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EDITORIAL

Decolonization strategies against multidrug resistant organisms in the ICU

Pedro Póvoa[1,2,3*], Paula Ramirez[4,5] and Stijn Blot[6]

Multiple-drug resistant organisms (MDRO) are a consequence of antibiotic pressure, selection, and infection control failure. Regional variation in MDRO rates is evident [1].

Important however, healthcare workers rarely become colonized with MDRO, probably because of a well-balanced microbiota offering 'colonization resistance' against new invaders. Antibiotics disrupt this equilibrium leading to an increased risk of MRDO colonization and infection, potentially taking months to restore.

Additionally, through horizontal transmission, the risk of MDRO colonization goes beyond antibiotic exposure. Our aim is to present practical recommendations for bedside clinicians concerning screening for MDRO and decolonization strategies (nasal, oropharyngeal, and skin).

Screening

Since intensive care unit (ICU) admits all types of patients, screening is a useful tool to monitor and identify MDRO colonization. This is an important step to implement enhanced contact precautions to prevent cross-colonization, through isolation and cohorting, elimination of reservoirs and outbreak identification [2]. Screening can be applied universally (all patients) or targeted by focusing on patients with a risk profile (e.g., prior hospitalization, long-term care facility resident, recent antibiotic exposure), possibly combined with predictive scoring systems. However, the performance of these clinical tools is poor [3].

*Correspondence: pedrorpovoa@gmail.com
[3] ICU4, Department of Intensive Care, Hospital de São Francisco Xavier, ULSLO, Estrada do Forte do Alto do Duque, 1449-005 Lisbon, Portugal
Full author information is available at the end of the article

MDRO detection could be done by classic culture methodology or by polymerase chain reaction (PCR)-based detection techniques using different types of kits for gene identification. Compared to the culture-based techniques, PCR-based techniques are faster (turnaround time of ± 2 h) but 3–4 times more expensive. Test results must be communicated immediately to ICU staff and infection control team, who must track patients' whereabouts and contacts.

Colonization by a MDRO during ICU stay is a dynamic process encompassing detection, spontaneous clearance, and infection [4]. Adequate identification of MDRO colonization requires regular screenings on admission and weekly thereafter.

Nasal decolonization

Nasal colonization by *Staphylococcus aureus* is a risk factor for post-operative surgical site infections (SSI). Nasal mupirocin bid for 5 days is the most frequently used methodology for nasal decolonization of methicillin-sensitive (MSSA) and methicillin-resistant *Staphylococcus aureus* (MRSA) (Table 1). However, literature is blurred by applying targeted nasal decolonization (screen-positive) and universal decolonization (all patients), or using it in combination with other strategies (e.g., chlorhexidine (CHG) bathing). A health technology assessment concluded that either targeted or universal nasal mupirocin decolonization alone may result in little or no risk SSI reduction [5]. However, the same review concluded that combined with CHG bathing, nasal mupirocin is likely to decrease the risk of SSI with *Staphylococcus aureus* (including MRSA) in patients undergoing cardiothoracic, vascular, orthopedic, gastrointestinal, or general surgery (Table 1).

MRSA colonization is frequent in ICUs and a predictor of ICU-acquired MRSA infection. A cluster-randomized trial assigned ICUs to different strategies [6], either a

Table 1 Decolonization strategies against multidrug-resistant organisms in the intensive care unit

Location	Intervention	Benefits	Adverse effects	Recommended
Nasal	Nasal mupirocin to MRSA carriers or universal	None	Mupirocin-resistant selection	NO
	Nasal mupirocin + CHG bathing before surgery	Decrease rate MRSA Decrease incidence BSI	Mupirocin-resistant Selection	NO
Oropharyngeal	Universal SOD (colistin + tobramycin + nystatin)	None	Antibiotic-resistant selection	NO
	Universal CHG mouthwashes	None	Increase mortality	NO
Gastrointestinal	Antimicrobials	None	Increase risk of MDRO	NO
Skin	Universal CHG bathing	Decrease incidence BSI (CLABSI and Gram-positive etiology) Decrease rate MDRO in endemic settings	Skin irritation	YES

CLABSI central line-associated bloodstream infection, *CHG* chlorhexidine, *BSI* bloodstream infection, *ICU* intensive care unit, *MDRO* multi-drug-resistant organisms, *MRSA* methicillin-resistant *Staphylococcus aureus*, *SOD* selective oral decontamination

targeted strategy (screening, isolation, nasal decolonization and CHG bathing) or a universal strategy (all patients exposed to nasal decolonization and CHG bathing) reduced clinical MRSA cultures and bloodstream infection from any pathogen, compared with baseline data. Following concerns regarding mupirocin resistance, povidone-iodine was evaluated as an alternative to the former, though found to be inferior in preventing *S. aureus* and MRSA clinical cultures [7].

Oropharyngeal decolonization

Selective oral decontamination with paste containing colistin, tobramycin and nystatin, thereby mainly targets Gram-negatives and yeasts. In a multicenter randomized controlled trial (RCT), its efficacy in the prevention of bloodstream infection with MDROs was investigated in patients anticipated to be ventilated > 48 h [8]. No significant reduction in absolute risk reduction versus baseline was observed (Table 1).

CHG mouthwashes have long been advocated in all ventilated patients to reduce ventilator-associated or post-operative pneumonia rates, albeit only supported by evidence in cardiosurgical patients. Since a decade, the safety of CHG mouthwashes is questioned. A meta-analysis of RCTs and three large cohort studies, indicated an increased risk of death associated with CHG mouthwash [9]. Following these data, a multicenter stepped-wedge cluster-randomized trial evaluated the effect of a de-adoption strategy of CHG mouthwash [10]. No differences in ICU mortality, time to infection-related ventilator-associated complications, time to extubation, or pain during oral care was observed. Interestingly, de-adopting CHG mouthwash resulted in lower oral care dysfunction scores, indicating that oral health is better pursued without the use of oral antiseptics. Therefore, the latest guidelines from the Society for Healthcare Epidemiology (SHEA), the Infectious Diseases Society of America (IDSA), and the Association for Professionals in Infection Control and Epidemiology (APIC), advise against CHG mouthwash (Table 1).

Skin decolonization

Skin disinfection could be useful to prevent nosocomial infections (specifically central line-associated bloodstream infection (CLABSI)) and to eliminate MDRO.

The agent of choice for skin disinfection is CHG due to its broad antimicrobial action and residual effect. Daily skin disinfection with CHG (liquid bathing agent or pre-packaged washcloths) was proposed for the prevention of nosocomial infections. Four randomized crossover trials involving 25 ICUs and 22,850 patients were evaluated in a meta-analysis, which found a reduction in nosocomial bloodstream infection (BSI) (odds ratio (OR): 0.74; 95% confidence interval (CI): 0.6–0.9), especially in CLABSI (OR: 0.5; 95% CI: 0.35–0.71). The effect remained significant for Gram-positive bacteria subgroup and not when Gram-negative bacteria were independently assessed, probably due to the greater CHG efficacy in Gram-positive and their predominance as CLABSI aetiology [11].

A recent cluster RCT including 72 ICUs with 76,815 patients showed that antiseptic bathing (CHG or octenidine) did not reduce CLABSI rates compared with controls [12]. However, a post hoc analysis comparing baseline versus intervention period demonstrated a decrease from 1.48 to 0.9 CLABSI/1000 days ($p = 0.0085$) in the CHG group; no difference was identified among controls [13]. Therefore, a universal CHG bathing strategy incorporation should be recommended for those ICUs with MDRO Gram-positive high prevalence or with high CLABSI incidence despite usual preventive measures.

MDRO Gram-positive bacteria acquisition declined statistically after CHG bathing in a systematic review including 16 studies [14]. However, information regarding MDR Gram-negative bacteria is scarce. A single study in an ICU endemic for multi-drug resistant *Klebsiella pneumoniae*, reduced the rate of colonized patients after 11 months using CHG washcloths ($\beta = -0.209$; $r2 = 0.549$; $p = 0.027$) [15] (Table 1). The universal use of CHG bathing has raised questions regarding reduced CHG-susceptibility or the acquisition of antiseptic resistance genes, antibiotic cross-resistance, decolonization failure, and unhealthy alteration in skin microbiome. So far, there is minimal evidence for any of these adverse consequences [16]. *Candida auris* (CA) is an emerging troublemaker pathogen in which the effectiveness of CHG has shown confounding results. Even the use of an isotonic hypochlorite solution was unable to achieve skin decolonization of CA [17]. The development of microbiome-based therapeutic approaches to prevent and treat CA is a promising option that could even be extended to restore skin microbiota in critically ill patients.

Take-home message

Universal screening for MDRO is important to identify colonized patients and implement the adequate preventive measures. Decolonization strategies are only recommended for skin with universal CHG bathing. With the growing problem of MDRO further research is needed to identify efficacious additional decolonization strategies.

Author details

[1] NOVA Medical School, NOVA University of Lisbon, Lisbon, Portugal. [2] Center for Clinical Epidemiology and Research Unit of Clinical Epidemiology, OUH Odense University Hospital, Odense, Denmark. [3] ICU4, Department of Intensive Care, Hospital de São Francisco Xavier, ULSLO, Estrada do Forte do Alto do Duque, 1449-005 Lisbon, Portugal. [4] Department of Critical Care Medicine, Hospital Universitario Y Politécnico La Fe, Valencia, Spain. [5] Centro de Investigación Biomédica en Red-Enfermedades Respiratorias (CibeRes, Carlos III Research Institute, CB06/06/0028 Madrid, Spain. [6] Department of Internal Medicine and Pediatrics, Ghent University, Ghent, Belgium.

Declaration

Conflict of interest

PP Lectures: Mundipharma, Gilead, MSD, Consulting: Gilead, Pfizer; PR Lectures: Pfizer, MSD, Shionogi, Gilead, Consulting: Pfizer, MSD, Shionogi, Gilead; SB none.

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