Influence of changing endotracheal tube cuff management on antibiotic use for ventilator-associated pneumonia in a tertiary intensive care unit

Jai N Darvall, Irani Thevarajan, Simon Iles, Thomas Rechnitzer, Tim Spelman and Nerina Harley

Ventilator-associated pneumonia (VAP) develops in up to one-quarter of all critically ill patients who are receiving mechanical ventilation (MV),[1] but when research is restricted to patients ventilated for > 48 hours, VAP incidence increases to as high as 28%–47%.[2-5] VAP is associated with outcomes including longer duration of MV, longer hospital stay and a higher mortality rate.[1,6] A 2005 meta-analysis of 51 randomised trials involving 4800 patients found that VAP also significantly increased hospital costs, with an increase of US$10 000 attributable to each VAP episode, and a doubling of mortality.[7]

Given the clinical significance of VAP, it is imperative to accurately establish its diagnosis. This has proved challenging at the bedside, however, with complex, subjective case definitions associated with low specificity, considerable interobserver variability, lack of an accepted gold standard, and poor agreement among competing diagnostic criteria.[1] A study of 255 critically ill patients receiving MV found that VAP rates, measured using four diagnostic strategies, including the Clinical Pulmonary Infection Score (CPIS) and the Johanson clinical criteria, varied between 4% and 48% in the same cohort.[8] The Centers for Disease Control and Prevention

Abbreviations

ANZICS APD	Australian and New Zealand Intensive Care Society Adult Patient Database
APACHE	Acute Physiology and Chronic Health Evaluation
CDC	Centers for Disease Control and Prevention
ETT	endotracheal tube
ICU	intensive care unit
IQR	interquartile range
IRR	incident rate ratio
IVAC	infection-related ventilator-associated complication
LOS	length of stay
MV	mechanical ventilation
PVAP	possible ventilator-associated condition
RMH	Royal Melbourne Hospital
SAPS	Simple Acute Physiology Score
SD	standard deviation
VAC	ventilator-associated condition
VAP	ventilator-associated pneumonia

ABSTRACT

Background: Routine deflation of the endotracheal tube (ETT) cuff of critically ill patients receiving MV is common in Australia and New Zealand. Literature about ventilator-associated pneumonia (VAP) and antibiotic use rates with different ETT cuff maintenance practices is lacking.

Objective: To determine the impact of a change in ETT cuff maintenance from a minimal leak technique to pressure manometry on the administration of antibiotics for VAP.

Design, setting and participants: A prospective, pre–post observational study conducted in a metropolitan tertiary referral intensive care unit. We analysed data from 178 patients receiving MV for > 48 hours during 13 weeks of minimal leak test ETT cuff technique (pre-intervention, n = 92) or 13 weeks of cuff pressure manometry (post-intervention, n = 86), separated by 3 weeks' "wash-out".

Main outcome measures: Primary outcome was the number of patients receiving antibiotics for the indication of VAP. Secondary outcomes were incidence of ventilator-associated surveillance events, lengths of stay (LOSs) and mortality.

Results: Antibiotics were administered for VAP in 24 patients (26.1%) in the pre-intervention period compared with 11 post-intervention patients (12.8%). The univariate antibiotic administraion rate per 100 ventilation days was 15.3% (95% CI, 12.6%–18.4%) v 6.8% (95% CI, 4.9%–9.3%), and the incident rate ratio (IRR) was 0.45 (95% CI, 0.31–0.64); $P < 0.001$). After adjustment for ventilation duration, IRR was 0.55 (95% CI, 0.24–1.27); $P = 0.160$. The ventilator-associated complication incidence rate was lower in the post-intervention group (11.4% v 16.3%; IRR, 0.70 [95% CI, 0.51–0.95]; $P = 0.018$). After adjustment for duration of MV, IRR was 0.66 (95% CI, 0.25–1.70); $P = 0.387$. Antibiotic administration for VAP was associated with increased ICU and hospital LOSs, but not with mortality.

Conclusions: ETT cuff pressure manometry is associated with a reduced rate of antibiotic administration for a diagnosis of VAP compared with a minimal leak test technique.

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(CDC) has attempted to address these shortcomings with a new surveillance approach which, although benefiting from more objective criteria, is not designed for diagnosis at the bedside.[9] Several studies report sensitivities of 20%–30% compared with existing methods, with a likely consequence being considerable underreporting of VAP.[10-13] Given these challenges, alternative clinically significant markers such as antibiotic use reduction have more recently been used as endpoints in literature examining VAP in critically ill patients.[14]

A major aetiological factor in the development of VAP is the transit of pooled pharyngeal fluid, potentially containing pathogenic microorganisms, past the endotracheal tube (ETT) cuff.[15,16] Despite the integral role of the ETT cuff, there is evidence of marked variation of cuff maintenance practice in ICUs, particularly in Australia and New Zealand. A 2008 survey of 92 ICUs in Australia and New Zealand showed four different techniques employed for cuff maintenance: cuff pressure manometry, cuff palpation, minimal occlusive volume testing and minimal leak testing. Minimal occlusive volume testing and minimal leak testing require cuff deflation.[17] Fifty ICUs (54%) used a technique for ongoing cuff maintenance involving regular deflation of the ETT cuff. A 2012 survey of South African intensive care units showed that only 52% of 100 respondents used cuff pressure manometry, and 46% used palpation or minimal occlusive volume testing requiring cuff deflation.[18] Despite this practice variation in ETT cuff management, there is a paucity of evidence about the effect of maintenance practice variation on the incidence of VAP or related factors.

Our aim was to assess the impact on antibiotic use of a change of ETT cuff maintenance practice in a metropolitan tertiary ICU. The change was from minimal leak testing, involving deflation of the cuff multiple times per day, to cuff pressure manometry. The primary endpoint was the antibiotic prescription rate for VAP. Secondary endpoints were the rates of ventilator-associated condition (VAC), infection-related ventilator-associated complication (IVAC), and possible VAP (PVAP), as recently defined by the CDC.

Methods

We conducted a prospective pre–post observational study between 23 March and 11 October 2015, within the Royal Melbourne Hospital (RMH) ICU, a 24-bed metropolitan ICU that admits over 2200 patients annually. Approval was obtained from the RMH Human Research Ethics Committee as a quality assurance project (QA2015099). All patients aged over 18 years who were receiving MV for > 48 hours with the RMH standard cuffed endotracheal tube (Mallinckrodt Pharmaceuticals) were included in the study. We excluded patients receiving MV via a tracheostomy.

Our research group had previously shown that the minimal leak test technique results in sub-optimal ETT cuff pressures,[18,19] which resulted in a change (independent of this study design) in June 2015 to cuff pressure manometry for patients receiving MV (cuff pressure maintained at 22–30 cmH_2O, checked once per nursing shift, ie, two to three times per day).

A pre-intervention 13-week period (March–June 2015) using the minimal leak test technique (air is withdrawn from the ETT cuff until a leak heard, before re-inflation of an amount necessary to stop the cuff leak, performed once per nursing shift), was compared with a post-intervention 13-week period (July–October 2015) during which cuff manometry was used, separated by a 3-week "washout" period. Our ICU employs several interventions designed to reduce VAP incidence, including elevation of the head of the bed to 30°, changing ventilator circuits every 7 days, and oral decontamination with chlorhexidine performed 4-hourly. These interventions remained the same throughout the study period.

The primary outcome was the number of patients receiving antibiotics for an indication of VAP. Given the complexity and subjectivity in defining VAP, a pragmatic endpoint was chosen. All antibiotics administered in the RMH ICU require an indication to be entered on the medication chart by the prescribing intensive care specialist. The antibiotic choice, dose and indication are checked and altered if necessary three times per week by infectious diseases physicians. These practices were maintained for our study and infectious diseases physicians were not informed about the change in ETT cuff management.

We identified antibiotic use as a measurable and reproducible surrogate marker of VAP, as well as a clinically relevant endpoint in its own right, that could be objectively assessed in the pre-intervention and post-intervention periods. We also chose this approach because we considered it likely that all patients diagnosed with VAP would be commenced on antibiotics, thus we would capture all affected patients.

Ventilator-associated event incidence

In addition to antibiotic administration for VAP, secondary outcomes were the incidence of VAC, IVAC and PVAP, as recently defined by the CDC.[9] These CDC definitions are not designed for the clinical diagnosis of VAP; they are for epidemiological and surveillance data collection. According to the CDC definitions, criteria for VAC are met if, after a period of stable oxygenation for at least 2 days, an increase in $Fio_2 \geq 0.2$ or PEEP ≥ 3 cmH_2O occurs for at least 2 further days. IVAC is diagnosed if, within 2 days before or after the onset of VAC, there is a new occurrence of hypothermia (< 36°C) or hyperthermia (> 38°C), or a leukocyte count of

< 4000/mm^3 or > 12 000/mm^3, in addition to at least one new antibiotic which is continued for at least 4 days. If this is combined with purulent respiratory secretions, or positive sputum, pleural fluid or bronchoalveolar lavage culture, the criteria for PVAP are met.

Additional secondary outcomes were hospital and ICU length of stay (LOS) and mortality.

Data collection

We recorded baseline patient data including age, sex and comorbidities. The comorbidities were classified as defined in the Australian and New Zealand Intensive Care Society Adult Patient Database (ANZICS APD), and included immunosuppression, haematological malignancy, cirrhosis or chronic liver disease, respiratory disease, cardiovascular disease, chronic renal failure, metastatic cancer and insulin-requiring diabetes mellitus. We also collected data relating to the patient's ICU admission diagnosis, whether they were electively or emergently admitted, and their Simple Acute Physiology Score (SAPS) II and Acute Physiology and Chronic Health Evaluation (APACHE) III score. Outcome data included daily antibiotic prescription, duration of MV, ICU and hospital LOS, and ICU and hospital mortality.

Sample size

We performed a power calculation based on previous literature informing VAP rates, assuming that 35% of control patients receiving MV for > 48 hours would be commenced on antibiotics for VAP, with an absolute reduction of antibiotic prescription of 50% to an antibiotic prescription rate for VAP of 17.5% in the intervention group. This was based on comparable literature relating to ETTs with integrated subglottic drainage, a meta-analysis of 13 randomised trials (including 2442 patients) showing a pooled risk ratio for VAP of 0.55 (95% CI, 0.46–0.66; $P < 0.001$).[20] At a power of 0.8 and alpha of 0.05, we estimated that we would require 220 patients (110 in each group). The observation period planned was considered a feasible timeframe, with 15%–20% of over 2200 patients admitted annually to the RMH ICU receiving MV for > 48 hours (220 patients over 6 months).

Statistical analysis

We tested continuous data for normality using the modified Jarque–Bera test. We summarised normally distributed data using means and standard deviations (SDs) and compared them using unpaired two-tailed *t* tests. Skewed data were summarised using medians and interquartile ranges (IQRs) and compared using Wilcoxon rank-sum tests. Categorical data were summarised using frequencies and percentages and compared them using the χ^2 test or Fisher exact test, as appropriate.

We analysed the impact of potential confounding covariates on the rate of antibiotic administration (such as ventilation duration) by multivariate negative binomial regression. The incident rate was calculated for antibiotic administration, VAC, IVAC and PVAP, and incident rate ratios compared between groups, using negative binomial regression. For all analyses, $P < 0.05$ was considered significant. All analyses were performed using Stata, version 14.1 (StataCorp).

Results

Patient characteristics

In the pre-intervention period (March–June 2015), 524 patients were admitted to the ICU. Of these, 92 received MV for > 48 hours for a total of 720 ventilation days, and we collected their data for our analysis. Of 504 patients admitted to the ICU in the post-intervention period (July–Oct 2015), 86 received MV for > 48 hours for a total of 614 ventilation days, and were included in our analyses (Figure 1). Patient characteristics are shown in Table 1. Age, sex, ANZICS APD-defined comorbidities, and SAPS II and APACHE III illness severity scores at admission were similar between groups. Durations of MV and ICU and hospital stays were also similar between groups (Table 2). Overall, between groups, there were no significant differences in the ICU or hospital LOSs, duration of MV, or ICU or hospital mortality (Table 2). ICU mortality was 15.1% in the intervention group and 20.7% in the control group ($P = 0.336$), and hospital mortality was 31.4% and 34.8%, respectively ($P = 0.631$).

Primary endpoint

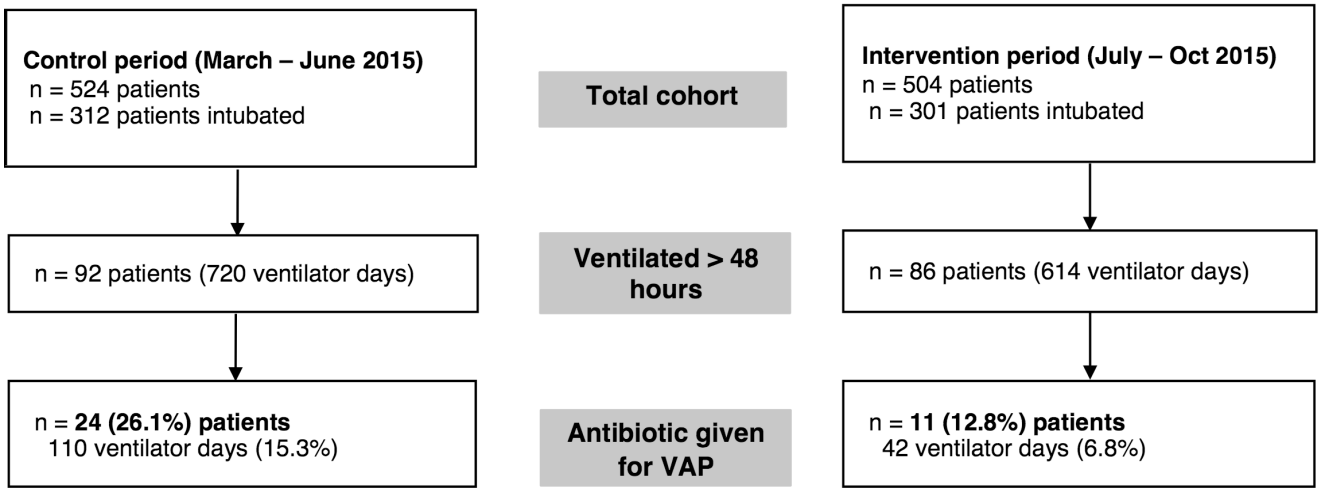
In the pre-intervention group, antibiotics were prescribed for VAP in 24 patients (26.1%) over 110 ventilation days. This was a VAP antibiotic rate of 15.28 prescription days per 100 ventilation days (95% CI, 12.56–18.41). In the post-intervention group, antibiotics were prescribed for VAP in 11 patients (12.8%) over 42 ventilation days, a VAP antibiotic rate of 6.84 prescription days per 100 ventilation days (95% CI, 4.93–9.25).

On univariate analysis, the VAP antibiotic incident rate ratio (IRR) for the post-intervention group v pre-intervention group was 0.45 (95% CI, 0.31–0.64), $P < 0.001$. When adjusted for ventilation duration, the IRR was 0.55 (95% CI, 0.24–1.27), $P = 0.160$.

Secondary endpoints

VAP antibiotic administration was associated with increased LOS, but not hospital mortality (Table 2). Seven of the 35 patients treated with antibiotics for VAP (20%) died compared with 26 of the 143 patients who were deemed not to have VAP (18.2%); $P = 0.804$.

Figure 1. Patient totals admitted in control and intervention periods



VAP = ventilator-associated pneumonia.

The rates of VAC, IVAC and PVAP are shown in Table 2. The VAC incidence rate was lower in the post-intervention group (11.4% v 16.3%; IRR, 0.70 [95% CI, 0.51–0.95]; P = 0.018). When adjusted for ventilation duration, the IRR was 0.66 (95% CI, 0.25–1.70; P = 0.387). PVAP was diagnosed in four pre-intervention patients (4.3%) v four post-intervention patients (4.7%); resulting in an unadjusted IRR of 1.15 (95% CI, 0.75–1.75; P = 0.500) and an adjusted IRR of 0.71 (95% CI, 0.08–6.53; P = 0.765).

Ventilation duration and ICU LOS were reduced in VAP antibiotic-treated patients, although these were not statistically significant reductions. The median duration of MV in the pre-intervention period was 10.9 days (IQR, 4.9–15.9 days] v post-intervention period, 8.3 days (IQR, 4.2–14.0 days); P = 0.434. The median pre-intervention ICU LOS was 13.5 days (IQR, 6.2–20.8 days) days v post-intervention ICU LOS, 10.5 days (IQR, 5.9–19.5 days); P = 0.845.

Relationship between antibiotic administration and CDC criteria

Of the 30 patients with a VAC, 14 (47%) were commenced on antibiotics for VAP, representing 10 of the total 13 patients with an IVAC (77%), and seven of eight patients with a PVAP (99.3% overall specificity) (Figure 2). Thus, among the 35 patients commenced on antibiotics for VAP, only 14 met the criteria for VAC (40%), 10 met criteria for IVAC (29%) and seven met criteria for PVAP (20% sensitivity).

Table 1. Baseline patient characteristics

Characteristic	Control period (n = 92)	Intervention period (n = 86)
Mean age, years (SD)	58.5 (18.5)	56.9 (17.4)
Female, *n* (%)	30 (32.6%)	27 (31.4%)
Type of patient, *n* (%)		
Medical	67 (72.8%)	62 (72.1%)
Surgical	25 (27.2%)	24 (27.9%)
Comorbidity, *n* (%)		
Haematological malignancy	4 (4.4%)	3 (3.5%)
Cirrhosis or chronic liver disease	0	3 (3.5%)
Immunosuppression	8 (8.7%)	10 (11.6%)
Chronic respiratory disease	7 (7.6%)	7 (8.1%)
Chronic cardiac failure	1 (1.1%)	5 (5.8%)
Chronic renal failure	0	2 (2.3%)
Metastatic cancer	1 (1.1%)	1 (1.2%)
Insulin-requiring diabetes mellitus	7 (7.6%)	6 (7.0%)
Mean SAPS II score, (SD)	46.9 (16.6)	47.2 (15.5)
Mean APACHE III score, (SD)	81.9 (29.0)	82.6 (28.9)

SAPS = Simplifed Acute Physiology Score. APACHE = Acute Physiology and Chronic Health Evaluation Score.

Discussion

Major findings

In this pre–post observational study, we showed that pressure manometry for ETT cuff maintenance, compared with a minimal leak test technique, was associated on univariate analysis with a lower incidence of antibiotic administration for VAP. After controlling for duration of MV, this association lost significance (P = 0.16) but the magnitude of reduction in VAP antibiotic administration rate remained similar (with incidence rate about halved). The sensitivity and specificity of the surveillance definition of PVAP, compared with antibiotic administration for VAP,

Table 2. Univariate ventilation and hospital outcomes

Characteristic	Control period (*n* = 92)	Intervention period (*n* = 86)	*P*
Antibiotics for VAP, *n* (%)	24 (26.1%)	11 (12.8%)	0.026
Median VAP antibiotic rate* (95% CI)	15.28 (12.56–18.41)	6.84 (4.93–9.25)	< 0.001
Median ICU LOS, days (IQR)	7.2 (4.6–12.2)	7.1 (4.8–12.1)	0.979
Antibiotics for VAP	13.5 (6.2–20.8)	10.5 (5.9–19.5)	0.845
No antibiotics for VAP	5.9 (4.3–10.4)	7.0 (4.5–12.0)	0.353
Median ventilation time, days (IQR)	4.4 (2.9–9.0)	4.6 (3.0–8.1)	0.479
Antibiotics for VAP	10.9 (4.9–15.9)	8.3 (4.2–14.0)	0.434
No antibiotics for VAP	3.9 (2.7–7.5)	4.5 (2.8–6.7)	0.746
Median hospital LOS, days (IQR)	22.5 (9–38)	18.5 (10–31)	0.554
ICU discharge status, *n* (%)			
Alive	73 (79.4%)	73 (84.9%)	0.336
Dead	19 (20.7%)	13 (15.1%)	
Hospital discharge status, *n* (%)			
Alive	60 (65.2%)	59 (68.6%)	0.631
Dead	32 (34.8%)	27 (31.4%)	
VAC, *n* (%)	20 (21.7%)	10 (11.6%)	
Median VAC rate,* (95% CI)	16.25 (13.44–19.48)	11.40 (8.89–14.40)	0.018
IVAC, *n* (%)	8 (8.7%)	5 (5.8%)	
Median IVAC rate,* (95% CI)	9.86 (7.70–12.44)	9.45 (7.17–12.21)	0.808
PVAP, *n* (%)	4 (4.3%)	4 (4.7%)	
Median PVAP rate,* (95% CI)	6.67 (4.92–10.18)	7.66 (5.62–10.18)	0.500

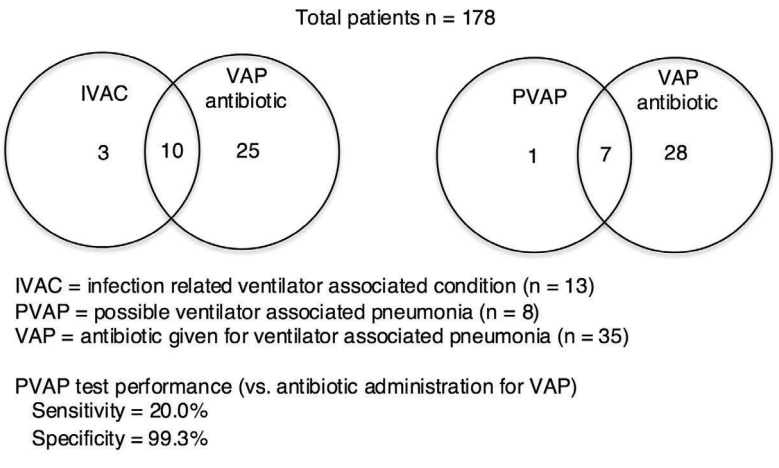
VAP = ventilator-associated pneumonia. ICU = intensive care unit. LOS = length of stay. VAC = ventilator-associated complication. IVAC = infection-related ventilator-associated complication. PVAP = possible ventilator-associated pneumonia. * Rates are per 100 ventilation days.

were 20% and 99.3%, respectively. Both duration of MV and ICU LOS were shorter in VAP antibiotic-treated patients in the post-intervention period, although differences were not statistically significant.

Strengths and limitations

Strengths of our study include that we collected complete data for all patients in the pre-intervention and post-intervention periods, as well as complete enrolment of all patients ventilated for > 48 hours during the study period. Comparative groups were reflected in the similarity of demographic characteristics at baseline. A further strength of our study was the consideration of both pragmatic clinical and objective surveillance endpoints.

Figure 2. Comparison between antibiotic administration for ventilator-associated pneumonia and surveillance definitions



Limitations include the single-centre design, the non-randomised nature of the study, that fewer than expected patients were ventilated for > 48 hours over the study period, and our inability to blind clinicians to the cuff maintenance technique. However, ICU specialists were not informed about the study, and we thought it was unlikely that a biased reduction in antibiotic prescription for patients would occur if the study purpose had become known. The primary endpoint (antibiotic us) is a surrogate marker for VAP incidence, but was deliberately chosen as a pragmatic, unambiguous and clinically relevant endpoint in its own right. Given the numerous competing diagnostic criteria

for VAP in existence, with poor agreement between them and the lack of an accepted gold standard, we identified antibiotic administration and indication as a clinically significant marker of pneumonia in ventilated patients. A reduction in antibiotic use for VAP is also recognised as an important endpoint in comparative literature.[14] A final limitation of our trial was the reliance on the antibiotic indication VAP when it was entered in the medication chart, as other indications could conceivably have been recorded, thus reducing the VAP antibiotic rate measured. Regular audit of these listed antibiotic indications is part of ongoing quality assurance within our ICU, and the fact that clinicians were unaware of the study purpose, and that the same method was used in the pre-intervention and post-intervention periods, led us to consider it unlikely that this would have affected the rate of VAP antibiotic prescribing. We did not record data on how often antibiotics were ceased or the indication altered by the reviewing infectious diseases physicians, which would have enhanced our study.

Importance of this study

Our study adds to the existing literature documenting safety concerns about the minimal leak test technique for ETT cuff maintenance. Earlier research by our group has shown the high rates of over-pressured and under-pressured ETT cuffs with this technique, with only 13 of 45 patients' ETT cuffs (29%) found to have been inflated with pressures in the safe range of 18–22 mmHg.[19] Our current study provides evidence confirming the biological plausibility of increased VAP rates associated with a cuff management technique involving cuff deflation, which must by definition result in aspiration of pharyngeal contents. This study is thus congruent with comparative literature assessing integrated subglottic drainage ETTs,[20] in which the magnitude of the reduction in VAP antibiotic rate seen in this study was similar.

This study also adds to previously published data suggesting that the CDC surveillance criteria for ventilator-associated events may not be well correlated with clinical markers of VAP at the bedside. We found that most patients commenced on antibiotics for VAP were not captured as having VAC, IVAC or PVAP. The rate of PVAP in the total cohort (eight of 178 patients who were ventilated for > 48 hours [4.5%]) is also very low compared with literature informing expected VAP rates, likely indicating poor sensitivity as observed in other studies. In a large Brazilian study of 801 patients, the CDC surveillance definition for PVAP, although 100% specific, was only 37% sensitive in diagnosing VAP, compared with the CPIS.[10] A similar study of five Belgian ICUs (which did not report PVAP rates), showed that IVAC only identified half of all patients with VAP, and that one-third of patients meeting the IVAC definition were not diagnosed with VAP.[11]

Duration of MV and ICU LOS were reduced in antibiotic-treated patients in the post-intervention period but these did not represent statistically significant differences. As absolute numbers of patients prescribed antibiotics for VAP in both pre-intervention and post-intervention periods were small, (11 post-intervention patients [13%] and 24 pre-intervention patients [26%]), it is likely that other factors affecting overall duration of MV and ICU stay (eg, other organ failure, surgical procedures, weakness resulting from critical illness) outweighed the effect of antibiotic reduction for VAP over the cohort as a whole.

Given the recent evidence of continued use of ETT management techniques involving cuff deflation in ICUs worldwide, particularly in the Australasian region, our study has important implications for practice. We suggest that the comparative safety of cuff pressure manometry, coupled with its ease of use, low cost and the availability of manometers, should mandate its use in critically ill patients receiving MV.

Future research could involve a randomised study of individual patients or a cluster design involving different ETT cuff-management protocols between ICUs. Such a study may benefit from the inclusion of a bedside diagnostic approach for VAP such as the CPIS, accepting limitations as discussed, or examination of pulmonary microbiology or colonisation rates. Based on the observed event rate difference between groups in this study, representing the best available precedent on which to base a larger trial, we estimate that a follow-up trial would need to include 478 patients, 239 in each group, at a power of 0.8 and alpha of 0.05. In our opinion, however, sufficient evidence now exists that a balance of indications for such a study would be problematic.

Competing interests

None declared.

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