

Ventilator-associated pneumonia in a tertiary paediatric intensive care unit: a 1-year prospective observational study

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Ventilator-associated pneumonia (VAP) refers to pneumonia that develops in patients on invasive mechanical ventilation. It is known to occur in as many as 10%–27% of adults on invasive mechanical ventilation.^{1,2} VAP has been shown to cause increased morbidity, mortality, duration of ventilation and hospitalisation, and health care costs.^{3–6} Data from the Australian Commission on Safety and Quality in Health Care suggest that there are more than 200 000 health care-associated infections (HAIs) in Australia every year, making HAI the single most common complication of hospitalisation. In the United States, VAP is the leading cause of death among all HAIs.⁷

Making an accurate diagnosis of VAP has been and remains a challenge to clinicians. There is no universally accepted “gold standard”, and although invasive diagnostic techniques including bronchoalveolar lavage (BAL) or protected brush specimens may be more specific, they are not practical for all patients, particularly children, and are not suitable for routine use as a surveillance tool. The current reference standard is the clinically applicable, age-specific diagnostic algorithm of the US National Nosocomial Infections Surveillance (NNIS) system (see Appendix).⁸ These criteria have the advantages of relative simplicity and low cost as a form of diagnostic testing.

Only a limited number of prospective studies have described the epidemiology of VAP in the paediatric population. It has been reported to affect 1.2%–22% of ventilated children,^{9–12} with an incidence density as high as 11.6/1000 ventilated days.⁴ Elward et al⁴ showed that genetic syndrome, reintubation, and transport out of the intensive care unit independently predicted VAP occurrence. Fayon et al⁹ identified immunodeficiency, immunosuppressant use and neuromuscular blockade as independent risk factors. Almuneef et al⁵ reported prior antibiotic use, continuous enteral feeds and bronchoscopy as significant predictors.

It is now accepted that HAIs are largely preventable, rather than unpredictable complications of medical care. It is important that the aetiological factors are clearly understood if appropriate preventive measures are to be undertaken. Literature on VAP in children is scant, and there is a clear need to enhance the existing knowledge on incidence, risk factors and health care burden in different populations, using consistent diagnostic criteria, to direct our search for solutions and improvements. The importance of improving paediatric-specific epidemiologic data for VAP cannot be overempha-

ABSTRACT

Objectives: To determine the incidence, risk factors and impact of ventilator-associated pneumonia (VAP) in a mixed tertiary paediatric intensive care unit.

Design: Prospective observational study.

Methods: Patients in the intensive care unit who were mechanically ventilated for more than 48 hours were assessed daily, according to criteria for a diagnosis of VAP. Potential risk factors for VAP, if present, were documented.

Results: Of 692 invasively ventilated patients, 269 (38.9%) were ventilated for >48 hours and met no exclusion criteria. Eighteen (6.7%) patients had episodes of VAP, and the VAP incidence density was 7.02 per 1000 intubation days. The mean admission Paediatric Index of Mortality 2 risk of death was similar in patients with and without VAP (0.084 v 0.056; $P=0.8$). Patients with VAP (compared with patients without VAP) had a longer median duration of ICU stay, (19.35 v 7.35 days; $P<0.001$), duration of ventilation (11.99 v 4.92 days; $P=0.024$) and duration of hospital stay (35.5 v 20 days; $P<0.001$). Univariate analysis showed that reintubation, absence of tube feeding and absence of stress ulcer prophylaxis were risk factors for VAP. While backward selection removed reintubation as a positive predictor during multivariate analysis, tube feeds (hazard ratio (HR), 0.27; 95% CI, 0.09–0.85; $P=0.02$) and stress ulcer prophylaxis (HR, 0.29; 95% CI, 0.11–0.76; $P=0.01$) were independently associated with reduced VAP incidence.

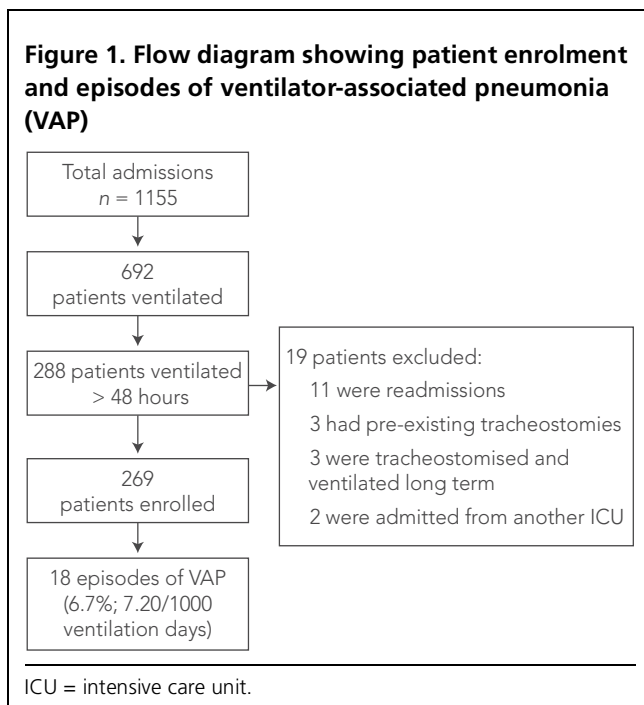
Conclusions: VAP in children is associated with significant morbidity and increased length of hospital stay. Enteral feeding and stress ulcer prophylaxis while intubated are associated with lower VAP hazards.

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sised, given the international expansion of mandatory reporting of HAIs. This study is one step forward in this direction.

Methods

This was a 1-year, single-centre, prospective, observational, quality assurance project performed between 1 February 2010 and 31 January 2011 in a tertiary, university-affiliated paediatric intensive care unit. It was designed to determine



the baseline incidence of VAP and associated risk factors. The project was prospectively approved by the Human Research Ethics Committee of The Children's Hospital at Westmead, and individual consent requirements were waived because the study was observational in nature and involved no new clinical interventions.

All children admitted to the ICU who required intubation for more than 48 hours were enrolled. Patients who had a pre-existing tracheostomy or had been intubated and ventilated at another hospital for more than 24 hours were excluded. For patients who were readmitted to the ICU for a second episode of ventilation during the same hospital admission, only the first episode was considered for enrolment purposes.

Data on baseline demographic variables and underlying illnesses, operations and procedures were collected on enrolment. These included sex, age, nutritional status (weight for age at admission, using World Health Organization criteria),¹³ type of admission (medical or surgical), underlying illness, type of intubation (emergency or elective), nature of tracheal tube (cuffed or uncuffed), presence of known genetic syndromes, airway anomalies, prematurity and chronic lung disease. We also collected the Paediatric Index of Mortality 2 (PIM2) score¹⁴ for enrolled patients, as determined at admission to ICU.

All enrolled patients were assessed daily by one or more members of the VAP surveillance team, comprising two ICU fellows (AG and SG) and an ICU nurse practitioner (OT) in conjunction with the treating intensivist or fellow. These investigators assessed each patient for the development of

VAP according to the Centers for Disease Control and Prevention (CDC) criteria⁸ (see Appendix). An opinion from a radiologist was sought for equivocal chest x-ray findings. Investigations including a full blood count, tracheal aspirate and/or a non-bronchoscopic alveolar lavage (nBAL) were performed whenever possible. When nBAL was performed, the semiquantitative culture cut-off point for potential infection was set at 10^5 colony forming units (CFU)/mL. Patients who fulfilled CDC and NNIS criteria were categorised as having VAP. Standard unit protocols for the care of the patients were followed, and their ongoing management was not affected by the study.

We also prospectively collected data on previously reported risk factors as well as hypothesised risk factors for VAP, including feeding type, use of gastric acid suppression, transfer out of ICU, transfusions, reintubation, head of bed elevation, use of renal replacement therapy, and usage of inotropes, steroids or immunosuppressant drugs. These were assessed daily, either until 48 hours after the patient was extubated or until the patient developed VAP. Further outcome data, including mortality, length of ICU stay and length of hospital stay, were also recorded and matched with the departmental database on a regular basis to ensure the accuracy of records.

Statistical analysis was performed using SAS 9.2 for Windows (SAS Institute Inc). Analysis of risk factors was modelled on the time-to-event (time-to-VAP) data, using proportional hazards (Cox) regression. Univariate analysis of the individual risk factors was performed, and those achieving statistical significance were analysed using a multivariate model. Non-parametric variables were expressed as a median and an interquartile range (IQR), and categorical variables were expressed as a proportion and a 95% confidence interval. A Wilcoxon rank-sum test was used for comparing the outcomes of patients with and without VAP.

Results

Out of 288 patients requiring ventilation for more than 48 hours, 19 met exclusion criteria, leaving 269 eligible patients (Figure 1). Of the 269 eligible patients, 167 (62%) were males. The median age of the patients was 8.97 months (IQR, 2.4–42.04). The most common underlying illnesses were cardiac in origin, and 42% of the patients were admitted after cardiac surgery. The median length of hospital stay before ICU transfer was 0.33 days (IQR, 0.14–3 days). The median weight for age in our cohort was in the 22nd percentile of WHO ideal weights for age (IQR, <3rd–60th percentiles). The baseline characteristics of the study population are summarised in Table 1.

There were 18 VAP episodes (6.7%), resulting in a VAP incidence of 7.02 per 1000 ventilation days (Figure 1). Nine

Table 1. Baseline characteristics of the study population (n = 269)

Characteristic	Median (interquartile range) or n (%)
Male	167 (62.08%)
Age	8.97 (2.4–42.04)
0–1 month	33 (12.27%)
2–12 months	113 (42.01%)
13 months–5 years	63 (23.42%)
6–12 years	38 (14.13%)
> 13 years	22 (8.17%)
Medical diagnosis	94 (34.94%)
Underlying reason for admission	
Cardiac	120 (44.61%)
Respiratory	36 (13.38%)
Trauma	21 (7.81%)
Hepatobiliary/gastrointestinal	19 (7.06%)
Cancer/bone marrow transplantation	12 (4.46%)
Central nervous system	25 (9.29%)
Other	36 (13.38%)
Postoperative cardiac patient	113 (42.01%)
Weight for age percentile*	22 (< 3–60)
Intubation characteristics	
Cuffed endotracheal tube	179 (66.54%)
Emergency intubation	116 (43.12%)
Reintubation	19 (7.06%)
PIM2 2008 risk of death	0.01 (0.006–0.044)
Pre-ICU length of hospital stay (days)	0.33 (0.14–3)
Outcome characteristics	
Ventilator-associated pneumonia	18 (6.69%)
Duration of intubation (days)	5.18 (3.58–8.92)
Duration of ICU stay (days)	7.88 (4.95–14.08)
Duration of hospital stay (days)	20 (10–50)
Patient outcome	
Discharged to ward	232 (86.25%)
Discharged home	4 (1.49%)
Discharged to other ICU	12 (4.46%)
Died or treatment withdrawn	21 (7.81%)

* Percentile of World Health Organization ideal. PIM2 = Paediatric Index of Mortality 2. ICU = intensive care unit.

of the 18 VAP cases were classified as “early VAP” (VAP occurring within 96 hours of intubation), and the other nine were classified as “late VAP”. Ninety per cent of the VAP cases occurred within 10 days of intubation. The odds ratio (OR) of developing VAP increased with duration of intubation, so the analysis of predictors was modelled on time-to-event data. The daily risk of VAP, censored by extubation, was about 1%, and rose slightly up to the fifth day of intubation, plateaued, and then fell away slightly over the second week

Table 2. Microbiological test results of VAP, and comparison of nBAL and ETA at the time of diagnosis

Day of VAP	nBAL	ETA
3	No growth	No growth
3	No growth	<i>Stenotrophomonas maltophilia</i>
3	<i>Pseudomonas, Candida</i>	<i>Candida</i>
4	<i>Haemophilus influenzae, Moraxella</i>	<i>H. influenzae, Moraxella</i>
4	No growth	No growth
4	No growth	No growth
4	No growth	No growth
4	Not sent	<i>Enterobacter aerogenes, E. cloacae</i>
4	Not sent	<i>Staphylococcus aureus</i>
5	<i>Candida, Pseudomonas, E. aerogenes</i>	<i>E. aerogenes</i> (previously colonised)
7	Not sent	<i>Pseudomonas</i>
8	<i>Acinetobacter</i>	<i>Acinetobacter</i>
8	<i>H. influenzae, Pseudomonas</i>	<i>Pseudomonas</i>
8	Not sent	<i>Staph. aureus</i> (previously colonised)
8	<i>S. maltophilia</i>	<i>S. maltophilia</i>
9	Not sent	MRSA
20	Not sent	<i>S. maltophilia, Pseudomonas</i>
28	No growth	No growth

VAP = ventilator-associated pneumonia. nBAL = non-bronchoscopic lavage. ETA = endotracheal aspirate. MRSA = methicillin-resistant *Staph. aureus*.

of intubation (data not shown). nBAL was performed in 13 patients with a clinical diagnosis of VAP, and the microbiological findings for early and late VAP are shown in Table 2.

Univariate analysis of predictors of VAP

Intrinsic predictors are patient-related factors present at the time of ICU admission, such as age, sex, underlying illness, nutritional status, pre-ICU length of stay in hospital, medical or surgical diagnosis, presence or absence of prematurity or chronic lung disease, known airway anomalies, blood infections at admission, underlying genetic syndrome and PIM2 scores. Most of these have been previously shown or hypothesised to be independent risk factors for VAP, but we did not find any statistically significant association between these factors and the risk of developing VAP (Table 3).

Extrinsic predictors are known or putative treatment-related predictors of VAP, as shown in Table 4. We did not analyse the effect of bed-head elevation as we observed

Table 3. Univariate analysis of intrinsic risk factors potentially associated with VAP (n = 269)

Risk factor	Patients	VAP events	Hazard ratio (95% CI)	P
Male	167	13	1.53 (0.54–4.33)	0.4
Age				
0–1 month	33	1	1.00	
2–12 months	113	6	2.22 (0.27–18.54)	0.5
13 months–5 years	63	4	2.22 (0.25–19.94)	0.5
6–12 years	38	3	2.94 (0.3–28.41)	0.4
> 13 years	22	4	5.49 (0.61–49.49)	0.1
Medical diagnosis	94	11	2.07 (0.8–5.37)	0.1
Underlying reason for admission				
Cardiac	120	5	1.00	
Respiratory	36	3	2.15 (0.51–9.06)	0.3
Trauma	21	2	1.62 (0.31–8.39)	0.6
Hepatobiliary/gastrointestinal	19	0	0	1.0
Cancer/bone marrow transplantation	12	1	1.15 (0.13–9.91)	0.9
Central nervous system	25	4	2.43 (0.65–9.11)	0.2
Other	36	3	1.25 (0.29–5.36)	0.8
Known GORD	10	1	2.61 (0.34–19.92)	0.4
Airway anomalies	29	3	1.79 (0.52–6.21)	0.4
Prematurity	20	1	0.61 (0.08–4.58)	0.6
Chronic lung disease	14	2	1.73 (0.4–7.53)	0.5
Known bloodstream infection	12	1	1.1 (0.14–8.35)	0.9
Genetic syndrome	16	1	1.45 (0.19–10.96)	0.7
Weight for age percentile*	NA	NA	1 (0.99–1.02)	0.7
PIM2 2008 risk of death	NA	NA	1.43 (0.06–32.89)	0.8

* Percentile of World Health Organization ideal. VAP = ventilator-associated pneumonia. GORD = gastro-oesophageal reflux disease. PIM2 = Paediatric Index of Mortality 2. NA = not applicable.

that almost all our patients had some degree of head elevation, but this was nearly always less than 30°. Only a small minority (those on high-frequency oscillator ventilation and those on extracorporeal membrane oxygenation) were managed in a horizontal position. The hazard of developing VAP was higher with patients requiring reintubation (hazard ratio [HR], 3.05; 95% CI, 1.08–8.63; $P=0.04$). Conversely, stress ulcer prophylaxis (HR, 0.32; 95% CI, 0.12–0.84; $P=0.02$) and tube feeding (HR, 0.32; 95% CI, 0.1–0.99; $P=0.05$) were associated with a lower hazard of VAP. No association was found between other known extrinsic predictors and VAP hazard.

Multivariate analysis of significant predictors

The predictors that approached significance in univariate models (reintubation, stress ulcer prophylaxis and tube feeding) were included in a multivariate analysis. Although backward selection removed the reintubation predictor, stress ulcer prophylaxis and tube feeding remained independent predictors of VAP. In the final model, the HR for stress ulcer prophylaxis was 0.29 (95% CI, 0.11–

0.76; $P=0.01$) and for tube feeding was 0.27 (95% CI, 0.09–0.85, $P=0.02$) (data not shown).

A total of 21 patients died (7.8%) (including two patients in the VAP group); none of these deaths were directly attributable to VAP. Overall, there were significant differences in the outcomes of the two groups (Table 5). The VAP group had more than twice the median duration of intubation, almost twice the median duration of hospital stay, and almost three times the median duration of ICU stay.

Discussion

This is the first prospective observational study attempting to describe VAP epidemiology in an Australian paediatric population. We found a VAP rate of 6.6% and an incidence density of 7.02 per 1000 invasive ventilation days. A study from Cincinnati reported a lower VAP rate of 2.8% and 5.6 per 1000 invasive ventilation days.¹⁵ Other studies have reported a higher incidence.^{4,5,12,16,17}

Although comparison with other paediatric data is difficult, given the differences in patient profiles, demographics, settings,

Table 4. Univariate analysis of extrinsic risk factors potentially associated with ventilator-associated pneumonia (VAP)

Characteristic	Patients	VAP events	Hazard ratio (95% CI)	<i>P</i>
Tube feeding (any)	242	14	0.32 (0.10–0.99)	0.05
Nasogastric tube feeding	224	12	0.45 (0.17–1.21)	0.10
Transpyloric tube feeding	24	2	0.75 (0.17–3.31)	0.70
Type of feed				
None	27	4	1.00	
Bolus	47	1	0.32 (0.04–2.98)	0.30
Continuous	176	11	0.32 (0.10–1.01)	0.05
Mixed	19	2	0.34 (0.06–1.99)	0.20
Inotropes	133	9	0.66 (0.26–1.70)	0.40
Postoperative cardiac	113	5	0.81 (0.29–2.30)	0.70
Steroids	71	6	0.97 (0.36–2.61)	1.00
Other immunosuppressants	25	3	1.09 (0.31–3.79)	0.90
ECMO	10	1	0.88 (0.12–6.67)	0.90
Transfer out of ICU	74	8	1.35 (0.53–3.43)	0.50
Renal replacement therapy	37	6	1.90 (0.71–5.11)	0.20
Stress ulcer prophylaxis	164	9	0.32 (0.12–0.84)	0.02
Reintubation	19	5	3.05 (1.08–8.63)	0.04
Neuromuscular blockade	99	9	0.67 (0.25–1.79)	0.40
Blood transfusion	80	5	0.36 (0.12–1.06)	0.07
Fresh frozen plasma transfusion	70	4	0.43 (0.14–1.36)	0.20
Platelet transfusion	55	5	0.75 (0.26–2.18)	0.60
Cuffed endotracheal tube	179	14	1.76 (0.58–5.36)	0.30
Emergency intubation	116	12	1.82 (0.68–4.88)	0.20
Pre-ICU length of stay	–	–	0.99 (0.96–1.02)	0.40

ECMO = extracorporeal membrane oxygenation.
ICU = intensive care unit.

variable diagnostic criteria and standards of care, our VAP rates were among the lowest published so far. We used the NNIS and CDC clinical criteria for establishing a diagnosis of VAP, as opposed to the microbiological criteria in some of the previous studies. Existing NNIS and CDC diagnostic criteria do not require microbiological evidence for a diagnosis of VAP (see Appendix), and it is well recognised that only half the patients meeting these criteria will have a likely bacterial pathogen isolated.¹⁸ Our study is consistent with this in that no bacterial pathogens were isolated from the lower airway in six of the 13 children in whom we performed nBAL. The daily hazard of VAP acquisition (cen-

Table 5. Comparison of duration of ventilation, ICU length of stay and hospital length of stay between patients with and without VAP

Outcome variable	With VAP, median days (IQR) or <i>n</i> (%)	Without VAP, median days (IQR) or <i>n</i> (%)	<i>P</i>
Duration of ventilation	11.99 (7.15–17.25)	4.92 (3.51–8.25)	0.024*
ICU stay	19.35 (9.73–26.73)	7.35 (4.94–13.76)	<0.001*
Hospital stay	35.5 (21–86)	20 (10–50)	<0.001*
Mortality	2 (11%)	19 (7.5%)	0.6†

* *P* value from Wilcoxon rank-sum test, comparing patients with VAP with patients without VAP. † *P* value from χ^2 test. ICU = intensive care unit. VAP = ventilator-associated pneumonia. IQR = interquartile range.

sored by extubation) was about 1%, and peaked between the second and fifth days of intubation. Although this change in daily VAP hazards was not statistically significant, a similar phenomenon has been observed in adult patients.¹⁹ This may be due to the high incidence of early VAP (50% in our study) and a decreased intrinsic risk in those ventilated longer. In a prospective paediatric study, Srinivasan et al found that 58% of their VAP cases were early VAP.¹⁷

We did not find any association between previously reported intrinsic risk factors and VAP. This is in agreement with findings of a recent study from Brazil.¹² However, we did find a higher VAP risk with reintubation, as previously reported by Elward et al.⁴ This is possibly due to an increased risk of aspirating oropharyngeal secretions during the act of reintubation.

Interestingly, we found a lower VAP risk in patients having gastric acid suppression for stress ulcer prophylaxis. It has been argued that acid suppression may predispose to bacterial colonisation of the upper gastrointestinal tract, thus increasing VAP risk.²⁰ In a retrospective study by Lopriore et al, there was no difference in upper airway colonisation with or without the use of ulcer prophylaxis in ventilated children.²¹ Yildizdaz et al, in their prospective study in children, reported similar findings.²² We are unable to explain the apparent protective effect of acid suppression in our cohort. The standard practice in our unit is to stop ulcer prophylaxis when enteral feeds are started. Due to this, our patient cohort may not have had increased residual gastric volumes and increased gastric pH at the same time, thus reducing the risk of bacterial aspiration. In a recent meta-analysis, histamine-2 (H₂) receptor blockers did not significantly increase the risk of hospital-acquired pneumonia (OR, 1.53; 95% CI, 0.89–2.61; *P*=0.12), but this

complication was increased in the subgroup of H₂-receptor blocker recipients who were fed enterally (OR, 2.81; 95% CI, 1.20–6.56; $P=0.02$).⁹ Clearly, data are inconclusive in this regard, and studies with larger cohorts may provide further clarification.

We also found enteral feeding to be associated with lower VAP risk (HR, 0.32; 95% CI, 0.1–0.99; $P=0.05$). Enteral nutrition in critically ill patients is associated with better immunocompetence, improved gut perfusion and preservation of gut flora. On the other hand, some studies of adult patients and one of paediatric patients have shown enteral feeds to be a risk factor for VAP, hypothesising microaspiration to be the underlying mechanism.⁵ There was no difference in risk of VAP with respect to the site of feeding (nasogastric or postpyloric) in our study. Kamat et al, in their prospective study in intubated paediatric patients, did not detect increased aspiration with nasogastric compared with postpyloric feeds.²³

Previously described risk factors, including comorbidities such as prematurity, chronic lung disease, genetic syndromes and airway anomalies, were not associated with VAP risk in our study, as was the case with use of blood products, neuromuscular blockers, steroids and immunosuppressants, or with transfer out of ICU.

VAP was associated with increased duration of ventilation and length of ICU and hospital stay in our cohort. Similar results have been shown in many adult and paediatric studies comparing matched cohorts, emphasising the burden imposed on health care costs. There was no significant difference in mortality in VAP versus no VAP groups, similar to other paediatric studies,^{4,5,17} but there were few deaths in our cohort and this analysis is underpowered.

We recognise the weaknesses of our study in being single centre. Furthermore, a low number of VAP events reduces statistical power. To detect an HR of approximately 0.3 with 80% power and 5% significance, about 22 VAP events need to be observed for a single predictor that occurs in 40% of subjects. For an HR of 0.6 we would need 125 events. The number of events required also increases if we wish to look at multiple predictors.

Lack of a gold standard for diagnosis of VAP is a universal limitation affecting VAP surveillance studies. A major limitation of the clinical approach to diagnosis is that it is oversensitive, resulting in diagnosis of VAP when another process is responsible for the clinical deterioration. Of our patients, 42% were admitted after cardiac surgery and may seem an overrepresentation of one subgroup. However, there was no difference in VAP incidence in this group when compared with the rest.

Despite these limitations, this study is important in several respects. It indicates the risk factors for, and importance and impact of, VAP in mechanically ventilated children. It adds to the existing epidemiologic data on paediatric VAP,

and represents the first Australian dataset in this area. Stringent daily VAP rounds ensured maximum achievable accuracy using observational techniques, and the patient cohort was a reasonable representation of overall ICU admissions. The findings of our study need to be confirmed in larger, adequately powered studies.

VAP is an important HAI, and establishing baseline epidemiologic data will enable preventive measures to be taken against modifiable risk factors. Effective preventive measures may allow a significant reduction in health care costs associated with the demonstrable adverse impacts of VAP. A large, multicentre study should be performed to better elucidate potentially modifiable risk factors.

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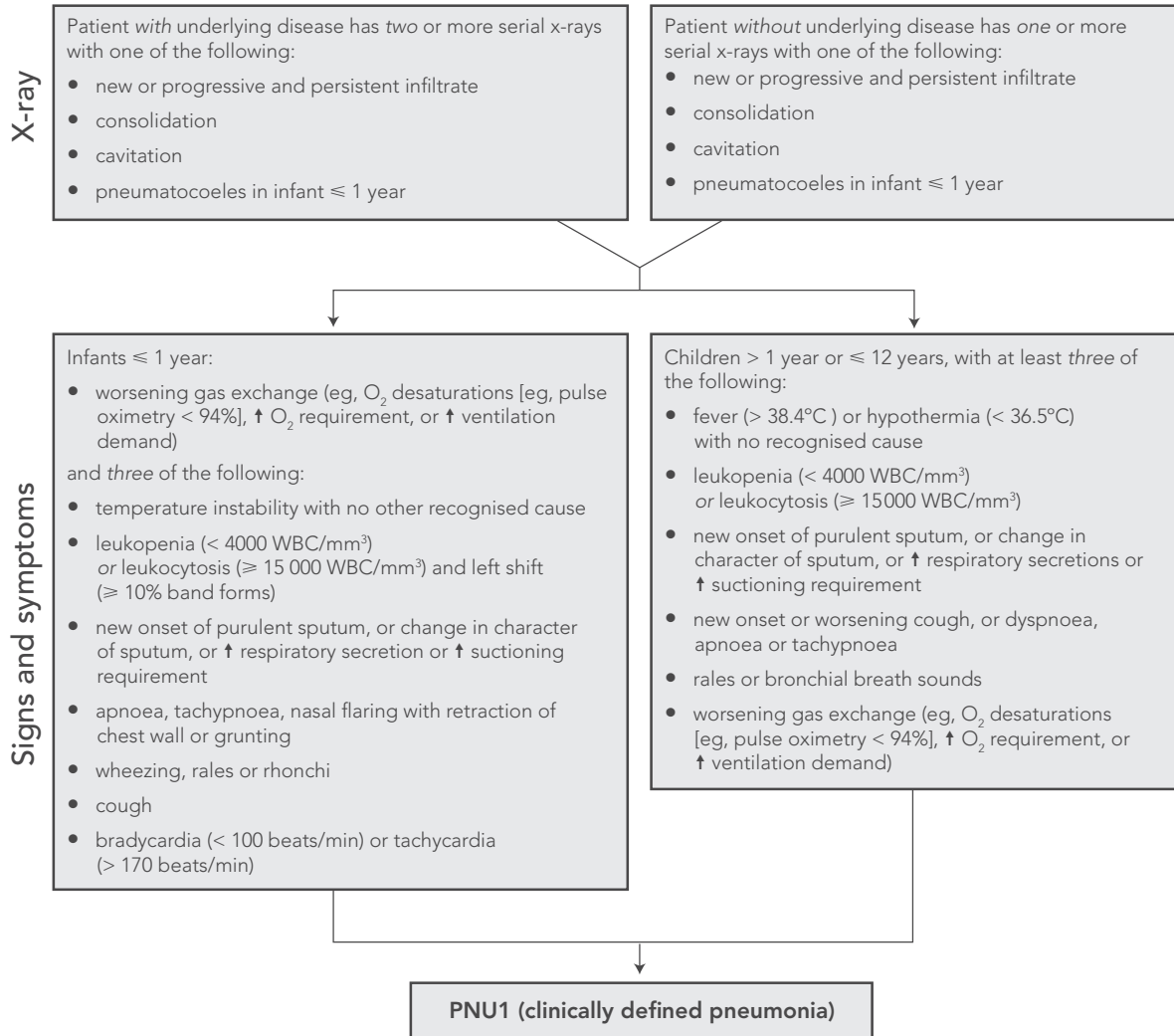
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Appendix. Diagnostic criteria of ventilator-associated pneumonia*



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