INFECTION CONTROL FOR HAEMODIALYSIS UNITS

APPENDICES

Appendix 1 – Population intervention comparator and outcome (PICO) strategy

Two questions relating to multi-resistant organisms were identified:

1) What is the epidemiology of multi-resistant organisms and blood stream infections (bacteraemia, fungaemia), in haemodialysis populations in Australia and New Zealand with particular reference to incidence, prevalence, nosocomial acquisition, morbidity and mortality?

2) What are the benefits and/or harms associated with screening for multiple resistant organisms (including culture, molecular methods/NAAT, serological testing, and frequency of testing)?

**Question 1**

A Population Intervention Comparator Outcome (PICO) search strategy was utilised to screen for relevant studies including prospective cohort; retrospective cohort; registry studies; case-control; cross sectional and surveillance studies.

**Population:** Australian and New Zealand haemodialysis patients

**Intervention/indicator:** Infections caused by multi-resistant organisms including blood stream infections and carriage caused by multi-resistant organisms

**Comparison/control:** Incidence, prevalence, nosocomial acquisition, morbidity, mortality in non-dialysis populations

**Outcomes:** Risk factors for infectious disease of interest in the haemodialysis population, mortality & morbidity, hospitalisation, access survival

Studies were excluded if they:

- Did not assess MROs
- Were not undertaken in Australia or New Zealand

**Question 2**

A PICO search strategy was utilised to screen for relevant studies including controlled trials; prospective cohort; case-control; historical control and diagnostic test studies.

**Population:** Haemodialysis patients: maintenance and temporary

**Intervention/indicator:** Screening and surveillance/monitoring for infectious organisms (including but not limited to, MRSA, VRE, CRE, ESBL).
Comparison/control: Alternative approaches to screening and surveillance including no screening

Outcomes: Rate of detection, rates of transmission of infection to other patients and/or staff, hospitalisations, hospital bed days, mortality, psychosocial (stigma, isolation), quality of life, impact on clinical contact, impact on delivered services (occupational therapy, etc.), impact on clinical decisions (e.g. vaccination, antibiotic prescribing)

Studies were excluded if they:
- Focused on antibiotic based interventions to reduce CVC line infections
- Did not assess MROs (this excluded studies of S. aureus decolonisation that did not assess MRSA)
- Only reported infection as a covariate (and not carriage following screening)
- Were solely modelling studies
Appendix 2 – Explanation of grades of evidence quality and strength of recommendation

The evidence and recommendations in this KHA-CARI guideline have been evaluated and graded following the approach detailed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group (www.gradeworkinggroup.org). A description of the grades and levels assigned to recommendations is provided in Tables 1 and 2.

Table 1. Final grade for overall quality of evidence

<table>
<thead>
<tr>
<th>Overall Evidence Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>A</td>
<td>High quality of evidence. We are confident that the true effect lies close to that of the estimate of the effect.</td>
</tr>
<tr>
<td>B</td>
<td>Moderate quality of evidence. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.</td>
</tr>
<tr>
<td>C</td>
<td>Low quality of evidence. The true effect may be substantially different from the estimate of the effect.</td>
</tr>
<tr>
<td>D</td>
<td>Very low quality of evidence. The estimate of effect is very uncertain, and often will be far from the truth.</td>
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Table 2. Nomenclature and description for grading recommendations

<table>
<thead>
<tr>
<th>Grade</th>
<th>Implications</th>
<th>Patients</th>
<th>Clinicians</th>
<th>Policy</th>
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<tr>
<td>Level 1</td>
<td>“We recommend”</td>
<td>Most people in your situation would want the recommended course of action and only a small proportion would not</td>
<td>Most patients should receive the recommended course of action</td>
<td>The recommendation can be adopted as a policy in most situations</td>
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<td>Level 2</td>
<td>“We suggest”</td>
<td>The majority of people in your situation would want the recommended course of action, but many would not</td>
<td>Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences</td>
<td>The recommendation is likely to require debate and involvement of stakeholders before policy can be determined</td>
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Appendix 3 – What is the evidence for multi-resistant organisms?

Australia and New Zealand

Garner 2013 [1]
A 10-year retrospective case control study comparing 134 VRE colonised or infected adult patients on renal replacement therapy (180 HDx, 31 PDx, 50 transplant) with 137 non-colonised age, gender and treatment matched controls at the Monash Medical Centre in Victoria, Australia. VRE screening by rectal swab was performed 3 to 6 monthly for all haemodialysis patients with the subsequent introduction of additional screening on admission and at weekly intervals whilst an inpatient. The study found no difference in mortality or number of admissions between colonised and uncolonised patients. However, there was an increased duration of hospital stay (7.29 days vs. 4.14 days p <0.001) which remained present even when analysis was restricted to patients who stayed 7 days or less, although the difference was of minimal clinical relevance (2.34 vs. 2.14 days). Peritoneal dialysis patients had a longer duration of stay than haemodialysis patients. The prevalence of VRE in nephrology patients rose from 1.23% in 2000 to 8.24% on 2010. 8 of 134 VRE-colonised progressed to clinically meaningful infection. The time from colonisation to infection varied from 1 to 18 months.

Graham 2008 [2]
This cross-sectional study screened faecal specimens of 56 community children; 97 community adults and 50 haemodialysis patients with no prior history of colonisation or infection with VRE in Melbourne, Victoria. It found VRE in 1 haemodialysis patient and one community patient. These findings are difficult to interpret given that patients with a prior history or known exposure to VRE were excluded and the study did not comment on whether the haemodialysis population was screened regularly or not. This study was primarily focused on identifying non-enterococcal vanB containing isolates. No year of collection was present in the study.

Burrell 2005 [3]
A cross-sectional survey of outpatient haemodialysis patients attending 12 Victorian in-centre haemodialysis units over six months in 2001 and 2002. Three rectal swabs and one faecal specimen was taken on at least three occasions. Three of 269 participants (1.1%) were colonised with VRE. The authors have since found intermittently high rates of VRE in the inpatient renal population (data not published).

Grayson 1999 [4]
Screening of 574 patients in the renal (356), oncology (84) and intensive care units (134) at Monash Medical Centre, Melbourne, Victoria over seven months from June 1997 after an initial case. Following the index case, nine renal inpatients and two patients undergoing in-centre haemodialysis or peritoneal dialysis were colonised (3.0%) which was higher than the number in the intensive care (0.7%) and oncology units (0%). Six isolates were clonal. Renal inpatients were screened using rectal swabs on admission and weekly thereafter, and outpatient haemodialysis patients every 3 months. Patients were nursed in transmission based precautions in single rooms. Nine colonised patients had received vancomycin in the previous month and four had also received ceftriaxone but no comparative data was available for non-colonised patients. Five of six renal patients with VRE on their initial swab had had a hospital admission in the previous three months compared to 36% of the non-colonised patients. The mean duration of the pre-swab inpatient stay for these six patients was 17.5 compared to 2.6 days (P<0.001). At the end of the study 9 of the 12 colonised patients had died but only one had a VRE infection. No comparative data was given. Seven patients were given oral antibiotics to clear the VRE but only two of four patients who were followed up had negative swabs (at day 13 and 18).
Infectious diseases in haemodialysis units

Padiglione 2003 [5]
A 15-month prospective cohort study from Victoria, Australia commencing in April 1998 was undertaken in 3458 adult patients admitted to haematology, renal, transplant and ICU units at three hospitals with identical infection control and isolation procedures for VRE to detect risk factors for VRE acquisition. Units undertook active screening of contacts of colonised patients. Single rectal swabs were taken at admission and every 7 days. Colonisation was detected in 1.91% of patients (66 patients) during 1.56% of admissions (0.45% at admission and 0.83% after admission). Baseline prevalence was 0.6%. No VRE infections occurred. The rate of new acquisition of VRE was 1.4/1000 patient days (24/16881) and was highest in renal units (3.23/1000 patient days). The majority of isolates were non-clonal. Risk of colonisation at baseline increased with time spent in a hospital prior to study entry – 0.4% if admitted directly to study unit compared to 0.8% if in hospital 1 to 8 days prior or 1.9% if in hospital >8 days prior. Risk of colonisation at baseline was also increased if there had been a previous hospital admission during the preceding three months (p=0.03). Univariable analysis found hospital admission in the previous 3 months to be a risk factor for new colonisation with VRE but this was not significant on multivariable analysis. Multivariable analysis found that management by a renal unit (vs. ICU) (HR 4.6, p=0.02) and recent ticarcillin-clavulanate (HR 3.6, p=0.03) or carbapenems (HR 2.8, p=0.05) but not vancomycin or broad spectrum cephalosporins were risk factors for acquisition. These results support the endogenous emergence of VRE or amplification of undetected colonisation rather than nosocomial spread in a setting where VRE patients are isolated. Incidence rate was potentially confounded by the use of only a single rectal swab on admission. The link between ticarcillin-clavulanate and carbapenems supports a study by Rice et al [6] and supports the theory that antibiotics with anaerobic activity promote VRE colonisation.

Pearman 2006 [7]
This study describes a clonal outbreak of VRE in Perth hospital in 2001 starting in ICU and Renal units and subsequent measures introduced to control the response. Control measures included cohorting positive and contact patients, screening all inpatients over one week, creating a dedicated VRE-ward cleaning service, environmental cultures post terminal cleaning, electronic flagging of medical records, screening ward contacts post discharge from hospital, special arrangements for discharged geriatric carriers and contacts to residential facilities. Four rectal swabs were required to detect >90% of carriers. The outbreak was terminated after five months and cost 2.7 million AUD. Subsequent on-going control measures were introduced including active surveillance of patients on high risk units and contact isolation of known carriers and unscreened ward contacts.

MDRGN

Pop-Vicas 2008 [8]
A prospective cohort study of 67 patients undergoing outpatient haemodialysis, in a US haemodialysis unit, who underwent screening swabs of their rectum nares and skin at baseline, 2 and 4 months, for multidrug resistant Gram negatives, MRSA and VRE and compared the risk factors for baseline and new colonisation compared to those who were not colonised. At baseline 11 (16%) were colonised by MDRGN, 9 (13%) by VRE and 3 (5%) by MRSA. Baseline colonisation with MDRGNs was associated with antibiotic use of greater than 7 days over the previous three months or residence of a long term care facility. 40% (22/55) of patients acquired an MRO over four months (20% MDRGN, 15% VRE, 13% MRSA). New acquisition of MDRGNs was associated with antibiotic use during follow up. Clonal spread of VRE (100% unrelated) or MDRGN (69% of MDRGN endogenous) was not the predominant mechanism, however, there was significant clonality demonstrated in MRSA isolates (6 of 7), consistent with nosocomial spread.
Bleumin 2012 [9]
A nested case control study of maintenance haemodialysis patients from January 2006 to June 2009 in an Israeli hospital to assess the risk factors and outcomes of carbapenem-resistant \textit{Klebsiella pneumoniae} (CRKP) infection or colonisation. 51 CRKP patients including 5 who were only colonised and 46 with infection were matched to 219 controls. 33\% of controls were screened for carriage. Patients aged 65 to 75 with no offspring were more likely to have CRKP. Previous hospitalisation, temporary HD catheters and previous isolation of VRE were associated with carriage. A continuous prospective cohort study demonstrated that CRKP carriage or infection was associated with increased mortality (HR 5.9) and shorter survival (median survival 1 month vs 30 months (p<0.001)). VRE carriage or infection was not associated with increased mortality.

Kruse 2010 [10]
A case control study undertaken in 2007 in Germany to investigate the source and risk factors for an outbreak of ESBL-producing \textit{Enterobacter cloacae} in the medical and surgical wards. 23 colonised patients were compared to 46 non-colonised controls, matched for ward and length of stay. Isolation was undertaken if a clinically overt infection was present. If only colonised, the decision to isolate depended upon the patient’s condition. The use of mobile dialysis units was associated with colonisation. In addition, colonised patients carried more invasive devices and were given a greater number of different antibiotics. In a quasi-experimental phase of the study, improved dialysis procedures, staff training and reinforced standard precautions led to a reduction in case numbers.

VRE

An observational study from Heidelberg, Australia, of 14 patients colonised with VRE (cVRE) and 7 patients previously colonised with VRE (pVRE) to determine the risk of environmental and healthcare worker contamination in outpatient rooms and after haemodialysis sessions. Chair cultures were positive in 58\% of haemodialysis sessions with cVRE patients, gown cultures in 30\% and patients’ hand cultures in 54\%. pVRE contamination occurred but was less common.

Servais 2009 [12]
A descriptive study with an embedded case control study detailing the bundle response to an outbreak of VRE in a French nephrology unit in 2007 including active screening using rectal swabs, isolation, separate wards for carriers, contact screening, automatic alerts and additional measures. 14 VRE positive and 125 VRE negative contacts (10.1\%) were identified with all carriers having identical strains of VRE on PFGE analysis. No new cases of VRE occurred after the bundle was introduced. A case control study to identify risk factors for VRE carriage revealed using multivariate analysis that VRE colonisation was associated with treatment with broad spectrum beta-lactams and the number of days in the nephrology ward. The measures introduced led to a 30\% reduction in haemodialysis. Three of the 14 VRE colonised patients had infection (infected peritoneal dialysis fluid, bacteraemia, polymicrobial angiocholitis).

Curtin 2010 [13]
An observational study assessing the impact of a community bundle program for outpatient haemodialysis patients with VRE or MRSA in Canada from 2005 to 2009, where screening of patients was performed yearly, post hospital admission or after return from another unit. Screening for VRE was via a rectal swab and MRSA was by swab of both nares, perineal swab and from wound or inflamed sites. The prevalence of VRE was 0 to 16\% in the units and MRSA was 0 to 33\%. There was only two episodes defined as nosocomial transmission of MRSA with the measures put in place.
Humphreys 2004 [14]
An observational study describing the response to a VRE outbreak in Ireland in 1999. Patients in the renal ward were screened by rectal swab on admission and weekly; with transmission based precautions, isolation and environmental cleaning put in place. 60 of 451 (13.3%) screened renal patients were colonised with VRE. VRE colonisation was associated with chronic haemodialysis, peritoneal dialysis, inpatient stay, multiple hospital admissions and increased age. Mortality was associated with age and positive VRE status. VRE colonisation often persisted on repeat screening. Control measures interfered with renal dialysis and as measures were commonly breached it was decided to discontinue routine screening and isolation unless a VRE carrier had diarrhoea, a discharging wound or VRE in a urinary catheter specimen. Spread of VRE and environmental contamination continued throughout the study. Only two clinically relevant cases of VRE infection occurred.

Axon 2004 [15]
A quasi-experimental study describing the effect of targeted active VRE screening with rectal swabs of haemodialysis patients in a US hospital in 2000 for the year prior to and the year after the program’s introduction. Screening and empiric isolation of patients occurred on admission, with weekly screening thereafter. There was an incidence rate of VRE colonisation in haemodialysis patients of 0.7 per 1000 patient days prior to the intervention compared to 6.2 per 1000 patient days after the intervention, although a reduction occurred in non-haemodialysis patients.

Diguio 2009 (in French) [16]
A quasi-experimental study describing the effect of stepwise infection control measures for VRE in a French Hospital from 2004 to 2008 to control an outbreak of VRE involving 19 patients. Initially patients were isolated, then geographically clustered, and then cohorted with specific staff with the number of VRE colonised patients reducing. Patients found these interventions difficult with a psychological impact due to having to change their long-standing dialysis times so they were next to different people to usual; missing out on hot meals in a common room and having to eat in bed. Isolated patients also felt forgotten by their medical teams and some were refused transfer to closer units. There was also a significant impact on the service with more blocked dialysis stations.

Dan 1999 [17]
A prospective cohort study of ICU and renal dialysis patients in Israel in 1996/7 to determine the prevalence of VRE colonisation. 114 dialysis patients underwent monthly rectal swabs with 92 completing four months or more of follow up (9 PDx and 83 HDx). Four dialysis patients had VRE colonisation (4.3%); one at baseline and three at month 5. Colonisation was transient. One dialysis patients had VRE in the blood but not the rectum. Compared to VSE patients, VRE patients were older and more commonly male with a shorter duration of dialysis, an increased cumulative hospital duration (26.3 vs 10.1 days, p=0.002) and an increased cumulative antibiotic duration (31 vs 15 days, p=0.05).

van der Steen 2000 (In Dutch – translation not available) [18]
An observational study describing the outbreak response to a VRE epidemic in an internal medicine/nephrology and dialysis ward in Amsterdam in 2000 involving 12 patients. Successful bundle measures to interrupt transmission included ward closure for new patients, cohorting, transmission based precautions and reduced antibiotic prescribing. Colonisation was related to earlier admission and previous use of ciprofloxacin, amoxycillin and co-amoxyclov.
Fishbane 1999 [19]
A 12-month prospective cohort study of 111 adult outpatient haemodialysis patients in New York, US, who were screened for rectal carriage of VRE at baseline. Patients with enterococcal infection in the previous year and hospital admission in the previous month were excluded. 10 (9%) had VRE on baseline which was associated with the volume of IV vancomycin exposure over the previous year. There was no difference in clinically relevant VRE infections on follow up (2 in the non-colonised group and 1 in the colonised). There was an incidence rate of 0.03 VRE cases per patient month.

Roghmann 1998 [20]
A prospective cohort study of 168 outpatient haemodialysis patients in a US hospital in 1994 and 1996 to assess VRE colonisation by stool culture with follow up for over a year for hospitalisation, VRE infection and survival. 16 patients were VRE colonised (10%) and 9 had additional VRE clinical isolates. Colonised VRE patients had less time on haemodialysis before screening (207 vs 822 days) and more hospitalisation in the year before (median 19 vs 3 days) on univariate analysis but a logistic regression model to adjust for other comorbidities found that only prior hospitalisation of more than 4 days was statistically significant. VRE colonised patients were more likely to develop VRE infection (25% vs 1%) but this was not associated with an increased risk of death using a multivariate model. The incidence rate of VRE infections in all patients was 2.3 per 100,000 patient days. Increased VRE with hospitalisation but not with longer haemodialysis suggests that VRE transmission occurs predominantly in the inpatient setting.

Atta 2001 [21]
A prospective cohort study of adult outpatient haemodialysis patients, who were VRE negative on rectal swab at baseline, was undertaken from December 1996 in a US centre with repeat swabs at 2 years and on admission to hospital. 10 of 124 patients were VRE positive at baseline (8.1%). Of 90 patients followed in the study, 16 (17.8%) became colonised with VRE, an incidence rate of one case per 9.8 patient years of follow up or 0.1 cases per patient year. 26% of those who received vancomycin developed VRE compared to 0% of those who did not (p=0.001). This association remained significant on multivariate analysis. VRE colonised patients also had higher exposure to aminoglycosides, anaerobic antimicrobials, hospital admissions (median 3.2 vs 1.5), duration of in-hospital stays (median 19.7 days vs 9.0 days) and ICU admissions. The unadjusted relative risk of death was higher in VRE colonised patients (p=0.005). The dialysis unit used standard precautions for all patients.

D'Agata 2001 [22]
A prospective cohort study of 119 haemodialysis patients admitted to a US hospital in 1998 who underwent rectal cultures for VRE colonisation on admission and every five days until discharge. 7 (6%) were colonised at admission. 6 of 38 patients (19%) acquired VRE with the mean time to first positive 12 days. Non-ambulatory status was associated with colonisation at admission (p=0.01) and vancomycin exposure was associated with VRE acquisition (p=0.02) on stepwise logistic regression. VRE acquisition was associated with epidemiologically linked patients and similar VRE genotypes. VRE colonised patients were placed in transmission based precautions. One VRE colonised and one non-colonised patient developed clinical infections.

Zacharioudakis 2015 [23]
A systematic review and meta-analysis of studies screening for VRE in chronic haemodialysis patients which included 23 studies and 4842 patients. The pooled VRE prevalence was 6.2% with significant variability (0-33.2%). VRE colonisation was associated with recent use of any antibiotic (especially vancomycin) and recent hospitalisation. VRE colonised patients were more likely to have a VRE infection (OR 21.62) in data extracted from four studies. The review describes haemodialysis patients as frequently being recognised as the source of VRE
outbreaks. Frequent hospitalisations, direct and indirect contacts between other patients (healthcare personnel and surfaces) and frequent use of antibiotics including vancomycin all increase the risk of VRE dissemination. Inclusion criteria required extractable data for VRE colonisation among long term dialysis patients in an outpatient setting. There was no language restriction imposed. Outbreak periods were excluded. Data was independently extracted by two authors and data quality was assessed. Studies reported data from 1995 to 2010. Differences in prevalence could be influenced by infection control practices, compliance with infection control practices, antibiotic consumption policies/antimicrobial stewardship and different MICs used to define vancomycin resistance.

MRSA

Lai 2011 [24]
A prospective cohort study of 306 outpatient haemodialysis patients in Taiwan from March 2007 to December 2008 comparing MRSA colonised patients to non-colonised patients without decolonisation. Colonisation was identified in 29 patients (9.48%) by at least one positive culture out of two consecutive weekly nasal swab cultures. There was a significant survival difference between colonised and non-colonised patients (p=0.02) with colonised patients 2.46 times more likely to die from any cause on multivariate analysis. Infection related mortality and S. aureus infection were increased in MRSA colonised patients (HR 4.99 and 4.31 respectively). Two MRSA carriers died because of MRSA associated infection and two others died from infection without documented pathogens. No non-carriers died from MRSA but four died from MSSA. All cause hospitalisation and infection from any micro-organism were not significantly different between MRSA carriers and non-carriers. Five of the 29 carriers had six MRSA infections between them while six of the 277 non-carriers had six MRSA infections between them. Isolation haemodialysis was undertaken in a separate room for patients with MRSA from sputum, dirty or open wounds and from urine or blood in addition to nasal swabs. Standard precautions were undertaken in MRSA nasal carriers without infection or patients with MRSA infection in urine or blood but no positive nasal swabs. However, MRSA carriers had significantly lower serum albumin levels and trends of higher recent hospitalisations and antibiotic use, suggesting that MRSA carriage may be a marker of a population that is at higher risk of death.

Johnson 2009 [25]
A prospective observational study assessing MRSA colonisation of hospitalised haemodialysis and peritoneal dialysis patients and healthcare workers in a US centre in 2006. Patients underwent nasal swabs of both anterior nares and rectal swabs if they consented, while HCWs underwent nasal swabs. 40 of 120 swabbed patients were colonised with S. aureus and 26 (65% of S. aureus and 21.7% of total) with MRSA. Colonised patients were older, and more likely to be diabetic. 15 patients consented to rectal culture and 2 were positive for S. aureus but both also had positive nasal swabs. There were no differences in patients colonised with MRSA and MSSA. 10 patients presented or developed a S. aureus infection with 8 colonised with S. aureus and 7 with MRSA. Of these MRSA infections, 5 were colonised with MRSA and 2 were not. Eight S. aureus infections occurred among 26 MRSA colonised patients and 1 infection among 14 MSSA colonised patients. Infections were all successfully treated. 31 of 100 HCWs (31%) were colonised with S. aureus and 6 with MRSA (6%).

Yeoh 2014 [26]
A retrospective cohort study of admitted chronic haemodialysis patients in a Singapore hospital from July 2010 to June 2011 to assess MRSA colonisation. MRSA screening was done on the day of admission by swabs of the nose, axillae, groin and wounds if present. The prevalence of MRSA carriage in this population was 15.1% (27/179) compared to 5.8% in all admitted patients. The incidence of MRSA colonisation was 10.1 per 1000 patient-days. 16 carriers had intermittent carriage. MRSA colonisation was associated with diabetes mellitus, Malay ethnicity, shorter
haemodialysis duration and use of tunnelled haemodialysis catheters. Relative risk of infection among MRSA carriers was increased (3.2x). MRSA carriers were more likely to present with infection and develop infection during hospitalisation. MRSA infection was more common in MRSA carriers (12.2% vs 2.5% p<0.05). MRSA colonisation rates are higher in patients on haemodialysis for less than 3 years (which was postulated to be related to more tunnelled catheters in this group or less inpatient admissions) and those with longer hospitalisation and more hospital admissions suggesting nosocomial origin.

Wang 2012 [27]
A case control study and prospective cohort study assessing S. aureus colonisation in the anterior nares of 541 outpatients on long term dialysis undertaken over 12 months from 2007 to 2008 in three Taiwanese hospitals. Patients were excluded if they had been admitted to hospital or undergone surgery in the previous month. 32 of 541 patients (5.9%) were positive for MRSA and 89 (16.5%) were positive for MSSA. Risk factors for MRSA colonisation included congestive heart failure, nursing home admission, nasogastric feeding in the last 3 months (MV analysis). At 12 months, of the 32 MRSA patients, 1 had MSSA infection and died from MSSA (3.1%) and 4 had MRSA infection and 3 died from MRSA (9.3%). In comparison, of the 63 MSSA colonised patients, 6 (9.5%) had MSSA infection and 1 (1.6%) died from this while 6 (9.5%) had MRSA infection and two (3.2%) died.

Aktas 2011 [28]
A six-month surveillance study in 30 haemodialysis patients, 40 peritoneal dialysis patients, 13 workers in the unit and 40 controls in Turkey. Cultures were nasal, axillary and perineal and were repeated after one week with colonisation defined as cultures being positive at both time-points. Only 1 MRSA isolate was identified from a haemodialysis patient that also had a clonally related bloodstream infection, although the relative timing of screening is unclear.

Grunewald 2013 [29]
A retrospective cohort study of 156 outpatient haemodialysis patients to assess MSSA and MRSA colonisation over 10 years in Germany ending in 2011. Swabs were taken from the nose, throat or groin. Screening by culture was undertaken in 2000, 2001, 2002, 2010. Patient were considered positive if one swab was positive. Some patients were also screened on hospital admission by PCR if considered high risk. There were 88 MSSA and 1 MRSA colonised patient identified over this time. The MRSA colonised patient was treated with local disinfection and cleared the MRSA on subsequent testing. This compares to the overall hospital MRSA screening rate of 4%. Morbidity and mortality of patients was not related to MSSA colonisation and the MSSA colonisation rate decreased over the study.

Lu 2008 [30]
A prospective surveillance study undertaken in Taiwan at three time periods from September 2002 to May 2003 for MRSA nasal carriage (swabbed both nares) in peritoneal dialysis patients, haemodialysis patients, healthcare workers and their families. MRSA colonisation was 2.36% (12/509) in haemodialysis patients and 2.41% in peritoneal dialysis patients. Four haemodialysis patients had subsequent MRSA infections over the one year follow up which were the same molecular type (PFGE) consistent with colonisation prior to infection. There was increased colonisation in family members of HCWs compared to family members of patients, and increased colonisation of patients compared to patients’ family members. MRSA carriage was associated with pulmonary disease, recent admission to hospital and recent antibiotic usage. The HCWs and family members had related MRSA strains suggestive of transmission.

Al-Said 2013 [31]
A retrospective observational study describing the effect of the implementation of an infection control bundle on the prevalence of haemodialysis related bacteraemia and vascular access infection over eight years from 2004 to 2011 in a Bahrain hospital. 118 patients were included with 9 patients having 15 episodes of dialysis related bacteraemia but only one episode of MRSA. This rate of bacteraemia was substantially lower than international data. The bundle included strengthening of standard precautions, biannual screening of staff and patients for MRSA and eradication with daily antiseptic baths and bactroban nasal cream if positive, strict dialysis protocols, isolation of MRSA infected patients in an isolation room, routine bactroban to exit site of catheters and preventing visitors.

Osono 2000 [32]
A quasi-experimental observational study assessing the efficacy of an infection control bundle including MRSA screening and isolation in a haemodialysis unit in Japan between 1993 and 1996. Inpatients and outpatients undergoing haemodialysis were screened by nose and throat swabs. Prevalence of MRSA infection was 4.5% prior to the protocol and 2.9% 2.5 years later. The majority of strains were not clonal suggesting that cross-transmission was rare (only occurring once between two hospitalised cases). Infection control measures including separate rooms with isolation, surveillance in all haemodialysis patients twice a year (nose and throat swabs) and follow up twice a month for four months until cleared, decolonisation with gentian violet skin ointment, povidone-iodine gargle and nasal GV or mupirocin ointment. Some patients had persistent colonisation despite decolonisation.

Kang 2012 [33]
An observational study from January to June 2011 assessing MRSA nasal colonisation in two outpatient haemodialysis centres in Taiwan and assessing the effectiveness of decolonisation. Prevalence of MRSA was 6.9% over two time points. There were no risk factors for MRSA carriage compared to patients without MRSA. 70% of the community and hospital based strains were epidemiologically linked. Decolonisation was effective in 95% of the 20 MRSA colonised patients using intranasal mupirocin ointment twice daily and 2% chlorhexidine shampoo once daily for five days with follow up sampling at one week, but only on one occasion. One MRSA colonised (9.1%) and one non-colonised patient developed MRSA infection (2/161 (1.24%)).

Lederer 2007 [34]
A quasi-experimental prospective observational study of 136 outpatient haemodialysis patients in 2004 and 2005 in Germany who underwent nasal screening for S. aureus and subsequent MRSA decolonisation using intranasal mupirocin ointment three times daily for five days. Screening occurred at the start of the trial and at all readmissions. MRSA positive patients also had swabs of skin and throat and were treated with antiseptic soap and fluids if positive on the skin. Follow up clearance swabs were taken at three days, one week, one and three months. The trial was instigated following an outbreak of MRSA wound infections. The prevalence of MRSA carriage was 12%. 6% of staff were MRSA carriers. All 16 MRSA positive patients had persistent carriage. MRSA carriage was associated with older age, more commonly having diabetes and increased hospitalisation of greater than 14 days over the preceding 3 months compared to MSSA carriers. MRSA isolates were not clonal including 2 isolates from staff. Mupirocin eliminated MRSA in all patients with no patients having a S. aureus infection over the subsequent 12 months (colonised or not colonised). Carriers were treated in a separate ward until decolonised.

Resic 2007 (abstract only; paper not translated) [35]
A cross-sectional study assessing the prevalence of MRSA colonisation in haemodialysis patients and staff in Bosnia and Herzegovina using nasal and throat cultures. 15.3% of patients and 11.6% of staff were colonised. Isolation was not undertaken but intensive antibacterial
prophylaxis was used. Decolonisation was successful in 34 patients (94.4%) using mupirocin ointment three times a day for 5 to 14 days.

**Schmid 2013 [36]**
A prospective interventional cohort study from 2004 to 2010 in a German haemodialysis unit that enrolled 289 haemodialysis outpatients and screened for nasal MRSA colonisation on first admission, transfer from another facility, following hospital admission, following holiday or following contact with an MRSA positive patient. MRSA positive patients underwent swabs of throat and skin and were treated in a separate ward and decolonised. Decolonisation was undertaken with mupirocin nasal ointment three times daily for five days and extranasal colonisation was treated with 0.2% chlorhexidine mouthwash (tds) or octenidine dihydrochloride antiseptic soap and 2% chlorhexidine body wash. Follow up swabs were taken at 3 to 5 days and at the subsequent two dialysis sessions. Clearance was defined as three negative swabs. This was confirmed with further swabs ten days later, then one, three and twelve months later. 34 MRSA carriers were identified (11.7%) with extranasal colonisation in 11 of these (32%). History of malignancy and an increased Charlson Comorbidity Index (age adjusted) were risk factors for carriage compared to non-carriage. MRSA carriage was associated with an increased all cause mortality (55.9% vs 37.4%). A higher age adjusted Charlson Comorbidity Index was associated with death in MRSA carriers. Decolonisation with mupirocin ointment was effective in 26 of 34 patients (76.5%) with persistence associated with a very poor survival (all cause mortality >85% compared to effective decolonisation patients with a mortality of 46.1%). The study suggests it is the overall state of health of a person that may predispose them to MRSA colonisation, meaning that MRSA may serve as a surrogate marker for poor health.

**Gomez-Gonzalez 2012 (abstract only; paper not translated) [37]**
A quasi-experimental observational study performed a Spanish hospital in 2008 and 2009 describing the implementation of active screening by nasal swabs for MRSA in acute and chronic haemodialysis patients and staff with isolation and decolonisation. The initial prevalence of MRSA in 54 patients was 29.6% with a cumulative incidence of 42.6% and 48 staff had a cumulative incidence of 39.5%. Five months follow up testing on 40 patients and 26 staff found only one positive staff member.

**Patel 2011 [38]**
A prospective cohort study of 103 outpatient haemodialysis patients in 2007 and 2008 from US to assess MRSA colonisation. Swabs were taken from nares, axillae and vascular access sites weekly for three weeks to assess baseline carriage. Screening was then performed monthly for five months. Standard precautions and universal gloving were used for all patients but only MRSA carriers with an increased risk of transmission (uncontained wound drainage) had additional precautions. The baseline prevalence was 12% (5% persistent and 7% intermittent). On univariable analysis, MRSA carriage was associated with a history of MRSA, failed renal transplantation, hospital admission within 6 months and receipt of first generation cephalosporin, cefepime or vancomycin. Six patients acquired MRSA (an incidence rate of 1.2 per 100 patient months) with an overall incidence of 18% (5 were colonised and 1 was infected). Isolates were clonally related suggestive of intrafacility transmission. The incidence rate of MRSA infection among carriers was 1.76 per 100 patient months (3 cases occurred in known carriers and one in a non-carrier). The overall MRSA infection rate was 3.9% over 12 months, with the rate in carriers 17.6%.

**Zacharioudakis 2014 [23]**
A meta-analysis to estimate the prevalence of MRSA colonisation in dialysis patients, time trends and long term risk of subsequent MRSA infections. 38 relevant studies were included involving 5596 patients. The prevalence of MRSA in haemodialysis patients was 7.2%, it increased over
time but remained stable after 2000. Haemodialysis colonisation was greater than peritoneal dialysis. Inpatients were more likely to be colonised (14.2% vs 5.4%). In four studies that reported long term data in outpatients, there was an increased risk of MRSA infection among colonised haemodialysis patients (19%) over 6 to 20 months compared to non-colonised patients (2%). In outpatient studies that performed multiple screenings, the prevalence of MRSA colonisation was not significantly different to the studies performing single screening (p=0.07). Studies that screened extranasal sites did not have a significantly increased prevalence compared to those only undertaking nasal screening (p=0.28).

Excluded from Review Tables:

Christiansen 2007 [39] (excluded from systematic review tables as not dialysis related)
This was a point-prevalence study of Enterococcus resistance in Australian centres in 2005. Twenty-two sites from Australia collected up to 100 consecutive isolates and tested them for susceptibility to ampicillin, vancomycin, high-level gentamicin and/or high-level streptomycin. High-level resistance to gentamicin was identified in 35.8% in *E. faecalis* and 52.2% in *E. faecium*. While high-level streptomycin resistance was found in 10.3% and 60.2% respectively. Compared to previous Australian Group on Antimicrobial Resistance surveys in 1995, 1999 and 2003, the proportions of vancomycin resistance and high-level gentamicin resistance in enterococci were found to be increasing.

Padiglione 2000 [40] (excluded from systematic review tables as healthy volunteers)
A cross-sectional study from Australia, including well subjects without diarrhea to assess the rate of faecal VRE colonisation. VRE was cultured from 2 (0.2%) of 1,085 specimens.

Descheemaeker 2000 [41] (excluded from systematic review tables as international prevalence study only)
A national prevalence study of intestinal GRE carriage among Belgian renal dialysis patients, conducted between May and September 1997. 1318 stool specimens were evaluated identifying 185 (14%) with glycopeptide-resistant *Enterococci*.

Boelaert 1989 [42] (excluded from systematic review tables as about *S. aureus* not MRSA)
A prospective placebo-controlled trial from a single centre in Belgium. 34 chronic haemodialysis patients were randomized to placebo or intranasal mupirocin, 3 times a day for two weeks and then three times a week. Nasal carriage of *S. aureus* was found in 40% of the haemodialysis patient population. The group treated with mupirocin had 6% of nasal cultures grow *S. aureus* vs 58% in the placebo-treated group. One *S. aureus* infection occurred in the mupirocin group compared to 6 in the placebo group (p ≤0.05).

Tacconelli E 2003 [43] (excluded from systematic review tables as about *S. aureus* not MRSA)
A systematic review to determine the overall benefit of mupirocin therapy in reducing the rate of *S. aureus* infection among haemodialysis or peritoneal dialysis patients. Ten studies with a total of 2445 patients were included. Use of mupirocin reduced the rate of *S. aureus* infections by 68% (95% confidence interval [CI], 57%-76%) among all patients undergoing dialysis; risk reductions were 80% (95% CI, 65%-89%) among patients undergoing HD and 63% (95% CI, 50%-73%) among patients undergoing PD. When data were stratified by type of infection, *S. aureus* bacteremia was found to be reduced by 78% among patients undergoing HD, and peritonitis and exit-site infections were found to be reduced by 66% and 62%, respectively, among patients undergoing PD. Mupirocin prophylaxis substantially reduced the rate of *S. aureus* infection in the dialysis population.
Kluytmans 1996 [44] (excluded from systematic review tables as about S. aureus not MRSA)
A prospective cohort study performed in a single centre in Holland. 226 chronic haemodialysis patients were screened monthly with nasal cultures and if found to be S. aureus carriers they were treated with intranasal mupirocin which was used twice a day for five days and then once a week for 12 months. The control group were a historic cohort from the same haemodialysis unit. 39% were identified as nasal carriers. Following the initial treatment, 66 nasal cultures (98.5%) became negative; after 3 months and 6 months, respectively, 63 (94%) and 61 (91%) of the treated carriers had negative cultures. The rate of bacteremia (defined as the number of episodes of S. aureus bacteremia per patient-year on haemodialysis) was significantly lower among the 226 patients in the study group (0.04 per patient-year) than among the 273 patients in the control group (0.25 per patient year, p < .001).

Yu 1986 [45] (excluded from systematic review tables as about S. aureus not MRSA)
A prospective cohort study from a single centre in the USA. Chronic haemodialysis patients were screened monthly with nasal cultures and if found to be S. aureus carriers they were treated with intravenous vancomycin, topical mupirocin, or oral rifampicin, or no treatment. S. aureus infections occurred significantly more frequently in carriers than in non-carriers (17/48 vs 3/26; p <0.05). Neither intravenous vancomycin nor topical mupirocin were effective at eliminating nasal carriage of S. aureus. Oral rifampin given for 5 days reduced S. aureus carriage (at 1 month follow up) but within 3 months, recolonisation had occurred in most carriers.

Perez Fontan 1993 [46] (excluded from systematic review tables as peritoneal dialysis)
A prospective cohort study from Spain in peritoneal dialysis patients. 94 patients with a follow-up of 1,097 patient-months were compared to a historic cohort of 74 peritoneal dialysis patients with follow-up of 1,043 patient-months. S. aureus nasal carriage was observed in 47.5% of the patients. Patients with S. aureus carriage were treated with mupirocin. The incidence of S. aureus peritonitis decreased from 1 episode over 58 patient-months in phase A to 1 episode over 548 patient-months in phase B, and the incidence of exit-site infection decreased from one episode over 55 patient-months in phase A to 1 episode over 137 patient-months in phase B. However, there was a simultaneous increase in the incidence of infections by other Gram positive and Gram negative bacteria and the overall rate of catheter loss after peritonitis was not significantly altered.

Zimmerman 1991 [47] (excluded from systematic review tables as peritoneal dialysis)
A randomized controlled trial in peritoneal dialysis patients from the USA. 64 patients received either oral rifampin 300 mg twice daily for 5 days every 3 months or no treatment. The rifampin-treated patients had a significant delay in time to first catheter-related infection (p < 0.015) and significantly fewer catheter-related infections overall (p < 0.001). There was no significant difference in peritonitis rates between groups and adverse effects necessitated withdrawal of rifampin in four patients.

The Mupirocin Study Group 1996 [48] (excluded from systematic review tables as peritoneal dialysis)
A randomized controlled trial in 9 European centres. 267 of 1144 screened peritoneal dialysis patients were carriers of S. aureus. Carriers were randomised to intranasal mupirocin (N = 134) or placebo (N = 133) and followed for up to 18 months. Nasal carriage fell to 10% in those subjects who received active treatment and 48% in those who used the placebo ointment. There was no significant difference in overall exit site infections, tunnel infection or peritonitis. There was no evidence of a progressive increase in resistance to mupirocin with time.

Bernardini 2005 [49] (excluded from systematic review tables as peritoneal dialysis)
A randomized controlled trial in 3 USA dialysis units. 133 peritoneal dialysis patients were randomised to daily mupirocin (66 patients) or gentamicin cream (67 patients) to the PD catheter exit site. Catheter infection rates were 0.23/yr with the gentamicin cream versus 0.54/yr with the mupirocin cream (P = 0.005). Time to first catheter infection was longer using gentamicin (P = 0.03). Peritonitis rates were 0.34/yr versus 0.52/yr (P = 0.03), respectively. Although there is no specific data for MRSA the authors comment that methicillin-resistant S. aureus PD-related infections are rare as a result of prophylaxis with exit site mupirocin, their previous standard of care.

Laupland 2003 [50] (excluded from systematic review tables as about S. aureus not MRSA)
Meta-analysis of the efficacy of intranasal mupirocin for eradication of S. aureus nasal carriage and for prophylaxis of infection. Sixteen randomized, controlled trials were appraised; 9 trials assessed eradication of colonisation as a primary outcome measure, and 7 assessed the reduction in the rate of infection. This included studies in dialysis patients by Perez Fontan [46] and The Mupirocin Study Group [48]. Mupirocin was generally highly effective for eradication of nasal carriage in the short term.

Loeb 2003 [51] (excluded from systematic review tables as not haemodialysis patients)
This review summarised the evidence for use of antimicrobial agents to eradicate MRSA. Six randomised controlled trials of patients colonised with MRSA comparing topical or systemic antimicrobials to placebo or no treatment, and trials comparing various combinations of topical or systemic agents to no treatment, placebo, or to topical or systemic agents were identified. 384 participants were included. No difference in MRSA eradication was detected in four studies: one that compared mupirocin to placebo, two that compared a systemic agent to no treatment (fusidic acid in one and rifampin or minocycline in the other) and one that compared mupirocin to topical fusidic acid and oral trimethoprim-sulfamethoxazole, examining nasal MRSA eradication as an outcome. One study compared minocycline to rifampin, with rifampin being more effective in relation to eradication of MRSA from all sites at day 30 (relative risk 0.16; 95% confidence intervals 0.02 to 1.00), but the difference at 90 days was not statistically significant (n = 18). Two studies (one testing novobiocin and rifampin, the other ciprofloxacin and rifampin, versus trimethoprim-sulfamethoxazole and rifampin) did not demonstrate a difference in eradication of MRSA at all sites (n = 94). Thus it was concluded that there was insufficient evidence to support use of topical or systemic antimicrobial therapy for eradicating nasal or extra-nasal MRSA and no demonstrated superiority of either topical or systemic therapy, or of combinations of these agents. Adverse events with systemic agents occurred in up to 20% of participants.

Perez-Fontan 2002 [52] (excluded from systematic review tables as peritoneal dialysis)
A descriptive study from a single centre in Spain. Standard therapy in asymptomatic peritoneal dialysis patients colonised with S. aureus was topical mupirocin. Compared to a historic cohort mupirocin-resistant S. aureus emerged in a significant proportion of PD patients and dialysis patients. It was also noted that there was a significant increase in the risk of S. aureus exit-site infection.

Batra 2010 [53] (excluded from systematic review tables as ICU patients)
Interrupted time-series analysis of MRSA acquisition in two 15-bed intensive care units in the UK. the effects of sequential introduction of an educational campaign, patient cohorting, and a chlorhexidine-based antiseptic protocol on transmission of strains was assessed. Patients with known MRSA infection had 1% chlorhexidine gluconate applied to the nostrils, around the mouth, and at tracheostomy sites 4 times daily; had 1% chlorhexidine acetate powder applied to groin, axillae, and skinfolds daily; and were washed daily with 4% chlorhexidine applied by a wet cloth. The antiseptic protocol was associated with a highly significant and immediate reduction in some
but not all strains of MRSA. There was only weak evidence of an effect of the other interventions on MRSA transmission.

Falgas 2006 [54] (excluded from systematic review tables as about *S. aureus* not MRSA)
A systematic review, which included four randomised controlled trials with 205 dialysis patients (3 PD and 1 HD), to determine the effectiveness and safety of oral rifampin with another regimen or no therapy in reducing *S. aureus*-related infections. Use of oral rifampin reduced infections with *S. aureus*. The review did not give specific data for MSRA. Development of toxicity and antimicrobial resistance occurred in a considerable proportion of patients.

Centers for Disease Control and Prevention 2007 [55]
Surveillance data from the Centers for Disease Control and Prevention (CDC) from 2005 was analyzed and highlighted that the incidence of invasive MRSA infection was much greater among dialysis patients than the general population (45.2 cases per 1,000 population versus 0.2 to 0.4 cases per 1,000 population).

Centers for Disease Control and Prevention 2010 [56] (excluded from systematic review tables as international prevalence study only)
Surveillance data from the US CDC from 2010 was analysed and highlighted that the incidence of invasive MRSA infection remained greater among dialysis patients. There were 39.4 cases per 1,000 population (95% CI 36.9 – 42.1), compared to 0.215 cases per 1,000 population (95% CI: 0.208 -0.222) in the general population.

Wang 2012 [57] (excluded from systematic review tables as international epidemiology study only)
This study from the US CDC highlighted that MRSA has molecular heterogeneity, with some strains having increased resistance to antimicrobial drugs, and increased capacity for invasive disease.

Park 2011 [58] (excluded)
A retrospective cohort study from Korea that found that a significant proportion of patients colonised with VRE cannot be detected by rectal cultures, and the duration of VRE colonisation in chronic haemodialysis patients tends to be prolonged.

D'Agata 2002 [59] (excluded as not MRO specific)
A review of the epidemiology of antimicrobial-resistant, Gram-positive pathogens in patients undergoing haemodialysis, with recommendations for limiting further dissemination.
REFERENCES


Infectious diseases in haemodialysis units