Multiple-site decontamination regimen without systemic antibiotics associated with reduced mortality in intubated patients

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Running Title: Multiple-site decontamination in ICU patients.

To the Editor

The results of a study on *Pseudomonas aeruginosa* ventilator-associated pneumonia, reported in this journal, suggested that initial combination therapy followed by early de-escalation had no impact on mortality, raising concerns about the appropriate management of pneumonia in the intensive care unit (ICU) [1]. Perspectives are different in ICUs with low multidrug-resistance prevalence rate, because antimicrobial therapy issues are simpler and infection prevention is more prominent. Selective digestive decontamination with systemic antibiotics has been shown to decrease ICU-acquired pneumonia and bloodstream infection and to reduce mortality in patients most often receiving mechanical ventilation. We performed a post-hoc analysis of an observational retrospective study in three ICUs with low multidrug-resistance prevalence rate. Mortality was compared for patients receiving standard care versus patients receiving a selective digestive combined with nasal and cutaneous decontamination regimen.

The study was conducted in three French ICUs with an average extended-spectrum beta-lactamase-producing Gram-negative bacilli prevalence rate of 6% [2]. ICU 1 was a medical ICU with 22 acute-care beds in a tertiary university hospital and ICUs 2 and 3 were polyvalent ICUs with 14 and 12 acute-care beds, respectively. In addition to standard care, ICU 1 used a multiple-site decontamination regimen for the prevention of acquired infections in intubated patients. Multiple-site decontamination is a variant of selective digestive decontamination and consists of the administration of topical antibiotics (tobramycin, polymyxin and amphotericin B) four times daily in the oropharynx and the gastric tube without systemic antibiotics, chlorhexidine body washing twice a day and a 5-day nasal mupirocin course in all intubated patients who had an expected intubation duration of 24 hours or more, throughout the duration of intubation. Full details about the multiple-site decontamination regimen have been reported elsewhere [3]. Patients in ICUs 2 and 3 received

standard care alone. Patients who required intubation for an expected duration greater than

two day were eligible for study and divided into two groups: multiple-site decontamination

group (ICU 1) and standard care group (ICUs 2 and 3).

Each center had a nosocomial infection committee for the prevention and prospective

census of acquired infections and applied the recommendations of the French Society for

Hospital Hygiene for the prevention and treatment of infection (available at

https://sf2h.net/publications/actualisation-precautions-standard-2017). Because report of

acquired infections is a routine care, the institutional ethics committee approved the study and

written informed consent was waived. Infection was considered ICU-acquired when it was

diagnosed 48 hours after admission or later and not incubating on admission. The diagnosis of

pneumonia was made on clinical signs (fever) radiological findings (new infiltrate on chest-

X-ray or CT scan), and a positive microbiological culture of an endotracheal aspirate ($\geq 10^6$

colony-forming units/mL) or a broncho-alveolar lavage ($\geq 10^4$ colony-forming units/mL) as

recommended by the Centers for Disease Control and Prevention [4]. Bloodstream infection

was diagnosed with at least one positive blood culture for a significant pathogen and two

positives blood cultures drawn on separate occasions for common skin contaminants as

defined by the CDC [4]. The primary endpoint was ICU mortality and secondary endpoints

were the incidence of pneumonia and bloodstream infection.

Statistical analysis was performed with R 3.4.3. Qualitative variables were expressed as

numbers (percent) and quantitative variables as medians (interquartile range [IQR]). The chi-

square test and the Fisher's exact test were used to compare categorical variables and the

Man-Whitney U test was used for continuous variables. Kaplan-Meier ICU survival curves

were compared with the log-rank test. Multivariate analysis was made using logistic

regression and the Cox proportional-hazards regression model when appropriate. The

following covariates including age, sex, reason for admission (medical/surgical) and

simplified acute physiology score II (SAPS II) at admission were included in the model, as performed in other studies [5]. All tests were two-sided, and a p-value ≤0.05 was considered statistically significant.

Among 3,861 admissions from January 2016 to September 2017, 1,368 patients were intubated longer than 2 days and were included in the study, respectively 676 and 680 in the multiple-site decontamination and standard care groups. Compared to the standard care group, patients in the multiple-site decontamination group were younger (62 [51–70] years versus 64 [53–74] years, p=0.005), had higher SAPS II score at admission (52 [38–65]) versus 50 [35–63] respectively, p=0.013), were less likely to be admitted for surgery (10% versus 17%, p<0.001) and had a longer length of stay in ICU (10 [3–17] days versus 8 [3–15] days, p=0.002) (Table 1).

The probability of remaining alive with time in ICU was higher in the multiple-site decontamination group (Figure 1, p=0.01). Compared to standard care, the adjusted hazard ratio for death in ICU at day-28 in the multiple-site decontamination group versus the standard care group was 0.75 (95% confidence interval 0.64–0.90, p=0.01). Crude mortality in ICU was 27.2% in the multiple-site decontamination group and 31.0% in the standard care group (adjusted OR 0.69 [0.52–0.90], p=0.007; Table 1). Compared to standard care, fewer patients acquired pneumonia (4.1% versus 12.6%, p=0.001), bloodstream infection (3.4% versus 6.7 %, p=0.006) and overall infections caused by *Pseudomonas aeruginosa* (1.0% vs 3.5%, p= 0.004) in the multiple-site decontamination group. Time to first acquired infection was similar in the multiple-site decontamination and the standard care groups (10 [6–25] days and 12 [5–26] days, p=0.97).

In this study conducted in ICUs with low-level antimicrobial resistance, the use of a selective digestive decontamination regimen was associated with a lower ICU mortality rate and lower acquisition rates of pneumonia and bloodstream infection than the use of standard

care alone. The relatively high rate of bloodstream infection in the standard care group, higher than usually reported by the Réa-Raisin surveillance network (available at http://www.cpias-ile-de-france.fr/surveillance/rea/2017/Rapport_REA2017.pdf), could be related to the 100% rate of intubation in our study population compared to only 59% to 67% in the Réa-Raisin database, depending on the year studied. Indeed, intubation >48 hours has been shown to increase the risk of acquired infection [3]. In our study, the incidence of pneumonia (combining ventilator-associated and other healthcare-associated pneumonia) compared favorably to the 12.5% mean rate reported by the French network for ventilator-associated pneumonia alone.

The favorable effect of infection prevention by selective digestive decontamination or selective oral decontamination regimens on mortality in ICU is controversial. In a large meta-analysis including 36 randomized controlled trials, total mortality was reduced in trials comparing a combination of topical and systemic antibiotics to controls, but not with topical antibiotics alone [6]. Selective oral decontamination has been shown to reduce mortality by 2.9 percentage points compared to standard care in the Netherlands [5]. However, compared to selective oral decontamination, selective digestive decontamination was associated to lower mortality. In contrast, in European ICUs with intermediate or high level antimicrobial resistance, a selective digestive decontamination regimen without systemic antibiotics did not decreased mortality compared to other interventions (chlorhexidine mouthwash, selective oral decontamination) or standard care [7].

In France, a multicenter controlled trial of selective digestive decontamination without systemic antibiotics performed in 1990 had not shown improved survival compared to placebos [8]. In contrast, our study, which shows for the first time a benefit on mortality with a selective digestive decontamination regimen in France, highlights the rationale of the recent French recommendations for the prevention of acquired pneumonia in ICUs with a prevalence

rate of multidrug resistant bacteria below 20% [9]. In a randomized controlled trial performed according to a 2x2 factorial design, Camus et al. reported for the first time that the combination of selective digestive decontamination using topical antibiotics alone with chlorhexidine body washing and nasal mupirocin decreased all-cause acquired infections compared to placebos [10]. Interestingly, although the study was not powered to assess mortality, ICU mortality tended to be lower with all-drugs regimen than with placebos (21.7% versus 32.5%, p=0.052) while the length of stay in ICU was similar in both groups [10].

The main limitations of the present study were the retrospective observational design, the existence of differences between groups at baseline and the possible reduced sensitivity of microbiological culture of respiratory samples for the diagnosis of pneumonia with multiple-site decontamination. However, patients in the multiple-site decontamination group were at higher risk for infection because they were more severe as evidenced by a higher severity score despite younger age and had a longer length of stay in ICU.

In conclusion, the association of oropharyngeal and digestive topical antibiotics (tobramycin, polymyxin and amphotericin B) with nasal mupirocin and chlorhexidine body wash was associated with lower ICU mortality in intubated patients hospitalized in ICUs with low multidrug resistance prevalence rate.

Competing interest :

The Authors have no conflict of interest to declare.

Ethic approval :

This observational retrospective study respects the MR003 convention. Patients were informed of the study and non-opposition was needed. By the French law, there was no need for patient's written approval. The local ethic committee approved the protocol (n°18.52).

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Table 1. Characteristics and outcomes of study patients.

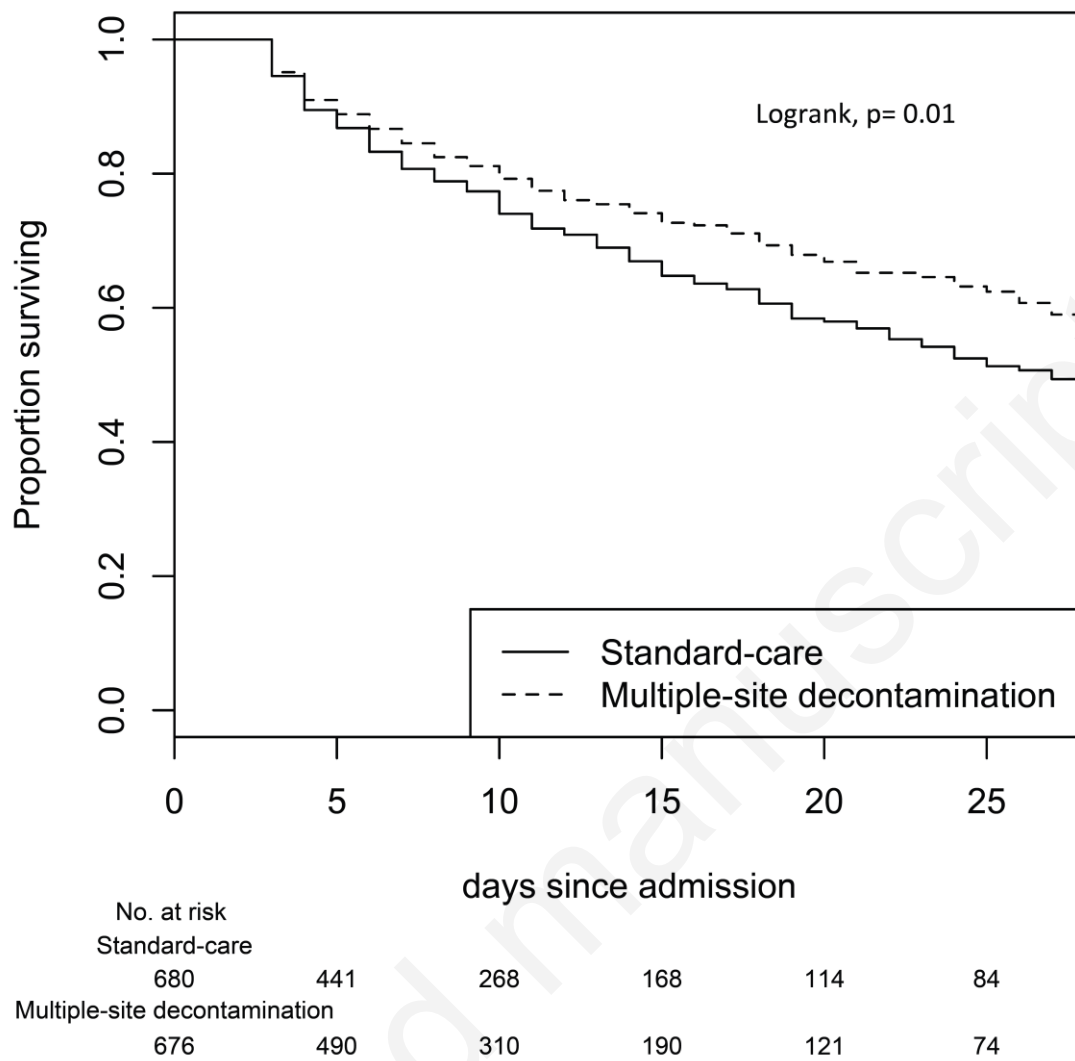| Variables	Multiple-site decontamination (n = 676)	Standard care (n = 680)	OR [95% CI]	p-value	Adjusted OR [95% CI]	p-value
Age, year (IQR)	62 (51–70)	64 (53 –74)				
Simplified Acute Physiology Score II (IQR)	52 (38 – 65)	50 (35– 63)				
Male – no. (%)	439 (64.9)	470 (69.1)				
Reason for admission						
Surgical – no. (%)	64 (9.5)	118 (17.4)				
Medical – no. (%)	612 (90.5)	387 (56.9)				
Not specified – no. (%)	0	175(25.7)				
Length of stay in ICU, days (IQR)	10 (3–17)	8 (3–15)				
Survivors, days (IQR)	11(3–17)	8 [3–16]				
Dead, days (IQR)	7 (3–14)	7(3–14)				
Death in ICU – no. (%)	184 (27.2)	211 (31.0)	0.83 [0.66 –1.05]	0.12	0.69 [0.52 – 0.90]	0.007
Infections acquired in ICU						
Pneumonia – no. (%)	28 (4.1)	86 (12.6)	0.30 [0.19 – 0.47]	< 0.001	0.28 [0.18 – 0.46]	< 0.001
Bloodstream infection – no. (%)	23 (3.4)	46 (6.7)	0.48 [0.29 – 0.81]	0.006	0.41 [0.24 – 0.71]	0.001
Infections caused by *Pseudomonas aeruginosa*– no. (%)	7 (1.0)	24 (3.5)	0.29 [0.12 – 0.69]	0.004	0.26 [0.11 – 0.63]	0.003

Figure 1. ICU survival of study patients.