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Occasional Survey

Management of Ventilator-associated Pneumonia in Paediatric Setting

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Abstract Ventilator-associated pneumonia (VAP) is the second commonest nosocomial infection in paediatric intensive care units. New definitions about VAP have been proposed recently for better epidemiological study and clinical trials. Management approach is mainly based on adult recommendation because of scanty paediatric studies. Multidrug resistant microorganisms can cause both the early and the late onset VAP. Possible risk factors for VAP include longer duration of ventilation, immunodeficiency, use of immunosuppressive drugs, neuromuscular blockade, genetic syndrome(s), reintubation and transport of critical patients. To have a more reliable diagnosis, quantitative or semi-quantitative bacterial cultures using bronchoscopic or nonbronchoscopic methods should be performed before initiation of the de-escalation therapy, which is the current trend of management. The threshold bacterial count of bronchoalveolar lavage in diagnosing pneumonia is still controversial in Paediatrics. Initial empirical treatment with combination antibiotics therapy providing a broad spectrum cover to decrease the mortality should be considered, which could later be narrowed to single sensitive antibiotic based on bacterial culture. Shorter duration of antibiotic(s) of 8 days is equally effective as the 15-day treatment except in Pseudomonas aeruginosa pneumonia. Good nursing care with utmost infection control practice is the paramount element in the prevention of VAP.

Key words Anti-bacterial agents; Child; Cross-infection; Pneumonia, bacterial; Ventilators, mechanical

Introduction

Nosocomial pneumonia (NP) / ventilator-associated pneumonia (VAP) are important entities in intensive care unit (ICU) / paediatric intensive care unit (PICU). Compared with those not having VAP, adult patients suffering from VAP have 2-time increase in the mortality rate [pooled odd ratio (OR) 2.03] and have longer ICU length of stay (mean 6.10 days). Each patient who had developed VAP incurred an additional hospital cost of at least USD $100191.[1] Guidelines on the management of VAP have been issued from American Thoracic Society (ATS) in 1995[2] and European Respiratory Society in 2001.[3] The ATS also revised the guidelines in 2004 after incorporating the recent important studies.[4] However these guidelines are restricted to the adult population. Here it is time to review any studies concerning the paediatric population on this matter, or whether the results of some of the adult studies could be applied to the paediatric population.

Definition of Ventilator-associated Pneumonia in Paediatrics

There are little articles concerning investigations/ management of NP /VAP in paediatric population. The main reason may be related to the small number of cases in each centre. The collaboration between different centres to produce multicentre, prospective, double blind randomised controlled studies is strongly indicated. The Pediatric Acute

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Lung Injury & Sepsis Investigators (PALISI) and International Sepsis Forum (ISF) reached a consensus in 2005 and published the proposed definitions of specific infections, including pneumonia, bacterial meningitis and central venous catheter-related infections, etc.[5] In the topic of pneumonia, it is divided into community-acquired pneumonia and nosocomial pneumonia.[6] There are two proposed definitions of pneumonia serving for different purposes. For hospital surveillance, the committee still adopts the CDC definition (Table 1). This is more sensitive but less specific for diagnosing pneumonia. However, for the enrollment in sepsis trial, or for the diagnosis or therapy, a stricter definition given by US FDA draft guideline for industry is used.[7] It is further subdivided into "definite" case if the pneumonia is confirmed microbiologically/ histopathologically, "probable" case if there is either positive Gram stain or presence of indirect evidence of pathogen, and lastly "possible" case without culture or histologic confirmation. For our daily practice in PICU, CDC criteria are more useful.

Epidemiology of Nosocomial Pneumonia and Ventilator-associated Pneumonia

Incidence of NP and VAP

The recent prospective study in one single paediatric intensive care unit in Montreal showed that the incidence of bacterial nosocomial pneumonia was 1.2%.[8] The study took place from July 1991 to July 1992 and it also included patient not requiring ventilation. Out of 960 patients enrolled, twelve patients had bacterial nosocomial pneumonia. Ventilated patients had the risk of 2.5% developing VAP, which was not statistically different from the above overall incidence rate (p=0.09). However, longer duration of ventilation was associated with higher significant rate of developing VAP, 5.3% for those ventilated >/= 2 days (p=0.0001), and 6.9% for those ventilated >/=3 days (p<0.0001).

National Nosocomial Infection Surveillance (NNIS) was conducted on 61 PICU in United States from January 1992 to December 1997.[9] 6290 cases of nosocomial infection (NI) were identified out of 110709 cases. Primary bloodstream infection ranked the most common NI (28%) and the NP ranked the second (21%) except in the age group of 5-12 year in which NP ranked the first. Furthermore 95% of NP was associated with mechanical ventilation. The pooled mean of VAP was about 5.9 cases per 1000 ventilator days, as compared with the figure 9.1 per 1000 ventilator days in adult counterpart.

European multicentric prospective study was performed from August 1996 to January 1997 to determine the sites and bacterial epidemiology of nosocomial infection in children.[10] The study involved 20 units in eight European

Table 1 Comparison of two definitions of nosocomial pneumonia proposed by CDC and US FDA draft guideline for industry[6]

	CDC criteria	**FDA draft**
Definition of nosocomial infection (NP)	New CXR features (A) Plus (B) and/or (C)	At least 3 days of hospitalisation, or less than 7 days after discharge. New CXR features (A) ***PLUS*** worsening gas exchange (if child <1yr) ***PLUS*** at least 3 traits out of the following categories 1. Clinical – symptoms or signs including sputum change (B); 2. Vital sign derangement – temperature or heart rate; 3. Laboratory abnormality in WBC – only required for children between 1-12 years.
New CXR features (A)	New/progressive infiltrate, cavitation, consolidation, or pleural effusion	Same as CDC
Change in sputum/ respiratory secretion (B)	Increased production or development of purulent sputum/secretion	Same as CDC
Microbiological/histologic evidence(s) (C)	Culture result, serological proof, or histopathologic evidence	Required to define "definite" case
Definition of VAP	NP occurring at or after 48 hrs after initiation of mechanical ventilation	Same as CDC

countries: 5 PICU, 7 neonatal units, 2 haematology-oncology units and 8 general paediatric units. The incidence of nosocomial infection was 2.5% (373/14675) with highest rate 23.5% in PICU. In PICU, the distribution of nosocomial infections in the decreasing order were pneumonia (33%), bacteremia (20%), urinary tract infection (15%), post-surgical wound infections (7%) and gastrointestinal infections (4%).

Risk Factors Causing NP/VAP

From Fayon's study, only three factors were identified as the risk factors of bacterial nosocomial pneumonia by the multivariate analysis: immunodeficiency (OR 6.9), use of immunosuppressive drugs (OR 4.8) and neuromuscular blockade (OR 11.4).[8] The same analysis, on the other hand, rejected the possible roles of respiratory failure, cardiovascular failure, neurological failure or haematological failure in the predisposition to nosocomial bacterial pneumonia. The effect of skeletal muscle paralysis on the development of pneumonia was also studied in one single PICU.[11] Those paralysed patients were found to have longer duration of mechanical ventilation and higher percentage (26%) to develop VAP (p=0.03)

A prospective study in St Louis Children's Hospital from September 1 1999 to May 31 2000 identified 34 episodes of VAP in 30 patients out of 911 PICU admission (3.3%).[12] The incidence of VAP in mechanically ventilated patients was 5.1% out of 595 patients. Univariate analysis identified the following risk factors causing VAP: Reintubation, tracheostomy, transfusion, transport out of PICU, presence of a central line, multiple central venous catheters, bronchoscopy, thoracocentesis, burn debridement, TPN, steroid, and histamine type 2 receptor blockers. Data on the use of neuromuscular blockade was not included in this study. However, after the multivariate analysis, only three factors were singled out, namely genetic syndrome which included neuromuscular abnormalities and craniofacial abnormalities (OR 2.37); reintubation (OR 2.71), which was probably related to aspiration of gastrointestinal contents during intubation; and finally transport out of the PICU (OR 8.9). The last risk factor was less understandable, but the authors postulated that during the transport, there might be higher chances of pooling of secretion in the alveoli, aspiration of oral secretion or breaches of proper infection control technique.

Outcome of NP/VAP

The overall mortality of NP/ VAP ranged from 8% to 20% in paediatric studies. Brown et al studied the infections in one single PICU.[13] Lower respiratory tract infection (not differentiating between hospital acquired or community acquired infection) had the highest mortality, 20.5%, compared with the overall mortality 3.4%. Fayon et al found that the death rate attributable to nosocomial pneumonia was 8%.[8] In the European multicentre trial, the mortality rate in PICU was 10%.[10] In the St Louis's group, the mortality rate was up to 20% (6/30) but was not statistically different from the non-VAP group (20% vs. 7%; p=0.065).[12]

Microbiology

Previous concept in adult's population usually divided NP/VAP into the early onset and the late onset types with different spectrums of pathogen.[2] The early onset nosocomial pneumonia that occurs during the first 4 days of hospitalisation is usually caused by the community-acquired pathogens, such as Streptococcus pneumoniae, Haemophilus influenzae, or Moraxella catarrhalis. The late onset pneumonia occurs on or after the fifth day and is frequently caused by potentially drug resistant nosocomial pathogens such as Pseudomonas aeruginosa, Acinetobacter, methicillin-resistant Staphylococcus aureus (MRSA), or multi-resistant gram negative bacilli.

In the epidemiological study of paediatric population, no such classification was made, probably related to the small number of patients involved. Several epidemiological studies detected similar pattern of pathogens with gram negative bacilli most predominant, followed by Staphylococcus aureus. NNIS identified that 67% of the pathogenic isolates were gram negative bacilli with Pseudomonas aeruginosa most common (22%).[9] Staphylococcus aureus was found in the 17% of the isolates. Viral pathogens were isolated in 37 cases, in which 27 cases (75%) were related to the respiratory syncytial virus. In the European study, Pseudomonas aeruginosa was the most common cause (35.6%) of NP.[10] Staphylococcus aureus ranked the second (18.6%), which was then followed by virus, Klebsiella and Serratia.

Only one study intended to compare different pathogens in the early onset and the late onset type of hospital acquired pneumonia in paediatric trauma patients.[14] The time frame in dividing the early versus the late onset infection was however taken on the seventh day after the trauma, which was different from the current conventional classification. The common organisms identified were Staphylococcus aureus (21%), Haemophilus influenzae (19%), Pseudomonas (11%), and Enterobacter (11%). In the early

onset pneumonia (diagnosed < or = 7 days after injury), Haemophilus species were more predominant whereas in late onset pneumonia (diagnosed >7 days after injury), Enterobacter and/or Pseudomonas were isolated primarily. Staphylococcus was equally prominent throughout the hospitalisation period.

Finally we should be vigilant that early onset VAP could also be caused by multi-drug resistant pathogens which are usually prevalent in hospital environment. Although there is no paediatric study detecting this causal relationship, one recent adult study may give some insight in which both Pseudomonas aeruginosa and MRSA were found as common in the early onset VAP as in the late onset VAP.[15] Some patients with certain risk factors might have been exposed to the more virulent bacteria before the current hospital admission complicated with the development of early onset VAP.[4]

Investigations for Ventilator-associated Pneumonia

Microbiological Investigations

As the number of paediatric patients suffering from VAP is small and it is difficult to perform invasive investigations, it is easier to use the experts' consensus according to the Delphi method as the gold standard in paediatric studies.[16,17] Its concept is to incorporate all the clinical, radiological and microbiological parameters together to give an overall impression of the diagnosis, which is then taken as the gold standard.

Bacteriolgoical investigations may be divided into the noninvasive and the invasive ones. The noninvasive methods include quantitative or semi-quantitative tracheobronchial aspiration. The invasive methods include quantitative culture derived from bronchoalveolar lavage (BAL), bronchoscopic protected specimen brush (PSB), nonbronchoscopic ("blind") bronchial suction, blind mini-BAL or blind PSB.

Adult study showed that quantitative culture of tracheal aspirate had high sensitivity but low specificity.[18] Analysis of receiver-operation curves using different cut-off values reached the best threshold value of 10^6 CFU/ml with the sensitivity 68% and the specificity 84%. However even when using that threshold value, there was still poor correlation between the micro-organisms identified by the tracheal aspirate and protected specimen brush (r=0.32), when the latter method was taken as the gold standard.

Different non-bronchoscopic techniques in obtaining bacterial cultures in paediatric patients have been mentioned previously in the literatures: protected specimen brush in newborn,[19] blind BAL using 4-F balloon wedge pressure catheter,[20] and blind BAL in mechanical ventilated infants using a sterile disposed feeding tube.[21] Recent study compared the usefulness of the blind PSB, blind BAL, and endotracheal aspirate (EA) in ventilated paediatric patients using the Delphi method as the gold standard.[16] They calculated that the best thresholds for different diagnostic tools were 10^3 CFU/ml in PSB culture, 1% in intracellular bacteria (ICB) in BAL and 10^4 CFU/ml in blind BAL. By combining the PSB, ICB and BAL results together, the sensitivity and specificity could be raised up to 90% and 88% respectively. On the other hand, endotracheal aspirate alone had high sensitivity 93% but very low specificity 41%. The major complications of non-bronchoscopic PSB or BAL were uncommon and the minor ones only included mild and self-limited bronchial haemorrhage (11%), moderate but persistent (>1 hr) increase in oxygen or ventilatory requirement (10%) or transient fever (6%).

Another study also compared quantitative culture, bacterial index in BAL, percentage of intracellular bacteria (ICB), gram stain all obtained in non-bronchoscopic BAL, together with endotracheal culture.[17] Bacterial index (BI) was calculated by the sum of the normal logarithm of each bacterial colony. The global value, which was defined as the sum of cases classified as true positives and true negatives divided by the total number of cases, was also calculated for each test to determine its usefulness. The results showed that blind BAL culture >/= 10^4 CFU/ml only had sensitivity 50%, specificity 80%, positive predictive value 56%, negative predictive value 71% and the global value 70%. On the other hand bacterial index of >5 in BAL was the best method with the sensitivity 78%, specificity 86%, positive predictive value 70%, negative predictive value 90% and the global value 90%. Intracellular bacteria and Gram stain from bronchoalveolar secretions were very specific (95% and 81%, respectively) but not sensitive 30% and 50% respectively. The conclusion from that study was that the bacterial index of >5 using the blind BAL was the most reliable diagnostic method for VAP. However an early adult study gave the opposite result.[22] In comparing the BI at a cut-off of > or =5 with BAL taking the threshold of 10^5 CFU/ml, BI was inferior to BAL as it was less specific than BAL, 87% versus 99% (P<0.0001) while there was no significant improvement in sensitivity 41% versus 33% respectively (P=0.77).

In paediatric population, there is no study investigating the threshold value of the bacterial count in bronchoscopic BAL to diagnose bacterial pneumonia. European Respiratory

Society Taskforce recommended "Results need to be interpreted based on quantitative cultures with the use of a diagnostic threshold and/or identification of intracellular bacteria on direct examination of the sample".[23] However no concrete figure was recommended by the Society. It is not sure whether the same threshold value 10^4 CFU/ml in the adult criteria could be applied to paediatric patients. Based on personal experience, Wood & Daines uses 10^5 CFU/ml as the diagnostic criteria of pneumonia for the common bacterial pathogen in the presence of significant number of neutrophils in BAL fluid.[24] Otherwise he takes the bacterial count of 5 x 10^5 CFU/ml in the BAL fluid as the clear-cut pneumonia. On the other hand, from the consensus between PALISI and ISF in formulating the definition of paediatric pneumonia, the group has also set the rule in diagnosing definite pneumonia with microbiological evidence (Table 2), most probably based on the adults' criteria.

In conclusion, bronchoscopic BAL seems to be the best modality for taking the microbiological culture. However, it may be limited by the small airway of the patient which may restrict the size of bronchoscope used. On the other hand, it is operator-dependent and thus urgent investigation might not be entertained before commencement of empirical antibiotics. Non-bronchoscopic investigations namely the protected specimen brush or non-bronchoscopic (blind) BAL are useful and the results are promising. However the threshold criterion for diagnosis in each method is still debatable based on the small number of studies available.

Ancillary Investigations

In adult studies, the following biochemical markers were found to be useful as diagnostic or prognostic factors.

Serum Procalcitonin as Diagnostic and Prognostic Factors[25]

Procalcitonin level was significantly increased in the VAP group compared with the non-VAP group: 11.5 ng/ml (95% confidence interval (CI), 5.9-17.0) versus 1.5 ng/ml (95% CI, 1.1-1.9). The best cut off value for the diagnosis was >3.9 ng/ml with sensitivity 41% and specificity 100%. Non-survivors were found to have higher serum level than survivors: 16.5 ng/ml (95% CI, 8.1-24.9) versus 2.9 ng/ml (95% CI, 1.2-4.7).

Soluble Triggering Receptor Expressed on Myeloid Cells (Soluble TREM-1) Measured in BAL Fluid[26]

It is a member of the immunoglobulin superfamily expressed in phagocytes which is specifically up-regulated by microbial products. One adult study showed that it was more accurate than clinical findings or laboratory values in identifying the presence of bacterial or fungal pneumonia. When the cut-off value of sTREM-1 >5 pg/ml in BAL fluid was used, the sensitivity and specificity were 98% and 90% respectively. By multiple logistic regression analysis, sTREM-1 with the above cut-off value was found to be the strongest independent predictor of pneumonia with odd ratio 41.5 when compared with the clinical pulmonary infection score >6, tumour necrosis factor or interleukin 1 beta in BAL.

C-reactive Protein (CRP) – Prognostic Factor of Outcome[27]

By the fourth day after starting the antibiotic treatment for VAP, the serum level of CRP >60% of the initial level was a marker of poor outcome (sensitivity 0.92; specificity 0.59). Furthermore, by dividing CRP patterns classified into 4 subtypes: fast response, slow response, non-response, and biphasic response, it was found that the non-response and a biphasic response pattern exhibited a mortality of 78% and 75%, respectively.

Management of Nosocomial Pneumonia and Ventilator-associated Pneumonia

De-escalation Therapy

There is no clinical trial in the literature investigating the treatment of VAP in paediatric population. Thus the management of paediatric VAP is mostly based on the results extrapolated from the adult studies. De-escalation therapy has become the standard treatment for VAP in adult population.[4] Studies have shown that the immediate

Table 2 Significant bacterial colony count from quantitative / semi-quantitative culture to define "definite" pneumonia adopted by PALISI and ISF consensus[6]

Specimen collection	Colony forming unit/mL
Endotracheal aspirate	>/= 10^6
Bronchoscopy with bronchoalveolar lavage	>/= 10^4
Protected specimen brush (bronchoscopic or blind)	>/= 10^3

administration of antimicrobial treatment is crucial and inappropriate treatment is associated with higher mortality from pneumonia. Furthermore even if the initially inappropriate anti-microbial treatment is later changed according to the bacterial culture and the antibiotic sensitivity, the mortality rate remains higher statistically when compared with those patients treated appropriately right at the beginning. One adult study showed that for those patients suffering from ICU acquired pneumonia and receiving empirical antibiotic(s) initially, 43.7% of cases required modification of the antibiotic treatment because of the isolation of a microorganism not covered by the initial antibiotic regimen (62.1%), lack of clinical response (36%), or development of antibiotic resistance (6.6%).[28] The risk factors which were associated with the initially inappropriate treatment and subsequent antibiotic modification included: (i) microorganism not initially covered by the empirical antibiotic [relative risk (RR) 22.02; 95% confidence interval (CI) 11.54 to 42.60; p<0.0001]; (ii) administration of more than one antibiotic (RR 1.29; 95% CI 1.02 to 1.65; p=0.021); (iii) previous use of antibiotics (RR 1.22; 95% CI 1.08 to 1.39; p = 0.0018). The attributable mortality was 16.2% in patients with appropriate initial therapy which was significant lower than that in patients with inappropriate initial treatment, 24.7% (p=0.034).

Another study discovered that the infection-related mortality rate (IRM) for adult patients receiving inadequate initial antimicrobial treatment for both community-acquired and nosocomial infections (42%) was significantly higher than the IRM for those receiving adequate initial antimicrobial treatment (17%) (RR 2.379; 95%CI 1.83 to 3.08; p<0.001).[29] Furthermore inadequate antimicrobial treatment of infection was found to be most important independent determinant of hospital mortality (adjusted OR 4.27; 95% CI 3.35 to 5.44; p<0.001). Prior antibiotic administration was an important contributing factor for the administration of inadequate antimicrobial treatment among ICU patients with clinically suspected infections. Ireguli et al further detected that in those adult patients with VAP, the delay of starting an initial appropriate antibiotic treatment for at least 24 hours were found to have higher hospital mortality rate by logistic regression analysis (adjusted OR 7.68; 95% CI 4.50 to 13.09; p<0.001).[30]

De-escalation therapy recommends that broad-spectrum antibiotics which could cover the common multi-resistant pathogens prevalent in the locality should be commenced immediately after an appropriate bacterial culture is taken. It has been argued that the indiscriminate use of broad-spectrum antibiotics may have serious adverse effects in critically ill patients as it will promote the development of secondary infections caused by multi-resistant and difficult-to-treat organisms. The essence of the de-escalation therapy is that once the pathogen(s) has/have been identified at around 48-72 hours and the antibiotic sensitivity is known, the treatment regimen should be reduced to narrow-spectrum antibiotics.[4]

Duration of Antimicrobial Therapy

The recommendation of the duration of antimicrobial therapy was previously based on expert opinion. In ATS 1995 guideline, it mentioned that for those adult patients with multilobar involvement, malnutrition, severe debilitation, cavitation or a necrotizing GNB pneumonia, 14-21 days of antibiotic(s) were indicated.[2] Shorter duration of 7-10 day therapy was only suggested for methicillin-sensitive Staphylococcus aureus (MSSA) and Haemophilus influenzae. ERS 2001 Taskforce did not discuss this issue.[3] For paediatric patients with VAP, 10-14 day antibiotic treatment has been recommended.[31] However it is based on ATS 1995 guideline.

One recent multi-centre prospective randomised controlled trial involving 51 French adult ICUs compared 8 days versus 15 days of antibiotic therapy in adult patients with VAP.[32] The primary outcomes of the study included patient mortality rate, the pulmonary infection recurrence rate and the antibiotic free days. The death rates and the overall pulmonary infection recurrence were similar in the two groups. There were more mean antibiotic free days in the group of 8-day regimen (13.7 days versus 8.7 days; p<0.001). The secondary outcomes of the study regarding the number of mechanical ventilation-free days, the number of organ failure-free days, and the length of ICU stay showed no differences in the two groups. However, those patients with VAP caused by non-fermenting gram-negative bacilli, including Pseudomonas aeruginosa, were found to have higher recurrence rate (40.6% versus 25.4%; risk difference, 15.2%; 90% CI 3.69%-26.6%). Another randomised controlled trial also showed that by following an well-defined antibiotic discontinuation policy, shorter duration of antibiotics could be attained, 6.0±4.9 days versus 8.0± 5.6 days in the conventional group (p = 0.001).[33] However, there were no statistical difference in the occurrence of the secondary episodes of VAP (17.3% versus 19.3%; p=0.667), the hospital mortality (32.0% versus 37.1%; p=0.357), and the ICU length of stay (6.8±6.1 days versus 7.0±7.3 days; p= 0.798). Based on the French multi-centre trial, the ATS 2004 guidelines recommend that if an appropriate antibiotic regimen is given initially, efforts should be made to shorten

the duration of therapy as short as 7 days, provided that the aetiologic pathogen is not Pseudomonas aeruginosa, and that the patient has a good clinical response with resolution of clinical features of infection (Level I recommendation).[4]

Monotherapy Versus Combination Antibiotic Therapy

Those who support the combination therapy claim that it is more advantageous in promoting synergistic effect, preventing the development of antibiotic resistance and also promoting the wider spectrum coverage. However no previous studies confirmed the first two assertions. On the contrary, two recent meta-analyses in adult population concerning the management of sepsis (not targeting at NP/VAP) favour monotherapy with no change in hospital mortality but with lesser degree of side effects. The first meta-analysis compared beta-lactam monotherapy with the combination therapy of beta-lactam and aminoglycoside for patients with neutropenic fever.[34] No significant difference in all-cause fatality was detected (RR 0.85; 95% CI 0.72 to 1.02). Monotherapy was preferred with lower failure rate (RR 0.92; 95% CI 0.85 to 0.99), though there was considerable heterogeneity among the trials. The rate of superinfection was similar in both groups. Adverse events, including those associated with severe morbidity, were significantly more common in the combination therapy group. The second meta-analysis compared the beta-lactam monotherapy with the combination therapy using beta-lactam and aminoglycoside in the treatment of sepsis in incompetent adult patients.[35] It also showed no difference in all cause fatality (RR 0.90; 95% CI 0.77 to 1.06). There was no advantage in using combination therapy to treat gram negative infections or Pseudomonas aeruginosa infection. Nephrotoxicity was, on the other hand, less common in monotherapy therapy group (RR 0.36; 95% CI 0.28 to 0.47). The above two meta-analyses supported the monotherapy approach. However from another study targeting at the documented Pseudomonas aeruginosa blood infection, inappropriate initial antimicrobial treatment was more common in the initial monotherapy group compared with initial combination therapy (65.5% vs. 79.4%; p=0.011), which in term caused higher hospital mortality (30.7% vs. 17.8%; p=0.018).[36] The above conclusions may be applied to patients with severe VAP and thus they should receive combination therapy initially. The therapy could be narrowed down to a single agent once the lower respiratory tract cultures do not yield a resistant pathogen such as Pseudomonas aeruginosa.[4]

There is no study concerning the antibiotic treatment of NP/VAP in paediatric population. Only two old studies discussing the management of pseudomonal pneumonia in patients of cystic fibrosis may give some insight. The results of both studies favoured monotherapy. In the study comparing piperacillin with ticarcillin plus tobramycin in the treatment of acute pulmonary exacerbations of cystic fibrosis, Pseudomonas aeruginosa was identified in 90% of sputum cultures.[37] The addition of tobramycin was found not to change the clinical outcome or development of bacterial resistance. However, the administration of tobramycin required monitoring of serum level and in most cases, adjustment of the drug dosage was required. Another prospective randomised trial compared the 14 day-regimen of ceftazidime monotherapy versus combination therapy for Pseudomonas pulmonary infections in cystic fibrosis.[38] The combination therapy regimen was ceftazidime plus sisomicin (C/S) or piperacillin plus sisomicin (P/S). The bacterial count of Pseudomonas aeruginosa in sputum dropped to less than 10^5 CFU/ml in a more significant percentage (60%) in C/S group when compared with the ceftazidime monotherapy group, or P/S group (both in 30%). However, there was no statistical difference in the 3 groups regarding the clinical and radiological improvement. A larger percentage of persistent resistant strains of P. aeruginosa, on the other hand, was seen after the combination therapy.

Role of Early Antibiotic Treatment of MRSA in Late Onset Type of VAP

By using statistical analysis, Lodise et al calculated the breakpoint, 44.75 hours, in dividing the antibiotic treatment into early treatment and late treatment for hospital-acquired staphylococcus aureus bacteremia.[39] Then by multivariate analysis, delayed treatment beyond the 44.75 hours were found to be an independent predictor of infection-related mortality (OR 3.8; 95% CI 1.3-11.0; p=0.01), and longer hospital stay (20.2 days versus 14.3 days; p=0.05). However in a recent retrospective cohort analysis by the same study group involving 60 adult patients with nosocomial bacteremic staphylococcal aureus pneumonia, no significant difference in the mortality or infected-related length of stay were found in comparing early appropriate antibiotic therapy at the onset of pneumonia versus late treatment using the same cut-off point of 44.75 hours.[40] Besides in the same study, there was no difference in the mortality between MSSA and MRSA pneumonia. It was argued that only 60 patients were involved in this study and such a small number of patients involved might not give an adequate power of the study to identify any genuine differences. From the above studies, it is still controversial

whether early empirical treatment to cover MRSA pneumonia is indicated. However if staphylococcal infection is strongly suspected, early antimicrobial therapy should be considered but from the above studies, the bottom line is 44.75 hours.

Choice of Antibiotic in Treating Staphylococcus Aureus Infection

One retrospective analysis of the two double-blind studies compared linezolid with vancomycin as the initial therapy in treating adult patients with gram-positive ventilator-associated pneumonia.[41] The group treated with linezolid had higher clinical cure rate and the odds ratios (OR) 1.8 for all patients, OR 2.4 for gram-positive VAP and OR 20.0 for MRSA VAP. The Kaplan-Meier survival curves also favoured linezolid therapy and the odds ratios of survival were 1.6 for all patients, 2.6 for gram-positive VAP and 4.6 for MRSA VAP. Concerning the paediatric population, a Phase III randomised, open label trial was conducted in comparing linezolid and vancomycin in the management of hospital-acquired pneumonia, catheter-related bacteremia and bacteremia of unknown source.[42] There was no differences between linezolid and vancomycin in the clinical cure rates of the above 3 kinds of infection. The only advantage in the linezolid treatment group was the lesser percentage of developing skin rash (0 versus 6.5%; p=0.009). Thus vancomycin is still the choice of drug in paediatric patients. The only advantage of linezolid may be that the antibiotic could be changed to the oral form when the condition becomes stable.

Suggested Management Protocol in Paediatrics

Guidelines for Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia have been published co-jointly by the American Thoracic Society and the Infectious Diseases Society of America.[4] Although it is mainly targeted at adult patients, a similar algorithm could be derived for paediatric patients (Figure 1). Based on the CDC criteria (Table 1), VAP is suspected clinically when there is an increase in sputum production or change in character of the purulent sputum from the endotracheal tube, and the CXR detects new lung infiltrate. Early quantitative or semi-quantitative culture using bronchoscopic or nonbronchoscopic approach should be obtained. Nonbronchoscopic BAL is an acceptable practice in paediatric patients in view of the technical difficulties. De-escalation treatment using broad-spectrum potent antibiotic(s), mostly two antibiotics, is then implemented promptly to cover the most likely pathogen(s) based on the local situation. The role of an early commencement of anti-staphylococcal antibiotic is still controversial. More studies in paediatrics are necessary to evaluate the efficacy of linezolid over vancomycin in treating staphylococcus aureus infection. The patient's clinical condition together with the laboratory parameters is monitored regularly. To reduce the chance of superinfection due to multi-drug resistance microorganism, single antibiotic of limited spectrum should be used once the sensitivity result is available. Shorter duration of antibiotic(s) (up to 8 days) is recommended for VAP except pneumonia caused by non-fermenting gram negative bacilli including Pseudomonas aeruginosa, in which short-course antibiotic treatment is associated with higher chances of relapse or superinfection.[32]

Prevention of Ventilator-associated Pneumonia

A few studies have investigated the issues to prevent the development of ventilator-associated pneumonia in paediatric setting. The most promising result only comes from the implementing good infection control measures together with proper nursing care.

Stress Ulcer Prophylaxis

Concerning stress ulcer prophylaxis, two paediatric studies showed that there was no effect of sucralfate on decreasing the risk of developing VAP when compared with ranitidine/omeprazole or no treatment.[43,44]

Selective Digestive Decontamination

Despite studies reporting the possible benefits of selective digestive decontamination in preventing VAP,[45] routine or indiscriminate use of selective digestive decontamination in preventing VAP should be cautioned as it may lead to emergence of antibiotic-resistant bacterial strains and superinfection by more virulent organism.[46] The guidelines published in 2003 by CDC in preventing health-care-associated pneumonia also holds reservation in giving a general recommendation on this issue, except that its use would probably be cost-effective on subsets of ICU patients, such as trauma and/or critically ill patients.[47]

Proper Infection Control Policy and Nursing Practice

The most important aspect in management of VAP is prevention. With the introduction of an educational program to respiratory care practitioners and ICU nurses, Babcock is able to demonstrate a reduction of VAP by 38-46%.[48] The education program includes a self-study module on

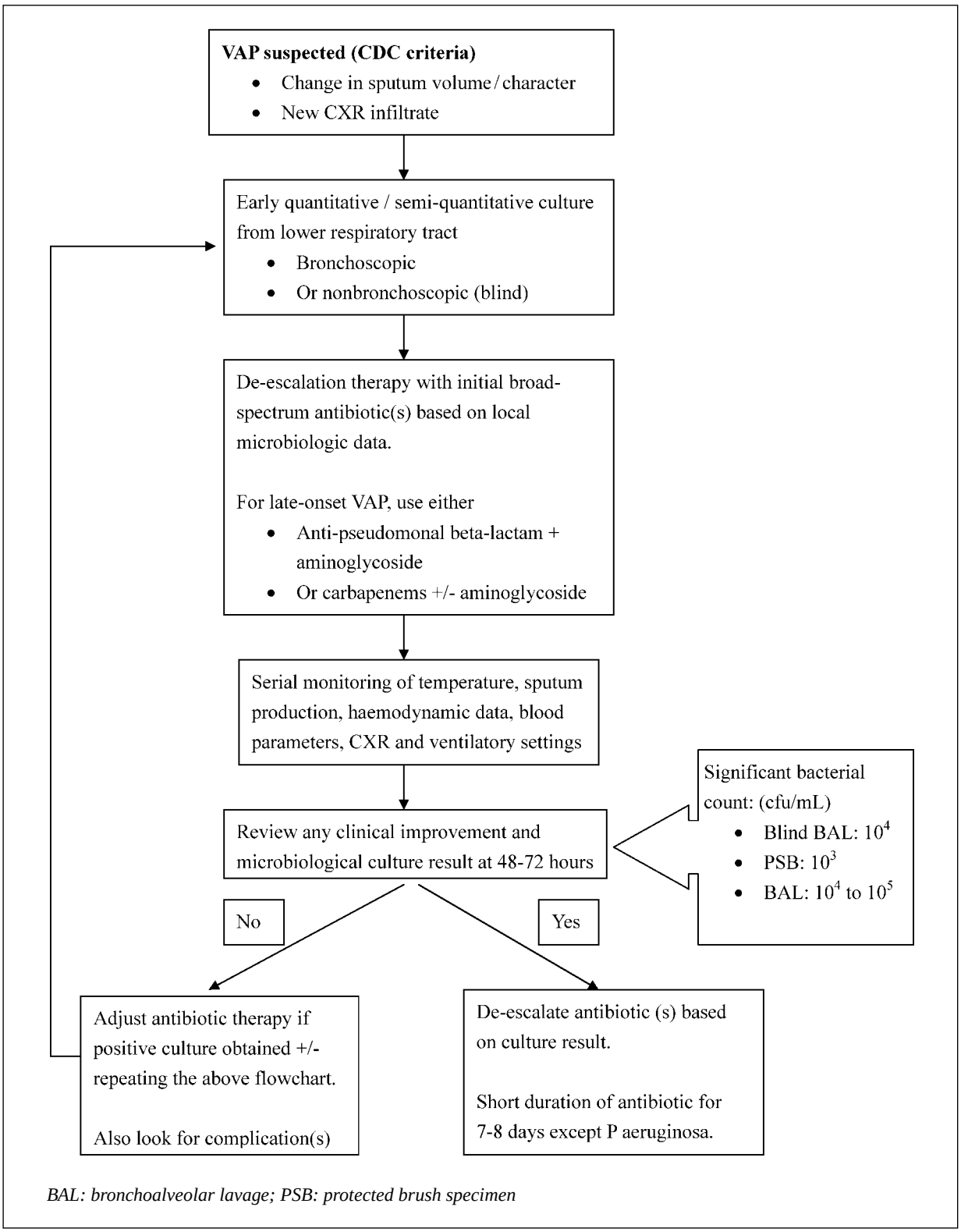

Figure 1 Suggested algorithm for paediatric patients with suspected ventilator-associated pneumonia (VAP).

the risk factors and strategies to prevent VAP, The essence of the preventive measures advocated in that module could be summarised by their acronym "WHAP VAP" , in which "W" stands for "wean the patient" as soon as possible, "H" for hand hygiene, "A" for aspiration precautions and "P" for "prevent contamination".

The guidelines published by CDC for preventing health-care pneumonia gives similar suggestion as mentioned in the above study module.[47] It also emphasises on strict handwashing practice, proper use of gloving, avoidance of nasal intubation and accidental extubation, as well as other nursing care issues. Non-invasive positive pressure ventilation is also recommended as it decreases the risk of pneumonia. However, the usefulness of heat-moisture exchanger mentioned in the above study module has been questioned by CDC due to inconsistent results from other studies. Further reviews and studies are necessary to evaluate the usefulness or cost-effectiveness of the following measures: comprehensive oral-hygiene program for ventilated patients; use of dual-lumen endotracheal tube to facilitate drainage of secretion around subglottic region; institution of strict-antibiotic-use control strategy in ICU, including scheduled change in the class of antimicrobial agents for empiric therapy of infection.

Conclusion

VAP is still an important disease entity in PICU though the number of patients is much lesser than that in adult ICU. Currently the management of paediatric VAP is mostly relied on the conclusion drawn from adult's studies. Hopefully in the near future after the consensus of the definition of NP/VAP in paediatric population and the collaboration between multiple paediatric centres, evidence-based recommendation could be drawn from the paediatric studies of adequate population size.

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