Preventing *Staphylococcus aureus* infection in the renal unit

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**Introduction**

*Staphylococcus aureus* is an important cause of morbidity and mortality in the renal unit setting. It is the leading cause of haemodialysis-related bacteremia and peritoneal dialysis catheter exit-site infection, and an important cause of peritoneal dialysis-related peritonitis. Since many such infections are potentially preventable, the institution of strategies that reduce infection rates represents an important element in the care of this patient group. This review examines the basis of prevention, together with its likely benefits and possible disadvantages.

Carriage of *S. aureus* is an important risk factor for infection with this organism. Carriers undergoing haemodialysis have higher rates of *S. aureus* bacteremia, and those receiving continuous ambulatory peritoneal dialysis (CAPD) have higher rates of exit-site infection and peritonitis, compared with non-carriers. Comparison of carriage and infecting *S. aureus* isolates indicates that individuals are commonly infected with their own carriage isolate, an observation that underpins prevention strategies.

A second factor that is likely to influence both carriage and disease is host genetic susceptibility. However, the genes involved have not been identified, and it is unclear whether susceptibility is to carriage alone with its inherent risks for infection, or whether additional genes influence the likelihood of sepsis once carriage is established.

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Acquired risk factors for *S. aureus* infection

Acquired factors also influence the likelihood of *S. aureus* infection and fall into two broad categories. The first is immune dysfunction: patients undergoing haemodialysis have decreased granulocytic chemotaxis, and lower immunoglobulin, complement and T cell levels. The second is the presence of prosthetic devices that not only breach the normal host defences and give direct access to normally sterile body sites, but provide a site of colonization to which staphylococci are well adapted. The importance of prosthetic material as a determinant of infection is reflected in the variable rates of sepsis associated with different types of haemodialysis vascular access. Endogenous arteriovenous fistulae are less prone to infection than prosthetic shunts, while intravenous haemodialysis catheters have the greatest associated risk and are a leading cause of *S. aureus* bacteraemia.

How can *S. aureus* infection be prevented?

Infection control measures

Good hospital infection control measures are central to the prevention of *S. aureus* infection. The evidence for this is two-fold. First, hand washing reduces transmission of pathogens between individuals, and from the hands of a given individual to their dialysis site. Second, improvement in infection control measures can lead to a reduction in the rate of infection. For example, one observational study introduced a package of measures including improved aseptic operative technique, provision of intensive training for nursing staff and patients in stringent aseptic care of the exit site, and avoidance of contact of the exit site with non-sterile water. These combined measures were associated with an overall 10-fold reduction in exit-site infection, a 2-fold reduction in peritonitis and 4.5-fold reduction in catheter loss from infection in patients undergoing CAPD. However, the use of face masks during manipulation of the peritoneal dialysis system makes no difference to the time to first episode of all-cause peritonitis. Asepsis during dialysis line insertion is also essential. The placement of peritoneal dialysis catheters and formation of fistulae are often performed in a theatre environment, ensuring high standards of aseptic technique. However, intravenous haemodialysis lines, particularly those that are intended to provide temporary access, may be inserted in a ward or radiology department setting. The importance of good asepsis during this procedure is exemplified by a study by Raad et al, which clearly demonstrated that maximal sterile barrier precautions during the insertion of non-tunelled catheters (mask, cap, sterile gloves, gown and a large drape) reduced the risk of catheter infection, compared with the use of sterile gloves and small drape alone. The role of prophylactic antibiotics for procedures to create haemodialysis access has not been studied at length. A single randomized study of 206 patients undergoing 408 permanent vascular access procedures compared infection rates following a single intravenous dose of vancomycin 6–12 h pre-operatively with no drug. Access infection rates were reported to be 1% in the vancomycin group and 6% in the controls, all of which were related to prosthetic grafts. Balanced against this practice is the likely selection of vancomycin-resistant bacteria in the host flora such as vancomycin-resistant enterococci. The risks and benefits of prophylactic antibiotics during the insertion of temporary haemodialysis catheters are currently unknown, but this approach is rendered less important by the treatment of *S. aureus* carriers with nasal mupirocin, as discussed below.

The role of antiseptics

**CAPD**

The reported effectiveness of antiseptics such as povidone-iodine present in dressings applied to the peritoneal dialysis catheter exit site has varied between studies. Povidone-iodine and non-occlusive dressings changed 2 or 3 times weekly were associated with a lower rate of exit-site infection compared with cleansing of the exit site with soap and water, although rates of peritonitis were not different. A second study reported that regular application of povidone-iodine delayed infectious complications (exit-site infections and peritonitis), while a third found that the number of *S. aureus* infections were reduced but those caused by *Pseudomonas aeruginosa* were increased. Thus, povidone-iodine appears to reduce *S. aureus* exit-site infections, but may not influence the overall rate at this site.

**Haemodialysis**

The application of povidone-iodine to the haemodialysis subclavian vein catheter exit site has been reported to reduce the risk of exit-site infections and incidence of septicaemia.
Eradication of *S. aureus* carriage

The dominant ecological niche for *S. aureus* carriage is the anterior portion of the nose. Organisms may also be found on the skin but elimination of nasal carriage by topical antibiotics generally leads to loss of carriage in other body sites. These observations have resulted in eradication strategies that focus predominantly on *S. aureus* eradication from the nose. Some individuals appear to have positive skin swabs and negative nose swabs, although this is the exception rather than the rule. It is unclear whether this represents true absence of nasal carriage or a low bacterial count in the nose that lies below the level of detection. Topical mupirocin is effective in temporary eradication of nasal carriage, is the most commonly used agent for this purpose, and will be the focus for the remainder of this review.

Infection rates following eradication of *S. aureus* carriage in the nose

**Haemodialysis patients**

Eradication of nasal carriage in haemodialysis patients by the application of topical mupirocin to the nose reduces the number of episodes of *S. aureus* infection per patient year. In a double-blind controlled trial in which the treatment arm received nasal mupirocin three times daily for 2 weeks, and then three times weekly for 9 months, the rate of *S. aureus* infection was 1 per 104 patient-months, compared with 6/147 patient months in the placebo arm. The same investigators have since described results for 7 years mupirocin use in *S. aureus* carriers in the same unit, reporting a 2.85-fold drop in the *S. aureus* bacteraemia year-incidence in all haemodialysis patients. A further study over 21 months of 226 patients, of which 67 were identified as carriers and treated with mupirocin, found a bacteraemia rate of 0.04 per patient year compared with 0.25 in a historical control group. In addition to reducing the burden of disease, this strategy has is cost-effective.

**CAPD patients**

A randomized, double-blind trial of placebo vs. mupirocin (twice daily for 5 days every 4 weeks) in *S. aureus* carriers reported that there was a significant reduction in *S. aureus* exit-site infection in the mupirocin arm, but all-cause exit-site infections were not significantly different between the two groups. In addition, there were no differences in the rate of tunnel infection or peritonitis. A further publication using the same data set reported that total antibiotic costs (including mupirocin) were significantly higher in the mupirocin group, and concluded that cost savings were unlikely to be sufficient to offset the cost of mupirocin and screening for nasal carriage of *S. aureus*. Similar outcomes were reported in a study of nasal mupirocin that used historical controls, in which there was a reduction in *S. aureus* peritonitis and exit-site infections but a simultaneous increase in the incidence of infections by other Gram-positive and Gram-negative bacteria. A recent study, again using historical controls, reported a reduction in peritonitis but no difference in *S. aureus* exit-site infections or tunnel infection. Overall, therefore, evidence for the efficacy of nasal mupirocin in preventing morbidity in CAPD patients is less convincing than that for haemodialysis patients.

Topical application of mupirocin to the dialysis catheter exit site

Mupirocin ointment applied to the intravenous catheter insertion site at the end of each dialysis session has been shown to be superior to povidone-iodine, being associated with a significant reduction in the risk of *S. aureus* skin and catheter colonization, exit site infection and bacteraemia. The peritoneal dialysis catheter exit site has been reported to be the most frequent colonizing site of strains causing peritonitis, and two studies have shown that topical application of mupirocin to the exit site was associated with a reduction in exit-site infection and peritonitis. However, the routine application of mupirocin to the exit site of all patients has potentially important implications for the emergence of drug resistance.

The practicalities of minimizing *S. aureus* infection

A range of non-antibiotic-related measures should be in place as part of an infection control programme. These include: (i) protocols for line insertion and line care; (ii) good mechanisms for recording line insertion, removal, and infective complications to facilitate audit; (iii) training and education of staff regarding line insertion, and of staff and patients in care of lines; and (iv) minimizing the time patients receive renal replacement therapy via temporary intravenous devices by good liaison with surgeons and timely fistula formation.

The institution of nasal mupirocin therapy requires that the following questions be addressed: (i) Which patient groups should be treated? The evidence for efficacy is good in haemodialysis
patients and has been recommended for carriers who need intravenous access.\textsuperscript{54} The evidence for efficacy of nasal mupirocin is less convincing for CAPD patients, and carriers in this patient group may be better served by topical mupirocin. (ii) Should mupirocin treatment be given to those with nasal swabs positive for \textit{S. aureus} or to all patients? Identifying and treating carriers alone will result in lower mupirocin costs and is likely to exert less pressure on bacteria to develop mupirocin resistance. Conversely, blanket treatment could reduce the costs associated with screening for carriage but may shorten time to the emergence of resistance. (iii) When should mupirocin be commenced, and how often should it be repeated? Mupirocin should ideally be commenced prior to the insertion of lines, or otherwise as soon as feasible. Nasal re-colonization over time by \textit{S. aureus} can be reduced by maintenance therapy, for example once per week after an initial eradication regimen of twice daily for 5 days.\textsuperscript{46}

\textbf{Conclusion}

The emergence of mupirocin resistance in the renal unit setting is reported to be low. For example, 7 years of follow-up in a unit that routinely uses mupirocin in haemodialysis \textit{S. aureus} carriers found two isolates with high-level resistance.\textsuperscript{46} However, it seems inevitable that resistance will ultimately occur, and strategies to reduce the speed with which this happens should be implemented at the same time as mupirocin is introduced. Measures include good infection control, reliable laboratory screening for resistance, good prescribing practices within a framework driven by protocol and audit, and the avoidance of blanket treatment, since a ‘treat-all’ policy represents a trade-off between short-term benefits and long-term emergence of resistance. Individual units will be required to develop tailored strategies for mupirocin use, a guiding principle of which must include informed and considered use of this valuable agent.

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