

The diagnostic dilemma of ventilator-associated pneumonia in critically ill children*

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Objective: A review of the existing literature on ventilator-associated pneumonia in children with emphasis on problems in diagnosis.

Data Sources: A systematic literature review from 1947 to 2010 using Ovid MEDLINE, PubMed, Cochrane Central Register of Controlled Trials, and ISI Web of Science using key words “ventilator associated pneumonia” and “children.” Where pediatric data were lacking, appropriate adult studies were reviewed and similarly referenced.

Study Selection: Two hundred sixty-two pediatric articles were reviewed and data from 48 studies selected. Data from 61 adult articles were also included in this review.

Data Extraction and Synthesis: Ventilator-associated pneumonia is the second most common nosocomial infection and the most common reason for antibiotic use in the pediatric intensive care unit. Attributable mortality is uncertain but ventilator-associated pneumonia is associated with significant morbidity and cost. Diagnosis is problematic in that clinical, radiologic, and microbiologic criteria lack sensitivity and specificity relative to autopsy histopathology and culture. Qualitative tracheal aspirate cultures are commonly used in diagnosis but lack specificity. Quantitative tracheal aspirate cultures have sensitivity (31–69%)

and specificity (55–100%) comparable to bronchoalveolar lavage (11–90% and 43–100%, respectively) but concordance for the same bacterial species when compared with autopsy lung culture was better for bronchoalveolar lavage (52–90% vs. 50–76% for quantitative tracheal aspirate). *Staphylococcus aureus* and *Pseudomonas* species are the most common organisms, but microbiologic flora change over time and with antibiotic use. Initial antibiotics should offer broad-spectrum coverage but should be narrowed as clinical response and cultures dictate.

Conclusions: Ventilator-associated pneumonia is an important nosocomial infection in the pediatric intensive care unit. Conclusions regarding epidemiology, treatment, and outcomes are greatly hampered by the inadequacies of current diagnostic methods. We recommend a more rigorous approach to diagnosis by using the Centers for Disease Control and Prevention algorithm. Given that ventilator-associated pneumonia is the most common reason for antibiotic use in the pediatric intensive care unit, more systematic studies are sorely needed. (*Pediatr Crit Care Med* 2011; 12:286–296)

KEY WORDS: ventilator; pneumonia; antibiotics; diagnosis; tracheal aspirates; bronchoalveolar lavage; nosocomial infection

Nosocomial infections are a major challenge in critical care medicine worldwide and are associated with significant increases in mortality, morbidity, and duration and cost of hospitalization. The Centers for Disease Control and Prevention (CDC) estimates there are 1.7 million nosocomial infections with approximately

90,000 attributable deaths yearly in the United States alone (1). Although regarded as an inevitable accompaniment of advanced medical care, the incidence of nosocomial infection in the United States is greater than all currently notifiable diseases and mortality exceeds that of any of the top ten leading causes of death (2, 3).

Intensive care units (ICUs) have the highest incidence of infections because of multiple risk factors, including frequent invasive procedures, use of medical devices, and prolonged exposure to multi-drug-resistant organisms (4–7). Gaynes et al showed that three or more therapeutic interventions or the use of any medical device correlated strongly with infection rates. Use of medical devices in pediatric intensive care units (PICUs) is comparable to that in adult ICUs and is a major factor in rates of nosocomial infections. The incidence of nosocomial infections in PICUs was reported to be as high as 23.5% in one European study (5), but the mean cumulative incidence of noso-

comial infections (defined as the number of infections per 100 discharges) in US PICUs has remained relatively constant at 14% (6, 8). The attributable mortality of PICU nosocomial infections has been estimated at 5–11% (9).

Pneumonia is second only to bacteremia as a cause of nosocomial infections in the PICU, accounting for 23% of nosocomial infections in a recent study conducted across 35 US PICUs (5) and 15% in studies by both the National Nosocomial Infections Surveillance System (NNIS) and Preventive Pediatric Network (5). In contrast, the European Multi-center Trial reported that pneumonia was the most common PICU nosocomial infection and was responsible for 53% of infections (8). The risk of developing nosocomial pneumonia (ventilator-associated pneumonia [VAP]) is six- to 13-fold greater in mechanically ventilated patients. Indeed, VAP is the most common infection encountered in mechanically ventilated patients (8) and 25–95% of

***See also p. 357.**

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The authors have not disclosed any potential conflicts of interest.

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DOI: 10.1097/PCC.0b013e3181fe2ffb

all nosocomial pneumonias occur in patients on mechanical ventilation (10).

Until recently, VAP was defined by the CDC as “pneumonia that develops in patients on mechanical ventilation for more than 48 hrs” (11). However, recognizing that the 48-hr time point may result in delayed diagnosis and treatment, the CDC guidelines were altered in 2007 to indicate that “there is no minimum period of time that the ventilator must be in place” to diagnose VAP (12). Based on the time of onset of pneumonia, VAP can be further categorized into “early” (within 1–4 days of ventilation) and “late” (>4 days of ventilation). Etiologically, in adults, late VAP is more commonly caused by antibiotic-resistant organisms and has a poorer prognosis relative to early VAP (13, 14), although this difference was not observed in the pediatric age group (15).

The pathogenesis of VAP begins with colonization of the lower respiratory tract from bacteria that enter the airway through the endotracheal tube. The complex interactions between the host's defenses and the virulence and quantities of bacteria establishing residence in the airways determine whether colonization will progress to actual infection. Tracheal colonization and tracheobronchitis (ventilator-associated tracheobronchitis) are thought to precede VAP, but it is difficult to distinguish among the three (16). In adults, tracheal colonization alone was not an independent risk factor for the development of VAP (17). More studies are needed to define ventilator-associated tracheobronchitis and determine whether there is a subsequent reduction in VAP incidence with antibiotic treatment (18, 19).

Given the life-threatening potential of VAP in critically ill patients, especially children, prompt and appropriate antibiotic therapy is essential. Accurate diagnosis of VAP, however, is problematic. A variety of invasive and noninvasive methods for microbiologic diagnosis are described and are generally paired with clinical and radiologic criteria, but none has proven adequately sensitive and specific against the gold standard of autopsy or direct lung tissue culture (20). The variability in diagnostic criteria used makes interpretation of published studies difficult at best, particularly in the pediatric literature, and greatly contributes to the indiscriminate use of antibiotics for “suspected VAP” in the PICU. In fact, a study in 1999 concluded that the greatest

reduction in antibiotic use in children would result from measures that can rule out VAP (21). This review focuses on the epidemiology, etiology, risk factors, therapy, and preventive measures of VAP with special emphasis on the diagnosis and its associated challenges in the pediatric population.

METHODOLOGY

A systematic literature search was done for the years 1947–2010 using the term “ventilator-associated pneumonia” limited to “children aged 0–18 yrs,” “human,” and “English language.” The search yielded 262 articles in PubMed, 190 in Ovid MEDLINE, nine in Cochrane Central Register of Controlled Trials, and 207 articles in ISI Web of Science databases. Abstracts of all articles and full texts of all relevant articles were reviewed by two of the authors (V.V. and D.F.W.). All articles with data on the epidemiology, risk factors, diagnostic techniques, antibiotic use, and preventive measures of VAP were included. References from these articles were also reviewed and new articles were included when appropriate. Articles with data not specific to VAP were excluded. Where specific pediatric data were absent or limited, adult studies were reviewed and are referenced.

The Epidemiology of VAP in Children

According to the NNIS, the incidence of VAP in US PICUs declined from six to 2.1 per 1000 ventilator days from 1999 to 2008 (22, 23), although another study reported a rate of 11.6 per 1000 ventilator days in 2002 (7). The incidence of VAP in other regions of the world may differ. Saudi Arabia, for example, reported an incidence of 8.9 per 1000 ventilator days (24). The 1999 NNIS study of 61 PICUs reported the highest incidence in children between 5 and 12 yrs (22), whereas a study by the Preventive Pediatric Network in 2002 reported the incidence in the 0–5 yrs age group was twice that of the 5- to 12-yr age group (5). The variable incidence may be consequent to several factors, among them differences in institutions, study methodologies (particularly the frequency and methods used for surveillance), and in the definition of VAP. In an effort to define VAP more precisely, the NNIS revised its diagnostic criteria in 2002 and introduced definitions for VAP diagnosis specific to age and

birth weight (25). Surveillance studies demonstrate that hospitals use modified NNIS criteria that underestimate the incidence of VAP (26). Pooled data on VAP, therefore, largely depend on the diagnostic criteria used by the majority of the participating institutions and fluctuations in the data likely reflect these differences. Pooled data in adults indicate VAP is associated with the highest mortality among nosocomial infections (1, 27), although heterogeneity among the studies is so high that a precise estimate of attributable mortality is difficult (27). The relatively lower incidence of VAP in children coupled with the difficulties in diagnosis make it problematic to establish a causal relationship of death with VAP. Although some PICUs (24) and neonatal ICUs (28, 29) studies have failed to show an association of VAP with mortality, a recent study reported a twofold mortality increase in children with VAP (19.1%) compared with those without (9.1%) (10). In addition to the time of onset of VAP, age may be an important determinant of lethality. Preterm neonates on mechanical ventilation >30 days who developed VAP had increased mortality (30), but, in contrast, no mortality increase was observed in children <18 yrs (mean age, 5.5 yrs) on mechanical ventilation >8 days (20% vs. 21%) (7).

VAP is clearly associated with increased morbidity. Multiple studies have linked VAP to an increased duration of ventilation of as much as 5–11 days and longer PICU stay by 20–34 days (7, 24, 31). The European Multicenter Trial found that VAP doubled the duration of PICU stay (8). Prolonged stay in the PICU resulting from VAP is also associated with increased hospital costs (32). A recent study in neonatal NICU and PICU units in California found that VAP increased costs by an average of \$55,882 (31).

Risk Factors for VAP in Children

The duration of mechanical ventilation is considered to be the greatest risk factor for the development of VAP (5, 10). Although there are no comparable data in children, in adult patients, the risk of VAP was reported to be 6.5% at 10 ventilator days and increases 1% with each subsequent ventilator day (33). Another study of 1014 adults found that the risk of VAP was maximal on day 5 but decreased thereafter (34).

Other known risk factors for development of VAP in children include genetic syndromes, immune deficiency, tracheal reintubation, transport out of the PICU, surgery, continuous enteral feedings, bronchoscopy, and medications, specifically steroids, H2 receptor antagonists, immunosuppressants, neuromuscular-blocking agents, narcotics, and prior antibiotics (7, 24, 31, 35, 36). Bloodstream infections (7, 30) and gastroesophageal reflux (37) have also been significantly associated with development of VAP in children. Trauma is associated with a higher incidence of VAP (13.8/1000 vs. 2.9/1000 ventilator days for nontrauma patients), but, unlike with adult trauma patients, there appears to be no increase in attributable mortality in pediatric trauma victims (38).

Diagnosis of VAP in Children

Direct examination and culture of lung tissue is the accepted gold standard for diagnosis of VAP (39). Because of the attendant risks, however, lung biopsy is rarely performed in immunocompetent children and autopsy data are increasingly rare. We are left with clinical, microbiologic, and radiologic criteria to diagnose VAP, most of which have been

derived primarily from adult studies. Data comparing these criteria with histopathology have also been obtained primarily from studies in adults, leaving us to extrapolate from these studies to treat children.

Clinical Criteria

Clinical criteria for diagnosing VAP include fever, leukocytosis or leukopenia, purulent secretions, new or worsening cough, dyspnea, tachypnea, crackles or bronchial breath sounds, and worsening gas exchange. These criteria are nonspecific and their sensitivity and specificity relative to pathology is poor (36, 40, 41). The clinical criteria for VAP are in many cases indistinguishable from those for generalized sepsis or systemic inflammatory response syndrome (33, 42). Consequently, clinical findings are generally considered in conjunction with radiology and microbiologic findings.

Radiologic Criteria

Radiologic criteria include the presence of new or progressive pulmonary infiltrates, cavitation, air bronchograms, or pneumatocele on chest radiograph. Air bronchograms have the highest correla-

tion with pneumonia with a sensitivity of 58–83%. In comparison, “evolving infiltrates” has a sensitivity of 50–78% (43, 44). Chest x-ray findings have only limited specificity (33–42%), however, because pneumonia in patients on mechanical ventilation has no consistent correlation to any of the radiologic signs (44). Radiologic criteria are especially difficult in children (particularly infants) because of the frequent development of atelectasis that is often indistinguishable from consolidation (36, 45). Acute respiratory distress syndrome, alveolar hemorrhage, and pulmonary infarction may also mimic consolidation radiologically (46). For these reasons it is recommended that if clinical and radiologic criteria suggest the diagnosis of VAP, microbiologic tests should be pursued for confirmation (47).

Microbiologic Criteria

Microbiologic evidence of the presence of pathogenic bacteria is critical because it can establish the causative organism and thereby guide treatment. Culture specimens can be obtained by a variety of invasive and noninvasive methods, as is discussed subsequently, but comparisons to histopathology and mi-

Table 1. Comparison of sensitivities and specificities of the various diagnostic techniques against the reference standard of histopathology and culture of biopsy specimens

Adult Studies	No. of Patients	Reference Standard Culture (>10 ³ CFU/g)	By Reference Standard		Tracheal Aspirate >10 ⁵ CFU/mL		Percent of Samples With Same Organism as Autopsy Culture ^a
			Positive for VAP	Negative for VAP	SN, %	SP, %	
Papazian et al, 1995	38	Histopathology and culture of biopsy	12	20	67	95	76
Fabregas et al, 1999	25	Histopathology and culture of biopsy	13	12	69	92	
Balthazar et al, 2001	37	Histopathology and culture of biopsy	20	17			
Torres et al, 2000	25	Histopathology and culture of biopsy	6	19	50	67	67
Torres et al, 1994	30	Histopathology alone	23	2	31	55	
Marquette et al, 1995	28	Histopathology alone	18	12	44 ^b	48 ^b	50
Torres et al, 1996	25	Histopathology alone	19	9	56	86	
Kirtland et al, 1997	39	Histopathology alone	9	30			
		Culture of biopsy specimen alone	16	23	31	100	69

CFU, colony-forming units; BAL, bronchoalveolar lavage; VAP, ventilator-associated pneumonia; SN, sensitivity; SP, specificity.

^aComparisons were made only for qualitative presence of one bacterial species in both specimens; ^bbronchoscopic blind aspirates.

crobiology obtained at autopsy have failed to demonstrate the superiority of one technique over another (Table 1). Causative organisms were missed altogether in 17–83% of cases (48), whereas they differed from biopsy cultures in as many as 10–83% of the cases, the difference being least with bronchoalveolar lavage. Differences in techniques, areas sampled at autopsy, numbers of specimens assessed, and statistical representation of data have all contributed to this disparity (49). Prior antibiotic use may also affect accuracy (40, 48), although not all studies agree (31). Furthermore, the correlation between the histopathology and microbiology of autopsy specimens is surprisingly poor (40, 49, 50), suggesting that neither can be used as the “gold standard” alone. Consequently, the combination of histopathology and microbiology has become the reference standard (48). The different techniques for obtaining cultures and their relative merits and limitations are as follows. *Bronchoscopic Bronchoalveolar Lavage.* Bronchoalveolar lavage (BAL) is the most widely used because of its ability to obtain specimens closest to the affected tissue while minimizing contamination (51–53). Mini-BAL is a modification whereby a smaller vol-

ume of saline is injected. Protected specimen brush substitute a brush to obtain secretions instead of saline instillation and aspiration. BAL has been extensively evaluated in adult studies. Two multicenter studies comparing the prognosis of patients with VAP identified by BAL vs. tracheal aspirate (TA) came to opposite conclusions. One study reported that bronchoscopic techniques had better outcome and less antibiotic use (52), whereas a subsequent study found no difference in hospital mortality, length of stay, duration of mechanical ventilation, or antibiotic use (54). Whereas the CDC recommends BAL cultures for the diagnosis of VAP, BAL has technical limitations and invasive risks in critically ill children (55, 56). Similarly, although protected specimen brush has a specificity and sensitivity comparable to BAL (57, 58), size considerations preclude its use in most children (45). Other limitations arguing against routine use of BAL are its higher cost, availability of skilled personnel, and the increased risk and difficulties in patients requiring high levels of mechanical ventilation (59, 60).

Nonbronchoscopic Bronchoalveolar Lavage. Nonbronchoscopic BAL (NB-BAL) has diagnostic accuracy comparable

to BAL and may be more suitable for children (55, 56, 61, 62). In this method, a double lumen plugged catheter is inserted into the endotracheal tube and advanced blindly until slight resistance is felt. The inner catheter is then extended and the plug expelled. Aliquots of warm sterile saline are injected, and the aspirate is collected through the catheter. Three adult studies comparing NB-BAL with pathology reported a sensitivity of 39%, 63%, and 80% and specificity of 100%, 83%, and 66%, respectively (Table 1) (48, 49, 63). A study in children comparing NB-BAL with pathology reported 100% sensitivity and specificity but was based on the results of just 17 autopsies (55). The concordance for repeated NB-BAL was reported to be 93% (61). In the pediatric population, the safety of NB-BAL has been primarily studied in infants. The first study reported no complications (64), but subsequent studies reported a few minor complications with transient decrease in oxygen saturation being the most common (65–67). A later study found that 7% had significant complications that required inotropes or an increase in ventilation for stabilization (68). In view of these associated risks, more studies are needed before this tech-

Table 1.—Continued

BAL >10 ⁴ CFU/mL			Nonbronchoscopic BAL >10 ⁴ CFU/mL			Protected Specimen Brush >10 ³ CFU/mL		
SN, %	SP, %	Percent of Samples With Same Organism as Autopsy Culture ^a	SN, %	SP, %	Percent of Samples With Same Organism as Autopsy Culture ^a	SN, %	SP, %	Percent of Samples With Same Organism as Autopsy Culture ^a
58	95	68				42	95	74
77	58		39	100		62	75	
90	94	90						
83	68	83	63	83	17	67	75	83
36	59		16	77		24	54	
50	45	52				36	50	59
47	100					58	89	
35	43		22	76				
11	80					33	63	
63	96	77				81	70	72

nique can be widely used across all age groups.

Tracheal Aspirate. TA involves culturing of secretions obtained through suctioning the endotracheal tube (as opposed to obtaining secretions through bronchoscopic BAL or advancing and wedging a catheter blindly as per NB-BAL). This approach has the advantage that sequential or repeated analysis can be safely performed. Feasibility, safety, and cost considerations clearly favor TA over other methods (54, 59, 69). Unfortunately, TA suffers from low specificity as a result of contamination from upper respiratory tract organisms (58, 62, 70). Although both qualitative and quantitative analyses are possible, TA cultures are generally analyzed qualitatively. The significance of TA cultures, especially qualitative cultures, in the diagnosis of VAP is unclear. The cultures are seldom "sterile" and the microbes isolated are often contaminated with oropharyngeal flora. Oropharyngeal flora are known to change determined by the individual's environment and prior antibiotic use. Sequential monitoring of TA in PICU patients has shown a trend toward change in flora from *Staphylococcus aureus* to *Pseudomonas* and *Candida* species along with the emergence of multidrug-resistant organisms (71). It is assumed that colonization of the tracheobronchial tree by pathogens precedes infection, but qualitative analysis of aspirates cannot definitively distinguish between the two (72). The value of TA cultures in initiating, continuing, or changing antibiotic therapy is therefore widely debated. Although some would argue that it occurs at the cost of sensitivity (73, 74), quantitative TA may improve specificity in distin-

guishing between infection and colonization (colony-forming units >10⁵ units). In fact, autopsy studies indicate that the specificity of quantitative TA is comparable to all other techniques (Table 1). It is rarely used in routine clinical practice, however, making the data insufficient for comparison.

Gram Stain. Gram stain of aspirates obtained by TA or BAL are often used to guide initial antibiotic therapy because results are available immediately and appropriate initial antibiotic therapy may improve clinical outcome (52). The parameters studied and cutoff values to predict VAP vary widely. Commonly used Gram stain parameters include: 1) >25 polymorphonuclear leukocytes per high-power field; 2) more than 2% inflammatory cells; 3) presence of polymorphonuclear leukocyte cells with intracellular organisms (ICO) with criteria for positivity ranging from 2–10% (75, 76). Autopsy studies show a broad range in sensitivity and specificity. One study reported that direct examination of BAL fluid had a specificity of 100%, comparable to mini-BAL or NB-BAL; however >7% of ICO on BAL fluid had low (>10% ICO on Gram examination of BAL fluid had a specificity of 100%, comparable to mini-BAL or NB-BAL; however >7% of ICO on BAL fluid had low (10% ICO on Gram-negative stain for BAL had a sensitivity and specificity of 50% and 55%, respectively, with a slight increase in sensitivity to 75% when >5% ICO was used (75). A third study showed that ICO in BAL fluid across all percentages was 37% sensitive but 100% specific in predicting VAP (78). However, >10% ICO from TA samples had 100% sensitivity and 86% specificity in predicting VAP (75, 77). The absence of

uniform standards in reporting results of Gram stains limits their value in the diagnosis of VAP (42, 79–81).

Etiological Organisms. In contrast to pneumonia in nonventilated patients, Gram-negative bacteria predominate in VAP. In the PICU, *Pseudomonas aeruginosa* is the most common followed closely by the Gram-positive organism, *S. aureus* (Table 2) (5). The predominance of *Pseudomonas* was shown in a study documenting the changes in tracheal flora over time by serial tracheal cultures (71). *Pseudomonas* was increasingly isolated over days of intubation and by the fourth day exceeded all other species in tracheal aspirate cultures. *Pseudomonas* is twice as common in PICUs relative to neonatal ICUs (33.3% vs. 17%), whereas *S. aureus* is twice as common in neonatal ICUs (38% vs. 17.6%) (15). The incidence of polymicrobial infection has been reported at 38% in the PICU (31) and 58% in the neonatal ICU (30).

Clinical Pulmonary Infection Score Criteria

The Clinical Pulmonary Infection Score (CPIS) was developed by Pugin et al (82) as a means of overcoming the limited sensitivity and specificity of isolated techniques through a combination of six clinical, radiologic, and microbiologic criteria: temperature, white cell count, sputum, oxygenation, culture of tracheal aspirates, and radiology. Each criterion is graded from 0 to 2 and a total score of >6 points suggests a diagnosis of VAP. In comparison to pathology, the CPIS score had 72–7% sensitivity and specificity between 42% and 85% (49, 83). The wide range in specificity has been attributed to

Table 2. Microbiology of ventilator-associated pneumonia

Pediatric Studies With "TA/BAL or Both"	Bacteria (%) → (in the Order of Decreasing Predominance)						
	<i>Pseudomonas</i>	<i>Staphylococcus aureus</i>	<i>Klebsiella</i>	<i>Enterobacter</i>	<i>Escherichia coli</i>	<i>Serratia</i>	<i>Haemophilus</i>
Bigham et al, 2009	19	14.3		7.1		9.5	9.5
Srinivasan et al, 2009	2.6	23.1		7.7	10.3	5.1	10.3
Almuneef et al, 2004	56.8	18.9	10.8	2.7			
Gaynes et al, 2003	10	27.8	7.2	18.1	5.0	4.7	
Grohskopf et al, 2002	10	30	10	10	5	5	
Elward et al, 2002	29.4	11.8	14.7	5.9	2.9	2.9	8.8
Raymond and Aujard, 2000	35.6	18.6	6.7	2.5		6.7	
Richards et al, 1999	21.8	16.9	5.3	9.3	3.6	3.6	10.2
Labenne et al, 1999	27.5	37.9	6.0		3.4		

TA, tracheal aspirate; BAL, bronchoalveolar lavage; CONS, coagulase-negative *Staphylococcus*.

^aThe specimens in the included studies were obtained by TA or BAL or both. When not reported, it is unclear if specific bacteria in the isolate was nonexistent or not examined for.

interobserver variation and has led to several modifications in its use. CPIS has also been used to determine treatment duration in patients (84). Some studies have used the CPIS score as their reference standard to compare the accuracies of diagnostic technique (85). There are no data regarding CPIS in children.

CDC Criteria

Similar to the CPIS, the CDC/NNIS criteria for the diagnosis of VAP include clinical, radiologic, and bacteriologic evidence (Fig. 1) (12, 86). Several studies have used the CDC criteria as their reference standard to compare the accuracies of diagnostic techniques (87, 88) and these have become the standard definition of VAP in many academic US teaching hospitals (89).

Antibiotic Therapy in VAP

VAP is the most common indication for initiation of empirical antibiotics in the PICU, accounting for nearly half of all antibiotic days (21). Clinical guidelines for initial antibiotic therapy in VAP in children have not been published (25) and practice is inconsistent and largely based on adult studies (53, 90). Several adult studies have shown that delay in initiation or inadequate initial antibiotic therapy is associated with poor prognosis (81, 91, 92). Important factors in the choice of empiric antibiotics include the predominant causative pathogens, antibiotic resistance patterns in the community, duration of intubation and hospitalization, prior or current antibiotic treatment, and disease conditions predisposing to specific pathogens (59, 70). Ini-

tial monotherapy with a broad-spectrum antibiotic has been shown to be effective in adult patients with CPIS scores <6 when the pathogens did not include *P. aeruginosa* (59). In another study, outcomes comparing mono- vs. polytherapy in adults with VAP were similar (93). In term infants, monotherapy with cefepime was safe and effective compared with ceftazidime and required less frequent dosing (94). Unfortunately, monotherapy carries the risk of undertreatment and potentially promoting drug resistance, particularly in patients with prior antibiotic therapy or late-onset VAP, both of which are strongly associated with multidrug-resistant organisms (13). This is the rationale for initial broad-spectrum antibiotics covering all likely pathogens (25, 36). Studies determining the optimal duration of antibiotic treatment are sparse (25). When preceded by appropriate initial empiric antibiotics, therapy for 8 vs. 15 days in adults showed no difference in mortality, morbidity, or cost (59, 95). Adult studies also suggest that it is safe to discontinue antibiotics after 3 days in patients with negative cultures and CPIS scores <6 (84, 95, 96). Prolongation of antibiotics despite negative culture reports accounts for 15% of all antibiotic days in children (21) but is often prompted by concern that cultures can be negative despite infection (97). Polytherapy has consequently resulted in greatly increased antibiotic use. A study of antibiotic prescription patterns in children showed an almost threefold increase in the use of cephalosporins from 1984–1994 alone (98). There are significant risks associated with prolonged use (>7 days) of broad-spectrum antibiotics, most

importantly colonization and superinfection with pathogenic and multidrug-resistant organisms (84). Prior exposure to broad-spectrum antibiotics has also been shown to lower the susceptibility to other potent antibiotics (13, 99). Furthermore, antibiotic treatment does not appear to eradicate even sensitive organisms. One study showed that despite optimum therapy with antibiotics having *in vitro* sensitivity and clinical resolution of signs and symptoms of VAP, multiple organisms including *Enterobacteriaceae*, *S. aureus*, *Haemophilus influenzae*, and *P. aeruginosa* were still recovered from subsequent TA cultures (100). Although these observations may relate more to the diagnostic accuracy and the use of TA cultures *per se*, they support a more conservative approach to the antibiotic therapy in suspected VAP (101).

Ensuring adequate coverage while avoiding overtreatment in suspected VAP is a clinical dilemma. Delayed or inadequate treatment is associated with poorer outcomes, whereas polypharmacy can result in the emergence of new and more virulent strains of bacteria. In line with adult recommendations (87, 101), the acceptable solution in children (Fig. 2) is to initiate broad-spectrum therapy and then narrow antibiotic coverage guided by culture results along with clinical and radiologic findings (24, 35, 58). As eloquently stated by Niederman (91), “the key decision point is not whether to start antibiotics but whether to discontinue them at day 2–3.” Although of limited diagnostic value, biomarkers like C-reactive protein or procalcitonin may be useful adjuncts to clinical signs in assessing treatment response (102–104). Soluble triggering

Table 2.—Continued

Bacteria (%) → (in the Order of Decreasing Predominance)						
<i>Streptococcus</i>	<i>CONS</i>	<i>Stenotrophomonas</i>	<i>Enterococcus</i>	<i>Acinetobacter</i>	<i>Candida</i>	Other Fungi
4.8		2.4			2.4	
2.6	5.1					2.6
2.7		5.4		5.4		
	1.8		1.3	6.9		
5.9		2.9	5.9		8.8	
	7.6				11.9	
3.4	0.9		1.0	3.1	2.0	0.5
13.0	6.0	3.4			3.4	

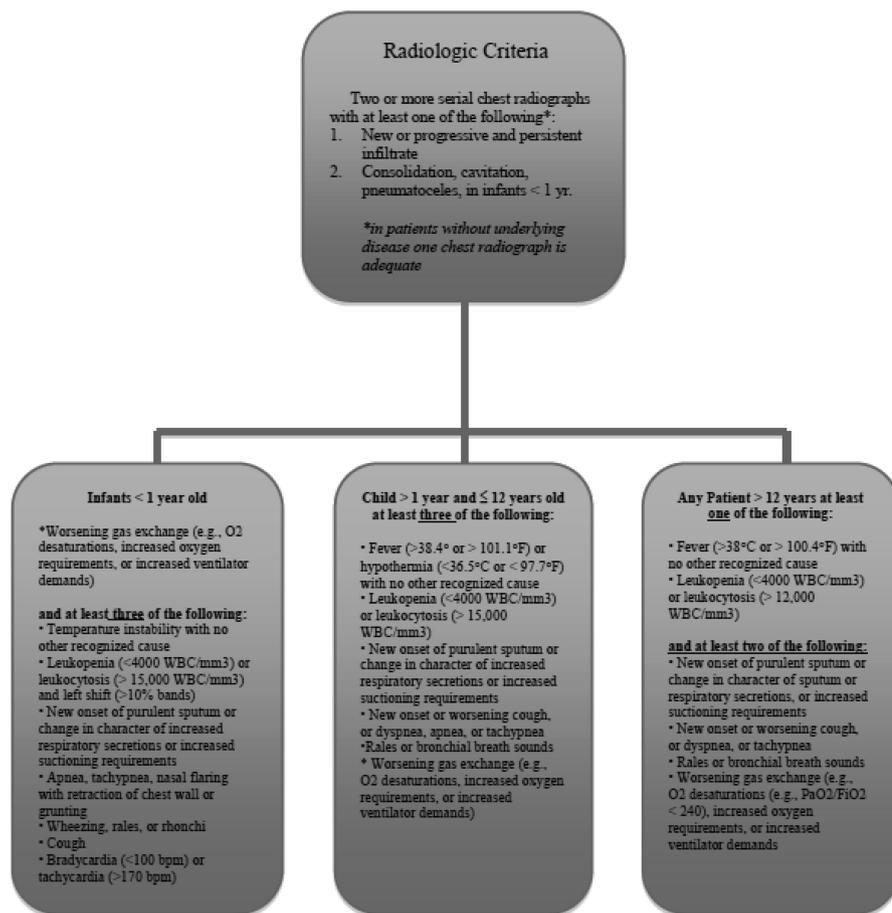


Figure 1. Centers for Disease Control and Prevention algorithms for clinically defined pneumonia. 1) Occasionally, in nonventilated patients, the diagnosis of health care-associated pneumonia may be quite clear on the basis of symptoms, signs, and a single definitive chest radiograph. However, in patients with pulmonary or cardiac disease (for example, interstitial lung disease or congestive heart failure), the diagnosis of pneumonia may be particularly difficult. Other noninfectious conditions (for example, pulmonary edema from decompensated congestive heart failure) may simulate the presentation of pneumonia. In these more difficult cases, serial chest radiographs must be examined to help separate infectious from noninfectious pulmonary processes. To help confirm difficult cases, it may be useful to review radiographs on the day of diagnosis, 3 days before the diagnosis, and on days 2 and 7 after the diagnosis. Pneumonia may have rapid onset and progression but does not resolve quickly. Radiographic changes of pneumonia persist for several weeks. As a result, rapid radiographic resolution suggests that the patient does not have pneumonia but rather a noninfectious process such as atelectasis or congestive heart failure. 2) Note that there are many ways of describing the radiographic appearance of pneumonia. Examples include, but are not limited to, “air-space disease,” “focal opacification,” and “patchy areas of increased density.” Although perhaps not specifically delineated as pneumonia by the radiologist, in the appropriate clinical setting, these alternative descriptive wordings should be seriously considered as potentially positive findings. 3) Purulent sputum is defined as secretions from the lungs, bronchi, or trachea that contain ≥ 25 neutrophils and ≤ 10 squamous epithelial cells per low power field ($\times 100$). If your laboratory reports these data qualitatively (eg, “many WBCs” or “few squames”), be sure their descriptors match this definition of purulent sputum. This laboratory confirmation is required because written clinical descriptions of purulence are highly variable. 4) A single notation of either purulent sputum or change in character of the sputum is not meaningful; repeated notations over a 24-hr period would be more indicative of the onset of an infectious process. Change in character of sputum refers to the color, consistency, odor, and quantity. Threshold values for cultured specimens used in the diagnosis of pneumonia. Specimen collection/technique values (CFU, colony-forming units). 1) Open-lung biopsy specimens and immediate post-mortem specimens obtained by transthoracic or transbronchial biopsy. Lung parenchyma $>10^4$ CFU/g tissue; 2) bronchoscopically obtained specimens, bronchoalveolar lavage $>10^4$ CFU/mL, protected specimen brushing $>10^4$ CFU/mL; 3) nonbronchoscopically obtained (blind) specimens, bronchoalveolar lavage $>10^4$ CFU/mL, protected BAL $>10^4$ CFU/mL. WBC, white blood cells.

receptor expressed on myeloid cells-1 in the BAL fluid has also been studied as a predictor of VAP in adults (105, 106). As previously mentioned, the fallibility of the various diagnostic techniques in reflecting the prevailing microbial status makes their use to guide therapy somewhat tenuous. Unfortunately, our clinical assessment tools are far from perfect (20). More studies are needed to formulate guidelines for antibiotic use in the pediatric age group.

Preventive Measures

The CDC guidelines recommend standard precautions, including washing hands before and after contact with patients and secretions, wearing gowns before procedures, and changing breathing circuits of ventilators only when they are visibly soiled (107). Indeed, changing the ventilator circuit every 7 days as opposed to 3 did not increase VAP incidence in the PICU but saved approximately \$22,000 a year in costs (108). Lateral positioning of infants has been found to decrease tracheal colonization and reduce the incidence of VAP (109). However, more studies are needed to confirm the consistency of these observations throughout the pediatric age group. Recommended preventive measures in adults include head-of-bed elevation, orotracheal (rather than nasotracheal) intubation when possible, closed endotracheal suctioning, subglottic drainage, and change of heat or moisture exchangers every 5–7 days (102, 107, 110). Use of probiotics (111), specialized endotracheal tubes (112, 113), decontamination of the oropharynx and digestive tract (115), and use of aerosolized antibiotics (115) are newer approaches to decrease VAP in adults. Data from randomized control trials indicate that use of probiotics (111), oral decontamination using antiseptics (116), and aerosolized antibiotics (115) lower the incidence of VAP but did not reduce mortality or the duration of mechanical ventilation. Data on the use of specialized endotracheal tubes are insufficient to comment on the benefits in mortality, duration of ventilation, and safety (112, 113). The major limiting factor in these studies is the timing and appropriateness of antibiotic therapy, which could contribute significantly to the observed outcomes (111). The effect of early tracheostomy on the incidence of VAP has been studied in randomized controlled trials in adults with equivocal results (117–121). The risks

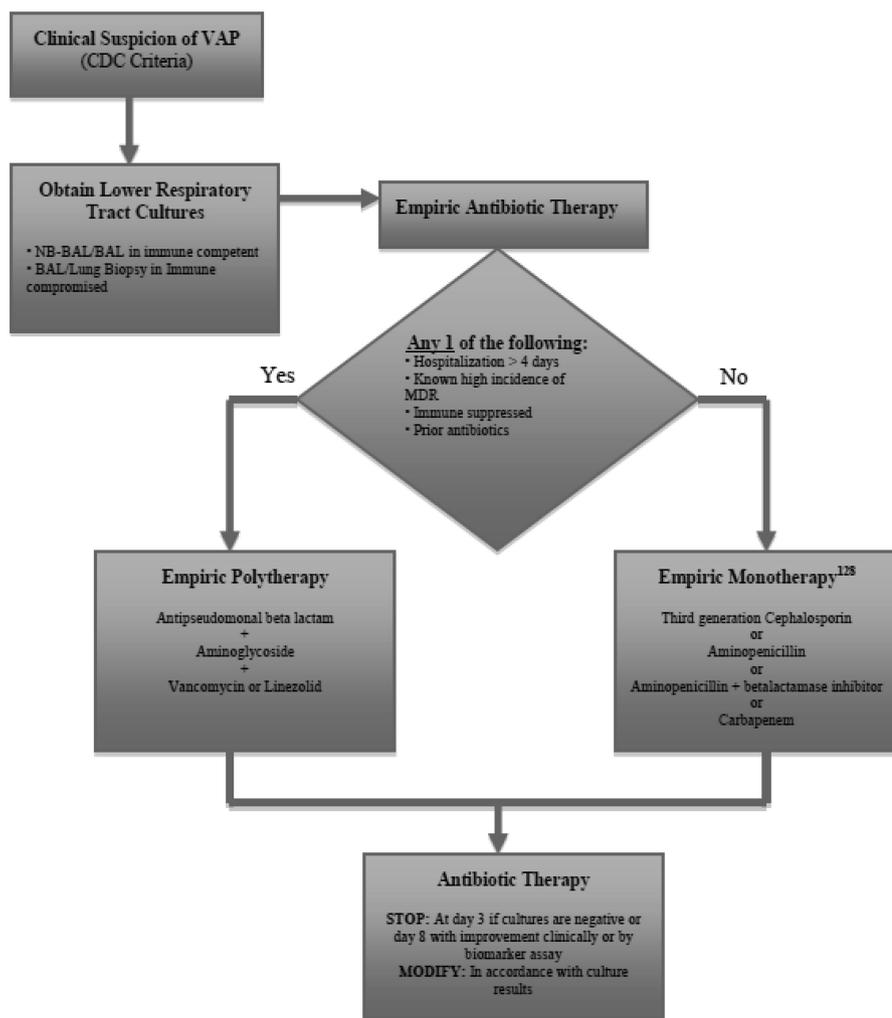


Figure 2. Treatment algorithm for ventilator-associated pneumonia (VAP). CDC, Centers of Disease Prevention and Control; BAL, bronchoalveolar lavage; NB-BAL, nonbronchoscopic BAL; MDR, multi-drug resistance.

and benefits of tracheostomy in children are more complex and this issue has not been studied in children. The “bundled” approach reported in adults (122–124) and recently by Bigham et al in children may be more effective (11). In addition to following CDC guidelines, Bigham et al used simple and inexpensive measures that included head end-of-bed elevation, drainage of ventilator circuit before repositioning patient, drainage of the ventilator circuit condensate every 2–4 hrs, rinsing of oral suction devices after use and storage in a plastic bag when not in use, regular mouth care every 2–4 hrs, and, whenever possible, using an endotracheal tube with dorsal lumen above the endotracheal tube cuff to help suction secretions. These measures aimed at reducing colonization of the tracheobronchial tree and aspiration of oropharyngeal secretions reduced VAP rate from 5.6 to

0.3 per 1000 ventilation days ($p < .0001$) at their institution (10). More studies focusing on a pediatric-specific VAP prevention bundle are needed (126).

Conclusions and Recommendations

Much of our understanding of VAP comes from adult studies and, consequently, many of our conclusions and recommendations are based largely on adult studies.

VAP is second only to bloodstream infection as a cause of pediatric nosocomial infection.

Although attributable mortality is uncertain, VAP clearly increases the duration of ventilation, length of ICU and hospital stay, and adds considerably to the cost of care.

Diagnosis is a critical issue and our current approach to the diagnosis of VAP in children is woefully inadequate. Clinical findings are often ambiguous and microbiologic diagnosis generally limited to blood cultures and tracheal aspirates, both of which lack specificity.

Identifying the causative organism(s) is important, but the best approach to microbiologic diagnosis is not clear. Lung biopsy and bronchoscopic BAL are the gold standards but are not routinely performed in children. In their absence, TA cultures are commonly substituted, but their lack of specificity makes their value questionable. This is one reason why “presumed VAP” accounts for more than half of all antibiotic days in the PICU.

We would recommend a more academic approach to microbiologic diagnosis with pursuit of minimally contaminated lower respiratory tract cultures through BAL or NB-BAL and support a stepwise approach similar to the NNIS criteria for children (Figs. 1 and 2). Qualitative TA aspirate are of little help in this decision.

The potential value of biomarkers such as C-reactive protein and procalcitonin should also be investigated. Empiric treatment in the critically ill but immunocompetent child should initially include coverage for both Gram-positive (with *S. aureus* most common) and Gram-negative (with *Pseudomonas* most common) organisms. The child already on or recently treated with broad-spectrum antibiotics merits additional consideration because of the possibility of altered microbiologic flora.

In the immunocompromised child, a more definitive approach using either BAL or lung biopsy should be seriously contemplated. Antibiotic coverage can be narrowed or possibly discontinued in the event negative cultures or subsequent clinical findings fail to support the diagnosis of VAP.

A shorter 7-day course of antibiotics is adequate in immunocompetent children when clinical improvement is seen. In nonresponders, active search for other causes and the possibility of antibiotic resistance should be considered. As a final note, we applaud the efforts of Bigham et al (10) at Cincinnati Children’s Hospital in using an evidence-based “bundle” of simple interventions to substantially decrease the incidence of this problem and, thereby, limit antibiotic use in their PICU.

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