High prevalence of mupirocin-resistant staphylococci in a dialysis unit where mupirocin and chlorhexidine are routinely used for prevention of catheter-related infections

In our centre, 65 % of newly diagnosed end-stage renal disease (ESRD) patients start haemodialysis with a tunnelled central venous catheter (CVC) (Teo *et al.*, 2010). The median lifespan of a CVC until transition to a permanent vascular access (arteriovenous fistula or graft) or to another treatment modality is 105 days (inter-quartile range: 69–193 days), while the median time to a CVC-related infection is 72 days (inter-quartile range: 21–151 days).

As part of a clinical process improvement project to reduce these infections, we implemented inpatient and outpatient antisepsis protocols from August 2008 comprising daily 2 % chlorhexidine bodywash along with application of 2 % mupirocin ointment to the anterior nares and CVC exit-sites of patients daily. These protocols are discontinued only upon CVC removal. Following these changes, the rate of infections did not change significantly from our historical (January 2007–July 2008) mean of 1–2 per 1000 catheter-days (Teo *et al.*, 2011). Antisepsis protocols have been shown to reduce the risk of infections (Batra *et al.*, 2010; Bleasdale *et al.*, 2007; McCann & Moore, 2010; Sheng *et al.*, 2009). However, emergence of mupirocin resistance has been documented in peritoneal dialysis patients, but is less well studied in haemodialysis patients (Tacconelli *et al.*, 2003). Also, whether chlorhexidine resistance develops as a result of this practice is unclear (Batra *et al.*, 2010). We performed this prospective surveillance study to determine the prevalence of mupirocin- and chlorhexidine-resistance genes in staphylococcal carriage following these practice changes.

After institutional review board approval, consenting general ward inpatients with

A supplementary figure showing PFGE patterns of mupirocin-resistant staphylococci from the dialysis unit patients is available with the online version of this paper.

ESRD dialysed via tunnelled CVC underwent anterior nares and catheter exit-site swabbing using sterile calcium alginate-tipped swabs upon each hospitalization between May and August 2009. Specimens were swabbed onto 5 % sheep blood agar plates and in cooked meat broth, and incubated at 35 °C overnight. If no staphylococci were seen on the primary plate, this was reincubated for another 24 h and the cooked meat broth was subcultured onto a CNA (Columbia agar with 5 % sheep blood containing colistin and nalidixic acid) plate. Staphylococci were identified by colony morphology, Gram stain and latex agglutination with Pastorex Staph Plus (Bio-Rad). Coagulase-negative staphylococci (CoNS) were not further speciated. Mupirocin MICs were determined via Etest (AB Biodisk), while the presence of *mec* and *ileS-2* genes encoding meticillin and high-level mupirocin resistance, respectively, was detected using a multiplex PCR protocol (Pérez-Roth *et al.*, 2001). We also tested for the presence of *smr* and *qacA/qacB* efflux genes, which are associated with reduced susceptibility to chlorhexidine (Noguchi *et al.*, 2005). Isolates were typed using PFGE (Maslow *et al.*, 1993).

Thirty-two patients were recruited, of whom nine patients were on their first hospitalization and haemodialysis. There were altogether 66 hospitalizations (minimum 1, maximum 5; median 1). All swabs were culture-positive, yielding 140 distinct *Staphylococcus* species isolates. These comprised 86 meticillin-resistant CoNS (MR-CoNS), 36 meticillin-susceptible CoNS (MS-CoNS), 11 meticillin-resistant *Staphylococcus aureus* (MRSA) and 7 meticillin-susceptible *S. aureus* (MSSA).

The distribution of organisms and antiseptic-resistance genes according to

mupirocin MIC is shown in Table 1. Staphylococcal isolates positive for *ileS-2* and high-level mupirocin resistance were isolated from 23 (71.9 %) previously hospitalized patients on initial swabs, but none were isolated from the remaining nine patients during their first hospitalization. However, three of these patients had acquired *ileS-2*-positive MR-CoNS by their second hospitalization, replacing initially mupirocin-susceptible MS-CoNS. Three (3/5) MRSA-positive patients were colonized with mupirocin-resistant MRSA, one of whom had concurrent mupirocin-resistant MR-CoNS isolated. No *S. aureus* isolate was found to have low-level mupirocin resistance. Mupirocin-resistant CoNS were more likely to be concomitantly meticillin resistant (chi-square; $P < 0.01$). The majority of staphylococcal isolates were positive for *qacA/B* (30 patients; 93.8 %) but *smr* prevalence was lower (18 patients; 56.3 %). One patient was colonized with mupirocin-susceptible MS-CoNS for all hospitalizations. Five patients were not readmitted.

PFGE results did not demonstrate any predominant CoNS clonal group (Supplementary Fig. S1 in JMM Online). All MRSA gel patterns were identical to that of the local dominant ST239 clone (Hsu *et al.*, 2005). The majority of subjects with repeat hospitalizations were colonized by CoNS with PFGE profiles that were identical to their initial results (Supplementary Fig. S1).

Our study demonstrated high rates of high-level mupirocin resistance among staphylococci isolated from patients subjected to daily chlorhexidine and mupirocin prophylaxis. Although chlorhexidine susceptibility was not formally tested, the high prevalence of *qacA/B* carriage and the isolation of staphylococci from patients who had daily chlorhexidine scrubs suggest that reduced susceptibility to chlorhexidine was common. PFGE data

Table 1. Distribution of mupirocin- and antiseptic-resistance genes by mupirocin MIC and organism type

Organism (no. of isolates)*	No. of patients†	Positive <i>ileS</i> -2 (%)	Positive <i>smr</i> (%)	Positive <i>qacA/B</i> (%)
High-level mupirocin resistance (MIC ≥ 512 $\mu\text{g ml}^{-1}$)				
Meticillin-resistant CoNS (66)	19	66 (100)	28 (42.4)	52 (78.8)
Meticillin-sensitive CoNS (11)	9	11 (100)	1 (11.1)	6 (66.7)
MRSA (6)	3	6 (100)	2 (16.7)	6 (100)
MSSA (1)	1	1 (100)	0 (0)	0 (0)
Low-level mupirocin resistance (MIC 8–256 $\mu\text{g ml}^{-1}$)				
Meticillin-resistant CoNS (10)	6	0 (0)	0 (0)	10 (100)
Meticillin-sensitive CoNS (1)	1	0 (0)	0 (0)	1 (100)
Mupirocin-susceptible (MIC < 8 $\mu\text{g ml}^{-1}$)				
Meticillin-resistant CoNS (9)	7	0 (0)	4 (44.4)	6 (66.7)
Meticillin-sensitive CoNS (25)	15	0 (0)	2 (8.0)	15 (60.0)
MRSA (5)	2	0 (0)	1 (20.0)	3 (60.0)
MSSA (6)	5	0 (0)	0 (0)	3 (50.0)

*CoNS, coagulase-negative staphylococci.

†Patients may have both mupirocin-resistant and non-resistant staphylococcal isolates (both *S. aureus* and coagulase-negative staphylococci) cultured over time.

(Supplementary Fig. S1) suggested that this resistance is not due to the spread of a particular CoNS clone, but rather results from transmission of mobile genetic elements such as plasmids on which *ileS*-2 and *qacA/B* may be found (Pérez-Roth *et al.*, 2001; Noguchi *et al.*, 2005).

Some limitations of this work include the relatively small number of patients and short duration of study. The initial prevalence of high-level mupirocin resistance and *qacA/B* carriage among staphylococcal isolates prior to the practice change is unknown. However, given the absence of mupirocin-resistant isolates in newly admitted patients, it is likely that the baseline prevalence was low.

In conclusion, the practice of daily chlorhexidine bodywash and mupirocin prophylaxis increases the prevalence of chlorhexidine- and mupirocin-resistance genes in staphylococci amongst haemodialysis patients using catheters. This limited study suggests that the benefit, if any, of prophylactic antiseptics in patients with long-term haemodialysis catheters may only be transient, and continued surveillance for risk–benefit assessments is necessary.

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