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Review

Controlling hospital MRSA

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ABSTRACT

Recent evidence from publications describing the success of interventions to control hospital meticillin-resistant *Staphylococcus aureus* (MRSA), often in the endemic setting, is reviewed. Overall, there is cautious ground for optimism that MRSA can be controlled in a cost-effective manner by employing a bundle approach, the mainstay of which is widespread admission screening to inform patient-specific control measures.

Contents

1. Introduction

Recent publications give some optimism that certain countries are observing significant declines in hospital meticillin-resistant *Staphylococcus aureus* (MRSA) rates, attributable to improved control measures [1,2]. Historically it has been debated whether control is possible, particularly in the endemic setting, or even a desirable use of scarce healthcare resources. Many have advocated so-called horizontal control where the emphasis is on all healthcare-associated infections, but this short review will demonstrate the recent effectiveness of vertical control of MRSA and will discuss the strength of evidence.

2. Causes of MRSA

Traditionally, MRSA has been thought of as a problem of infection control, but there are mounting data showing both the importance of antibiotic use and the benefits of antibiotic stewardship. Cephalosporins and quinolones in particular are prone to predisposing patients to carry MRSA and may even modulate pathogenicity and transmissibility as well as acquisition of further resistances [3,4]. A recent whole-genome sequencing study concluded that maintenance of ciprofloxacin resistance in MRSA UK15 was critical to this clone's success in recent years [5]. Other agents that MRSA is also frequently resistant to, such as macrolides and other β-lactams, may also play a role [6]. It is safe to conclude that without antibiotics there would be no MRSA and that the antimicrobial era has been primarily responsible for driving the rapid evolution of *S. aureus* since the second world war, in a truly epic battle of survival of the fittest. Even in community- and livestock-associated MRSA we see the influence of antimicrobial selection pressure [7].

Transmission of MRSA in the hospital requires a source, which is usually patients in the endemic setting and rarely staff. Patients will normally acquire their MRSA in hospital and many will become chronically colonised, remaining colonised on subsequent admissions, contaminating fomites, of which hand-touch sites are generally regarded as the most important [8], and generally greatly contributing to the hospital MRSA colonisation pressure unless isolated, decontaminated or decolonised.

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3. Recent evidence on what works

There are many aspects of improved infection control that can potentially have an impact on MRSA rates. Understanding the pathogenesis and epidemiology of MRSA has helped us to design the best 'bundled' interventions. Short of a 100% efficient screening and decolonisation protocol immediately affected at hospital admission, bundles are needed to give a fail-safe control programme.

It is clear from national data recently published in the UK [2] and France [1] that there have been significant successes in controlling MRSA in the past few years.

Two recent publications from the USA give apparently contradictory results on the implementation of infection control bundles based on admission screening [9,10]. A programme of universal surveillance, contact precautions, hand hygiene and institutional culture change was associated with a significant decrease in healthcare-associated transmission of and infection with MRSA in the Veterans Affairs (VA) hospitals network [9]. Evaluation was by interrupted time-series (ITS) analysis. In another cluster randomised trial of admission surveillance and expanded barrier precautions in intensive care units (ICUs), the intervention was not effective in reducing the transmission of MRSA or vancomycin-resistant enterococci, although the authors admitted that use of barrier precautions by providers was less than what was required [10]. More importantly, the mean time to feed back positive admission cultures to the wards was >5 days, although this was not discussed in the paper. Arguably this amounts to a non-intervention, as many patients will have died or been discharged by the time positive cultures were notified and barrier precautions implemented! In contrast to this ICU study, a similar intervention on a UK ICU, analysed by ITS, recently reported a 5-year follow-up on its original 2-year study and confirmed continuing success in controlling MRSA [11]. To the author's knowledge, this is the longest duration study of robust design in the literature.

The VA programme was criticised in an important paper using a mathematical model [12]. These authors maintained that only a very small part of the reduction in MRSA could robustly be attributed to the intervention bundle but, in this author's opinion, many of the assumptions used to populate the model were invalid. For instance, the baseline assumption that risk of infection is the same in those colonised on admission versus during hospitalisation is debatable. Patients newly colonised are recognised to be at several fold increased risk of developing infection on that admission. Also, their conclusion that the only function of universal screening and isolation is to reduce nosocomial transmission is also incorrect. Knowledge of MRSA status may also improve patient management, e.g. with more rapid appropriate treatment of serious infection and decolonisation associated reduced risk of developing infection. It may also bolster other aspects of infection control, not necessarily associated specifically with MRSA. Indeed, control of MRSA has been described as a good marker for standards in other aspects of infection control [13]. Finally, we should not ignore other types of benefits from screening programmes not captured in the VA study, including the connection between nosocomial and community MRSA, reduction in risks of transmission beyond hospitalisation, and improved outcomes from MRSA infection.

Nevertheless, it has to be admitted that universal screening is not universally popular! Recent successes in the control of MRSA bacteraemia in the USA have been attributed to 'reliable application of evidence-based "bundles" of care practices and decision-support checklists, especially when combined with strong leadership commitment, teamwork, communication, peer behaviour norms, real-time feedback of adherence data, and accountability' [14].

In another recent study in a UK hospital [15] between 2006 and 2010, the prevalence density of all *S. aureus* bacteraemia declined by 41%, from 0.73 to 0.50 cases/1000 acute occupied bed-days (AOBDs) ($P = 0.002$ for trend) and 30-day mortality decreased from 26% to 14% ($P = 0.013$). Significant reductions were observed only in MRSA bacteraemia, not meticillin-susceptible *S. aureus* (MSSA) bacteraemia. Admissions screened for MRSA increased from 43% during selective screening to >90% within 4 months of implementation of universal screening, which included isolation or cohorting of positive cases and decontamination using chlorhexidine bathing and nasal mupirocin. In multivariate time-series analysis ($R^2 = 0.45–0.68$), universal screening was associated with a 19% reduction in the prevalence density of MRSA bacteraemia [−0.035, 95% confidence interval (CI) −0.049 to −0.021/1000 AOBDs; $P < 0.001$], a 29% fall in hospital-associated incidence density (−0.029, 95% CI −0.035 to −0.023/1000 AOBDs; $P < 0.001$) and a 46% reduction in 30-day mortality (−15.6, 95% CI −24.1% to −7.1%; $P < 0.001$). Importantly, the time to report positive cultures was <48 h. The method of MRSA detection from screening swabs was a chromogenic agar, and several are available, which give reasonable performance with 16–24 h of incubation [16]. It is not clear from the literature what benefits are to be gained from more rapid and even more sensitive molecular tests, although near-patient application of these is likely to prove beneficial in certain circumstances. The extra costs may, however, be difficult to justify. Rather than universal screening, costs may be saved by targeted or risk-assessed screening [17], and computer-based electronic prediction programmes [18] may be helpful here. In the author's experience, however, it can be difficult to implement risk assessment without dedicated personnel.

Positive associations with fluoroquinolone and cephalosporin use suggested that antibiotic stewardship measures targeted against these agents reduced the prevalence density of MRSA bacteraemia by 0.027 [15]. Rates of bacteraemia and 30-day mortality were also positively associated with hospital-wide consumption of fluoroquinolone and cephalosporin antibiotics 1–6 months earlier. Assuming an average regimen of seven defined daily doses, the number needed to treat to cause one additional case of MRSA bacteraemia was 179 for cephalosporins and 204 for fluoroquinolones.

An important paper from the UK argues that the decline in MRSA in UK hospitals is strain-specific and preceded intensification of infection control measures such as widespread adoption of universal screening [19]. The authors did not, however, use time-series analysis or account for autocorrelation or autoregression of resistance. This is essential as successive observations of resistance are not independent. Resistance is an ecological phenomenon dependent upon population-level determinants. While the authors argue the merits of randomised controlled trials, these would necessarily require multicentre involvement, but contamination between intervention and control areas would be problematic: the global spread of resistant pathogens invalidates assumptions of closed populations even at international levels.

Other issues to consider when designing future intervention studies include the prolonged timescales required to capture delayed effects from changes in care, standardisation of interventions, and risks of selection bias.

Another paper, analysing the benefits of a national hand hygiene campaign by ITS analysis, could only show reductions in MRSA rates in the last year of the 4-year study [20]. We too have found no strong association with improved hand hygiene in our MRSA rates [15]. Experience from Hong Kong during the severe acute respiratory syndrome (SARS) outbreak confirms this, suggesting that significant environmental contamination by MRSA can confound benefits of hand hygiene (W.H. Seto, personal communication). Further confirmation of this can be gleaned from

the few studies on environmental MRSA contamination and the importance of cleaning/disinfection [8].

Chlorhexidine bathing is a very common intervention in hospitals these days, and not just for control of MRSA. Current evidence suggests it is a very important part of MRSA control bundles, particularly where there is a lack of isolation facilities. It is also an integral part of decolonisation strategies. Worries about resistance are widespread, although there is little evidence that this is likely to be a major problem in the near future [11]. Probably only high-level resistance will be a significant clinical issue in MRSA. Of more concern perhaps is the selection of less susceptible Gram-negative bacteria such as *Pseudomonas* spp. that may colonise or infect after chlorhexidine use, or even contaminate chlorhexidine-containing products [21].

Finally, the cost effectiveness of MRSA control is often debated with concern, in particular about the use of universal screening. Whilst broad use of molecular screening methods may not be cost effective, it is difficult to argue against the use of conventional culture-based screening as part of a bundle of control measures, even in the epidemic setting. Hospitals do, however, really need to evaluate their own interventions to see what works, and this is easily done with the use of routine laboratory and pharmacy data, analysed on a monthly basis by ITS analysis. Also, considering MRSA is an extra burden of serious staphylococcal infection and not just a replacement for MSSA, it is hard to think control measures are not cost effective [22]. Recent work from the UK even demonstrates the value of rapid molecular typing in controlling an outbreak [23].

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Competing interest

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