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Ceftriaxone Therapy of Serious Bacterial Infections in Adults

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We evaluated the efficacy and safety of ceftriaxone in 50 adults with serious infections, usually giving 1 g every 12 h. Of the 35 patients who could be evaluated for clinical efficacy, 15 had failed on previous therapy, 15 had nosocomial infections, and all but 1 had underlying diseases. One patient had three sites of infection. Favorable responses were seen in 34 of 37 infections, including 11 of 13 respiratory tract infections, all 7 urinary tract infections, all 12 skin and soft tissue infections, 1 of 2 bone and joint infections, a catheter-related septicemia, a liver abscess, and an otitis media and externa. Favorable bacteriological responses were seen for 48 of 58 organisms. This included 6 of 7 *Staphylococcus aureus* strains, 14 of 16 other aerobic gram-positive cocci, 18 of 20 *Enterobacteriaceae*, 6 of 9 *Pseudomonas aeruginosa*, and 1 of 2 anaerobes. Peak plasma ceftriaxone levels on day 1 were 152 μg/ml by bioassay and 78 μg/ml by high-pressure liquid chromatography. Four of the 31 initial isolates of aerobic gram-negative rods developed resistance to ceftriaxone on disk diffusion testing. Diarrhea occurred in 3 of 50 patients. All three had received a higher than usual dose. Drug administration was stopped twice, once for a thrombocytopenia and once for a thrombocytopenia with leukopenia. Neither problem could be attributed exclusively to ceftriaxone. Other adverse reactions were eosinophilia, abdominal pain, inguinal candidiasis, and nonsuppurative phlebitis. Even among debilitated adults, ceftriaxone was safe and effective in a twice daily regimen.

Ceftriaxone is a new broad-spectrum cephalosporin active in vitro against a wide range of aerobic and anaerobic gram-positive and gram-negative bacteria (1, 3, 5). Ninety percent of *Staphylococcus aureus* isolates are inhibited by 3.1 μg/ml, *Streptococcus pneumoniae* by 0.25 μg/ml, *Haemophilus influenzae* by 0.01 μg/ml, most *Enterobacteriaceae* by 0.2 μg/ml, *Serratia marcescens* and *Bacteroides fragilis* by 25 μg/ml, and *Pseudomonas aeruginosa* by 50 μg/ml (5). As a single chemotherapeutic agent, ceftriaxone would be expected to be effective in the treatment of a broad range of bacterial infections when given as infrequently as twice daily, since the half-life in healthy subjects is 6 to 8 h and peak plasma levels of 150 μg/ml can be achieved after a 1-g intravenous dose (6, 9). Therefore, we evaluated its efficacy and safety in a population of debilitated, hospitalized adults with acute, serious infections requiring systemic antimicrobial therapy.

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MATERIALS AND METHODS

Patients. Between January and December 1981, 50 adults hospitalized at the St. Paul-Ramsey Medical Center, St. Paul, Minn., and the Omaha Veterans Administration Medical Center and the St. Joseph Hospital, Omaha, Neb., were enrolled in the study after informed consent was obtained. Pregnant women; individuals with penicillin or cephalosporin allergy, ceftriaxone-resistant organisms, or a baseline serum creatinine concentration exceeding 5.0 mg/dl; and patients who had received one or more antibiotics effective against the isolated pathogen within 3 days of enrollment were excluded. The study was approved by the institutional review board for each hospital. The usual dose of ceftriaxone was 1 g given intravenously over 20 to 30 min every 12 h for a period usually ranging from 5 to 15 days. Clinical response determined the duration of therapy.

Specimens for bacteriological cultures were obtained during the 48 h before the first dose of ceftriaxone, on day 4 of therapy, and at the end of therapy. In urinary tract infections, a urine culture was repeated 1

week and 1 month after therapy. Before therapy, every 4 days during therapy, and at the end of therapy specimens were obtained for a complete blood count, platelet count, differential leukocyte count, prothrombin time, blood urea nitrogen determination, serum creatinine determination, liver function tests, and urinalysis. X rays were obtained when clinically indicated. Plasma specimens for measurement of peak and trough ceftriaxone levels were obtained on days 1 and 4 of therapy. Levels in specimens from St. Paul were measured with a agar well diffusion method with *Escherichia coli* as the test organism, and the other levels were measured by high-pressure liquid chromatography (done by Hoffmann-LaRoche Inc., Nutley, N.J.) (6).

Bacteriological studies. Specimens for culture were processed in a routine manner. Ceftriaxone susceptibility testing was performed by using a disk diffusion method with a 30-μg ceftriaxone disk supplied by the manufacturer (Hoffmann-LaRoche). Organisms with a zone size of ≥16 mm were considered to be susceptible, a 13- to 15-mm zone indicated intermediate susceptibility, and a zone of 12 mm or less indicated resistance to ceftriaxone. According to the manufacturer, who supplied these criteria, corresponding minimum inhibitory concentrations (MICs) are ≤16, 32, and ≥64 μg/ml, respectively.

Diagnostic criteria. Diagnostic criteria were similar to those noted elsewhere (2). A roentgenographic pulmonary infiltrate, positive sputum culture, and compatible Gram stain of sputum were required for the diagnosis of pneumonia. Roentgenographic evidence of pleural effusion and positive culture of that fluid were required for the diagnosis of empyema. Clinical deterioration in pulmonary status, positive sputum culture, and compatible Gram stain of sputum were required for the diagnosis of bronchitis. Local or systemic signs of urinary tract infection coupled with a catheter or midstream urine culture demonstrating 10^5 or more organisms per ml were required for the diagnosis of urinary tract infection. Signs of local inflammation coupled with a positive culture obtained aseptically were required for the diagnosis of soft tissue, bone, or joint infection. Local inflammation with purulent discharge from which a positive culture was obtained was required for the diagnosis of otitis media and externa. Growth of an organism in at least one pretreatment blood culture obtained in a compatible clinical setting was required for the diagnosis of bacteremia.

Response. A clinical cure was defined as complete resolution of all clinical signs and symptoms of infection at the time the drug was discontinued. Patients were clinically improved when there was incomplete resolution of clinical signs and symptoms of infection or if relapse occurred after discontinuation of the antibiotic. Individuals in whom there was no apparent response to therapy were identified as clinical failures. A bacteriological cure occurred when the initially identified pathogen was eliminated during therapy and was not isolated from posttherapy cultures. In cases where there was clinical resolution of the infection and no material available for culture at the termination of treatment, a qualified bacteriological cure was noted. Urinary tract infections were designated as reinfected when the original uropathogen was eliminated but when a recurrent infection with another species occurred. A bacteriological failure was defined as the persistence of the initial pathogen at the completion of a course of ceftriaxone.

RESULTS

Patient characteristics. Although 37 men and 13 women were enrolled, 15 were excluded from evaluation of efficacy. They were evaluated only for ceftriaxone levels and toxicity. Failure to isolate a susceptible pathogen from pretreatment culture excluded seven patients. Four were excluded because they lacked indicated follow-up cultures, two because of administration of subsequent antimicrobial agents obscuring follow-up, one because of administration of concomitant antimicrobial agents expected to be effective against the infecting pathogen, and one because therapy was given for less than 3 days.

The remaining 26 men and 9 women ranged in age from 18 to 90, with a mean of 60. Nearly all (34 of 35) had underlying disease, 15 had failed on other therapy as manifest by positive posttreatment cultures, and 15 had nosocomial infections. None was leukemic or leukopenic, but one was receiving azathioprine and prednisone for giant cell arteritis.

Twenty-six of the 35 patients received 1 g of ceftriaxone every 12 h. This dose was reduced to 250 mg every 12 h in one patient (patient 33) who developed uremia due to hypotension, sepsis, and aminoglycoside treatment. Larger doses delivered at more frequent intervals (up to 2 g every 6 h) were given to two patients with *P. aeruginosa* infections and to six patients with infected foot ulcers. Twenty-nine patients received a 5- to 15-day course of therapy. Three individual patients with foot ulcer, anaerobic empyema, and osteomyelitis, respectively, received 20- to 43-day courses. In two patients, courses were shortened to 3 to 4 days; this was a result of suspicions of clinical failure (which were not confirmed). A course was shortened to 4 days by death caused by an arrhythmia subsequent to placement of a pulmonary artery catheter.

Types of infections and etiological organisms. Among the 35 patients there were 37 infections (Table 1). One patient (patient 5) had three infections: two discrete sites of cellulitis in addition to a pneumonia. There were 13 lower respiratory infections, 7 urinary tract infections, 12 skin and soft tissue infections, an arthritis, an osteomyelitis, a catheter-related septicemia, a liver abscess, and an otitis media and externa.

Among the 58 organisms isolated there were 23 aerobic gram-positive cocci (40%), including 7 isolates of *S. aureus* (12%), 20 *Enterobacteriaceae* (34%) representing 12 species, and 11 nonfermenting aerobic gram-negative bacilli (19%), 9 of which were *P. aeruginosa*. Also

TABLE 1. Site of infection, bacteriology, length of therapy, and response in 35 clinically evaluated patients

Patient no.	Age and sex	Infection site	Pathogen(s) isolated	Days of therapy	Clinical response	Bacteriological response
1	72, F	Pneumonia	*S. pneumoniae*	6	Improved	Cured
2	53, M	Pneumonia (bacteremic)	*S. pneumoniae*	4	Improved	Cured
3	86, M	Pneumonia	*S. pneumoniae*	4	Failed	Cured
4	76, M	Pneumonia	Group B *Streptococcus*,	15	Improved	Cured
			S. aureus,			Cured
			Morganella morganii,			Cured
			Serratia liquefaciens,			Cured
			A. calcoaceticus subsp. *anitratus*			Failed
5	65, M	Pneumonia	Group B *Streptococcus*,	6	Improved	Failed
			S. aureus			Failed
		Abdominal wall cellulitis	Group B *Streptococcus*,		Cured	Cured
			Klebsiella pneumoniae			Cured
		Scrotal cellulitis	Group B *Streptococcus*,		Cured	Qualified cure
			S. aureus			Qualified cure
6	52, M	Pneumonia	Group C *Streptococcus*	11	Cured	Cured
7	36, M	Pneumonia	*S. marcescens*	8	Failed	Failed
8	80, M	Pneumonia	*Citrobacter diversus*	15	Improved	Qualified cure
9	25, M	Pneumonia	*P. aeruginosa*	11	Improved	Failed
10	18, M	Pneumonia	*H. influenzae*	3	Improved	Cured
11	79, M	Empyema	*S. aureus*	12	Improved	Cured
12	76, M	Empyema	*B. fragilis*	21	Improved	Failed
13	65, M	Bronchitis	*P. aeruginosa*,	11	Improved	Cured
			H. influenzae			Cured
14	56, F	Urinary tract	*P. aeruginosa*	6	Cured	Cured
15	85, M	Urinary tract	*K. pneumoniae*	8	Cured	Cured
16	59, M	Urinary tract	*K. pneumoniae*	11	Cured	Cured
17	70, F	Urinary tract	*E. agglomerans*	10	Reinfected	Reinfected
18	71, M	Urinary tract	*M. morganii*	8	Reinfected	Reinfected
19	89, M	Urinary tract	*Citrobacter freundii*	9	Reinfected	Reinfected
20	85, F	Urinary tract	*E. coli*	8	Cured	Cured
21	90, F	Foot ulcer	Group B *Streptococcus*,	9	Cured	Cured
			S. epidermidis			Cured
22	72, M	Foot ulcer	Group B *Streptococcus*,	13	Cured	Cured
			S. epidermidis			Cured
23	59, M	Foot ulcer	Nonenterococcal group D *Streptococcus*,	8	Improved	Cured
			S. aureus,			Cured
			E. cloacae,			Cured
			P. aeruginosa			Cured
24	76, F	Foot ulcer	*S. epidermidis*	10	Improved	Cured
25	82, M	Foot ulcer	*S. epidermidis*,	6	Cured	Failed
			Moraxella sp.			Cured
26	67, F	Foot ulcer	*Enterobacter aerogenes*	7	Cured	Cured
27	69, M	Foot ulcer	*Proteus vulgaris*,	5	Improved	Cured
			P. aeruginosa			Cured
28	20, M	Cellulitis	*S. aureus*	6	Cured	Cured
29	55, M	Cellulitis	*S. marcescens*	21	Cured	Cured
30	19, F	Cellulitis	*P. aeruginosa*	12	Improved	Failed
31	30, M	Arthritis	*E. cloacae*,	9	Failed	Failed
			E. coli,			Cured
			S. aureus,			Cured
			Non-group D alpha-hemolytic *Streptococcus*,			Cured
			Anaerobic gram-positive coccus			Cured
32	25, M	Osteomyelitis	*P. aeruginosa*	43	Cured	Qualified cure
33	63, M	Bacteremia	*S. marcescens*	6	Improved	Qualified cure
34	31, M	Liver abscess	*E. agglomerans*,	15	Improved	Cured
			P. aeruginosa			Failed
35	57, F	Otitis media and externa	*Proteus mirabilis*,	12	Improved	Qualified cure
			P. aeruginosa			Qualified cure

noted were two isolates (3%) of *H. influenzae* and two anaerobes (3%).

Single pathogens were isolated in 24 of the 37 infections, including all urinary tract infections and bacteremias. At least two organisms were isolated from 3 of 13 respiratory infections, 5 of 7 foot ulcers, 2 of the 5 cases of cellulitis, and the arthritis, the liver abscess, and the otitis media and externa. Five organisms were isolated from secretions suctioned from the endotracheal tube of a patient (patient 4) with aspiration pneumonia and five from synovium of the arthritis patient (patient 31).

All tested aerobic isolates were susceptible to ceftriaxone on disk diffusion testing. For five aerobic isolates, bacteriological success was obtained, but susceptibility results were not available. The two anaerobic isolates were susceptible by broth diffusion or disk diffusion testing.

Ceftriaxone levels. St. Paul-Ramsey Medical Center plasma ceftriaxone levels measured by bioassay (mean ± standard deviation) were less on day 1 for 17 patients (peak, 152.5 ± 91.4 μg/ml; trough, 26 ± 15.9) than for the 13 patients studied on day 4 (peak, 179.2 ± 105.6; trough, 36.3 ± 28.9). Similarly, in Omaha, day 1 peak levels measured by high-pressure liquid chromatography among 15 patients were 78.5 ± 44.9 with day 1 troughs among 13 patients of 40.2 ± 15.9. Among the 11 Omaha patients studied on day 4, the peak was 142.5 ± 40.6, and the trough was 62.7 ± 30.4 (Fig. 1).

In one patient, cerebrospinal fluid ceftriaxone levels were 14.8 and 32.9 μg/ml as measured by high-pressure liquid chromatography.

Response to therapy. (i) Respiratory infections. The mean age of the 13 patients with respiratory tract infections was 60.2; five were over 75 years of age, and all three under age 50 had spinal cord injuries or were unconscious. An obtunded head trauma patient had persistent *S. marcescens* in his sputum (patient 7) and required other antimicrobial agents. An 86-year-old man (patient 3) had a stormy course of pneumococcal pneumonia, dying subsequent to pulmonary artery catheter insertion. Nonetheless, his autopsy lung cultures were negative. Four other patients had persistence of pathogens yet showed clinical improvement (patients 4, 5, 9, and 12).

(ii) Urinary tract infections. The mean age among the four men and three women with urinary tract infections, all of which were nosocomial, was 73.6 years. One patient had diabetes mellitus, two had neurogenic bladders, and one had both conditions. All patients showed clinical improvement and were abacteriuric at the end of therapy. Four patients maintained sterile urine cultures throughout follow-up (4 weeks for two patients, 1 week for two patients). Two patients had reinfections with new organisms at 1 week posttherapy, and one had a reinfection with a new organism at 4 weeks posttherapy. Of three patients with reinfection, one (patient 18) had a neurogenic bladder and one (patient 19) had metastatic adenocarcinoma of the prostate. A reason for reinfection was not apparent in the other (patient 17).

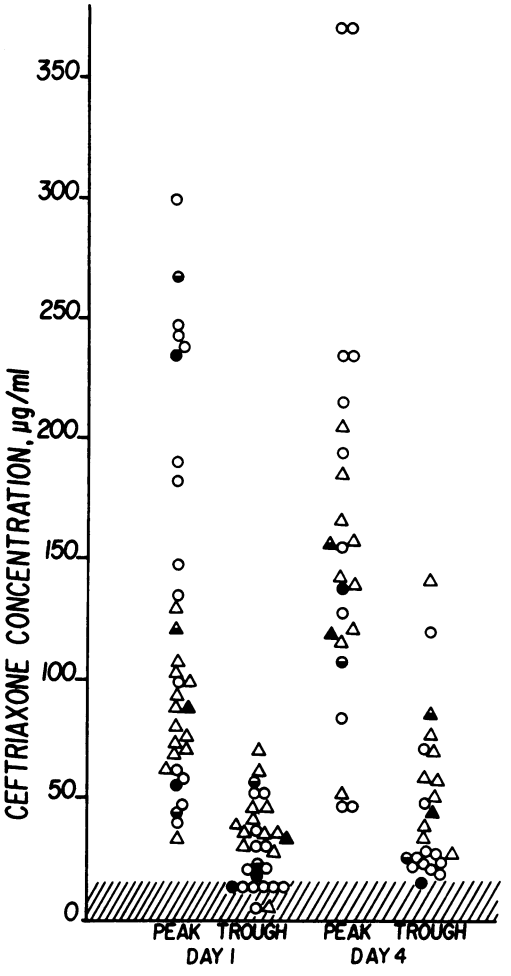

FIG. 1. Peak and trough plasma ceftriaxone concentrations measured on days 1 and 4 by high-pressure liquid chromatography (△, clinical successes; ▲, failures; ▲, unevaluable cases) and bioassay (○, clinical successes; ●, failures; ◒, unevaluable cases). Shading indicates levels below 16 μg/ml, which is the breakpoint for susceptibility testing by dilution.

(iii) Skin and soft tissue infections. The 12 skin and soft tissue infections included 7 foot ulcers, 6 of them in diabetics. The other five soft tissue infections included a patient with separate infections on the abdomen and scrotum (patient 5), a patient who failed on other therapy (patient 28), and two traumatic wounds (patients 29 and 30). All of the three infections with *S. aureus* and

three with *P. aeruginosa* showed clinical and bacteriological response, except for a traumatic wound which healed clinically despite the persistence of *P. aeruginosa* (patient 30). *Staphylococcus epidermidis* persisted in a foot ulcer that nonetheless improved clinically (patient 25).

(iv) Bone and joint infections. A patient with traumatic osteomyelitis in whom tobramycin had failed (patient 32) responded to ceftriaxone. However, *Enterobacter cloacae* persisted in a patient (patient 31) who had arthritis of the knee.

(v) Bacteremias. Two patients were bacteremic: patient 2 with pneumococcal pneumonia and patient 33 with an infected intravenous catheter. Both cleared their bacteremias on ceftriaxone.

(vi) Miscellaneous infections. Other infections responding to ceftriaxone included a nosocomial liver abscess from which *Enterobacter agglomerans* and *P. aeruginosa* were isolated, which had failed to respond to gentamicin and vancomycin. The *E. agglomerans* was eradicated with ceftriaxone but the *P. aeruginosa* persisted, and other antibiotics were required. In addition, one patient with gram-negative otitis media and externa which had failed on topical neomycin was successfully treated.

Emergence of resistance among gram-negative bacilli. Among 24 patients who could be evaluated, from whom a total of 31 isolates of aerobic gram-negative bacilli were recovered, 18 isolates were eradicated. In one patient with a healing *P. aeruginosa* osteomyelitis, attempts were not made to reculture the organism. Of the 12 isolates that were recovered on repeat culture, 7 remained susceptible on disk diffusion testing, and testing was omitted in 1. Thus, emergence of resistance during therapy occurred in only four cases, two of which involved *P. aeruginosa*. In one, the initial zone diameter decreased from 20 to 6 mm (patient 30), and in another (patient 9), the zone size decreased from 18 to 12 mm and, subsequently, to no inhibition. Yet, in both cases clinical improvement ensued, and antimicrobial agents were stopped. One patient with pneumonia caused by susceptible *Acinetobacter calcoaceticus* subsp. *anitratus* initially improved and no longer required mechanical ventilation. However he subsequently deteriorated, and a resistant (12 mm) strain of the same species grew from his blood. In the last instance (patient 31), *E. cloacae* isolated from a joint became resistant during therapy (reduction of zone size from 30 mm to no inhibition) and was associated with unequivocal clinical failure requiring other antibiotics for cure.

Toxicity. Only 6 of the 50 patients (12%) receiving at least one dose of ceftriaxone had clinically evident adverse reactions. Three individuals (6%) developed diarrhea, one of whom had *Clostridium difficile* toxin isolated from the stool. However, his *C. difficile* stool culture was negative, proctoscopy showed only mild erythema without pseudomembrane formation, and he had been given ampicillin concurrently for an enterococcal urinary tract infection. Nevertheless, the diarrhea did not resolve until he received a 7-day course of metronidazole. The diarrhea was self-limited in the other two patients, one of whom had a normal proctoscopic examination. Each patient received a dose of ceftriaxone in excess of the recommended protocol dosage of 1 g every 12 h. Two patients had received 2 g every 8 h and the third a dose of 1.5 g every 12 h. Other adverse reactions which occurred in one patient each included spontaneously remitting abdominal pain, inguinal candidiasis, nonsuppurative phlebitis, and eosinophilia. Ceftriaxone was discontinued in two patients because of suspected toxicity. One individual had thrombocytopenia and the other thrombocytopenia and leukopenia, neither of which could be attributed exclusively to ceftriaxone. No coagulation, renal, or hepatic function test abnormalities were attributed to ceftriaxone, and there was no evidence of clinically apparent allergic manifestations. Ceftriaxone was well tolerated by all patients, and none complained of infusion-related pain. No deaths were attributed to ceftriaxone.

DISCUSSION

Our experience in a patient population characterized by serious underlying disease, nosocomial infections, and failure on other therapy confirms the previously reported efficacy of ceftriaxone in adults (2). Bacteriological response was obtained against 48 of 58 isolates (83%), and clinical response was obtained in 34 of 37 infections (92%), similar to previously reported rates (2).

Success is of interest because ceftriaxone was administered only twice a day to patients with serious infections. Indeed, our patients had therapeutic serum levels with twice daily dosing. Even trough levels exceeded the MICs of most bacterial pathogens (5). Peak and trough serum ceftriaxone levels resembled those obtained by others (2, 6). This was reassuring, since early studies, done on normal volunteers, showed concentration-dependent protein binding (9), a phenomenon that might be altered in a debilitated population. The relatively long half-life of ceftriaxone would facilitate two types of studies modifying the dosing regimen: (i) more frequent dosing to determine whether cephalosporin levels continuously exceeding MICs enhance efficacy (4); and (ii) less frequent dosing to determine whether the frequency of drug administration can be minimized and outpatient

therapy promoted. The relatively high cerebrospinal fluid levels achieved in one patient suggest that ceftriaxone may be effective in the treatment of meningitis caused by a variety of bacteria. Our patient's cerebrospinal fluid concentrations of ceftriaxone exceeded the MICs for *S. pneumoniae, Neisseria meningitidis*, and *H. influenzae* by more than 100-fold (5). In two cases of clinical and bacteriological failure (patients 7 and 31), plasma levels of ceftriaxone exceeded the MICs of the infecting organisms. The tendency for day 4 levels to exceed day 1 levels may reflect the time needed to reach steady state (7).

Ceftriaxone was found to be very safe in our population of elderly, debilitated individuals with serious underlying disease. The contributory role of ceftriaxone in patients with hematological abnormalities and *C. difficile* toxin-associated diarrhea remains unclear since other host and drug-related factors may have contributed. It is intriguing, however, that all three patients with antibiotic-related diarrhea received higher doses of ceftriaxone than individuals in whom diarrhea did not occur. It is possible that the diarrhea is a dose-related phenomenon and does not occur in patients receiving relatively low doses of ceftriaxone.

Emergence of resistance during treatment with expanded spectrum cephalosporins raises much concern (8). However, we documented emergence of resistance in only 4 of 31 gram-negative rod isolates by using disk zone size criteria. These may represent superinfection with resistant organisms or induction of resistance in the flora present at the onset of therapy. In only two of these episodes was it associated with clinical failure. Whether it is an uncommon event or a frequent menace to the seriously ill deserves more study. None of our patients on this expanded-spectrum cephalosporin developed an enterococcal superinfection (10).

In view of the relative safety, unique pharmacokinetic properties, and excellent clinical and bacteriological efficacy of ceftriaxone in this debilitated adult population, additional clinical studies with this promising antibiotic are indicated.

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