Considerations Unique to Pediatrics for Clinical Trial Design in Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia

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**Background.** A need exists for new antimicrobial agents to treat neonates, infants, and children for hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) caused by nosocomial antibiotic-resistant pathogens. Current and clear guidance on approval of new agents for all pediatric age groups is lacking.

**Methods.** Studies on HAP and VAP in the neonatal and pediatric age groups were collected using PubMed (National Library of Medicine). Published articles were reviewed for pediatric-specific definitions of HAP and VAP, diagnostic techniques, rates of disease, risk factors, characteristics, and outcomes.

**Results.** Definitions of HAP and VAP in neonatal and pediatric age groups vary considerably. No well-studied, sensitive, and specific microbiologic testing techniques exist. Morbidity and mortality associated with VAP in neonates, infants, and children have been documented.

**Conclusions.** Investigation and approval of new agents for HAP and VAP in all pediatric age groups is needed. A uniform definition of HAP and VAP is required that is relevant for clinical trials and balances the risks of experimental therapy and sampling procedures for study patients with potential benefits for both the patient under investigation and the hospitalized children who may develop nosocomial pneumonia.

To accurately determine the impact of new therapeutic interventions for hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) in neonates, infants, and children, clear definitions of these entities are important. For many reasons, the study of pediatric HAP and VAP has been less robust than that in adults. Nonetheless, these nosocomial infections result in measurable morbidity and mortality in all pediatric age groups. HAP and VAP, defined as pneumonia developing 48 h after hospital admission, was either the most common or second most common nosocomial infection in pediatric intensive care units (ICUs) [1–3]. Adequate, well-controlled studies of new antimicrobials, based on appropriate and realistic clinical trial designs, are critically needed. However, unique problems exist for the study of HAP and VAP in pediatric age groups with respect to definitions of disease, risk factors, and outcomes related to clinical trial design, including risks and benefits of invasive diagnostic techniques, varying age-dependent tissue-site antibiotic exposures, and the ethical dilemmas of experimentation in seriously ill children.

**DEFINING HAP AND VAP IN PEDIATRICS**

Definitions of HAP and VAP in adults have not, to date, been uniformly accepted by the infectious diseases, pulmonary, and critical care communities. It has been even more difficult to establish definitions acceptable to the US Food and Drug Administration (FDA) and the pharmaceutical industry for use in clinical trial designs that lead to approval of drugs as safe and effective for these indications. Although rates of HAP and VAP, as defined by the US Centers for Disease Control and Prevention (CDC), have been collected for pediatric patients over the past decade, few independent studies have attempted to characterize HAP and VAP in neonates and older children with analysis of risk factors and outcomes. Underlying comorbidities in children with HAP and VAP may differ substantially from those in adults. Unique congenital anatomic or acquired cardiopulmonary disease and frequent respiratory tract viral infections may obscure an accurate
diagnosis of HAP or VAP. Infants and children are widely recognized to be susceptible to viral pathogens causing lower respiratory tract infection, with documented nosocomial spread. However, many infections due to these nosocomial viral pathogens are not diagnosed easily by currently available commercial techniques, confusing the interpretation of fever and deterioration in respiratory status in a child known to be colonized in the lower respiratory tract with bacterial pathogens. To further complicate definitions, each age group in pediatrics has distinctive characteristics with respect to susceptibility to infection and to comorbid conditions, from the most extremely premature neonates to young infants, children, and adolescents. Furthermore, differences exist between adults and children with respect to populations defined to have health care–associated pneumonia. In adults, a significant proportion of patients with health care–associated pneumonia are residents from long-term chronic care facilities, a population that contributes very little to the burden of health care–associated pneumonia in infants and children. Similarly, comorbid conditions in adults that represent risk factors for health care–associated pneumonia, such as outpatient hemodialysis, are relatively uncommon in children, whereas pediatric comorbidities, such as neonatal chronic lung disease (formerly, bronchopulmonary dysplasia), do not occur in adults [4]. Therefore, HAP more accurately reflects the disease described in pediatric patients.

**Definition of pediatric HAP and VAP for surveillance.**

For epidemiologic surveillance of nosocomial infections, a sensitive case definition of HAP and VAP that comprises virtually all cases, including those in patients who may not have true infection, is appropriate and reasonable, and is used by the CDC in the National Nosocomial Infections Study (NNIS). Since 2005, these data have been reported through the National Healthcare Safety Network. Definitions are generally broad (Figure 1) [5] and collect rates of infection across all health
care institutions in the United States. Data on VAP rates among neonates and children are collected through voluntary reporting by hospitals to the CDC [6–9]. Additional data have been collected and reported by the CDC from pediatric ICUs through collaboration with the National Association of Children’s Hospitals and Related Institutions [2]. Differences in rates of nosocomial pneumonia have been frequently observed between CDC-generated national statistics and single-center statistics and are believed to be a function of the differences in the types and severity of underlying pediatric diseases treated at each institution. Institution-specific information that would allow for adjustments in rates of nosocomial infection on the basis of comorbidities or acuity of illness have not generally been integrated into data collected by the CDC. The CDC’s most current published rate of VAP with use of National Healthcare Safety Network definitions, which is likely to be higher than the rate of true infection, is 2.1 cases/1000 ventilator-days [9]. However, Elward et al [10], using NNIS definitions, reported a much higher rate of 11.6 cases/1000 ventilator-days at the pediatric ICU at St. Louis Children’s Hospital. Bigham et al [16], using NNIS definitions, documented varying rates at Cincinnati Children’s Hospital over several years (from 5.6 cases/1000 ventilator-days in 2004 to 8.8 cases/1000 ventilator-days in 2005); after implementation of a VAP-prevention bundle during 2006–2007, the rate decreased to 0.3 cases/1000 ventilator-days. Another recent prospective study from Children’s Hospital and Research Center Oakland did not report rates of infection, but with a diagnosis made either by NNIS definitions or by a “qualified intensivist with a diagnosis based on clinical assessment of clinical, laboratory, radiographic, and culture results” [11, p 1109]. These investigators documented that 32% of pediatric patients admitted to the ICU develop VAP [11]. Other centers prospectively studying VAP have used more specific definitions, such as those required by Labenne et al [17], including fever (temperature ≥38°C), a decrease of ≥25% of the ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen, and/or C-reactive protein level ≥50 mg/L, and presence of a new and persistent pulmonary infiltrate on the chest radiograph in a child who is not receiving antimicrobial therapy or has had no change in antimicrobial therapy during the preceding 3 days.

With respect to neonates, reports from both the CDC and single institutions have revealed that the risk of VAP generally increases as postconceptional age decreases [8, 12–14]. Currently, rates reported by the CDC with use of National Healthcare Safety Network criteria for neonates (by birth weight) in level-III neonatal ICUs are 2.6 cases/1000 ventilator-days among those with a birth weight <750 g, 2.1 cases/1000 ventilator-days among those with a birth weight of 751–1000 g, 1.5 cases/1000 ventilator-days among those with a birth weight of 1001–1500 g, 1.0 cases/1000 ventilator-days among those with a birth weight of 1501–2500 g, and 0.9 cases/1000 ventilator-days among those with a birth weight ≥2500 g [9]. Using NNIS definitions for neonates, Apisarnthanarak et al [13] reported rates of VAP in the neonatal ICU at St. Louis Children’s Hospital of 6.5 cases/1000 ventilator-days among neonates with estimated gestational age <28 weeks, and 4 cases/1000 ventilator-days among those with an estimated gestational age ≥28 weeks.

Risk factors, characteristics, and outcomes of VAP in neonates and children. Limited prospective studies have been performed for HAP and VAP in neonates, infants, and children. Most published studies of pediatric HAP and VAP have used CDC surveillance-based definitions to collect patient data for analysis [10, 13, 15, 16]. Some centers have also used diagnosis of VAP by a panel of experts, based on clinical, laboratory, radiographic, and culture results [11, 17, 18]. Once defined, these populations were analyzed for risk factors, characteristics, and outcomes [1, 10–16, 19].

Risk factors for pediatric VAP, as assessed in a prospective study involving children receiving mechanical ventilation who received a diagnosis of VAP at Hospital St. Justine in Montreal, included immunosuppressant drugs, immunodeficiency, and neuromuscular blockade [19]. Risk factors identified at St. Louis Children’s Hospital in a prospective cohort of patients receiving mechanical ventilation who received a diagnosis of VAP based on NNIS criteria included genetic syndrome, translocation out of the pediatric ICU (eg, for imaging or surgery), reintubation, and transfusion [10]. Another prospective cohort study, from Saudi Arabia, documented prior antibiotic use, continuous enteral feeding, and bronchoscopy to be associated with VAP [15]. A recently published prospective study involving children who received a diagnosis of VAP based on NNIS criteria or a diagnosis by an intensivist at Children’s Hospital Oakland, California, found that female sex, postsurgical diagnosis (need for surgery in an operating room), narcotic use, and enteral feeds were independently associated with VAP. Transfusion was associated with protection from VAP in that report [11]. Of interest, another prospective study in a neonatal ICU at St. Louis Children’s Hospital that also used NNIS definitions identified a risk factor in a multivariate analysis of previous bloodstream infection, although the organism isolated from the blood was always different from that causing VAP [13].

Consistently reported adverse clinical outcomes resulting from VAP have included increased duration of mechanical ventilation and increased length of hospital stay—factors that can both be used to measure an antibiotic-attributable treatment effect in neonates [13] and older children [2, 10, 11, 15, 16]. Some centers have also documented an increase in mortality among both neonates [13] and older children with VAP [2, 11, 16].
**MICROBIOLOGY OF PEDIATRIC VAP**

The organisms cultured from lower respiratory tract specimens from neonates, infants, and children that are presumed to cause VAP are similar to those cultured from specimens from adults [1, 10, 11, 13, 15–17, 20]. *Pseudomonas aeruginosa*, *Klebsiella* species, *Enterobacter* species, and nontypable *Haemophilus influenzae* are the most common gram-negative isolates. *Staphylococcus aureus*, including the more recently emerged methicillin-resistant strains, has been documented to be the most common gram-positive isolate.

**CLINICAL TRIAL ISSUES EXCLUSIVE TO CHILDREN**

Epidemiology-based case definitions are not suitable as enrollment criteria for pediatric HAP and/or VAP clinical trials, because the most important children to identify and enroll in a prospective study are those with true infection. Studying only children with true disease will maximize information learned regarding investigational antibiotic- and comparator-attributable clinical and laboratory outcomes and will minimize the risk of unnecessary investigational drug exposure. The statistical power of a study to assess differences between treatment groups is enhanced when a high proportion of microbiologically and clinically evaluable patients are enrolled.

**Pediatric severity-of-illness scoring systems.** A clinical trial design to assess new antimicrobial therapy must use a validated severity-of-illness measure to adequately characterize the severity of lower respiratory tract disease to accurately assess the potential benefit derived from investigational therapy. No such well-validated scoring system exists for neonates, infants, and children.

For adults, the Clinical Pulmonary Infection Score and similar scoring systems have been used to describe severity of infection and prognosis [21]. Such scoring systems have been used to describe the natural history of disease and have the potential to assess the benefit of investigational therapy. Various scoring systems have been proposed for pediatric patients in ICUs, including the Pediatric Risk of Mortality Score [22] and the Pediatric Logistic Organ Dysfunction Score [23, 24], although no single pediatric score has been studied or validated as well as those in adults. Many scoring systems are designed to be performed at the time of admission to the hospital to assess mortality risk and may not be relevant to the status of the patient several days after hospital admission, when HAP or VAP may occur. A pediatric scoring system that is capable of documenting the severity of illness on a daily basis should be able to define the severity of disease both on the day that HAP or VAP is diagnosed and on each day that the child is receiving investigational or control therapy, allowing for an accurate evaluation of treatment effect. Furthermore, it is likely that scoring systems would need to be validated in all pediatric age groups, including neonates with extremely low birth weight, term neonates, infants, children, and adolescents, because each age group displays different degrees of innate immune deficiency and different degrees of organ function stability during infection.

**Defining effective antiinfective drug exposure for neonates and children.** Many antibiotics are currently approved for children for specific indications based on microbiologic and clinical efficacy data in adults, with supporting pharmacokinetic and safety data in children, as represented by linezolid, the only FDA-approved antibiotic for pediatric nosocomial pneumonia. Although this approach provides many advantages for the availability of approved antibiotics for treatment of HAP and VAP in children, the assumption that drug exposure in all lung tissues (respiratory tract mucosa from the trachea to the respiratory bronchioles and alveoli, consolidated lung, epithelial lining fluid, and empyema) is similar, the assumption that lung tissue reactivity and/or inflammation is equivalent in children and in adults, and results for the equivalent drug exposure and equivalent organism clearance at the site of infection may not be accurate.

Moreover, drug exposure in the plasma compartment and, subsequently, at the site of infection varies among pediatric age groups on the basis of age-specific drug distribution and elimination. Pulmonary tissue drug exposure (eg, entry, tissue binding, and tissue half-life) is, therefore, also not likely to be equivalent in all pediatric age groups, particularly in extremely premature neonates, whose lung anatomy has not developed to the point of demonstrating mature aveloi [25].

The actual site of infection in the lung in children with HAP and VAP may also vary on the basis of the pathogen causing infection, with more invasive organisms, such as *P. aeruginosa* and enteric gram-negative bacilli, and community-associated methicillin-resistant *S. aureus* more likely to be associated with lung parenchymal damage, necrotizing pneumonia, and abscess formation. The epithelial lining fluid, a tissue site associated with microbiologic and clinical cure in community-associated pneumonia, may not be the most appropriate site to measure antibiotic exposure in HAP or VAP in children.

An additional consideration for pediatric age groups is defining the treatment duration necessary to produce a microbiologic and clinical cure in community-associated pneumonia, may not be the most appropriate site to measure antibiotic exposure in HAP or VAP in children.

**Diagnostic techniques in neonatal and pediatric HAP and VAP.** To establish the diagnosis of VAP in adults, the sensitivity, specificity, and positive and negative predictive values of various microbiologic sampling techniques (endotracheal aspiration, bronchoscopy with bronchoalveolar lavage [BAL],
blind BAL, and blind protected specimen brush) that can quantitatively or qualitatively identify the density of organisms present in the lower respiratory tract need to be established; these data are presented for adult patients in other articles in this supplement [26, 27]. Similar, in-depth data do not exist for neonates, infants, and children. Labenne et al [17] from Paris compared culture of endotracheal aspirate specimens with culture of samples obtained by blind protected specimen brush or blind bronchoalveolar lavage for 103 children receiving mechanical ventilation who had new onset of pulmonary infiltrates in the context of fever, >25% decrease in the ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen, and/or elevated C-reactive protein level, with no changes in antibiotic therapy in the preceding 72 h. Children with severe underlying lung disease and those who were immunocompromised were excluded. The diagnosis of VAP was made by microbiologic or histologic confirmation or by clinical assessment by 2 senior physicians who were unaware of culture results, based on CDC NNIS criteria. A summary of the findings is shown in Table 1, although a more detailed analysis of the sensitivity and specificity at each bacterial density threshold was also undertaken by the authors. Minor complications from the sampling procedure were not uncommon. Major complications were unusual, but 3 newborns developed postprocedure pneumothorax. As observed by other researchers, endotracheal aspirate culture was sensitive but not sufficiently specific to be useful in clinical trials. Specificity increased with the use of relatively high thresholds for bacterial densities in protected specimen brush samples and blind BAL fluid samples. Additional specificity was obtained when the presence of ≥1% of polymorphonuclear cells documented to harbor intracellular bacteria in blind BAL fluid samples was added to the blind BAL bacterial density criteria.

Similar data are presented in Table 2 for blind BAL fluid samples collected from 30 children receiving mechanical ventilation in Montreal, comparing the clinical opinions of 3 experts (who retrospectively reviewed each case based on clinical, microbiological, and radiologic data while being blinded to BAL fluid culture results) using clinical criteria from CDC NNIS definitions [28], quantitative culture of blind protected BAL fluid samples, gram-stained smear of BAL fluid samples, histologic examination for intracellular bacteria, and nonquantitative endotracheal aspirate cultures [18]. In addition, a bacterial index was calculated on the basis of the total numbers of all bacteria isolated on culture [29]. Similar to Labenne et al [17], Gauvin et al [20] noted that culture of endotracheal aspirate samples had insufficient specificity, and both quantitative culture and Gram stain of blind BAL fluid samples achieved greater specificity (50% for each in this study) than did testing of endotracheal aspirate samples. Such low specificity of testing of blind BAL fluid samples in this study, even for a group of children with a high pretest probability of VAP, may not be sufficient for use as criteria to define microbiologically evaluable children in clinical trials. Gauvin et al [20] also validated the reproducibility of the blind BAL technique by collecting samples again from the children 2 h after the initial procedure. The safety of blind BAL techniques has also been

### Table 1. Sensitivity and Specificity of Different Microbiologic and Histologic Techniques to Diagnose Ventilator-Associated Pneumonia

<table>
<thead>
<tr>
<th>Testing technique</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
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<tbody>
<tr>
<td>EA qualitative culture</td>
<td>93</td>
<td>41</td>
</tr>
<tr>
<td>PSB culturea</td>
<td>69</td>
<td>95</td>
</tr>
<tr>
<td>ICB in blind BAL fluid sampleb</td>
<td>55</td>
<td>89</td>
</tr>
<tr>
<td>Blind BAL fluid culturec</td>
<td>72</td>
<td>88</td>
</tr>
<tr>
<td>Combination of ICB and blind BAL fluid culture</td>
<td>79</td>
<td>88</td>
</tr>
<tr>
<td>Combination of PSB culture, ICB, and blind BAL fluid culture</td>
<td>90</td>
<td>88</td>
</tr>
</tbody>
</table>

**NOTE.** Derived from [17]. BAL, bronchoalveolar lavage; EA, endotracheal aspirate; ICB, intracellular bacteria; PSB, protected specimen brush.

a Positive threshold for PSB specimen quantitative culture: 1 × 10³ colony-forming units (cfu)/mL.
b Positive threshold for microscopic quantification of ICB in BAL fluid sample: 1%.
c Positive threshold for blind BAL fluid quantitative culture: 1 × 10⁴ cfu/mL.

### Table 2. Diagnosis of Ventilator-Associated Pneumonia: Sensitivity and Specificity of Centers for Disease Control and Prevention (CDC) National Nosocomial Infections Study Clinical Assessment and Blind Bronchoalveolar Lavage Microbiologic and Histologic Assessment, Compared with Expert Opinion

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
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<tbody>
<tr>
<td>CDC clinical criteria [28]</td>
<td>100</td>
<td>15</td>
</tr>
<tr>
<td>EA qualitative culture</td>
<td>90</td>
<td>40</td>
</tr>
<tr>
<td>ICB in BAL fluid samplea</td>
<td>30</td>
<td>95</td>
</tr>
<tr>
<td>BAL fluid cultureb</td>
<td>50</td>
<td>80</td>
</tr>
<tr>
<td>BAL fluid Gram stain</td>
<td>50</td>
<td>81</td>
</tr>
</tbody>
</table>

**NOTE.** Derived from [18]. EA, endotracheal aspirate; ICB, intracellular bacteria.
a Positive threshold for microscopic quantification of ICB in BAL fluid sample: 1%.
b Positive threshold for blind BAL fluid quantitative culture: 1 × 10⁴ colony-forming units (cfu)/mL.
described by other investigators who provided important information on the risks involved in these procedures, particularly among younger infants [30–32].

Although nonspecific markers of acute inflammation, including C-reactive protein and procalcitonin, have been investigated to differentiate bacterial from nonbacterial (primarily viral) illness in neonates, infants, and children in both outpatient and inpatient settings, these tests have not yet been applied to pediatric HAP or VAP populations to determine their role in diagnosis [33, 34]. Imaging techniques (chest radiograph or chest CT) are frequently used to support a diagnosis of HAP or VAP. However, chest radiographs have been shown to be neither sensitive nor specific in the diagnosis of community-acquired pneumonia [35–38]. Although CT provides better resolution than chest radiographs to differentiate between atelectatic and consolidated lung [39], it is associated with additional radiation risks that regulatory agencies, physicians, parents, and institutional review boards may not be willing to accept for a research study [40].

**UNIQUE CHALLENGES IN PEDIATRIC INVESTIGATION OF HAP AND VAP**

Children, as defined by regulatory agencies, comprise a vulnerable population. Unique ethical issues apply to children when enrolling them in clinical trials of experimental antinfective therapy, because the risks and benefits among children may be different from those for adults for both efficacy and safety, making it more difficult to justify clinical research protocols with unknown benefit but defined and potentially substantial risks to children. Furthermore, risks and benefits may differ when considering each age group in pediatrics, from premature newborns to adolescents.

For intubated infants with VAP, access to the lower respiratory tract is relatively easy. One of the most effective techniques for assessing the presence of pathogens in infected lung tissue in adults is bronchoscopy. However, accepting the risk of bronchoscopy in children presents ethical challenges when performed for a microbiologic diagnosis for research purposes only. For neonates, because of the small size of airways, bronchoscopy may not be possible. Samples collected by blind BAL or blind protected specimen brush are less likely to cause trauma than a bronchoscope, but these sampling procedures are also associated with some risk. Endotracheal samples, which may be obtained routinely as part of clinical care with minimal risk, have been shown to be highly sensitive but insufficiently specific to diagnose VAP [17, 18].

Even more difficult to assess are nonintubated neonates, infants, and children with HAP, for whom sampling of lower respiratory tract secretions can be even more challenging. Young infants are not likely to be able to produce sputum. Ethical considerations about the invasive nature and risks of transtracheal aspiration or intubation for the sole purpose of acquiring a microbiologic sample for research are substantial.

To approach parents for enrollment of their seriously ill child in an investigational trial represents unique challenges for the pediatric investigator, often leading to low enrollment in these clinical trials. After the news that their newborn’s or child’s health has deteriorated, with new evidence of pneumonia, possibly life-threatening, parents are approached by the investigator with a request that they take an additional risk for their child in testing an experimental agent. Parents, understandably, are often unwilling to agree to any additional risk that they can avoid. Invasive sampling techniques may be necessary to document a microbiologic etiology, as outlined above, and lead to additional risks of adverse outcomes. Informed consent documents clearly need to state not only that the new investigational agent may be ineffective, leading to deterioration, but also that sampling techniques, used only for purposes of the research study, may also place the child at increased risk of deterioration. Investigators are required to explain these risks to both parents so that they understand and then request both parents to sign the informed consent document.

**NEXT STEPS FOR CLINICAL TRIAL DESIGN FOR HAP AND/OR VAP IN CHILDREN**

A need to define HAP and VAP for clinical trials. A clear need exists to achieve a consistent and reproducible diagnosis of HAP and VAP in all pediatric age groups with use of clinical, laboratory, and imaging criteria that address the needs of regulatory agencies to best understand the safety and efficacy of new agents [3, 41]. Novel laboratory techniques for assessing infection in children are needed, including pathogen-specific molecular techniques (eg, polymerase chain reaction), to support the diagnosis of HAP or VAP in neonates and children without requiring more invasive sampling procedures.

Lack of current gram-negative agents in pediatric age groups. No FDA-approved antibiotic with gram-negative activity exists for the treatment of nosocomial pneumonia for any pediatric age group. Placebo-controlled trials in HAP and/or VAP would be unethical; therefore, it is important to establish unique ways to approve antibiotics for these indications in children. The possibility of conducting pediatric noninferiority trials with the experimental agent, compared with one approved for adults, should be considered until a drug with gram-negative activity that is well studied in children has received FDA approval for pediatric HAP and/or VAP. End points that should be considered include resolution of specific signs and symptoms of pneumonia, as measured by a validated scoring system; improvement or lack of progression of abnormalities on chest radiograph; duration of mechanical ventilation (for those receiving mechanical ventilation); duration of intensive care unit stay; duration of hospitalization; duration of a requirement for...
oxygen; duration of fever; and if applicable, time to return to school (or other functional outcome that is age appropriate). Historical control data may be needed to justify a noninferiority margin. Optimally, phase 3 studies should be performed in each pediatric age group for each antiinfective agent, but the size of the clinical trials and the costs involved may exceed those traditionally taken on by industry and may require collaborative efforts by industry, the FDA, and the National Institutes of Health.

**Approaches to the approval of agents for children.** The single antibiotic that is currently FDA-approved to treat nosocomial pneumonia in children, linezolid, received approval on the basis of "evidence from adequate and well-controlled studies in adults, pharmacokinetic data in pediatric patients, and additional data from a comparator controlled study of gram-positive infections in pediatric patients ranging in age from birth through 11 years" [42, pp 17, 18]. The present approach used by the FDA represents a compromise between the risks of subjecting children to invasive procedures performed in adults and the benefits of having basic dose and safety information available on antiinfectives for children in all age groups. However, the strategy of using phase 1 and phase 2 data for children, linked to phase 3 data for adults, does not adequately address the possibility that drug exposures or duration of treatment for microbiologic and clinical cure in each pediatric age group may be different from those in adults. Neonates represent an age group for which even fewer data on appropriate and safe treatment administration exist, because the lower age limit in most pediatric studies of antiinfectives is 2 months. It is essential to perform, at a minimum, pharmacokinetic and basic safety studies in neonates, even though the risks of investigation are highest in this age group.

Until noninvasive, sensitive, and specific diagnostic tests are available to establish a bacterial etiology of HAP and VAP in children, continuing to use phase 1 pharmacokinetic and phase 2/3 clinical efficacy and safety data for infants and children, linked to phase 3 adult data, appears to be the only current option for investigation and approval of antimicrobial agents for children. Research to create noninvasive diagnostic techniques for children is essential for optimal pediatric clinical trial design for HAP and VAP. In addition, the creation of a validated clinical scoring system, such as the Clinical Pulmonary Infection Score for adults, for each pediatric age group, from neonates to adolescents, represents another essential area for research and will allow both investigators and regulators to analyze, with greater accuracy, the relevant differences in clinical response to different antimicrobial treatment regimens.

Enhanced postmarketing safety surveillance programs that are monitored by the FDA may ensure that potentially life-saving antiinfectives are made available for pediatrics, with more long-term safety assessments that can detect a new adverse event profile that substantially changes the risk-benefit assessment in the use of these antibiotics in children.

**Timely availability of agents.** Because the pathogens causing HAP and VAP in children are the same as those in adults, there is also a critical need for the timely availability of new agents in children. New agents that show promise against multidrug-resistant pathogens in phase 2 studies in adults and have entered into phase 3 comparative clinical trials with an acceptable safety profile and preliminary efficacy data should enter into pediatric investigations. Current timelines for drug development postpone useful data collection in the pediatric age groups by several years until the phase 3 data in adults are collected, analyzed, and presented to the FDA. Initial pediatric data on pharmacokinetics and safety in several age groups should already be available to those who care for children at the time the investigational antibiotic receives approval from the FDA for adult indications. Although safety data in adults may reveal toxicities that would preclude the study of agents in children, the delay in acquiring pediatric data forces those who care for children to use agents without scientific guidance on age-specific pharmacokinetics, subjecting neonates, infants, and children to possible drug toxicities that may not be seen in adults.

**SUMMARY**

Although a need for agents to treat neonates, infants, and children with HAP and VAP due to nosocomial antibiotic-resistant pathogens clearly exists, the framework for conducting adequate and well-controlled trials in children does not yet exist. Better definitions of HAP and VAP are needed for clinical trials, with sensitive and specific microbiologic sampling techniques that demonstrate an acceptable risk-benefit profile for parents, investigators, and human research committees. A current strategy to approve agents for children that have been approved for adults, supported by basic pharmacokinetic and safety data, is an important means to provide access to new agents for those who care for children but should not be considered an optimal long-term strategy for investigating new agents in neonates, infants, and children.

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