Eradication of methicillin-resistant *Staphylococcus aureus* from the lower respiratory tract of patients with cystic fibrosis

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DR BURDGE, EM NAKIELNA, MA NOBLE. Eradication of methicillin-resistant *Staphylococcus aureus* from the lower respiratory tract of patients with cystic fibrosis. Can J Infect Dis 1995;6(2):97-101. Two of 95 patients followed in an adult cystic fibrosis clinic consistently grew methicillin-resistant *Staphylococcus aureus* (MRSA) on sputum culture. Sputum Gram stain consistently showed +4 polymorphonuclear leukocytes and +4 Gram-positive cocci in clusters. Both patients were co-infected with *Pseudomonas aeruginosa* and required multiple hospitalizations for treatment of pulmonary exacerbation, resulting in significant infection control concerns. Multiple courses of antibiotics, including ciprofloxacin and clindamycin regimens, failed to eliminate the MRSA. A combination of oral rifampin and clindamycin was successful in eradicating the organism from both patients. Over a 12-month period following therapy, in both patients none of 13 sputums showed Gram-positive cocci in clusters on Gram stain and none of 13 sputum cultures grew MRSA. Successful eradication of MRSA has greatly simplified infection control measures on subsequent hospitalizations, reducing costs and enhancing patient comfort.

Key Words: *Cystic fibrosis, Eradication of infection, Infection control, Methicillin-resistant Staphylococcus aureus*

Éradication d'un *Staphylococcus aureus* méthicillino-résistant dans les voies respiratoires inférieures de patients atteints de fibrose kystique

RÉSUMÉ : Deux patients sur 95 suivis dans une clinique pour fibrose kystique chez l'adulte ont présenté avec constance une culture des expectorations positives à l'égard d'un *Staphylococcus aureus* méthicillino-résistant. La coloration de gram des expectorations a révélé la présence de +4 leucocytes polymorphonucléaires et +4 cocci gram-positifs en amas. Les deux patients étaient co-infectés par *Pseudomonas aeruginosa* et ont nécessité de multiples hospitalisations pour le traitement d'exacerbations pulmonaires qui ont beaucoup inquiété les autorités de lutte contre l'infection. De multiples antibiothérapies, y compris de la ciprofloxacine et de la clindamycine ont échoué à éliminer le *S aureus* méthicillino-résistant. Une association de rifampine et de clindamycine orale a réussi à éradiquer l'organisme chez les deux patients. Sur une période de 12 mois suivant le traitement, les deux patients n'ont présenté aucune croissance de cocci gram-positifs en amas sur 13 cultures et aucune de ces 13 cultures n'a permis d'isoler le *S aureus* méthicillino-résistant. L'éradication complète de cette souche a grandement simplifié les mesures de lutte contre l'infection lors d'hospitalisations subséquentes, réduisant ainsi les coûts et améliorant le confort des patients.

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CYSTIC FIBROSIS (CF) REMAINS THE MOST COMMON SEMILETHAL genetic disease of Caucasians (1). While the majority of CF patients die prematurely of respiratory failure, many are now reaching adulthood. Recent Canadian Cystic Fibrosis Foundation data indicate that the median age of survival for Canadian CF patients reached 30.9 years in 1991 (2). CF, therefore, has clearly become an adult disease that internists, chest physicians and gastroenterologists will encounter with increasing frequency.

Patients with CF develop chronic lower respiratory tract infection, usually initially with *Staphylococcus aureus* and later with *Pseudomonas aeruginosa* (3,4). Once infection develops, it usually persists, and infection combined with host inflammatory and immune response leads to progressive pulmonary damage, bronchiectasis, chronic obstructive pulmonary disease, and eventually respiratory failure and death. Although chronic *S aureus* infection of the lower respiratory tract is extremely common in this patient group, methicillin-resistant strains of *S aureus* (MRSA) have been infrequently encountered (3,5). Two of 95 patients followed in our adult CF clinic consistently grew MRSA on sputum culture. Sputum Gram stain consistently showed +4 polymorphonuclear leukocytes (PMNs) and +4 Gram-positive cocci in clusters, and MRSA was believed to be infecting the lower respiratory tract. Both patients were chronically co-infected with *P aeruginosa* and required multiple hospitalizations for treatment of pulmonary exacerbation. Given the potential for MRSA to cause serious nosocomial infection (6-9), each hospitalization resulted in considerable anxiety about potential spread of the organism. In accordance with recommended infection control practices (6,9) strict isolation precautions were instituted. This resulted in increased expense and decreased patient comfort. The clinical significance of MRSA in the lower respiratory tract of these patients was not totally clear, but because it may have been contributing to pulmonary disease, and because of the major infection control implications, we elected to try to eradicate the organism from the lower respiratory tract.

CASE PRESENTATIONS

Case one: A 28-year-old female with known CF required several hospitalizations each year for treatment of pulmonary exacerbation. Pulmonary function testing revealed forced expiratory volume in 1 s (FEV_1) of 2.19 L (70% predicted) and forced vital capacity (FVC) of 2.97 L (77% predicted). Shwachman score was 85/100. Sputum consistently grew *P aeruginosa*. Methicillin-sensitive *S aureus* (MSSA) was isolated from sputum cultures in October and November 1987. Throughout 1988 and 1989 no *S aureus* was isolated from sputum. MRSA was first isolated January 18, 1990 and subsequently grew from 10 of 11 sputum cultures between January 1990 and June 1991. Sputum Gram stains consistently demonstrated +3 or +4 PMNs and +3 or +4 Gram-positive cocci in clusters in addition to Gram-negative rods. During the 18 months that MRSA was consistently isolated from sputum, four courses of oral ciprofloxacin, and four courses of high dose parenteral tobramycin and ceftazidime therapy were administered. None of these interventions, directed primarily against *P aeruginosa* infection, eradicated MRSA. A three-week course of oral rifampin 600 mg daily and clindamycin 600 mg tid was given in June 1991. Over the subsequent 12 months (July 1991 to July 1992), none of 13 sputum Gram stains showed Gram-positive cocci in clusters, and none of 13 sputum cultures grew MRSA. Since eradication of MRSA there has been no obvious change in her clinical status, or in the frequency of hospital admissions.

Case two: A 31-year-old female with known CF averaged four hospital admissions yearly for treatment of pulmonary exacerbation. Pulmonary function testing revealed FEV_1 of 1.0 L (27% predicted) and FVC of 1.68 L (37% predicted). Shwachman score was 40/100. For many years, the sputum consistently grew *P aeruginosa* and no *S aureus*. MRSA was first isolated from sputum in November 1988, and subsequently grew from 20 of 29 cultures through June 1991; 12 of 12 cultures from June 1990 through June 1991 grew MRSA. During this time sputum Gram stain consistently demonstrated +3 or +4 PMNs, +3 or +4 Gram-positive cocci in clusters and Gram-negative rods. After the first isolation of MRSA, five courses of parenteral tobramycin, ceftazidime and clindamycin, two courses of tobramycin and ceftazidime, one course of tobramycin, ceftazidime and ciprofloxacin, one course of tobramycin and ticarcillin, and multiple courses of oral cephalexin and ciprofloxacin were administered for treatment of pulmonary exacerbation. None of these interventions eradicated the MRSA. A two-month course of oral rifampin 600 mg daily and clindamycin 600 mg tid was instituted in June 1991. Over the subsequent 12 months (July 1991 to July 1992), none of 13 Gram stains showed Gram-positive cocci in clusters, and none of 13 sputum grew MRSA. In 1992 the patient became infected with *Pseudomonas cepacia*, and subsequently deteriorated and died in March 1993 of *P cepacia* pneumonia.

MICROBIOLOGICAL METHODS

Expectorated sputum from all CF patients was routinely inoculated onto 5% sheep blood agar (with *S aureus* streak), MacConkey agar, colistin-nalidixic acid agar and *P cepacia* agar. A mannitol salt agar plate containing D-mannitol 10 g/L and sodium chloride 75 g/L, highly selective for *S aureus*, was added to the routine CF sputum protocol for a three-month period from June 1991 through September 1991. During this time, 95 sputum specimens were cultured from 49 adult CF patients; 35 of 95 (37%) cultures grew *S aureus*, but no MRSA was detected. It was concluded that the routine CF sputum microbiology protocol was highly sensitive for the detection of MRSA, and that other CF patients in the authors' centre were not colonized or infected (10).

S aureus isolates were identified according to standard methods. Susceptibility testing was performed at the University Hospital, Vancouver microbiology laboratory. All *S aureus* isolates were tested for cloxacillin resistance to 4 mg/mL by agar dilution method. Initial screen for intrinsic methicillin resistance was accomplished using an amoxicillin-clavulanate disc; a 20 mm or greater zone of inhibition was interpreted as hyperbeta-lactamase production, while less than 20 mm was interpreted as intrinsic methicillin resistance (11). Minimum

inhibitory concentration testing was performed by microbroth dilution technique (Sensititre, Radiometer/Copenhagen Company, Ohio) using a sensititre AGPMI multititre panel in accordance with the manufacturer's instructions. *S aureus* ATC 29213 was run as a simultaneous control with patient isolates.

MICROBIOLOGICAL RESULTS

Isolates from both patients had zone sizes of 16 to 17 mm around the amoxicillin-clavulanate disc, consistent with intrinsic methicillin resistance. In vitro sensitivity data are summarized in Table 1.

TABLE 1
Results of in vitro sensitivity testing

Antibiotic	MIC (mg/L)	
	Patient 1 isolate	Patient 2 isolate
Ampicillin	16	16
Cephalothin	4	8
Chloramphenicol	8	8
Clindamycin	0.12	0.12
Erythromycin	0.25	0.25
Gentamicin	32	32
Imipenem	0.25	0.25
Oxacillin (2% NaCl)	ô32	ô32
Penicillin	ô4	ô4
Rifampin	1	1
Tetracycline	1	1
TMP-SMX	0.25/4.75	0.25/4.75
Vancomycin	1	1

MIC Miminum inhibitory concentration; TMP-SMX Trimethoprim-sulfamethoxazole

DISCUSSION

Factors associated with acquisition of MRSA include duration of hospitalization, prior administration of one or more antibiotics and duration of prior antibiotic therapy (7). Patients with CF who receive multiple courses of prolonged combination antipseudomonal antibiotic therapy therefore appear to be at particularly high risk of colonization and infection with MRSA. There is, however, surprisingly little published information regarding MRSA in this population. Szaff and Hoiby (5) report that MRSA in CF patients in Denmark is a 'rare occurrence', and in a recent review of the microbiology of airway disease in patients with CF, Gilligan (3) states only that his experience confirms that MRSA is 'not a concern' in the CF population. Boxerbaum and colleagues (12) retrospectively reviewed throat and sputum cultures from 452 CF patients during 1986 and found that 14 (3%) patients at Rainbow Babies and Children's Hospital, Cleveland, Ohio were colonized with MRSA. None of these patients was treated specifically for the MRSA, and the study is limited by its retrospective nature and the lack of patient follow-up. There is no other previously published study on MRSA in this population.

In general, infection of the lower respiratory tract in CF patients, once established, is very difficult to eradicate. This is particularly true of chronic *P aeruginosa* infection where even prolonged courses of combination parenteral antipseudomonal therapy usually fails to eradicate the organism from the lung. Michel (13) reviewed the published studies of antipseudomonal therapy in CF patients between 1980 and 1987 and reported that only 13 of 64 studies had more than 30% patients with negative sputum cultures after therapy. MSSA has proven to be less problematic than *P aeruginosa* in these patients, and the prevalence of MSSA infection decreases with age (3,4). Szaff and Hoiby (5) reported reasonable success in controlling MSSA infection by repeatedly treating patients with positive sputum cultures with fusidic acid in combination with oxacillin. Nevertheless, chronic MSSA infection can also be extremely difficult to eradicate. In a study of clindamycin therapy of staphylococcal infection in CF patients, Shapera et al (14) noted that MSSA persisted in 59% of treated patients. Pittman et al (15) studied the phage type of *S aureus* isolated from CF patients and found that, in 65 patients from whom *S aureus* was isolated on more than one occasion, the phage type remained consistent in 52, suggesting persistent infection with the same organism despite prolonged antistaphylococcal therapy.

Given the difficulty in eradicating *P aeruginosa* or MSSA from patients with CF, it is anticipated that eradication of MRSA from the lower respiratory tract would be extremely difficult. Frénay et al (16) recently reported an adult CF patient with long term carriage of MRSA in whom repeated courses of neomycin-bacitracin and mupirocin nasal creams, hexachlorophane disinfectant soap and oral vancomycin all failed to eradicate the organism. Several courses of intravenous antibiotics were also unsuccessful, and MRSA continued to be present in the anterior nares, throat and sputum over the 27-month study period. To date, we know of no other published report of any attempt to eradicate MRSA from a patient with CF.

It is noteworthy that in both of the present cases, the load of MRSA in the lower respiratory tract was very heavy as assessed by sputum Gram stain, where +3 and +4 Gram-positive cocci in clusters were consistently reported. In both patients multiple nonrifampin-containing antibiotic regimens failed to eradicate the organism.

Ciprofloxacin has been reported to be useful in treatment of MRSA (17-19), but multiple courses of ciprofloxacin failed to eradicate the organism in either of these individuals. In our second patient, multiple clindamycin-containing antibiotic regimens also were unsuccessful at eradicating MRSA. Only when rifampin in combination with clindamycin was used was eradication successful. Rifampin is thought to be the drug that most effectively eradicates MRSA from mucosal surfaces (20), although failure can occur when it is used alone (21). Most authors currently recommend the use of rifampin in combination with a second active drug such as ciprofloxacin, clindamycin, trimethoprim-sulfamethoxazole or vancomycin when attempting eradication of MRSA (8,18,22). We chose to use clindamycin in combination with rifampin because of good absorption by the oral route, activity in vitro against our two patients' isolates, and ability to concentrate in macrophages and PMNs (23). More prolonged therapy than is usually employed for eradication of MRSA from mucosal surfaces

(20), although failure can occur when it is used alone (21). Most authors currently recommend the use of rifampin in combination with a second active drug such as ciprofloxacin, clindamycin, trimethoprim-sulfamethoxazole or vancomycin when attempting eradication of MRSA (8,18,22). We chose to use clindamycin in combination with rifampin because of good absorption by the oral route, activity in vitro against our two patients' isolates, and ability to concentrate in macrophages and PMNs (23). More prolonged therapy than is usually employed for eradication of MRSA from mucosal surfaces was administered because we believed that we were dealing with lower respiratory tract infection in patients with bronchiectasis on the basis of CF lung disease.

Many studies have shown that treatment of MRSA can result in only very transient eradication of the organism and that recolonization frequently occurs (19,22). The absence of MRSA on multiple sputum cultures from our two patients over a one-year period post-treatment is strong evidence for successful long term eradication.

Successful treatment of MRSA in these individuals has greatly simplified infection control measures on subsequent hospitalizations (including to the obstetrics hospital). Substantial cost-savings have been realized by this success, and the patients have been much more comfortable out of strict isolation. While the role of treatment of carriers as an infection control measure remains debatable, antimicrobial therapy has previously been reported to be useful in assisting in the control of an outbreak of MRSA and in prevention of significant clinical infection (20,24).

CONCLUSIONS

Prolonged eradication of MRSA from the sputum of CF patients may be possible by use of rifampin and clindamycin therapy. These results may also be of practical interest in the management of MSSA infection in patients with CF. Further investigation into the prevalence and role of MRSA in patients with CF is warranted.

REFERENCES

1. di Sant'Agnese PA, David PB. Research in cystic fibrosis. N Engl J Med 1976;295:481,537,597.
2. Canadian Cystic Fibrosis Foundation. Report of the Canadian patient data registry (National), 1991. Toronto: Canadian Cystic Fibrosis Foundation, 1991.
3. Gilligan PH. Microbiology of airway disease in patients with cystic fibrosis. Clin Microbiol Rev 1991;4:35-51.
4. Hoiby N. Microbiology of lung infections in cystic fibrosis patients. Acta Paediatr Scand Suppl 1982;301:33-54.
5. Szaff M, Hoiby N. Antibiotic treatment of *Staphylococcus aureus* infection in cystic fibrosis. Acta Paediatr Scand 1982;71:821-6.
6. Haley RW, Hightower AW, Khabbaz RF, et al. The emergence of methicillin-resistant *Staphylococcus aureus* infections in United States hospitals. Possible role of the house staff-patient transfer circuit. Ann Intern Med 1982;97:297-308.
7. Thompson RL, Cabezudo I, Wenzel RP. Epidemiology of nosocomial infections caused by methicillin-resistant *Staphylococcus aureus*. Ann Intern Med 1982;97:309-17.
8. Locksley RM, Cohen ML, Quinn TC, et al. Multiply antibiotic-resistant *Staphylococcus aureus*: Introduction, transmission, and evolution of nosocomial infection. Ann Intern Med 1982;97:317-24.
9. Brumfitt W, Hamilton-Miller J. Methicillin-resistant *Staphylococcus aureus*. N Engl J Med 1989;320:1188-96.
10. Burdge DR, Nakielna EM, Noble MA. Detection of methicillin-resistant *Staphylococcus aureus* (MRSA) in the sputum of patient with cystic fibrosis (CF); Lack of increased sensitivity using mannitol salt agar. XIth International Cystic Fibrosis Congress, Dublin, August 1992. (Abst TP13)
11. McDougal LK. Acquired oxacillin resistant *Staphylococcus aureus*. Clin Microbiol Newletter 1987;9:144-6.
12. Boxerbaum B, Jacobs MR, Cechner RL. Prevalence and significance of methicillin-resistant *Staphylococcus aureus* in patients with cystic fibrosis. Paediatr Pulmonol 1988;4:159-63.
13. Michel BC. Antibacterial therapy in cystic fibrosis. A review of the literature published between 1980 and February 1987. Chest 1988;94(Suppl):1295-405.
14. Shapera RM, Warwick WJ, Matsen JM. Clindamycin therapy of staphylococcal pulmonary infections in patients with cystic fibrosis. J Pediatr 1981;99:647-50.
15. Pittman FE, Howe C, Goode L, di Sant'Agnese PA. Phage groups and antibiotic sensitivity of *Staphylococcus aureus* associated with cystic fibrosis of the pancreas. Pediatrics 1959;24:40-2.
16. Frénay HME, Vandenbroucke-Grauls CMJE, Molkenboer MJCH, Verhoef J. Long-term carriage, and transmission of methicillin-resistant *Staphylococcus aureus* after discharge from hospital. J Hosp Infect 1992;22:207-15.
17. Piercy EA, Barbaro D, Luby JP, MacKowiak PA. Ciprofloxacin for methicillin-resistant *Staphylococcus aureus* infections. Antimicrob Agents Chemother 1989;33:128-30.
18. Smith SM, Eng RH, Tecson-Tumang F. Ciprofloxacin therapy for methicillin-resistant *Staphylococcus aureus* infections or colonizations. Antimicrob Agents Chemother 1989;33:181-4.
19. Mulligan ME, Ruane PJ, Johnston L, et al. Ciprofloxacin for eradication of methicillin-resistant *Staphylococcus aureus* colonization. Am J Med 1987;82(Suppl 4A):215-9.
20. Yu VL, Goetz A, Wagener M, et al. *Staphylococcus aureus* nasal carriage and infection in patients on hemodialysis. Efficacy of antibiotic prophylaxis. N Engl J Med 1986;315:91-6.
21. Canawati HN, Tuddenham WJ, Sapico FL, Montgomerie JZ, Aeilts GD. Failure of rifampin to eradicate methicillin-resistant *Staphylococcus aureus* colonization. Clin Ther 1982;4:526-31.
22. Chambers HF. Treatment of infection and colonization caused by methicillin-resistant *Staphylococcus aureus*. Infect Control Hosp Epidemiol 1991;12:29-35.
23. Klempner MS, Styrt B. Clindamycin uptake by human neutrophils. J Infect Dis 1981;144:472-9.
24. Ward TT, Winn RE, Hartstein AI, Sewell DL. Observations relating to an inter-hospital outbreak of methicillin-resistant *Staphylococcus aureus*: Role of antimicrobial therapy in infection control. Infect Control 1981;2:453-9.