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EMERGENCE OF MUPIROCIN-RESISTANT *STAPHYLOCOCCUS AUREUS* IN CHRONIC PERITONEAL DIALYSIS PATIENTS USING MUPIROCIN PROPHYLAXIS TO PREVENT EXIT-SITE INFECTION

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¨ ***Objective:*** **To determine the prevalence of the carriage of *Staphylococcus aureus* (SA), methicillin-resistant *Staphylococcus aureus* (MRSA), and mupirocin-resistant *Staphylococcus aureus* (MuRSA) in chronic peritoneal dialysis (CPD) patients after 4 years of prophylactic mupirocin application to the exit site, in a peritoneal dialysis unit.**

¨ ***Methods:*** **Three swabs were collected from the nares, axillae/groin, and exit site, respectively, from 149 patients on CPD between May and July 2001. All swabs were cultured on solid selective agar (mannitol salt agar) and in mannitol salt broth. *Staphylococcus aureus* isolates were tested for methicillin resistance using oxacillin screening plates, and mupirocin resistance using E-test strips. Low-level MuRSA was defined as minimum inhibitory concentration (MIC) of 4 mg/mL or more, and high-level MuRSA as MIC of 256 mg/mL or more.**

¨ ***Results: Staphylococcus aureus*** **was isolated from 26 (17%) patients (25 from nares/axilla/groin, and 1 from the exit site). High-level MuRSA was isolated from 4 patients (3% of the total study population; 15% of total SA isolates). No MRSA was detected. One patient with high-level MuRSA had peritonitis due to SA, resulting in treatment failure and catheter loss, soon after the swabs were collected for the study.**

¨ ***Conclusion:*** **We report the emergence of high-level MuRSA in CPD patients after a 4-year practice of continuous use of mupirocin in a small number of patients in our unit. Our results may have significant implications for the future practice of prophylactic use of mupirocin by CPD patients to prevent exit-site infection.**

KEY WORDS: Mupirocin-resistant *Staphylococcus aureus*; chronic peritoneal dialysis; mupirocin prophylaxis.

Despite major advances in peritoneal dialysis (PD) technology, infective complications remain the major cause of morbidity and technique failure in chronic peritoneal dialysis (CPD) patients. *Staphylococcus aureus* (SA) is an important cause of peritonitis and exit-site infection (ESI) and is associated with a high incidence of PD catheter removal (1). Nasal carriage of SA is shown to be associated with an increased incidence of ESI and peritonitis due to SA (2). Accordingly, topical or systemic antibiotic therapy to eradicate nasal carriage of SA has been successful in reducing the incidence of ESI, but not peritonitis due to SA (3,4). The topical application of mupirocin to the exit site has been shown to significantly reduce not only the incidence of ESI but also peritonitis (5–7). Indeed, it has been shown that the site most frequently colonized with strains of SA identical to those causing peritonitis episodes was the catheter exit site, followed by the nares and fingernails (8). However, widespread use of any antibiotic risks the emergence of resistant strains, as shown by the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) as a major pathogen in hospital-acquired infections during the past 10 – 15 years (9).

More recently, the emergence of mupirocin-resistant *Staphylococcus aureus* (MuRSA) has been reported on a worldwide basis in nondialysis patients (10–14). We previously reported in a point prevalence study that there was no evidence of MuRSA in CPD patients after a 1-year practice of prophylactic application of mupirocin to the exit site (15). Recently, Rosales *et al*. reported increasing resistance to mupirocin in a significant portion of CPD patients and partners during the previous 4 years (16).

The objectives of our study were to determine the prevalence of SA, MRSA, and MuRSA carriage in CPD patients after 4 years' prophylactic use of mupirocin in our PD unit, and to compare the prevalence of SA carriage and drug-resistant SA carriage with the results of our previous study of 1-year's use of mupirocin in the CPD population in our PD unit (15).

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MATERIAL AND METHODS

Patients undergoing CPD for end-stage renal disease, who were visiting our outpatient PD clinic between May and July 2001, were asked to participate in a surveillance study done as a part of a screening program established between our CPD and Infection Prevention and Control Units. Three standard cotton swabs were collected, one each from the anterior nares, axillae/inguinal areas bilaterally, and exit site of the PD catheter. All specimens were inoculated onto selective solid agar (mannitol agar plates) and in mannitol salt broth (7.5% NaCl). For each patient, the swabs taken from the nares, axillae, and groin were pooled when inoculating culture plates and broth, whereas the swabs collected from the exit site were cultured separately. All cultures were incubated aerobically at 35°C. The plates were reviewed at 24 hours and again after 48 hours if no growth was observed. Putative SA colonies were identified on the basis of positive Gram stain, catalase test, coagulase tube test, and Pastorex Staph Plus rapid agglutination slide test (Bio-Rad, Montreal, Quebec, Canada). All strains of SA isolated were tested for methicillin and mupirocin resistance. Methicillin resistance was tested using methicillin screening plates containing oxacillin 6 mg/mL and 4% NaCl. Mupirocin resistance was tested using E-test strips (AB Biodisk, Solna, Sweden). Low-level resistance was defined as minimum inhibitory concentration (MIC) of 4 mg/mL or more (17), and high-level resistance as MIC of 256 mg/mL or more (18).

Clinical data were collected from patients at the time of swab collection. The following demographic data were collected: age, sex, etiology of end-stage renal disease, modality of CPD (automated vs CAPD), presence of diabetes, use of immunosuppressive drugs, hospitalization, antibiotic use (for at least 48 hours), surgery during the preceding 6 months, presence or absence of mupirocin application to exit site, and frequency of mupirocin application to the exit site per week. Mupirocin users were classed as intermittent users if they were applying mupirocin to the exit site 1 – 4 times per week, or continuous users if they were applying mupirocin 5 – 7 times per week.

The two-tailed Student's t-test was used to compare continuous data, and chi-square test to compare categorical data. A p value of less than or equal to 0.05 was considered significant. The prevalence of SA, MRSA, and MuRSA carriage was compared to our previously reported study done after mupirocin had been used for 1 year on the exit sites of our CPD population (15).

RESULTS

Of the 150 patients who were asked to participate in the study, 149 had surveillance swabs taken. The patients' clinical characteristics are given in Table 1. *Staphylococcus aureus* was isolated from 26 (17%) patients (25 from nares/axillae/groin and 1 from an exit site). Mupirocin resistance was found in 4 of 26 (15%) SA isolates and all were high-level MuRSA. All 4 MuRSA were isolated from patients using mupirocin intermittently. There was no methicillin resistance observed in any of the SA isolates. One patient from whom MuRSA was isolated developed peritonitis due to SA with high-level resistance to mupirocin 1 day after the swab was collected, and lost the PD catheter, indicating failure of treatment with mupirocin. The clinical characteristics of MuRSA carriers and noncarriers are compared in Table 2.

Carriage of SA, MRSA, and MuRSA in the present study (n = 149) and that in a similar study (n = 167) previously reported by us after 1 year's use of prophylactic mupirocin in our unit (15) is compared in Table 3.

DISCUSSION

Mupirocin is a carboxylic acid that inhibits bacterial protein synthesis by binding isoleucine t-RNA synthetase (IleS) (19). Mupirocin has been in clinical use in nondialysis hospitalized patients for prophylaxis against nasal carriage of SA since the late 1980s (20). Soon after its introduction into clinical practice for bacterial skin infections in the UK in 1985, the first reports of MuRSA appeared in 1987 (21,22). It is only recently that increased incidence of MuRSA has been reported in nondialysis patients worldwide (10–14,23) with widespread use of mupirocin for elimination of nasal carriage of SA. Low-level resistance is common but has little clinical significance (20,24). High-level resistance has major clinical implications but fortunately is rare. The level of mupirocin resistance is related to alterations in IleS. Low-level resistance is probably due to mutations in a chromosomally encoded *IleS*; it is stable and nontransferable (20). Low-level MuRSA strains can be eradicated with higher concentrations of mupirocin (25). High-level resistance is due to acquisition of an additional novel *IleS*; it is plasmid mediated and transferable (24,26). MuRSA is more commonly seen in MRSA strains (10,11) and in the setting of widespread clinical use of mupirocin (11–13).

The point prevalence of SA carriage in our study was 17%. This is lower than the prevalence of 45% reported by Luzar *et al.* in patients undergoing catheter insertion (2), but similar to the 23% reported by Davies *et al.* (27), and the 12% reported by Hanslik *et al.* (28). However, a point prevalence study such as ours may underestimate the true incidence of SA carriage, as intermittent carriage is common in CPD patients. Surveillance studies have shown an incidence of nasal SA carriage of 44% – 66% (29–32).

We compared the prevalence of carriage of SA, MRSA, and MuRSA after 1-year's (15) and 4-years' prophylactic use of mupirocin in our CPD population. During this interval, we observed no change in the prevalence of SA carriage (16% vs 17%), and the prevalence of MRSA

TABLE 1
Comparison of Patient Characteristics Between *Staphylococcus aureus* (SA) Carriers and Noncarriers

	All patients (*n*=149)	SA carriers (*n*=26)	Non SA carriers (*n*=123)
Age (mean years ±SD)	57.3±16.2	54.6±19	58.0±15
Male	69 (46%)	15 (58%)	54 (44%)
Diabetes mellitus	50 (34%)	7 (27%)	43 (35%)
Etiology of ESRD			
Diabetic nephropathy	36 (24%)	6 (23%)	30 (24%)
Glomerulonephritis	57 (38%)	13 (50%)	44 (36%)
Hypertensive nephrosclerosis	19 (13%)	2 (8%)	17 (14%)
Chronic interstitial nephritis	8 (5%)	1 (4%)	7 (6%)
ADPKD	9 (6%)	1 (4%)	8 (6.5%)
Other/Unknown	20 (13%)	3 (11.5%)	17 (14%)
Dialysis modality (CAPD:APD)	67:82	16:10	51:72
Immunosuppressive drugs	25 (17%)	2 (8%)	23 (19%)
Hospitalization during the preceding 6 months	48 (32%)	5 (19%)	43 (35%)
Surgical procedure during the preceding 6 months	30 (20%)	4 (15%)	26 (21%)
Antibiotic therapy during the preceding 6 months	36 (24%)	2 (8%)	34 (28%)[a]
Exit-site care (self:others)	118:31	20:6	98:25
Mupirocin application to exit site	139 (93%)	22 (85%)	117 (95%)
Mupirocin use (intermittent:continuous)	35:104	5:17	30:87
Duration of mupirocin use (months±SD)	23.8±18	19.2±17.3	24.4±17.8
Frequency of mupirocin use (applications per week±SD)	3.6±2.1	3.2±2.3	3.6±2.0

ESRD = end-stage renal disease; ADPKD = autosomal dominant polycystic kidney disease; CAPD = continuous ambulatory peritoneal dialysis; APD = automated peritoneal dialysis.
[a] $p = 0.035$.

TABLE 2
Comparison of Clinical Characteristics Between Mupirocin-Resistant *Staphylococcus aureus* (MuRSA) Carriers and Non MuRSA/SA Carriers

	MuRSA carriers (*n*=4)	Non MuRSA & non SA carriers (*n*=145)
Age (mean years ±SD)	42.3±5.6	57.8±16.2
Immunosuppressive drugs	1	24
Hospitalization during the preceding 6 months	0	48
Surgical procedure during the preceding 6 months	1	29
Antibiotic therapy during the preceding 6 months	0	36
Diabetes mellitus	1	35
Mupirocin use (intermittent:continuous)	4:0	31:114
Duration of mupirocin use (months±SD)	15.5±8.4	23.9±18.2

TABLE 3
Comparison of Prevalence of Carriage of *Staphylococcus aureus* (SA), Methicillin-Resistant SA (MRSA), and Mupirocin-Resistant SA (MuRSA) After 1 Year and 4 Years of Prophylactic Use of Mupirocin

	1-Year's use (*n*=167)	4-Years' use (*n*=149)
SA carriers	27 (16%)	26 (17%)
MRSA carriers	2 (1%)	0
MuRSA carriers	0	4 (3%)[a]

[a] $p = 0.033$.

decreased from 8% to 0% of SA isolates. However, we observed an emergence of MuRSA after 4-years' use of mupirocin in 3% of patients (15% of SA isolates), which was not evident after 1-year ($p = 0.033$). MuRSA is generally associated with MRSA and other multidrug-resistant SA; however, in our study we observed MuRSA in 3% patients, in the absence of MRSA. This observation is reassuring in that there are still good therapeutic options to eradicate MuRSA with antibiotics; therapeutic options to eradicate multidrug-resistant MuRSA are limited. The administration of antibiotics during the preceding 6 months had a negative correlation with SA carrier

status, indicating systemic antibiotic administration for other infections may have eliminated or suppressed the likelihood of finding SA. The number of MuRSA carriers was too small to identify any meaningful risk factors. However, it is of interest to note that all 4 MuRSA carriers in our study were applying mupirocin to the exit site intermittently, and tended to be younger compared to noncarriers (42.3 ± 5.6 vs 57.8 ± 16.2 years, $p = 0.058$).

Recently, Rosales *et al.* reported on the emergence of MuRSA in PD patients and their partners during the previous 4 years (16). Our results lend support to these reports. Furthermore, our results may have major implications for the future practice of prophylactic mupirocin use in CPD patients. Failure to identify the emergence of high-level MuRSA in CPD patients may result in treatment failure due to peritonitis with SA and catheter loss, as observed in one of our patients. Our results imply that the emergence of high-level MuRSA would be expected to appear in CPD populations using prophylactic mupirocin at the exit site for extended periods (months to years).

It should be emphasized that mupirocin prophylaxis has been very effective in preventing infective complications in CPD patients (5–7). The prevalence of MuRSA was not widespread in our study and we do not recommend discontinuation of the present practice of prophylactic mupirocin application in CPD patients. We suggest that large PD centers using mupirocin in CPD patients should have periodic surveillance, at least yearly, to detect the emergence of MuRSA strains so that appropriate measures may be implemented to avoid its spread, loss of treatment efficacy, and deleterious patient outcomes.

The eradication of MuRSA has not been well studied. However, eradication of MuRSA would not be difficult, as several alternative systemic and topical antibiotics have been shown to be effective in eradicating MuRSA. Topical agents that have been shown to be effective *in vivo* in eliminating MuRSA strains are polysporin (33) and tea tree oil (34); and *in vitro*, povidone–iodine (35), azelaic acid, nitrofurazone, and silver sulfadiazine (36). Alternatively, combined topical agents such as bacitracin and fusidic acid, and systemic antibiotics such as rifampicin or ciprofloxacin may be used (37).

It is important to prevent the emergence of MuRSA in CPD populations, as it would be unfortunate to lose a very effective drug through injudicious use. Its use may be restricted to only carriers of SA rather than using it in an unrestricted fashion. However, this strategy would be difficult to implement, as it would involve the considerable cost of frequent screening of CPD patients to identify intermittent carriers of SA (38). Alternatively, other strategies need to be explored to prevent the emergence of MuRSA. In our study, all 4 carriers of MuRSA were using mupirocin intermittently, but this number is too small to attain any statistical significance from which to draw meaningful conclusions. However, the effect of intermittent compared to continuous use of mupirocin on the emergence of MuRSA needs to be tested in a controlled study. Also, the use of mupirocin alternating with another topical agent, such as polysporin, merits clinical evaluation.

In conclusion, we report the emergence of high-level mupirocin resistance to *Staphylococcus aureus* in 3% of CPD patients (15% of SA isolates) after 4 years of prophylactic use of mupirocin at the exit site. Our results may have major implications for the future use of continuous mupirocin prophylaxis in CPD patients, given the serious clinical consequences of clinical failures with increasing mupirocin resistance.

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