A Randomized Clinical Trial of Moxalactam Alone versus Tobramycin plus Clindamycin in Abdominal Sepsis

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One hundred patients with intraabdominal infections were assigned randomly in double-blind fashion to receive either the combination of tobramycin plus clindamycin (TM/C) or moxalactam (MOX) alone. Fifty patients comprised each group, but one patient in each group died of infection before 48 hours treatment. In the remaining 98 patients, the average age was 62 years, initial serum albumin was 3.0 mg/dl, serum creatinine was 1.5 mg/dl, and over half of the patients were nutritionally deficient by the prognostic nutritional index criteria. In approximately one-half of the patients, the source of infection was perforated colon or perforated appendix. There were no significant differences in demographic factors between these groups, except that those who were given TM/C were older, while those who were given MOX had a more serious long-term prognosis due to underlying disease. The average length of treatment was 11 days, and the average hospitalization time was 24 days. Clinical response to therapy was identical, since 74% of the TM/C patients and 76% of the MOX patients had satisfactory responses. Bacteria persisted at the site of infection in 63% of the TM/C patients and in 65% of the MOX patients, with the most common isolate being *Staphylococcus epidermidis*. Pseudomonas infections were the most difficult to cure in both groups. The two regimens differed only in side effects; TM/C was a more frequent ($p < 0.05$) cause of nephrotoxicity, and elevated prothrombin time/partial thromboplastin time (PT/PTT) was more frequently ($p < 0.05$) observed in MOX. All PT/PTT elevations responded to injections of vitamin K, and no serious bleeding occurred. Choice between these regimens depends on the risk of renal versus hematologic side effects, rather than efficacy.

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THE PATHOGENESIS of intraabdominal sepsis has been elucidated in animal models over the past 5 years.[1] Abdominal sepsis is a two-stage mixed infection with aerobic gram-negative rods as a cause of initial sepsis, followed (in case of survival) by abscesses caused by anaerobes. The combination of an aminoglycoside plus clindamycin is active against both aerobes and anaerobes, and has emerged as the standard therapy, in conjunction with appropriate surgical intervention.[2] Aminoglycosides that are marketed in the United States, including gentamicin,[3,4] tobramycin,[5] and amikacin[6] have been combined with clindamycin to successfully treat intraabdominal sepsis. The choice of aminoglycoside is determined commonly by organism sensitivity, cost, or nephrotoxic potential. Metronidazole,[5] chloramphenicol,[4] and ticarcillin[4] plus an aminoglycoside have shown equivalence to clindamycin plus an aminoglycoside in clinical trials. Recently, cefoxitin,[6] cefamandole,[7] cefotaxime,[8] and moxalactam[9] have been proposed as alternatives to the combination of aminoglycosides and clindamycin in such infections.

Although these newer cephalosporins may be effective in surgical infections, recent studies are deficient in four major areas. They have included large numbers of soft tissue or wound infections, which are often a more benign process responsive to drainage alone.[6-9] Second, previous trials span the age range of 20 to 85 years. A younger, healthy patient is not at equivalent risk for sequelae of intraabdominal sepsis to an older patient with chronic diseases. Third, preoperative nutritional status has not been evaluated in relation to outcome in other trials. This factor is a major determinant of sequelae,[10,11] and younger patients with abdominal sepsis who are free of significant malnutrition do not respond to sepsis in an identical manner as do malnourished geriatrics.

No study of abdominal sepsis has yet matched groups on age and nutritional status, and, in addition, previous studies have not limited their study populations to those who require aminoglycosides. If the infection would be cured by a second generation cephalosporin such as cefoxitin or cefamandole, then this patient may have a low pretreatment risk of sequelae.

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This study was designed to address previous deficiencies in a randomized, clinical trial of moxalactam alone versus the standard treatment of abdominal sepsis. Age criteria was restricted to include only those patients over 40 years old. Our study excluded trauma patients, gunshot and stabbing victims, and those with surgical wound infections. This trial was carried out in a subpopulation that was representative of the high risk, nutritionally deficient, older patients with sepsis due to intraabdominal catastrophe.

Methods

One hundred consecutive patients with presumed or proven abdominal sepsis were entered into this trial. Four other suitable patients were approached, but refused to give consent, and were excluded. Patients were not approached if they were not candidates for tobramycin plus clindamycin (TM/C) or if the patient's age was below 40 years. Patients with a history of major allergy to penicillin were excluded. They were also excluded if not expected to survive 48 hours or if gram negative bacteria were known to be resistant *in vitro* to either TM/C or MOX. Patients were included if they were a failure on previous antimicrobial therapy, providing other criteria were met. After informed consent was obtained, patients were given one of the regimens based on order of entry, using a previously randomized list kept blind from the investigators by the pharmacy. After entry, the study regimen was made known to the investigators as well as to patients, if they requested. Almost two-thirds of patients were entered without knowledge of the pathogen, since most were given the first dose prior to a surgical procedure. The other one-third had gram negative organisms resistant to first or second generation cephalosporins.

Baseline laboratory testing included SMA 6 and 12 profiles, CBC with differential, prothrombin time/partial thromboplastin time (PT/PTT), and total iron-binding capacity. Total iron-binding capacity, serum albumin and triceps skin fold measurements were used in calculation of prognostic nutritional index (PNI), as described by Buzby.[10] A urinalysis was taken for cast count, and a 24-hour urine collection was started to quantitate excretion of *beta* 2-microglobulin (B2M), alanine aminopeptidase (AAP), creatinine, protein, and excretion rate of study drug. We assayed B2M[12] and AAP as previously described. Blood testing was repeated at 24- to 48-hour intervals during the study, and for 5 to 10 days post-treatment. Daily 24-hour urines were collected whenever the patient was catheterized.

Tobramycin dosage initially was 2.0 mg/kg, followed by adjustments based on measured serum concentrations. The moxalactam starting dose was 2.0 g every 8 hours, with empiric increases to 4.0 g every 8 hours if pseudomonas was isolated, or if the clinical condition of the patient was not improving by day 2 of treatment. The MOX dosage was decreased to 1–2 g every 12 hours in cases of severely impaired renal function. The dose of clindamycin was 600 mg every 6 hours, empirically reduced to 600 mg every 8 hours if major liver disease was present.

Peak and trough antibiotic concentrations were measured every 2 days during therapy. On study days 3 to 6, a full kinetic profile (eight blood samples and interval urine) was taken over one dosing interval.

Tobramycin was assayed using EMIT (Syva Company, Palo Alto, CA). Moxalactam was assayed via high pressure liquid chromatography (HPLC)[14] or bioassay, with good agreement between methods. Desired therapeutic ranges for tobramycin were maintained at peaks 4.0 to 12.0 μg/ml, and valleys 0.5 to 2.0 μg/ml. Moxalactam peaks were maintained above 150 μg/ml.

Bacteria were isolated from aerobic and anaerobic cultures taken before or within 8 hours of the first dose. Aerobic isolates were tested for sensitivity to MOX and TM/C using Autobac (Pfizer Labs, Groton, CT) or Kirby Bauer Disks.

The patients were followed until death or discharge, and complete clinical and demographic data were collected. Any patient readmitted was noted. Follow-up was complete, since nearly all patients were seen post discharge by their physicians who, in turn, advised us of their subsequent progress.

Clinical and bacteriologic responses were assessed separately. Satisfactory clinical response was defined as absence of signs and symptoms of infection at completion of treatment. Recurrent symptoms were termed satisfactory with recurrence. Unsatisfactory responses included those who failed to improve, had changes in therapy, or died of infection. The clinical requirement for another antibiotic or antifungal was considered a regimen failure, and patient response was defined as unsatisfactory, even though all patients were treated by the investigators as needed.

Bacteriologic response was differentiated into 4 categories: post-treatment eradication, eradication plus colonization, eradication plus superinfection, or persistence of the organism as a pathogen. In the case of multiple pathogens, the same criteria were used for each pathogen. A global assessment of response was made also.

Significant change in renal function was defined as a rise in creatinine of more than 0.5 mg/dl during or within 10 days posttreatment. Changes in creatinine were ascribed to the antibiotic if they were preceeded by significant renal tubular damage, such as B2M excretion above 50 mg/24 hours[15] or AAP excretion above 50 mU/24 hours.

Elevation of PT/PTT above the normal range was considered significant, and all patients were treated with vitamin K at the time of elevation. Except for two cases of elevated PT/PTT due to heparin, all these cases were attributed to the antibiotic.

Statistical analysis was performed using chi square or unpaired T-test. Statistical significance was defined as $p < 0.05$.

Results

Study Groups

The 100 study patients comprised two randomly divided groups, 50 patients receiving MOX and 50 receiving TM/C. Two patients (one MOX, one TM/C) died in the first 24–48 hours of the study. These two patients rapidly deteriorated, and both were excluded from further analysis because they died before surgery. In the remaining 98 patients, no additional antibiotics were given, and no other protocol violations occurred. The 98 study patients were derived primarily (77%) from the practice of three general surgeons, and six surgical residents managed the postoperative course of 71% of the patients. There were no differences between the three surgical groups in patient response, cures, or complications.

These 98 patients had multiple underlying diseases, as shown in Table 1. The most frequent were malnutrition and cardiac disease. Renal disease, age above 70 years, and malignancies were observed commonly, while liver disease and neutropenia were rare. Half of the patient population had three or more diseases. Less than 20% of the patients had no disease, most of whom had a perforated appendix as their primary reason for admission. The duration of abdominal symptoms prior to randomization and surgery did not differ between MOX and TM/C, and averaged 36 hours.

TABLE 1. *Associated Diseases in the Patients Treated with Either Moxalactam alone (MOX) or Tobramycin plus Clindamycin (TM/C)*

Diagnosis*	MOX 49 Patients	TM/C 49 Patients
Diabetes	12%	12%
Carcinoma	37%	26%
Pulmonary	31%	20%
Cardiac	41%	51%
G.I. carcinoma	20%	22%
Malnutrition	59%	51%
Liver disease	4%	4%
Renal disease	31%	49%
Neutropenia	0%	0%
Age above 70 years	20%	41%†
Three or more above	49%	53%
No associated disease	16%	18%

* Criteria for diseases: pulmonary (COPD only), cardiac (clinical CHF or by EKG), malnutrition (PNI > 60), liver disease (biopsy proven), renal disease (CCR < 50 ml/min), neutropenia (WBC < 1000).

† Significant difference ($\chi^2 = 4.8$, $p < 0.05$).

TABLE 2. *Demographic Features of 100 Patients Treated for Abdominal Sepsis after Randomization to Either Moxalactam Alone (MOX) or Tobramycin plus Clindamycin (TM/C)*

	MOX	TM/C
Number Studied	49	49
Age (years)	59 ± 16	65 ± 16
Sex (m/f)	22/27	29/20
Baseline lab data		
Serum creatinine (mg/dl)	1.5 ± 1.9	1.3 ± 0.6
Serum albumin (gm/dl)	3.0 ± 0.6	3.1 ± 0.7
Initial PNI	66 ± 20	63 ± 22
Type of infection—peritonitis and/or abscess after		
Perforated upper G.I.*	6	7
Hepatobiliary/pancreatic†	9	10
Perforated small bowel	5	5
Perforated colon	17	12
Perforated appendix	4	9
Miscellaneous‡	8	6
Underlying prognosis		
Less than 1 month (%)	8	6
One month to 1 year (%)	35	12§
Over 1 year (%)	26	53‖
Positive blood cultures (%)	10	10
First infections (%)	69	80
Failures of prior Tx (%)	31	20
Treatment		
Duration (days)	10 ± 4	12 ± 6
Total dose (g)	62 ± 37	2.2 ± 2.0
ICU management (days)	13 ± 18	8 ± 9

* Includes perforated stomach and duodenal ulcers.

† Includes infections of liver, biliary system, suphrenic and pancreatic abscesses. Uncomplicated cholecystitis was excluded.

‡ Includes operations where the bowel was not entered, such as abdominal aortic graft infections, or those cases where no infection was found at laparotomy.

§ Significant difference at $p < 0.05$.

‖ Significant difference at $p < 0.01$.

As shown in Table 2, initial creatinine tended to be above normal, and initial albumin and PNI was often low. Positive blood cultures were relatively infrequent, and, when noted, the patient usually died. Appendix and colon perforations were found in about half of the study group, while upper gastrointestinal and small bowel perforations comprised most of the remainder. There were no cases of cholecystitis or appendicitis in either group, and there were no significant differences between MOX and TM/C patients in any of the surgical diagnosis categories. Exclusive of infection, many patients had a generally poor long-term prognosis, since only 30% of patients were expected to survive 5 years. There were two differences between MOX and TM/C patients in long-term prognosis, as more TM/C patients than MOX patients were expected to survive over 1 year ($p < 0.05$) and fewer TM/C patients than MOX patients

TABLE 3. *Bacteria Isolated and Response of Bacteria to Treatment with Either Moxalactam Alone (MOX) or Tobramycin plus Clindamycin (TM/C)*

	MOX	TM/C
Number studied	49	49
Initial isolate		
Aerobes only (%)	49	43
Anaerobes only (%)	0	2
Aerobes and anaerobes (%)	39	41
No pathogens (%)	12	14
Initial sensitivity to study drug		
Gram-neg sensitive (%)	96	100
Gram-pos sensitive (%)	26	38*
During treatment		
Eradication	10/43 (23%)	10/42 (24%)
Erad with colonization	18/43 (42%)	13/42 (31%)
Erad with superinfection	10/43 (23%)	9/42 (21%)
Bacterial persistence	5/43 (12%)	10/42 (24%)
Post-treatment persistence†		
Enterococci	28/49, 8 (29%)	19/49, 8 (42%)
Anaerobes	4/49, 1 (25%)	5/49, 4 (20%)
Pseudomonas	14/49, 4 (29%)	6/49, 5 (83%)‡
Candida	13/49, 1 (8%)	8/49, 1 (13%)
S. epidermidis	15/49, 5 (20%)	23/49, 5 (22%)

* Tobramycin sensitivity is shown.

† Post-treatment persistence of each bacteria are given as follows: number persistent/total patients, number of persistent bacteria considered pathogenic (per cent pathogenic). Persistent bacteria in the face of clinical deterioration was considered pathogenic.

‡ Significant difference at $p < 0.05$.

were expected to survive between 1 month and 1 year ($p < 0.05$). The only other demographic difference between the 49 MOX patients and the 49 TM/C patients was that more TM/C-treated patients were over 70 years of age ($p < 0.05$), as shown in Table 1.

Bacteriology

Bacteria isolated from study patients are shown in Table 3. Because of patient entry prior to surgery based on symptoms, 12% to 14% of patients had no bacteria isolated. In a portion of these, infection was not found at laparotomy, or, in some cases, infection was noted, but organisms were not isolated. Two such negative cases were perforations of the appendix, and one was a gangrenous terminal ileum.

In patients who were culture-positive, aerobes were found invariably, and concomittant anaerobes were present in about half of them. No differences were noted between MOX and TM/C groups as to type of bacteria found. The specific pathogens found in the initial cultures of the 98 patients included *Escherichia coli,* the most frequent in 53% of cultures, enterococci in 47%, bacteroides species in 37%, Klebsiella in 15%, Pseudomonas in 15%, Enterobacter in 18%, Proteus in 10%, *Staphylococcus epidermidis* in 21%, and *Candida* in 11%. Three isolates per patient was average.

The aerobic pathogens isolated were sensitive to the study drug in 96% of MOX cases and 100% of TM/C cases. Enterococcus was nearly always MOX-resistant and was usually resistant to TM or clindamycin. Because of frequent isolation in benign clinical situations, *enterococcus* and *S. epidermidis* was not considered a pathogen, unless it was a single isolate and the patient showed clinical deterioration.

During therapy, bacteriologic failures were more frequent than clinical failures, to the point where cultures were scrutinized only when clinical deterioration occurred. By the end of therapy, the bacterial flora in 98 patients were substantially different than those at initial culture. *S. epidermidis* increased to 46% (20% of these were pathogenic), enterococcus declined to 18%, Candida rose to 16%, Pseudomonas was unchanged at 16%, bacteroides declined to 9%, and *E. coli* dropped to 7%.

Table 3 also shows the post-treatment persistence of bacteria in both groups. Colonization was frequent, and when clinical deterioration occurred in the colonized patients, this was termed superinfection. Pseudomonas was responsible for superinfection in four of the 14 Pseudomonas-colonized MOX cases and five of the six TM/C cases ($p < 0.05$). *S. epidermidis* caused superinfection in five of 25 colonized MOX cases and in five of 23 TM/C cases. Candida superinfection was rare. Most of the patients with Candida, Pseudomonas, and *S. epidermidis* superinfections died. Anaerobes were seldom identified in the cultures of superinfected cases. Pseudomonas superinfection was the only significant bacteriologic difference between the TM/C and the MOX group.

Clinical Response

Clinical response was satisfactory in 75% of patients, with no differences between MOX and TM/C. Table 4 further defines the less than satisfactory responses by diagnosis. Most failures were ascribed to gram-negative aerobic superinfection or acquired resistance. The most common sites were biliary/pancreatic and colon. In eight of the nine TM/C failures, cultures revealed organisms sensitive to TM/C, while cultures showed sensitive organisms in three of the six MOX failures, and the other three showed a resistance to MOX. All clinical failures were also bacteriologic failures, although the converse was not generally true. Study mortality rate was 13%. Most of the patients who died, did so with infection as a major contributing factor.

Adverse Reactions

Approximately half of the patients had side effects, as listed in Table 4. An increase in serum creatinine (>0.5 mg/dl) occurred in six (12%) MOX and 14 (29%)

TM/C patients ($p < 0.05$). Nephrotoxicity due to renal tubular damage (as assessed by increased excretion of B2M, AAP, and casts) was less frequent than creatinine rise, since it occurred in 4% of MOX patients and 18% of TM/C patients ($p < 0.05$).

Moxalactam was associated more frequently ($p < 0.01$) with alteration of PT/PTT (45%), although changes in clotting times were noted also in 16% of TM/C patients. All patients with elevated PT/PTT were treated with vitamin K every 12 hours for two doses, and the elevated PT/PTT values were usually normalized within 24 hours. Bleeding requiring more than 2 units of packed cells occurred in only two patients, both treated with MOX. However, this difference was not statistically significant. Mild allergic dermatologic reactions were observed in five patients, with no differences between regimens. Diarrhea, elevations in liver enzymes, thrombophlebitis, and eosinophilia were encountered but could not be clearly related to either regimen. These abnormalities were reversible.

TABLE 4. *Clinical Response and Adverse Reactions during Treatment with Moxalactam Alone (MOX) or Tobramycin plus Clindamycin (TM/C)*

	MOX	TM/C
Number studied	49	49
Overall outcome		
Satisfactory (%)	76	74
Satisfactory with recurrence (%)	12	8
Unsatisfactory (%)	12	18
Late abscesses	1/49	3/49
Mortality rate (%)	14	12
Clinical failures by category (failures/total in category)		
Upper G.I.	0/6	1/7
Hepatobiliary/pancreatic	4/9	7/10
Small bowel	0/5	2/5
Colon	6/17	2/12
Appendix	0/4	1/9
Miscellaneous	2/8	0/6
Adverse reactions‡		
All creatinine elevations (%)	12*	29
Renal tubular damage (%)	4*	18
PT/PTT rise (%)	45†	16
Bleeding (%)	4	0
Allergy (%)	2	6
None (%)	45	57

* Significantly different from tobramycin/clindamycin at $p < 0.05$.
† Significantly different from tobramycin/clindamycin at $p < 0.01$.
‡ Some of the reactions occurred in the same patients, so the total exceeds 100%.

Discussion

This study was designed to test the efficacy and safety of moxalactam in a subpopulation of older, critically ill adults who had major underlying diseases, poor nutritional status defined as PNI $\geq$ 50, and intraabdominal sepsis requiring intensive care unit (ICU) management. The intervening variables were well balanced between regimens by the blind randomization.

The findings regarding nephrotoxicity are not necessarily representative of previous studies of surgical infection.[4–9] The greater average age, the abnormal renal function, and the critically ill status of the patients and long course of treatment all contributed to a higher incidence of changed renal function. Tobramycin was selected as our reference aminoglycoside primarily because of significantly greater gentamicin nephrotoxicity in previous studies of these patients.[16,17] Tobramycin nephrotoxicity was more frequent in this study than in previous series,[16] but in this study, the tobramycin cumulative dosage was higher and therapy was continued longer. Secondly, over 80% of this population had abdominal sepsis, while in our previous studies, about 50% had abdominal infections and a large portion had pneumonia.[16,17] In all previous trials of nephrotoxicity in ICU patients, the absence of a non-aminoglycoside-treated control has prevented full appreciation of the acute renal failure incidence in these patients due to aminoglycosides versus other insults. Since MOX has no nephrotoxicity in animals,[18] the MOX patients might be considered a control group given a non-nephrotoxic substance. The results suggest that approximately one-half of the acute renal failure in this surgical population was linked directly to aminoglycoside use. These mild and generally reversible creatinine elevations occurred, even though dosages of tobramycin were adjusted to the recommended serum concentration range, using measured serum concentrations.

Although the study population here is unique because of the restrictive exclusion criteria, several previous clinical trials bear some similarity to this study population. Stone performed a series of trials in surgical patients and has compared gentamicin plus clindamycin to cefamandole,[7] moxalactam,[9] and cefotaxime.[8] The two study populations differ; his patients are generally 15 to 20 years younger, in a better state of health, and most do not appear seriously malnourished. In addition, trauma cases and/or sepsis from soft tissue or wound infections, comprised a large portion of the group. Finally, the dose of clindamycin in one of these studies[9] has been challenged. All of the Stone studies find the cephalosporin regimen equivalent to the aminoglycoside/clindamycin regimen, as did this study. However, it is difficult to define the role of third generation cephalosporins in a series of trials which demonstrate both second and third generation cephalosporins equivalent to aminoglycoside plus clindamycin.

Tally[6] and Drusano[22] conducted randomized trials of cefoxitin alone or with amikacin, versus amikacin plus clindamycin. In both studies, at least half of the patients had surgical infections other than abdominal sepsis. The

mean age of their patients was younger, and it is not possible to assess nutritional status or underlying disease severity from the data provided. The protocol of Tally provided for empiric use of amikacin until cultures were back or for addition of amikacin to cefoxitin if cultures grew resistant organisms. Amikacin was added to cefoxitin in 38% of the patients,[6] an indication that cefoxitin alone is not generally considered equivalent to aminoglycoside/clindamycin by these investigators. The high initial isolation of Pseudomonas and Enterobacter resistant to cefoxitin in our study patients also would have precluded the use of cefoxitin alone in our population.

Bacteriologic confirmation of infection was achieved in 88% of patients, and initial gram-negative isolates were nearly always sensitive to the study regimens. Although most patients were entered before culture of the surgical infection site, patients with a large left shift were identified nearly always correctly as having intraabdominal perforations. A large left shift was also one of the most useful indicators of the need for further surgery or abscess later in the course of therapy. The findings generally agree with those of previous studies.[10]

The clinical findings suggest that the enterococcus has a low pathogenic potential. This bacteria was universally resistant to MOX and frequently to TM/C. The enterococcus was often the sole bacteria found at the wound site on days 3 to 5, but it disappeared with wound healing. Eight patients had superinfections including this organism, but enterococcus was the sole isolate in only two cases. Our data are in contrast to one previous report,[20] but the reference study was an open trial and patients are not necessarily comparable.

Pathogenic *S. epidermidis* has been noted recently in surgical infections.[21] *S. epidermidis* was usually resistant to both regimens, and although uncommonly pathogenic, superinfections were serious problems, accounting for one fatality in each regimen. This organism should be considered a pathogen in surgical patients if fever and leukocytosis returns after an initial response, in conjunction with its isolation.

Anaerobes were found initially in almost one-half of these 98 study patients, with bacteroides species being most common. Others have found these organisms present in abdominal infections as frequently as 80%.[4,5] Anaerobic isolation procedures were not rigorous, and the actual presence of anaerobes in our population was probably higher than our cultures reveal. Nevertheless, in the presence of prior or concommittant surgical drainage, both MOX and clindamycin apparently provided effective anaerobic coverage, as there were almost no cases of subsequent abscesses requiring drainage (Table 4).

The present study population was selected carefully to study the subpopulation of older, seriously ill patients who require aminoglycoside plus clindamycin for treatment of intraabdominal sepsis. Most patients had both aerobes and anaerobes. Moxalactam was as effective as the combination but was responsible for significantly less nephrotoxicity. However, MOX was not free of adverse reactions, since elevated PT/PTT occurred in 22 (45%) of the patients, while it was observed in eight (16%) of the TM/C patients. The latter finding has not been reported previously and probably reflects the poor health of these patients, combined with intense surveillance. Vitamin K was given within 24 hours of the first PT/PTT elevation, and no hazardous bleeding was noted. However, the data support the prophylactic use of vitamin K in older, malnourished patients who are treated with MOX, as recommended in the package literature. Those given TM/C should also have clotting profiles monitored closely.

Drug costs were not different between the two regimens. The average cost of the moxalactam plus three fluid administration sets per day was $75.10, compared to the TM/C regimen with 7 I.V. fluid sets costing $71.75 per day. Factors such as tobramycin levels, PT determinations, and nursing and pharmacy time were not considered in these calculations.

As amply documented in the literature, cure of abdominal sepsis can be effected by surgical correction of the underlying condition, but in older patients, only when adequate surgery is combined with effective antimicrobial coverage. Nutritional support has a major adjunctive role, since the patients with the highest baseline malnutrition can be considered likely to heal slowly, develop leaks around anastamoses, form abscesses, and develop resistant organisms.[10,11] In almost all our clinical failures, resistant aerobes were identified as the cause. Pseudomonas was implicated most often in failure of both TM/C and MOX, and neither agent can be considered a universal antidote to this pathogen. *S. epidermidis* was also particularly troublesome, and it will be interesting to see if gram-positive bacteria return as the gram-negative spectrum is optimized further by the newer cephalosporins. In spite of the development of new antibiotics, the patient with weakened host resistance continues to have a high mortality due to infection. Nevertheless, moxalactam in combination with vitamin K is a major advance in safety and can be considered equivalent in efficacy to the standard regimen.

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References

1. Weinstein WM, Onderdonk AB, Bartlett JG, et al. Antimicrobial therapy of experimental intraabdominal sepsis. J Infect Dis 1975; 132:282–286.
2. Bartlett JG, Miao PVW, Gorbach SL. Empiric treatment with clindamycin and gentamicin of suspected sepsis due to anerobic and aerobic bacteria. J Infect Dis 1977; 135(Suppl):80–85.
3. Stone HH, Kolb LD, Geheber CE. Use of aminoglycosides in surgical infections. Ann Surg 1976; 183:660–666.
4. Harding GKM, Buckwold FJ, Ronald AR, et al. Perspective, randomized comparative study of clindamycin, chloramphenicol, and ticarcillin, each in combination with gentamicin, in therapy for intraabdominal and female genital tract sepsis. J Infect Dis 1980; 142:384–393.
5. Smith JA, Skidmore AG, Forward AD, et al. Prospective, randomized, double blind comparison of metronidazole and tobramycin with clindamycin and tobramycin in the treatment of intraabdominal sepsis. Ann Surg 1980; 192:213–220.
6. Tally FP, McGowan K, Kellum JM, et al. A randomized comparison of cefoxitin with or without amikacin and clindamycin plus amikacin in surgical sepsis. Ann Surg 1981; 193:318–323.
7. Stone HH, Morris ES, Kolb LD, et al. Clinical comparison of cefamandole versus gentamicin in the treatment of peritonitis (Abst). Clin Pharmacol Ther 1979; 25:251.
8. Stone HH, Geheber CE, Kolb LD, Dunlop WE. Clinical comparison of cefotaxime versus the combination of gentamicin plus clindamycin in the treatment of peritonitis and similar polymicrobial soft-tissue surgical sepsis. Clin Ther 1981; 4(Suppl A):67–80.
9. Stone HH, Haney BB, Kolb LD, et al. Clinical comparison of moxalactam versus the combination gentamicin—clindamycin in peritoneal and soft tissue sepsis (Abst 248). Presented at the 20th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, 1980.
10. Buzby GP, Mullen JL, Matthews DC, et al. Prognostic nutritional index in gastrointestinal surgery. Am J Surg 1980; 139:160–167.
11. Dionigi P, Nazari S, Bonoldi AP, et al. Nutritional assessment and surgical infections in patients with gastric cancer or peptic ulcer. J Parent Enteral Nutr 1982; 6:128–133.
12. Schentag JJ, Plaut ME. Patterns of urinary beta 2-microglobulin excretion by patients treated with aminoglycosides. Kidney Int 1980; 17:654–661.
13. Mondorf AW, Breier J, Hendus J, et al. Effect of aminoglycosides on proximal tubule membranes of the human kidney. Eur J Clin Pharmacol 1978; 13:133–142.
14. Ziemniak JA, Chiarmonte DA, Miner DJ, Schentag JJ. HPLC determination of d and l moxalactam in human serum and urine. J Pharm Sci 1982; 71:399–402.
15. Schentag JJ, Cerra FB, Plaut ME. Clinical and pharmacokinetic characteristics of aminoglycoside nephrotoxicity in 201 critically ill patients. Antimicrob Agents Chemother 1982; 21:721–726.
16. Schentag JJ, Plaut ME, Cerra FB. Comparative nephrotoxicity of gentamicin and tobramycin: pharmacokinetic and clinical studies in 201 patients. Antimicrob Agents Chemother 1981; 19:859–866.
17. Schentag JJ, Plaut ME, Cerra FB, et al. Aminoglycoside nephrotoxicity in critically ill surgical patients. J Surg Res 1979; 26:270–279.
18. Luft FC, Arnoff GR, Evan AP, et al. Effects of moxalactam and cefotaxime on rabbit renal tissue. Antimicrob Agents Chemother 1982; 21:830–835.
19. Lennard ES, Dellinger EP, Werta MJ, Minshew BH. Implications of leukocytosis and fever at conclusion of antibiotic therapy for intraabdominal sepsis. Ann Surg 1982; 195:19–24.
20. Yu VL. Enterococcal superinfection and colonization after therapy with moxalactam, a new broad-spectrum antibiotic. Ann Intern Med 1981; 94:784–785.
21. Christensen GD, Bisno AL, Parisi JT, et al. Nosocomial septicemia due to multiple antibiotic-resistant *Staphylococcus epidermidis*. Ann Intern Med 1982; 96:1–10.