRE in 126 U.S. ICUs ($P < 0.001$ by linear regression analysis) although lack of individual-level data in studies such as this one make it difficult to determine if the association is causative in nature.¹⁸ In a recent review by Harbarth et al, the authors noted that many studies reporting a link between IV Vancomycin and VRE did not control for other confounders such as length of stay and use of other antibiotics.¹⁹ It is also difficult to determine true *de novo* acquisition of VRE in retrospective studies since these studies often did not demonstrate that VRE-positive patients were truly VRE negative at study entry.

Nevertheless, the rate of VRE in nosocomial infections is higher in the U.S. than anywhere else in the world with 17% of U.S. isolates identified as resistant strains in 1999.²⁰ The epidemiology of VRE in the U.S., however, is different from that in Europe. Strong data exist to support a link between oral administration of vancomycin (now widely discouraged) and nosocomial VRE infections in the U.S.²¹ In Europe, the spread of VRE was associated with the use of oral avoparcin as a growth promoter in animal feeds, which is now banned.²¹ Use of broad spectrum cephalosporins and/or anti-anaerobic antibiotics may have had a more pronounced influence than vancomycin on increasing VRE.¹⁹

Conclusions

In summary, there are clinical advantages and disadvantages for prescribing glycopeptides (e.g., vancomycin) for the treatment of serious gram-positive infections in the U.S. (**Table 2**). Advantages (the pros) include low initial acquisition costs (although administrative costs need to be considered), no metabolic interactions with other drugs, a

Table 2

Pros and Cons of Glycopeptide Use

Pros

- Low initial acquisition costs
- No metabolic drug interactions
- Predictable PK profile with BID dosing
- Favorable safety profile, in general
- Documented efficacy, familiar antibiotic

Cons

- Reduced efficacy compared with beta-lactams
- IV or IP administration
- Modest to poor CSF penetration (particularly in adults)
- A few potential toxicity issues
- Recent emergence of resistance (VRE, VISA/VRSA)

predictable pharmacokinetic profile with twice-daily dosing, a generally favorable safety profile, and documented efficacy as a known and familiar antibiotic. Clinical disadvantages (the cons) include reduced efficacy compared with beta-lactams for MSSA infections, the need for par-

enteral administration, modest to poor CSF penetration (particularly in adults), a few potential toxicity issues, and the recent emergence of resistance among enterococci and *Staphylococcus aureus* strains.

REFERENCES:

1. National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. 5th ed. Approved standard M7-A5. Wayne, PA: National Committee for Clinical Laboratory Standards; 2000.
2. Hubert SK, Mohammed JM, Fridkin SK, Gaynes RP, McGowan Jr JE, Tenover FC. Glycopeptide-intermediate *Staphylococcus aureus*: evaluation of a novel screening method and results of a survey of selected U.S. hospitals. *J Clin Microbiol* 1999;37:3590-3593.
3. Moore MR, Perdreau-Remington F, Chambers HF. Vancomycin treatment failure associated with heterogenous vancomycin-intermediate *Staphylococcus aureus* in a patient with endocarditis and in the rabbit model of endocarditis. *Antimicrob Agents Chemother* 2003;47:1262-1266.
4. Fridkin SK, Hageman J, McDougal LK, Mohammed J, Jarvis WR, Perl TM, Tenover FC, Vancomycin-Intermediate *Staphylococcus aureus* Epidemiology Study Group. Epidemiological and microbiological characterization of infections caused by *Staphylococcus aureus* with reduced susceptibility to vancomycin, United States, 1997-2001. *Clin Infect Dis* 2003;36:429-439.
5. Small PM, Chambers HF. Vancomycin for *Staphylococcus aureus* endocarditis in intravenous drug users. *Antimicrob Agents Chemother* 1990;34:1227-1231.
6. Dhawan VK, Yeaman MR, Bayer AS. Influence of in vitro susceptibility phenotype against thrombin-induced platelet microbicidal protein on treatment and prophylaxis outcomes of experimental *Staphylococcus aureus* endocarditis. *J Infect Dis* 1999;180:1561-1568.
7. Dhawan VK, Bayer AS, Yeaman MR. Thrombin-induced platelet microbicidal protein susceptibility phenotype influences the outcome of oxacillin prophylaxis and therapy of experimental *Staphylococcus aureus* endocarditis. *Antimicrob Agents Chemother* 2000;44:3206-3209.
8. Cantoni L, Wenger A, Glauser MP, Bille J. Comparative efficacy of amoxicillin-clavulanate, cloxacillin, and vancomycin against methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* endocarditis in rats. *J Infect Dis* 1989;159:989-993.
9. de Gorgolas M, Aviles P, Verdejo C, Fernandez Guerrero ML. Treatment of experimental endocarditis due to methicillin-susceptible or methicillin-resistant *Staphylococcus aureus* with trimethoprim-sulfamethoxazole and antibiotics that inhibit cell wall synthesis. *Antimicrob Agents Chemother* 1995;39:953-957.
10. Fantin B, Pierre J, Castela-Papin N, Saint-Julien L, Drugeon H, Farinotti R, Carbon C. Importance of penicillin alone or in combination with sulbactam in experimental endocarditis due to methicillin-resistant *S. aureus*. *Antimicrob Agents Chemother* 1996;40:1219-1224.
11. Entenza JM, Hohl P, Heinze-Krauss I, Glauser MP, Moreillon P. BAL9141, a novel extended-spectrum cephalosporin active against methicillin-resistant *Staphylococcus aureus* in treatment of experimental endocarditis. *Antimicrob Agents Chemother* 2002;46:171-177.
12. Sakoulas G, Eliopoulos GM, Moellering Jr. RC, Wennersten C, Venkataraman L, Novick RP, Gold HS. Accessory gene regulator (*agr*) locus in geographically diverse *Staphylococcus aureus* isolates with reduced susceptibility to vancomycin. *Antimicrob Agents Chemother* 2002;46:1492-1502.
13. Matzke GR, Zhanel GG, Guay DR. Clinical pharmacokinetics of vancomycin. *Clin Pharmacokinet* 1986;11:257-282.
14. Shah NP, Reddy P, Paladino JA, McKinnon PS, Klepser ME, Pashos CL. Direct medical costs associated with using vancomycin in methicillin-resistant *Staphylococcus aureus* infections: an economic model. *Curr Med Res Opin* 2004;20:779-790.
15. Rao N, Ziran BH, Wagener MM, Santa ER, Yu VL. Similar hematologic effects of long-term linezolid and vancomycin therapy in a prospective observational study of patients with orthopedic infections. *Clin Infect Dis* 2004;38:1058-1064.
16. Centers for Disease Control and Prevention. National nosocomial infections surveillance (NNIS) system report, data summary from January 1992-April 2000, issued June 2000. *Am J Infect Control* 2000;28:429-448.
17. Kirst HA, Thompson DG, Nicas TI. Historical yearly usage of vancomycin. *Antimicrob Agents Chemother* 1998;42:1303-1304.
18. Fridkin SK, Edwards JR, Courval JM, Hill H, Tenover FC, Lawton R, Gaynes RP, McGowan JE, Jr.: Intensive care antimicrobial resistance epidemiology (ICARE) project and the national nosocomial infections surveillance (NNIS) system hospitals. *Ann Intern Med* 2001;135:175-183.
19. Harbarth S, Cosgrove S, Carmeli Y. Effects of antibiotics on nosocomial epidemiology of vancomycin-resistant enterococci. *Antimicrob Agents Chemother* 2002;46:1619-1628.
20. Low DE, Keller N, Barth A, Jones RN. Clinical prevalence, antimicrobial susceptibility, and geographic resistance patterns of enterococci: results from the SENTRY antimicrobial surveillance program, 1997-1999. *Clin Infect Dis* 2001;32 (Suppl 2):S133-145.
21. Goossens H. Spread of vancomycin-resistant enterococci: differences between the United States and Europe. *Infect Control Hosp Epidemiol* 1998;19:546-551.
22. Schwaber MJ, Wright SB, Carmeli Y, Venkataraman L, DeGirolami PC, Gramatikova A, et al. Clinical implications of varying degrees of vancomycin susceptibility in methicillin-resistant *Staphylococcus aureus* bacteremia. *Emerg Infect Dis* 2003; 9:657-664

Requests for credit must be received no later than May 31, 2006

Target Audience: Physicians; clinical microbiologists; pharmacists; hospital epidemiologists; public health authorities; health care professionals in training; and others interested in the epidemiology, recognition, and management of infections due to resistant staphylococci.

Learning Objective: After reading this publication, the reader should be able to list the advantages and disadvantages of glycopeptide use for the treatment of serious infections.

CME Self Assessment Examination

Volume VIII, Issue 1

(At least three of the five answers must be correct in order to obtain a CME certificate)

See mailing instructions and other pertinent information on the reverse side.

- 1) Evidence for the significance of heteroVISA includes all except:
 - a) Case reports of relapse of *S. aureus* bacteremia after completion of vancomycin therapy
 - b) Prevalence rates of >50% for hVISA in clinical laboratories
 - c) Demonstration of higher mortality rates among bacteremic patients infected with hVISA
 - d) Persistence of bacteremia with hVISA strains during vancomycin therapy in a rabbit endocarditis model
- 2) With regard to glycopeptide pharmacology, which of the following statements is true?
 - a) CNS concentrations are poor in the absence of inflamed meninges
 - b) Vancomycin is 100% bioavailable when administered orally
 - c) There is excellent penetration of drug into the epithelial lining fluid of the lung
 - d) Because of extensive hepatic metabolism, glycopeptides frequently interact with drugs metabolized thru the CYP450 system.
- 3) "Red man syndrome" and toxic epidermal necrolysis occur with equal frequency among patients receiving vancomycin.
 - a) True
 - b) False
- 4) The total daily cost of therapy with vancomycin, including the cost of drug, administration and laboratory monitoring, is approximately:
 - a) \$8-14
 - b) \$36-44
 - c) \$58-86
 - d) \$95-120
- 5) Data from rabbit models of infective endocarditis suggest that oxacillin is a more rapid staphylocidal agent than vancomycin against organisms susceptible to both.
 - a) True
 - b) False

Answer: _____

Answer: _____

Answer: _____

Answer: _____

Answer: _____

CME Evaluation

Your input is important to us in improving this publication and identifying areas of need for other CME programs. Please circle the choice that best answers the following:

- 1. This content meets the educational objectives.
 - A. Agree B. Neutral C. Disagree
- 2. Considering my experience, the material presented was:
 - A. Satisfactory B. Too Elementary C. Too Technical
- 3. I gained information which will be of use to me.
 - A. Agree B. Neutral C. Disagree
- 4. The format is clear, readable, and useful.
 - A. Agree B. Neutral C. Disagree
- 5. There was commercial bias in this publication.
 - A. Yes B. No

If yes, please give examples: _____

Suggested topics for future issues or other comments about this publication: _____

Please provide all the information below so that you may obtain CME credit (**Please print legibly or we will be unable to process your certificate**).

Name/Degree _____

Title _____

Affiliation _____

Address _____

City _____ State _____ Zip _____

E-Mail _____

Telephone _____ Fax _____

Check the appropriate box:

I am an MD and/or DO and wish to receive 1.0 (one) AMA/PRA Category 1 credit.

I am not an MD and/or DO but wish to receive a certificate of completion.

Signature/Date _____



EDUCATION PREVENTION RESEARCH

4733 Bethesda Avenue, Suite 750
Bethesda, MD 20814

CME Accreditation

The National Foundation for Infectious Diseases (NFID) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide Continuing Medical Education (CME) for physicians. NFID takes responsibility for the content, quality, and scientific integrity of this CME activity.

NFID designates this CME activity for a maximum of one (1.0) Category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

The 1.0 credit hour is based upon the approximate time it should take to read this publication and complete the self-assessment examination.

Credit will be granted only up to 6 months following the publication date. **Requests for credit must be received no later than May 31, 2006.**

CME Disclosure

As a sponsor accredited by the ACCME, NFID must insure balance, independence, objectivity, and scientific rigor in its educational activities. All authors are required to disclose any relevant financial interest or other relationship with the manufacturer(s) of any product or service discussed in an educational presentation and with the commercial supporter of this activity. Disclosure information is reviewed in advance to manage and resolve any conflict of interest that may affect the balance and scientific integrity of an educational activity.

Dr. Murray is a consultant for Aventis, AstraZeneca, Cubist Pharmaceuticals, Eli Lilly, Genome Therapeutic Corporation, NABI Pharmaceuticals, Pfizer, Inc., Vicuron Pharmaceuticals, and Wyeth.

CME Instructions

To receive CME credits after reading this publication, complete the self-assessment examination, the CME evaluation, and your contact information. Return the examination and evaluation form, including your complete contact information, **via fax to 301-907-0878** or by mail to:

NFID Office of CME
4733 Bethesda Avenue, Suite 750
Bethesda, Maryland 20814

No fee is required. Please allow 4-6 weeks for processing your certification. Inquiries may be directed by phone to 301-656-0003 ext. 19 or by email to info@nfid.org