

## Randomized, Prospective, and Double-Blind Trial of New $\beta$ -Lactams in the Treatment of Appendicitis

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**A prospective, randomized, and double-blind study was conducted with 864 patients operated on for appendicitis. In early cases, including normal and acute appendicitis, one dose of antibiotic was given. The rate of postappendectomy septic complications in patients who received cefotaxime, cefoperazone, or moxalactam was very low (about 3%), and there was no statistical difference between the drugs. For late cases, including gangrenous and perforated appendicitis, the antibiotics were continued for 5 days. Moxalactam decreased significantly the septic complications in these patients when compared with the other two drugs. It is safe, free from serious toxic side effects, and more convenient and easier to administer than combination antibiotic therapy. The main disadvantage of moxalactam is its high cost, but this has to be balanced against the savings in nursing time, the cost of monitoring renal function and serum level when aminoglycosides are used, and the reduced usage and manipulation of infusion sets.**

The incidence of sepsis after appendectomy increases as appendicitis progresses (3, 15, 20), and it is more than 50% in perforated cases (11, 15). Systemic antibiotics have been widely used to decrease wound and intraperitoneal sepsis (10). The choice of antibiotics is, however, still controversial (10). Evidence is now accumulating that antibiotics directed against both aerobes and anaerobes are more effective than antibiotics directed against either type of organism alone (7, 18, 26).

With the introduction of the new cephalosporins, a single agent can now be used against the bacteria commonly encountered in appendicitis. In *in vitro* bacteriological sensitivity studies on bacteria isolated from appendicitis, cefotaxime, cefoperazone, and moxalactam compared favorably with combination drugs such as aminoglycosides and metronidazole (19). In *in vivo* appendectomy studies, they also are very effective (2, 17, 28). They are safe and free from serious toxic side effects (8, 27) and are more convenient and easier to administer than combination therapy (28). Because the costs, antimicrobial activities, pharmacokinetics, and degree of penetration into peritoneal fluid differ quite significantly among these three cephalosporins (32), a randomized trial was conducted to compare their effectiveness in appendicitis.

### MATERIALS AND METHODS

All patients admitted to the Government Surgical Unit, Queen Mary Hospital, Hong Kong, between September 1982 and August 1984 and undergoing appendectomy through a gridiron incision were included in this study. During this period, 22 such patients were not included, 18 because they had received other antibiotics before admission, 2 because of pregnancy, and 2 because of a history of sensitivity to cephalosporins.

The patients were randomly allocated into three groups after informed consents were obtained. One group received cefotaxime, one group received cefoperazone, and one group received moxalactam. A sample size was determined at the beginning of the trial, and the treatment codes were

not broken until the results were analyzed. A sealed envelope contained the random code number which defined the antibiotic group. The antibiotic was given to the patient intravenously just before the operation. Because the antibiotics were contained in identical bottles, the surgeon had no idea what antibiotic the patient had received. If the appendix was normal or acutely inflamed, no further antibiotic was given. If the appendix was gangrenous or perforated or if there was an abscess, the antibiotic was continued for 5 days. The dose of antibiotic was 1 gm intravenously every 8 h. Appropriately reduced doses of 25 mg/kg of body weight were administered to 86 children under 12 years of age. The drugs used in this study were provided by Hoechst-Roussel Pharmaceuticals, Inc. (Somerville, N.Y.), Pfizer Inc. (New York, N.Y.), and Eli Lilly & Co. (Indianapolis, Ind.).

Appendectomies were performed in the usual manner. A drain was used only in patients with an abscess, and it was brought out through a separate incision some distance away from the main wound. In 161 patients, a detailed bacteriological study was performed, including aerobic and anaerobic cultures from the blood, appendicular lumen, mucosa, serosa, fossa, and the wound after closure of the peritoneum (19). For the rest of the patients, only fossa swabs were taken for aerobic and anaerobic cultures by using the Culturette and Anaerobic Culturette manufactured by Marion Scientific, Div. Marion Laboratories, Inc. (Kansas City, Mo.). The specimens were sent to the laboratory for plating and culture as soon as possible. All resected specimens were sent to the laboratory for histological section.

The patients were routinely examined before being discharged from the hospital and during follow-up visits at 2 and 6 weeks after the operation. All patients with suspicion of postappendectomy sepsis were evaluated by one independent assessor.

Postappendectomy sepsis includes wound infection, intraperitoneal abscess, and clinical sepsis which were defined as follows.

**Wound sepsis.** We used the criteria of Ljungqvist (23) for wound sepsis, based on the clinical appearance of the wounds combined with the results of culture to determine

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whether the wounds were infected or clean. Wounds with purulent discharge and wounds with serous discharge which gave positive bacteriological cultures were classified as infected. Also included as infected were wounds with serous discharge after the patients had returned home. Because the patients had left the hospital, cultures could not be taken.

**Intraperitoneal abscess.** The diagnosis of intraperitoneal abscess was made by (i) laparotomy, (ii) discharge of a pelvic abscess per rectum, and (iii) ultrasound and clinical evidence of an abscess.

**Clinical sepsis.** Clinical sepsis was defined as persistent pyrexia postoperatively with a daily peak temperature over 38°C for at least 5 days. A specific septic focus could not be identified as the response clinically to a change of antibiotics.

## RESULTS

Of the 872 patients who were entered into this trial, 289 received cefotaxime, 285 received cefoperazone, 290 received moxalactam, and 8 were excluded from the study. (In the latter group, three patients [including one with serious antibiotic dosing errors, one with incomplete follow-up, and one with Meckel's diverticulitis] received cefotaxime, four patients [including one with serious antibiotic dosing errors, one with carcinoma of the colon, one with a tubo-ovarian abscess, and one with pelvic infection] received cefoperazone, and one patient [with incomplete follow-up] received moxalactam.)

The incidence of sepsis after appendectomy is shown in Table 1. In early appendicitis, the sepsis rate was very low in each of the three groups (about 3%), and there was no statistical difference between them. For late appendicitis, moxalactam reduced significantly postoperative sepsis when compared with cefotaxime or cefoperazone.

The various types of postappendectomy sepsis are shown in Table 2. Wound sepsis was the commonest infection. Intraperitoneal abscess and clinical sepsis were uncommon, but additional antibiotics, which consisted usually of an aminoglycoside and metronidazole, were required in all these patients, and reoperation had to be done in the four patients with intraperitoneal abscesses.

All intraperitoneal abscesses and clinical sepsis presented with fever soon after surgery. The presentation of wound sepsis, however, could be early (before 7 days) or delayed (after 7 days). Delayed wound infection occurred in 21 of 46 patients with wound sepsis (45.6%). This percentage was

TABLE 1. Postoperative sepsis in relation to degree of appendicitis

Type and degree of appendicitis	No. of patients/no. infected (% infected) <sup>a</sup> given the following drug:		
	Cefotaxime	Cefoperazone	Moxalactam
Early	212/6 (2.8)	207/4 (1.9)	215/7 (3.3)
Normal	29/	25/	28/
Acutely inflamed	183/6	182/4	187/7
Late	77/18 (23.4)	78/16 (20.5)	75/6 (8)
Gangrenous	16/3	15/3	18/2
Perforated	53/12	53/11	50/3
Abscessed	8/3	10/2	7/1

<sup>a</sup> Total percent infected was 8.3, 7, and 4.5 for patients taking cefotaxime, cefoperazone, and moxalactam, respectively. Differences were not statistically significant by corrected chi-squares, except for late cases ( $P < 0.05$  for cefotaxime:moxalactam [ $\chi^2 = 5.65$ ]) and late cases ( $P < 0.02$  for cefoperazone:moxalactam [ $\chi^2 = 3.90$ ]).

TABLE 2. Types of postappendectomy sepsis

Type of case and sepsis	No. of patients given the following drug:		
	Cefotaxime	Cefoperazone	Moxalactam
Early			
Wound infection	6	4	6
Intraperitoneal abscess			
Clinical			1
Late			
Wound infection	14	12	4
Intraperitoneal abscess	1	2	1
Clinical	3	2	1

roughly the same in patients who received any of the antibiotic regimens in this study (Table 3). Thus, about half of the cases of wound infection were detected after the patients had returned home. In the cases of early wound sepsis, the infections were all deep. In 6 of 21 cases of delayed wound sepsis, the infections were superficial, and they all healed with dressings alone. All cases of early or delayed deep wound sepsis required secondary suturing.

Routinely, aerobic and anaerobic cultures were taken from the appendicular fossa during the operation. Positive cultures were obtained from 274 patients (31.7%), and pure growth of bacteria occurred in 131 patient cultures (15.2%). A positive culture increased the risk of postappendectomy sepsis. When a mixed growth of aerobes and anaerobes was isolated, the subsequent sepsis was 26.7, 21.3, and 9.8% for patients who received cefotaxime, cefoperazone, and moxalactam, respectively. The corresponding figures fell to 8.5, 9.8, and 4.7%, respectively, when the isolates were pure aerobes or pure anaerobes, and they further fell to 4, 3, and 3%, respectively, when no organisms were isolated. The commonest organisms isolated from the appendicular fossa swabs, infected wounds, or intraperitoneal abscesses were *Escherichia coli* and *Bacteroides fragilis* in either pure or mixed growth.

With the standardized single disk susceptibility test (1), almost all aerobes isolated (with the exception of *Pseudomonas aeruginosa* and *Streptococcus faecalis* which were only occasionally isolated) were susceptible to cefotaxime, cefoperazone, and moxalactam. When the agar diffusion (disk) test for anaerobes (29) was used, only 51.6, 62.8, and 73.1% of *B. fragilis* isolated was susceptible to cefotaxime, cefoperazone, and moxalactam, respectively.

## DISCUSSION

The use of systemic antibiotics in gangrenous and perforated appendices is a widely accepted practice (6). However, its use in normal and acute nonperforating appendices is still questioned (14). Several studies have clearly documented

TABLE 3. Early and delayed wound sepsis

Type of wound sepsis (% of patients)	No. of patients given the following drug:		
	Cefotaxime	Cefoperazone	Moxalactam
Early (<7 days)			
Deep (54.4)	11	9	5
Superficial			
Delayed (>7 days)			
Deep (32.6)	7	4	4
Superficial (13)	2	3	1

infective complications after normal appendectomy (12, 22, 24), and these include not only wound infections but also occasional pelvic abscesses (6). Moreover, many antibiotics are effective in decreasing postoperative sepsis when compared with placebos in acute nonperforating appendicitis (5, 13, 31). Thus, it seems logical to give systemic antibiotics to all patients with appendicitis.

Systemic antibiotics should be given before or at least during operations (10). The efficacy of the antibiotics has been shown to be greatest if they are in the circulation when the bacteria lodge in the tissues. Efficacy decreases progressively until the antibiotics become of no real value when started 3 h thereafter (4, 25). A single dose of antibiotic is effective (11, 16, 21), especially in early appendicitis with little peritoneal contamination. In late appendicitis with severe peritoneal soiling, the antibiotics should be continued for a full course.

The choice of antibiotics is still controversial (10). Antibiotics directed against aerobes and anaerobes are more effective than antibiotics directed against either organism alone (7, 18, 26). Cefotaxime, cefoperazone, and moxalactam have the broad antibacterial activity of the combination therapy of an aminoglycoside and clindamycin or metronidazole, but they have much lower nephrotoxicity and ototoxicity (8, 27). In *in vitro* bacteriological studies on bacteria commonly isolated from appendicitis (19) and in *in vivo* appendectomy studies, they are effective (2, 17, 28). They are more convenient to use and easier to administer and do not require the frequent intravenous infusions of combination therapy.

In our study, cefotaxime, cefoperazone, and moxalactam were all very effective in decreasing septic complications of early appendicitis to about 3%. In gangrenous and perforated appendices, moxalactam was more effective than cefoperazone and cefotaxime. This was probably owing to the greater effectiveness of moxalactam against *B. fragilis*, which is very commonly isolated in late cases (19, 22). There are few antibiotic regimens that can reduce the incidence of postoperative sepsis in perforated appendicitis to less than 25%, and there are even fewer regimes that can reduce it to less than 10% (9). The rate of postappendectomy septic complication for perforated appendicitis was 24.6, 20.6, and 7% for cefotaxime, cefoperazone, and moxalactam, respectively, in this study.

The main disadvantages of moxalactam are its high cost and its reported side effects of bleeding owing to hypoprothrombinemia and platelet dysfunction (30). The high cost of moxalactam has to be balanced against the savings in nursing time, the cost of monitoring of renal function and serum level when aminoglycosides are used, and the reduced usage and manipulation of infusion sets. Such savings are especially marked when a complete course of the drug is used therapeutically for gangrenous and perforated appendicitis, whereas it is small and unimportant when only one prophylactic dose is used for early cases. The side effects of moxalactam are minimal, and we did not encounter any bleeding diathesis in our cases. Because of its effectiveness, we recommend its use in appendicitis, especially in late cases with severe peritoneal soiling and when the use of aminoglycosides has to be avoided.

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