Methicillin-Resistant *Staphylococcus aureus* Strains in New York City Hospitals: Inter-Hospital Spread of Resistant Strains of Type 88

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Received 9 February 1984/Accepted 29 May 1984

A survey of methicillin-resistant strains of *Staphylococcus aureus* received for phage typing indicated a marked increase of resistant strains received in 1982 and 1983. Of 62 hospitals in New York City which sent strains for phage typing, 35 had methicillin-resistant isolates. A significant development was the presence of strains of the same phage type at several hospitals, indicating a possible inter-hospital spread of these strains. Among strains present at several hospitals, the largest group was of experimental phage type 88. Strains of type 88 were received from 23 hospitals, representing 56% of all methicillin-resistant strains received from New York City hospitals. Strains of type 88 were resistant to all antistaphylococcal antibiotics, with the exception of vancomycin, and represented a major source of nosocomial infections at 13 hospitals. As experimental phage 88 is not routinely used for typing in U.S. laboratories, the nationwide distribution of strains of type 88 is difficult to assess.

There are few data available concerning the regional epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) strains (6, 12, 13). Data from the general population refer mainly to drug addicts (14), whereas data regarding hospital outbreaks, in most instances, refer to individual hospitals (3, 7-11) or hospital services, especially burn units (5). In New York City, the Staphylococcal Phage Typing Unit of the Bureau of Laboratories receives specimens for phage typing from most hospitals in the city. In addition, hospitals are requested to send MRSA isolates as part of a long-term survey of the incidence of MRSA strains in New York City hospitals, thus allowing us to follow from inception the emergence of MRSA strains in these hospitals. This survey began in 1977 when the first MRSA strains were received by our laboratory. Initially (1977 to 1978), we received strains of phage type 92 from six hospitals (17), with a relatively large number of isolates at two hospitals. In 1979 to 1980, the number of hospitals with MRSA strains increased to 10. Strains of experimental phage type 92 were replaced by a variety of phage types, with most hospitals harboring a predominant endogenous phage type (16). Recent data accumulated in 1982 to 1983 indicated a marked increase in the number of hospitals with MRSA isolates and in the total number of strains. A significant development was the presence in various hospitals of MRSA strains of the same phage type, especially experimental phage type 88, indicating a probable inter-hospital spread of MRSA strains.

**MATERIALS AND METHODS**

Screening for methicillin-resistant strains. The strains investigated included *S. aureus* strains routinely received for phage typing by the Phage Typing Unit of the Bureau of Laboratories, New York City Department of Health, as well as strains obtained in a collaborative survey of the incidence of MRSA strains in New York City hospitals. With few exceptions, the strains received were from different patients. The strains were screened for methicillin and gentamicin resistance on agar plates with 10 μg each of methicillin and gentamicin per ml. Representative MRSA strains and, in some instances, methicillin-susceptible isolates of the same phage type as the MRSA strains were tested in the same manner as in previous surveys (3, 16, 17) for susceptibility to each of the following: amikacin, chloramphenicol, clindamycin, erythromycin, gentamicin, penicillin, rifampin, tetracycline, trimethoprim-sulfamethoxazole, and vancomycin.

**Phage susceptibility.** All strains were tested for phage susceptibility with the international set of *S. aureus* phages and an additional set of experimental phages routinely used in our laboratory (4, 16). The international phages were used at routine test dilution concentration and, in some instances, at 100× routine test dilution. The experimental phages were used at 100× routine test dilution concentration.

**Biochemical tests.** Acid production from mannitol and growth response was tested on mannitol salt agar plates (Difco). The same medium with 0.9% NaCl and 1% mannitol or 1% lactose was used for additional carbohydrate tests. Plasmid DNA electrophoresis was performed in the same manner as previously described (15), except that the lysostaphin concentration was increased to 100 μg/ml, and the cells were kept for 5 min at room temperature after the addition of 1% dodecyl sulfate in 0.2 M NaOH.

**RESULTS**

Distribution of methicillin-resistant strains. Table 1 summarizes the distribution of MRSA strains received for phage typing from hospitals in New York City. In the period between January 1982 and October 1983, we received *S. aureus* strains for phage typing from 62 hospitals. MRSA strains were found at 35 hospitals. When compared with previous surveys of MRSA strains isolated in New York City, there was a marked increase in both the number of strains and in the number of hospitals: from 1977 to 1978, 125 strains were received from 6 hospitals (17); from 1979 to 1980, 195 strains were received from 10 hospitals (16); and from 1982 to 1983, 2,309 strains were received from 35 hospitals. Of the strains tested, 1,825 (79%) were isolated at 13 large hospitals, each with over 750 beds. Of the 188

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strains received from hospitals with less than 500 beds, 94 came from a single hospital.

Bacteriophage susceptibility. Of the MRSA strains tested, only 33.9% were typable by the international set of phages, although 62% were typable by experimental phages routinely used in our laboratory; those were mainly experimental phage 88 (56%). The ratio of strains typable by the international phages was significantly higher with methicillin-susceptible strains isolated in the same period (74.2%). A new group of methicillin-resistant strains which emerged in 1982 was of variable susceptibility to international phages 85 and 81 but of consistently high susceptibility to experimental phage 208.

Antibiotic susceptibility and acid production from mannitol and lactose. The initial screening data indicated that 79% of the MRSA strains were resistant to gentamicin (Table 1). Antibiotic susceptibility was tested with 430 strains originating from 28 different hospitals. These strains were representative for the main phage types. Strains susceptible to experimental phage 88, representing the largest group of isolates, were resistant to chloramphenicol, clindamycin, erythromycin, gentamicin, penicillin, rifampin, streptomycin, and tetracycline. The strains were susceptible to vancomycin and varied in their susceptibility to amikacin and trimethoprim-sulfamethoxazole. For the remaining strains, the order of frequency of resistance was as follows: penicillin, tetracycline, gentamicin, streptomycin, erythromycin, clindamycin, chloramphenicol, and rifampin. All strains tested were susceptible to vancomycin. Strains of type 88 produced acid from mannitol but not from lactose, whereas strains susceptible to phages 85, 81, and 208 were mannitol negative and lactose positive.

Strains present in several hospitals. Strains susceptible to phages 85, 81, and 208 were isolated at 13 hospitals. In most instances, these strains were found at hospitals in which MRSA strains of other phage types were predominant, notably experimental phage type 88. Strains susceptible to phages 85, 81, and 208 exhibited heterogeneous resistance to methicillin and were resistant to gentamicin, penicillin, streptomycin, and tetracycline. They varied in the resistance to clindamycin and erythromycin and were susceptible to chloramphenicol and rifampin.

Strains of experimental phage type 88 represented the main group of methicillin-resistant strains (Table 1). Strains of this type were received from 23 hospitals and were the predominant strain at 13 hospitals. Twelve of these were hospitals with 500 beds or more. The largest number of strains was received from three hospitals (257, 253, and 217 strains), accounting for 54% of isolates of type 88. Two of these hospitals were affiliated and partly shared their medical staff. Strains of type 88 were obtained from blood cultures, cerebrospinal fluid, wound infections, sputum, urine, and asymptomatic carriers. Starting in 1982, there was a marked increase in the number of strains isolated from blood cultures. Only in a few instances could the index cases be identified; one was an intravenous drug addict without known prior hospitalization. In 1979 to 1980, strains of type 88 were first received from a burn unit in a university-affiliated hospital and, subsequently, from two additional hospitals, all three hospitals being located in Manhattan (16). Strains of type 88 are still endemic at these hospitals. Subsequently, MRSA strains of type 88 were received from hospitals located in the boroughs of Bronx (two hospitals), Brooklyn (three hospitals), and Queens (three hospitals). The largest number of isolates was, however, obtained in Manhattan (15 hospitals). MRSA strains of type 88 tended to persist at hospitals from which we received at least 20 isolates, being consistently the main group of MRSA strains received from these hospitals. In several instances, the incidence of type 88 strains was reduced by isolation and cohorting of patients, but they were never completely eradicated.

Variations in antibiotic and phage susceptibility. Strains of type 85, 81, and 208, which are susceptible to methicillin, were isolated at the same hospitals in which methicillin-resistant strains of the same phage type were isolated. Methicillin-susceptible strains retained gentamicin resistance and were mannitol negative. Strains susceptible to phage 84 (group III) were isolated at the same hospitals in which strains of type 88 were isolated. These strains exhibited the resistance spectrum of type 88 strains, including rifampin resistance and were susceptible to experimental phages 88 or 89, 88, and 89. Some strains also became susceptible to phages 83A and 85. The strains carried a very large plasmid and a small chloramphenicol plasmid characteristic for strains type 88 (15) and did not produce acid from lactose. In mixed culture with strain 766, these strains acquired phage-mediated novobiocin resistance (15). This appears to indicate that some MRSA strains classified as belonging to the international phage group III are closely related to strains of type 88.

Both clinical isolates and in vitro derivatives of strains of type 88 were obtained which lost gentamicin and clindamycin or methicillin and cadmium resistance. These susceptible derivatives showed no detectable changes in their plasmid DNA electrophoretic pattern or phage susceptibility. Chloramphenicol-susceptible derivatives lacked the small chloramphenicol plasmid. We obtained in vitro and also from cul-

<table>
<thead>
<tr>
<th>Hospital group</th>
<th>No. of hospitals</th>
<th>No. of MRSA strains</th>
<th>Met + Gent</th>
<th>Phage type</th>
<th>85/81 (Exp 208)</th>
<th>Exp 88</th>
<th>Other</th>
<th>NT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over 1,000 beds</td>
<td>6</td>
<td>655</td>
<td>521</td>
<td>4</td>
<td>118</td>
<td>8</td>
<td>72</td>
<td>4^*</td>
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<td>1,170</td>
<td>891</td>
<td>19</td>
<td>224</td>
<td>6</td>
<td>127</td>
<td>6^*</td>
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<tr>
<td>500–750 beds</td>
<td>13</td>
<td>296</td>
<td>296</td>
<td>10</td>
<td>102</td>
<td>8</td>
<td>8</td>
<td>109</td>
</tr>
<tr>
<td>250–500 beds</td>
<td>9</td>
<td>188</td>
<td>148</td>
<td>2</td>
<td>69</td>
<td>9</td>
<td>1</td>
<td>68</td>
</tr>
<tr>
<td>%</td>
<td>79</td>
<td>1.52</td>
<td>0.025</td>
<td>1.3</td>
<td>9</td>
<td>56</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

* Met + Gent, Resistant to gentamicin and methicillin; I, international phage group I; II, international phage group II; III, international phage group III; Misc, miscellaneous phage types (81, 94 and 96); 85/81 (Exp 208), weak susceptibility to phages 85 and 81, susceptible to experimental phage 208; Exp 88, susceptible to experimental phage 88. Other, susceptible to experimental phages other than 88; NT, not typable.

* Data in parentheses indicate number of hospitals at which strains of type 85/81 (Exp 208) were isolated.

* Data in parentheses indicate number of hospitals at which the majority of the isolates were of phage type 88.

Data from Table 1.
tures of type 88 received from two hospitals susceptible isolates which retained resistance to penicillin and tetracycline and, in several instances, resistance to streptomycin and clindamycin. These strains were characterized by the appearance of at least three additional plasmids, possibly originating from the very large plasmid present in strains of type 88. They became susceptible to a large number of phages of groups I and III as well as several experimental phages. Their lysogenic phage had the same host spectrum as phage 188 present in strains of type 88 and promoted acquisition of novobiocin resistance from strains of type 766 (15). These strains are presently under investigation.

**DISCUSSION**

Large urban centers such as New York City pose specific epidemiological problems due to the size and mobility of their population and the concentration in a limited area of a sizable number of large health care facilities. Under these circumstances, the inter-hospital spread of nosocomial infections can be of epidemiological significance. In the case of MRSA strains, the investigation of inter-hospital transfer of MRSA strains is facilitated by the existence of a central phage typing facility. This organizational setup imposes certain limitations in the interpretation of our data. Large hospitals with well-staffed epidemiological control services are probably overrepresented in this survey.

The factors affecting the inter-hospital spread of MRSA strains are only partly understood. Among them are common medical staff in affiliated hospitals, prior hospitalization of patients in hospitals with endemic MRSA strains, and the spread of resistant strains among drug addicts (14). A still unknown factor is the prevalence of MRSA strains in the general population. A preliminary investigation of *S. aureus* strains isolated at pediatric clinics yielded no methicillin-resistant strains among the 400 strains tests (S. Schaefer, unpublished data).

A comparison of phage types and resistance patterns of MRSA strains isolated in New York City over a period of 6 years indicated major shifts in both the predominant phage types and resistance spectra. The first methicillin-resistant strains received by our laboratory were of experimental phage type 92 (17). The strains of type 92 were predominantly gentamicin susceptible. During a subsequent survey in 1979 to 1980 (16), strains of type 92 were replaced by other phage types at each of the hospitals in which they were initially isolated, mostly by gentamicin-resistant MRSA strains. In contrast to the strains isolated in 1977 to 1978, the strains isolated in 1979 to 1980 showed a variety of phage susceptibility patterns, with some of the hospitals having characteristic endemic strains. At that time, there was apparently only a limited inter-hospital spread of MRSA strains.

The main epidemiological feature observed in 1982 to 1983 was the presence of strains of the same phage type at several hospitals, especially the emergence of strains of type 88 as the main MRSA isolate at a large number of hospitals. The consistent presence of rifampin resistance, lysisogeny for phage 188, and the small chloramphenicol plasmid (15) in all strains tested in this respect seems to indicate a common origin of these strains. The causes for the spread of strains of type 88 are difficult to assess. Contributing factors could be the tendency of these strains to persist in the hospital environment. As our laboratory is apparently the only Public Health Laboratory in the United States using phage 88 for *S. aureus* phage typing, it could be interesting to ascertain the incidence of MRSA strains of type 88 among "nontypable" strains isolated in other regions of the United States.

**LITERATURE CITED**


