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Antimicrobial Chemotherapy of Septicemia Due to Methicillin-Resistant *Staphylococcus aureus*

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The outcome of treatment of 48 episodes of septicemia due to methicillin-resistant *Staphylococcus aureus* (MRSA) in 44 patients was assessed. Twenty-six of the patients died; nineteen of them died of infection, and infection was a major contributing factor to the deaths of the remaining seven patients. Fourteen of fifteen patients treated with inadequate antibiotic therapy died, and the other patient developed a mycotic aneurysm of the femoral artery, for which amputation was necessary. Eight of eleven patients treated with amikacin (alone or combined with another antimicrobial) died, and three recovered slowly; only one recovered fully without sequelae. In an additional two patients who failed to respond to amikacin, treatment was changed to vancomycin. Vancomycin was used to treat 18 episodes of MRSA septicemia in 17 patients. In 14 of these episodes the patients recovered fully. One patient died of uncontrolled infection, and in three, infection was a contributing factor but not the major cause of death. Vancomycin was confirmed as antibiotic of choice in treating MRSA septicemia.

Since 1976, methicillin-resistant *Staphylococcus aureus* (MRSA) has been a serious problem in Dublin hospitals (3, 4, 10) as well as in other centers (7, 8, 17, 21–23, 25–28). From 1979 to 1983, approximately 30% of *S. aureus* strains isolated from blood cultures taken from patients in our hospitals were MRSA. Initially, we treated severe MRSA infection with a variety of antimicrobial agents other than vancomycin. Since August 1980, we have used vancomycin as the drug of first choice in treating severe MRSA infection. Here we report the results of treatment of MRSA septicemia.

MATERIALS AND METHODS

Patients. The patients involved in this study were in nine Dublin hospitals; the hospitals contained a total of about 3,000 beds and included all specialties except neurosurgery. The clinical staff took blood cultures from patients with symptoms suggesting bacteremia or septicemia. Septicemia was defined as isolation of an organism from blood cultures on two or more occasions when the symptoms were still present. Detailed clinical records were kept in the laboratories, and the charts were reviewed on recovery and again on discharge or at the time of death.

From 1978 through 1983, there were 48 episodes of MRSA septicemia in 44 patients. In 41 of the episodes, MRSA was in pure culture. In six episodes it was combined with *Pseudomonas aeruginosa* (three times), *Streptococcus* sp. (once), *Bacteroides* sp. (once), and *Proteus morganii* (once). One patient developed superinfection with *Candida albicans* and subsequently had mixed septicemia with MRSA and *C. albicans*.

Processing of blood culture specimens. Eight of the hospitals were served by a central microbiology laboratory. Blood cultures were incubated at 37°C in the hospital of origin pending transport to the central microbiology laboratory. The other hospital was served by an on-site microbiology laboratory. During the period of study, two systems of blood culture were in operation.

(i) Before August 1982, a conventional system of blood culture processing was used (29). A 10-ml sample of blood was taken aseptically, and 5 ml was put into each of two bottles, containing nutrient broth no. 2 (Oxoid Ltd., London, England) for aerobes and Brewer thioglycolate for anaerobes. Both bottles were routinely subcultured at 24, 48, and 72 h and 5 days. If the fluid medium appeared cloudy, dark, or frothy in the first 24 h (or at routine subculture), a Gram stain and culture were performed. With this system, most of the positive blood cultures were not detected until 48 h after sampling. Identification and antibiotic susceptibilities were not available until 18 to 24 h later.

(ii) Since August 1982, the Bactec blood culture system (Johnston Laboratories, Towson, Md.) has been in routine use in our laboratories. A 10-ml sample of blood is taken aseptically, and 5 ml is put into each of two bottles, enriched trypic soy broth (6B; Difco Laboratories, Detroit, Mich.) for aerobes and prereduced enriched trypic soy broth (7D) for anaerobes. The aerobic bottles are routinely screened every 8 h for the first 36 h and subsequently once daily until 5 days after sampling. The anaerobic bottle is screened daily for 7 days. Samples from bottles showing growth index on screening are Gram stained, and subculture and direct susceptibility testing and identification are performed. With this method, positive bottles are usually detected on first and second sampling, and identification and antibiotic susceptibilities are available within 24 h of sampling.

MRSA isolates. Antibiotic susceptibility testing was performed by the Stokes disk diffusion method on diagnostic sensitivity test agar (Oxoid) with the following disks and disk contents: penicillin G (2 U), tetracycline (10 μg), erythromycin (15 μg), trimethoprim (1. 25 μg), sulfamethoxazole (100 μg), gentamicin (10 μg), amikacin (30 μg), fusidic acid (10 μg), rifampin (30 μg), chloramphenicol (30 μg), clindamycin (2 μg), and vancomycin (30 μg). Single disks and Multidiscs (Mast Laboratories Ltd., Liverpool, England) were used. The plates were incubated overnight at 37°C. Methicillin

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TABLE 1. Clinical details of patients treated with inadequate antimicrobial therapy

Patient no.	Age (yr)	Sex	Principal infected site	Underlying condition	Treatment	Outcome
1	66	F	A.V. fistula[a]	Multiple myeloma; acute on chronic renal failure	Nil	Died
2[b]	63	M	CVP line[c]	Postoperative resection of upper lobe of right lung	Cloxacillin (4 days) then fusidic acid (3 days)	Died
3[d]	77	M	CVP line	Postoperative cystectomy; carcinoma of bladder	Nil	Died
4	63	M	Burns	25% second- and third-degree burns	Ampicillin	Died
5	65	M	Burns, desloughing		Nil	Died
6[d]	31	M	Burns, desloughing	80% third-degree burns	Vancomycin and amikacin[e]	Died
7	40	M	Decubitus ulcer	Alcoholic hepatitis and pneumonia	Amoxycillin	Died
8	57	F	Decubitus ulcer	6-mo postoperative aortic valve replacement	Nil	Died
9[b]	66	F	Varicose ulcer	Recovered from thrombocytopenia and MRSA septicaemia 3 weeks earlier	Cloxacillin	Died
10	45	M	Mediastinitis and sternal osteomyelitis	6-week postoperative aortic and mitral valve replacement	Cloxacillin	Died
11	64	F	Abdominal wound infection and peritonitis	Postoperative, laparotomy; gastic ulcer	Amphotericin B	Died
12[d]	38	F	Peritonitis (?)	Chronic renal failure	Cefuroxime	Died
13[b]	69	M	Urinary tract infection; endocarditis	Posttransurethral resection of prostate	Lincomycin and fusidic acid	Died
14[b]	77	M	Urinary tract infection; multiple catheterization	Atheroma	Nil	Mycotic aneurysm of femoral artery and second septicemia
15	70	M	Unknown	Bleeding esophageal varices	Nil	Died

[a] A.V., Arteriovenous.
[b] Patients still living when antimicrobial susceptibilities became available.
[c] CVP, Central venous pressure.
[d] Bactec system used.
[e] Inadequate dosage.

resistance was tested on a blood agar plate at 30°C with a 10-μg methicillin disk by the method of Hewitt et al. (9). The Oxford strain of *S. aureus* (NCTC 6571) was used as the control organism in all antibiotic susceptibility tests. MRSA isolates were resistant to penicillin, methicillin, erythromycin, and gentamicin. There was a variable resistance to trimethoprim and sulfamethoxazole: repeated testing of the same or serial isolates gave equivocal results. Isolates from 29 patients were susceptible to tetracycline. One patient was infected with a chloramphenicol-resistant MRSA, and isolates from three patients were resistant to fusidic acid and amikacin. All isolates were susceptible to rifampin and vancomycin. Isolates obtained during and after treatment showed no change in disk susceptibility patterns.

Choice of antibiotic. After isolation of MRSA from blood cultures, the significance of the isolate was discussed with the clinicians, and advice was given on antibiotic treatment. The choice of antibiotic was limited. Amikacin alone, or with another antibiotic, was usually recommended before August 1980. Cotrimoxazole, tetracycline, chloramphenicol, clindamycin, fusidic acid, or rifampin were sometimes used, alone or in combination. By August 1980 it was clear that these were of limited value in the treatment of MRSA infection. Consequently, vancomycin was recommended as treatment of choice and, to date, it remains the antibiotic of first choice for septicemia or other severe MRSA infection.

Dosage. The antibiotics chosen were administered parenterally, usually by the intravenous route as bolus injections, with the exception of vancomycin. Rifampin was given orally to two patients as part of combination therapy, as the intravenous preparation was unobtainable locally.

When amikacin was given, the dosage schedule was calculated by use of a nomogram for kanamycin (18), as it has been suggested that in view of the similar activity, toxicity, and pharmokinetics of the two drugs, the kanamycin nomogram could be used for amikacin (5). Assay of levels in serum was performed in four patients only, and peak levels were therapeutic.

Vancomycin is a potentially toxic drug (6). Infusion into a large vein has been reported to reduce the incidence of thrombophlebitis associated with its administration (6, 12). Vancomycin powder for injection (Eli Lilly & Co., Indianapolis, Ind.) was suspended in 20 ml of water for injection and diluted up to 200 ml in 0.9% (wt/vol) NaCl or 5% (wt/vol) glucose. This solution was infused over 40 min to prevent the anaphylactoid reaction that may follow rapid infusion (1). It was administered via a subclavian line or antecubital fossa long line throughout. The following dosage schedule (4) which gave therapeutic levels in the blood was used: body weight of <45 kg, dose of 0.5 g each 12 h; body weight of 45 to 60 kg, dose of 0.75 g each 12 h; body weight of >60 kg, dose of 1.0 g each 12 h. For patients in renal failure, a loading dose of 1 g was given and subsequent dosage was based on levels in serum. When assays could not be performed (such

TABLE 2. Clinical details of patients treated with antimicrobial agents (other than vancomycin) thought to be appropriate

Patient no.[a]	Age	Sex	Principal infected site[b]	Underlying condition[b]	Treatment	Outcome
16	51	M	A.V. fistula	Chronic renal failure secondary to inferior vena caval thrombosis	Tetracycline	Recovered; 1 yr later, septic arthritis
17[c]	46	M	CVP line	Postoperative vagotomy and pyloroplasty	Amikacin, chloramphenicol, clindamycin, rifampin	Pulmonary emboli
18	55	F	I.V. site; endocarditis	Postoperative renal transplant	Amikacin	Died
19[d]	48	M	CVP line	Multiple complications of resection of stomach carcinoma	Amikacin for 24 h	Continuing septicemia; changed to vancomycin
20[c]	29	F	Wound sepsis and CVP line	Postpartum	Amikacin and cefuroxime	Failed; changed to vancomycin
21[c]	58	M	CVP line; cellulitis	Postoperative CABG	Amikacin and cloxacillin	Full recovery
22[c]	79	M	Varicose ulcer	Maturity-onset diabetes mellitus	Amikacin, cefuroxime, rifampin, chloramphenicol	Died
23[c]	58	M	Sternal wound infection; osteomyelitis and mediastinitis	Postoperative aortic valve replacement	Amikacin, cefuroxime	Died
24[c]	29	F	Biliary tree	Postoperative cholecystectomy tear of common bile duct	Amikacin, chloramphenicol, amphotericin B	Died
25	58	F	Intraperitoneal abscess	Postoperative repair of stricture of common bile duct	Amikacin	Slow recovery
26	85	M	Operative wound infection	Postoperative ascending cholangitis perforated gall bladder and peritonitis	Amikacin and cloxacillin	Died
27	55	M	Operative wound infection	Postoperative renal transplant	Amikacin, amikacin and chloramphenicol, amikacin	Died
28	69	M	Operative wound infection	Postoperative bilateral total hip replacement	Netilmicin and cefamandole	Died
29[c]	33	M	Pneumonia and flail chest	Multiple injuries	Amikacin then chloramphenicol	Died
30[d]	26	M	Wound infection	Multiple injuries	Amikacin	Recovered, later septic arthritis
16	52	M	Septic arthritis	Chronic renal failure on hemodialysis previous shunt infection	Cotrimoxazole	Full recovery
31[c]	66	M	Chest wound infection and empyema	Postoperative gastrectomy	Amikacin	Slow recovery and chronic discharging sinus

[a] There were 17 episodes in 16 patients.
[b] Abbreviations: A.V., arteriovenous; CVP, central venous pressure; I.V., intravenous; CABG, coronary artery bypass graft.
[c] Initially treated with other antimicrobial agents for up to 72 h pending results of susceptibility testing.
[d] Bactec system used.

as at weekends), the interdose interval was increased, taking into account the degree of renal failure pending assay of levels in serum.

RESULTS

The patients were divided into three groups on the basis of antibiotic treatment.

(i) Group 1. Patients receiving inadequate therapy. Inadequate therapy included no administration of antimicrobial agent, administration of an agent to which the MRSA isolate was resistant on disk sensitivity testing, or administration of the correct antibiotic in subtherapeutic dosage. This group contained 15 patients, 6 females and 9 males. The age range was 31 to 77 years (mean, 59.5 years). Clinical details are shown in Table 1. Eleven of these patients died of septicemia after an illness lasting from 6 h to 14 days (mean, 3 days). One patient in this group (no. 14) survived. He presented 6 weeks later with septicemia and mycotic aneurysm of the femoral artery. It was necessary to amputate the leg; the septicemia was successfully treated with vancomycin.

(ii) Group 2. Patients receiving antimicrobial agents, other than vancomycin, to which MRSA was susceptible. This group contained 16 patients, who had 17 episodes of septicemia. These will be considered to be 17 patients for the purpose of this analysis. There were 4 females and 13 males. The age range was 26 to 79 years (mean, 52.8 years). Clinical details are shown in Table 2. Eight of these patients were treated for up to 72 h with other antimicrobial agents pending results of antimicrobial susceptibility testing. Fourteen patients were treated with amikacin, sometimes in combination with another agent. Seven of these patients (50%) died of uncontrolled infections. One of these seven patients had mixed septicemia with *C. albicans* terminally, for which amphotericin B was also administered. Two patients (no. 19 and 20) who failed to respond to amikacin were changed to vancomycin therapy. Only 1 of the 14 recovered fully; the remain-

TABLE 3. Clinical details of patients treated with vancomycin

Patient no.[a]	Age	Sex	Principal infected site	Underlying conditions	Treatment	Outcome
20	29	F	CVP[b] line	Postpartum hepatorenal failure, large bowel perforation	Vancomycin	Recovered
32	60	M	CVP line	Parenteral nutrition; carcinoma	Vancomycin	Recovered
19[c]	48	M	CVP line	Multiple complications of resection of carcinoma of stomach	Vancomycin	Died
9[c]	66	F	CVP line	Thrombocytopenia	Vancomycin	Recovered
33	52	M	CVP line and burns	60% second- and third-degree burns	Vancomycin	Recovered
33	52	M	CVP line and burns	60% second- and third-degree burns	Vancomycin and amikacin	Recovered from septicemia, died of unknown cause
34	49	M	Pacemaker	Postmyocardial infarction, arhythmia	Vancomycin	Recovered
35	72	F	Burns		Vancomycin and amikacin	Died on day 5 of treatment (unknown cause)
36[c]	9	F	Burns		Vancomycin	Recovered
37[c]	70	F	Operative wound	Old CVA[d] reduction of open fracture of femur	Vancomycin	Recovered
38[c]	61	F	Operative wound	Perforated gangrenous bowel and CVA	Vancomycin	Died
39	63	M	Operative wound and pneumonia	Postoperative abdominoperineal resection for adenocarcinoma of rectum	Vancomycin	Recovered
14	77	M	Amputation stump	None	Vancomycin	Recovered
40	57	M	Pneumonia	Acute alcoholic hepatitis	Vancomycin	Recovered
41	68	F	Pneumonia and empyema thoracis	Postoperative, gastric ulcer, splenic bed abscess	Vancomycin and metronidazole	Recovered
42[c]	67	M	Pneumonia	Postoperative	Vancomycin	Recovered
43	17	M	Inhalation injury, pneumonia and empyema thoracis	Burns	Vancomycin and amikacin	Recovered
44	70	F	Unknown	Aplastic anemia secondary to cotrimoxazole	Vancomycin	Recovered

[a] There were 18 episodes in 17 patients.
[b] CVP, Central venous pressure.
[c] The Bactec system was used.
[d] CVA, Cardiovascular accident.

ing 4 recovered slowly, with continuing septicemia for 14 days in patient 17 and development of chronically discharging sinuses in patient 31.

One patient who was treated with tetracycline seemed to make full recovery. This patient represented 14 months later with septic arthritis and septicemia due to an indistinguishable strain. It was concluded that the organism had not been eradicated in the first episode. The second episode was successfully treated with cotrimoxazole. The final patient in this group was treated with netilmicin and cefamandole; septicemia was not controlled by this regime.

(iii) Group 3. Patients receiving vancomycin therapy. A total of 18 episodes of MRSA septicemia in 17 patients were treated with vancomycin. There were 7 females and 11 males. The age range was 17 to 77 years (mean, 52.8 years). Clinical details are shown in Table 3. Vancomycin was administered within 18 h of onset of symptoms in 13 patients. Of the 18 patients, 4 (22%) died. In two of these the infection was the cause of death, but in the other two the infection was controlled and there was a sudden deterioration and death on day 5 of vancomycin treatment in one and after a 26-day course of vancomycin and amikacin in the other. Neither patient had an autopsy performed. Infection was not the cause of death in these two patients, but may have been a contributing factor.

DISCUSSION

A variety of treatment regimes have been advocated for treating septicemia and other severe MRSA infections. Because of the increasing number of infections with these organisms reported from various centers, we thought that it was important to analyze the outcome of our cases of MRSA septicemia.

Patients were divided into three groups for analysis. There was a predominance of males in all three groups. In group 1, the mean age (59.5 years) was higher than in the other two groups (both with a mean of 52.8 years). The high mortality (94%) in group 1, in which the patients had inadequate therapy or no therapy, indicates the pathogenicity of these strains.

Before mid-1980, we used amikacin as the drug of choice to treat severe MRSA infections, on the basis of results of laboratory susceptibility testing. This drug was occasionally combined with a cephalosporin because of reports of in vitro synergy of such combinations against MRSA (2, 13, 18). The results for group 2 were somewhat better than those in group 1, but only 18% recovered fully. These data are consistent with earlier findings of low efficacy of gentamicin treatment in patients infected with gentamicin-susceptible *S. aureus* strains (14). Clearly, aminoglycosides are suboptimal ther-

apy of severe staphylococcal infection. In the present study, the dosage of amikacin was based on body weight and renal function; however, serum assay was not performed in the majority of cases. Factors which may be important in treatment failure could be related to low antibiotic levels in serum, the metabolism of the organisms (15, 16), or possibly an in vitro diffusion block. Another factor that may have an important effect on outcome is the time interval between onset of septicemia and initiation of appropriate antibiotic therapy. Antibiotic susceptibilities were not available until 2 to 4 days after sampling in the majority of patients subsequently treated with amikacin, and initial treatment was with an antimicrobial agent to which the MRSA isolate was resistant in vitro.

Because of the poor results of treatment with other antimicrobial agents, we decided to use vancomycin as the drug of choice for MRSA septicemia in 1980. Of the 18 patients treated with vancomycin (group 3), 14 (72%) made a full recovery. In 13 of the septicemia episodes in group 3, vancomycin therapy was administered within 18 h of the onset of symptoms. A rapid blood culture system and increased awareness of the possibility of MRSA septicemia both contributed to this earlier treatment, which may have influenced the outcome. Of the patients who died, only one (6%) had uncontrolled infection. However, MRSA was usually not eradicated from the carrier sites or the lesions. In three patients, continuing carriage was the probable source of reinfection, which was fatal in one patient. There may be a place for a controlled trial of vancomycin versus vancomycin and rifampin (19).

This report shows there is a high mortality from untreated or inadequately treated MRSA septicemia. Cloxacillin has no place in the treatment of such infections. The response to amikacin was poor. Vancomycin is confirmed as the antibiotic of choice. The studies of Karchmer et al. (11) with prosthetic valve endocarditis indicate that vancomycin is the treatment of choice in severe infection with methicillin-resistant *S. epidermidis* also.

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