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Adjunctive Antimicrobial Therapy for Complicated Appendicitis: Bacterial Overkill by Combination Therapy

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Abstract. Although single antimicrobials with broad-spectrum aerobic and anaerobic coverage are effective in patients with appendicitis, many general surgeons continue to use multiple agents. A prospective, double-blind, randomized trial was designed to detect any clinical correlate of in vitro susceptibility advantage of multiple antimicrobials as adjunctive therapy for 114 patients undergoing operation for complicated appendicitis. There was clinical resolution of intraabdominal infections with no occurrence of postoperative infectious complications in 90% (36 of 40) of the cefotetan group and 86% (31 of 36) of the clindamycin/amikacin group ($p = 0.11$). The number of patients who had changes in antibiotic therapy due to postoperative complications was higher in the clindamycin/amikacin group: five (12.5%), compared to one (2.8%) in the cefotetan group ($p = 0.07$). Although *Bacteroides fragilis* group organisms resistant to cefotetan were identified, none was responsible for the postoperative infections. Adverse drug events in 28% of the cefotetan group and 26% of the clindamycin/amikacin group consisted primarily of transient elevations of liver function tests. Monotherapy with a second-generation, broad-spectrum cephalosporin, such as cefotetan, given twice a day is an economical and effective adjunctive regimen in patients with complicated appendicitis for which operation is the definitive treatment. Aminoglycosides and other, more potent antimicrobials should be reserved for resistant organisms or nosocomial infections.

Carefully selected cephalosporin monotherapy for the adjunctive treatment of complicated appendicitis has been shown to be as effective as combination therapy of an aminoglycoside plus clindamycin or metronidazole [1–6]. The Antimicrobial Agents Committee of the Surgical Infection Society has recommended both combination and single-agent regimens (including cefotetan) for the treatment of community-acquired infection of mild to moderate severity [7]. Combinations of antimicrobials continue to be used by surgeons on the theoretic grounds that in vitro susceptibility testing shows that cephalosporins lack activity against certain of the *Bacteroides fragilis* group of organisms. The pathogenic role of the *B. fragilis* group members other than *B. fragilis* in intraabdominal and postoperative infections following appendectomy is not clearly established [5].

We report the results of a double-blind comparison of cefotetan versus amikacin plus clindamycin to determine the efficacy and safety of these agents, as well as the role of resistant *B. fragilis* group isolates in the outcome of operation for complicated appendicitis. In this blinded study the treating surgeon was compelled to decide on a change of therapy based on the patient's clinical condition and intraoperative culture results rather than a preconceived expectation of antimicrobial activity.

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Methods

Over 4 years a prospective, double-blind, randomized comparison of the safety and efficacy of intravenous cefotetan and amikacin plus clindamycin for the treatment of complicated appendicitis was carried out at Harbor/UCLA Medical Center, a 500-bed, urban, public hospital. Patients suspected of having complicated appendicitis (gangrenous, perforated appendicitis or appendiceal abscess) who signed a written informed consent approved by the hospital's Institutional Review Board received a single dose of antibiotic from one of the treatment groups prior to surgery based on a computer-generated randomization table. Excluded from the study were patients who were hypersensitive to the study drugs or penicillin, had received prior antibiotics, required concomitant antimicrobial therapy for another infection focus, had received any other investigational drug, had a serum creatinine level higher than 2.5 mg/dl, had impaired immunologic function or leukopenia less than 1500/mm^3, had evidence of central nervous system infection, had a history of active colitis or liver disease, or were pregnant or nursing. All antibiotics were given by intravenous infusion over 30 to 60 minutes for at least 5 days in the following doses: cefotetan, 2 g every 12 hours; amikacin, an initial dose of 500 mg followed by 7.5 mg/kg body weight every 12 hours; and clindamycin, 600 mg every 6 hours. Antimicrobials other than the study drugs were not permitted during the course of the study through the follow-up visit. Antibiotics were not changed postoperatively if the patient's clinical condition appeared to be satisfactory, even if resistant bacteria were isolated from cultures obtained during surgery. If resistant organisms were isolated and in the opinion of the surgeon the patient was not responding adequately to the antibiotics, therapy was changed to provide coverage for all isolates and the patient was considered a clinical failure.

Blood cultures were obtained for all patients who had signs of sepsis prior to the start of antimicrobial therapy. Cultures of peritoneal fluid or other appropriate intraabdominal sources were obtained during the initial operation. Specimens for culture obtained during surgery were placed in Anaport tubes (Scott Laboratories, West Warwick, Rhode Island, U.S.A.). Susceptibil-

Table 1. National Committee for Clinical Laboratory Standards recommended interpretive standards used for bacteria isolated in the present study.

Standard	Criterion for diagnosis	Susceptible	Intermediate	Resistant
Aerobes				
Cefotetan	Disk zone	≥ 16	13–15	≤ 12
Clindamycin	Disk zone	≥ 21	15–20	≤ 14
Amikacin	Disk zone	≥ 17	15–16	≤ 14
Cefotetan	MIC	≤ 16	32	≥ 64
Clindamycin	MIC	≤0.5	1–2	≥ 4
Amikacin	MIC	≤ 16	32	≥ 64
Anaerobes				
Cefotetan	MIC	≤ 32		≥ 64
Clindamycin	MIC	≤ 4		≥ 8

ity of aerobic organisms were determined by the Kirby-Bauer and Sensititre (Radiometer America, Westlake, Ohio, U.S.A.) methods. Anaerobes were identified by the technique recommended by the Virginia Polytechnic Institute Anaerobic Laboratory Manual [8], and susceptibilities were determined by methods recommended by the National Committee for Clinical Laboratory Standards [9, 10]. Susceptibilities of each isolate were interpreted using the guidelines outlined in Table 1. For purposes of this analysis, all isolates recovered from the peritoneal cavity were considered pathogens. Skin incisions were left open in 94% (32 of 34) of patients who received cefotetan and 90% (26 of 29) of patients who received clindamycin/amikacin because class IV contamination (gross contamination or abscess) was present. In all patients with intraabdominal abscesses at operation, either a Penrose or a Jackson-Pratt drain was placed through a stab wound separate from the incision. Routine laboratory tests were done preoperatively, weekly, while the antibiotic was administered, and at the end of therapy to monitor hematologic parameters and renal and hepatic function. For the purpose of determining adverse events reflected in clinical laboratory values, elevated liver function tests were considered clinically significant if the results were beyond the normal range and were twice the baseline value. Any elevation of prothrombin time (PT) and activated partial thromboplastin time (PTT) was considered clinically significant. Amikacin serum levels were monitored and serum concentrations determined within 48 hours of the initiation of therapy in 28 of 55 (51%) of the patients receiving this drug. In an additional 15 patients blood specimens were obtained at 54 to 174 hours of therapy. Details of the operative procedures and findings were recorded. Patients were assessed for signs of infection daily during hospitalization and at each outpatient visit for at least 4 weeks postoperatively. Culture specimens were obtained from the site of the postoperative infection whenever possible.

Patients were considered to have a *satisfactory* clinical course if there was no evidence of the intraabdominal or wound infection or persistent fever during the postoperative period, which included the 4 to 6 weeks after discharge from the hospital. Persistence of original pathogens at the primary site of infection, persistent bacteremia with one of the initial isolates but no other source of infection, or development of a superinfection requiring additional antibiotic or surgical intervention was considered *unsatisfactory*. A *clinical failure* was defined as the presence of any of the following: recurrence of infection at the original site, wound with purulent drainage, or increasing or persistent fever higher than 38.5°C for three consecutive days postoperatively with no identifiable source of sepsis.

Wound infections were considered *major* if they required surgical drainage or a change in antibiotic therapy; they were deemed *minor* if they could be successfully treated with topical antiseptics and aggressive wound care. *Bacteriologic efficacy* was considered satisfactory or presumed satisfactory if there was eradication of the pathogens at the original site of infection, eradication of original pathogens with a new pathogen present without clinical evidence of a new infection, or no material was available for culture.

Statistical analysis of the data was performed using Mann-Whitney analysis for continuous variables and Fisher's exact test or χ^2 for categorical variables of appropriate sample sizes with the Statpro statistical package (Penton Software, New York, NY, U.S.A.).

Results

A group of 114 hospitalized patients with suspected complicated appendicitis were randomized to this study. Of these patients, 113 qualified for evaluation using our protocol: 58 patients received cefotetan and 55 clindamycin/amikacin. A subgroup of 89 patients received a full course of antimicrobial therapy, 76 of whom had complicated appendicitis and 13 acute appendicitis. Of the other, nonevaluable patients, 13 had a diagnosis other than complicated appendicitis: five gynecologic illnesses, four unknown abdominal pain, one liver abscess, one gastritis, one greater omentum hemorrhage, and one cecal diverticulitis. Of the remaining 12 patients, five received a different antimicrobial when uncomplicated appendicitis was observed during surgery, six had protocol violations, and one was randomized but no antibiotic was given. There was no statistical difference in demographic details of the 76 evaluable complicated appendicitis patients between the two arms of the study (Table 2), nor were there any differences when the evaluable acute appendicitis patients were included.

Preoperative blood culture specimens were obtained from 31 of the 89 (35%) patients. One patient in each arm of the study had a positive blood culture, *Escherichia coli* in one and *Klebsiella pneumoniae* in the other. Sixty-three positive peritoneal cultures were obtained from the 76 patients with complicated appendicitis at the time of initial operation; there were a total of 409 isolates, of which 198 were aerobes and 211 anaerobes. Among the 34 patients receiving cefotetan with positive intraoperative cultures, 97% of the cultures were positive for aerobic organisms, 91% for anaerobic organisms, and 88% for polymicrobes. Among the 29 positive cultures in the clindamycin/amikacin group, 100% were positive for aerobic organisms, 79% for anaerobic organisms, and 79% for polymicrobes. None of these differences was significant. The patients with bacteria isolated from intraoperative cultures of peritoneal fluid or intraabdominal abscess are enumerated in Tables 3 and 4. The patients with organisms resistant to the antibiotic received are also indicated.

Among the patients with gangrenous and perforated appendicitis, 90% (36 of 40) of those receiving cefotetan and 86% (31 of 36) of those receiving clindamycin/amikacin experienced clinical resolution of their intraabdominal infection with no postoperative infectious complications (Table 5). Among all of the clinically evaluable patients, including those with acute appendicitis, 91% (43 of 47) of

Table 2. Demographic comparison of evaluable gangrenous and perforated appendicitis.

Parameter	Cefotetan	Clindamycin/ amikacin	*p* Value
Evaluable patients (no.)	40	36	
Age, mean (range)	29 (18–60)	29 (18–55)	0.95
Sex, M/F (% male)	37/3 (93)	30/6 (83)	0.22
Admission WBC (cells $\times 10^3$ mm^3)	16.0 ± 4.4	14.8 ± 5.0	0.17
Admission temperature (°F)	101.4 ± 1.5	100.8 ± 1.5	0.11
Onset (days)	2.7 ± 2.1	2.6 ± 1.4	0.80
Amikacin peak (μg/ml)	—	27.9 ± 9.7	
Diagnosis			0.37
Gangrenous appendicitis	3 (8%)	2 (6%)	
Perforated appendicitis	37 (92%)	31 (86%)	
Concurrent disease			0.54
Diabetes	1 (3%)	2 (6%)	
Substance abuse	3 (8%)	5 (14%)	
Other	11 (28%)	6 (17%)	
Operation			0.16
Appendectomy	18 (45%)	20 (56%)	
Appendectomy with drainage	22 (55%)	14 (39%)	
Exploration with drainage	0	2 (6%)	
Length of surgery (min)	76.5 ± 26.2	79.1 ± 28.0	0.68
Cultures			
Positive intraabdominal	34 (85%)	29 (81%)	0.61
Positive blood	1 (3%)	1 (3%)	0.30
Other findings			
Abscess	17 (43%)	13 (36%)	0.57
Abdominal drainage			0.74
Penrose	20 (50%)	16 (44%)	
JP	2 (5%)	1 (3%)	
Wound closure			0.57
Primary	5 (13%)	8 (22%)	
Delayed primary	32 (80%)	25 (69%)	
Secondary	1 (3%)	2 (6%)	

Values are given as number of patients, procedures, or diagnosis; or the mean ± SD of the parameter measured unless otherwise stated.

Table 3. Patients with aerobic and facultative bacteria from intraabdominal cultures, by drug received.

Bacterium	No. resistant/total no.	
	Cefotetan	Clindamycin/ amikacin
Escherichia coli	0/25	1/21
Pseudomonas aeruginosa	8/8	0/6
Pseudomonas spp.	2/2	0/1
Comamonas testosteroni	0/2	0/2
Klebsiella spp.	0/4	0/4
Enterobacter cloacae	0/1	0/1
Other gram-negative rods	0/5	0/4
Streptococcus spp.	4/29	0/11
Enterococcus species	10/11	6/10
Staphylococcus epidermidis	0/3	2/5
Staphylococcus spp.	0	0/2

Table 4. Patients with anaerobic bacteria from intraabdominal cultures, by drug received.

Bacterium	No. resistant/total no.	
	Cefotetan	Clindamycin/ amikacin
Bacteroides		
fragilis	2/17	2/12
thetaiotaomicron	11/13	2/10
uniformis	5/5	1/7
distasonis	4/4	2/3
ovatus	2/2	1/4
stercoris	2/2	0/1
merdae	2/3	0
vulgatus	0/2	1/4
eggerthii	0	0/1
caccae	0	0/1
species	4/8	1/6
Eubacterium spp.	8/24	0/14
Clostridium spp.	3/8	3/17
Other gram-negative rods	1/11	2/9
Other gram-positive rods	1/4	0/2
Peptostreptococcus spp.	0/8	0/7

Table 5. Gangrenous and perforated appendicitis outcomes.

Parameter	Cefotetan	Clindamycin/ amikacin	p Value
Evaluable patients	40	36	
Clinical outcome			0.11
Cure	36 (90)	31 (86)	
Failures			
Wound	4	1 (3)	
Major	1	1	
Minor	3	0	
Intraabdominal abscess	0	2 (6)	
Febrile morbidity	0	2 (6)	
Days to morbidity	3.0 ± 1.4	6.0 ± 3.5	0.16
Antibiotic days	6.9 ± 1.7	6.5 ± 2.4	0.39
Satisfactory bacterial outcome	31 (91%)	24 (83%)	0.57
Febrile days	1.9 ± 1.4	1.8 ± 1.7	0.74
Hospital days	7.9 ± 1.9	8.2 ± 3.8	0.68
Additional surgery	0	1 (percutaneous)	
Additional antibiotic	1 (3%)	5 (14%)	0.07

See footnote to Table 2 relative to the presentation of values.

the cefotetan group and 88% (37 of 42) of the clindamycin/amikacin group had a satisfactory clinical course. None of the 13 patients with acute appendicitis who received a complete course of antibiotic therapy had an infectious complication. Of the four postoperative wound infections in the cefotetan arm, one was major and three were minor. Of the five patients with postoperative complications in the clindamycin/amikacin arm, one patient had a major wound infection with extensive cellulitis, one had an intraabdominal abscess that was drained percutaneously, one had a cecal fistula, and two had prolonged fever. In all other patients the postoperative infections resolved without additional intervention. There were no postoperative deaths.

Bacteriologic response was satisfactory in 91% (31 of 34) of the cefotetan group and 83% (24 of 29) of the clindamycin/amikacin group (Table 5). Table 6 enumerates the patients with each organism isolated from postoperative infections, including those resistant to the antimicrobial regimen received. Although the difference was not significant ($p = 0.07$), the numbers of patients whose antimicrobial therapy was changed because of postoperative infection were different between the two groups: one patient (2%) for cefotetan and five patients (12%) clindamycin/amikacin, respectively. The average length of time from operation to the beginning of postoperative morbidity was 3 days for patients

Table 6. Patients according to isolates from postoperative complication cultures.

Bacterium	No. resistant/total no.	
	Cefotetan	Clindamycin/ amikacin
Aerobes		
Escherichia coli	0	0/2
Pseudomonas aeruginosa	1/2	0
Streptococcus alpha group D	0/1	0
Viridens streptococcus	0/1	0
Enterococcus avium	0	1/1
Anaerobes		
Bacteroides		
fragilis	0	0/1
distasonis	0/1	0
uniformis	0/1	0
Porphyromonas asaccharolytica	0	1/1
Eubacterium lentum	0/1	0
Eubacterium limosum	1/1	0

Table 7. Adverse drug events.

Parameter	Cefotetan	Clindamycin/ amikacin	*p* Value
Patients (no.)	58	55	
Adverse events			0.66
Patients (no.)[a]	16 (28%)	14 (26%)	
Elevated Liver Function	13 (22%)	13 (24%)	
Elevated PT/PTT	2 (3%)	2 (4%)	
Nausea/vomiting	1 (2%)	0	
Diarrhea	1 (2%)	0	
Headache	1 (2%)	0	
Rash/itch	0	1 (2%)	
Days to adverse event (mean ± SD)	6.56 ± 1.75	5.57 ± 2.03	0.16

[a]In some patients more than one event occurred.

receiving cefotetan and 6 days for patients receiving clindamycin/amikacin. There was no difference in postoperative febrile days or days in hospital for the two arms of the study.

In the patients receiving cefotetan there were 18 adverse drug events, which occurred in 28% (16 of 58) of patients; and in those who received clindamycin/amikacin, there were 16 events in 26% (14 of 55) of patients (Table 7). Elevated liver function tests accounted for 72% (13 of 18) and 81% (13 of 16) of the events in those receiving cefotetan and clindamycin/amikacin, respectively. PT or PTT prolongation was observed in two patients in each group. No clinically significant increase in serum creatinine or urea nitrogen was noted. Diarrhea occurred in a single cefotetan patient and resolved rapidly with antidiarrheal medication. One patient in each arm had the study antibiotic stopped because of an adverse event: The patient on cefotetan experienced headache with nausea and vomiting; and the patient on clindamycin/amikacin had rash, puritus, shortness of breath, and periorbital edema. The average length of time to the occurrence of adverse events was 6.6 ± 1.8 days in the cefotetan group and 5.6 ± 2.0 days in the clindamycin/amikacin group.

Discussion

Cephalosporins are well established antimicrobials for the treatment of community-acquired intraabdominal infections; yet many surgeons prefer multiple agents, usually combinations of aminoglycosides, antianaerobic agents, and penicillins. This study was designed to evaluate the efficacy of a broad-spectrum, second-generation cephalosporin (cefotetan) versus combination therapy in patients with gangrenous or perforated appendicitis, a moderately severe infection.

Our goal was to look for a difference in postoperative infectious complications between the patients receiving cefotetan and those receiving clindamycin/amikacin for intraabdominal infections where operation is the major component of cure and the use of adjunctive antimicrobials might be simplified. No postoperative infectious complications occurred in patients without perforation. Only one wound infection in the cefotetan group was considered serious enough to necessitate a change in antibiotic therapy. The other wound infections responded to aggressive wound care. Failures in the combination therapy group included a single patient with an intraabdominal abscess, which was treated with percutaneous drainage. Other complications in this group included one wound infection with right-sided cellulitis extending from nipple to thigh; one cecal fistula, which closed without additional therapy; and two patients with prolonged postoperative fever (for 3 days or more). All of the patients with infectious complications in the combination group had their antibiotic coverage changed.

More than 75% of the peritoneal culture specimens from the operative site proved to have multiple microbes. The intraoperative culture results suggested that the antimicrobial agent given preoperatively may affect which bacteria are involved in the intraabdominal infection. There were significantly more cephalosporin-treated patients in whom *Streptococcus* species, not including enterococcus, were isolated (85% versus 38%, $p < 0.01$); whereas significantly more patients receiving clindamycin/amikacin harbored *Clostridium* species (59% versus 24%, $p = 0.01$, according to the initial peritoneal fluid cultures. All other isolates had similar distributions between the two groups. Although these patients received only a single dose of antibiotic prior to surgery—which we speculate would have little effect on the infectious flora in peritoneal fluid—it is of interest to note the absence of coverage for these specific isolates in the two patient groups.

In vitro susceptibility of *B. fragilis* to cefotetan is reported to be ≥87%, and susceptibility of the *B. fragilis* group is 36% to 96% depending on the species and institution [11, 12]. Our results indicate that the organisms of the *B. fragilis* group, other than *B. fragilis,* exhibited resistance to the cephalosporin. In the operative cultures, 56% (24 of 43) of the *B. fragilis* group members were resistant to cefotetan; however, results of postoperative infectious cultures indicate that these organisms are not significant pathogens in this study. In a study of early therapy with cephalosporins (including cefotetan) in a mouse model of intraabdominal infection with *E. coli, B. fragilis,* and *B. thetaiotaomicron,* Brook concluded that antibiotic administration early in the infectious process suppressed the number of bacteria present at the infection site independent of their in vitro susceptibility [13]. Thus the effect of low inoculum could be one explanation for the discrepancy between in vitro susceptibility and in vivo efficacy. Although *Pseudomonas* species isolated in 10 (29%) of the initial cultures were resistant to cefotetan, *P. aeruginosa* was isolated from the wounds of only two patients with postoperative wound infections. More data are needed concerning the relatively high recovery of *Pseudomonas* species in patients with appendicitis (approximately

20%) [14, 15] and the importance of this pathogen in postoperative infections where the operation is the definitive treatment.

The role of enterococci in enterogenous infections continues to be a puzzle [16]. Our results do not indict enterococci as significant pathogens. Enterococci were present in 33% of our patients with positive peritoneal fluid cultures; 76% of these patients had resistant species, yet in only one patient was an enterococcus isolated from a postoperative infection site—even though neither drug regimen has strong coverage for this group of organisms.

Sheikh et al. [17] speculated on several factors that may contribute to the finding that some organisms, though resistant to cefotetan, are not implicated in postoperative infectious complications. Such factors include the synergistic interaction of isolates in mixed infections, an operation that is a curative procedure, and problems with anaerobic susceptibility testing.

In our study, both antimicrobial regimens were given with few adverse events. Serum creatinine and urea nitrogen, monitored throughout the hospital course, provided no evidence of nephrotoxicity in any of the patients. Marginally elevated SGOT, SGPT, and PT, which returned to normal at the end of therapy, occurred in one-fourth of the patients. Gastrointestinal disturbances were infrequent, occurring in 2% of patients. Hence these antimicrobial regimens can be given safely for treatment of appendicitis, with no difference in the two regimens in regard to adverse effects.

This study demonstrates the importance of conducting clinical trials in a blinded fashion in order to prevent bias toward one of the treatment modalities. In five patients receiving clindamycin/amikacin the study antibiotic was discontinued and therapy changed to other antibiotics, whereas only one patient receiving cefotetan had a change in study antibiotic. Had our study been conducted as an open comparison, we speculate that the outcome for this variable would probably have been quite different, as surgeons, influenced by the broader in vitro spectrum of the two-antibiotic regimen, would probably have favored the maximum combination therapy.

Beyond the issues of nephrotoxicity and ototoxicity, which were not factors in this study, the problems with aminoglycoside therapy are twofold. First, there may be a delay in achieving therapeutic serum levels; and although the amikacin levels in this study reached an average peak serum level of 28 μg/ml within 48 hours, several patients had much lower peaks, and the average trough level was 2.5 μg/ml. Second, obtaining adequate monitoring on a timely basis can be difficult. Of the 55 patients receiving clindamycin/amikacin, in only 51% were blood samples obtained owing to the difficulty of obtaining them on weekends, holidays, and in the evening.

Antimicrobial agents represent the single largest expense of any drug group, typically accounting for 20% to 40% of a hospital's drug budget [18]. Rapp et al. [19] reported that monotherapy with cephalosporins was less expensive than combination therapy that included gentamicin. Sochalski et al. [20] demonstrated an approximately 40% decrease in cost per day for twice-daily cefotetan monotherapy compared to a regimen of ampicillin/aminoglycoside/clindamycin, without incorporating the costs associated with monitoring serum creatinine and aminoglycoside levels. Twice-daily dosing with a single drug reduces the pharmacy and nursing costs; and the safety profile of cephalosporins eliminates the expense of monitoring renal function and serum drug levels, which is necessary with combination therapy.

When selecting antimicrobial therapy for surgical infections, surgeons should rely on the outcome data from clinical trials.

Résumé

Bien qu'un seul antibiotique avec un large spectre couvrant les germes aérobies et anaérobies soit reconnu comme efficace dans l'appendicite, beaucoup de chirurgiens continuent d'utiliser une polyantibiothérapie. Dans un essai contrôlé en double aveugle, nous avons testé la corrélation clinique avec la sensibilité in vitro d'une association de plusieurs antibiotiques comme traitement complémentaire chez 114 patients ayant eu une appendicite compliquée. Quatre-vingt pour-cent (36/40) des patients ayant eu du céfotétan et 86% (31/36) des patients ayant eu l'association clindamycine/amikacine n'ont pas eu de complications infectieuses postopératoires ($p = 0.11$). Il a été nécessaire de changer les antibiotiques en raison d'une complication postopératoire plus souvent chez les patients ayant eu l'association clindamycine/amikacine, (5 (12%) comparé à 1 (2%)) dans le groupe céfotétan ($p = 0.07$). On a identifié des organismes *Bacteroides fragilis* résistants au céfotétane mais aucun n'était responsable d'infection postopératoire. Il y a eu des effets secondaires non désirables, essentiellement une perturbation des tests de la fonction hépatique, chez 28% et chez 26% des patients ayant pris respectivement du céfotétane et l'association clindamycine/amikacine, respectivement. Une monothérapie avec une céphalosporine de deuxième génération du type céfotétan, donnée deux fois par jour, est efficace et économique dans le traitement de l'appendicite compliquée mais opéréc. Les aminosides et les autres antibiotiques plus puissants doivent être réservés pour les germes résistants ou les infections nosocomiales.

Resumen

Aunque los antibióticos únicos de amplio espectro de cobertura aeróbica y anaeróbica son eficaces en la apendicitis, muchos cirujanos continúan utilizando agentes múltiples. Se diseñó un ensayo clínico prospectivo, doble ciego y aleatorizado con el fin de correlacionar la susceptibilidad in vitro de agentes antimicrobianos múltiples como terapia adyuvante en el manejo de 114 pacientes sometidos a operación por apendicitis complicada. 90% (36/40) de los pacientes en el Grupo de cefotetan y 86% (31/36) en el Grupo que recibió clindamicina/amikacina tuvieron resolución clínica de sus infecciones intraabdominales sin recurrencia de complicaciones sépticas postoperatorias ($P = 0.11$). El número de pacientes que tuvieron cambio en la terapia antibiótica por complicaciones postoperatorias fue más alto en el Grupo clindamicina/amikacina, 5 (12%) comparados con 1 (2%) en el Grupo cefotetan ($P = 0.07$). Aunque se identificaron microorganismos del Grupo de los *Bacteroides fragilis* resistentes a cefotetan, ninguno fue responsable de infecciones postoperatorias. Se presentaron reacciones farmacológicas adversas en 28% del Grupo cefotetan y en 26% del Grupo clindamicina/amikacina, las cuales consistieron primordialmente en elevaciones pasajeras de los valores de las pruebas de función hepática. La monoterapia con una cefalosporina de amplio espectro de segunda generación, tal como el cefotetan, administrado en dos dosis diarias constituye un régimen económico y eficaz en la apendicitis complicada en la cual la cirugía representa el tratamiento definitivo. Los aminoglucósidos y otros agentes antimicrobianos más potentes deben ser

reservados para el tratamiento de infecciones nosocomiales por microorganismos resistentes.

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Invited Commentary

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Hopkins et al. have conducted an interesting and highly useful study of adjunctive antimicrobial therapy for complicated appendicitis. Their thesis is that single-drug, broad-spectrum coverage is as efficacious as the use of combination antibiotic use. In fact, their use of the phrase "overkill" to describe their view of multiple antibiotic use in such patients is more than apt. This is an area, and a thesis, that has been propounded before by several investigators. The publication of additional studies is not without merit, however, because it is obvious that physicians' treatment patterns remain, for the most part, unchanged.

This prospective, randomized trial has both clinical and theoretic goals. First, patient outcomes are compared. Did one of the antibiotic regimens result in fewer patient complications? Which regimen cost more? Bacteriology of peritoneal cavity cultures, as well as of wounds and blood where appropriate, were also compared. Thus data speaking to several differing issues are available.

In my view, it is not at all surprising that no difference was found in any of the parameters of clinical outcome between the group receiving cefotetan versus those administered the clindamycin/amikacin combination. The congruency of outcomes was noted in mortality, wound failure, days given the antibiotic(s), hospital stay, or days patients had fever. Of most importance, there were no deaths in either group, and the rate of reoperative intervention was both minimal and not significantly different between the treatment groups. This result speaks to the efficacy of prompt, well planned operative procedures *along with* the use of antibiotics started preoperatively. Such data underline the secondary role of choosing the broad-spectrum antibiotic regimen.

The analysis of the patients' bacteriology in both treatment groups yielded some interesting data. There were quite a few patients whose peritoneal cultures yielded organisms not susceptible to the specific antibiotic regimen given. These organisms included *Bacteroides* species, *Pseudomonas* species, *Clostridium* species, and enterococcus. Despite these findings, only a handful developed wound complications related to these pathogens. Once again, it is obvious—at least to this observer—that the choice of antibiotic plays a secondary role in patient management.

In summary, I believe that this study, along with others that have preceded it, show conclusively that expensive multidrug therapy for complicated appendicitis adds significant incremental costs without resulting in significant clinical benefit. It may be true that the inability to show any significant differences might be due to a type II error that would be corrected by carrying out a study based on thousands of patients. However, in practical terms of a given surgeon's experience, such *statistical* differences would, if found, mean little. Thus I believe that the standard for treatment of complicated appendicitis should include a timely and appropriate operation along with the administration (begun preoperatively) of a single broad-spectrum second-generation cephalosporin.