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 sepsis. 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 tryptic soy broth (6B; Difco Laboratories, Detroit, Mich.) for aerobes and prereduced enriched tryptic 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 μg), 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 Multidisks (Mast Laboratories Ltd., Liverpool, England) were used. The plates were incubated overnight at 37°C. Methicillin
TABLE 1. Clinical details of patients treated with inadequate antimicrobial therapy

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

<sup>a</sup> A.V., Arteriovenous.<br>
<sup>b</sup> Patients still living when antimicrobial susceptibilities became available.<br>
<sup>c</sup> CVP, Central venous pressure.<br>
<sup>d</sup> Bactec system used.<br>
<sup>e</sup> 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
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 myotic 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

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Sex</th>
<th>Principal infected site</th>
<th>Underlying conditions</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>29</td>
<td>F</td>
<td>CVP line</td>
<td>Postpartum hepatorenal failure, large bowel perforation</td>
<td>Vancomycin</td>
<td>Recovered</td>
</tr>
<tr>
<td>32</td>
<td>60</td>
<td>M</td>
<td>CVP line</td>
<td>Parenteral nutrition; carcinoma of stomach</td>
<td>Vancomycin</td>
<td>Recovered</td>
</tr>
<tr>
<td>33</td>
<td>52</td>
<td>M</td>
<td>CVP line and burns</td>
<td>60% second- and third-degree burns</td>
<td>Vancomycin</td>
<td>Recovered</td>
</tr>
<tr>
<td>34</td>
<td>49</td>
<td>M</td>
<td>Pacemaker</td>
<td>Postmyocardial infarction, arrhythmia</td>
<td>Vancomycin</td>
<td>Recovered</td>
</tr>
<tr>
<td>35</td>
<td>72</td>
<td>F</td>
<td>Burns</td>
<td>Vancomycin and amikacin</td>
<td>Vancomycin</td>
<td>Died on day 5 of treatment (unknown cause)</td>
</tr>
<tr>
<td>36</td>
<td>9</td>
<td>F</td>
<td>Burns</td>
<td>VR</td>
<td>Vancomycin</td>
<td>Recovered</td>
</tr>
</tbody>
</table>
| 37          | 70  | F   | Operative wound         | Old CVA
d' reduction of open fracture of femur | Vancomycin | Recovered |
| 38          | 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 |
| 40          | 57  | M   | Pneumonia               | None | Vancomycin | Recovered |
| 41          | 68  | F   | Pneumonia and empyema thoracies | Acute alcoholic hepatitis | Vancomycin | Recovered |
| 42          | 67  | M   | Pneumonia               | Postoperative, gastric ulcer, splenic bed abscess | Vancomycin and amikacin | Recovered |
| 43          | 17  | M   | Inhalation injury, pneumonia and empyema thoracies | Burns | Vancomycin | Recovered |
| 44          | 70  | F   | Unknown                 | Aplastic anemia secondary to cotrimoxazole | Vancomycin | Recovered |

* There were 18 episodes in 17 patients.
* CVP, Central venous pressure.
* The Bactec system was used.
* CVA, Cardiovascular accident.

DISCUSSION

A variety of treatment regimes have been advocated for treating sepsis 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 sepsis.

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. Three of the 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 (10%) 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 vanco-
mycin and rifampin (19).

This report shows there is a high mortality from untreated or inadequately treated MRSA septicemia. Cloxacin has no place in the treatment of such infections. The response to amikacin was poor. Vancomycin is confirmed as the antibi-
otic 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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