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Name	Inselspital Bern
Kunden Adresse	Gastroenterologie Zbinden Marie-Louise, Postfach 19 B84053
Benutzer_Nr.	marie-louise.zbinden@insel.ch
E-Mail-Adresse	2011-09-01 14:56:02
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## UNIDENTIFIED CURVED BACILLI IN THE STOMACH OF PATIENTS WITH GASTRITIS AND PEPTIC ULCERATION\*

BARRY J. MARSHALL                      J. ROBIN WARREN

*Departments of Gastroenterology and Pathology,  
Royal Perth Hospital, Perth, Western Australia*

**Summary** Biopsy specimens were taken from intact areas of antral mucosa in 100 consecutive consenting patients presenting for gastroscopy. Spiral or curved bacilli were demonstrated in specimens from 58 patients. Bacilli cultured from 11 of these biopsies were gram-negative, flagellate, and microaerophilic and appeared to be a new species related to the genus *Campylobacter*. The bacteria were present in almost all patients with active chronic gastritis, duodenal ulcer, or gastric ulcer and thus may be an important factor in the aetiology of these diseases.

### Introduction

GASTRIC spiral bacteria have been repeatedly observed, reported, and then forgotten for at least 45 years.<sup>1-3</sup> In 1940 Freedburg and Barron stated that "spirochaetes" could be found in up to 37% of gastrectomy specimens,<sup>4</sup> but examination of gastric suction biopsy material failed to confirm these findings.<sup>5</sup> The advent of fiberoptic biopsy techniques permitted biopsy of the antrum, and in 1975 Steer and Colin-Jones observed gram-negative bacilli in 80% of patients with gastric ulcer.<sup>6</sup> The curved bacilli they illustrated were said to be *Pseudomonas*, possibly a contaminant, and the bacteria were once more forgotten. The repeated demonstration of these bacteria in inflamed gastric antral mucosa<sup>7</sup> prompted us to do a pilot study in twenty patients. Typical curved bacilli were present in over half the biopsy specimens and the number of bacteria was closely related to the severity of the gastritis. The present study was designed to confirm the association between antral gastritis and the bacteria, to discover associated gastrointestinal diseases, to culture and identify the bacteria, and to find factors predisposing to infection.

\*Based on paper read at Second International Workshop on Campylobacter Infections (Brussels, 1983).

## Patients and Methods

### Patients

All patients referred for gastroscopy on clinical grounds were eligible for the study which continued until there were 100 participants who gave informed consent and in whom biopsy was considered to be safe. The study was approved by our hospital's human rights committee.

### Questionnaire

Where possible patients completed a clinical questionnaire designed to detect a source of infection or show any relationship with "known" causes of gastritis or *Campylobacter* infection, rather than give a detailed account of each patient's history. The emphasis was on animal contact, travel, diet, dental hygiene, and drugs, rather than symptoms.

### Endoscopy

The gastroscopies were done by colleagues at the Royal Perth Hospital. Participants fasted for at least 4 h before endoscopy. An Olympus GIF-K fiberoptic gastroduodenoscope was used. Routine biopsies were done when indicated. For the study two extra specimens were taken from an area of intact antral mucosa, at a distance from any focal lesion such as an antral ulcer. When the mucosa appeared inflamed the specimens were taken from a red area, otherwise any part of the antrum was used. One biopsy was immediately fixed in phosphate-buffered formalin for histological examination, the other was placed in chilled anaerobic transport medium and taken to the microbiology laboratory within 1 h. In a few cases an extra specimen was taken for ultrastructural examination.

The gastroenterologist dictated his report soon after the endoscopy. We had not planned to analyse these reports so a standard terminology was not used and no special attention was paid to minor endoscopic lesions. Findings of doubtful clinical significance, such as mild endoscopic gastritis or duodenogastric bile reflux, may thus have been under-reported. (Hereafter the term "gastritis" refers to a histological grade of chronic gastritis unless stated otherwise.) Before we analysed the data, the endoscopy reports were coded for the major diagnoses.

### Histopathology

Sections were stained with haematoxylin and eosin (H & E) and graded for gastritis (by J. R. W.) as 0 (normal), inflammatory cells rarely seen; 1 (normal), lymphoid cells present but within normal limits and with no other evidence of inflammation (see below); 2 (chronic), chronic gastritis; or 3 (active), active chronic gastritis.

Gradings were based solely on the type of inflammatory cells. Other types of mucosal change, such as gland atrophy or intestinal metaplasia, were noted separately, but were not used as evidence of inflammation. "Chronic gastritis" indicated inflammation with no increase in polymorphonuclear leucocytes (PMNs). There were either increased numbers of lymphoid cells or normal cell numbers with other evidence of inflammation such as oedema, congestion, or cell damage. The term "active" was used to indicate an increase in PMNs.<sup>8</sup> The gastritis was considered active if a few PMNs infiltrated one gland neck or pit, if occasional PMNs were scattered throughout the superficial epithelium, or if there was an obvious increase in PMNs in the lamina propria.

Later, sections stained with Warthin-Starry silver stain were examined for small curved bacilli on the surface epithelium. Numbers of bacteria were graded as 0, no characteristic bacteria; 1, occasional spiral bacteria found after searching; 2, scattered bacteria in most high-power fields or occasional groups of numerous bacteria; or 3, numerous bacteria in most high-power fields.

### Microbiology

Tissue smears were Gram stained and examined for curved bacilli resembling *Campylobacter*. The remaining tissue was minced, plated on non-selective blood and chocolate agar, and cultured at 37°C under microaerophilic conditions as used for *Campylobacter* isolation.<sup>9</sup> At first plates were discarded after 2 days but when the first positive plate was noted after it had been left in the incubator for 6 days during the Easter holiday, cultures were done for 4 days.

### Analysis of Results

Questionnaires, gastroscopy reports, and histopathology and microbiology results were coded independently in separate departments. Complete results for individual patients were not known until the statistician had received all the data. The findings were tested for positive correlation with the presence of either bacteria or gastritis, by the chi-squared method. Fisher's exact test of significance was used for all the 2 × 2 tables in this paper.

## Results

In 12 weeks 184 patients were examined by the gastroenterology unit. Of the 84 patients excluded, 5 refused consent, 4 had contraindications to biopsy, and 75 patients, mostly unbooked cases, could not be invited to participate. These patients closely matched the study group for age, sex, and incidence of peptic ulcers (table I).

### Questionnaires

99 patients completed the questionnaires. The only symptom which correlated with gastritis or bacteria was "burping" which was more common in patients with bacteria ( $p=0.03$ ) or gastritis ( $p=0.007$ ). This association remained when patients with peptic ulcer were excluded. None of the other questionnaire responses showed any relationship to the presence of gastric bacteria or gastritis.

### Endoscopy

There was a very close correlation between both gastric ulcer and duodenal ulcer and the presence of the bacteria (table II). Most patients with peptic ulcer also had gastritis (29/31;  $p=0.0002$ ).

TABLE I—COMPARISON OF PARTICIPANTS WITH EXCLUDED PATIENTS

	Study group (n = 100)	Exclusions (n = 84)
Mean age (range)	55 (20–88) yr	57 (18–88) yr
Males	63 (63%)	55 (65%)
Females	37 (37%)	29 (35%)
Gastric ulcer	22 (22%)	19 (23%)
Duodenal ulcer	13 (13%)	8 (10%)

TABLE II—ASSOCIATION OF BACTERIA WITH ENDOSCOPIC DIAGNOSES

Endoscopic appearance*	Total	With bacteria	p
Gastric ulcer	22	18 (77%)	0.0086
Duodenal ulcer	13	13 (100%)	0.00041
All ulcers	31	27 (87%)	0.0005
Oesophagus abnormal	34	14 (41%)	0.996
Gastritis†	42	23 (55%)	0.78
Duodenitis†	17	9 (53%)	0.77
Bile in stomach	12	7 (58%)	0.62
Normal	16	8 (50%)	0.84
Total	100	58 (58%)	

\*More than one description applies to several patients (eg, 4 patients had both gastric and duodenal ulcers).

†Refers to endoscopic appearance, not histological inflammation.

TABLE III—HISTOLOGICAL GRADING OF GASTRITIS AND BACTERIA

Gastritis	Bacterial grade				Total
	Nil	1+	2+	3+	
Normal*	29	2	0	0	31
Chronic	12†	9	7	1	29
Active	2	5	15	18	40
Total	43	16	22	19	100

\*Gastritis grades 0 and 1 normal.

†1 case showed bacteria on gram stained smear.

TABLE IV—RELATION BETWEEN GASTRITIS AND BACTERIA IN PATIENTS WITHOUT PEPTIC ULCER

Gastritis	Bacteria			Total
	No	Yes	Total	
Normal	28	1	29	
Chronic	8	12	20	
Active	2	18	20	
Total	38	31	69	

### Histopathology

Gastritis could usually be graded with confidence at low magnification. There was some difficulty with about 25 cases where the changes were mild or the specimens were small, superficial, or distorted. To ensure that gradings were reliable, single H & E sections from the last 40 cases were examined "blind" by another pathologist who agreed with the presence or absence of gastritis in 36 cases (90%), and gave an identical grading in 32.

Gradings for bacteria by silver staining were more straightforward. The bacteria stained well and were easily differentiated from contaminant bacteria or debris. Silver staining was the most sensitive method of detecting the spiral bacteria. Silver stained sections and Gram stained smears were both done in 96 cases and spiral bacteria were seen in 56 of them; 32 with both stains, 23 with silver alone, and 1 case with the Gram stain alone.

The correlation between gastritis and bacteria, defined by Gram and/or by silver staining, was remarkable (table III). Gastritis was present in 55/57 biopsy specimens with bacteria ( $p=2 \times 10^{-12}$ ). When the 31 patients with peptic ulcer were excluded, the correlation persisted, implying that the presence of bacteria was not secondary to an ulcer crater (table IV).

### Microbiology

Specimens for culture were received from 96 patients and 11 were culture positive, all being seen with Gram and silver staining also. No spiral bacteria were grown from the first 34 cases, probably because the cultures were discarded too soon.



**Electron micrograph from a mucosal biopsy with active chronic gastritis.**

Upper: many profiles of sectioned pyloric campylobacter are located on the luminal aspect of mucus-secreting epithelial cells; plasma membranes are intact, but indented and almost devoid of microvilli (bar = 1  $\mu$ m).

Lower: at higher magnification groups of transversely and longitudinally cut sheathed flagella are visible (arrows; bar = 100 nm).

The bacteria were S-shaped or curved gram-negative rods, 3  $\mu$ m  $\times$  0.5  $\mu$ m, with up to 1½ wavelengths. In electron micrographs they had smooth coats and there were usually four sheathed flagella arising from one end of the cell. They grew best in a microaerophilic atmosphere at 37°C; a campylobacter gas generating kit was sufficient (Oxoid BR56). Moist chocolate or blood agar was the preferred medium. Growth was evident in 3 days as 1 mm diameter non-pigmented colonies. In artificial media the bacteria were usually larger and less curved than those seen on Gram stains of fresh tissue. They formed coccoid bodies in old cultures. The bacteria were oxidase +, catalase +, H<sub>2</sub>S +, indole -, urease -, nitrate -, and did not ferment glucose. They were sensitive to tetracycline, erythromycin, kanamycin, gentamicin and penicillin, and resistant to nalidixic acid. DNA base analysis gave a guanine + cytosine content of 36 mol%, a value in the range for campylobacters.

**Sources of Bias**

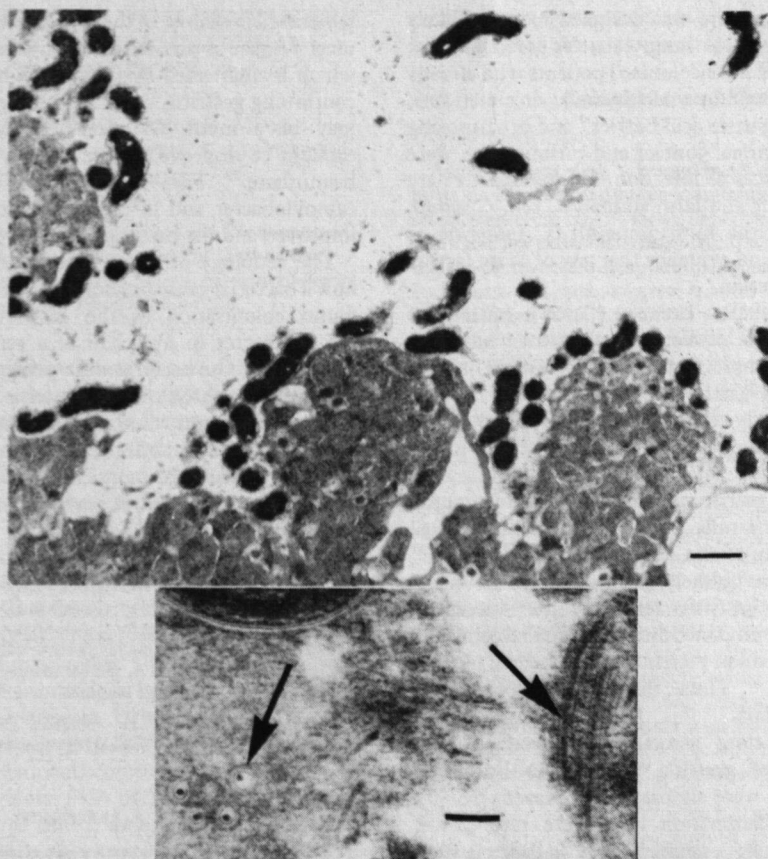
The patient sample was from a defined population with gastric symptoms expected to have some gastroenterological abnormality. The biopsy tissue studied was from apparently intact mucosa—ie, not the sort of specimen a pathologist usually sees. We attempted to limit bias by making the study consecutive and blind, and were partly successful. The study was not strictly consecutive since 84 patients had to be excluded. However, gastroscopy reports and laboratory investigations were completed serially and usually independently (“blind”) except that clinically relevant

material was sent (to J. R. W.) with study biopsies, mainly from cases of gastric ulcer. However, an independent blind assessment of gastritis in 40 cases matched the study results well.

**Discussion**

The spiral bacteria of the human gastric antrum have never been cultured before, and their association with active chronic gastritis has not been described. They are a new species closely resembling campylobacters morphologically and in respect of atmospheric requirements and DNA base composition, but their flagellar morphology is not that of the genus *Campylobacter*.<sup>9</sup> Campylobacters have a single unsheathed flagellum at one or both ends of the cell whereas the new organism has four sheathed flagella at one end.<sup>7,10</sup> If it is premature to talk of “*Campylobacter pyloridis*”<sup>11</sup> perhaps the name “pyloric campylobacter” will do to define the site where these organisms are commonly found and to indicate the similarity to known *Campylobacter* spp.

There was no well-defined clinical syndrome associated with pyloric campylobacter. Only “burping” was significantly associated. Others have described this symptom in patients with non-ulcer dyspepsia and PMN infiltration of the antrum is also common in such patients.<sup>12,13</sup> We expected abdominal pain to correlate with pyloric campylobacter or gastritis, but it did not. Perhaps, since most patients undergoing gastroscopy have pain (75% in our study) the question “Do you have abdominal pain—yes or no?” was too general.



Electron micrograph from a mucosal biopsy with active chronic gastritis.

Upper: many profiles of sectioned pyloric campylobacter are located on the luminal aspect of mucous-secreting epithelial cells; plasma membranes are intact, but indented and almost devoid of microvilli (bar = 1  $\mu$ m).

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Much of the questionnaire was designed to select likely sources or causes of pyloric campylobacter infection. For example, bacteria might have colonised patients who already had gastritis and were taking antacids, milk, or cimetidine, thus impairing their "gastric acid barrier" and predisposing them to infection.<sup>14</sup> Animal contact and carious teeth were also considered as sources of infection. Campylobacters are commensals of domestic and farm animals (*C. coli*, *C. jejuni*), and they also inhabit the human mouth (*C. sputorum* ss *sputorum*).<sup>15</sup> We found no evidence that any of these factors predisposed to the infection.

The absence of a relation between "known causes" of gastritis and the presence of histological gastritis has been noted by others. For example, analgesic abusers often have no gastritis, even when a gastric ulcer is present;<sup>16</sup> alcohol consumption is not clearly related to gastritis;<sup>17</sup> the quantity of bile in the stomach (duodenogastric reflux) is not obviously related to the state of gastric mucosa;<sup>18</sup> autoimmune disease is an unlikely cause, since gastric autoantibodies are uncommon except in pernicious anaemia, where the main histological changes are in the body of the stomach, not the antrum.<sup>19</sup> Gastric ulcer seems an unlikely primary cause of antral gastritis because the gastritis remains after successful treatment of the ulcer with cimetidine or carbenoxolone, and gastritis is just as common in patients with duodenal ulcer as with gastric ulcer.<sup>6,20-23</sup> Thus, the aetiology of chronic gastritis remains uncertain.

We have found a close association between pyloric campylobacter and antral gastritis. When PMN infiltrated the mucosa the bacteria were almost always present (38/40). In the absence of inflammation they were rare (2/31), suggesting that they are not commensals. The bacteria were not cultured unless the patient had histological evidence of both gastritis and pyloric campylobacter. We know of no other disease state where, in the absence of complicating factors such as ulceration (table IV), bacteria and PMNs are so intimately related without the bacteria being pathogenic.

How does pyloric campylobacter survive? The bacteria were usually in close contact with the mucosa, often in grooves between cells, within acinus-like infoldings of the epithelium or within the mucosal pits (figure). The surface mucus coating was superficial to the bacteria and any foreign material or organisms from the oral flora were present above the mucus, rarely mixed with it, and not beneath it: the mucus appeared to form a stable layer over the spiral bacteria. The antrum secretes mainly mucus, and the deeper levels of the surface mucus coating are slightly alkaline.<sup>24</sup> Thus pyloric campylobacter grows in a near-neutral environment, in close contact with the mucosa and protected from the bactericidal gastric juice. The absence of these bacteria from past reports of gastric microbiology may be because only gastric juice was cultured.<sup>25,26</sup> Even salmonellae cannot survive the low intragastric pH for more than a few minutes.<sup>14</sup> Where gastric biopsy material has been cultured,<sup>6,27,28</sup> microaerophilic techniques were not used and pyloric campylobacter did not grow.

Peptic ulcer was the only endoscopic finding associated with histological gastritis and pyloric campylobacter. This was surprising since the bacteria were not prominent on gastric ulcer borders and in duodenal ulcer no correlation would be expected. Perhaps the mucus coating is deficient or unstable near ulcer borders, thus allowing damage to the bacteria as well as the mucosa. Within a few millimetres of an ulcer, both pyloric campylobacter and gastritis were usually present. Other studies have shown continuing gastritis after ulcer healing with cimetidine and we have observed the persistence of pyloric campylobacter colonisation in such

patients. The failure of the H<sub>2</sub> receptor antagonists to prevent ulcer relapse is attributed to an underlying ulcer diathesis which is unaffected by therapy. A bacterial aetiology, with continuing gastritis, could be the explanation. The diathesis may be a myth. Of ulcer-healing agents the only one thought to improve relapse rates is tripotassium dicitrate-bismuthate.<sup>29</sup> This compound is bactericidal to pyloric campylobacter and in patients treated with it the gastritis improved and the bacteria disappeared.<sup>30</sup>

The aetiology of peptic ulceration is unknown but until now a bacterial cause has not really been considered. We have found colonisation of the gastric antrum with pyloric campylobacter in over half of a series of cases at routine endoscopy. The bacteria were present almost exclusively in patients with chronic antral gastritis and were also common in those with peptic ulceration of the stomach or duodenum. Although cause-and-effect cannot be proved in a study of this kind, we believe that pyloric campylobacter is aetiological related to chronic antral gastritis and, probably, to peptic ulceration also.

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Correspondence should be addressed to: B. M., Department of Microbiology, Fremantle Hospital, PO Box 480, Fremantle 6160, Western Australia.

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## AZTREONAM COMPARED WITH GENTAMICIN FOR TREATMENT OF SERIOUS URINARY TRACT INFECTIONS

FRED R. SATTLER                      JAMES E. MOYER  
MARGARET SCHRAMM                JEFFREY S. LOMBARD  
PETER C. APPELBAUM

*Division of Infectious Diseases and Epidemiology, Department of Medicine, Division of Urology, Department of Surgery, and Department of Pathology, Pennsylvania State University College of Medicine, Hershey, Pennsylvania USA*

**Summary** 52 patients with serious urinary tract infections were randomised to receive either aztreonam (35) or gentamicin (17). In the aztreonam group 23 patients had unqualified cures, 6 cures with relapse, and 6 cures with reinfection; the comparable numbers in the gentamicin group were 9, 1, and 4. There were no failures with aztreonam and 3 with gentamicin. The most important determinant of outcome was the presence or absence of urological abnormalities. 11 further patients, with renal failure or gentamicin-resistant isolates, treated with aztreonam were all cured. Toxic effects were limited to symptomless liver-function-test abnormalities with aztreonam, whereas deterioration in renal function occurred in 4 gentamicin-treated subjects. Urinary colonisation with group D streptococci occurred in 14 of 46 aztreonam-treated patients (1 required treatment) compared with only 1 of 17 gentamicin-treated patients. 97% of 309 consecutive gram-negative urinary isolates tested, including 50 *Pseudomonas aeruginosa*, were susceptible in vitro to aztreonam and 91% to gentamicin. Aztreonam may prove an effective and safe alternative to the aminoglycosides.

### Introduction

AZTREONAM is the first of a class of synthetic antimicrobials called monobactams. These are monocyclic  $\beta$ -lactam drugs that lack the two-ring configuration of penicillin and cephalosporin molecules. In vitro aztreonam inhibits the growth of most Enterobacteriaceae, including multiply drug resistant strains of *Serratia marcescens*, at concentrations of 2  $\mu$ g/ml or less.<sup>1-3</sup> Moreover, more than 90% of *Pseudomonas aeruginosa* isolates are inhibited by concentrations of 16  $\mu$ g/ml and less.<sup>1-3</sup> In human beings, 1 or 2 g given intravenously produces serum concentrations of at least 100–200  $\mu$ g/ml.<sup>4,5</sup> In addition, the serum half-life of approximately 2 h is suitable for a dose interval of 8 or 12 h.<sup>4,5</sup> These in-vitro and pharmacological properties suggest that aztreonam has the potential to replace the aminoglycosides for therapy of gram-negative infections. We have compared aztreonam with

gentamicin in the treatment of serious urinary tract infections in patients requiring parenteral therapy.

### Patients and Methods

#### Comparative Study

Adult patients with a presumptive diagnosis of urinary tract infection who required systemic antibiotic therapy were eligible for study. Minimum criteria for enrolment included: fever  $\geq 37.8^\circ\text{C}$  or signs and symptoms of urinary tract infection;  $\geq 10$  leucocytes per high power field of urinary sediment; and microscopic evidence of bacteriuria ( $\geq 1$  gram-negative rod/oil immersion field in fresh uncentrifuged urine or bacteria too numerous to count per high power field in unstained sediment of fresh urine collected by clean catch or catheterisation). Patients who had had an indwelling Foley catheter or nephrostomy tube in the preceding 48 h were excluded. All patients gave informed consent.

A pharmacist assigned the enrolled patients to receive aztreonam (1 g every 8 h) or gentamicin (1 mg/kg every 8 h) in a 2:1 manner according to a table of random numbers. If bacteraemia was suspected the doses were increased to 2 g and 1.7 mg/kg, respectively. In patients with creatinine clearances below 30 ml/min, the dose of aztreonam was halved and that of gentamicin was changed according to serum drug levels. Both drugs were given by intravenous infusion over 20–30 min or intramuscularly if there was inadequate venous access; the two routes of administration give similar areas under the serum concentration curve and the proportions in the two groups receiving the drugs intramuscularly were similar. Treatment was continued for 5–10 days in uncomplicated cases. Patients with bacteraemia were treated for 10–14 days. Treatment was discontinued if pretreatment urine cultures did not grow  $\geq 10^5$  gram-negative organisms/ml.

#### Open Study

Other patients were treated with aztreonam in an open, unrandomised way if their infecting organisms were known to be resistant to gentamicin or if they had renal failure (creatinine clearance  $< 50$  ml/min). Enrolment, treatment, and follow-up evaluation were otherwise carried out as in the comparative study.

#### Laboratory Studies

Urine was collected for culture and sensitivity testing<sup>6</sup> before treatment, after 2–4 days of treatment, and at the end. Test-of-cure cultures were obtained 5–9 days and 4–6 weeks after the last day of treatment. Blood samples for cultures were collected before treatment and, if positive, after 24–48 h of treatment, and 24 h after the completion of treatment. Haematology and chemistry test results were monitored for drug-related toxic reactions. These tests were done before the study, every 3–5 days during treatment, and on the last day of treatment.

#### Definitions of Outcome

**Unqualified cure.**—Urine cultures were sterile at the completion of treatment and 5–9 days and 4–6 weeks later.

**Cure with relapse.**—Urine cultures at the end of treatment and 5–9 days later were sterile but those at 4–6 weeks grew  $\geq 10^5$  colony-forming units/ml (cfu/ml) of the original infecting organism.

**Cure with reinfection.**—Urine cultures at the end of treatment and 5–9 days later were sterile but those at 4–6 weeks grew  $\geq 10^5$  cfu/ml of an organism different from the original infecting isolate.

**Failure.**—Urine culture during treatment or 5–9 days later grew  $\geq 10^5$  cfu/ml of the original infecting organism.

**Superinfection.**—Urine culture during therapy or up to 5–9 days after treatment grew an organism different from the original infecting organism and corresponding gram stain of uncentrifuged urine showed  $\geq 1$  organism per oil immersion field.

### Results

#### Comparative Study

From July 1, 1982, to Feb 28, 1983, 60 patients were enrolled in the comparative study. 8 patients (6 in the

#### B. J. MARSHALL AND J. R. WARREN: REFERENCES—continued

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