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ORIGINAL

Personalized automatic management of tracheal cuff pressure and subglottic secretions drainage to prevent pneumonia in critically ill intubated patients. The MICROINHALO multicenter randomized controlled trial

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Abstract

Purpose: The MICROINHALO trial investigated whether personalized management of endotracheal tube cuff pressure (P*cuff*) based on exhaled CO_2 measurement combined with automatic subglottic space drainage (SSD) may prevent tracheal colonization in critically ill intubated patients.

Methods: This cluster-randomized, international, open-label trial (NCT05403320) enrolled adult patients at 10 ICUs. They were randomly assigned to receive either an endotracheal tube equipped with automatic P*cuff* management and SSD, or a conventional one with manual P*cuff* management and manual SSD. The primary endpoint of the study was the rate of bacterial tracheal colonization ($> 10^3$ CFU/mL) on day 3 after intubation.

Results: Among 270 randomized patients, 250 were included in the analysis: 127 allocated to the automatic management group and 123 to the manual management group. Bacterial tracheal colonization on day 3 occurred in 47 (37%) patients in the automatic management group and in 51 (41.5%) patients among controls (absolute difference − 4% [95% CI − 16 to 8], $P = 0.52$). The rate of clinically diagnosed (12.6% vs. 24.4%, $P = 0.016$) and microbiologically confirmed ventilator-associated pneumonia (VAP) (10.2% vs. 19.5%, $P = 0.039$) was significantly lower in the automatic management group, along with a lower percentage of P*cuff* values outside the safety range (10.2% vs. 24.4%, $P < 0.001$) and a higher daily SSD volume (25 [8–41] mL vs. 10.5 [6–17] mL, $P < 0.001$).

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Conclusions: Among critically ill intubated patients, personalized automatic management of tracheal cuff pressure and subglottic secretion drainage was not superior to manual management to prevent tracheal colonization. Further research is warranted to confirm the observed effect on VAP rate reduction.

Graphical abstract:

PERSONALIZED AUTOMATIC MANAGEMENT OF TRACHEAL CUFF PRESSURE AND SUBGLOTTIC SECRETIONS DRAINAGE TO PREVENT PNEUMONIA IN CRITICALLY ILL INTUBATED PATIENTS

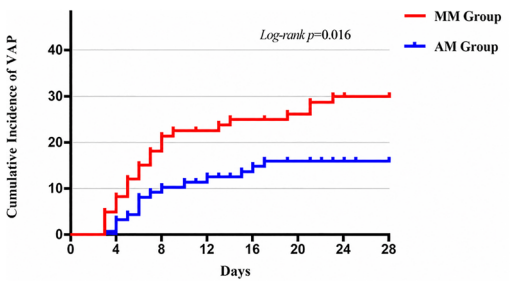
The MICROINHALO multicenter randomized controlled trial

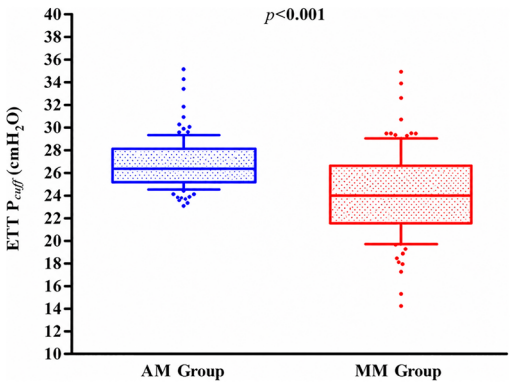
Study design

Multicenter cluster-randomized trial in 250 critically ill intubated patients comparing automatic personalized cuff-pressure control + automatic subglottic secretion drainage vs manual management.

Findings

- **Primary endpoint not met:** Day-3 tracheal colonization was similar between groups: **37.0% vs 41.5%.**
- Automatic management achieved **better cuff-pressure control**, with fewer values outside the 20–30 cmH_2O safety range: **10.2% vs 24.4%**.
- It also enabled **greater subglottic secretion drainage:** median daily volume **25 mL vs 10.5 mL.**
- **VAP rates were lowe**r with automatic management: clinically diagnosed VAP **12.6% vs 24.4%;** microbiologically confirmed VAP **10.2% vs 19.5%.**
- No clear differences were observed in **ventilator-free days, antibiotic-free days, ICU/hospital length of stay, or mortality.**





Take-home message

Automatic personalized airway management did not reduce early tracheal colonization but may reduce VAP through improved cuff sealing and more efficient secretion drainage.

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ICM Intensive Care Medicine

Keywords: Ventilator-associated pneumonia (VAP), Infection prevention, Tracheal cuff pressure, Subglottic secretions

Introduction

Ventilator-associated pneumonia (VAP) represents the most frequently encountered nosocomial infection in Intensive Care Unit (ICU) patients, being still associated with relevant morbidity, mortality and additional healthcare-related costs [1, 2]. Among international recommendations to prevent VAP, both the use of endotracheal tubes (ETTs) with subglottic secretions drainage (SSD) ports and frequent cuff-pressure (P*cuff*) monitoring are considered additional approaches which may lower VAP rates in certain patient populations [3, 4]. Microaspiration of oropharyngeal secretions also has a key role in VAP development. Indeed, the drainage of above the ETT-cuff secretions and the maintenance of P*cuff* in a safety range (usually between 20 and 30 cmH_20) are physiologically sound interventions to prevent secretions migration and pneumonia occurrence [5, 6]. Many observational and interventional studies have investigated the clinical impact of the above prevention measures in patients with an expected mechanical ventilation (MV) duration ≥ 72 h, usually documenting a clear trend toward VAP reduction [7, 8]. Clinical data regarding the superiority of different P*cuff* control systems and SSD modalities are still unclear, although a recent meta-analysis showed a reduced risk of VAP associated with automatic continuous ETT P*cuff* control (OR 0.51, 95% CI 0.31 – 0.82) [9]. Similarly, the large body of evidence supporting the benefits of SSD derives from studies where manual intermittent subglottic secretions suction and lavage were performed [10, 11].

Recently, an innovative technology for the management of intubated patients (AnapnoGuard™ [AG] 100 System) has been developed. The system provides continuous P*cuff* control, detecting air leakage from the lungs by measuring the carbon dioxide (CO_2) level in the subglottic space, indeed personalizing inflation values to the lowest levels sealing the tracheal mucosa. Concomitantly, it automatically evacuates secretions from the subglottic area by simultaneously rinsing/venting the space from one port of the tube, while performing intermittent suctioning through dedicated ports. This innovative technology has received both Food and Drug Administration (FDA) and European Conformity (CE) approval and it has been shown to be feasible and safe in preclinical and preliminary clinical investigations [12, 13]. Then, in a pilot randomized trial, the use of this technology was associated with a higher rate of P*cuff* determinations in the safety range and a higher amount of aspirated subglottic secretions, appearing safe in terms of post-extubation throat pain, hoarseness and tracheal mucosa oedema [14, 15]. Thus, we decided to conduct a randomized control trial to investigate whether a technology based on a personalized automatic management of P*cuff* and SDD could reduce tracheal colonization and ventilator-associated pneumonia (VAP) in intubated critically ill patients.

Take-home message

This randomized trial investigated if a personalized and automatic Pcuff management based on exhaled CO2 measurement combined with automatic subglottic space suctioning and rinsing may help prevent microaspiration and ventilator-associated pneumonia (VAP) in orotracheally intubated critically ill patients. The study failed to demonstrate a superiority of the personalized automatic management to prevent early tracheobronchial colonization (37% vs 41.5%), although showing a significant lower rate of Pcuff measurements outside the 20–30 cmH_2O safety range (10.2% vs. 24.4%) and a significantly higher median daily SSD volume (25 mL vs. 10.5 mL). The rates of clinically diagnosed (12.6% vs. 24.4%) and microbiologically confirmed (10.2% vs. 19.5%) VAP were significantly lower in patients undergoing the automatic management of Pcuff and subglottic secretions drainage. The findings do not support the hypothesis that a personalized automatic management of tracheal cuff pressure and subglottic secretions drainage reduces early tracheal colonization in patients undergoing invasive mechanical ventilation. However, the observed potential to prevent clinically- and microbiologically-diagnosed VAP warrants further confirmatory research.

Methods

Study design and participants

The MICROINHALO trial was a cluster-randomized international multicentre open-label controlled trial, conducted in ten ICUs in Italy and Israel between June 2022 and April 2024 (*see appendix page 3 for the full list of study centres*). The study was approved by the Catholic University's Ethical Committee (approval number P/4739/CE/2022) and by the Institutional Review Board of all centres and was prospectively registered with ClinicalTrials.gov (NCT05403320) before the inclusion of the first patient. Written informed consent was provided by the patients/their legal representative or next of kin, before enrolment, according to local regulations. Patients older than 18 years were considered for enrolment if they required invasive mechanical ventilation (IMV) with an expected duration > 48 h. They were excluded in the presence of the following criteria: IMV in the previous 14 days, contraindication for enteral feeding, enrolment in another study that could interfere with the current trial, clinical evidence of inhalation before intubation, pregnancy.

Randomization procedure

Because intubation is an urgent intervention in critically ill patients with acute respiratory failure, individual randomization was considered unpractical. Hence, we decided to implement a cluster randomization based on predetermined clusters of 9 consecutive patients, stratified by centres, with each cluster being assigned to one

of the study groups. Inclusion in a single cluster was anticipated to cover 4–6 weeks in each centre and at each cluster change the appropriate endotracheal tubes were made available for all future patients at the centres. Cluster size has been set at "9" to reduce as much as possible the intra-cluster correlation [16]. Patients randomized in the automatic management (AM) group were intubated with AnapnoGuard ETT [ID 8.0/7.5 mm, polyvinylchloride (PVC) tube with ellipsoidal shape, thin wall polyurethane (PU) cuff] with dual suction lines and an extra venting line. They were indeed connected to the AnapnoGuard 100 control unit (Hospitech Respiration LTD., Petach-Tikva, Israel), which provided automatic continuous P*cuff* regulation and evacuation of SS from above the cuff (*see appendix page 4 for further details on the system function*). Patients randomized in the manual management (MM) group were intubated with the TaperGuard Evac ETT (Mallinckrodt Medical, Athlone, Ireland; ID 7.5/8.0 mm), incorporating a dorsal additional lumen ending above the PU conic cuff. In this group ETT P*cuff* was manually kept constant within the 20—30 cmH_20 interval using a portable manometer (monitored at least every h8) and subglottic secretions were manually drained with a 10 mL syringe, with an intended frequency of one suction per hour, through the only dedicated lumen.

Study outcomes

The primary outcome of the study was the proportion of patients with bacterial tracheobronchial colonization ($>10^3$ colony-forming units [CFU]/mL) measured from tracheal aspirate, without clinical and radiological signs of VAP on Day 3 after randomization. Secondary outcomes were: proportion of patients who developed VAP and the time to event, total/daily subglottic secretion volume, out-of-range cuff pressure values, prevalence of patients with gastric and oropharyngeal microaspiration, number of antibiotic-free days and ventilator-free days, length of ICU and hospital stay, in-hospital mortality, 28-day mortality, 60-day mortality, 90-day mortality, post-extubation stridor. To assess robustness of findings under different prior assumptions, a post-hoc exploratory Bayesian analysis was conducted on the primary and main secondary outcomes (*see appendix pages 6–8 for further details*).

Data collection and definitions

In both groups, to diagnose tracheobronchial colonization ($>10^3$ CFU/mL, measured from tracheal aspirate), quantitative tracheal aspirate was performed after intubation, and after 72 h. In patients with suspected VAP, quantitative tracheal aspirate or bronchoalveolar lavage was performed to confirm the diagnosis (*see appendix page 4 for VAP diagnostic criteria*). In both groups, identical measures for the prevention of VAP were established (*see appendix page 4 for VAP prevention bundle details*). Only in the coordinating centre tracheal aspirates were collected to measure pepsin and amylase, at least 12 h after intubation. (*see appendix pages 4, 5 for details on variables and definitions*) [15, 17].

Statistical analysis

We estimated a prevalence of 30% tracheal colonization in the control group [18, 19]. Hypothesizing a 50% reduction in the automatic management group, with a two-sided confidence interval with an alpha error of 5% and a power of 80%, we expect that the minimum sample size needed for each group to reach the primary endpoint would be of 120 patients ($N=240$). However, hypothesizing a drop-out rate of the 10% (mainly patients extubated or dead within 48 h of IMV), we expect to enrol at least 135 patients per group, for an overall sample size of 270 patients. The tracheobronchial colonization rate was estimated on the basis of the results of two randomized controlled studies [18, 19] where this outcome was investigated and the 50% relative reduction in the experimental group was based on the finding of previous results from our group [14]. Data were analysed on a modified intention-to-treat principle; indeed, we included all randomized patients who required mechanical ventilation for more than 48 h, except those who secondarily withdrew consent, who were already ventilated during in the previous 14 days and who did not reach DAY 3 because extubated or dead (drop-out population). No interim analysis was planned. All included variables were summarized by descriptive statistics techniques. In depth, data were reported as absolute and percentage frequencies as for qualitative variables, whilst quantitative data were expressed either as mean ± standard deviation (SD) or median with interquartile range (IQR). Quantitative data distribution was previously assessed by the Shapiro–Wilk test. Between-groups differences were assessed, as for qualitative variables, either by the Fisher exact test or the Chi-square test, with Yates correction, as appropriate. Quantitative data, instead, were assessed either by the Student's t-test or the non-parametric Mann Whitney U test, according to their distribution. VAP occurrence (either clinically diagnosed and microbiologically confirmed) was assessed by Kaplan–Meier survival analysis and appropriate curves were plotted. A pre-specified subgroup analysis of the primary endpoint was performed in patients with Day 0 negative TA and with Day 3 positive TA at any count.

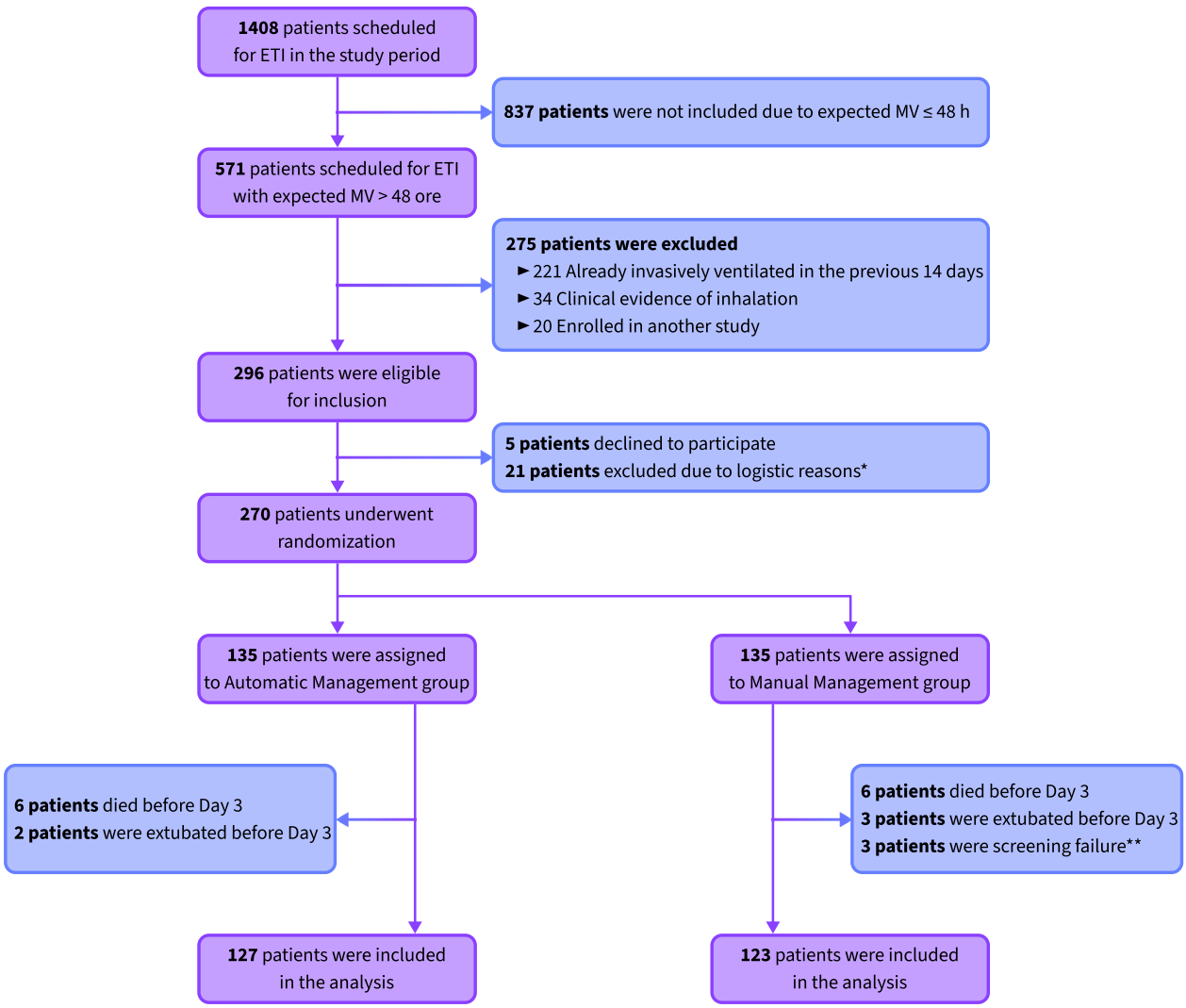


Fig. 1 Flow chart of the study inclusion process[#]. [#]7053 patients were admitted in the study period in all the participating ICUs. *Emergency intubation without availability of study endotracheal tubes. **Already mechanically ventilated in the previous 14 days

All statistical analyses were performed using SPSS version 26 (IBM SPSS). Data were further graphed with GraphPad Prism version 6.0 (GraphPad Software, San Diego, CA).

Results

During the study period, among 1408 patients scheduled for ETI in the study centres, 837 were not included due to IMV expected ≤ 48 h and 301 were excluded according to protocol criteria (Fig. 1). Of the remaining 270, 17 died or were extubated before Day 3 and three were secondarily found to be already mechanically ventilated in the previous 14 days. Finally, 250 patients were included in the analysis: 127 in the automatic management group and 123 in the manual management group. No patients were lost at follow-up, and no follow-up data were missing. Demographics and comorbidities were similar between the groups with a median Charlson index of 5 [IQR, 3–7] and no significant differences in terms of main severity scores and organ dysfunctions (Table 1). Of note, 50.8% of the patients were intubated with a diagnosis of suspected pneumonia (Supplementary Table 1, *appendix page 9)*, with overall septic shock and ARDS rates of 24% and 16.8%, respectively (Table 1).

Table 1 Baseline patients' characteristics

Variables	No. of patients	
	Automatic management ($n=127$)	Manual management ($n=123$)
Demographics and comorbidities		
Age, years	66 [55.5–75]	65 [55–72.5]
Sex (male)	81 (63.8)	82 (66.7)
Body mass index, kg/m^2	26.3 [24.2–30.3]	26.6 [24.2–31]
Chronic Heart Disease	36 (28.3)	34 (27.6)
Peripheral Vascular Disease	48 (37.8)	32 (26)
COPD	23 (18.1)	27 (21.9)
Chronic Neurologic disorder#	16 (12.6)	7 (5.7)
Diabetes	26 (20.5)	34 (27.6)
Chronic renal disease	20 (15.8)	25 (20.3)
Chronic liver disease	12 (9.5)	9 (7.3)
Immunosuppression*	36 (28.3)	40 (32.5)
Charlson index	5 [3–7]	5 [3–7]
Recent hospitalization**	50 (39.4)	46 (37.4)
*Day 0—presenting features****		
Hospital LOS, days	2 [0–6]	1 [0–5.5]
Respiratory failure	67 (52.8)	56 (45.5)
Cardiovascular failure	19 (15)	17 (13.8)
Renal failure	8 (6.3)	10 (8.1)
Neurological failure	57 (44.9)	49 (39.8)
SAPS II score	44 [34–53]	46 [38–58]
SOFA score	7 [5–10]	8 [5–12]
ARDS	24 (18.9)	18 (14.6)
Septic Shock	34 (26.8)	26 (21.1)
Suspected pneumonia	68 (53.5)	59 (47.9)
Positive TA (any count)	67 (52.8)	58 (47.1)
WBC (10^9/L)	12.8 [8–17.1]	12.4 [7.9–19.1]
Previous antibiotics	68 (53.5)	62 (50.4)
On-going antibiotics	94 (74)	96 (78.1)
Lowest PaO_2/FiO_2 ratio	183 [119–279]	178 [123–260]
Lowest PEEP value	5 [5–8]	5 [5–8]
Controlled MV	104 (81.9)	102 (82.9)

Categorical variables are expressed in count and percentage; continuous variables are expressed in median and interquartile range

COPD Chronic Obstructive Pulmonary Disease, *SAPS II* Simplified Acute Physiology Score II, *SOFA* Sequential Organ Failure Assessment, *ARDS* Acute Respiratory Distress Syndrome, *TA* Tracheal Aspirate, *WBC* White Blood Cell, *PEEP*: Positive End Expiratory Pressure, *MV* Mechanical Ventilation, *LOS* Length of Stay

16 patients with neurological disorders in the AM group: 10 with motor disorders and 6 with cognitive disorders. Seven patients with neurological disorders in the MM group: 6 with motor disorders and 1 with cognitive disorder. Among them 6 patients in the AM group and 4 in the MM group were intubated due to primary neurological failure

*Including patients with active solid and haematological neoplasms, chronic steroids, immunosuppressive agents, solid organ and stem cells transplantation, WBC < 1000 *10^9/L, acquired immunodeficiency syndrome

**Previous three months

***At enrolment, patients may have more than a clinical presenting feature

Primary outcome

The proportion of patients with bacterial tracheobronchial colonization (> 10^3 CFU/mL), measured from tracheal aspirate, on Day 3 after randomization did not significantly differ between the two arms: ($n=47$) 37% in patients randomized to the automatic management group vs. ($n=51$) 41.5% among controls, [absolute difference − 4 (− 16 to 8) $p=0.52$] (Table 2).

The primary outcome measure was also similar considering only new isolated bacteria (> 10^3 CFU/mL) on Day 3: ($n=33$) 26% in the AM group vs. ($n=35$) 28.5% in the MM group [OR (95%CI) 0.88 (0.51–1.54), $p=0.67$] (Fig. 2). No intergroup differences were documented analysing Day 3 tracheal bacterial colonization at any count: ($n=63$) 49.6% in the AM group vs. ($n=63$) 51.2% among controls [OR (95%CI) 0.94 (0.57–1.54), $p=0.8$] (Fig. 2). Post-hoc Bayesian sensitivity analysis on the primary outcome did not reach conventional decision thresholds for superiority (posterior probability of ~ 72–79%) (*see appendix page 6 for further details on the analysis*).

Day 3 microbiological isolates were also similar, with an overall predominance of Gram-negative bacteria ($n=83/127$; 65.4%) compared with Gram-positive ones ($n=44/127$, 34.6%), including 47 multidrug-resistant (MDR) strains (Supplementary Table 2, *appendix page 10*) [20].

Secondary outcomes

Three of the pre-specified secondary outcomes (VAP rate, P*cuff* control and SS drained volume) significantly differed between the two arms (Table 2).

In the AM group ($n=16$), 12.6% of patients developed clinically diagnosed VAP and among them 13 (10.2%) were microbiologically confirmed. Conversely, in the MM group ($n=30$), 24.4% of patients had a clinical diagnosis of VAP, and among them 24 (19.5%) were microbiologically confirmed [OR (95%CI) 0.45 (0.23–0.87), $p=0.016$ and 0.47 (0.23–0.97), $p=0.039$, respectively]. Survival analysis confirmed a significantly lower rate of both clinically diagnosed and microbiologically confirmed VAP in the AM group than in the MM group ($p=0.016$ and $p=0.032$ by log-rank test) (Fig. 3a and b). In the automatic management group, the occurrence rate of clinically and microbiologically diagnosed VAP was 12.5/1000 MV days and 10.2/ 1000 MV days with a median time to event of 6 [IQR, 4.75–10.6] days and 7 [IQR, 6–12] days, respectively. In the manual management group, the occurrence rate of clinically and microbiologically diagnosed VAP was 24.6/1000 MV days and 19.7/1000 MV days with a median time to event of 6 [IQR, 4–8] days and 6.5 [IQR, 4–8.75] days, respectively. Overall, among

Table 2 Primary and secondary outcomes

Variables	No. of patients				
	Automatic management group ($n=127$)	Manual management group ($n=123$)	Absolute or mean difference (95% CI)	OR (95% CI)	*P* value
Primary outcome					
Day 3 tracheal colonization > 10^3 UFC/mL	47 (37)	51 (41.5)	− 4 (− 16 to 8)	0.83 (0.5–1.38)	0.52
Secondary outcomes					
Clinically diagnosed VAP	16 (12.6)	30 (24.4)	− 12 (− 21 to − 2)	0.45 (0.23–0.87)	**0.016**
Microbiologically confirmed VAP	13 (10.2)	24 (19.5)	− 9 (− 18 to 0)	0.47 (0.23–0.97)	**0.039**
Mean daily SS volume, mL[#]	25 [8–41]	10.5 [6–17]	17.45 (10.99 to 23.91)		**< 0.001**
ETT P*cuff* value out of the safety range*	264 (10.2)	541 (24.5)	− 14 (− 16 to − 12)	0.35 (0.3–0.41)	**< 0.001**
Post-extubation stridor	3 (2.4)	2 (1.6)	1 (− 5 to 5)	1.46 (0.24–8.91)	1
Tracheostomy	21 (16.5)	16 (13)	4 (− 5 to 12)	1.32 (0.66–2.68)	0.48
IMV free-day (28d)	21 [16–23]	20 [14.25–24]	− 0.19 (− 1.56 to 1.94)		0.89
Antibiotics free-days (28d)	19 [9.5–22]	19 [11.25–23]	− 0.31 (− 2.45 to 1.83)		0.65
ICU free-days (28d)	17 [7–22]	18 [7–22]	0.16 (− 2.04 to 2.36)		0.77
Hospital LOS	23 [7–52]	21 [7.5–41.5]	5.1 (− 5.85 to 16.01)		0.39
28-day mortality	53 (41.7)	54 (43.9)	− 2 (− 14 to 10)	0.92 (0.55–1.51)	0.7
60-day mortality,	56 (44.1)	60 (48.8)	− 5 (− 17 to 8)	0.83 (0.50–1.36)	0.37
90-day mortality	59 (46.5)	61 (49.6)	− 3 (− 15 to 9)	0.88 (0.54–1.45)	0.53
In-ICU mortality	49 (38.6)	52 (42.3)	− 4 (− 16 to 8)	0.86 (0.52–1.42)	0.78
In-Hospital mortality	59 (46.5)	61 (49.6)	− 3 (− 15 to 9)	0.88 (0.54–1.45)	0.53

Categorical variables are expressed in count and percentage; continuous variables are expressed in median and interquartile range

UFC Unit Forming Colonies, *VAP* Ventilator Associated Pneumonia, *SS* Subglottic Secretions, *ETT Pcuff* Endotracheal Tube Cuff Pressure, *IMV* Invasive Mechanical Ventilation, *ICU* Intensive Care Unit, *LOS* Length of Stay

[#] A total of 7031 SS effective aspirations were performed in the MM group with a median daily frequency of 10 (IQR 8–12)

[*] Number of ETT P*cuff* values below 20 cmH20 and above 30 cmH20 among 2592 measures in the Automatic Management group and 2205 measures in the Manual Management group. Missing values in the MM group were 45 (2%)

37 patients with microbiologically confirmed VAP, 51 bacteria were isolated with a predominance of Gram-negative isolates ($n=40$, 78.4%) and an overall MDR rate of 35.3% ($n=18$) (Supplementary Table 3, *appendix page 11*). Bayesian sensitivity analysis suggested a benefit for both endpoints (posterior probability of ≈99% and ≈98%, respectively) (*see appendix pages 7, 8 for further details on the analysis*).

Of note, among 46 clinically VAP cases, 31 patients (22/30 in the MM group and 9/16 in the AM group) underwent TA for VAP diagnosis, while 15 (8/30 in the MM group and 7/16 in the AM group) underwent BAL. Conversely, among 39 microbiologically confirmed VAP cases, in 24 patients (18/26 in the MM group and 6/13 in the AM group) TA was performed for VAP diagnosis, whereas 15 (8/26 in the MM group and 7/13 in the AM group) received a BAL.

Regarding tracheal surveillance cultures after Day 3, 25 samples were positive for any bacterial growth in the AM group (including 7 cases of clinically diagnosed VAP, of which 3 were microbiologically confirmed) and 27 in the MM group (including 3 cases of clinically diagnosed VAP, all microbiologically confirmed).

Among patients with positive DAY 0 TA, 45 (21 in the AM group and 24 in the MM group) showed MDR bacteria. However, only 31 samples (14 in the AM group and 17 in the MM group) were collected from patients with pneumonia at enrolment (Supplementary Table 1, *appendix page 9).* The rate of appropriate antibiotic therapy was 9/14 (64%) in the AM group and 9/17 (53%) in the MM group, using carbapenems and large-spectrum beta-lactam–beta-lactamase inhibitors for Gram-negative bacterial pneumonia, and linezolid or glycopeptides for methicillin-resistant *Staphylococcus aureus* pneumonia.

Regarding P*cuff* control, the rate of measures out of the 20–30 cmH20 safety range was 10.2% in the AM group compared with 24.5% among controls [OR (95% CI 0.35 (0.3–0.41), $p<0.001$] (Table 2). More in detail, all the 264 out-of-range P*cuff* measures in the AM group were above 30 cmH20, automatically set to seal the trachea. Conversely, of the 541 out-of-range measures in the MM group, 377 were below the threshold: 137 between 19 and 16 cmH20 (indeed related to the disconnecting-reconnecting manoeuvre) and 240 below 16 cmH20. Further, the AM group also showed significantly higher

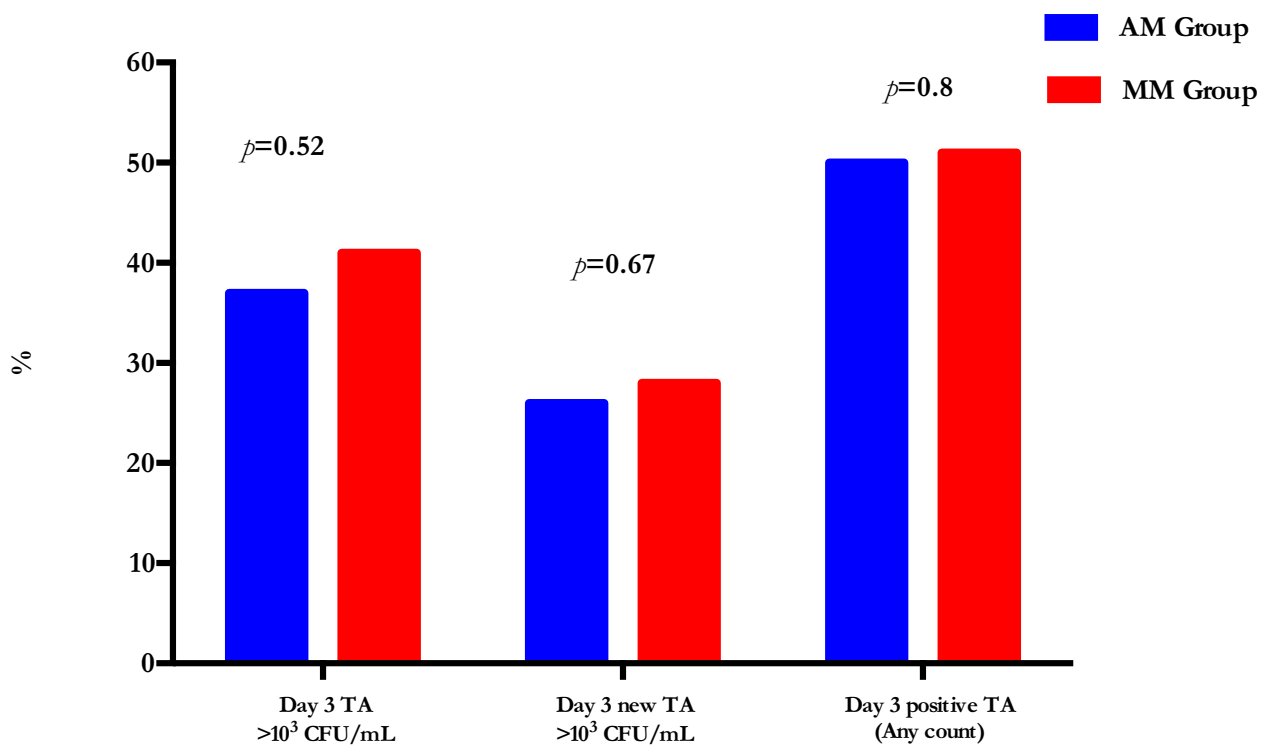
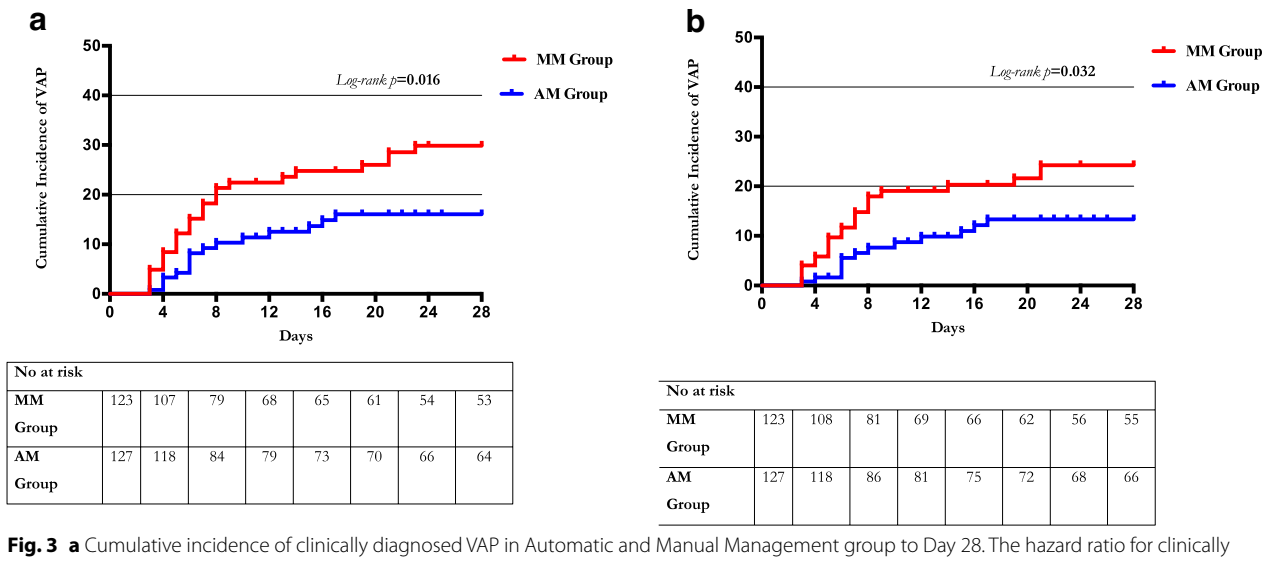


Fig. 2 Day 3 tracheal colonization in the Automatic Management and Manual Management groups. Day 3 new TA: tracheal aspirate positivity (10^3 CFU/mL) with a germ absent on Day 0 sampling; *AM*, automatic management; *MM*, manual management

per-patient mean ETT P*cuff* values: 27.1 [IQR, 26.4–28.3] cmH20 vs. 24.7 [IQR, 22.1–27.1], $p < 0.001$ (Fig. 4a).

The automatic system drained a significantly higher amount of subglottic secretions with per-patient daily volumes of 25 [IQR, 8–41] mL vs. 10.5 [IQR, 6–17] mL



No at risk								
MM Group	123	107	79	68	65	61	54	53
AM Group	127	118	84	79	73	70	66	64

No at risk								
MM Group	123	108	81	69	66	62	56	55
AM Group	127	118	86	81	75	72	68	66

Fig. 3 **a** Cumulative incidence of clinically diagnosed VAP in Automatic and Manual Management group to Day 28. The hazard ratio for clinically diagnosed VAP in the Automatic Management group is 0.49 (95% CI 0.27–0.87). *AM* automatic management, *MM* manual management. **b** Cumulative incidence of microbiologically confirmed VAP in Automatic and Manual Management group to Day 28. The hazard ratio for microbiologically confirmed VAP in the Automatic Management group is 0.49 (95% CI 0.26–0.94).*AM* automatic management, *MM* manual management

compared with manual aspiration, $p<0.001$ (Table 2). Such a difference was confirmed also for per-patient total SS volume: 126 [IQR, 45–249] mL vs. 49 [IQR, 30–119.5] mL, $p<0.001$ (Fig. 4b). No other significant intergroup differences were found regarding the other secondary outcomes (Table 2), including antibiotic-free days, but patients diagnosed with VAP had a longer antibiotic course (median IQR: 15 days [10–27]), compared with those without VAP (8 days [5–14]). In this regard, 76% of the patient population was already receiving antimicrobials at ICU admission due to the presence of an existing infection: about 50% of subjects were admitted with pneumonia, with a 10% higher rate in the AM group (53.5% vs 47.9%; Table 1).

Finally, in the coordinating centre, ten patients in both AM and MM groups underwent 83 tracheal aspirates for measuring alpha-amylase and pepsin levels, as a surrogate of oropharyngeal and gastric microaspirations. All the results for pepsin and amylase levels are reported in Supplementary Table 4, *appendix page 12*.

Discussion

In this multicentre international trial on critically ill intubated patients, the use of a system allowing a personalized automatic regulation of tracheal cuff pressure and subglottic secretions drainage did not reduce the bacterial tracheal colonization rate ($>10^3$ CFU/mL) on Day 3 after intubation, compared to completely manual intermittent management. However, in those managed with the personalized and automatic system, narrower P*cuff* control and larger subglottic secretions drainage were documented, alongside a lower rate of both clinically diagnosed and microbiologically confirmed VAP. No differences were documented in terms of mechanical ventilation duration, ICU length of stay and mortality.

P*cuff* control represents a hallmark in the management of intubated patients. Effectively sealing the trachea may help reduce the migration of subglottic secretions into the lower respiratory tract, provided that cuff pressure is maintained within a safe range of 20–30 cmH_2O. Furthermore, P*cuff* monitoring protects capillaries from hyperinflation injuries that lead to stenosis and tracheomalacia [21, 22]. One of the seminal papers supporting the benefits of strict P*cuff* control was from *Nseir and coll.* where the authors observed that patients randomized to receive a continuous pneumatic control of the endotracheal cuff at 25 cmH_20 had a significant reduction of gastric microaspirations, tracheal bacteria count and VAP rate (9.8% vs. 26.2%, $p=0.032$) [23]. Although subsequent observational data confirmed that continuous *Pcuff* control could reduce lower respiratory tract infections in mechanically ventilated patients [24, 25], two randomized studies recently challenged the potential benefits of such a strategy [26, 27]. A recent systematic review and meta-analysis has confirmed that the use of continuous P*cuff* control devices is associated with a reduced risk of VAP (OR, 0.51), although these data were based on a very low certainty of evidence due to lack of blinding, potential commercial conflict of interests and high heterogeneity [9]. That said, it is not surprising that this measure is not considered as a 'generally recommended' preventive practice in the current update of international VAP prevention guidelines [4]. In our trial, patients managed with the automatic and personalized system, likewise in studies on other electronic or pneumatic devices, had a significantly better P*cuff* control with a lower rate of out-of-limits measures, although setting the pressure slightly

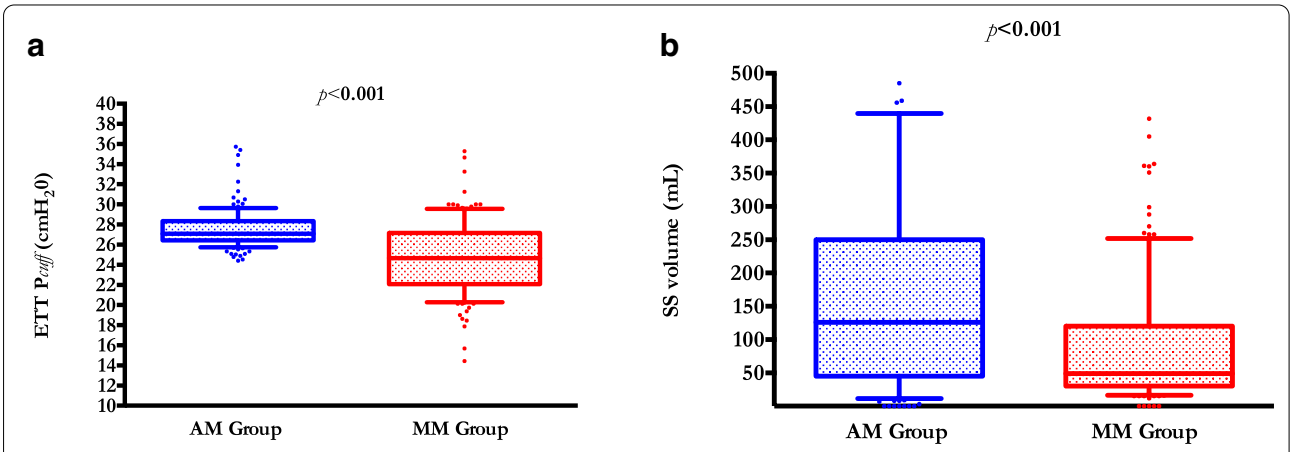


Fig. 4 **a** Per patient mean ETT P*cuff* values in Automatic and Manual Management groups. *ETT*, Endotracheal tube, *Pcuff*, cuff pressure, *AM*, automatic management, *MM*, manual management. **b** Per-patient total volume in Automatic and Manual Management groups. *SS*, subglottic secretions, *AM*, automatic management, *MM*, manual management

higher according to CO_2 leak detections [14, 15]. These results may be explained by the technology surrounding the study device, which intermittently detects air leakages from the lungs by measuring the carbon dioxide (CO_2) level in the subglottic space and inflates the cuff to the lowest value efficiently sealing tracheal mucosa.

For many years, subglottic secretions drainage has been considered a major target of many technological innovations aimed to reduce VAP rate. From a pathophysiological viewpoint, impeding oropharyngeal and gastric secretions to overcome ETT cuff toward the lower respiratory tract has a strong clinical rationale, alongside the reduction of ETT biofilm and the preservation of lung eubiotic microbiota [11, 28]. The first randomized trial using an ETT with a separate dorsal lumen for continuous aspiration demonstrated the safety of this device, which was associated with a trend toward reduced and delayed onset of ventilator-associated pneumonia (VAP) [29]. A few years later, two large-scale randomized studies reproduced these results, by demonstrating the potential benefit of SSD as a standard of care for the prevention of VAP [30, 31]. Similar results have been recently reinforced by a systematic review and meta-analysis of 20 randomized studies, showing a clear reduction of VAP rate (risk ratio (RR) 0.56, 95% CI 0.48–0.63; $I^2=0\%$, $p=0.841$) [10]. Current guidelines support the use of ETT with an SSD additional port for patients who are expected to require prolonged (> 48—72 h) mechanical ventilation, with a moderate strength of evidence [4]. Interestingly a recent randomized trial including about 1000 patients did not show any improvement in terms of quality of life and cognitive function in patients intubated with ETT with subglottic ports and a polyurethane cuff, not even reducing the incidence of possible VAP [32]. Indeed, it has been already observed that uncontrolled negative-pressure aspiration, especially in the presence of vacuum effect-like phenomenon in the subglottic space, may lead to severe mucosal lesions and airway bleeding [33].

In our trial, patients managed with the AG 100 system had a significantly higher daily and per-patient aspiration of SS compared with commonly reported drained volumes obtained manually or with other automatic suction systems. This may suggest that the availability of two ports for suctioning and an additional channel for saline rinsing plus air venting allows a more efficient cleaning of the subglottic space, alongside a protective effect on tracheal mucosa from suction-induced lesions [14, 15]. Although a more effective P*cuff* control and a better SS drainage were observed in the AM group, the trial failed to demonstrate the superiority of the study technology on bacterial tracheal colonization at Day 3. However, about 50% of enrolled patients received ETI or were admitted to the ICU for pneumonia, with a positive TA bacterial culture at Day 0. In addition, during the first 2 days of intubation, patients' secretion production is generally lower than in the following days, potentially blunting the potential benefits of a completely automatic and personalized system, compared with the standard manual practice.

Regarding pulmonary infections prevention, patients randomized to the automatic and personalized system had a significantly lower rate of both clinically diagnosed (24.4% vs. 12.6%; $p=0.016$) and microbiologically confirmed (19.5% vs. 10.2%; $p=0.039$) VAP, compared with controls. In this regard, it is clinically sound that stricter control of cuff pressure and more efficient secretions drainage may contribute to the reduction of lower respiratory tract infections in ventilated patients. However, it is important to note that in most patients in whom VAP was diagnosed, a tracheal aspirate was chosen as the diagnostic procedure, potentially increasing the risk of overdiagnosis. Interestingly, a recent meta-analysis of 18 randomized studies comparing continuous vs. intermittent P*cuff* control showed that, when the drainage of subglottic secretions is combined with automatic control of cuff pressure, the highest effect on VAP reduction may be obtained (RR=0.39; $p<0.001$) [21]. Similarly, a network meta-analysis of 22 randomized trials confirmed that the synergistic effect of antimicrobial coating, cuff design optimization and subglottic secretions drainage is effective in preventing VAP [34].

Said that, the absence of any difference between study groups in antibiotic consumption, duration of mechanical ventilation, ICU length of stay, and mortality appears in contrast with the observed reduction of VAP rates in the AM group. The lack of correlation between VAP prevention and improvement of the above-mentioned outcomes remains a matter of debate. For instance, current international IDSA-SHEA-APIC guidelines stratify preventive measures that primarily reduce VAP incidence (subglottic secretion drainage and, to a lesser extent, strict P*cuff* control), from those that also impact broader outcomes such as MV duration, ICU LOS and mortality (i.e. avoidance of intubation, minimization of sedation, and early mobilization, etc.). One possible explanation lies in the well-known heterogeneity of low respiratory tract infections in mechanically ventilated patients, which is strongly influenced by individual risk profile, antibiotic therapy appropriateness, and clinical severity.

Some limitations of this study should be acknowledged. First, we did not perform serial surveillance tracheal aspirates over Day 3, but we only collected data on the VAP rate. In addition, a Day 3 tracheal aspirate may not represent an objective surrogate of VAP development risk, especially in a population with a very high percentage of Day 0 tracheal colonization due to concomitant

pneumonia. In such a population a later tracheal aspirate could have been more clinically informative, although increasing the drop-out rate. Of note, the median time to VAP occurrence was 6 days among controls and 7 days in the AM group, which were far from the day of microbiological sampling for the primary outcome.

Second, about 15% of the patients underwent tracheostomy, although maintaining electronic continuous P*cuff* control. This aspect may limit the generalizability of the observed results to the overall population of mechanically ventilated patients and the potential impact on more objective clinical outcomes like MV duration, ICU LOS and mortality. Further, we compared a specific personalized automatic system with the manual P*cuff* and SSD management of intubated patients. Thus, it remains unknown whether this new technology may add a real plus-value over other modalities of continuous P*cuff* control and subglottic secretions drainage.

Conclusions

This trial showed that a new system for the management of critically intubated patients, based on personalized control of cuff pressure and automatic subglottic space drainage and rinsing, did not reduce Day 3 tracheal colonization. However, compared with the standard-of-care manual management, it allowed for a more accurate P*cuff* control and efficient subglottic secretions drainage, which may explain the documented reduction in VAP rate. These findings are hypothesis-generating, warranting further investigations in future trials.

Supplementary Information

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Author contributions

GDP and MA conceived the study, participated in protocol development, study design, and data interpretation, and co-wrote the first draft of the report. GDP coordinated the study. GDP, SLC, MV, AC, LD, MG, SB, CE, DLG, RG, GL, VP, GP, MS, EST, AC, CP, MS, TB, AU, MG, MC, GS, GC, MA participated in data collection and data interpretation, and were involved in critical appraisal and revision of the manuscript. GDP provided statistical expertise and review of the report. All authors had full access to all the data in the study and approved the final manuscript for submission.

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Data availability

Data are available with publication by the corresponding author by a signed data access agreement.

Declarations

Conflicts of interest

Maurizio Cecconi is a Section Editor for Intensive Care Medicine. He has not taken part in the review or selection process of this article. Other authors declare no competing interests.

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