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## **Continuous pneumatic regulation of tracheal cuff pressure to decrease ventilator-associated pneumonia in mechanically ventilated trauma patients: the AGATE multicenter randomized controlled study**

### **SHORT RUNNING HEAD**

#### **Continuous regulation of tracheal cuff pressure**

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#### **COMPETING INTEREST**

All investigators declare no competing interests.

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## **ABBREVIATION LIST**

HT	Hazard ratio
ATS	American Thoracic Society
CDC	Centers for Disease Control and prevention
CI	Confidence Interval
CPIC	Clinical Pulmonary Infection Score
HAI	Healthcare-associated infections
ICU	Intensive Care Unit
OR	Odd Ratio
VAE	Ventilator-associated Events
VAP	Ventilator-associated pneumonia

## **ABSTRACT**

**Background:** Ventilator-associated pneumonia (VAP) is the most frequent healthcare-associated infection in severely ill patients and aspiration of contaminated oropharyngeal content around the cuff of the tracheal tube is the main route of contamination.

**Research question:** Is continuous regulation of tracheal cuff pressure using a pneumatic device superior to manual assessment three times daily using a portable manometer (routine care) in preventing VAP in severe trauma patients?

**Study design and methods:** In this open-label, randomised-controlled superiority trial conducted in 13 French intensive care units, we enrolled adults (age  $\geq 18$  years) suffering from severe trauma (Injury severity score  $>15$ ) and requiring invasive mechanical ventilation for 48 hours or longer. Patients were randomly assigned (1:1) via a secure web-based random number generator in permuted blocks of variable sizes to one of two groups according to the method of tracheal cuff pressure control. The primary outcome was the proportion of patients developing VAP within 28 days following the tracheal intubation, as determined by two assessors masked to group assignment, in the modified intention-to-treat population. This study is closed to new participants.

**Results:** 434 patients were recruited between 31/07/2015 and 15/02/2018, of which 216 were assigned to the intervention group and 218 to the control group. 73 patients (33.8%) developed at least one episode of VAP within 28 days following the tracheal intubation in the intervention group compared with 64 patients (29.4%) in the control group (adjusted sub-distribution HR 0.96 [95% CI 0.76-1.20];  $p=0.71$ ). No serious adverse events related to the use of the pneumatic device were noted.

**Interpretation:** Continuous regulation of cuff pressure of the tracheal tube using a pneumatic device was not superior to routine care in preventing VAP in severe trauma patients.

**Clinical trial Registration:** <https://clinicaltrials.gov> - NCT02534974.

**Keywords** pneumonia; ventilator-associated; infection; intensive care; tracheal cuff pressure

Severe trauma is the leading cause of death worldwide and the third highest cause of death in France after cardiovascular disease and cancer. Most deaths occur within the first 24 hours following the trauma and are directly related to hemorrhagic shock or intractable neurologic injuries. About one quarter of deaths occur later and are mainly due to healthcare-associated infections (HAI) <sup>1,2</sup>. Neurological disorders, need for mechanical ventilation and the early post-traumatic immune suppression are major factors contributing to the high incidence of HAI, particularly ventilator-associated pneumonia (VAP) <sup>3-5</sup>. VAP occurs in 35% to 60% of patients with severe trauma <sup>6,7</sup> and contributes to increased morbidity and mortality <sup>8</sup>. Moreover, VAPs are responsible for more than half of antibiotic prescriptions in the intensive care units (ICU) and therefore, contribute significantly to the spread of bacterial resistance <sup>9</sup>.

Aspiration of bacterial-contaminated oropharyngeal or gastric contents plays a major role in the development of VAP <sup>10</sup>. Maintaining the tracheal cuff pressure at an optimal level is therefore of critical importance. Cuff under-inflation increases the risk of bacterial aspiration and then VAP. Cuff over-inflation increases the risk of ischemia of the tracheal mucosa and, upon removal, tracheal edema and later tracheal stenosis <sup>11</sup>.

Regular control of tracheal cuff pressure is therefore recommended, but the optimal method has yet to be clearly established. Intermittent manual control using a portable manometer is the reference method, but it requires fine tuning and it is frequently accompanied by episodes of under-inflation and/or over-inflation <sup>12</sup>. Indeed, the diameter of the trachea around the cuff frequently varies in different situations, such as patient mobilization, swallowing movements, respiratory efforts and coughing. Use of automatic devices allows the cuff pressure to be continuously maintained in the target values <sup>13</sup> but few studies showing a decline in the incidence of complications are available.

The impact of continuous control of cuff pressure in preventing VAP has only been evaluated in three small prospective studies <sup>14-16</sup>. All were conducted in single centers <sup>14-16</sup>, one was observational <sup>16</sup> and another one used VAP as secondary outcome only <sup>14</sup>. Few surgical patients were included and none were trauma patients, though they represent the most at-risk population for VAP among critically ill patients <sup>17</sup>. One study showed no benefit of using a continuous control device of tracheal cuff pressure on VAP, while the two

others reported a lower VAP incidence with the use of such devices<sup>14-16</sup>. A meta-analysis of the three trials suggested a benefit of continuous control of tracheal cuff pressure in reducing the risk of VAP (HR 0.47 [95% CI 0.31-0.71]) without any significant impact on other outcomes, such as antibiotic usage, duration of mechanical ventilation or ICU length of stay<sup>18</sup>. Therefore, the real impact of these automatic devices remains uncertain<sup>19,20</sup>, and learned societies do not recommend their systematic implementation for the purpose of VAP prevention<sup>21,22</sup>.

Given these concerns, we designed a multicenter randomized trial to determine whether continuous regulation of tracheal cuff pressure using a pneumatic device is superior to intermittent control of tracheal cuff pressure using a portable manometer in reducing the incidence of VAP in severe trauma patients.

## **METHODS**

### **Study design**

The AGATE trial was an investigator-initiated, multicenter, randomized, controlled, open-label superiority trial. Patients were recruited from 13 ICUs in 13 French University hospitals. The study protocol has been previously published<sup>23</sup>.

### **Participants**

We enrolled adult patients ( $\geq 18$  years) suffering from severe trauma (Injury severity score<sup>24</sup>  $> 15$ ) and requiring invasive mechanical ventilation for 48 hours or longer. The expected time on mechanical ventilation was based on the physician's experience and initial assessment of injuries. Patients were included as soon as possible after ICU admission and no later than 24 hours after trauma and 15 hours after tracheal intubation. We excluded patients likely to die within 48 hours after admission, having their trachea intubated via the nasal route, being ventilated with a tracheotomy, or having any contraindication to the head-up position.

### **Randomization and blinding**

A statistician, who was neither involved in screening patients nor in assessing outcomes, provided a computer-generated numbered list. Randomization was carried out by the attending physician through a secure web-based randomization system with stratification according to center and neurologic compromise (Glasgow Coma Scale <8 or ≥8) at the time of inclusion, to account for differences in patient treatment between centers and the heightened VAP risk in patients with altered consciousness<sup>25</sup>. Patients were randomly assigned (1:1) in permuted blocks of variable size to one of the two treatment groups based on the method used to monitor the tracheal cuff pressure.

Blinding of the participants and medical staff was not feasible due to the nature of the intervention.

However, the microbiologists who tested the pulmonary and blood samples in each center, the outcome assessors (NM and OM) and the statistician (DF) were blinded to group assignment.

## **Procedures**

According to the randomized group assignment, the cuff pressure of the tracheal tube was monitored either manually every 8 hours (control group) using a portable manometer<sup>21</sup> or automatically and continuously (intervention group) through the use of a pneumatic device (Nosten<sup>®</sup>, Leved, France), aiming at keeping tracheal tube cuff pressure between 25 and 30 cm H<sub>2</sub>O.<sup>26</sup> The Nosten<sup>®</sup> device is a CE-labeled mechanical device consisting of a 200 mL sterile, single-use, cylindrical cuff connected to the tracheal tube cuff by a plastic tube (e-Figure 1). A weight mounted on an articulated arm exerts a constant pressure on this cuff, which is adjustable by moving another weight along the arm. Any pressure variation in the tracheal tube cuff due to a change in tracheal diameter is immediately compensated for by the disproportion between the volumes of both cuffs to immediately adjust the cuff volume of the tracheal tube, keeping the cuff pressure constant. ICUs teams were trained by the manufacturer before beginning the study, and training reminders were issued regularly throughout the study to ensure that the pneumatic device was used appropriately, according to the manufacturer's recommendations. We required all study centers to follow French recommendations<sup>21</sup>, similar to the CDC recommendations for VAP prevention<sup>27</sup>. These recommendations are described in detail elsewhere;<sup>23</sup> specifically patients added regular decontamination of the nasal and



oropharyngeal cavities through suitable oral care, following each ICU protocol. Prophylactic antibiotic treatments were administered by attending physicians and followed the French recommendations of 2017.<sup>28</sup> Most often, the duration was limited to the operating period, but could be extended to 48 hours for fractures operated on within the first 6 hours following trauma. Curative antibiotic therapy should be limited to infections for which the bacterial origin was documented, or probable, and in cases where other anti-infectious measures were insufficient, in accordance with the 2008 recommendations of the official French health authority on the proper use of antibiotics<sup>29</sup>. None of the patients received polyurethane-cuffed, tapered-cuff shape tracheal tubes or with subglottic secretion drainage. No modification was allowed during the study duration.

The patients were monitored from randomization through to their discharge from the ICU without exceeding 60 days following inclusion. Any patient who left the ICU was considered having exited the study. Any readmission into the ICU (even within 60 days following the trauma) was not taken into account. Attempted detection of VAP signs were performed on a daily basis while the patient was being mechanically ventilated. A thoracic X-ray aimed at detecting VAP was required within a few hours whenever at least two of the following clinical signs of VAP were observed in the same clinical examination: fever  $\geq 38.0^{\circ}\text{C}$  or hypothermia  $\leq 36.0^{\circ}\text{C}$ , purulent endotracheal secretions or either hyperleucocytosis ( $\geq 12\,000/\text{mL}$ ) or leucopenia ( $\leq 4000/\text{mL}$ ). Whenever the patient met the clinical and radiological criteria on the same day, the modified clinical pulmonary infection score (CPIS) was calculated<sup>30</sup>, and bacterial analysis of the respiratory tract was carried out. The type of sampling (bronchoalveolar lavage, blind protected telescoping catheter or tracheal aspirates) was left to the discretion of the attending physician. We routinely obtained sets of aerobic and anaerobic blood cultures in patients with fever (body temperature  $\geq 38.5^{\circ}\text{C}$ ), hypothermia ( $\leq 36.5^{\circ}\text{C}$ ), or other symptoms, such as chills (a sensation of cold, with convulsive shaking of the body) or sudden shock (systolic blood pressure  $< 90$  mm Hg or decrease of 40 mm Hg or more in systolic pressure compared with baseline in patients with arterial hypertension), and when a VAP was suspected.

## Outcomes

The primary outcome was the proportion of patients who developed VAP at day 28 in the ICU. The diagnosis of VAP was based on the American Thoracic Society (ATS) definition<sup>31</sup> and centralized by two outcome assessors (NM and OM) blinded to group assignment because current definitions may result in misdiagnosis<sup>32</sup>. In case of disagreements, conflicts were discussed between the two experts to reach a consensus.

Additional pre-specified outcomes were the (1) proportion of patients who developed VAP in the ICU, (2) proportion of patients who developed bacteremic VAP in the ICU, (3) proportion of patients who developed early ( $\leq 7$  days) or late ( $> 7$  days) VAP in the ICU, (4) time until the first diagnosis of VAP, (5) proportion of patients who developed ventilator-associated events (VAE) according to the Centers for Disease Control and Prevention definition<sup>27</sup>, (6) number of ventilator-free days, (7) number of antibiotic-free days, (8) length of stay in the ICU, (9) proportion of patients who died during their ICU stay, (10) proportion of patients who required corticosteroids or bronchodilators within 48 hours of tracheal extubation (Definitions are available in the online data supplement).

## Statistical analysis

The sample size of 440 ( $n = 220$  in each group) was computed on an estimated 20% VAP incidence in the control group and a 50% reduction in the intervention group, with a two-sided  $\alpha$  risk of 5% and power of 80%, and a maximum patient loss of 10%. The VAP incidence in the control group was estimated on unpublished analysis of the AtlanRea database, a French research network dedicated to trauma patients to which several participating study centers belong. The 50% reduction in VAP in the experimental group was based on the finding of previous studies<sup>14,16</sup>.

Data were analyzed on a modified intention-to-treat principle (all randomized patients except those who withdrew consent). No interim analysis was planned. Continuous variables are expressed as means  $\pm$  standard deviation (SD) or median and IQR and compared using student t-test or Mann-Whitney U-test for normally and non-normally distributed continuous variables, respectively. Categorical variables are given as

number (percentage) and compared using Chi-2 or Fisher exact tests. Treatment effects on time until VAP occurrence were assessed using competing risks regression (Fine and Gray model), with mortality and tracheal extubation before VAP occurrence being considered as competing risks, and expressed as adjusted sub-distribution hazard ratio (aSHR) with 95% confidence intervals (95% CI). The proportionality of VAP occurrence hazard risk was tested using Schoenfeld residuals. Treatment effects on other outcomes were assessed using logistic regression models and expressed as adjusted odds-ratio (aOR) with 95% CI. Mortality between study groups was compared using a Cox regression model and expressed as adjusted hazard ratio (aHR) with 95% CI. The proportionality of mortality hazard risk was tested using Schoenfeld residuals. Treatment effects were adjusted for stratification factors (center and Glasgow Coma Scale <8 or ≥8) and unbalanced variables.

All tests were two-tailed with no adjustment for multiple testing. Analyses were done using SAS 9.3 software (SAS Institute Inc, Cary, NC, USA) and R statistical package version 3.6.2 or later (The R Foundation for Statistical Computing, <https://www.R-project.org/>).

### **Ethical approval**

The study protocol was approved by the ethics committee of Poitiers University hospital (France) and was carried out according to the principles of the Declaration of Helsinki and the Clinical Trials Directive 2001/20/EC of the European Parliament.

### **Study registration**

The study is registered with ClinicalTrials.gov, NCT02534974.

## **RESULTS**

Between July 31, 2015 and February 15, 2018, we screened 711 potentially eligible patients and randomly assigned 437 to one of the study groups (figure 1). Two patients assigned to the experimental group and one patient assigned to the control group withdrew consent and were subsequently excluded from analyses.

Therefore, 434 patients were included in the modified intention-to-treat analysis (216 in the experimental group and 218 in the control group). Baseline characteristics (Table 1 and e-Table 1), number of patients under mechanical ventilation for 48 hours or more (191 [88%] versus 182 [83%] in the experimental and control groups, respectively) and therapeutics received during ICU stay (e-Table 2) were overall comparable between study groups. Antibiotic prophylaxis was more frequent in the control group than the experimental group (Table 1) and was included in the multivariate model (e-Table3).

Investigators declared 248 events (127 [51.2%] in the experimental group and 121 [48.8%] in the control group) as possible VAP. After blinded adjudication, only 159 [64.1%] of them (82/216 [38.0%] in the experimental group and 77/218 [35.3%] in the control group) met all ATS criteria for VAP. The CPIS score at the day of VAP diagnosis (7 [6-8] in the experimental group compared with 7 [7-8] in the control group,  $p = 0.63$ ) was comparable between the study groups. Microbiological methods used to diagnose VAPs were similar between study groups (e-Table 4). Twenty-two patients developed at least 2 VAPs while on mechanical ventilation. Overall, 73 (33.8%) of 216 patients in the experimental group and 64 (29.4%) of 218 patients in the control group developed at least one episode of VAP within 28 days of mechanical ventilation (aSHR 0.96 [95% CI 0.76 – 1.20]) (Table 2, figure 2), with no difference between centers (e-Table 5). The proportionality of hazard was respected for VAP occurrence and for mortality (e-figure 2 and e-figure 3). The proportion of patients developing VAP before or after the day 8 of mechanical ventilation and the proportion of bacteremic VAP were comparable between the two study groups (table 2), as were the pathogens isolated in microbiological cultures (Table 3). Similarly, the number of patients presenting ventilator-associated events, ventilator-free days, antibiotic-free days, length of stay in the ICU or hospital, and in-ICU mortality were comparable between the study groups (Table 2).

No serious issues were reported with the use of the pneumatic device. Median time of device interruption was 3 hours [1-8] overall, corresponding to 1.4% [0.5-3.7] of mechanical ventilation time. These interruptions were mainly for patient transfer to the radiology department or the operating room. Use of steroids and/or  $\beta$ -2 agonists after scheduled tracheal extubation was comparable between the two study groups (Table 2 and e-Table 2) (22/174 [13%] patients in the experimental group compared with 18/168

[11%] in the control group,  $p = 0.57$ ). The numbers of patients having a tracheostomy were comparable between groups (38/216 [18%] in the experimental group compared with 33/218 [15%] in the control group,  $p = 0.49$ ).

## DISCUSSION

We report the first large-scale study comparing the efficacy of two modalities of tracheal cuff pressure control in reducing ventilator-associated complications in severe trauma patients. Continuous control of tracheal cuff pressure using a pneumatic device failed to reduce the incidence of VAP compared with routine care.

We included severe trauma patients requiring prolonged (>48 hours) mechanical ventilation because they represent the most vulnerable ICU population for developing VAP. These healthcare-associated infections typically occur at the end of the first week, when the decline in immune defenses in response to the post-traumatic anti-inflammatory reaction is maximal<sup>33,34</sup>. In the intervention group, we chose a pneumatic rather than an electronic device because the former has several advantages, including a shorter response time with fewer periods of insufficient or excessive tracheal cuff pressure and therefore a reduced risk of microbial aspiration and tracheal injury, no need for electronic supply, lower acquisition costs and easier handling. The number of patients who developed VAP in the control group was greater than the number used to determine the sample size for the study. This could be explained by the exclusion of patients with a high probability of death or of having their trachea extubated within 48 hours of enrolment in the study. This resulted in an increased probability of showing a benefit of the intervention.

Devices that automatically control tracheal cuff pressure are expected to keep pressure in the target range longer, but their impact on preventing VAP was mixed before starting the present study. In a single French medical ICU<sup>14</sup>, 122 patients were randomly assigned to receive continuous control of cuff pressure using a pneumatic device similar to the one used in the present study ( $n=61$ ) or routine care ( $n=61$ ). The percentage of patients with abundant micro-aspiration defined as the primary outcome (18% vs 46%; OR [95% CI], 0.25 [0.11-0.59]), bacterial concentration in tracheal aspirates (mean  $\pm$  SD  $1.6 \pm 2.4$  vs  $3.1 \pm 3.7$  log<sub>10</sub> cfu/ml;  $p =$

0.01) and VAP rate (9.8 vs 26.2%; 0.30 [0.11-0.84]) were significantly lower in the intervention group compared with the control group. By contrast, in a second randomized study of 142 patients from two medical ICUs of a single hospital,<sup>15</sup> VAP rate with clinical criteria (22% vs 29%) and microbiological confirmation (15% vs 15%), distribution of early and late onset and causative microorganisms were comparable for the automatic and control groups, respectively. In a last observational single-center study involving 284 patients, the use of an electronic device was associated with fewer occurrences of VAP than an intermittent control protocol (11% versus 22%;  $p = 0.02$ ).<sup>16</sup> Unfortunately, all these studies suffered from several limitations. They are single-center studies, thus limiting the external validity of their findings. The diagnosis of VAP was not assessed blindly to the intervention, leading to potential interpretation bias. Among the 2 studies showing a decrease in VAP incidence in the intervention group, one was not randomized and the other did not include VAP as the primary outcome.

To the best of our knowledge, the AGATE trial is the first multicenter randomized study adequately powered to evaluate the potential benefit of an automatic device for continuous cuff pressure monitoring in reducing VAP. Despite inclusion of more than 400 critical care patients, we were unable to demonstrate any reduction in VAP with the use of a pneumatic automatic device. This resulted in the absence of positive impact in the number of days without antibiotics or mechanical ventilation, length of stay and mortality. Several factors may explain our findings. First, we cannot exclude the possibility that significant aspiration of contaminated oropharyngeal or gastric contents may have occurred prior to insertion of the tracheal tube. Indeed, severe trauma is generally associated with immediate neurological disorders, a major risk factor for aspiration,<sup>25,35</sup> while delay between trauma and insertion of the tracheal tube was higher than 1 hour in more than 50% of included patients, and possible up to 24 hours as per study protocol. Second, similarly, we cannot rule out significant aspiration of contaminated oropharyngeal or gastric contents prior to pneumatic device placement, as the assessment of trauma and the frequent need for surgery may have delayed admission to the ICU and therefore inclusion of patients in the study, up to a maximum of 15 hours after tracheal intubation as per study protocol. Third, despite randomization, the number of patients receiving antibiotic prophylaxis was higher in the control group than in the intervention group. Since antibiotic administration is

a well-known protective factor for early-onset VAP, this variable was included in our multivariate analyses to account for this imbalance between study groups. Finally, patients were provided with recommended VAP prevention measures,<sup>21</sup> including the semi-recumbent position, a protective lung ventilation strategy, early enteral nutrition, extubation as early as possible, and adherence to hygiene guidelines. Tracheal tubes with subglottic secretion drainage were not used in any of the study participants because this device was not recommended in France at the beginning of the study and most patients had their trachea intubated before being admitted to the ICU. Use of a device to continuously control cuff pressure may become useless in patients when a care bundle approach including regular control of cuff pressure is adequately applied.<sup>36</sup> Periods of over-inflation of the tracheal cuff may cause edema of the tracheal mucosa<sup>37</sup> reducing the diameter of the airway and possibly resulting in respiratory failure after scheduled tracheal extubation. In our study, use of the pneumatic device was not associated with a reduction in steroid or  $\beta$ -2 agonist administration after scheduled tracheal intubation. These unexpected results could be explained by periods of over-inflation in the control group not being frequent or long enough to cause damage to the tracheal mucosa.

Our study suffers from several limitations. First, we only included patients with severe trauma and requiring prolonged mechanical ventilation. As previously discussed, it is possible that, in these patients, aspiration of contaminated oropharyngeal or gastric contents occurs very early after the trauma, before tracheal intubation and/or placement of the pneumatic device, accounting the absence of any impact on early-onset VAP incidence. A study will have to be conducted in non-trauma patients to confirm our findings in other severely ill populations. Second, because of the device evaluated, the investigators could not be blinded to the treatment received, resulting in an open clinical trial suffering from its inherent methodological bias. Nevertheless, all centers were already implementing recommended measures to prevent VAP before starting the study, and the diagnosis of VAP was done by two assessors blinded to group assignment. Third, compliance with French recommendations on VAP prevention (such as head-up elevation) was not systematically sought. However adherence to these guidelines was observed in 42-47% of the 1856 patients enrolled in the Pneumocare study, a randomized cluster trial conducted in 35 French intensive care units, of

which many participated in this study.<sup>36</sup> Four, we did not record cuff pressure values in the control group at each evaluation. Therefore, it is impossible to determine whether or not pressure adjustments were frequent. Nevertheless, episodes of under- or over-inflation of the tracheal tube cuff frequently occur between two assessments, resulting in an under-evaluation of these events in the absence of continuous monitoring.<sup>12</sup> Five, cuff pressure values were not recorded in the experimental group either. Studies that recorded cuff pressure continuously over 24 to 48 hours with the use of a pneumatic device observed episodes of under- or over-inflation in less than 5% of the recording time.<sup>14,26</sup> Although unlikely, we cannot totally rule out the possibility that episodes of under-inflation were more frequent in our study. In order to evaluate the device as real life to facilitate the generalizability of our findings, caregivers were asked to follow the manufacturer's recommendations. These recommendations require checking the device at each nurses round and, in case of anomaly detection, to measure the cuff pressure and, as usual, to check the cuff pressure every 8 hours or sooner, if an air leak is detected on the ventilator. Finally, the impact of the intervention on late-onset VAP related to multidrug resistant micro-organisms was not sought. However, since late-onset VAP were uncommon, the study was underpowered to address this issue.

## **INTERPRETATION**

Continuous regulation of tracheal cuff pressure using a pneumatic device was not superior to intermittent control of tracheal cuff pressure using a manual manometer in reducing the incidence of VAP in severe trauma patients. Further studies taking into account the limitations of the present study are required to definitely conclude on the absence of benefit of the intervention.



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## **GUARANTOR STATEMENT**

Prof. Olivier Mimoz is the guarantor of the content of the manuscript, including data and analysis.

## **AUTHORS' CONTRIBUTIONS**

NM and OM conceived the study. JK and DF did the statistical analyses. OM, NM and DF drafted the first version of the manuscript. All the investigators mentioned as co-authors helped collect the data, amended the first version of the manuscript, and read and approved the final manuscript.

## **FINANCIAL DISCLOSURES**

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## **ROLE OF SPONSORS**

The University Hospital of Poitiers, France, was the sponsor of the study, and the French Ministry of Social Affairs and Health was the founder. Neither the sponsor nor the funder had a role in the trial initiation, study design, choice of devices, data collection, data analysis, data interpretation, writing of the report, or the decision to submit. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

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## **TAKE-HOME POINT**

### **Study question**

Is continuous regulation of tracheal cuff pressure superior to manual assessment every 8 hours using a portable manometer (routine care) in preventing ventilator-associated pneumonia?

### **Results**

Seventy-three patients (33.8%) in the experimental group and 64 patients (29.4%) in the control group developed at least one episode of VAP within 28 days of mechanical ventilation (aSHR 0.96 [95% CI 0.76 – 1.20]).

### **Interpretation**

In this large multicenter, randomized, controlled study with severe trauma patients, continuous monitoring of tracheal cuff pressure using a pneumatic device did not prevent VAP compared with routine care. Further studies taking into account the limitations of the present study are required to definitely conclude on the absence of benefit of the intervention.

## **FIGURES LEGEND**

Figure 1. Trial profile.

Figure 2. Cumulative incidence (with 95% CI) and adjusted subdistribution Hazard Ratio (aSHR) for ventilator-associated pneumonia by study group allocation.

**Table 1: Baseline characteristics of the modified intention-to-treat population**

	<b>Intervention group (n=216)</b>	<b>Control group (n=218)</b>
Age, years	45 ± 20	44 ± 20
Male sex	171 (79%)	166 (76%)
BMI, kg/m <sup>2</sup>	25 ± 5	25 ± 4
Medical history		
Diabetes mellitus	6 (3%)	7 (3%)
Obesity (BMI >30 kg/m <sup>2</sup> )	22 (11%)	21 (10%)
Malnutrition (BMI <20 kg/m <sup>2</sup> )	4 (2%)	7 (3%)
Alcoholism	31 (16%)	34 (18%)
Smoking	42 (24%)	46 (25%)
Cirrhosis	2 (1%)	1 (0%)
Gastro-esophageal reflux	2 (1%)	3 (1%)
Glasgow coma scale on the scene	7 (4-13)	7 (4-12)
ISS score	29 (21-34)	27 (22-35)
Trauma to tracheal intubation time, minutes	62 (36-167)	66 (35-147)
Trauma to randomization time, hours	10 (6-14)	10 (6-13)
Etomidate use for tracheal intubation	132 (61%)	124 (57%)
Thiopental use for tracheal intubation	6 (3%)	2 (1%)
Gastric tube	123 (57%)	116 (53%)
Orotracheal route	104 (85%)	93 (80%)
Nasotracheal route	19 (15%)	23 (20%)
Aspiration before tracheal intubation	37 (17%)	35 (16%)
Antibiotic prophylaxis	120 (56%)	140 (64%)

Data are n (%), median (IQR) or mean ± SD. BMI=body-mass index. ISS=injury severity score.

**Table 2: Primary and secondary outcomes**

	<b>Intervention group (n=216)</b>	<b>Control group (n=218)</b>	<b>Treatment effect [95% CI]</b>	<b>P value</b>
<b>VAP</b>				
At day 28	73 (34%)	64 (29%)	0.96 [0.76-1.20]	0.71
At day 60	73 (34%)	65 (30%)	0.96 [0.76-1.20]	0.73
Early ( $\leq 7$ days)	52 (24%)	55 (25%)	0.97 [0.66-1.45]	0.90
Late ( $> 7$ days) at day 28	27 (12%)	18 (8%)	1.05 [0.63-1.74]	0.85
With bacteremia, at day 28	2 (1%)	4 (2%)		0.69
Time until first diagnosis, days	5 (4-8)	5 (4-6)		0.25
<b>Ventilator associated events</b>				
Ventilator-associated condition	66 (31%)	56 (26%)	1.26 [0.83-1.92]	0.28
Infection-related VAC	63 (29%)	54 (25%)	1.24 [0.81-1.90]	0.33
Possible VAP	30 (14%)	31 (14%)	0.96 [0.55-1.67]	0.89
Steroids or $\beta$ -2 agonist after scheduled tracheal extubation	22/174 (13%)	18/168 (11%)	1.26 [0.65-2.46]	0.57
<b>Duration of Mechanical Ventilation, hours</b>				
Ventilator-free days at day 28	14 (0-23)	12 (0-23)		0.54
Ventilator-free days at day 60	46 (27-55)	44 (0-55)		0.44
Antibiotics-free days at day 28	20 (12-28)	20 (5-28)		0.66
Antibiotics-free days at day 60	52 (44-60)	52 (40-60)		0.60
ICU length of stay, days	14 (8-26)	14 (6-22)		0.38
Hospital length of stay, days	25 (13-46)	24 (12-43)		0.45
ICU mortality at day 28	42 (19%)	52 (24%)	0.78 [0.52-1.18]	0.24
ICU Mortality at day 60	44 (21%)	57 (26%)	0.72 [0.46-1.13]	0.16

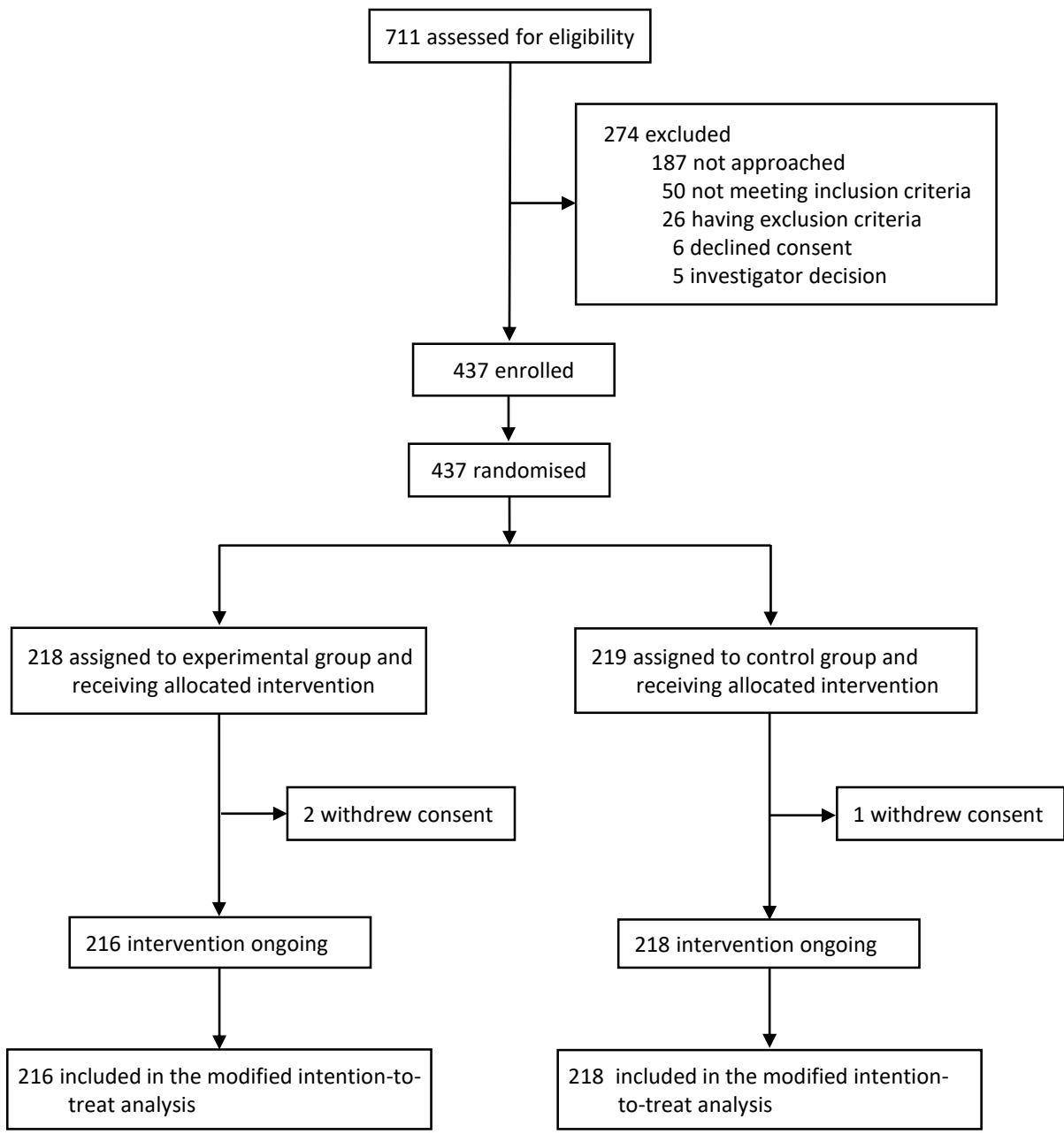
Data are n (%), median (IQR), or n/N (%). VAP=ventilator-associated pneumonia. VAC=ventilator-associated complication. ICU=intensive care unit

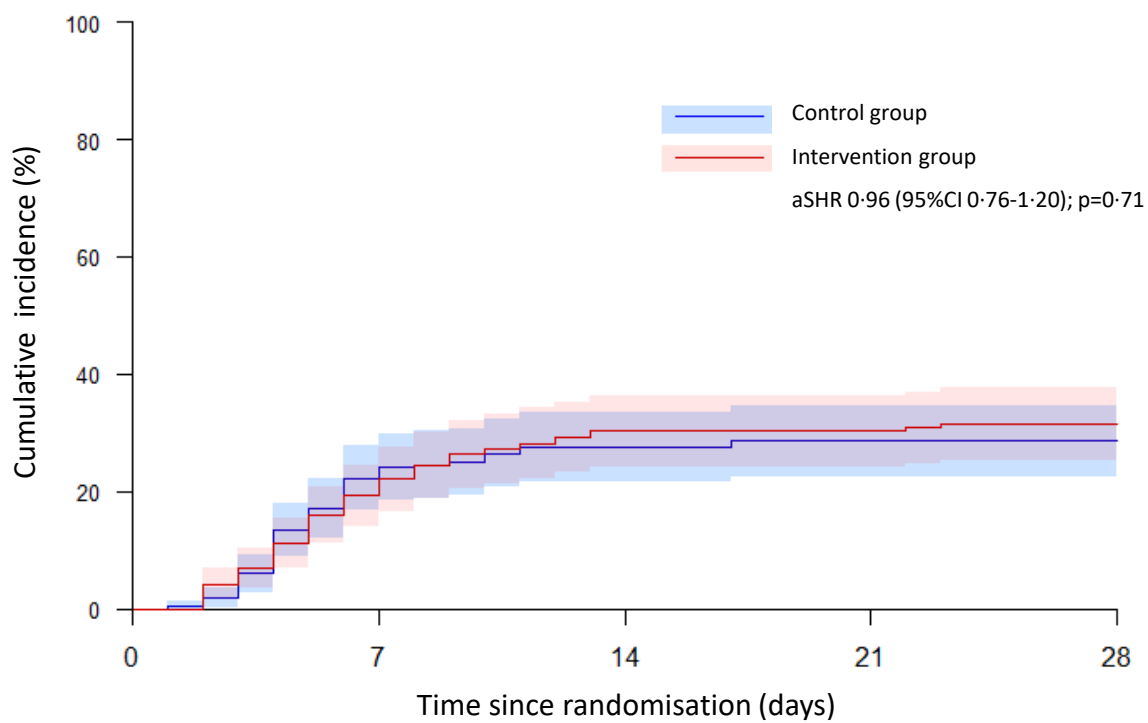


**Table 3. Microbiological documentation of the 159 ventilator-associated pneumonia occurrences.**

	Intervention group		Control group	
	(n=82 VAP)		(n=77 VAP)	
	Early VAP (n=52)	Late VAP (n=30)	Early VAP (n=55)	Late VAP (n=22)
<i>Staphylococcus aureus</i>	21 (30%)	9 (22%)	27 (32%)	6 (21%)
<i>Streptococcus pneumoniae</i>	6 (9%)	2 (5%)	3 (4%)	1 (4%)
<i>Haemophilus influenzae</i>	9 (13%)	3 (7%)	14 (17%)	1 (4%)
<i>Escherichia coli</i>	13 (19%)	6 (15%)	6 (7%)	3 (11%)
<i>Proteus sp.</i>	3 (4%)	1 (2%)	5 (6%)	1 (4%)
<i>Klebsiella pneumoniae</i>	1 (0%)	4 (10%)	9 (11%)	2 (7%)
<i>Enterobacter cloacae</i>	7 (10%)	6 (15%)	7 (8%)	3 (11%)
<i>Serratia marcescens</i>	2 (3%)	1 (2%)	3 (4%)	2 (7%)
<i>Pseudomonas aeruginosa</i>	4 (6%)	5 (12%)	6 (7%)	5 (18%)
<i>Acinetobacter baumannii</i>	3 (4%)	3 (7%)	1 (1%)	1 (4%)
<i>Stenotrophomonas sp.</i>	0 (0%)	0 (0%)	2 (2%)	1 (4%)
<b>Total</b>	69	40	83	26

Data are n (%). VAP=ventilator-associated pneumonia. More than one microorganism was recorded in some cases.





**Number at risk**

	0	7	14	21	28
Control group	218	71	31	11	4
Intervention group	216	86	22	10	2