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Perspective

Multiple-site decontamination in critically ill patients requires careful implementation

Yuetian Yu[a,b,1], Bin Lin[b,c,1], Lihui Wang[a], Chunhui Xu[d], Cheng Zhu[e,*], Yuan Gao[a,*]

[a] Department of Critical Care Medicine, Renji Hospital, Shanghai Jiao Tong University, School of Medicine, Shanghai 200127, China
[b] Key Laboratory of Intelligent Pharmacy and Individualized Therapy of Huzhou, Huzhou 313100, Zhejiang Province, China
[c] Department of Pharmacy, Changxing People's Hospital; Changxing Branch, Second Affiliated Hospital of Zhejiang University School of Medicine, Huzhou 313100, Zhejiang Province, China
[d] State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin 300020, China
[e] Department of Disease Prevention and Control, Ruijin Hospital, Shanghai Jiao Tong University, School of Medicine, Shanghai 200025, China

A B S T R A C T

The EPIC III study showed that 52% of patients admitted to the intensive care unit (ICU) have infectious diseases and that the incidence of ICU-acquired infections is increasing, leading to longer ICU stays and higher mortality rates. Multiple-site decontamination, a type of selective decontamination program, has been associated with a reduction in the incidence of ICU-acquired infection and decreased mortality rates in some critically ill patients. However, the standardized implementation and actual effectiveness of multiple-site decontamination require further investigation.

1. Definition and development of multiple-site decontamination

The concept of decontamination originated in the 1960s, initially targeting patients with malignant hematological tumors who were immunosuppressed and susceptible to secondary infections, as well as those undergoing solid organ transplantation. By the 1980s, its application had expanded to critically ill patients in the intensive care unit (ICU). Selective digestive decontamination (SDD) is one of the most common methods currently used. It involves the application of non-absorbable local antibacterial and antifungal drugs to the oral cavity and upper gastrointestinal tract of mechanically ventilated (MV) patients. While the specific implementation and drug protocols may vary, SDD typically includes oral administration of aminoglycosides (e.g., tobramycin, gentamicin), polymyxins (e.g., colistin, polymyxin B), and antifungal agents (e.g., amphotericin B, miconazole). Short-term intravenous administration of third-generation cephalosporins (e.g., cefotaxime) or fluoroquinolones (e.g., ciprofloxacin) can also be included [1,2].

In recent years, the concept of multiple-site decontamination (MSD) has emerged, combining selective oropharyngeal decontamination with comprehensive body washing using chlorhexidine and nasal application of mupirocin, in addition to SDD. The primary aim of MSD is to prevent the excessive growth of antibiotic-resistant bacteria in the patient's oral cavity, skin, mucosa, and upper gastrointestinal tract. It seeks to prevent ventilator-associated pneumonia (VAP) by inhibiting the colonization of these microorganisms in the stomach and their subsequent microaspiration into the lungs. Additionally, it aims to reduce the translocation of intestinal microbiota and ICU-acquired bloodstream infec-

Abbreviations: ICU, intensive care unit; SDD, selective digestive decontamination; MV, mechanically ventilated; MSD, multiple-site decontamination; VAP, ventilator-associated pneumonia; BSIs, bloodstream infections; ICHs, immunocompromised hosts; ICU-AI, ICU-acquired infections; RR, relative risk; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; MDRO, multidrug-resistant organism; OR, odds ratio.

* Corresponding authors.
E-mail addresses: zhucheng1203@163.com (C. Zhu), 17811@renji.com (Y. Gao).

[1] Yuetian Yu and Bin Lin contributed equally to this work and should be considered co-first authors.

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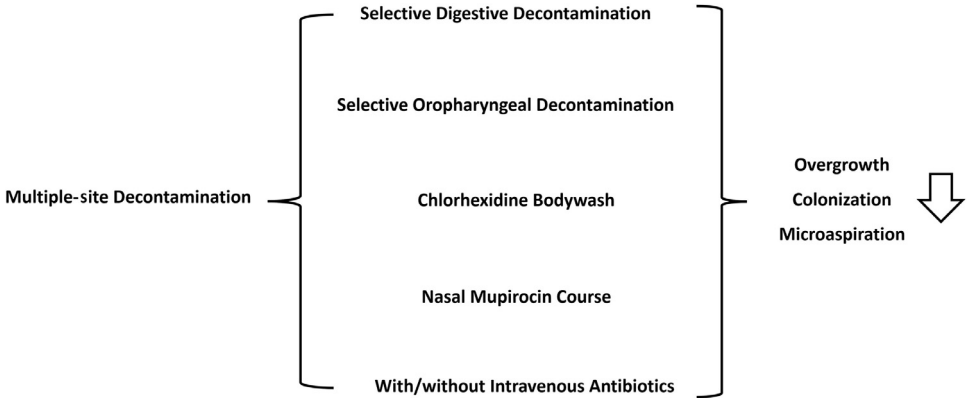

Fig. 1. Multiple-site decontamination.

tions (BSIs) resulting from skin and mucosal damage (Fig. 1).

2. Clinical evidence of multiple-site decontamination

Table 1 summarizes key studies evaluating the efficacy of MSD in ICUs and includes some important studies related to SDD. The methods and main results of the MSD-related studies are as follows.

- In 2023, Massart et al. [3] evaluated 295 immunocompromised hosts (ICHs) in French ICUs, dividing patients into an MSD group and a standard prevention group. The MSD protocol involved daily use of gentamicin (543 mg/day), colistin (400 mg/day), and amphotericin B (2000 mg/day) in the oropharynx and gastric tube; daily full-body bathing with 4% chlorhexidine; and a 5-day course of mupirocin applied to both nasal cavities without intravenous antibiotics. The study showed that MSD reduced the incidence of ICU-acquired infections (ICU-AI) (relative risk [RR], 0.39; 95% confidence interval [CI], 0.20–0.87) and lowered overall ICU mortality (hazard ratio [HR], 0.58; 95% CI, 0.34–0.95).
- Massart et al. [4] conducted a retrospective observational study in 2022 involving 461 MV patients from 15 ICUs in France, with 89 patients receiving MSD. The study showed reductions in ICU-AI (RR, 0.56; 95% CI, 0.38–0.83), VAP (RR, 0.52; 95% CI, 0.33–0.89), and in-hospital mortality (16.9% vs. 30.1%, $P = 0.017$) in the MSD group [4].
- In 2023, Massart et al. [5] examined 241 patients who underwent venovenous extracorporeal membrane oxygenation (VV-ECMO) for acute respiratory distress syndrome in 3 ICUs in France, with 69 patients in the MSD group and 172 patients in the standard treatment group. The study showed a decrease in ECMO-related infections (RR, 0.42; 95% CI, 0.23–0.60) and multidrug-resistant organism (MDRO) infections (RR, 0.13; 95% CI, 0.03–0.56) in the MSD group, but there was no significant difference in the mortality rate (45% vs. 43%, $P = 0.90$) [5].
- Also in 2023, Massart et al. [6] analyzed 346 MV patients from 5 ICUs in western France, including 334 in the MSD group and 1012 in the standard care group. A previous before-and-after study showed that MSD reduced the incidence of ICU-AI (RR, 0.33; 95% CI, 0.18–0.60), VAP (3.6% vs. 16.2%), and BSI (3.0% vs. 7.2%) ($P < 0.05$) [6]. By contrast, the four

Table 1
Important studies evaluating the impact of decontamination in the ICU.

Study/Year	Study Type	Intervention Group	Control Group	Outcomes
Recent studies focused on MSD				
Nicolas Massart et al. (2023) [3]	Before after study	MSD	Standard care	MSD reduces the incidence of ICU-AI and all-cause mortality
Nicolas Massart et al. (2022) [4]	Retrospective observational study	MSD	Standard care	MSD reduces the incidence, VAP and all-cause mortality, but not the incidence of BSI
Nicolas Massart et al. (2023) [5]	Retrospective observational study	MSD	Standard care	MSD decreases the incidence of ECMO-AI and MDRO infection, but not the all-cause mortality
Nicolas Massart et al. (2023) [6]	Retrospective observational study	MSD	Standard care	MSD decreases the incidence of ICU-AI, VAP, BSI, but not the incidence of MDRO infection
Nicolas Massart et al. (2023) [7]	Before after study	MSD	Standard care	MSD decreases the incidence of IFI
Recent studies focused on SDD				
Plantinga et al. (2018) [8]	Meta-analysis of six RCTs	SOD or SDD	Standard care	SDD improves ICU and hospital survival
Wittekamp et al. (2018) [9]	Three-arm cluster crossover trial	CHX 2%, SOD or SDD	Standard care	SDD does not decrease the incidence of ICU-BSI
Myburgh et al. (2022) [10]	Cluster crossover trial	SDD	Standard care	No difference can be found in mortality, MV time and long of ICU stay
Hammond et al. (2022) [11]	Meta-analysis of 32 RCTs	SDD	Standard care	SDD reduces the incidence of VAP and ICU-BSI

Abbreviations: CHX, chlorhexidine; IFI, invasive fungal infection; SOD, selective oral decontamination; RCT, randomized controlled trial.

SDD studies listed in Table 1 remain controversial in terms of their impact on the incidence of ICU-AI, mortality, length of ICU stay, and other outcomes.

Recent analyses indicate that high-risk populations for ICU-acquired MDRO infections include ICHs, patients with severe COVID-19, patients undergoing VV-ECMO, and patients with ARDS. Some studies have revealed ICU-AI rates as high as 56% [12]. Adopting selective decontamination strategies with or without systemic antibiotics may reduce the occurrence of VAP and BSI in critically ill patients, decrease MDRO infections, and potentially reduce broad-spectrum antibiotic use. In the current era of global antibiotic resistance, these findings are encouraging. However, most studies were conducted in ICUs with low MDRO detection rates, such as in France and the Netherlands, while ICUs with higher MDRO rates have reported opposite outcomes.

As part of MSD, the role of chlorhexidine gluconate bathing in reducing hospital-acquired MDRO infections remains unclear. In areas with a high MDRO prevalence, such bathing significantly reduced the risk of MDRO and hospital-acquired BSIs. However, a randomized controlled trial in France showed no reduction in ICU-AI compared with placebo. Later studies revealed that combining mupirocin and chlorhexidine gluconate with oral-pharyngeal and digestive tract decontamination had a synergistic preventive effect, with encouraging results across AI, VAP, BSI, and MDRO [13]. Moreover, several studies showed lower overall mortality rates in the MSD group than in controls. The attribution of VAP-related mortality remains controversial. Smet et al. [14] indicated that MV patients with moderate to severe conditions have higher VAP-related mortality, but many confounding factors affect these rates. Determining the true efficacy of MSD will require further adjustment or subgroup analysis.

3. Controversies regarding widespread settlement in multiple regions

Despite studies showing that SDD can reduce ICU-AI rates and its recommendation in some guidelines as a standard strategy for preventing VAP, the implementation of SDD in ICUs remains low. International guideline groups have consistently not recommended routine use of this intervention, mainly because of the lack of standardized methods and concerns about increased antibiotic resistance. Excessive antibiotic use, particularly local application, is associated with higher detection rates of MDRO, especially methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*, which are prevalent in ICU-AI. SDD may also be linked to increased MDR bacteria in patients with inflammatory bowel disease, likely because of disruptions in the intestinal microbiota balance from local antibiotics. However, elucidating the true impact of SDD on host microbiota still requires long-term follow-up with large sample sizes.

Most research on the impact of SDD on antibiotic resistance patterns comes from France and the Netherlands, countries with a lower prevalence of MDRO. A recent study included patients from five Dutch ICUs with an average follow-up of 7 years. The study showed that after implementing a decolonization strategy, the detection rate of tobramycin-resistant pathogens decreased over time, while resistance to colistin remained unchanged (0.5%) [15]. Further analysis is needed to determine whether data from countries with lower antibiotic resistance apply to those with higher resistance rates.

A systematic review of antibiotic-resistant bacteria emergence after SDD showed no increase in colonization or infection rates of methicillin-resistant *Staphylococcus aureus* (odds ratio [OR], 1.46; 95% CI, 0.90–1.68) or vancomycin-resistant *Enterococcus* (OR, 0.63; 95% CI, 0.39–1.02). Resistance to aminoglycosides (OR, 0.73; 95% CI, 0.51–1.05) or quinolones (OR, 0.52; 95% CI, 0.16–1.68) did not increase, while resistance to glycopeptides (OR, 0.58; 95% CI, 0.46–0.72) and third-generation cephalosporins (OR, 0.33; 95% CI, 0.20–0.52) significantly decreased [16]. Although concerns about increased resistance rates exist, published clinical trials do not support this claim. In fact, SDD is associated with reduced overall antibiotic use and decreased prescription of "wild-type" antibiotics. The amount of antibiotics used in SDD is negligible relative to total hospital usage.

Another barrier to SDD implementation is the lack of standardized, commercially prepared, and tested drug formulations. Most studies rely on formulations prepared in hospital pharmacies or at the bedside, complicating consistent implementation.

Patients with traumatic brain injury are particularly prone to VAP because of their impaired consciousness and decreased immune function. Long-term antimicrobial use for infection prevention or treatment in these patients can lead to drug-resistant bacteria. Young et al. [17] performed a post hoc analysis of nearly 6000 patients with traumatic brain injury and found lower mortality rates in the SDD group than in the conventional treatment group (32.3% vs. 38.0%, $P = 0.004$). However, further analysis of factors such as pathogen resistance and changes in intestinal microbiota was not conducted. The generalizability and long-term effects of SDD and MSD in these patients require further clarification through large-sample randomized controlled trials [17].

4. Limitations and prospects of multisite extensive decontamination

The primary goal of implementing MSD is to reduce the emergence and spread of MDR pathogens. However,

some studies suggest that MSD may alter patients' internal microecological balance, potentially inducing MDR pathogen production. Wand et al. [18] found that exposure of *Klebsiella pneumoniae* to chlorhexidine may induce mutation of the *smvR* gene, enhancing the efflux pump mechanism and further mutating the *PhoPQ* gene, ultimately leading to colistin resistance in *Klebsiella pneumoniae* [18].

Some clinical studies have analyzed the impact of MSD on the minimum inhibitory concentration of pathogens, antibiotic resistance, and patient microflora. Although some studies show that MSD can reduce all-cause mortality, it also increases the detection of antibiotic-resistant bacteria. Machuca et al. [19] evaluated the use of oral aminoglycoside antibiotics for patients colonized with *Klebsiella pneumoniae* carbapenemase (KPC)-producing *Klebsiella pneumoniae* and found a secondary gentamicin resistance rate of 13.6% in the decolonization group, higher than in the control group (3.0%, $P = 0.008$). Another single-center study implementing SDD for patients at risk of resistant bacterial infection detected two colistin-resistant strains and five gentamicin-resistant strains in the SDD group, while none were found in the control group [20]. Later research by Oren et al. [21] reached similar conclusions.

MSD has gradually become a standard practice for preventing ICU-AI in European countries such as France and the Netherlands, where MDRO detection rates are lower. It remains uncertain whether findings from studies by Massart et al. apply to regions with higher MDRO detection rates, such as the United States or Asia. The true impact of MSD on the ICU environment and host microbiota also requires long-term follow-up studies with large sample sizes. Additionally, the heterogeneity in defining ICHs may necessitate subgroup analyses of the effectiveness of preventive strategies across different settings. With the increasing use of novel biological agents and immunosuppressive therapies in clinical practice, there is also a need for standardized definitions and classifications of ICHs.

Finally, all completed MSD research, primarily observational studies by Massart et al., lack blinded or randomized controlled trial designs, affecting the reliability and generalizability of the results. Large-sample randomized controlled trials are necessary to evaluate the real effects of MSD, and further analysis is required to determine the contribution of each component of MSD.

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CRediT authorship contribution statement

Yuetian Yu: Conceptualization, Data curation. **Bin Lin:** Data curation, Writing – original draft. **Lihui Wang:** Validation, Writing – review & editing. **Chunhui Xu:** Data curation, Software. **Cheng Zhu:** Methodology, Writing – original draft. **Yuan Gao:** Writing – review & editing.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data available statement

Not applicable.

Ethics statement

Ethical approval was not required.

Informed consent

Not applicable.

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