ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 1979, p. 468-474
0066-4804/79/10-0468/07$02.00/0

Vol. 16, No. 4

Urinary Casts as an Indicator of Renal Tubular Damage in Patients Receiving Aminoglycosides

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Received for publication 16 July 1979

We assessed the value of quantitative cast excretion as an early marker of renal tubular damage in 154 seriously ill patients. One hundred twenty-four of these received aminoglycoside antibiotics, and 30 of the 124 experienced a rise in serum creatinine of 0.5 mg/dl or more during therapy. The remaining 30 of the 154 patients were treated with other antibiotics and served as controls. Casts were quantitated in random urines collected before morning diuretic doses. Cast counts in control patients averaged 44 ± 51 casts during the intensive care unit admission. Patients given aminoglycosides without a significant rise in serum creatinine of 0.5 mg/dl or more excreted 153 ± 196 casts, significantly more than controls. In comparison to both the control and nontoxic patients, the 30 nephrotoxic patients excreted significantly more casts (625 ± 364) and were significantly higher as early as 9 days before serum creatinine first rose. Daily urinary cast counts are a rapid and inexpensive means of identifying early renal tubular damage in critically ill patients given aminoglycosides.

Aminoglycoside antibiotics such as gentamicin, tobramycin, amikacin, and netilmicin are highly effective in the treatment of serious gram-negative infections. However, their use in critically ill patients may be associated with acute, nonoliguric renal insufficiency. Although serum creatinine and creatinine clearance are commonly employed to monitor the renal function of treated patients, both are tests of glomerular filtration rate rather than renal tubular function, the location of aminoglycoside-related damage. Because of considerable lag time between tubular injury and creatinine clearance rise, measurement of serum creatinine and creatinine clearance provides essentially no early warning of proximal tubular damage. Moreover, aminoglycosides accumulate rapidly in renal tissue, produce damage, and persist in the kidney long after treatment ends, so stopping therapy only after glomerular filtration rate falls will not prevent further progression of the renal failure (9).

The need for more sensitive renal monitoring techniques has increased interest in proximal tubular tests such as urinary enzymes (6, 7) and urinary β_2-microglobulin (8, 10). These tests clearly are more sensitive than is serum creatinine. However, in addition to aminoglycosides, many clinical tubular insults alter the excretion of urinary enzymes (14) and urinary β_2-microglobulin (3), thus diminishing their diagnostic value.

Although it appears unlikely that an aminoglycoside-specific renal tubular marker will be discovered, tests of renal tubular function, if frequently employed, may give early warning of tubular damage before a decline in glomerular filtration rate occurs. However, daily measurement of β_2-microglobulin and most urinary enzymes is limited in availability and is expensive and time consuming. Therefore, we explored the measurement of urinary cast excretion as an early marker of renal tubular damage, because the identification of a renal tubular marker with adequate sensitivity, low cost, and general availability can potentially decrease both the incidence and the severity of aminoglycoside-related renal damage.

MATERIALS AND METHODS

Patients. A total of 124 patients receiving aminoglycosides and 30 similar intensive care unit (ICU) patients who did not receive aminoglycosides comprised the study group. Of the 124 treated patients, 25 received gentamicin, 70 received tobramycin, 18 received amikacin, and 11 received netilmicin. These patients and the 30 controls were managed in acute-care units for gram-negative infections complicating either medical or surgical problems. The majority of patients were over 60 years old, and most had creati-

nine clearances below 60 ml/min. Associated medical diagnoses frequently included congestive heart failure, diabetes, cerebrovascular accident, gastrointestinal bleeding, shock, malnutrition, diverticulitis, and mesenteric insufficiency. Malignancy, when present, was generally not the reason for ICU admission. Most surgical patients had postoperative pneumonia or abdominal infections complicating lower bowel resections, or gastrointestinal cancer, or both. Most medical patients had pneumonia, in many cases associated with chronic lung disease. Control patients were similar in terms of clinical conditions, but usually had less severe infections. Control patients received either no antibiotics, cephalosporins, or clindamycin instead of aminoglycosides.

Dosing and blood levels. All patients were given recommended loading dosages of aminoglycosides, followed by maintenance doses adjusted according to measured peak and trough serum concentrations. Desired peak concentrations were 4.0 to 10.0 μg/ml for gentamicin, tobramycin, and netilmicin, and 20 to 30 μg/ml for amikacin. Desired trough concentrations were 0.5 to 2.0 μg/ml for gentamicin, tobramycin, and netilmicin, and 2.0 to 5.0 μg/ml for amikacin. These levels were exceeded in patients who responded poorly to usual dosing, when potential benefits appeared to exceed risks.

Most patients concurrently received one to four drugs typical of those given to older adults. Digoxin and loop diuretics such as furosemide were given to the majority of patients.

Assessment of renal damage. Of the 124 patients treated with aminoglycosides, 30 (24%) experienced a 0.5-mg/dl or greater rise in serum creatinine during or within 5 days after aminoglycoside treatment. All patients with significant creatinine increases were judged nephrotoxic. In this manner, the assumption was made that casts are nonspecific indicators of damage to renal tubules, rather than being specific for aminoglycosides, since many patients also had other potential causes of renal damage present. Our purpose was to compare cast excretion among sick patients, sick patients given aminoglycosides, and sick patients with aminoglycoside nephrotoxicity.

Mean ± standard deviation (SD) cast counts were illustrated with respect to time in reference to day 0. In nontoxic patients and in the 30 control patients, day 0 represented the day of first aminoglycoside dose and day of first ICU admission, respectively. In the nephrotoxic patients, day 0 was the day of the first rise in serum creatinine. It was necessary to illustrate nephrotoxic patients in this synchronizing manner to allow for comparison and because creatinine did not rise on the same day in all patients.

Assays. Serum aminoglycoside concentrations were measured by both microbiological and radioimmunoassay techniques as previously described (9). Daily serum creatinine and daily 24-h urine creatinine clearances were determined by standard autoanalyzer methods.

A variation of the Addis count (1) was used to count casts. A 12-ml random sample of urine was collected daily in the morning for the duration of treatment and for at least 5 days after the drug was discontinued. Four drops of 40% Formalin were added to each sample for preservation of casts. Urines with pH greater than 6.5 were acidified to pH < 5.0 (2, 11). The samples were centrifuged at 2,000 rpm for 5 min and aspirated to 1.0 ml. The samples were stained with a modified Sternheimer-Malbin stain prepared by mixing equal volumes of crystal violet and safranin. The stained sample was loaded into a standard hemacytometer and counted under low power (100×). High power (450×) was used to confirm the identity of cellular casts. The total number of casts present in the four large areas of the chamber was employed as a raw number in an equation to determine the number of casts per milliliter of urine:

$$\text{casts per milliliter} = [(\text{raw number}) \times (\text{sediment volume})]/[(\text{starting volume}) \times (0.0036)].$$

Sediment volume is the volume of the suspended pellet (usually 1.0 ml), starting volume is the volume of the sample collected (usually 12.0 ml), and 0.0036 is the volume of the four counting chambers. All casts were recorded, but only hyaline and granular casts were totaled to arrive at the final value, since these casts appear most useful in the evaluation of proximal tubular status (11). Cellular casts such as red and white cell casts were rarely observed in our 154 patients, and their inclusion would not have altered results.

All cast counts were performed by two individuals who were not aware of the clinical status of the patients. Several times during the study the two individuals cross-checked for accuracy, with good agreement.

Reproducibility in quantitative cast counts depended on the number of casts present in the sample. Reproducibility was lower below 400 casts per ml, as the coefficient of variation calculated by counting 15 volumes of the same urine on 5 consecutive days ranged from 75% below 400 casts per ml to 12% above 500 casts per ml.

Chi-square, two-tailed unpaired Student's t tests, and two-way analysis of variance were employed to test the significance of our findings.

In this study, results of cast counts were not employed to make therapeutic decisions regarding aminoglycoside dosing or discontinuance.

RESULTS

Clinical comparisons of patient groups. Clinical characteristics of the three groups are summarized in Table 1. Only body weight differed significantly among the three groups. By chi-square analysis, the three groups of patients did not differ in the following conditions: CHF, diabetes, gastrointestinal bleeding, pneumonia, shock, positive blood cultures, malignancy, assisted ventilation, or mortality.

Serum creatinines and cast counts of the three groups are shown in Table 2, with results expressed as both absolute values and percent change from base-line values. Base-line serum creatinine did not differ among groups, and patients in both nontoxic and control groups re-

TABLE 1. *Clinical characteristics of the patient population*

Patient group	No. of patients	Age (yr)[a]	Sex (% male)	Wt (kg)[a]	Duration of treatment (days)[a]	Total dose given (mg)[a]	Concurrent diuretics (%)
Control	30	67 ± 11	59	78 ± 18	NA[b]	NA	69
Nontoxic	94	63 ± 15	60	67 ± 14[c]	9 ± 7	1,508 ± 1,250	58
Nephrotoxic	30	65 ± 19	77	64 ± 15[d]	10 ± 6	1,980 ± 2,423	65

[a] Values given as mean ± SD.
[b] NA, Not applicable.
[c] Indicates significant difference ($P < 0.05$) versus control group.
[d] Indicates significant difference ($P < 0.01$) versus control group.

TABLE 2. *Serum creatinines and cast counts in the patient groups*

Patient group	No. of patients	Serum creatinine (mg/dl ± SD)			% Change in serum creatinine (± SD)		5-Day cast counts[c] (mean value ± SD)
		Base line[a]	Day +1[b]	Highest creatinine	Day +1	Highest change	
Control	30	1.2 ± 0.8	1.3 ± 1.0	1.6 ± 1.6	2.0 ± 26	9.7 ± 23	44 ± 51
Nontoxic	94	1.7 ± 1.6	2.0 ± 1.8	2.0 ± 1.8	17 ± 45	30 ± 40[d]	153 ± 196[d]
Nephrotoxic	30	1.6 ± 0.9	2.5 ± 1.0[d]	3.2 ± 1.7[d]	68 ± 65[e]	118 ± 108[e]	625 ± 364[e]

[a] Base-line values represent the day of ICU admission in control patients, and the day treatment started in nontoxic and nephrotoxic patients.
[b] These values represent the day after ICU admission in control, 1 day after the last dose in nontoxic, and 1 day after the first creatinine increase in nephrotoxic.
[c] Mean ± SD cast count for the first 5 days in ICU (control group), last 5 days of treatment (nontoxic group), and last 5 days before creatinine rise (nephrotoxic group).
[d] Significant difference ($P < 0.01$) versus control group.
[e] Significant difference ($P < 0.01$) versus nontoxic and control groups.

mained within the criteria for stable renal function. However, nontoxic patients had a slightly greater average creatinine increase within the nontoxic limits. The 30 nephrotoxic patients by definition had greater creatinine increases than nontoxics during therapy, and, in most cases, creatinine continued to rise for several days after the last dose. Measured creatinine clearances changed in inverse proportion to changes in serum creatinines. Incomplete 24-h urine collections occasionally caused fluctuations in measured creatinine clearances. Thus, we found daily use of serum creatinine more useful for monitoring these drugs once base-line function was established from a 24-h urine collection.

Cast counts in patient groups. The cast counts of these 154 patients are also shown in Table 2. Mean cast counts are given for the first 5 days in the ICU for the control group, the last treatment days for the nontoxic group, and the last 5 days before serum creatinine rose in the nephrotoxic group. Cast counts differed significantly among the three groups, counts were higher in nephrotoxic than in nontoxic patients, and in both groups urinary casts exceeded those found in control patients.

Figure 1 shows the mean ± SD cast counts on each day for the 94 nontoxic patients given the four aminoglycosides. Over the entire study period illustrated in Fig. 1, the mean ± SD counts were stable and averaged 118 ± 186 casts per ml. This value is lower than the value observed in the last 5 days of therapy, 153 ± 196 casts per ml (Table 2). In the 30 control patients, the cast count averaged 44 ± 51 casts per ml during the ICU period. The control and nontoxic groups differed significantly ($P < 0.01$) in these average values, perhaps due to mild aminoglycoside renal effects not sufficiently damaging to raise serum creatinine in nontoxic patients, or possibly effects related to the more severe infections present in aminoglycoside-treated patients.

In spite of the fact that cast counts clearly distinguished between the nephrotoxic, nontoxic, and control patient groups, the cast counts did not demonstrate any average differences among the four aminoglycosides used in this study (Fig. 2). A crossover study to assess comparative drug toxicity was not done.

Figure 3 compares the daily cast counts between the 94 nontoxic and 30 nephrotoxic study patients. Each point is the mean ± SD of all cast counts performed that day. When the cast counts of the 30 nephrotoxic patients were synchronized in relation to the treatment day that creatinine first rose, all nephrotoxic patients had elevated cast counts preceding serum creatinine rises. The cast counts rose significantly

above mean values in the nontoxic patients as early as 9 days before creatinine rose. All patients who later developed a rise in serum creatinine had at least three daily cast counts above 500. This pattern was never observed in nontoxic patients, even though nontoxic values occasionally exceeded 500 casts on a single determination.

A two-way analysis of variance was performed to test the interaction of cast counts between nontoxic and nephrotoxic groups as a function of time. Over the analysis period of 16 days on either side of serum creatinine rise, there was a significant interaction ($P < 0.01$) between cast excretion and time, indicating that these two groups diverged as a function of time. The two-way analysis of variance also showed differences between nontoxic and toxic groups ($P < 0.01$), as well as differences between days ($P < 0.05$). When t tests were performed to determine

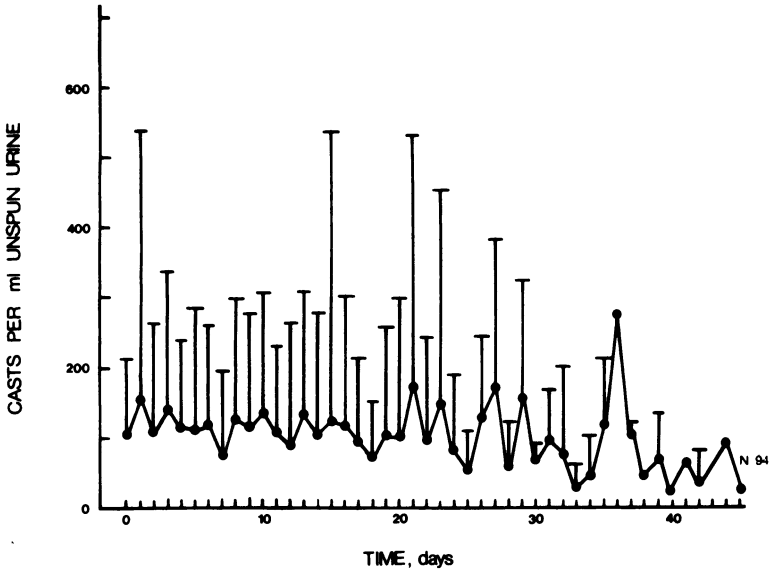

FIG. 1. *Cast counts (mean ± SD) in 94 aminoglycoside-treated patients who were not nephrotoxic. Counts represent the total granular and hyaline counts and are expressed as casts per milliliter of unspun urine plotted versus time. Each point represents mean ± SD of all patients on each day.*

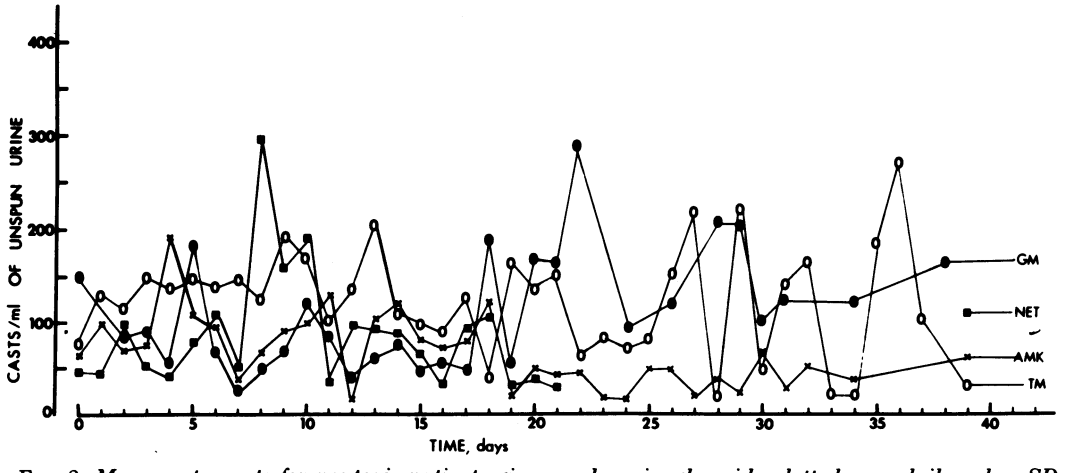

FIG. 2. *Mean cast counts for nontoxic patients given each aminoglycoside plotted as a daily value. SD values were similar between drugs and were excluded for clarity in presentation of the daily values. The 30 nephrotoxic patients were also excluded before preparing this figure. There were no significant differences between the four aminoglycosides by Student's t test.*

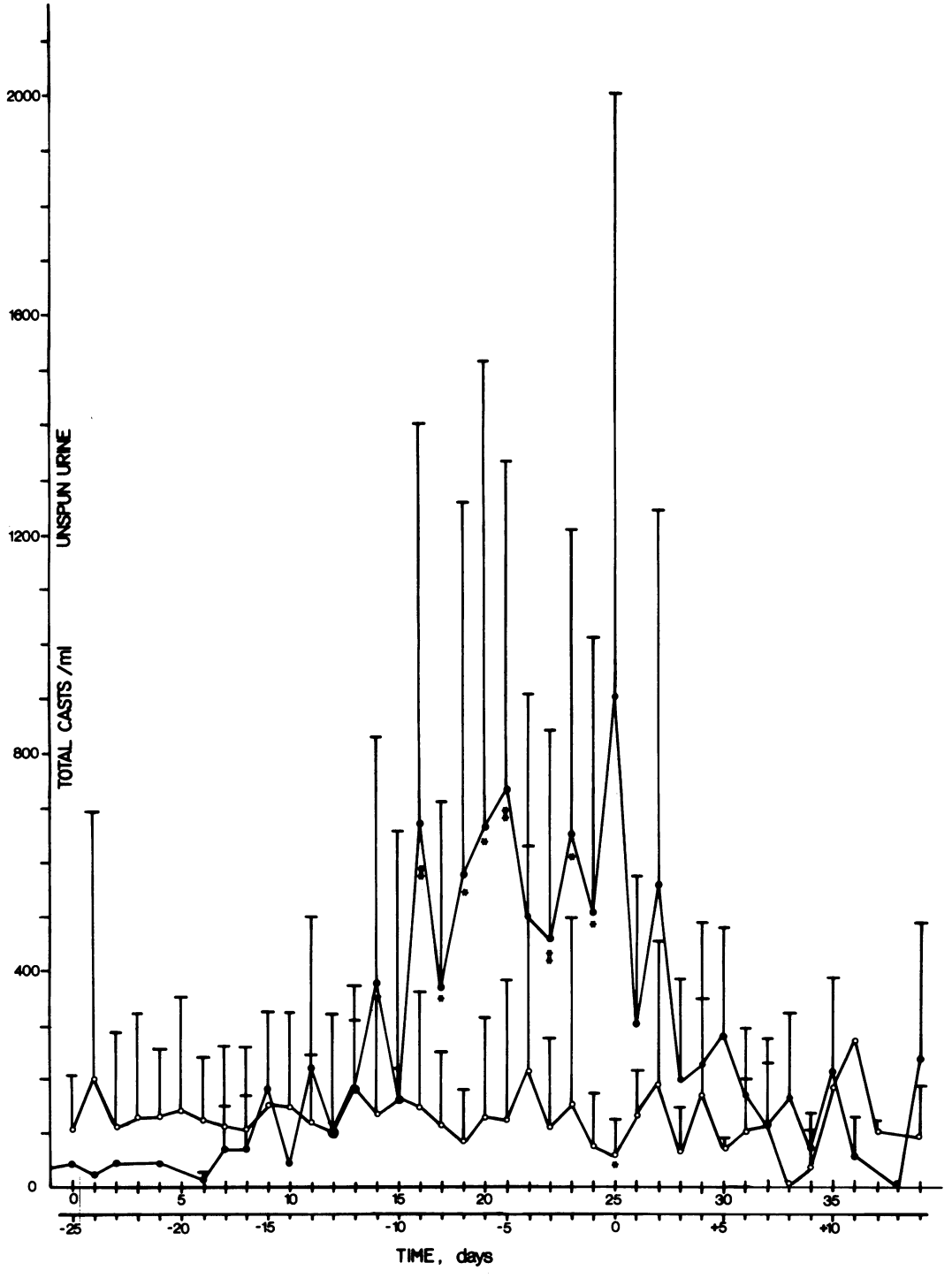

FIG. 3. *Cast counts of 30 nephrotoxic patients (●) compared with 94 nontoxic patients (○). The nephrotoxic patients were illustrated on the lower time scale (day 0 is day of first creatinine increase) to achieve synchronization. This was required because day of first creatinine rise differed between patients. Vertical bars represent ± 1 SD from the mean of all patients on the study day. Statistical differences are shown as: * = $P < 0.05$; ** = $P < 0.01$.*

the day of first significant cast elevation, this difference was first apparent 9 days before creatinine rose and continued until day 0 (Fig. 3).

Figure 3 also demonstrates that the cast counts dropped to normal in nephrotoxic patients shortly after serum creatinine began to rise. This effect was noted whether aminoglycoside dosing was continued, stopped, or continued at a reduced dosing rate in response to changing serum creatinines.

DISCUSSION

Although the package inserts for all available aminoglycosides recommend urinalysis as a means of monitoring therapy, this technique has apparently received little attention. Indeed, except for occasional diagnostic use of 12 or 24 Addis counts (1), quantitative cast excretion has not been clinically employed. Major reasons for the general neglect of urinalysis probably stem from the difficulties encountered standardizing the test and the fact that many clinical insults increase cast excretion in ICU patients. This predictable absence of diagnostic specificity is a major reason why urinary casts are seldom looked for in critically ill patients. Our results do not establish a high cast count as specifically diagnostic of aminoglycoside nephrotoxicity but clearly demonstrate that an elevation in cast excretion provides 5 to 9 days of warning to adjust aminoglycoside dosage or intervene and combat other renal insults. In this manner, use of casts can be an effective early marker of renal tubular damage regardless of its specific cause, and lack of diagnostic specificity presents only minor problems.

Although clinical laboratories have been reluctant to employ this technique because it is difficult to automate, interest in the use of casts as a diagnostic method has been increasing (4, 12), and it is probable that application of this test to the serial monitoring of renal tubular status may also become popular. A cast count can be rapidly performed with a hemacytometer, a microscope, and minimal instruction, establishing rapid turnaround time and negligible expense as two major advantages over other commonly used aminoglycoside monitoring techniques. Although frequent and probably daily cast counts are needed to provide meaningful data, this disadvantage is also inherent in the use of serum creatinines, aminoglycoside serum levels, urinary enzymes, and urinary β_2-microglobulin. When compared with β_2-microglobulin and urinary enzymes, cast counts have a clear advantage in that they apparently can be performed on a random urine, provided that a concentrated and acidic urine specimen is collected.

In view of their speed and low cost, cast counts can logically serve as a screening method to identify patients who should also have the more expensive aminoglycoside blood level measurements. However, before cast counts are widely employed and again misunderstood, we emphasize that they are essentially useless and potentially misleading if done only after serum creatinine begins to rise above base line. For unknown reasons, casts disappear from the urine as serum creatinine begins to rise, perhaps because damaged and nonfiltering nephrons do not produce them or stasis prevents their excretion. In addition, because other insults also transiently elevate cast excretion (5, 13), it seems prudent to document at least three successive cast counts above 500 before concluding that serious damage has occurred. Finally, since we did not use cast counts to make clinical decisions, a prospective study will be required to determine whether decreasing aminoglycoside dosages in response to elevated cast counts will prevent or minimize the resulting creatinine rise. Indeed, since casts in the urine indicate that some damage to renal tubules has already occurred, it remains to be prospectively determined whether even this early intervention can benefit these critically ill patients.

ACKNOWLEDGMENTS

We thank the attending, house, and nursing staff of the Millard Fillmore and Buffalo General Hospitals for assistance throughout this study. E. DeGlopper, G. Calleri, J. Acquard, and D. Chiarmonte provided technical assistance.

This work was supported by Public Health Service grant GM 20852 from the National Institute of General Medical Sciences, and in part by grants from the Eli Lilly Co. and The Schering Corp.

LITERATURE CITED

1. **Addis, T.** 1926. The number of formed elements in the urinary sediment of normal individuals. J. Clin. Invest. **2**:409.
2. **Burton, J. R., J. W. Rowe, and R. N. Hill.** 1975. Quantitation of casts in urine sediment. Ann. Intern. Med. **83**:518–519.
3. **Fredriksson, A.** 1975. Renal handling of β_2-microglobulin in experimental renal disease. Scand. J. Clin. Lab. Invest. **35**:591–600.
4. **Haber, M. H., and L. E. Lindner.** 1977. The surface ultrastructure of urinary casts. Am. J. Clin. Pathol. **68**: 547–552.
5. **Imhof, P. R., J. Hushak, G. Schumann, P. Dukor, J. Wagner, and H. M. Keller.** 1972. Excretion of urinary casts after the administration of diuretics. Br. Med. J. **2**:199–202.
6. **Mondorf, A. W., M. Zegelman, J. Klose, J. Hendus, and J. Breier.** 1978. Comparative studies on the action of aminoglycosides and cephalosporins on the proximal tubule of the human kidney. J. Antimicrob. Chemother. **4**(Suppl. A):53–58.
7. **Patel, V., F. C. Luft, M. N. Yum, B. Patel, W. Zeman, and S. A. Kleit.** 1975. Enzymuria in gentamicin-induced kidney damage. Antimicrob. Agents Chemother.

7:364–369.

8. **Peterson, P. A., P. E. Ervin and I. Berggard.** 1969. Differentiation of glomerular, tubular and normal proteinuria: determinations of urinary excretion of β_2-microglobulin, albumin and total protein. J. Clin. Invest. **48**:1189–1198.
9. **Schentag, J. J., T. J. Cumbo, W. J. Jusko, and M. E. Plaut.** 1978. Gentamicin tissue accumulation and nephrotoxic reactions. J. Am. Med. Assoc. **240**:2067–2069.
10. **Schentag, J. J., T. A. Sutfin, M. E. Plaut, and W. J. Jusko.** 1978. Early detection of aminoglycoside nephrotoxicity with urinary β_2-microglobulin. J. Med. **9**:201–209.
11. **Schreiner, G.** 1957. The identification and clinical significance of casts. Arch. Intern. Med. **99**:356–369.
12. **Schumann, G. B., S. Harris, and J. B. Henry.** 1978. An improved technique for examining urinary casts and a review of their significance. Am. J. Clin. Pathol. **69**: 18–23
13. **Stewart, H. J., and N. S. Moore.** 1930. The number of formed elements in the urinary sediment of patients suffering from heart disease. J. Clin. Invest. **9**:409.
14. **Stroo, W. E., and J. B. Hook.** 1977. Enzymes of renal origin in urine as indicators of nephrotoxicity. Toxicol. Appl. Pharmacol. **39**:423–434.