Ciprofloxacin-Resistant Methicillin-Resistant *Staphylococcus aureus* in New York Health Care Facilities, 1988

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Abstract: The emergence in 1988 of ciprofloxacin-resistant methicillin-resistant *Staphylococcus aureus* (MRSA) in New York City was studied in nine hospitals and eight nursing homes. Of the 43 hospitalized patients studied, 21 were admitted from home, while nine of the 12 nursing home patients were transferred from a hospital. Twenty-four of the 55 patients had been treated previously with ciprofloxacin, and 26 had an identifiable risk factor for a nosocomial infection. MRSA was a contributing factor in at least five of the 21 deaths. MRSA resistance to ciprofloxacin was detected within three months of the drug's commercial availability, apparently emerged independently at a number of the health care facilities, and has become widespread. If such resistance is found in a health care facility, ciprofloxacin may not be useful as a first line antibiotic. (*Am J Public Health* 1990; 80:810–813.)

Introduction

Staphylococcus aureus caused a pandemic of nosocomial infections in the 1950s.[1] Shortly after methicillin was introduced into clinical practice, methicillin-resistant *S. aureus* (MRSA) emerged as a prominent cause of nosocomial infections first in Europe and later in the United States.[2–7] Patients can introduce MRSA into a health care facility from the community and cause intra- and inter-institutional spread.[8–11] Ciprofloxacin, an oral fluoroquinolone antibiotic that became commercially available on October 22, 1987, has bacteriocidal activity *in vitro* against MRSA[12] and is reportedly useful for the treatment of infections with susceptible staphylococci of the skin and skin structures,[13] for which it is marketed, bones,[14] and the lower respiratory tract.[15] This report examines the emergence of MRSA resistant to ciprofloxacin in New York City hospitals and nursing homes in 1988.

Methods

The Bureau of Laboratories Phage Typing Unit of the New York City Department of Health is the reference laboratory in New York City for bacteriophage typing of *S. aureus* isolates voluntarily submitted by hospitals, nursing homes, and other laboratories. All facilities do not submit isolates for typing and individual facilities do not necessarily submit all their isolates. The method of phage typing has been previously described in detail.[16–18] In summary, isolates are initially tested for phage susceptibility using the international set of *S. aureus* phages (at routine or 100X routine test dilution concentration) and then are tested using an experimental set of phages (at 100X routine test dilution). In addition, isolates are tested for acid production from mannitol, for growth response on mannitol salt agar plates (Difco Laboratories), and for susceptibility to a standard panel of antibiotics.[17–19] Ciprofloxacin susceptibility has been tested since May 1987 and resistance to ciprofloxacin was defined as a minimal inhibitory concentration ≥ 4.0 μg/mL. Isolates that differed by ≥ 3 of 13 findings in their antibiogram and biochemistry profiles were categorized as different.

The Phage Typing Unit MRSA laboratory records were reviewed for all isolates submitted between May 1, 1987 and June 30, 1988 that were resistant to ciprofloxacin. Isolates from 67 patients in 14 New York City hospitals and 14 patients in nine nursing homes (seven in New York City, two in bordering counties) were identified. The infection control practitioners of these 23 facilities were requested to complete for each patient a standardized data collection form based on the Centers for Disease Control National Nosocomial Infections Surveillance System Infection Worksheet. Data were collected concerning demographic factors, medical history, surgical procedures, cultures obtained, antibiotic treatment, hospital course, and outcome. Data were also collected concerning any patient at the facility who had a culture that revealed MRSA resistant to ciprofloxacin that was not submitted to the Phage Typing Unit.

Data on 43 patients were submitted by nine (64.3 percent) of the hospitals which are located in Manhattan (five) and Brooklyn (four) [the five nonparticipating hospitals are in Manhattan (two), Queens (two), and Brooklyn (one)]. Data on 12 patients were submitted by eight (88.9 percent) of the nursing homes which are located in the Bronx (four), Manhattan (one), Queens (one), Westchester (one), and Nassau (one); (the nonparticipating nursing home is in Brooklyn). Patients with positive cultures from normally sterile body sites or who were treated with antibiotics for positive cultures were considered infected; all others were considered colonized.

The data were coded and computerized using DBase III software. Statistical methods used included chi-square tests

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for independence and Fishers exact test. Odds ratios (OR) and 95% confidence intervals (CI) were calculated.

Results

The Patients

The first positive culture for ciprofloxacin-resistant MRSA in New York City was obtained from a patient in late January 1988. Prior to that time, ciprofloxacin-resistant MRSA had not been reported in New York City. Of the 55 patients on whom we have reports, 30 were males, 25 were females, and the age range was 23 to 96 years, with a mean of 67.5 years and a median of 73 years. The mean age of the nursing home patients (71.8 years) was five years greater than that of the hospital patients. The principal diagnoses at admission were cerebrovascular accident (16.4 percent), pneumonia (12.7 percent), atherosclerotic heart disease (9.1 percent), sepsis (9.1 percent), and gangrene/cellulitis (7.3 percent), with other diagnoses accounting for two or fewer patients each. Two patients had the acquired immunodeficiency syndrome (AIDS). In addition, seven patients had insulin dependent diabetes mellitus and four had a reported history of intravenous drug use; none were on hemodialysis.

Almost half of the hospitalized patients were admitted from home, while three-fourths of the nursing home patients were transferred from a hospital (Table 1). The median time from admission to the first positive culture for MRSA was 25 days for 38 of the hospital patients and 340 days for the nursing home patients. Of the nine hospital patients who had a positive culture within one week of admission, five were admitted from home, including the two patients with a positive culture on the day of admission, three were admitted from a nursing home, and one was transferred from another hospital. The one nursing home patient who had a positive culture within one week of admission had been transferred from a hospital. At least 26 (47.3 percent) of the patients had at least one prior culture negative for ciprofloxacin-resistant MRSA and 14 patients had previous treatment with systemic antibiotics.

The culture source of each patient's initial MRSA isolate is listed in Table 2. All eight bacteremic patients and 20 of the 22 patients with positive pulmonary or sputum cultures were hospitalized. Of the 22 patients with a sputum or pulmonary source, 13 had definite radiologic evidence of pneumonia and three had possible radiologic evidence of pneumonia. Almost half of the patients had an identifiable risk factor for a nosocomial infection. Of the 21 deaths, MRSA was estimated by the clinical staff to have contributed to the deaths of at least five.

At least one antibiotic had been used for 52 of the 55 patients and 24 were treated with ciprofloxacin, 19 of whom began taking ciprofloxacin at least two days before the first MRSA positive culture was obtained. None of eight patients with a culture positive for MRSA within one week of admission received ciprofloxacin (data were unavailable for one patient). Twenty-two additional patients who did not receive ciprofloxacin were infected or colonized with ciprofloxacin-resistant MRSA. Ciprofloxacin use among the nursing home patients (75.0 percent) was greater than its use among the hospital patients (OR = 5.6, 95% CI = 1.1, 27.0).

TABLE 1—Places from Which Patients Were Admitted, by Patient's Facility at Time of Culture

Admitted From	Facility at Culture: Hospital, n	Facility at Culture: Nursing Home, n	Total, n
Home	21	1	22
Hospital	6	9	15
Nursing Home	12	1	13
Other/Unknown	4	1	5
Total	43	12	55

TABLE 2—Initial Source of Ciprofloxacin-resistant Methicillin-resistant *Staphylococcus aureus*, Site-Specific Risk Factors, and Deaths

Methicillin-resistant *Staphylococcus aureus* Source	Number	Nosocomial Risk Factor	Number with Risk Factor	Number Who Died
Blood	8	Central venous catheter	7	3
Pulmonary/sputum	22	Ventilator	8	15
Urine	8	In-dwelling catheter	5	2
Wound	14	Previous incision	4	1
Other	3	Invasive procedure	2	0
Total	55	Any noted above	26	21

The MRSA Isolates

The phage susceptibility of the ciprofloxacin-resistant MRSA are listed by facility in Table 3. The distribution of phage types differed between the hospitals and the nursing homes, with 57 percent of the isolates from the hospital patients that were typed susceptible to experimental phage 88 and 64 percent of the isolates from the nursing home patients that were typed susceptible to phages of International Group III. When facilities were grouped by geographic location, no singular or unique pattern was identified.

Ten facilities identified more than one patient with ciprofloxacin-resistant MRSA. The antibiograms, biochemistry tests, and phage typing of the isolates from nine of these facilities are available. Table 4 lists the number of different phage types and antibiogram/biochemistry patterns by facility. Three hospitals and one nursing home identified isolates with multiple phage groups and multiple antibiogram/biochemistry patterns. In one hospital (M-2) there was a close association between the phage groups and the antibiogram/biochemistry patterns, in two of the facilities (hospital K-1 and nursing home B-1) there was a variable association, and in one hospital (M-4) there was no association.

Discussion

In this investigation, we document the emergence of ciprofloxacin-resistant MRSA in New York City health care facilities, which was first noted in 1988.[19] The data are incomplete and represent a minimal account, however, because not all facilities report MRSA and submit all isolates to the NYCDOH and not all facilities that did submit isolates participated in this survey. In addition, this retrospective analysis was limited to MRSA isolates and not other *S. aureus* isolates. Finally, the patients may have been misclassified as being infected or colonized, because patients could have been treated with antibiotics inappropriately and because not all culture data were provided on each patient. Nevertheless, several important conclusions can be reached.

The ciprofloxacin-resistant strains appear to have emerged independently at a number of the health care facilities. This was also seen in the broader survey of reported quinolone-resistant *S. aureus* isolates in New York City.[19]

TABLE 3—Phage Susceptibility of Ciprofloxacin-resistant Methicillin-resistant *Staphylococcus aureus* by Facility

Facility*	International Group 2	International Group 3	Experimental Phage 88	Other Experimental#	Not Typable	Not Typed	Total
Hospitals							
M-1		2				9	11
M-2		5	1		1	1	8
M-3			8				8
M-4			2		1		3
M-5			1				1
K-1			2	1	3		6
K-2						3	3
K-3			2				2
K-4			1				1
Subtotal		7	17	1	5	13	43
Nursing Homes							
B-1	1	1	1				3
B-2		1					1
B-3		1					1
B-4		1					1
X-1			1	1			2
X-2		1				1	2
X-3		1					1
X-4		1					1
Subtotal	1	7	2	1		1	12
Total	1	14	19	2	5	14	55

*Facilities: M = Manhattan, K = Brooklyn, B = Bronx, X = Other locations for nursing homes (1 each in Manhattan, Nassau, Queens, Westchester)
#Experimental phages excluding phage 88

The distribution of ciprofloxacin-resistant MRSA detected may represent either actual differences between hospitals and nursing homes, differences in community flora, or selective underreporting by facilities in other New York City boroughs. If the difference between the facilities is real, it is possible that MRSA isolates with this resistance pattern are transferred only between similar facilities locally, and we did note a few patients who may have been the vectors of transmission between facilities. Although nursing home patients have been prospectively implicated as a source of MRSA in Chicago hospitals,[8] half of the hospital patients we studied came from their homes, and colonized nursing home residents did not appear to be the major source of ciprofloxacin-resistant MRSA in the hospitals. Similarly, although the majority of the nursing home patients came from hospitals, many had a prior culture negative for ciprofloxacin-resistant MRSA and this admission pattern may be the usual one for nursing home residents.

TABLE 4—Phage Group, Antibiogram, and Biochemistry Patterns of Ciprofloxacin-resistant Methicillin-resistant *Staphylococcus aureus* by Facility

Facility*	Number of Isolates	Number of Different Phage Groups	Number of Different Antibiogram/Biochemistry Patterns
M-1	11	1	3
M-2	8	3	3
M-3	8	1	1
K-1	6	3	3
B-1	3	3	2
M-4	3	2	2
X-1	2	2	1
K-3	2	1	2
X-2	2	1	1

*See footnote Table 3.

Ciprofloxacin-resistant MRSA, which contributed to almost one-fourth of the deaths and which resulted in an outbreak that eventually affected over 40 patients in one of the hospitals (Michael S. Simbercoff, MD: personal communication) appears as virulent as other *S. aureus* strains.[20] In this investigation, the majority of patients had MRSA resistant to ciprofloxacin without prior ciprofloxacin treatment. Therefore, ciprofloxacin may not be useful as a first line antibiotic, especially in facilities where ciprofloxacin-resistant MRSA is already prevalent.[21] Although data indicating that the prevention of resistance to ciprofloxacin by combination chemotherapy are few, ciprofloxacin may best be used in combination with other agents.[22–25]

We recommend that isolates of *S. aureus* be tested for susceptibility to ciprofloxacin in all health care facilities where ciprofloxacin is used. This increased testing provides clinicians with additional information necessary to prescribe appropriate treatment and allows additional surveillance opportunities to further define the spread of ciprofloxacin-resistant MRSA. In New York City, the Phage Typing Unit received 717 ciprofloxacin-resistant *S. aureus* isolates from 31 hospitals and 28 nursing homes from July 1 to December 31, 1988, 23 percent of the 3134 MRSA isolates submitted for phage typing (New York City Department of Health: unpublished data).

MRSA, in general, is becoming more problematic to health care facilities in New York. In a 1987 New York State Department of Health statewide survey, 40 (36 percent) of 111 acute care hospitals reported that they were adversely affected by MRSA. Furthermore, 23 outbreaks of nosocomial MRSA were reported in New York City health care facilities between July 1, 1987 and December 31, 1988 (New York State Department of Health: unpublished data). In response, the Department is promoting policies for health care facilities, based in part on those of the Los Angeles County Department of Health[26] and the Centers for Disease

Control[27,28] which emphasize the importance of traditional infection control measures, i.e., surveillance, handwashing, barrier precautions, epidemiologic assessment and appropriate cultures, individualized treatment, and intra- and inter-facility communication. Additional prevention and control measures have been described elsewhere[29] and have been discussed in a recent review.[30] Health care facilities may also find the surveillance of certain prescribed antibiotics and their control useful.[30–33] Finally, health care facilities need to work together to control the spread of MRSA and to provide the appropriate level of care for colonized or infected patients.

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