Eur J Clin Microbiol Infect Dis
DOI 10.1007/s10096-008-0469-7

REVIEW

Can we do better in controlling and preventing methicillin-resistant *Staphylococcus aureus* (MRSA) in the intensive care unit (ICU)?

H. Humphreys

Received: 13 November 2007 / Accepted: 23 January 2008

Abstract Methicillin-resistant *Staphylococcus aureus* (MRSA) is prevalent in many hospitals, but many of its most serious clinical manifestations, such as bloodstream infection and ventilator-associated pneumonia, are seen in the intensive care unit (ICU). Many interventions to prevent and control MRSA were initially pioneered in the ICU and subsequently extended to the rest of the hospital. Recent studies confirm how many of these are effective. Active surveillance reveals higher numbers of cases when compared with the sole use of clinical specimens to identify MRSA-positive patients. Although one recent study from the UK has suggested that isolation has no impact on MRSA transmission in the ICU, current recommendations include isolation or cohorting, combined with decolonisation (e.g., mupirocin to the nose and chlorhexidine baths) as major control measures. However, the excessive use of mupirocin for nasal MRSA decolonisation leads to resistance. Improved compliance with hand hygiene recommendations and better antibiotic stewardship are also important. Rapid diagnosis such as PCR may utilise isolation facilities more effectively by identifying MRSA patients earlier. However, all these measures must be combined with adequate numbers of staff and suitable space and facilities, e.g., single rooms, to be maximally effective. Finally, while much can be done within the ICU itself, MRSA in the ICU often reflects the difficulties elsewhere in the acute hospital and the health service generally, in terms of the control and prevention of healthcare-associated infection.

Declaration The author is in receipt of financial support for research from Steris and 3M. He has also recently received lecture fees from 3M.

H. Humphreys
Department of Clinical Microbiology,
Royal College of Surgeons in Ireland,
Dublin, Ireland

H. Humphreys (✉)
Department of Clinical Microbiology,
RCSI Education and Research Centre, Beaumont Hospital,
P.O. Box 9063, Dublin 9, Ireland
e-mail: hhumphreys@rcsi.ie

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a worldwide cause of healthcare-associated infection, and many of its more serious clinical manifestations are seen in the intensive care unit (ICU). The prognosis from MRSA infections is often more grave than that from infections caused by methicillin-susceptible *S. aureus* (MSSA). In a meta-analysis of 31 cohort studies of *S. aureus* bacteraemia, mortality was significantly higher with MRSA than with MSSA [1]. Although controversies remain about the optimal diagnosis of ventilator-associated pneumonia (VAP), in patients with infection caused by MRSA, the median length of ICU stay is significantly longer even when patients receive appropriate initial antibiotic treatment [2]. The additional length of stay in ICU, the requirement for additional investigations and the use of more expensive antibiotics mean that MRSA has a significant impact on ICU costs. The cost attributable to MRSA infection was $9,275 during the mid-1990s in a French ICU, and after assessing the likely costs of control measures themselves, it was considered cost effective to have an effective control

programme in place to reduce infection [3]. Strategies to control and prevent MRSA include active surveillance with screening to identify cases, antibiotic stewardship, decolonisation or MRSA eradication from carriage sites, isolation, appropriate general infection prevention measures, such as hand hygiene, and adequate numbers of staff [4].

The principles of control and prevention of MRSA in the ICU are broadly similar to those in the rest of the hospital, and indeed many of them were first implemented in the ICU. However, there are particular challenges in applying such measures to an acutely ill patient population where patients require multi-therapeutic and diagnostic interventions, often as an emergency, and/or, in less than ideal circumstances. Recent published studies have emphasised the importance of MRSA in critically ill patients, but also that prevention and control measures are effective.

Surveillance

MRSA rates vary, and this partly depends on the approach to detection, i.e., surveillance and screening. Recent data from German ICUs that take part in a national surveillance system reveal that the percentage of total isolates of *S. aureus* that are MRSA ranges from 0% to 64%, with a mean of 24% [5]. In North America, clinical specimens indicate that prevalence varies, but that without routine surveillance of MRSA, the occurrence of MRSA is significantly underestimated [6, 7]. In one study, routine surveillance for MRSA on admission, weekly screens and screening on discharge increased the detection of MRSA by 58% compared to the use of clinical specimens alone [7].

In an interrupted time series, Huang and colleagues assessed the effect of maximally sterile central venous catheter placement, the introduction of alcohol hand rubs, a hand hygiene campaign and enhanced ICU surveillance of MRSA infections [8]. Over a period of 16 months, the incidence of MRSA in the bloodstream in the ICU decreased significantly. Routine surveillance cultures and subsequent contact isolation precautions were considered to be the most influential interventions in achieving this reduction, even if the study could not specifically quantitate the contribution of each intervention [8]. In a medical and surgical ICU in Denver, CO, active surveillance on admission, and weekly thereafter, resulted in a statistically significant fall in noscomial MRSA infections, i.e., from 4.5 to 2.8 infections per 1,000 days [9]. This decrease in MRSA infections is encouraging despite the emergence in North America and in some other countries of increasing numbers of community-associated MRSA where patients, not previously exposed to healthcare, may present to acute hospitals with MRSA, adding to the overall burden of MRSA in the ICU.

Isolation, cohorting and decolonisation

Isolation or patient cohorting is a major component of any MRSA control policy. However, in a prospective 1-year study in three intensive care units in London, there was no difference in the rate of transmission when patients with MRSA were or were not isolated [10]. However, this study was characterised by sub-optimal patient screening, the failure to provide designated non-nursing as well as nursing staff for patients in MRSA isolation, poor compliance with hand hygiene protocols (i.e., only 21%), and delays in the availability of MRSA results, leading to patients who were positive not being isolated for 2 or more days. Intuitively, isolation makes sense, and this is borne out in part by some anecdotal reports involving ICUs that, however, fall short of being considered randomised trials. In a 14-bed combined medical and surgical ICU in Montreal, Canada, MRSA acquisition was higher in open bays than in single rooms, despite the fact that the sickest patients were often to be found in single isolation rooms [11]. Surgical ICUs in Germany were found to be an independent risk factor for MRSA infection, and the routine isolation of patients with MRSA was a protective factor on multivariate analysis of national surveillance data [12].

Decolonisation, usually with a combination of mupirocin to the nose and body washes using chlorhexidine or an equivalent, are a component of most MRSA control programmes. However, a recent systematic review of interventions to prevent and control MRSA has emphasised that the currently available evidence does not support the routine use of topical and or systemic antimicrobial therapy in every colonised patient for eradicating nasal and extra-nasal MRSA [13]. However, in the ICU a case can be made for the routine decolonisation of many patients colonised with MRSA, given the clinical consequences for the colonised patient developing serious infection, e.g., bloodstream infection against a background of multiple organ failure, and the risk of spread to other vulnerable patients. In a non-controlled study of over 2,000 patients in a 13-bed general ICU, 2% mupirocin applied to the nose three times daily for 5 days and a chlorhexidine bath once daily for 3 days resulted in a fall in nosocomial MRSA infections and a statistically significant reduction in all *S. aureus* infections [14]. The widespread use of mupirocin leads to resistance, and this occurs in patients administered repeated courses, especially where MRSA colonisation is associated with a device, e.g., an endotracheal tube, that needs to remain *in situ* for a prolonged period. Of 302 MRSA isolates recovered from patients in a surgical intensive care unit, 13.2% were mupirocin resistant, and this was more likely to occur in older patients and was associated with a higher mortality [15]. MRSA eradication from the nose in the setting of mupirocin resistance is challenging, as the options are

limited and the use of systemic antibiotics, such as rifampicin, fusidic acid, co-trimoxazole, etc., may be associated with severe side effects.

Hand and environmental hygiene

Hand hygiene is another key component of any infection prevention strategy, but it is often difficult to determine the impact of increased compliance when other measures are being undertaken at the same time. In a longitudinal observational study of a 350-bed tertiary referral hospital, which included a 35-bed intensive care unit, the introduction of antimicrobial hand hygiene gel to the intensive care unit and a hospital-wide MRSA surveillance feedback programme resulted in a reduction in the rate of new patients with MRSA in the ICU [16]. This was accompanied by an increase in the use of hand hygiene products from 78.1 litres per 1,000 patient days to 102.7 litres per 1,000 patient days [16]. While actual compliance with hand hygiene recommendations is preferable as an indicator of improved practice, measuring the consumption of hand gel is an indication of improved practice. However, hand hygiene compliance levels are often linked to patient-staff ratios, particularly nursing staff levels. In a cohort study of a 12-bed ICU, observation of 125 staff-patient contacts revealed 59% compliance with hand-hygiene procedures, and on multivariate analysis, exposure to relative staff deficits was the only variable significantly associated with clustered cases of MRSA [17]. The authors predicted that an average increase of 12% in hand hygiene compliance would have significantly limited transmission potential.

Environmental hygiene may also be important in MRSA control, but the literature by and large fails to suggest a direct correlation between MRSA in the environment and infection rates. Although a recent study carried out in a non-ICU clinical area showed heavy contamination of environmental surfaces and positive air samples and demonstrated that 70% of patient and environmental isolates were indistinguishable [18], it can't be assumed that patients acquired their isolate from the environment. In a recent UK study of 114 ICU patients, 47 bed areas were found to be contaminated with MRSA, but only one patient developed infection with an MRSA strain identical to that in that patient's environment [19].

Rapid detection

Current techniques to detect MRSA are slow and somewhat cumbersome. However, rapid diagnostic tests, which include the use of PCR, offer hope for early identification of positive patients (i.e., within hours rather than 2–3 days) and consequently the possibility of earlier isolation and the institution of barrier precautions. Initial non-controlled trials offer promise in this area. In a study from Switzerland, PCR to detect MRSA decreased the overall time to notification, but only when this was combined with pre-emptive isolation was there a significant reduction in MRSA infections in a medical ICU; there was no change in the surgical ICU [20]. Cunningham and colleagues in Plymouth, UK, demonstrated a mean reduction in the incidence of transmission from 13.89 per 1,000 patient days to 4.9 per 1,000 patient days in critical care patients, following the introduction of PCR to detect MRSA colonisation [21]. The earlier identification of patients carrying MRSA may also be used to guide appropriate antimicrobial chemotherapy in those patients not responding to antibiotics [22].

Mathematical modelling

Mathematical modelling using simulated scenarios has helped determine the relative impact of different measures on MRSA transmission even if conclusions from such studies are only as good as the quality of the model itself. In one such model, it has been suggested that although eradication of endemic MRSA is possible, it is far easier to prevent MRSA from becoming endemic in the first place [23]. Furthermore, the level of resource provision and the chance to combine a number of different interventions will determine whether such measures succeed or fail. In a model using four compartments, applied specifically to the intensive care unit of an 800 bed tertiary referral hospital, daily prevalence data were collected over 999 days [24]. The model predicted that MRSA acquisitions would increase substantially if hand hygiene compliance fell below 40% and that MRSA decolonisation attempts have only a modest impact on transmission. A recent study that combined many of the components of current models such as early identification of MRSA patients, isolation and patient decolonisation, resulted in reduced MRSA rates, a fall in mean ICU length of stay and also a decline in bloodstream infection due to coagulase negative staphylococci [25].

While control measures are often effective in the ICU in preventing and controlling MRSA despite the particular challenges that exist in this clinical area, such as high bed occupancy levels, inadequate numbers of isolation rooms and, in many ICUs, insufficient numbers of nursing staff, the aggressive enforcement of known control measures in the form of healthcare bundles markedly reduces healthcare-associated infections; in one study central-line-associated sepsis and bloodstream infections were practically eradicated [26]. Similarly, there is a strong case to be made for the utilization of care bundles applied to antimicrobial

prescribing in the ICU where assertive antibiotic stewardship programmes can result in reducing unnecessary antibiotic use [27].

Conclusions

In healthcare systems where MRSA is endemic, and where patients re-admitted to the hospital have a high likelihood of MRSA, e.g., Ireland, the UK, Spain, etc., the emphasis may be on control. In contrast, prevention and eradication are possible where MRSA levels are very low, e.g., the Netherlands and the Scandinavian countries. Nonetheless, recent studies demonstrate the possibilities of real reductions in MRSA in the ICU when well recognised interventions are successfully implemented. A combination of earlier detection of MRSA, isolation with selective patient decolonisation, compliance with best professional practice, such as with hand hygiene and antibiotic stewardship, will reduce MRSA colonisation and infection in the ICU, and given the severity of illness in such a group of patients, will almost certainly lead to reduced bed stay and reduced morbidity and contribute to improving mortality rates. However, the ICU is not an isolated clinical area, but rather exists and provides a key clinical service in a healthcare environment that often fails to adequately prevent and control healthcare-associated infection through inadequate space and isolation facilities and as a consequence of deficiencies in staffing.

References

1. Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y (2003) Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: A meta-analysis. Clin Infect Dis 36:53–59
2. Shorr AF, Combes A, Kollef MH, Chastre J (2006) Methicillin-resistant *Staphylococcus aureus* prolongs intensive care unit stay in ventilator-associated pneumonia, despite initially appropriate antibiotic therapy. Crit Care Med 34:700–706
3. Chaix C, Durand-Zaleski I, Alberti C, Brun-Buisson C (1999) Control of endemic methicillin-resistant *Staphylococcus aureus*. A cost-benefit analysis in an intensive care unit. J Am Med Ass 282:1745–1751
4. Coia JE, Duckworth GJ, Edwards DI et al. (2006) Guidelines for the control and prevention of meticillin-resistant *Staphylococcus aureus* (MRSA) in healthcare facilities. J Hosp Infect 63S:S1–S44
5. Meyer E, Schwab F, Gastmeier P, Jonas D, Rueden H, Daschner FD (2006) Methicillin-resistant *Staphylococcus aureus* in German intensive care units during 2000–2003; Data from project SARI (Surveillance of antimicrobial use and antimicrobial resistance in intensive care units). Infect Control Hosp 27:146–154
6. Huang SS, Rifas-Shiman SL, Warren DK et al. (2007) Improving methicillin-resistant *Staphylococcus aureus* surveillance and reporting in intensive care units. J Infect Dis 195:330–338
7. Warren DK, Guth RM, Coopersmith CM, Merz LR, Zack JE, Fraser VJ (2007) Impact of methicillin-resistant *Staphylococcus aureus* active surveillance program on contact precaution utilization in a surgical intensive care unit. Crit Care Med 35:430–434
8. Huang SS, Yokoe DS, Hinrichsen VL et al. (2006) Impact of routine intensive care unit surveillance cultures and resultant barrier precautions on hospital-wide methicillin-resistant *Staphylococcus aureus* bacteraemia. Clin Infect Dis 43:971–978
9. Clancy M, Graepler A, Wilson M, Douglas I, Johnson J, Price CS (2006) Active screening in high-risk units is an effective and cost-avoidant method to reduce the rate of methicillin-resistant *Staphylococcus aureus* infection in the hospital. Infect Control Hosp Epidemiol 27:1009–1017
10. Cepeda JA, Whitehouse T, Cooper B et al. (2005) Isolation of patients in single rooms or cohorts to reduce spread of MRSA in intensive-care units: A prospective two-centre study. Lancet 365:295–304
11. Bracco D, Dubois M-J, Bouali R, Eggimann P (2007) Single rooms may help to prevent nosocomial bloodstream infection and cross-transmission of methicillin-resistant *Staphylococcus aureus* in intensive care-units. Intensive Care Med 33:836–840
12. Gastmeier P, Schwab F, Geffers C, Rüden H (2004). To isolate or not to isolate? Analysis of data from the German nosocomial infection surveillance system regarding the placement of patients with methicillin-resistant *Staphylococcus aureus* in private rooms in intensive care units. Infect Control Hosp Epidemiol 25:109-113
13. Loveday HP, Pellowe CM, Jones SRLJ, Pratt RJ (2006) A systematic review of the evidence for interventions for the prevention and control of meticillin-resistant *Staphylococcus aureus* (1996–2004): Report from the Joint MRSA Working Party (Subgroup A). J Hosp Infect 63S:S45–S70
14. Sandri AM, Dalarosa MG, de Alcântara LR, da Silva Elias L, Zavascki AP (2006) Reduction in incidence of nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) infection in an intensive care unit: role of treatment with mupirocin ointment and chlorhexidine baths for nasal carriers of MRSA. Infect Control Hosp Epidemiol 27:185–187
15. Jones JC, Rogers TJ, Brookmeyer P et al (2007) Mupirocin resistance in patients colonized with methicillin-resistant *Staphylococcus aureus* in a surgical intensive care unit. Clin Infect Dis 45:541–547
16. Harrington G, Watson K, Bailey M et al (2007) Reduction in hospital wide incidence of infection or colonisation with methicillin-resistant *Staphylococcus aureus* with use of antimicrobial hand hygiene gel and statistical process control charts. Infect Control Hosp Epidemiol 28:837–844
17. Grundmann H, Hori S, Winter B, Tami A, Austin DJ (2002) Risk factors for the transmission of methicillin-resistant *Staphylococcus aureus* in an adult intensive care unit: Fitting a model to the data. J Infect Dis 185:481–488
18. Sexton T, Clarke P, O'Neill E, Dillane T, Humphreys H (2006) Environmental reservoirs of methicillin-resistant *Staphylococcus aureus* in isolation rooms: Correlation with patient isolates and implications for hospital hygiene. J Hosp Infect 62:187–194
19. Wilson AP, Hayman S, Whitehouse T et al. (2007) Importance of environment for patient acquisition of methicillin-resistant *Staphylococcus aureus* in the intensive care unit: A baseline study. Crit Care Med 35:2275–2279
20. Harbarth S, Masuet-Aumatell C, Schrenzel J et al. (2006) Evaluation of rapid screening and pre-emptive contact isolation for detecting and controlling methicillin-resistant *Staphylococcus aureus* in critical care: an interventional cohort study. Critical Care 10:R25 (DOI 10.1186/cc3982)
21. Cunningham R, Jenks P, Northwood J, Wallis M, Ferguson S, Hunt S (2007) Effect on MRSA transmission of rapid PCR testing of patients admitted to critical care. J Hosp Infect 65:24–28

22. Rajan L, Smyth E, Humphreys H (2007) Screening for MRSA in ICU patients. How does PCR compare with culture? J Infect 55:353–357
23. Cooper BS, Medley GF, Stone SP et al. (2004) Methicillin-resistant *Staphylococcus aureus* in hospitals and the community: Stealth dynamics and control catastrophes. Proc Nat Acad Soc 101:10223–10228
24. McBryde ES, Pettitt AN, McElwain DLS (2007) A stochastic mathematical model of methicillin resistant *Staphylococcus aureus* transmission in an intensive care unit: Predicting the impact of interventions. J Theor Biol 245:470–481
25. Gould IM, MacKenzie FM, MacLennan G, Pacitti D, Watson EJ, Noble DW (2007) Topical antimicrobials in combination with admission screening and barrier precautions to control endemic methicillin-resistant *Staphylococcus aureus* in an Intensive Care Unit. Int J Antimicorb Ag 29:536–543
26. Pronovost P, Needham D, Berenholtz S et al. (2006) An intervention to decrease catheter-related bloodstream infections in the ICU. N Engl J Med 355:2725–2732
27. Cooke FJ, Holmes AH (2007) The missing care bundle: Antibiotic prescribing in hospitals. Int J Antimicrob Ag 30:25–29