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Individualizing Gentamicin Dosage Regimens in Burn Patients with Gram-Negative Septicemia: A Cost–Benefit Analysis

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Abstract □ Services provided by a clinical pharmacokinetics laboratory were evaluated in terms of an accepted cost–benefit model, and a model to evaluate clinical services provided by the pharmacist is presented. A retrospective study was conducted to evaluate the impact, in terms of patient outcomes, of individualizing gentamicin dosage regimens in severely burned patients. Analysis was conducted using multivariate statistical techniques and appropriate nonparametric and parametric tests to determine significant differences. This analysis provided the necessary data to quantify the impact of the pharmacokinetic service. The findings suggest that significant differences do exist in comparing individually dosed patients against those who were not, based upon discriminant and multiple regression analyses and/or nonparametric tests. Furthermore, the results will be useful for insurance companies, third-party payers, and government agencies in deciding which innovative clinical services should be reimbursed.

Keyphrases □ Gentamicin—dosage regimens individualized in burn patients, cost–benefit analysis □ Cost–benefit—analysis, gentamicin dosage regimens individualized in burn patients □ Dosage regimens—gentamicin, individualized in burn patients, cost–benefit analysis □ Antibacterials—gentamicin, dosage regimens individualized in burn patients, cost–benefit analysis

The new roles of the pharmacist go beyond the distribution function and center around optimal utilization of drug knowledge. The main thrust of clinical pharmacy is aimed at enhancing the benefits of drug therapy and correcting detected deficiencies in drug use. The ultimate goal of the clinical pharmacist is to be recognized as a drug therapy specialist who provides judgmental services (1, 2).

BACKGROUND

The expanded role of the pharmacist includes offering new services such as counseling patients with respect to drug therapy, conducting drug histories, providing therapeutic advice to physicians, and applying pharmacokinetic principles in monitoring and adjusting dosage regimens (3).

Few pharmacists would argue that these additional clinical services do not provide added benefit to the treatment of patients and the cure of disease. However, health administrators and other policy decision makers emphasize that innovative health services that further expand the health-care system must be sufficiently evident to the buyer that he/she is willing to pay the increased price over that in which the service is not provided. Unfortunately, furnishing this information has been a serious problem that may partially explain the slow acceptance of the clinical pharmacy concept by the consumer and other health-care providers.

In the past few years, the health-care system has been faced with the growing rate of inflation and the reality that resources for medical care are clearly finite. It was suggested (4, 5) that future medical innovations be evaluated in terms of social and medical priorities relative to costs incurred. The ever increasing problem of rising costs and limited resources has led many leaders in pharmacy to the realization that innovative clinical services must be cost justified (6).

Economists have suggested that cost–benefit or cost–effectiveness analyses are necessary to evaluate rationally innovative health services that result in increased costs to the system. This analysis is often necessary to gain acceptance from the health-care sector (7–9). It was proposed that the utilization of such a valuable tool in evaluating the benefits and costs of clinical pharmacy services may be one solution to increasing acceptance of such services by the medical profession, third-party payers, and consumers (10–15).

In examining the scope of services provided by the clinical pharmacists, the application of clinical pharmacokinetic principles to individualize drug dosage regimens has the greatest potential for directly affecting patient outcome with respect to drug therapy. Burn patients treated with gentamicin often receive subtherapeutic doses, theoretically leading to a decrease in a positive therapeutic effect and, thus, altering the chances for positive patient outcome (18–20).

The present study attempted to evaluate whether a clinical pharmacokinetic service staffed by clinical pharmacists has a measurable and positive impact on the care and outcome of burn patients with Gram-negative septicemia. A cost–benefit method was employed for this evaluation.

EXPERIMENTAL

A retrospective cohort study was conducted to evaluate the impact, in terms of patient outcomes, of individualizing gentamicin dosages for burn patients with Gram-negative septicemia. Data were abstracted[1]

[1] To avoid bias, data were abstracted by hospital auditors unconnected with the project. The abstractors had prior experience in chart review and medical care audits.

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Table I—Comparison between Nonkinetics and Kinetics Study Groups of Selected Independent Variables

Patient Variable	Nonkinetics (Mean ± *SD*)	Kinetics (Mean ± *SD*)
Age, years	34.1 ± 22.1	39.1 ± 24.1
Weight, kg	62.1 ± 25.4	67.5 ± 25.5
Percent body surface area burned	47.0 ± 19.8	50.7 ± 21.1
Delay in admission, hr	6.8 ± 6.7	4.9 ± 4.7
Onset of sepsis, days	9.4 ± 2.1	9.3 ± 2.2
Percent of females	23.1	27.3

Table II—Gentamicin Dosage Regimen Comparison for the First Septic Episode

Dosage Variable	Nonkinetics Group (Mean ± *SD*)	Kinetics Group (Mean ± *SD*)	Test Value	Significance Level
Dosage, mg/kg/day	4.4 ± 4.5	7.4 ± 2.8	$t_{(103)} = 4.13$	0.001
Dosage interval, hr	8.1 ± 2.9	5.3 ± 1.7	$t_{(103)} = 5.24$	0.001
Duration of therapy[a], days	8.3 ± 2.3	10.3 ± 4.8	$t_{(53)} = 2.28$	0.05

[a] Determined for surviving patients only.

from the medical charts of patients admitted to the burn center[2] during 1972–1976.

Based on a predetermined set of criteria, the "treatment" group was selected from burn victims whose gentamicin dosage regimens were individualized by the pharmacokinetic service from the second half of 1974 through 1976. The comparison group (serving as the "control") consisted of burn patients admitted to the burn care center prior to the implementation of the pharmacokinetic service, during 1972 through the first half of 1974. Their gentamicin dosage regimens were determined *via* traditional recommendations.

For admission to the study, patients must have had:

1. At least one Gram-negative septic episode (documented by either a blood culture or clinical observation).
2. Gentamicin treatment for at least 3 days.
3. At least a third-degree burn or a combination of second- and third-degree burns.
4. Less than 24 hr between time of burn and time of admission (patient must not have been a referral case).
5. No prior renal disease.
6. An internally consistent and complete data base on the relevant variables.

Analysis Design—As previously mentioned, this study consisted of a retrospective cohort design in which many of the variables that could potentially affect patient outcome were not controlled as would be the case in an experimental design approach. In other words, this epidemiological approach affords no way of knowing that the two groups were equivalent before the implementation of the pharmacokinetics service. As a result, various multivariate statistical techniques, such as multiple regression and discriminant analyses, were utilized to measure adequately the impact of the pharmacokinetics service while treating the independent variables as covariates.

Independent Variables—When using a multivariate technique, independent variables for the multivariate model must be selected carefully. Variables were selected on the basis of support from the literature in terms of their impact on patient outcome in burn wound victims. The variables collected in this study were: type of burn, sex, age, total body surface area burned (percent), delay between injury and admission (hours), onset of sepsis (days from burn injury), disease complications (*e.g.*, pulmonary and cardiovascular), preexisting disease, blood culture, type of topical treatment, pharmacokinetic protocol (yes or no), gentamicin dosage (interval and duration), and carbenicillin dosage and interval.

Patient Outcome Variables—Several dependent variables were chosen to detect significant differences between patients whose gentamicin dosages were pharmacokinetically determined and those for which the dosage regimen was determined *via* traditional mechanisms. The patient "outcome" variables were: survival, length of infection, length of stay, number of adverse drug reactions, and number of septic episodes.

Cost–Benefit Model—The mathematical statement of the cost–benefit model used in this study was:

$$BC_{pv} = \frac{\sum_{t=1}^{n} B_t/(1+r)^t}{\sum_{t=1}^{n} C_t/(1+r)^t} \qquad \text{(Eq. 1)}$$

where B_t is the total economic value of all benefits (Σb_i) that accrue to a program in time period t, C_t is the total economic value of all costs (Σc_j) that are incurred by a program in time period t, r is the annual opportunity cost or discount rate, n is the economic life of the proposal, and BC_{pv} is the benefit-to-cost ratio at present value.

With this model, programs under evaluation would be socially valuable or would be considered a desirable use of resources as long as the BC_{pv} is greater than 1.0.

Pharmacokinetics Service Costs—Two major types of costs, the fixed and operating costs, were incurred in the implementation and operation of the pharmacokinetics service. The fixed costs included the cost of the physical facility based on the size in square feet, the annual maintenance expenditures, and equipment costs that were depreciated over a 20-year straight line.

The operating costs measured in this project included: administrative, professional staff, and supportive personnel salaries; equipment leasing fees; subscription fees for professional journals and miscellaneous references; and medical supplies (*e.g.*, drug assay kits, syringes, and needles).

The total annual cost was determined by the simple addition of the fixed and operational costs. However, the cost per gentamicin serum determination was computed by dividing the total costs by the number of gentamicin samples obtained and analyzed for the period in which the costs were incurred.

Direct and Indirect Benefits—Direct benefits were regarded as the incremental reduction in the direct costs associated with the particular program. In this study, direct benefits were estimated based on significant changes observed in the two study groups. The relative contribution of the pharmacokinetics service to explaining observed changes was estimated using both regression and discriminant analyses. The variables measured to estimate the direct benefits were: length of hospital stay, length of infection, number of septic episodes, and number of adverse drug reactions.

A reduction in one or more dependent variables provided an estimate of the benefits derived by the burn patient in this study. The following formula was used to determine the dollar value associated with the direct benefits accrued:

$$DB = IX_1LOS + JX_2LOI + KX_3NSEP + LX_4ADR \qquad \text{(Eq. 2)}$$

where:

DB = direct benefits in dollar value
LOS = observed change (days) in length of stay between the two study groups
LOI = observed change (days) in length of infection between the two study groups
$NSEP$ = observed change in the number of septic episodes between the two study groups
ADR = observed change in the number of adverse drug reactions between the two study groups
X_1, X_2, X_3, X_4 = relative contribution of the pharmacokinetics service in explaining the observed change in the respective dependent variables, estimated using multivariate techniques
I = medical and hospitalization costs per day of hospitalization
J = incremental medical and hospitalization costs per day of infection
K = incremental medical and hospitalization costs per septic episode
L = incremental medical and hospitalization costs per adverse drug reaction

Indirect benefits were regarded as a measure of the productivity losses attributed to an increased length of hospital stay and/or to persons who would have died if the pharmacokinetics service were not in effect.

[2] The burn care center at St. Paul-Ramsey Medical Center is a 24-bed facility, one of the largest in the upper midwest of the United States and the major center in Minnesota. Approximately 190 patients are admitted annually.

Table III—Stepwise Summary of Discriminant Analysis for Mortality during the Study Period, 1972–1976

Step	Variable	Wilks Lambda	Significance Level	Change in r^2	Rao's V	Change in Rao's V	Significance Level
1	Age	0.87	0.001	0.13	15.81	15.81	0.001
2	Percent body surface area burned	0.76	0.001	0.12	29.88	14.07	0.001
3	Pharmacokinetics	0.63	0.001	0.13	44.73	14.85	0.001
4	Disease complications	0.60	0.000	0.03	49.03	4.30	0.007
5	Blood culture	0.56[a]	0.000	0.03	53.15	4.12	0.009

[a] χ^2 (5 df) = 47.1; $p < 0.0001$.

Morbidity savings (MBS) were calculated using:

$$MBS = X_1(E_a)LOS \quad \text{(Eq. 3)}$$

where X_1 is the relative contribution of the pharmacokinetics service in explaining the observed change in the length of stay between the two study groups, LOS is the observed change (days) in the length of stay between the two study groups, and E_a is the average earnings at age group a. Morbidity savings were calculated separately for males and females.

The following formula was used to compute the mortality savings (the average per capita income was adjusted for sex):

$$L_t = \sum_{t=i}^{n} Y_n(1 + r)^{-(t-i)} \quad \text{(Eq. 4)}$$

where L_t is the expected total earnings up to time t, Y is the average per capita income in the age group where the midpoint of the group is age i, n is the number of years of expected earnings, and r is the discount rate. The measure of output loss for an individual was the year-round, full-time earnings, which include wages and salaries before deduction of the proposed measure of expected earnings in the arithmetic average or mean.

The discount rates were chosen from those studies conducted in recent years. A sensitivity analysis approach was used. The rates used were 1, 6, and 10%.

RESULTS AND DISCUSSION

Data were abstracted from the medical charts of 832 burn patients; 105 patients met the criteria for admission to the study, representing approximately 12.6% of the burn patients admitted to the sponsoring hospital. The nonkinetics group consisted of 39 patients, whereas 66 patients were in the kinetics study group.

Comparison of Independent Variables between Kinetics and Nonkinetics Study Groups—In terms of the independent variables collected, few significant differences were detected. There were no significant differences in the demographic factors, percent body surface area burned, delay in admission, or the number of days for onset of sepsis. Table I shows that over 90% of the patients in both groups were inflicted with a flame injury. The incidence of preexisting diseases was 21.1 and 22.7% in the nonkinetics and kinetics groups, respectively, and was not significantly different. The predominant preexisting diseases were hypertension, diabetes mellitus, and emphysema.

In terms of disease complications, no significant differences between the groups were detected. Twenty-three (60.5%) nonkinetics patients had one or more complications, whereas 40 (62.5%) kinetics patients developed at least one disease complication. The various complications detected were pneumonia, cardiovascular problems, GI disorders, and renal failure. The number of patients having a positive blood culture was 23 (59%) for the nonkinetics group and 37 (56.1%) for those patients whose gentamicin dosage regimen was individualized by the pharmacokinetics service. This difference was not significant using χ^2 analysis.

Table IV—Discriminant Analysis Coefficients for the Mortality-Dependent Variable during the Study Period, 1972–1976

Independent Variable	Standardized Coefficient	Unstandardized Coefficient
Age	−0.92	−0.04
Percent body surface area burned	−0.60	−0.03
Pharmacokinetics	−0.63	−1.3
Disease complications	−0.42	−0.53
Blood culture	−0.40	−0.80
Constant		+3.21

Table II shows significant differences in the dosage, interval, and duration of gentamicin therapy between the two study groups, supporting the hypothesis that burn patients may require higher dosages to obtain therapeutic serum levels. The mean dosage in the nonkinetics group fell within the manufacturer's recommended dosage; patients in the pharmacokinetics group were given higher dosages at significantly shorter intervals. These findings further support those of Zaske *et al.* (17), which suggest the measurement of serum gentamicin levels in all burn patients with life-threatening infections.

The antibiotic carbenicillin is often used in conjunction with gentamicin for patients with *Pseudomonas* infections. In the nonkinetics group, 51% of the patients received carbenicillin and 58% of the kinetics patients received the drug. The average doses were 410 and 439 mg/kg/day in the nonkinetics and kinetics groups, respectively. These differences were not statistically significant (t = 1.12; 56 df; n.s.). In terms of topical therapy, no significant differences were observed. All patients received silver sulfadiazine with either povidone-iodine or mafenide.

Finally, the antibiotic sensitivity patterns were examined for the study period to detect any significant changes in susceptibility of the bacterial organisms to gentamicin. The results indicated nonsignificant changes over the 6-year period.

Pharmacokinetics Service Annual Costs—*Fixed Costs*—The annual fixed costs of $778.00 were relatively small compared to the other costs. The fixed costs for the pharmacokinetics office facility and equipment were depreciated in accordance with the depreciation schedules used by the sponsoring hospital.

Operating Costs—The total annual cost to operate the pharmacokinetics service was approximately $73,915. Salaries accounted for the largest percentage, but the costs of the gentamicin blood sample assays were similar. A breakdown of the laboratory costs showed that the average cost to assay a blood sample of gentamicin was $7.72.

Total Annual Costs—The total annual costs, $74,693, included the fixed and operating costs associated with operating the pharmacokinetics service. The total annual costs divided by the total annual number of gentamicin blood samples (4305) provided an estimate of $17.35 for the cost per gentamicin blood sample[3].

Total Cost per Burn Patient—The cost per burn patient whose gentamicin dosage regimen was determined by the pharmacokinetics service was approximated by multiplying the total cost per blood sample ($17.35) by the mean number of gentamicin samples (6.8) obtained per burn patient in the study. Rounding the 6.8 to 7.0 yielded a cost of approximately $122.00/patient for individualized gentamicin dosage. Since the total number of patients was 66, the total costs for individualizing the gentamicin dosages was approximately $8052. This figure represented the denominator in the cost–benefit model.

Benefit Determinations—Each patient outcome variable was analyzed using the appropriate multivariate analytical techniques to determine the relative contribution of the pharmacokinetics service.

Prior to multivariate analysis, Kendall's tau correlation coefficients were obtained for the independent variables collected. If any two variables had a correlation greater than 0.40, then one was deleted to help minimize the problems of multicollinearity.

After the elimination of those variables, which were highly intercorrelated, the following multivariate linear model was developed:

$$Y = B_1(\text{type of burn}) + B_2(\text{sex}) + B_3(\text{age}) + B_4(\text{percent of body surface area burned}) + B_5(\text{delay before admission}) + B_6(\text{onset of sepsis}) + B_7(\text{disease complications}) + B_8(\text{preexisting diseases}) + B_9(\text{blood culture}) + B_{10}(\text{topical therapy}) + B_{11}(\text{carbenicillin dose}) + B_{12}(\text{pharmacokinetics}) + \text{constant} \quad \text{(Eq. 5)}$$

[3] St. Paul-Ramsey Medical Center currently charges the patient $21.00/sample.

Table V—Mortality Rates between the Two Study Groups [a]

	Nonkinetics Group	Percent	Kinetics Group	Percent
Survived	13	33.3	42	63.6
Died	26	66.7	24	36.4
Total	39	100	66	100

[a] χ^2 (1 *df*) = 7.85; $p < 0.005$.

Variables not included were gentamicin dosage and interval, weight, and carbenicillin interval.

Mortality—Discriminant analysis was used to determine the relative influence of the various independent variables on explaining observed changes in those patients who died and those who survived Gram-negative sepsis secondary to the burn injury. In addition, it allowed the quantification of the relative contribution of the pharmacokinetics service to explain the observed differences between the two study groups.

Table III summarizes the discriminant analysis for mortality. As specified in the model, all variables were included in the analysis. The step-down analysis was repeated until the change in Rao's V was not significant. This procedure was followed for all multivariate analyses. The final model was significant ($p < 0.0001$), as indicated by the overall significance of Wilks lambda. The canonical correlation was 0.66. Examination of the standardized coefficients (Table IV) shows that the pharmacokinetics service was positively correlated with survival, whereas age, percent body surface area burned, disease complications, and blood cultures were negatively correlated with survival.

The findings also suggest a significant impact of the pharmacokinetics service in terms of reducing mortality. Pharmacokinetics explained 13% of the variance in the observed mortality rates between the two study groups. As predicted, age and percent of body surface area burned were also good predictors in explaining this variance. The findings support the hypothesis that a significant reduction in the mortality rate between the two study groups can be attributed to the pharmacokinetics service.

The observed change in the percentage of patients that died between the nonkinetics and kinetics study groups was approximately 30.3% (Table V). This percentage represents a difference of 20 lives saved between the two groups. The results of the discriminant analysis indicated that the pharmacokinetics service accounted for approximately 13% of the variance, equivalent to 2.6 lives saved. In terms of sex differences, the ratio of male to female in the kinetics population was 8 to 3. The 2.6 lives saved can then be transformed into 1.9 males and 0.7 females for the purposes of estimating dollar value of lives saved. This information was incorporated into the cost–benefit formula using the average earnings[4] for both the male and female wage earners.

These estimates were based on the mean ages of the males and females in the kinetics study group, 35 and 27 years, respectively. Table VI provides a summary of the mortality savings for the respective discount rates.

Length of Stay and Length of Infection—Table VII shows that the mean length of hospital stay and the mean length of infection were greater for the kinetics group. The mean length of infection was 10.3 days for the kinetics group and 8.1 days for the nonkinetics group. The mean length of stay was 72.3 days for the nonkinetics group and 93.2 days for the kinetics group. These findings were significantly different and contradict the hypotheses that the pharmacokinetics service would reduce the lengths of infection and hospital stay. A possible explanation is that the increased probability of survival, as described earlier, may have affected the ratio of severe patients in the kinetics group as compared to the nonkinetics group, which may have ultimately affected the length of stay and the length of infection. This decrease may be reflected by the survival of patients who would have normally died if their gentamicin dosages were not individualized by the clinical pharmacokinetics service.

In addition, the mean length of stay of patients who died was greater for those in the kinetics group *versus* the nonkinetics group. However, this difference was not statistically significant. The mean length of infection for patients that died was 5.7 and 11.2 days for patients in the nonkinetics and kinetics groups, respectively. This difference was significantly different (Table VII). These findings give further support to the explanation given with regard to the stated hypotheses. In other words, this finding, which is opposite to the stated hypothesis, may be a reflection of patients who would have normally died if their gentamicin dosages were not individualized by the clinical pharmacokinetics service.

[4] Source: U.S. Bureau of the Census, "Incomes in 1975 of Families and Persons in the United States," *Current Population Reports*, Series P-60, No. 102, U.S. Government Printing Office, Washington, D.C., 1977.

Table VI—Cost–Benefit Ratios for Selected Discount Rates

Parameter	Discount Rate 1%	Discount Rate 6%	Discount Rate 10%
Mortality savings, dollars	911,520	331,068	171,931
Morbidity losses, dollars	29,798	29,798	29,798
Pharmacokinetics service costs, dollars	8,052	8,052	8,052
Total costs, dollars	37,850	37,850	37,850
Benefit-to-cost ratio	24.0	8.7:1	4.5:1

Multiple regression analysis was used to determine the relative contribution of the independent variables identified earlier to explaining variances in the length of infection and the length of stay between the study groups. Patients who died were analyzed separately from those who survived.

In examining the regression analysis in the length of infection for those patients that survived, the significance of the *F* statistic was not significant at any level of the analysis. In other words, none of the variables entered in the model were significant contributors to explaining variance between the study groups.

Table VIII provides a summary of the regression analysis for the length of infection in those patients that died. The pharmacokinetics service accounted for approximately 32% of the variance. The significance of the *F* statistic shows that the model was significant to $p < 0.001$. Examination of the sign of the standardized coefficients showed that the pharmacokinetics variable was positive, indicating that patients whose gentamicin dosage regimen was determined by the pharmacokinetics service experienced longer periods of infection before they actually died (Table IX).

In summary, the contribution of the pharmacokinetics service for those patients who survived was not significant using multiple regression. However, regression analysis for those patients that died indicates that a significant portion (32%) of the observed change can be attributed to the pharmacokinetics service. As noted earlier, however, this change was not in the direction hypothesized. Table VII shows that the mean length of infection was greater for the kinetics group. The mean difference in the length of infection for those patients that died was 5.5 days. Multiplying this observed change by 32% yields the increase in the length of infection attributable to the pharmacokinetics service. Rounded to the nearest day, approximately 2 days/patient that died can be attributed to the pharmacokinetics service. If this number is multiplied by the number of patients in the kinetics group (24), the total number of additional days of infection was approximately 48 days. The incremental cost per day of infection over and above the normal daily medical and hospitalization charges was estimated to be $531.00, using the records supplied by the sponsoring hospital. If this figure is multiplied by 48 days, the additional cost attributed to the pharmacokinetics service was $24,488.

Finally, in examining the regression analyses for the length of hospital stay, the pharmacokinetics service did not contribute significantly to explaining the variance observed between the two study groups and was not included in the cost–benefit model as a result of the analyses.

Number of Septic Episodes per Patient—In examining the number of septic episodes per patient, there was a significant difference between the two study groups (Table X). In the nonkinetics group, three (7.7%)

Table VII—Length of Infection and Length of Stay Comparisons for Patients Who Died and Survived in Study Groups

Patient Outcome Variable	Nonkinetics Group (Mean ± *SD*)	Kinetics Group (Mean ± *SD*)	Test Value	Significance Level
Length of stay, days				
Survived	72.3 ± 24.3	93.2 ± 32.4	$t_{(53df)} = 2.11$	0.05
Died	26.3 ± 31.2	36.1 ± 30.4	$t_{(48df)} = 1.12$	n.s.
Length of infection, days				
Survived	8.1 ± 2.3	10.3 ± 4.8	$t_{(53df)} = 2.28$	0.05
Died	5.7 ± 3.2	11.2 ± 4.9	$t_{(48df)} = 4.64$	0.001

Table VIII—Stepwise Summary for Regression Analysis for Length of Infection in Patients Who Died [a]

Step	Variable	Significance Level	Multiple R	r^2	Change in r^2	Overall F	Significance Level
1	Pharmacokinetics	0.000	0.56	0.32	0.32	22.23	0.001
2	Preexisting diseases	0.003	0.66	0.44	0.12	18.20	0.001
3	Topical therapy	0.081	0.69	0.47	0.03	13.72	0.001
4	Carbenicillin dose	0.152	0.73	0.53	0.03	9.93	0.001
5	Sex	0.152	0.73	0.53	0.03	9.93	0.001
6	Age	0.459	0.73	0.54	0.01	8.28	0.001
7	Disease complications	0.576	0.74	0.54	0.001	7.03	0.001
8	Percent body surface area burned	0.640	0.74	0.54	0.001	6.07	0.001
9	Onset of sepsis	0.756	0.74	0.54	0.001	5.28	0.001
10	Blood culture	0.806	0.74	0.54	0.001	4.65	0.001
11	Delay in admission	0.812	0.74	0.54	0.001	4.13	0.001

[a] The F level for "type" was insufficient to be included in the analysis.

patients had more than one spetic episode. One of the three patients had three septic episodes. All three of these patients died as a result of the Gram-negative sepsis.

In the kinetics group, 15 (22.7%) patients had at least two septic episodes, which was significantly different from the nonkinetics group ($\chi^2 = 3.91, p < 0.05$). Twelve patients had two septic episodes while the remaining patients experienced three septic episodes. Also, seven of the 15 patients died as a result of the sepsis.

These findings do not support the main hypothesis that fewer patients in the kinetics group would experience more than one septic episode as compared to the nonkinetics group. A possible explanation parallels that given for the unexpected findings associated with the length of infection and the length of stay. That is, the survival of patients who would have normally died if the pharmacokinetics service were not in effect significantly offset this patient outcome variable.

The relative contribution of the pharmacokinetics service to explaining observed changes in the number of septic episodes per patient between the two study groups was determined using discriminant analysis. The dependent variable was separated for those patients who had one septic episode *versus* those patients experiencing more than one septic episode. This analysis was conducted separately for those patients that survived and those that died.

Table XI provides a summary of the multivariate analysis for patients that survived. Age contributed the most to explaining variance, with a 0.87 Wilks lambda. The pharmacokinetics service was second, explaining approximately 9% of the variance as indicated by the change in Wilks lambda. The canonical correlation was 0.55.

Examination of the standardized coefficients showed that age and the time at which the patient developed sepsis were negatively associated with the increase in the number of septic episodes between the two study populations (Table XII). In other words, the older the patient and the later the patient developed sepsis from the time of admission, the fewer were the number of septic episodes. The pharmacokinetics service, however, was positively related to the number of septic episodes.

The results of the discriminant analysis indicate that the pharmacokinetics service contributed significantly (9%) to explaining the variance between the two study groups in the number of septic episodes for those patients that survived (Table XI). The regression analysis was not significant for those patients that died.

Multiplying the mean length per septic episode (10.3 days) by the increase in the number of septic episodes (0.25) per kinetics patient that survived provided an estimate of the increase in the number of days of infection per patient between the two study groups (2.6 days). The number of patients that survived in the kinetics group was 42; thus, the increase in the total number of days of infection due to patients having more than one septic episode was approximately 110 days. Multiplying this number by the relative contribution of the pharmacokinetics service (9%) showed that the increase in the total number of days of infection attributable to the service was 10 days. Multiplying this number by the incremental cost per day due to the infection ($531.00) showed that the total cost due to the increase in the number of septic episodes attributable to the pharmacokinetics service was $5310.00.

Table IX—Regression Coefficients for Length of Infection in Patients Who Died

Independent Variable	Standardized Coefficient	Unstandardized Coefficient
Pharmacokinetics	0.43	4.17
Preexisting disease	0.34	2.16
Topical therapy	−0.18	−1.02
Carbenicillin dose	0.26	0.01
Sex	−0.18	−1.94
Age	−0.04	−0.01
Disease complications	0.06	0.46
Percent body surface area burned	−0.05	−0.01
Onset of sepsis	−0.05	−0.23
Blood culture	−0.03	−0.32
Delay in admission	−0.03	−0.03
Constant		6.13

Incidence of Adverse Drug Reactions—The reported incidence of nephrotoxicity and ototoxicity ranges from 5 to 10% (20). Three (7.7%) patients in the nonkinetics group possibly had renal complications secondary to gentamicin therapy. It is difficult to distinguish renal toxicity due to gentamicin and that due to a secondary complication of the burn injury or to other underlying conditions following the burn injury. There was no evidence of nephrotoxicity in the pharmacokinetics group.

In reviewing the medical charts, no patient complaints of any hearing deficit could be found. Also, for those patients whose hearing was tested, no impairment of auditory function was detected. A possible explanation for the low incidence of detected ototoxicity could be the difficulty in abstracting this information from medical charts. In addition, it was apparent that few patients (0.8%) were given auditory examinations; thus, an accurate estimate of the incidence of ototoxicity could not be obtained.

In summary, evidence was insufficient to conclude that the incidence of gentamicin-related adverse drug reactions was significantly reduced by the pharmacokinetics service and was deleted from the cost–benefit model. However, the frequency of nephrotoxicity observed with the nonkinetics group was similar to the reported incidence of from 5 to 10%.

Benefit-to-Cost Ratio—Table VI provides a summary of the costs and benefits. The ratios were calculated for the respective discount rates. The morbidity losses due to the increase in the length of infection and the number of septic episodes per patient were added to the pharmacokinetics service costs.

The benefit-to-cost ratios were greater than one for each discount rate. The 6% discount rate was the mean of those rates previously reported. The ratio (8.7:1) for this discount rate may represent the most reasonable estimate of worth for the pharmacokinetics service. These findings indicate that the benefits associated with the pharmacokinetics dosage intervention for burn patients with secondary Gram-negative septicemia outweigh the costs associated with operating the service.

CONCLUSION

The objectives of this study were accomplished. It was undertaken

Table X—Number of Septic Episodes per Patient between Study Groups [a]

Number of Septic Episodes per Patient	Nonkinetics Group	Percent	Kinetics Group	Percent
1	36	92.3	51	77.3
2	2	5.1	12	18.2
3	1	2.6	3	4.5
Total	39	100	66	100

[a] χ^2 (1 df) = 3.91; $p < 0.05$.

Table XI—Stepwise Summary of Discriminant Analysis for Number of Septic Episodes in Patients Who Survived [a]

Step	Variable	Wilks Lambda	Significance Level	Change in r^2	Rao's V	Change in Rao's V	Significance Level
1	Age	0.87	0.002	0.13	7.37	7.37	0.007
2	Pharmacokinetics	0.78	0.002	0.09	14.22	6.86	0.009
3	Onset of sepsis	0.70[a]	0.002	0.08	18.01	3.79	0.050

[a] χ^2 (3 *df*) = 15.35; $p < 0.002$.

partially to apply a practical cost–benefit decision model that could be used by the decision maker to determine the desirability of establishing and operating a clinical pharmacokinetics service within the hospital environment. Beginning with a considerable volume of theoretical, economic, and mathematical literature, this work set out to bridge the gap between the theoretical discussion of cost–benefit analysis and its practical application to evaluating clinical pharmacy services.

Cost–benefit analysis proved to be a satisfactory technique in evaluating the use of clinical pharmacokinetics in the treatment of burn patients. A major contribution of cost–benefit analysis was identifying the specific costs and benefits associated with the pharmacokinetics program. This step is important if one is ultimately interested in making the operation more efficient in terms of maximizing the cost–benefit ratio.

The major conclusion to be made from this study is that the pharmacokinetics service evaluated may be beneficial not only to the burn patient who develops Gram-negative infections secondary to a third-degree burn wound but also to society. In other words, this study demonstrated that the ability of the pharmacist to provide services related to the application of pharmacokinetics in the treatment of burn wound infections may improve the quality, as well as the cost–benefit, of patient care as related to drug therapy.

As stated by McLeod (3), the continued success of clinical pharmacy will be proportional to its contribution to patient care and public welfare. It appears that cost–benefit analysis can be a mechanism to document successfully and accurately the contributions of the clinical pharmacist.

Table XII—Discriminant Analysis Coefficients for Number of Septic Episodes in Patients Who Survived

Variable	Standardized Coefficient	Unstandardized Coefficient
Age	−0.99	−0.05
Pharmacokinetics	0.70	1.63
Onset of sepsis	−0.47	−0.05
Constant		0.76

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Effect of Obtrusive Measures on Antibiotic Compliance

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Abstract □ The influence of compliance measurement activities on patient behavior was studied. The project measured the relationship among physical capsule counts, patient interviews, and the amounts of excreted ampicillin. The capsule counts and patient interviews were conducted in a manner that disguised their intent. Sixty college-age patients were assigned to one of three experimental groups: a telephone interview, a personal interview and capsule count, or a control group. Stimulation (interviews) occurred on the 2nd day of the prescribed regimen, and urine was collected on random days thereafter. Results indicated that both stimulation types were associated with more positive compliance rates. The influence diminished rapidly. The reactive influence of experimentor intervention associated with personal and phone communication was demonstrated.

Keyphrases □ Compliance—effect of measurement activities on patient behavior □ Dosage regimens—effect of compliance measurement activities on patient behavior

Since 1954, when Jenkins (1) reported that the "average patient" consumed only about half of the total number of prescribed doses, members of the health community have responded with increased interest in the prevalence, associated factors, and methods of improving medication compliance. Most published research studies regarding

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