Commentary

Rapid molecular detection of methicillin-resistant *Staphylococcus aureus*: a cost-effective tool for infection control in critical care?

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See related research by Harbarth *et al.* in issue 10.1 [http://ccforum.com/content/10/1/R25]

Abstract

Control strategies for methicillin-resistant *Staphylococcus aureus* (MRSA) in critical care remain debated. Timely detection of MRSA carriers is crucial to an effective isolation policy. In this issue, Harbarth and colleagues report rapid MRSA screening among intensive care unit-admitted patients using a PCR assay. Pre-emptive isolation for all admissions until screened negative for MRSA was associated with a reduction of intensive care unit-acquired MRSA infections in one of two study units. The data provide preliminary evidence to the effectiveness of a MRSA control strategy combining rapid screening by a molecular method and preventive isolation. Further controlled studies are needed to evaluate the cost-effectiveness of this intervention.

Evaluation of rapid MRSA screening and preventive isolation

The study reported by Harbarth and colleagues in the previous issue of *Critical Care* is the first clinical investigation to evaluate the impact of a novel molecular assay for rapid screening of methicillin-resistant *Staphylococcus aureus* (MRSA) carriage in the intensive care setting [1]. The authors conducted a multistep intervention cohort study over a period of 32 months in two adult intensive care units (ICUs) in a university hospital.

During a baseline phase, screening for MRSA was performed by culture methods in high-risk patients admitted to these ICUs. In a first intervention phase, all admissions were screened for MRSA by PCR. The median time intervals between ICU admission and notification of screening test results in the intervention and baseline phases were compared. In a second intervention phase, all patients were placed in contact isolation on ICU admission pending rapid screening results, and the incidence of ICU-acquired MRSA infection was compared with that of the pre-intervention period, with adjustment for MRSA colonization pressure.

The implementation of rapid PCR screening reduced the time to detection of MRSA carriers from 4 days to 1 day. After implementing extensive on-admission PCR screening and pre-emptive contact isolation, a substantial decrease of MRSA infections was observed in the medical ICU but not in the surgical ICU. Using the PCR method, the number of unnecessary isolation days was markedly reduced as compared with the same isolation policy supported by conventional screening methods.

Rationale for improved MRSA control by rapid screening

Harbarth and colleagues' study is important because it addresses an unmet medical need [2]. MRSA has become endemic in many hospitals worldwide where it is causing excess nosocomial infection, particularly in the intensive care setting. There is mounting public concern about this situation, as evidence shows that invasive MRSA infection is associated with a significant increase in mortality and prolonged hospital care [3,4]. MRSA transmission occurs via healthcare workers' hands that become contaminated during patient care. MRSA colonization places the individual patient at increased risk of infection and constitutes up to 70% of the patient reservoir for cross-transmission [1,4]. As confirmed by Harbarth and colleagues, only a small minority of MRSA carriers can be detected by culture of clinical samples whereas performing selective culture of mucocutaneous colonization sites was 10-fold more sensitive in this endemic ICU setting [1].

The optimal MRSA control strategy remains debated, although the 'search-and-destroy' approach that combines active screening, strict isolation and decolonization of carriers has demonstrated its efficacy in keeping hospitals free of

ICU = intensive care unit; MRSA = methicillin-resistant *Staphylococcus aureus*; PCR = polymerase chain reaction.

endemic MRSA in The Netherlands and Scandinavia [5,6]. Clinical practice recommendations include MRSA carrier screening to inform patient isolation and decontamination procedures, and thereby to more effectively control cross-infection [4]. Several studies have indeed indicated that this approach is also cost-effective in endemic ICU settings with prevalence rates of MRSA carriage on admission ranging from 4% to 20% [4,7].

Conventional methods are unfortunately too slow for early identification of MRSA carriers. Culture-based screening methods usually require 48–96 hours before MRSA identification. New-generation selective agar media with chromogenic enzyme substrates perform better but still require 24–48 hours for presumptive MRSA detection [8]. During this delay of several days between sampling and reporting of detection results, MRSA carriers may constitute a source of cross-colonization if no contact isolation precautions are taken. To address this diagnostic delay, a cautious alternative is to place ICU-admitted patients in pre-emptive isolation until proven MRSA-negative.

Technological advances in molecular detection of MRSA

Molecular assays that detect MRSA in the range of 10 genome copies within 2–6 hours have recently been developed for screening specimens [8]. The majority of these multiplex PCR assays simultaneously detect the methicillin resistance determinant *mecA* and another gene that is specific to *S. aureus*, such as the thermonuclease *nuc* gene or the cell wall biosynthesis *femA* gene.

The IDI-MRSA system (GeneOhm Sciences, San Diego, CA, USA) targets MRSA-specific DNA elements that bridge the mobile genetic cassette carrying *mecA*, called Staphylococcal Chromosome Cassette mec, and the *S. aureus*-specific chromosomal junction (*orfX*). This design prevents false-positive signals occurring from mixed flora specimens containing methicillin-susceptible *S. aureus* and methicillin-resistant coagulase-negative staphylococci [9]. Clinical evaluations of this assay have shown that MRSA could be detected from nasal swabs within 2 hours with high sensitivity and specificity [9,10].

Real-time multiplex PCR on the LightCycler system (Roche Applied Sciences, Indianapolis, IN, USA) has also shown promising performance on testing nasal swabs from neonates and from adult patients in one study [11].

The assay evaluated in the study by Harbarth and colleagues used an immunomagnetic separation step for selective MRSA concentrations from swab specimens prior to DNA extraction and real-time multiplex PCR. It was initially reported as very sensitive but not very specific [12], although results reported here showed lower sensitivity and higher specificity [1]. Mathematical modeling suggest that using a rapid PCR assay for MRSA admission screening and patient isolation should reduce significantly the incidence of hospital-acquired MRSA infection and should prove cost-saving [13,14].

A technology assessment challenge

Will such prediction prove correct in critical care? The findings of Harbarth and colleagues [1] provide preliminary evidence for the medical utility of this new diagnostic technology. This study provides the first detailed analysis of diagnostic delays for MRSA screening. It demonstrated that a screening time of 1 day is feasible using real-time PCR, thereby enabling a preventive isolation strategy that appeared to contribute to a reduction of ICU-acquired infections in one of two units. Why this strategy had no impact in another ICU remains unclear. As recognized by the authors, their study had several limitations. Firstly, they used different timings for implementing the components of their combined intervention in the two ICUs. Secondly, the impact on MRSA acquisition and transmission in the ICU could not be assessed because no screening was performed during the ICU stay and bacterial isolates were not genotyped. Finally, the model used for measuring the effect attributable to the intervention did not adjust for several important confounders. Nevertheless, the authors should be commended for performing this intervention study that documents the benefit of replacing conventional screening by rapid PCR testing and re-organizing critical care towards systematic use of barrier precautions.

Commercial PCR tests are becoming available for fast MRSA detection. As these tests are more expensive and skill-intensive than conventional tests, controlled trials funded by independent health technology assessment agencies must determine the potential medical and economic benefit of control strategies using this technology in acute care [8]. Study endpoints should include the number of unisolated MRSA patient-days avoided, the number of unnecessary pre-emptive isolation days avoided, the increase in the MRSA decolonization rate, the decrease in the MRSA transmission and infection rate, the decrease in MRSA-related mortality, the cost saving due to shorter patient hospital stay and ICU stay, and the decreased use of glycopeptides. Although such studies will be costly, the burden of disease caused by uncontrolled MRSA infection in critically ill patients and the potential benefits of improved control warrant the effort.

Competing interests

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