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Enterococcal Superinfection and Colonization with Aztreonam Therapy

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Patients were given aztreonam (SQ 26,776) parenterally for the treatment of various gram-negative infections. During or shortly after therapy, 8 (17.8%) of 45 patients became infected with or colonized by enterococcus. These eight cases included eight urinary tract isolates; one of these cases subsequently developed bacteremia. Five patients required further antimicrobial therapy directed against enterococcus. Patients receiving aztreonam are at risk for the development of enterococcal superinfection or colonization.

Aztreonam is a new beta-lactamase-stable antimicrobial agent which is structurally classified as a monobactam (6). According to its pharmacokinetic profile, it can be administered parenterally every 8 h (5, 9). Its in vitro activity is directed against *Haemophilus influenzae*, *Neisseria* spp., and gram-negative bacilli, including *Pseudomonas aeruginosa* (3–5). However, it is inactive in vitro against anaerobes, as well as against gram-positive cocci (enterococci, nonenterococcal streptococci, and staphylococci) (3, 4).

We report eight cases of enterococcal superinfection or colonization, including one bacteremia, during or shortly after aztreonam therapy.

Aztreonam (SQ 26,776; E. R. Squibb & Sons, Princeton, N.J.) was used to treat patients with various gram-negative bacterial infections under an open investigational protocol approved by the Hahnemann University Human Studies Committee. Written, informed consent was obtained from each patient or the nearest relative of each patient. Aztreonam was administered intravenously in a usual dose of 1 g every 8 h and, in some cases, up to a maximum of 8 g/day. A penicillinase-stable penicillin, vancomycin, clindamycin, or metronidazole could be administered concurrently with aztreonam when either gram-positive bacteria or anaerobes were simultaneously involved as pathogens. Appropriate aerobic and anaerobic cultures of blood, sputum, bile, bone, wound exudate, and urine were obtained before and, when possible, during and 1 to 5 days after aztreonam therapy (5 to 9 days after therapy for determination of urinary tract infections). Cases were considered clinically able to be evaluated for safety and efficacy when the patient had received aztreonam for a minimum of 5 days.

Enterococcus was identified by its ability to grow in 6.5% NaCl broth and to hydrolyze esculin in medium containing 40% bile. Enterococcal isolates were not identified. MICs were determined by a microtiter broth dilution technique similar to the one described by Gavin and Barry (1). Briefly, each bacterial suspension was obtained by inoculating Mueller-Hinton broth with 0.1 ml of an overnight culture, incubating the solution, and adjusting the density of the fresh bacterial suspension with a spectrophotometer to contain 10^8 CFU/ml. The antimicrobial solutions and their serial twofold dilutions were inoculated (Dynatech MIC-2000) with 0.001 ml of a 1:10 dilution of the bacterial suspension for a final concentration of 10^4 organisms per 0.1 ml. MICs were determined visually after incubation for 24 h at 35°C. The MIC was defined as the lowest concentration of the antibiotic that prevented visible growth.

Superinfection was defined as the development of signs or symptoms of infection during treatment or within the period of posttreatment follow-up, which were due to a pathogen which was not originally present at the subsequently infected site and not recognized as the original causative pathogen. Colonization was defined as the isolation of a significant growth ($\geq 10^5$ bacteria for a urinary tract infection) of a previously undetected bacteria at a site in the absence of signs or symptoms of infection at the site.

Cases in which enterococcus was cultured from any body site (even an uninfected site) before therapy were excluded from analysis.

A total of 56 patients were enrolled in the aztreonam treatment protocol. Two patients received aztreonam for less than 4 days, and their cases were excluded from analysis. Nine patients had enterococcus isolated in pretreatment cultures (three urinary tract, three skin, two biliary tree, and one bacteremia). These cases were also excluded from further analysis. Two of these patients had enterococcus originally isolated at a site distinct from where it was subsequently cultured. Both patients had skin infections from which enterococcus was isolated. One developed symptomatic urinary tract infection, related to a Foley catheter, which was treated with ampicillin. This patient received no antibiotic concurrently with aztreonam. The second patient developed enterococcal bacteremia on day 23 of aztreonam therapy and was treated with vancomycin. This patient received clindamycin concurrently with aztreonam. Both of these cases were excluded from further analysis because enterococcus was isolated from an initial culture, although the subsequent infection was probably not related to the original enterococcal isolate.

Of 45 of the remaining patients, 8 (17.8%) had enterococcus isolated from cultures during or after aztreonam therapy (Table 1). The MIC of aztreonam was >128 μg/ml for all enterococci tested. All eight patients had enterococcus isolated in the urine. Of eight patients, four (50%) required therapy for symptomatic enterococcal urinary tract infection. All four of these patients responded to additional therapy. Four of eight patients were determined to have enterococcal colonization and did not initially require therapy. However, one patient developed enterococcal bacte-

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TABLE 1. Description of eight patients from whom enterococcus was isolated during or after aztreonam therapy

Patient no.	Underlying condition	Concurrent antibiotic	Original infection[a]	Original pathogen	Aztreonam		Site of enterococcus	Enterococcus isolated on (day):	Status of enterococcus
					Dose (g/day)	Duration (days)			
1	Endometrial carcinoma, hydronephrosis, nephrostomy tube	None	UTI	*Enterobacter aerogenes*	3	5	Urine	4 of therapy	Infection
2	Organic brain syndrome, Foley catheter	None	UTI	*Escherichia coli*	3	10	Urine	10 of therapy	Infection
3	Subarachnoid hemorrhage, Foley catheter	None	UTI	*Enterobacter aerogenes* *Serratia liquefaciens*	3	10	Urine	5 posttherapy	Infection
4	Multiple sclerosis, Foley catheter	Clindamycin	UTI	*Proteus mirabilis* *Escherichia coli*	2	11	Urine	8 of therapy	Infection
5	Craniotomy, Foley catheter, tracheostomy	Clindamycin	Pneumonia	*Pseudomonas aeruginosa*	3	7	Urine Blood	6 of therapy 2 posttherapy	Infection
6	Paraplegia, diabetes, Foley catheter	None	UTI	*Pseudomonas aeruginosa*	3	13	Urine	9 of therapy	Colonized
7	Cerebrovascular accident, Foley catheter	Clindamycin	UTI	*Proteus mirabilis* *Escherichia coli*	3	6	Urine	5 of therapy	Colonized
8	Dementia, hip fracture, Foley catheter	None	Urosepsis	*Proteus mirabilis*	3	10	Urine	10 posttherapy	Colonized

[a] UTI, Urinary tract infection.

remia 3 days after the organism had colonized the urinary tract. This patient also responded to additional therapy. Therefore, a total of five patients required therapy for enterococcal superinfection, whereas three patients had colonization which did not require therapy.

Seven of eight patients had an indwelling Foley catheter and one patient had a nephrostomy tube as predisposing factors for urinary tract colonization or infection. As an additional predisposing factor, three of eight patients received a concurrent antimicrobial agent having no enterococcal activity (clindamycin) for all or part of the treatment course. Two of these patients became superinfected, whereas one became colonized with enteroccoccus. Five of eight patients from whom enterococcus was isolated received no concurrent antibiotic. In these five cases, superinfection or colonization could be directly linked to aztreonam therapy. Overall, 13 of 45 patients received a concurrent antibiotic without enterococcal activity (12 clindamycin and 1 metronidazole). Of 13 patients, 3 (23%) had enterococcal superinfection or colonization. Of 45 patients, 22 received no concurrent antibiotic. Of 22 patients, 5 (22.7%) had enterococcal superinfection or colonization.

The average duration of aztreonam therapy in patients who developed enterococcal superinfection or colonization was 11.7 (range, 5 to 17) days. The average time to superinfection or colonization was 10.1 (range, 4 to 20) days.

It is critical to emphasize that in any clinical situation the distinction must be drawn between colonization and actual infection, lest patients be subjected unnecessarily to additional antimicrobial therapy. Similarly, the clinician should be wary of the fact that colonization may predispose certain individuals to future superinfection (7, 8).

Previous reports have implicated the broad-spectrum antimicrobial agent moxalactam as being associated with enterococcal superinfection and colonization (2, 10). Aztreonam has a relatively narrow spectrum of activity as compared with moxalactam, particularly against anaerobic bacteria and gram-positive cocci. It was hoped that the narrower spectrum of this agent would preserve normal colonization resistance preventing such superinfection problems.

However, in the present study, 45 aztreonam treatment courses were complicated by eight cases (17.8%) of enterococcal infection or colonization. In five of the eight cases, additional antimicrobial therapy was required during or after aztreonam therapy for enterococcal superinfection. This represents a considerable risk of enterococcal superinfection (11.1% of all treatment courses). Clinicians using aztreonam alone or in combination with other antimicrobials inactive against enterococcus must be aware of this possible complication of therapy.

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