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Once-Daily Amikacin Dosing in Burn Patients Treated with Continuous Venovenous Hemofiltration▽

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Amikacin clearance can be increased in burn injury, which is often complicated by renal insufficiency. Little is known about the impact of renal replacement therapies, such as continuous venovenous hemofiltration (CVVH), on amikacin pharmacokinetics. We retrospectively examined the clinical pharmacokinetics, bacteriology, and clinical outcomes of 60 burn patients given 15 mg/kg of body weight of amikacin in single daily doses. Twelve were treated with concurrent CVVH therapy, and 48 were not. The pharmacodynamic target of ≥10 for the maximum concentration of drug in serum divided by the MIC (C_{max}/MIC) was achieved in only 8.5% of patients, with a small reduction of C_{max} in patients receiving CVVH and no difference in amikacin clearance. Mortality and burn size were greater in patients who received CVVH. Overall, 172 Gram-negative isolates were recovered from the blood cultures of 39 patients, with amikacin MIC data available for 82 isolates from 24 patients. A 10,000-patient Monte Carlo simulation was conducted incorporating pharmacokinetic and MIC data from these patients. The cumulative fraction of response (CFR) was similar in CVVH and non-CVVH patients. The CFR rates were not significantly improved by a theoretical 20 mg/kg amikacin dose. Overall, CVVH did not appear to have a major impact on amikacin serum concentrations. The low pharmacodynamic target attainment appears to be primarily due to higher amikacin MICs rather than more rapid clearance of amikacin related to CVVH therapy.

Aminoglycosides are an important therapeutic option in critically ill patients with sepsis, and achieving a pharmacodynamic target of ≥8 to 10 for the maximum concentration of drug in serum divided by the MIC (C_{max}/MIC) is recommended (14, 16). While aminoglycoside therapy has traditionally been given in multiple daily doses, limited clinical evidence supports once-daily maintenance dosing of 15 mg/kg of body weight for amikacin and offers advantages in cost and convenience (9, 12). However, aminoglycoside clearance can be enhanced in critically ill patients and patients with burn injury (8, 19, 21), making this target more difficult to achieve. Increased amikacin doses could therefore be required in this population to ensure clinical efficacy.

In our burn intensive care unit (ICU), we have observed that patients with severe burn injury often develop clinical sepsis or septic shock along with acute kidney injury, leading to concurrent antimicrobial and renal replacement therapies. Continuous venovenous hemofiltration (CVVH) is most often used since data from our center indicate a survival advantage over historical controls who largely did not receive any form of renal replacement (4, 5). However, the clinical impact of CVVH therapy on aminoglycoside pharmacokinetics in burn patients is uncertain. We therefore conducted a Monte Carlo simulation using pharmacokinetic and MIC data from burn patients to determine whether CVVH compromised our ability to achieve a C_{max}/MIC of ≥8 to 10 using standard once-daily amikacin doses of 15 mg/kg.

MATERIALS AND METHODS

Clinical data. We reviewed the medical records of patients admitted to the burn ICU of the United States Army Institute for Surgical Research (USAISR) from 2006 to 2009. Patients were included if they received single daily amikacin doses of approximately 15 mg/kg. Patients were excluded if they were less than 18 years of age, pregnant, admitted for reasons other than a primary thermal burn injury, admitted within 72 h of the burn injury, or lacked sufficient amikacin serum concentrations to calculate pharmacokinetic parameters. Patients admitted after 72 h from the injury were included to ensure that pharmacokinetic measurements would take place in the second phase of burn injury, which is characterized by a hypermetabolic state. Amikacin doses, amikacin serum concentrations, CVVH treatment parameters, age, sex, and total body surface area burned (TBSA) were recorded. The study was approved by the Institutional Review Board.

Pharmacokinetic data. Amikacin serum concentrations were determined after the first dose in the course of routine clinical care by the automated fluorescence polarimetry method of the clinical laboratory. Each amikacin dose of approxi-

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TABLE 1. Clinical and pharmacokinetic variables in burn patients receiving amikacin

	Without CVVH	With CVVH	P
Patients (No.)	48	12	
Age (years)	37.9 ± 20.2	28.3 ± 8.4	0.11
TBSA (%)	38.4 ± 21.8	74.0 ± 15.9	<0.001
Weight (kg)	94.9 ± 20.7	83.3 ± 20.9	0.10
Dose (mg)	1320.0 ± 286.4	1158.3 ± 357.9	0.17
Dose (mg/kg)	14.2 ± 2.9	13.9 ± 26	0.32
C_{max} (μg/ml)	36.3 ± 10.2	29.1 ± 14.5	0.05
C_{min} (μg/ml)	1.6 ± 4.3	1.5 ± 1.6	0.02
$T_{1/2}$ (h)	4.75 ± 5.24	5.49 ± 2.35	0.003
CL_{amik} (L/h)	7.8 ± 3.7	8.8 ± 8.9	0.37
AUC_{24} (mg · h/L)	239.0 ± 262.7	214.8 ± 113.8	0.52
V (L/kg)	0.60 ± 1.01	0.84 ± 1.06	0.36

Data are expressed as mean ± SD, unless otherwise noted.

TBSA, % total body surface area burned; C_{max}, maximum concentration; C_{min}, minimum concentration; k, rate constant of elimination; $T_{1/2}$, half-life of elimination; CL, amikacin clearance; AUC, area under the curve; V, apparent volume of distribution.

mately 15 mg/kg was infused over 60 min. One postdistributional amikacin concentration was drawn ≥1 h after the end of the infusion, and a second amikacin concentration was obtained 8 to 12 h after the end of the infusion. The patient was excluded if the second concentration was below the limit of detection. The first-dose pharmacokinetic parameters were calculated from these two postdistributional concentrations using a one-compartment model by a modification of the two-point method of Sawchuk and Zaske (18). The following pharmacokinetic parameters were calculated for each patient: volume of distribution of the central compartment (V), total clearance (CL), elimination half-life ($t_{1/2}$), area under the concentration-time curve over 24 h (AUC_{24}), maximum concentration in serum at the end of the infusion (C_{max}), and concentration in serum 24 h after the start of the infusion (C_{min}). Pharmacy records were used to obtain the timing and dose delivered; while nursing records were used to obtain the time of sample collection. Each patient contributed data from a single dose only once to the analysis.

Bacteriology. Amikacin MICs were determined for Gram-negative bloodstream isolates using the Vitek 2 instrument (bioMérieux, Durham, NC), the Phoenix instrument (Becton, Dickinson and Co., Franklin Lakes, NJ), or by CLSI broth microdilution (6). Only those isolates obtained within 30 days before or after amikacin therapeutic drug monitoring were reviewed for analysis. CLSI interpretive criteria were utilized (6). Due to previously documented inaccuracies with the Vitek 2 instrument (1), all *Acinetobacter baumannii* isolates reported as susceptible to amikacin were confirmed by CLSI criteria (7) according to the standard procedures of the clinical laboratory. For Monte Carlo simulations, only MICs from the Phoenix instrument or broth microdilution were used.

Monte Carlo simulations. We used Oracle Crystal Ball (Fusion Edition; Oracle USA, Inc., Redwood City, CA) to conduct multiple 10,000-subject Monte Carlo simulations in order to determine the cumulative fraction of response (CFR) for CVVH and non-CVVH patients against common Gram-negative isolates. C_{max} and AUC_{24} were modeled as a log-normal distribution using the mean and standard deviation values derived from the study population. Custom distributions were created for the *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *A. baumannii* isolates obtained from these patients. Pharmacokinetic and microbiologic data were integrated by dividing the C_{max} and AUC_{24} probability distribution by the customized MIC distribution. Finally, the CFR was determined, representing the combined probability of achieving C_{max}/MIC ratios of 8 and 10 and AUC_{24}/MIC ratios of 100, 125, 150, and 175 (15). A 20 mg/kg dose of amikacin was also modeled in the same manner, and peaks were estimated according to a 1-h infusion model.

Statistics. Proportions were compared using the chi-square distribution. The Kolmogorov-Smirnoff test was used to check the continuous data for normality. The means of continuous variables were compared using Student's t test or the Mann-Whitney U test as appropriate. The Wilcoxon rank-sum test was used to compare serial creatinine values. All calculations were performed using SPSS for Windows, version 16.0 (Chicago, IL).

TABLE 2. Gram-negative bacteria isolated in study patient blood cultures

Bloodstream isolates (n = 172)	Amikacin Susceptibility	No. with amikacin MIC data	Amikacin MIC50/ MIC90
Pseudomonas aeruginosa (55)	65.4%	26	16/≥64
Klebsiella pneumoniae (39)	65.5%	29	16/≥64
Acinetobacter baumannii (35)	39.1%	23	≥64/≥64
Other Enterobacteriaciae (43)			

Stenotrophomonas maltophilia (11), *Enterobacter aerogenes* (9), *Aeromonas hydrophilia* (6), *Serratia marcescens* (4), *E. coli* (3), *Pantoea aglommerans* (2), *Haemophilus influenza* (2), *Serratia liquefaciens* (2), *Klebsiella oxytoca* (2), *Proteus mirabilis* (1), *Enterobacter cloacae* (1).

RESULTS

Patient and infection characteristics. Sixty patients received amikacin and had sufficient dosing and postinfusion data to calculate pharmacokinetic parameters (Table 1). In-hospital mortality was 35%, and 20 patients (51.3%) developed recurrent bacteremia after amikacin therapy. The majority of patients also received imipenem therapy. In the 48 patients who did not receive CVVH, the mean and standard deviation for serum creatinine were 1.0 ± 0.3 mg/dl, and the mean creatinine clearance was 134 ± 35 ml/min. Twelve patients were simultaneously treated with CVVH. Of these, 10 patients were treated using the Prismaflex system with an HF1400 polyarylethersulfone (PAES) filter with a 1.4-m^2 surface area (Gambro, Lakewood, CO) and 2 were treated using the NxStage system using a CAR-500 polyethersulfone (PES) filter with a 1.5-m^2 surface area (NxStage Medical, Inc., Lawrence, MA). The mean hemofiltration rate was 30.0 ± 13.5 ml/kg/h (range, 10.6 to 55.6 ml/kg/h; median, 26.9 ml/kg/h). Clearance of amikacin in CVVH recipients correlated with effluent rates (r = 0.82).

One hundred seventy-two Gram-negative bloodstream isolates were recovered from 39 patients within 30 days of the amikacin dose. The predominant pathogens and amikacin MIC data for 82 isolates are listed in Table 2. The other isolates recovered included *Stenotrophomonas maltophilia* (11 isolates), *Enterobacter aerogenes* (9 isolates), *Aeromonas hydrophilia* (6 isolates), *Serratia marcescens* (4 isolates), *Escherichia coli* (3 isolates), *Pantoea aglommerans* (2 isolates), *Haemophilus influenzae* (2 isolates), *Serratia liquefaciens* (2 isolates), *Klebsiella oxytoca* (2 isolates), *Proteus mirabilis* (1 isolate), and *Enterobacter cloacae* (1 isolate).

Pharmacokinetic data. Among those patients receiving CVVH therapy, the amikacin C_{max} and C_{min} were significantly lower and $t_{1/2}$ was significantly longer (Table 1). C_{max} was noted to be significantly lower in association with more rapid amikacin clearance and a larger volume of distribution as the total body surface area burned (TBSA) exceeded 25% (Table 3). Considering the amikacin C_{max} values in individual patients relative to the MICs of bacteria recovered from them, the target ratio of C_{max}/MIC of ≥10 was satisfied for only 7 of 82 isolates (8.5%) collected from 7 different patients. The amikacin MICs of those isolates were 2 or 4 μg/ml, in contrast to ≥8 μg/ml for the remaining 75 isolates for which a C_{max}/MIC ratio of ≥10 was not satisfied.

Although the amikacin 15 mg/kg CFR given a C_{max}/MIC of ≥10 was higher for patients not receiving CVVH, it was less

TABLE 3. Comparison of amikacin pharmacokinetic parameters according to %TBSA

	<25% TBSA	≥25% TBSA	P
C_{max} (mean ± SD, μg/ml)	41.4 ± 8.8	33.2 ± 11.5	0.01
CL_{amik} (mean ± SD, L/h)	5.6 ± 2.3	8.6 ± 5.4	0.005
V (mean ± SD, L/kg)	0.36 ± 0.07	0.72 ± 1.13	0.03

TABLE 4. Cumulative fraction of response (CFR) in burn patients with or without concurrent CVVH therapy

Bloodstream isolates	15 mg/kg[a]		20 mg/kg[a]		20 mg/kg[b]	
	CVVH	No CVVH	CVVH	No CVVH	CVVH	No CVVH
A. baumannii	2%	3%	3%	4%	4%	4%
P. aeruginosa	20%	23%	23%	23%	24%	23%
K. pneumoniae	30%	36%	41%	42%	44%	43%
Other Enterobacteriaceae[c]	36%	44%	50%	51%	53%	54%

[a] C_{max}:MIC ≥ 10.
[b] C_{max}:MIC ≥ 8.
[c] Includes *Escherichia coli*, *Klebsiella* spp., *Proteus* spp., *Enterobacter* spp. and *Serratia* spp.

than 50% for all isolates (Table 4). The CFRs remained less than 60% for all isolates for a theoretical 20-mg/kg amikacin dose using a lower threshold of C_{max}/MIC of ≥10. Amikacin 20 mg/kg CFRs were modeled for AUC_{24}/MIC ratios of 100, 125, and 150 since some studies have proposed these as potential pharmacodynamic targets. CFRs were less than 15% for all isolates at an AUC_{24}/MIC of 100 and less than 5% for an AUC_{24}/MIC of 150 (data not shown).

DISCUSSION

Optimizing antimicrobial therapy is critical to ensure favorable clinical outcomes for life-threatening bacterial infections. Previous studies have indicated that critical illness (17, 18) and burn injury (21) are risk factors for inadequate aminoglycoside dosing, even when 20 mg/kg of amikacin is administered as a single daily dose (8). Based on previous data indicating significant survival advantages in burn patients who develop acute renal insufficiency (4, 5), CVVH is often used for renal replacement therapy in our burn ICU. However, it is unclear whether and to what extent CVVH therapy affects aminoglycoside clearance and whether increased clearance might offset the survival benefits of CVVH therapy. With this in mind, we used data previously collected for clinical care to calculate pharmacokinetic parameters for amikacin in severely burned patients with and without exposure to concurrent CVVH therapy and then used a Monte Carlo simulation to estimate the CFR for these patients.

For aminoglycosides, which exert concentration-dependent bactericidal activity, optimal efficacy is achieved when the C_{max}/MIC ratio is ≥8 to 10 (14, 16). Our data show that this pharmacodynamic target was achieved infrequently, for only 8.5% of the isolates when using an average dose of 14.1 mg/kg. Amikacin AUC_{24}/MIC ratios of >150 were nearly unattainable using a 15-mg/kg dose. We did observe increased amikacin clearance with more extensive burns. Patients had lower C_{max} values due to large volumes of distribution and increased clearance. This resulted in more difficult attainment of a C_{max}/MIC of ≥10. This finding agrees with prior observations of increased amikacin clearance above a total body surface area burned (TBSA) threshold of 15% (8).

The lack of pharmacodynamic target attainment in many of our patients may also be due in part to high MICs of isolates for which this target was not met. An isolate with a MIC of up to 16 μg/ml is considered susceptible by CLSI guidelines, whereas the European susceptibility breakpoint is ≤8 μg/ml. In order to achieve a C_{max}/MIC of 8 for CLSI susceptible isolates, the amikacin peak would have to be unacceptably high at 128 μg/ml. Monte Carlo simulation data incorporating MIC and pharmacokinetic data from within our burn ICU indicate that a 20-mg/kg amikacin dose would not be sufficient to significantly improve the CFR for accepted C_{max}/MIC or AUC_{24}/MIC indices. While achieving a C_{max} of 64 μg/ml for isolates with MICs of 8 μg/ml may be considered safe, daily doses greater than 35 mg/kg would likely be required given the V of 0.6 liters/kg in our burn patients. Such doses may increase the likelihood of toxicity resulting from continuously elevated trough concentrations. However, it is notable that once-daily doses of amikacin as high as 50 mg/kg were recently used to cure refractory *P. aeruginosa* infections in two patients, apparently without toxic effects of therapy. In these patients, continuous venovenous hemodiafiltration (CVVHDF) was used adjunctively to achieve low trough concentrations between doses (13).

Interestingly, the amikacin serum concentrations, pharmacokinetic parameters, and CFRs in burn patients undergoing CVVH were similar to those in non-CVVH patients. One reason for this finding may be the greater relative %TBSA-to-body weight ratio in the CVVH group. Indeed, our study and others have demonstrated that a greater %TBSA may lead to increased loss of aminoglycosides through the burn wound. The prescribed CVVH doses and filter membranes used at our institution may also result in amikacin clearances similar to those in patients without acute kidney injury. These findings are notable because a maximum empirical amikacin dose of 7.5 mg/kg every 24 h is recommended for nonburn critically ill patients undergoing CVVH (10, 20). Following these empirical dosing guidelines would likely result in peaks of less than 15 μg/ml, which is a C_{max} below the target for all isolates in our study which had MICs of ≥2 μg/ml. The 20-mg/kg modeled amikacin dose would increase CFR in CVVH recipients, and the C_{min} would likely remain below 2 to 4 μg/ml. One challenge to high-dose amikacin in CVVH patients would be unplanned clotting of the continuous renal replacement therapy (CRRT) circuit. If this were to occur shortly after the administration of a dose, a patient would be exposed to prolonged concentrations of amikacin until CVVH could be resumed. After comparing the high efficiency of amikacin drug removal observed with CVVH in this study to the solute clearance observed in other reports, we strongly recommend that aminoglycoside dosing guidelines in patients undergoing CRRT be institution specific. Using Monte Carlo simulations that incorporate these CRRT factors in addition to institution-specific

MIC distributions should further guide empirical dosing recommendations.

This study has limitations. The number of patients receiving concurrent CVVH therapy was small, reducing the sensitivity for detecting an increase in amikacin clearance attributable to CVVH (a type II error). While it would be interesting to perform a population pharmacokinetic model on our amikacin serum concentrations, the more precise estimates from such modeling would be unlikely to significantly change the study conclusions. We also described the amikacin pharmacokinetics using a 1-compartment model, which would underestimate the amikacin peak concentration. However, amikacin peak concentrations according to a two-compartment model would probably remain less than 50 to 60 mg/liter, and few isolates had MICs of less than 8 μg/ml. Widely accepted pharmacodynamic targets would still not be met in CVVH and non-CVVH burn patients receiving once-daily amikacin doses of 15 mg/kg. Pharmacokinetic calculations are exquisitely sensitive to the elapsed time from the start and end of infusion, and we were unable to verify the accuracy of the times recorded on laboratory samples. However, the resulting pharmacokinetic parameters are largely consistent with those of other studies (3, 8, 11). We deliberately used only bloodstream isolates for the calculation of C_{max}/MIC ratios, and thus, these findings cannot be directly extrapolated to isolates recovered from other body compartments. The evaluation of clinical pharmacodynamic targets for amikacin in bacteremic patients is of significant interest. However, many of the patients included in this study received concomitant antimicrobial therapy.

In conclusion, critically ill burn patients are at increased risk for inadequate dosing with amikacin. Although increased clearance and volume of distribution may be contributing factors with larger surface area burns, the low CFR for a C_{max}/MIC of $\geq$10 that we observed is also attributable to high MICs among the recovered bacterial isolates. In addition, it appears that high-dose daily aminoglycoside dosing may be appropriate given the high efficiency of drug removal observed while receiving CVVH according to our institution's CRRT prescribing practices. It should be noted that the CVVH recipients in this study had TBSAs greater than 60%. As therapeutic options are progressively limited by increasing antimicrobial resistance and rising MICs, new dosing strategies may be necessary in order to deliver effective antimicrobial therapy to critically ill and severely burned patients. It might be possible to give higher amikacin doses and use CRRT to enhance drug removal and minimize toxicity. Clinical trials are needed to further assess this idea.

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REFERENCES

1. **Akers, K. S., et al.** 2010. Aminoglycoside resistance and susceptibility testing errors in *Acinetobacter baumannii-calcoaceticus* complex. J. Clin. Microbiol. **48:**1132–1138.
2. **Akers, K. S., et al.** 2009. Tetracycline susceptibility testing and resistance genes in isolates of *Acinetobacter baumannii-Acinetobacter calcoaceticus* complex from a U.S. military hospital. Antimicrob. Agents Chemother. **53:** 2693–2695.
3. **Armendariz, E., L. Chelluri, and R. Ptachcinski.** 1990. Pharmacokinetics of amikacin during continuous veno-venous hemofiltration. Crit. Care Med. **18:**675–676.
4. **Chung, K. K., et al.** 2008. Continuous renal replacement therapy improves survival in severely burned military casualties with acute kidney injury. J. Trauma **64**(Suppl. 2)**:**S179–S187.
5. **Chung, K. K., et al.** 2009. Continuous venovenous hemofiltration in severely burned patients with acute kidney injury: a cohort study. Crit. Care **13:**R62.
6. **Clinical and Laboratory Standards Institute.** 2009. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard, 8th ed. CLSI document M07-A8. Clinical and Laboratory Standards Institute, Wayne, PA.
7. **Clinical and Laboratory Standards Institute.** 2009. Performance standards for antimicrobial disk susceptibility tests; approved standard, 10th ed. CLSI document M02-A10. Clinical and Laboratory Standards Institute, Wayne, PA.
8. **Conil, J. M., et al.** 2006. Increased amikacin dosage requirements in burn patients receiving a once-daily regimen. Int. J. Antimicrob. Agents. **28:**226–230.
9. **Fayed, D. F., et al.** 1996. Efficacy and safety of once-daily amikacin in combination with ceftazidime in critically ill adults with severe gram-negative infections. J. Chemother. **8:**457–464.
10. **Heintz, B. H., G. R. Matzke, and W. E. Dager.** 2009. Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. Pharmacotherapy **29:**562–577.
11. **Joos, B., M. Schmidli, and G. Keusch.** 1996. Pharmacokinetics of antimicrobial agents in anuric patients during continuous venovenous haemofiltration. Nephrol. Dial. Transplant. **11:**1582–1585.
12. **Karachalios, G. N., et al.** 1998. Prospective randomized study of once-daily versus twice-daily amikacin regimens in patients with systemic infections. Int. J. Clin. Pharmacol. Ther. **36:**561–564.
13. **Layeux, B., F. S. Taccone, D. Fagnoul, J. L. Vincent, and F. Jacobs.** 2010. Amikacin monotherapy for sepsis caused by panresistant *Pseudomonas aeruginosa*. Antimicrob. Agents Chemother. **54:**4939–4941.
14. **Moore, R. D., P. S. Lietman, and C. R. Smith.** 1987. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. J. Infect. Dis. **155:**93–99.
15. **Mouton, J. W., M. N. Dudley, O. Cars, H. Derendorf, and G. L. Drusano.** 2005. Standardization of pharmacokinetic/pharmacodynamic (PK/PD) terminology for anti-infective drugs: an update. J. Antimicrob. Chemother. **55:**601–607.
16. **Mueller, E. W., and B. A. Boucher.** 2009. The use of extended-interval aminoglycoside dosing strategies for the treatment of moderate-to-severe infections encountered in critically ill surgical patients. Surg. Infect. (Larchmt.) **10:**563–570.
17. **Rea, R. S., et al.** 2008. Suboptimal aminoglycoside dosing in critically ill patients. Ther. Drug Monit. **30:**674–681.
18. **Sawchuk, R. J., and D. E. Zaske.** 1976. Pharmacokinetics of dosing regimens which utilize multiple intravenous infusions: gentamicin in burn patients. J. Pharmacokinet. Biopharm. **4:**183–195.
19. **Taccone, F. S., et al.** 2010. Revisiting the loading dose of amikacin for patients with severe sepsis and septic shock. Crit. Care **14:**R53.
20. **Trotman, R. L., J. C. Williamson, D. M. Shoemaker, and W. L. Salzer.** 2005. Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy. Clin. Infect. Dis. **41:**1159–1166.
21. **Zaske, D. E., R. J. Sawchuk, and R. G. Strate.** 1978. The necessity of increased doses of amikacin in burn patients. Surgery **84:**603–608.