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## ONCE-DAILY AMINOGLYCOSIDES IN PATIENTS WITH NEUTROPENIC FEVER

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### Introduction

Over the past few decades, several antibiotic regimens have been proposed for the empiric treatment of febrile neutropenic patients. Parenteral aminoglycosides continue to be important in the treatment of this patient population.<sup>1</sup> Consensus guidelines and treatment algorithms routinely recommend an aminoglycoside to be used in conjunction with a beta-lactam antibiotic for their synergistic activity and for coverage against Gram-negative pathogens. The latest guidelines from the Infectious Diseases Society of America specifically recommend an aminoglycoside to be used with an antipseudomonal beta-lactam antibiotic in dual therapy.<sup>2</sup>

Traditionally, aminoglycosides have been administered in multiple daily doses, typically every 8 to 12 hours, with adjustments made to the dosing interval for impaired renal function. Although these drugs are highly effective, their utilization has been limited due to concerns about toxicities and the subsequent need for frequent monitoring. Over the past several years, much has been learned about the efficacy and toxicities of the aminoglycosides, and a new dosing strategy emerged with the "once-daily" administration. Once-daily aminoglycoside (ODA) dosing regimens have now been studied extensively and discussed in several review articles.<sup>3,5</sup> ODA has been shown to be as effective as and no more toxic than the traditional multiple-daily-dosing regimens. However, few studies have involved neutropenic patients.

Initially, studies were lacking in the neutropenic patient population, primarily because of apprehension associated with allowing extended "drug-free intervals," that is, the period of time that the serum concentration of the aminoglycoside is undetectable. It is known that aminoglycosides have a postantibiotic effect (PAE), but there was uncertainty that the PAE would last for the duration of the drug-free interval with ODA dosing due to the absence of neutrophils.<sup>6</sup> Therefore, the possibility that bacterial regrowth could occur after the PAE in an immunocompromised patient was a concern with ODA administration. More recent studies that focus on ODA dosing specifically in neutropenic patients alleviate this concern by demonstrating equal or better outcomes.<sup>1,7-11</sup>

The purpose of this review is to explain the rationale behind ODA administration and evaluate its clinical utility in the neutropenic host.

### Rationale for Once-Daily Administration

Several potential advantages are associated with ODA regimens. First, this schedule optimizes the pharmacodynamics of aminoglycosides. Second, it is thought that ODA dosing may reduce the incidence of adaptive resistance by providing higher peak serum concentrations of the drug and a subsequent drug-free interval. Third, substantial reductions in direct and indirect costs

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have been demonstrated with ODA over traditional dosing.

### *Pharmacodynamics*

Aminoglycosides demonstrate concentration-dependent killing.<sup>12-14</sup> Once-daily administration is designed to take advantage of the pharmacodynamics by optimizing concentration-dependent bactericidal activity with high peak concentrations while reducing toxic exposure with drug-free intervals. Concentration-dependent bactericidal activity is optimized for aminoglycosides by attaining a peak concentration:minimum inhibitory concentration (MIC) ratio of at least 8:1 to 10:1.<sup>15,16</sup> Higher concentrations obtained by ODA dosing may lead to better outcomes and a reduction of resistant organisms.<sup>17,18</sup>

It is well known that elevated trough levels of aminoglycosides increase the incidence of nephrotoxicity due to increased drug accumulation. Toxicity can be delayed or avoided by giving the aminoglycosides adequate time for renal elimination, thereby reducing the saturable binding to the renal proximal tubular cells.<sup>19</sup> Nicolau et al<sup>20</sup> found that, compared with Hartford Hospital historical controls, nephrotoxicity was reduced from 3%-5% to 1.2% with an institutional switch to ODA dosing. Higher doses of aminoglycosides associated with the extended interval dosing are no more nephrotoxic and may be less nephrotoxic than traditional dosing.<sup>21-28</sup>

Aminoglycosides can cause both cochlear and vestibular toxicities

by accumulating in the affected tissue and destroying the sensory hair cells.<sup>29</sup> Few studies objectively assess the comparative incidence and severity of ototoxicity associated with ODA vs traditional dosing. There are no standards established for assessing, measuring, or defining aminoglycoside-related ototoxicity. Cochlear hearing loss begins with more unnoticed, high-pitched sounds (>10,000 Hz), before progressing to lower-pitched speech pattern-type sounds (<8,000 Hz).<sup>30</sup> This can be difficult to assess because baseline examinations are not routinely performed in the acute care setting, and some patients, especially critically ill or sedated patients, may not be assessable. Vestibular toxicity may be masked initially because of a patient's response to visual cues, which can be used for compensation. As with nephrotoxicity, it has been theorized that the incidence of ototoxicity may be reduced or delayed in extended-interval dosing due to a reduction in accumulation of aminoglycoside.<sup>31</sup>

Studies that have investigated ototoxicity in comparative trials have shown no significant increase in incidence with ODA dosing.<sup>20-28</sup> Rather, the risk of ototoxicity seems to be related to duration of treatment. One study by Warkentin et al<sup>32</sup> assessed the incidence of toxicity in 33 febrile neutropenic bone marrow transplant patients receiving gentamicin 5 mg/kg per day in a noncomparative trial. All patients were given vancomycin, and 17 had received cisplatin. All had normal renal function prior to therapy, and gentamicin levels were not moni-

tored unless renal function deteriorated. Ototoxicity occurred in 4 patients (12%), and nephrotoxicity occurred in 1 (3%). All patients who developed ototoxicity had normal renal function before and during treatment. The mean duration of gentamicin treatment was 20 days in the ototoxic patients compared with 9 days of therapy in those who did not express ototoxicity ( $P=.001$ ). At this time, it is thought that the ototoxicity seen with ODA is more dependent on the duration of treatment than anything else. The incidence of ototoxicity has not been shown to be significantly different with extended-interval dosing.<sup>20-28</sup>

An antibiotic provides a PAE if it continues to suppress bacterial growth after serum levels drop below the MIC. Aminoglycosides possess a PAE that is linked to (1) the species of bacteria, (2) the MIC of the bacterial strain, and (3) the serum concentration as a factor of the duration of exposure (area under the curve [AUC]) achieved. The PAE is likely due to irreversible binding at the 30S ribosome, causing nonlethal damage to the bacterial cell. The duration of aminoglycoside therapy and the presence of neutrophils are other factors that may play a role.<sup>5,33,34</sup>

The PAE demonstrated by aminoglycosides is one component of ODA therapy that allows drug-free intervals without compromising patient outcomes. Another component is the concomitant administration of a second antibiotic. Aminoglycosides are not typically given as single-

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agent therapy but are given in combination with an antipseudomonal beta-lactam. This approach not only provides synergistic antibacterial activity, but also provides antibacterial coverage during the aminoglycoside-free interval for any time outside of the PAE.<sup>20</sup>

### *Adaptive Resistance*

Aminoglycosides have been associated with a first-exposure effect called adaptive resistance, which most commonly occurs with *Pseudomonas aeruginosa*.<sup>35</sup> This phenomenon is manifested after the first dose by the down-regulation of aminoglycoside uptake for subsequent doses. When this occurs, there is less bacterial killing with the later doses, as well as shorter PAEs. It is most likely to occur with first doses that provide low peak serum concentrations. Peak concentrations of 8 to 10 times the MIC can reduce the emergence of resistance. Once the first-exposure effect develops, the down-regulation can last for hours; however, it will eventually dissipate.<sup>35-39</sup> A study by Daikos et al<sup>38</sup> evaluated gentamicin and netilmicin against *P aeruginosa* strains and other aerobic Gram-negative bacilli. The surviving bacteria showed down-regulation after the first dose and were resistant to later doses. Cross-resistance between the aminoglycosides was also demonstrated. Down-regulation of uptake occurred within 2 hours of the first dose but dissipated after 6 to 7 hours without aminoglycoside exposure. Once-daily dosing provides the high serum concentrations necessary to avoid inducing a first-exposure effect, and it extends the time

interval between doses to overcome the onset of adaptive resistance.

### *Costs*

The administration of ODA can reduce costs and conserve resources. Nursing, pharmacy, and laboratory personnel workload would be reduced due to less frequent dosage administration and serum concentration monitoring. A direct cost savings would result from fewer doses given and fewer serum levels to process. Once-daily administration could allow lower-risk patients to be treated as outpatients, resulting in the elimination of many costs associated with an inpatient stay.<sup>40</sup> Also, if the regimen results in the increased efficacy of the first-line treatment, the resulting reduction in the number of changes to a more expensive second-line treatment can provide an indirect cost savings.<sup>10</sup>

In 1996, Nicolau et al<sup>41</sup> reported the impact of a hospital-wide conversion to ODA at the 850-bed Hartford Hospital. The result was a 40% decrease in the orders for gentamicin and tobramycin serum concentrations compared with their historical controls for traditional aminoglycoside dosing. The switch eliminated 350 aminoglycoside serum concentration orders per month, resulting in an annual savings of more than \$100,000.

### *Clinical Efficacy in Neutropenic Patients*

Clinical efficacy in immunocompetent patients has been documented in several studies and meta-

analyses.<sup>21-28</sup> These studies have shown that the efficacy of ODA is at least equal to traditional dosing. It is important to note that the aminoglycoside was administered in combination with a beta-lactam antibiotic in most of the studies. Differences in toxicity between the two regimens either were insignificant or favored the ODA regimen.

More recently, studies in neutropenic patients have been conducted. Both noncomparative and comparative trials have been conducted to evaluate the efficacy and safety of the ODA regimen. Noncomparative trials have shown ODA regimens to be safe, effective, and tolerable.<sup>40,42-44</sup> Other trials have compared ODA dosing directly to traditional dosing regimens.<sup>1,7,11</sup>

A meta-analysis by Hatala et al<sup>45</sup> pooled three small studies with one larger study, totaling over 800 patients, that met criteria to evaluate both efficacy and toxicity of ODA vs traditional dosing in neutropenic immunocompromised patients (Table). All studies were randomized and combined an aminoglycoside with a beta-lactam antibiotic. Patients were not stratified into groups according to risk factors, but most of the patients evaluated had neutropenic fever due to a hematologic malignancy (71% to 91%) and had severe neutropenia (50% to 66% with an absolute neutrophil count of <100/ $\mu$ L). Efficacy was evaluated based on bacteriologic cure, clinical cure, and mortality (all causes). Once-daily dosing was equally efficacious compared with traditional aminoglycoside dosing in both

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hematologic malignancies and solid tumors, as well as in bacteremic and nonbacteremic patients. There was no difference in the clinical response rate when analyzed according to neutrophil count at study entry. The bacteriologic cure pooled risk ratio was 1.00 and the clinical cure pooled risk ratio was 0.97, indicating that there was no difference found in cure rates by either definition. In addition, ODA dosing was found to have a trend toward reduced mortality and nephrotoxicity compared with traditional dosing in these patients, with pooled risk ratios of 0.93 and 0.78, respectively. There was no significant heterogeneity found between risk ratios of individual studies. Ototoxicity was evaluated only in one trial. The risk ratio was 1.69, with a wide confidence interval (95% CI, 0.49-5.86) reflecting the small sample size. Additional studies are needed to assess the comparative incidence of ototoxicity with both dosing regimens.

Bakri et al<sup>10</sup> conducted a retrospective, comparative, sequential, nonrandomized study of once-daily and multiple-daily dosing of gentamicin in 52 febrile neutropenic patients with acute myeloid leukemia over a 2-year period. In the first year, 27 patients received azlocillin 5 g three times daily (t.i.d.) and gentamicin 80 mg t.i.d., with desired gentamicin serum levels being 1 to 2 mg/L and 6 to 8 mg/L for the trough and peak, respectively. In the second year, 25 patients received azlocillin with gentamicin 7 mg/kg per day, following the Hartford Hospital protocol and nomogram.<sup>46</sup> During both years, teicoplanin and ceftazidime were used as a second-line regimen if clinical failure was evident. Response was defined as complete resolution of signs and symptoms of infection for 48 hours and was evident in 52% of the ODA patients vs 18.2% of those receiving the traditional regimen ( $P=.112$ ). The poor response rate in the multiple-daily group was attributed to the

failure to achieve therapeutic levels in the first 48 hours of treatment, resulting in a switch to the second-line regimen. Three patients (12%) in the once-daily group developed toxicity (1 nephrotoxicity, 1 ototoxicity [auditory], and 1 with both nephrotoxicity and ototoxicity [both auditory and vestibular]). The two cases of ototoxicity were described as severe and irreversible. In the multiple-daily group, 1 patient (3.7%) experienced nephrotoxicity, and there were no reported incidences of ototoxicity. The mean duration of treatment of those who did and did not experience toxicity was 16 and 9.7 days ( $P=.066$ ), respectively, in the once-daily group, and 3 and 7.4 days, respectively, in the multiple-daily group.

## Serum Drug Level Monitoring

The goal of ODA is to obtain a peak concentration-MIC ratio that

exceeds 10:1 while maintaining a drug-free interval of at least 2 to 4 hours. Because of the high serum concentrations obtained with ODA and the essential drug-free period, traditional monitoring of peaks and troughs is not applicable. Monitoring strategies for ODA may include obtaining a random serum concentration 2 to 4 hours prior to the next dose to ensure adequate renal clearance that provides a sufficient drug-free period. A concentration of less than 0.5 µg/mL is desired before redosing. Another widely accepted approach is to obtain a single midpoint blood sample 6 to 14 hours postinfusion and apply this value to a concentration-time curve nomogram, such as the Hartford Hospital ODA nomogram.<sup>20</sup> The value will be plotted on the nomogram to determine the appropriate dosing interval. In most instances, a single serum sample is adequate to determine subsequent dosing. However, individuals with altered pharmacokinetic/dynamic states (eg, sepsis, ascites) may require several samples to determine optimal dosing. Serum drug levels should be obtained every 5 to 7 days or more frequently if clinically indicated.

## Conclusions

ODA dosing in combination with an antipseudomonal beta-lactam antibiotic has become an acceptable regimen over the past 5 to 10 years for immunocompetent patients with pneumonia, urinary tract infections, pelvic inflammatory disease, and abdominal infections due to suspected susceptible

pathogens. The pharmacodynamics of this class of drugs has become better understood, allowing more studies in immunocompromised patients to emerge. Once-daily administration optimizes aminoglycoside pharmacodynamics by increasing concentration-dependent killing, providing a possible reduction in toxicity, avoiding adaptive resistance, and utilizing the PAE.

In all studies performed, ODA combined with a beta-lactam antibiotic in febrile neutropenic patients has shown equivalent outcomes in mortality, equivalent or better outcomes in clinical cure, and no difference or significantly less nephrotoxicity when compared to traditional dosing. Otitotoxicity needs to be investigated further, but no increase in incidence has been attributed to the ODA dosing regimen. While providing equivalent or better outcomes in efficacy and toxicity, ODA dosing also substantially reduces direct and indirect costs associated with therapy, making it a viable, cost-effective method of treatment in this patient population.

## References

1. The International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer. Efficacy and toxicity of single daily doses of amikacin and ceftazidime for infection in patients with cancer and granulocytopenia. *Ann Intern Med.* 1993; 119(7 pt 1):584-593.
2. 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.
3. Preston SL, Briceland LL. Single daily dosing of aminoglycosides. *Pharmacotherapy.* 1995;15:297-316.

4. Rice DAK. Once daily aminoglycosides. *Clin Trends Pharm Pract.* 1996;10:9-15.
5. Freeman CD, Nicolau DP, Belliveau PP, et al. Once-daily dosing of aminoglycosides: review and recommendations for clinical practice. *J Antimicrob Chemother.* 1997;39:677-686.
6. McDonald PJ, Wetherall BL, Pruul H. Postantibiotic leukocyte enhancement: increased susceptibility of bacteria pretreated with antibiotics to activity of leukocytes. *Rev Infect Dis.* 1981;3:38-44.
7. Gibson J, Johnson L, Snowdon L, et al. Single daily ceftriaxone and tobramycin in the empirical management of febrile neutropenic patients: a randomised trial. *Int J Hematol.* 1993;58:63-72.
8. Rozdzinski E, Kern W, Reichle A, et al. Once-daily versus thrice-daily dosing of netilmicin in combination with beta-lactam antibiotics as empirical therapy for febrile neutropenic patients. *J Antimicrob Chemother.* 1993;31:585-598.
9. Hansen M, Achen F, Carstensen C, et al. Once- versus thrice-daily dosing of netilmicin in febrile immunocompromised patients: a randomized, controlled study of efficacy and safety. *Journal of Drug Development.* 1988;1(suppl 3):119-124.
10. Bakri FE, Pallett A, Smith AG, et al. Once-daily versus multiple-daily gentamicin in empirical antibiotic therapy of febrile neutropenia following intensive chemotherapy. *J Antimicrob Chemother.* 2000;45:383-386.
11. Charnas R, Luthi AR, Ruch W. Once daily ceftriaxone plus amikacin vs three times daily ceftazidime plus amikacin for treatment of febrile neutropenic children with cancer. *Pediatr Infect Dis J.* 1997;16: 346-353.
12. MacArthur RD, Lolans V, Zar FA, et al. Biphasic, concentration-dependent and rate-limited, concentration-independent bacterial killing by an aminoglycoside antibiotic. *J Infect Dis.* 1984;150:778-779.
13. Moore RD, Smith CR, Lietman PS. The association of aminoglycoside plasma levels with mortality in patients with gram-negative bacteremia. *J Infect Dis.* 1984;149: 443-448.
14. Dudley MN, Zinner SH. Single daily dosing of amikacin in an in vitro model. *J Antimicrob Chemo.* 1991;27(suppl C):15-19.
15. Begg EJ, Peddie BA, Chambers ST, et al. Comparison of gentamicin dosing regimens using an in-vitro model. *J Antimicrob Chemother.* 1992;29:427-433.
16. Blaser J, Stone BB, Groner MC, et al. Comparative study with enoxacin and

netilmicin in a pharmacodynamic model to determine importance of ratio of antibiotic peak concentration to MIC for bactericidal activity and emergence of resistance. *Antimicrob Agents Chemother.* 1987;31:1054-1060.

17. Moore RD, Lietman PS, Smith CR. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. *J Infect Dis.* 1987;155:93-99.

18. Ericsson CD, Fischer RP, Rowlands BJ, et al. Prophylactic antibiotics in trauma: the hazards of underdosing. *J Trauma.* 1989;29:1356-1361.

19. Verpooten GA, Giuliano RA, Verbist L, et al. Once-daily dosing decreases renal accumulation of gentamicin and netilmicin. *Clin Pharmacol Ther.* 1989;45:22-27.

20. Nicolau DP, Freeman CD, Belliveau PP, et al. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. *Antimicrob Agents Chemother.* 1995;39:650-655.

21. Ali MZ, Goetz MB. A meta-analysis of the relative efficacy and toxicity of single daily dosing versus multiple daily dosing of aminoglycosides. *Clin Infect Dis.* 1997;24:796-809.

22. Bailey TC, Little JR, Littenberg B, et al. A meta-analysis of extended-interval dosing versus multiple daily dosing of aminoglycosides. *Clin Infect Dis.* 1997;24:786-795.

23. Ferriols-Lisart R, Alos-Alminana M. Effectiveness and safety of once-daily aminoglycosides: a meta-analysis. *Am J Health Syst Pharm.* 1996;53:1141-1150.

24. Hatala R, Dinh T, Cook DJ. Once-daily aminoglycoside dosing in immunocompetent adults: a meta-analysis. *Ann Intern Med.* 1996;124:717-725.

25. Munckhof WJ, Grayson ML, Turnidge JD. A meta-analysis of studies on the safety and efficacy of aminoglycosides given either once daily or as divided doses. *J Antimicrob Chemother.* 1996;37:645-663.

26. Barza M, Ioannidis JP, Cappelleri JC, et al. Single or multiple daily doses of aminoglycosides: a meta-analysis. *BMJ.* 1996;312:338-345.

27. Blaser J, Konig C. Once-daily dosing of aminoglycosides. *Eur J Clin Microbiol Infect Dis.* 1995;14:1029-1038.

28. Galloe AM, Graudal N, Christensen HR, et al. Aminoglycosides: single or multiple daily dosing? A meta-analysis on efficacy and safety. *Eur J Clin Pharmacol.* 1995;48:39-43.

29. Brummett RE, Fox KE. Aminoglycoside-induced hearing loss in humans. *Antimicrob Agents Chemother.* 1989;33:797-800.

30. Kibbler CC, McWhinney PH, Warner P, et al. Ototoxicity associated with a once daily dose amikacin regimen in febrile neutropenic patients. *J Antimicrob Chemother.* 1992;29:463-464.

31. Tran Ba Huy P, Deffrennes D. Aminoglycoside ototoxicity: influence of dosage regimen on drug uptake and correlation between membrane binding and some clinical features. *Acta Otolaryngol.* 1988;105:511-515.

32. Warkentin D, Ippoliti C, Bruton J, et al. Toxicity of single daily dose gentamicin in stem cell transplantation. *Bone Marrow Transplant.* 1999;24:57-61.

33. Craig WA. Post-antibiotic effects in experimental infection models: relationship to in-vitro phenomena and to treatment of infections in man. *J Antimicrob Chemother.* 1993;31(suppl D):149-158.

34. Spivey JM. The postantibiotic effect. *Clin Pharm.* 1992;11:876-877.

35. Karlowsky JA, Zelenitsky SA, Zhanel GG. Aminoglycoside adaptive resistance. *Enterococcus faecium* in a multiple-dose, in vitro pharmacodynamic model. *Pharmacotherapy.* 1997;17:549-555.

36. Lacy MK, Nicolau DP, Nightingale CH, et al. The pharmacodynamics of aminoglycosides. *Clin Infect Dis.* 1998;27:23-27.

37. Craig WA. Once-daily versus multiple-daily dosing of aminoglycosides. *J Chemother.* 1995;7(suppl 2):47-52.

38. Daikos GL, Jackson GG, Lolans VT, et al. Adaptive resistance to aminoglycosides antibiotics from first-exposure down-regulation. *J Infect Dis.* 1990;162:414-420.

39. Daikos GL, Lolans VT, Jackson GG. First-exposure adaptive resistance to aminoglycoside antibiotics in vivo with meaning for optimal clinical use. *Antimicrob Agents Chemother.* 1991;35:117-123.

40. Rapoport BL, Sussmann O, Herrera MV, et al. Ceftriaxone plus once daily aminoglycoside with filgrastim for treatment of febrile neutropenia: early hospital discharge vs standard in-patient care. *Chemotherapy.* 1999;45:466-476.

41. Nicolau DP, Wu AH, Finocchiaro S, et al. Once-daily aminoglycoside dosing: impact on requests and costs for therapeutic drug monitoring. *Ther Drug Monit.* 1996;18:263-266.

42. Cornely OA, Bethe U, Salzberger B, et al. Randomized controlled monocentric comparison of once daily ceftriaxone with tobramycin and cefotaxime three times daily with tobramycin in neutropenic fever. *Ann Hematol.* 2001;80:103-108.

43. Gilbert C, Meisenberg B, Vredenburg J, et al. Sequential prophylactic oral and empiric once-daily parenteral antibi-

otics for neutropenia and fever after high-dose chemotherapy and autologous bone marrow support. *J Clin Oncol.* 1994;12:1005-1011.

44. Cooke RP, Grace RJ, Gover PA. Audit of once-daily dosing gentamicin therapy in neutropenic fever. *Int J Clin Pract.* 1997;51:229-231.

45. Hatala R, Dinh TT, Cook DJ. Single daily dosing of aminoglycosides in immunocompromised adults: a systematic review. *Clin Infect Dis.* 1997;24:810-815.

46. Nicolau D, Quintiliani R, Nightingale CH, et al. Once-daily aminoglycosides. *Conn Med.* 1992;56:561-563.

47. Van der Auwera P, Meunier F, Ibrahim S, et al. Pharmacodynamic parameters and toxicity of netilmicin (6 milligrams/kilogram/day) given once daily or in three divided doses to cancer patients with urinary tract infection. *Antimicrob Agent Chemother.* 1991;35:640-647.