An outbreak of infection caused by a gentamicin-resistant Staphylococcus aureus

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SYNOPSIS An outbreak of infection caused by a strain of Staphylococcus aureus resistant to gentamicin and tobramycin and other antibiotics occurred in two wards in a hospital. Eight patients were colonized, of whom six had clinical infections. Previous administration of gentamicin appeared to predispose the patients to infection with the strain. Restriction of the use of gentamicin and tobramycin is essential to preserve their value in serious infections.

Gentamicin is widely regarded as an extremely valuable agent in treating serious infections when the pathogens are unknown or where there is resistance to other antimicrobial agents. Although reports of increasing resistance among Gram-negative bacilli have been appearing in the literature (Greene et al., 1973; Whitelaw et al., 1974; Shafi and Datta, 1975), resistance in Staphylococcus aureus has been rare. We report here an outbreak caused by a strain of Staph. aureus resistant to many antibiotics including gentamicin and tobramycin. The occurrence of this outbreak, similar to that described by Speller et al. (1976) in another British city, points to the likelihood that more will occur, and that great care will have to be taken to preserve the value of aminoglycosides.

Description of the strain

All the isolates of the gentamicin-resistant Staph. aureus came from patients and staff in a general medical ward and an ophthalmic ward (Table 2).

The strain of Staph. aureus was coagulase-positive, fermented mannitol, and was markedly pigmented. Bacteriophage typing of all the isolates of the gentamicin-resistant Staph. aureus demonstrated a common phage-type 54/77/83A/84. Some of the isolates were also typed by Dr V. G. Alder using additional phages (90 and 92) with which they gave positive reactions. The staphylococci were tested for sensitivity to antibiotics by a routine disc diffusion technique using Oxoid Diagnostic Sensitivity Test agar with 5% lysed horse blood, and low content discs as specified by Garrod et al. (1973). The strain was resistant to penicillin, tetracycline, erythromycin, clindamycin, fusidic acid, gentamicin, tobramycin, and streptomycin; sensitive to methicillin (tested at 30°C), cotrimoxazole, and chloramphenicol, and moderately sensitive to neomycin. It is of interest that Staph. aureus isolates from two patients who were admitted on the medical ward just before the epidemic started had an identical phage-type to that of the epidemic strain. The antibiogram was also identical except that the isolates were sensitive to gentamicin and tobramycin (Table 1).

Minimum inhibitory concentrations (MIC) and minimum bactericidal concentrations (MBC) of the aminoglycoside antibiotics (Table 1) were determined by the agar plate dilution method. Membrane filters on the surface of the drug-containing plates were transferred to drug-free plates to determine the MBC of each drug. Oxoid Diagnostic Sensitivity Test agar was used with a final inoculum of 5 × 10^4 colony-forming units. Studies to investigate the possible presence of aminoglycoside-inactivating enzymes were performed by the method of Broughall and Reeves (1975). The strain possessed both adenyl transferase and acetyl transferase activity against gentamicin and tobramycin but no activity against amikacin. Transduction experiments were performed by the technique of Lacey (1972). For these experiments typing phages 77, 83A, and 84 of the International Basic Set were propagated on the donor strain. The recipients PS77, PS83A, and PS84 were lawned on agar plates containing gentamicin at a concentration of 8 mg/l. All three phages transduced the resistance at a frequency of one transductant per 3 × 10^6 phage particles. Transduction was also attempted in mixed culture experiments by the method of Lacey (1972) using phages 77, 83A, and...
Table 1 | Sensitivity of Staph. aureus to aminoglycoside antibiotics

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Gentamicin-resistant strain</th>
<th>Gentamicin-sensitive strain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC (mg/l)</td>
<td>MBC (mg/l)</td>
</tr>
<tr>
<td>Amikacin</td>
<td>4</td>
<td>64</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>16</td>
<td>&gt;256</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>&gt;256</td>
<td>&gt;256</td>
</tr>
<tr>
<td>Neomycin</td>
<td>32</td>
<td>16</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>64</td>
<td>&gt;256</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>16</td>
<td>&gt;256</td>
</tr>
</tbody>
</table>

Table 2 | The patients and previous antimicrobial therapy

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>First isolation of Staph. aureus</th>
<th>Previous antimicrobial therapy</th>
<th>Gentamicin</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Date</td>
<td>Site(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General medical ward</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>23 Dec 1975</td>
<td>Wound</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>6 Jan 1976</td>
<td>Sputum, skin rash</td>
<td>+ (t)</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>9 Jan</td>
<td>Nose</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>20 Jan</td>
<td>Sputum</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>22 Jan</td>
<td>Scalp lesion</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>27 Jan</td>
<td>Abcess</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>3 Feb</td>
<td>Nose</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Ophthalmic ward</td>
<td></td>
<td>Conjuinctiva</td>
<td>+ (t)</td>
<td>-</td>
</tr>
</tbody>
</table>

(t) = Topical preparation.

84. The potential recipients were novobiocin-resistant, rifampicin-resistant mutants of the propagating strains of Staph. aureus. The medium for selection of transductants was Oxoid Diagnostic Sensitivity Test agar containing novobiocin, 5 mg/l, rifampicin, 50 mg/l, and gentamicin, 8 mg/l. The gentamicin-resistance marker failed to transduce in these mixed culture experiments.

The outbreak

Patient 1 (Table 2) was a woman who had had a panproctocolectomy for ulcerative colitis. She was given oral neomycin as part of her preoperative bowel preparation and three doses of lincomycin intramuscularly to cover the operation. Seven days after the operation she started a four-day course of gentamicin, 120 mg every 8 hours. Nineteen days after the operation the gentamicin-resistant strain of Staph. aureus was isolated from a wound swab. No special control of infection measures were taken for this patient.

Patient 2, a man with ankylosing spondylitis, renal amyloidosis, and psoriasis, was admitted to the same ward four days before patient 1 was discharged and while her wound was still infected with the Staph. aureus. He had been prescribed gentamicin cream for a rash on the scrotum and perineum two weeks before his admission. He continued to apply this cream for a few days while in hospital without informing the medical staff. A heavy growth of the resistant strain was isolated from his sputum and skin rash. There was clinical and radiological evidence of bronchopneumonia. He was immediately isolated and barrier nursed. Oral fluclouacillin therapy was started and the rash was treated with chlorhexidine dusting powder. He was sufficiently well to be discharged 24 days after admission. However, nasal and skin swabs still demonstrated the presence of the staphylococcus.

At the time of his infection patient 2 was in a four-bedded ward. Nasal swabs were taken from the other three occupants and from one of these (patient 3) the staphylococcus was isolated. Patient 3 was treated with 0.5% neomycin/0.1% chlorhexidine nasal cream (Naseptin) and discharged as soon as possible. Three further patients became infected during the following two weeks. The staphylococcus was isolated from a conjunctival swab from patient 4 who had been transferred from the general medical ward to an ophthalmic ward, sputum from patient 5, and a swab from a scalp lesion on patient 6. Patient 4 had received gentamicin eye-drops before the isolation of the staphylococcus. She was treated with chloramphenicol eye-drops, neomycin/chlorhexidine nasal cream, and oral fluclouacillin. Patient 5 was discharged immediately, and patient 6 was isolated and barrier nursed. Chlorhexidine 0.05% solution was applied to the scalp lesion and neomycin/chlorhexidine cream to the nose.

Patient 7 developed a buttock abscess from which a heavy growth of the epidemic staphylococcus was obtained. He was isolated and barrier nursed. Oral fluclouacillin therapy was given; he was later transferred to the infectious diseases unit in another hospital. At this stage all patients and staff who were, or had been, present in the general medical ward had nasal swabs taken. Two nurses and one patient (8) were found to be colonized with the epidemic staphylococcus. The patient was given neomycin/chlorhexidine nasal cream and discharged. The nurses were sent off duty and given a two-week course of neomycin/chlorhexidine nasal cream, povidone-iodine hair shampoo, and hexachlorophane bath concentrate. The ward was closed to admissions and transfers. Swabs from the nurses after the courses of treatment showed that the staphylococcus had been eliminated from both. No further patients have been infected with the staphylococcus at one month after patient 8 was colonized.
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Discussion

Recently, gentamicin-resistant strains of Staph. aureus have been described by Soussy et al (1975) and Porthouse et al (1976). In both of these instances the strains were single isolates and were not multiresistant. Sedimentation analysis of DNA and loss of the resistance at high frequency strongly suggested a plasmid locus for the resistance (Soussy et al, 1975). Our strain is resistant to aminoglycosides by nature of the possession of inactivating enzymes, as were the strains described by Porthouse et al (1976) and Speller et al (1976). Genes coding for drug-inactivating enzymes are usually plasmid borne. The transduction of gentamicin resistance at high frequency in our preliminary studies gives some support to a plasmid locus. Our strain is similar to that described by Speller et al (1976) in being multiresistant, differing only in its sensitivity to fusidic acid. However, the two strains had quite different phage types. The appearance of two isolates with the same phage type as the epidemic strain which were gentamicin-sensitive raises the interesting possibility that a plasmid bearing a gentamicin-resistance marker was transduced into a sensitive staphylococcus already present in the hospital. The phage-typing records of the hospital revealed that no other staphylococci of this phage type had been isolated during the preceding 12 months.

The sudden appearance of gentamicin-resistant strains of Staph. aureus in hospitals some 11 years after the introduction of the drug is similar to the delay in appearance of neomycin-resistant strains which did not appear for nine years after its introduction (Lacey, 1973). The sudden dissemination of neomycin-resistant strains often followed its topical use (Lowbury et al, 1964; Alder and Gillespie, 1967). In the outbreak reported here, six patients had clinical infections; three of these had been treated with gentamicin, two of them by topical administration. Three of the eight patients had received other antibiotics to which the strain was resistant. Our experience and that of Speller et al (1976) and Warren and Roberts (1976) show that both systemic and topical gentamicin therapy can lead to dissemination of resistant strains. Lacey (1975) had predicted that widespread gentamicin resistance in Staph. aureus would occur in a similar manner to neomycin-resistance. With the appearance of different phage-types resistant to gentamicin causing outbreaks of infection it would appear that this prediction is already coming true. The increasing and sometimes indiscriminate use of gentamicin and tobramycin will exert strong selective pressure to enable resistant strains to spread.

We strongly support the conclusions of Speller et al (1976) that the usefulness of gentamicin and tobramycin can be preserved only by the restriction of their use by rational prescribing of antibiotics. The frequent use of topical preparations of gentamicin should be actively discouraged.

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References


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