Nosocomial Pneumonia in Pediatric Patients

Practical Problems and Rational Solutions

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Abstract

Nosocomial pneumonia is a common hospital-acquired infection in children, and is often fatal. Risk factors for nosocomial pneumonia include admission to an intensive care unit, intubation, burns, surgery, and underlying chronic illness. Viruses, predominantly respiratory syncytial virus (RSV), are the most common cause of pediatric nosocomial respiratory tract infections. Gram-negative bacteria (*Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*) are the predominant bacterial pathogens, and are associated with a high mortality rate. *Staphylococcus aureus* and *Staphylococcus epidermidis* are the most common Gram-positive bacteria causing nosocomial pneumonia; infections with these organisms have a better outcome than those with Gram-negative organisms. An increasing problem is the emergence of multiresistant Gram-positive and Gram-negative nosocomial pathogens.

Distinguishing nosocomial pneumonia from other pulmonary processes may be difficult; diagnosis is based on clinical signs, radiological findings, and microbiological results. Recommended empiric therapy should consider factors such as the time of onset of illness, severity of disease, and specific risk factors for nosocomial pneumonia, including use of mechanical ventilation, underlying disease, or recent use of antibacterials. The resident local hospital flora should be considered when selecting therapy for nosocomial pneumonia. Early initiation of appropriate empiric therapy reduces morbidity and mortality. For empiric treatment of bacterial nosocomial pneumonia, an intravenous antibacterial regimen that includes coverage of Gram-negative bacilli and Gram-positive organisms should be used. A carbapenem or ureidopenicillin derivative (piperacillin) plus a β -lactamase inhibitor should be used where extended spectrum β -lactamase-producing Enterobacteriaceae are endemic. Therapy should be modified when a specific pathogen and its antimicrobial susceptibility are identified.

Effective prevention of nosocomial pneumonia requires infection control measures that affect the environment, personnel, and patients. Of these, hand hygiene, appropriate infection control policies, and judicious use of antibacterials are essential.

Nosocomial pneumonia (NP) is defined as pneumonia occurring at or beyond 48 hours after admission to hospital that was not present nor incubating at the time of admission.^[1] Ventilator associated pneumonia (VAP) is pneumonia that develops in mechanically ventilated patients later than 48 hours after intubation. Pneumonia is a common hospital-acquired infection, especially in infants and children requiring intensive care support. Moreover, NP is the leading cause of fatal nosocomial infection.

NP occurs as a complication of altered pulmonary or systemic antimicrobial defenses, resulting in invasion of the lower respiratory tract by a pathogenic organism. Causative organisms may derive either from the child's own flora (endogenous) or an environmental source (exogenous). Endogenous infection often occurs via subclinical aspiration of both oropharyngeal and gastric secretions or hematogenous spread from an infected distant site. Exogenous infection may result from colonization of the child's upper respiratory tract by flora present in the hospital or staff. The role of invasive diagnostic techniques, the optimal samples for diagnosis, and the most effective treatment regimens for NP remain controversial. This article reviews the epidemiology, risk factors, and etiology of NP in children, and discusses diagnosis, treatment, and prevention.

1. Epidemiology

The incidence of NP varies from 16 to 29% of hospitalized pediatric patients.^[2] Differences in study methodology, patient population, case definitions of NP, and institutional practices may explain this variability. Overall, NP accounts for 10 to 15% of all nosocomial infections in children.^[3] Importantly, pneumonia is the most common fatal nosocomial infection, with mortality ranging from 20 to 70% depending on the organism and underlying illness.^[2]

Children in pediatric intensive care units (PICUs) have a higher incidence of NP than those in general wards.^[3,4] A 5-year multicentered survey of nosocomial infection in 61 North American PICUs reported that NP was the second most common infection, accounting for 21% of hospital-acquired infections.^[5] Others have reported that pneumonia is the most common bacterial nosocomial infection in PICUs, accounting for 35 to 67% of nosocomial infection.^[6-8] This may reflect the increased risk for NP associated with mechanical ventilation, as the incidence of NP is increased by 6- to 20-fold in ventilated patients.^[9]

Neonatal NP encompasses only infections that are truly hospital-acquired and, therefore, excludes pneumonia acquired by vertical transmission. Nosocomial infections in the neonatal nursery are uncommon, but rates of infection in neonatal intensive care units (NICUs) tend to be higher than in PICUs.^[10]

2. Risk Factors

Loss of the normal barriers against infection and change in the nasopharyngeal flora during hospitalization result in increased respiratory tract colonization by potential pathogens. Risk factors for NP in children include intubation, prolonged hospitalization, underlying illness, immunosuppression, or recent antimicrobial therapy. Specific children at risk of NP are detailed below.

2.1 Children Admitted to a Pediatric Intensive Care Unit

The severity of the underlying illness and use of invasive modalities of care are important risk factors for NP. A prospective study of 960 admissions to a PICU identified three independent risk factors for NP: immunodeficiency, pharmacological immunosuppression, and neuromuscular blockade.^[11]

A study of 500 children admitted to a Brazilian PICU (where pneumonia was the predominant nosocomial infection), identified length of stay, parenteral nutrition and device utilization ratio (defined as central venous catheter days + urinary catheter days + mechanical ventilation days divided by the number of days in the PICU) as independent risk factors for nosocomial infection.^[6]

Medical equipment necessary for the survival of severely ill patients predisposes to the development of NP. A nasogastric tube provides a direct route for pathogens from the upper gastrointestinal tract to the oropharynx. Endotracheal intubation is the most important factor predisposing to NP.^[3] An endotracheal tube stents the vocal cords, allowing gastric contents into the trachea. Although the risk of pneumonia increases with the duration of intubation, the period of highest risk is within the first 2 weeks.^[12] In a study where the mean duration of endotracheal intubation was 9.2 days, 96% of endotracheal tubes were partially colonized, and 84% completely colonized, by bacteria.^[13] A study of 63 consecutive patients admitted to a PICU reported that all children with endotracheal tubes had hospital-acquired organisms in tracheal aspirates, colonization occurring at a mean of 5 days.^[14] Colonization of ventilator tubing and condensate may also be a source of bacterial contamination.^[15] Nebulizers inserted into the respiratory circuit may cause the inhalation of aerosolized bacteria.^[16] Frequent manipulation of ventilator tubing is another risk factor for NP.^[17] A prospective 4-year study in adults found that delaying ventilator circuit change intervals beyond 2 days to between 7 and 30 days was associated with a reduced risk of VAP and significant reductions in morbidity and cost,^[18] which confirmed similar findings of earlier studies.^[19,20]

H₂ receptor antagonists, used to prevent stress ulceration, increase the gastric pH, often with a resultant rise in bacterial growth.^[21] A number of meta-analyses have found that use of

sucralfate was associated with a reduced incidence of NP when compared with the use of either antacids alone or in combination with H₂ antagonists;^[22-24] however, the effect of H₂ antagonists on the incidence of NP is controversial as some studies have reported no difference when compared with placebo, whereas others have suggested that the use of sucralfate may be protective, reducing the incidence of NP compared with H₂ antagonists.^[22-26]

2.2 Infants Admitted to a Neonatal Intensive Care Unit

With the increasing survival of low birthweight infants and longer duration of NICU stay, the incidence of neonatal nosocomial infection has risen.^[10] Low birthweight and the degree of low bodyweight are major risk factors for neonatal nosocomial infection because of poor immune defenses and the need for life support systems such as endotracheal intubation, mechanical ventilation, and invasive monitoring that interfere with normal defense barriers.^[10,27]

Colonization with normal flora prevents growth of pathogenic bacteria and fungi. As this process has not yet developed at birth, neonates may be particularly susceptible to the ecologic influence of antibacterials, resulting in colonization with pathogenic bacteria.^[28] Furthermore, the type and antimicrobial sensitivity of the resident flora in a NICU may be directly influenced by the selection of antimicrobial regimens.^[29]

2.3 Children with Burns

NP is a significant cause of morbidity and death in children with burns. In a pediatric burns unit, 17.5% of patients developed VAP at a rate of 11.4/1000 ventilator days within a 2 year period.^[30] Inhalation injury was a major risk factor. Moreover, the incidence of pneumonia was related to the extent of burn injury, occurring in 86% of those with more than 30% burn surface area.

2.4 Children after Surgery

Postoperative patients have an increased risk of NP, especially after thoracic, thoraco-abdominal, or upper abdominal surgery.^[3,31] Reasons include postoperative intubation and mechanical ventilation, impaired clearance of secretions due to pain or sedation, and chest tubes that provide a portal of entry into the lower respiratory tract.

2.5 Children with Underlying Chronic Illness

Children at risk of aspiration include those with tracheo-oesophageal fistulae, gastrointestinal reflux, swallowing incoordination and myopathies. Cardiac disease, immunodeficiency,

and malnutrition are risk factors for more severe disease and associated high mortality.^[3,32] Children with cystic fibrosis are frequently colonized by *Pseudomonas aeruginosa*. Major risk factors for NP in a developing country prior to the HIV epidemic were malnutrition, age <2 years, and prolonged hospitalization.^[33] Increased numbers of HIV-infected children can be expected to develop NP as a result of the rising number of HIV-positive patients requiring hospitalization, particularly in sub-Saharan Africa.

2.6 Children in Resource-Poor Settings

Poor hand hygiene is probably the most important factor in the spread of nosocomial pathogens and is exacerbated by chronic overcrowding and understaffing.^[34] For this reason, nosocomial infection occurs more commonly in resource-constrained environments. For example, Cotton et al.^[33] reported 22.5 nosocomial infections per 100 children admitted to a general ward at Baragwanath Hospital, Soweto, South Africa. In contrast, Welliver and McLaughlin^[35] documented 4.1 nosocomial infections per 100 discharges in a North American children's hospital.

3. Etiological Organisms

The type and antimicrobial resistance of pathogens causing NP depend on the local prevalence and susceptibility patterns, which differ according to specific regions, institutions, and units. A number of bacteria, viruses, and fungi cause NP (table I).

Gram-negative bacilli predominate and are associated with a high mortality rate of around 50%.^[3] *Escherichia coli*, *Klebsiella pneumoniae* and *P. aeruginosa* are the most common bacteria, comprising up to 73% of all isolates.^[4,5,11] In PICUs, *P. aeruginosa* was the most commonly identified species causing NP.^[5,8] Moreover, *P. aeruginosa* has been associated with the highest mortality rate, ranging from 70 to 80%. *Enterobacter* species have been increasingly reported in PICUs.^[5] Other Gram-negative bacilli implicated in NP include *Acinetobacter*, *Serratia*, and *Proteus* species. *Legionella pneumophila* has rarely been found as a cause of NP; Levy and Rubin^[36] reported nosocomial *L. pneumophila* pneumonia in nine neonates, eight of whom had risk factors such as prematurity, congenital heart disease, bronchopulmonary dysplasia, or corticosteroid therapy. *Acinetobacter* infections have been associated with contaminated respiratory support equipment, while outbreaks of *Legionella* have been ascribed to contaminated water.^[37,38] Antibacterial resistance has become more prevalent in Gram-negative hospital pathogens.^[39] These bacteria have had a major impact on outcome and cost as they have doubled the case fatality rates and significantly prolonged hospital stay.

Table I. Infectious agents causing nosocomial pneumonia in children**Aerobic bacteria****Gram-negative bacteria**

Klebsiella pneumoniae
Pseudomonas aeruginosa
Escherichia coli
Enterobacter spp.
Acinetobacter spp.
Proteus spp.
Citrobacter spp.
Serratia marcescens
Haemophilus influenzae
Legionella pneumophila
Moraxella catarrhalis

Gram-positive bacteria

Staphylococcus aureus
Staphylococcus cohnii
Staphylococcus epidermidis
Streptococcus pneumoniae

Anaerobic bacteria

Prevotella spp.
Peptostreptococcus spp.
Fusobacterium spp.
Bacteroides spp.

Viruses

Respiratory syncytial
 Parainfluenza
 Influenza A and B
 Adenovirus
 Varicella-zoster
 Cytomegalovirus
 Herpes simplex
 Measles

Fungi

Aspergillus spp.
Candida spp.
Pneumocystis carinii

the predominant staphylococcal species; 91% were methicillin-resistant.^[44]

An increasing problem is the emergence of extended spectrum β -lactamase (ESBL)-producing nosocomial pathogens, resistant to third-generation cephalosporins such as cefotaxime and ceftriaxone.^[45] Hospital surveys report that the majority of *K. pneumoniae*, *P. aeruginosa*, and Enterobacteriaceae are resistant to third-generation cephalosporins.^[46-49]

Anaerobic bacteria are infrequently reported, possibly due to difficulties in identification; however, by using protected specimen brushes and appropriate transport and culture media, anaerobic bacteria were recovered in 23% of adults with VAP; the most frequently isolated anaerobic strains were *Prevotella* species and *Fusobacterium nucleatum*.^[50,51] The majority produced ESBL.

Viruses, predominantly respiratory syncytial virus (RSV), are the most common cause of pediatric nosocomial respiratory tract infection.^[2,52,53] Transmission rates for RSV are approximately 45% in the absence of infection control measures.^[53] Children with underlying cardiac, pulmonary and immunodeficiency disease are at particular risk for severe RSV infection. Other respiratory viruses such as adenovirus, influenza and parainfluenza virus are isolated less frequently, but immunocompromised children and neonates may develop severe infection.^[53-55] For example, during an outbreak of adenovirus in a PICU, the nosocomial acquisition rate was 12% and the associated case fatality rate 67%.^[56]

Fungal NP occurs in immunosuppressed children, probably exacerbated by frequent use of broad-spectrum antibacterials for suspected bacterial infections. Children who have neutropenia are at particular risk for infection with *Aspergillus* and *Candida* species. Reports of clusters of *Pneumocystis carinii* pneumonia (PCP) in hospitals implicate nosocomial acquisition in immunosuppressed children who were not taking chemoprophylaxis.^[57]

4. Diagnosis

Diagnosis may be difficult, as acute respiratory distress syndrome, atelectasis and pulmonary edema can mimic NP. In addition, cultures from sputum or endotracheal suctioning frequently represent colonizing organisms. Most case definitions of NP include clinical symptoms, signs, and radiological changes, whereas those from the Centers for Disease Control and European Nosocomial Infection Survey also contain laboratory evidence.^[58] American Thoracic Society (ATS) guidelines for the diagnosis of NP in adults include clinical, radiological, and bacteriological evaluation.^[59]

NP should be suspected when there is an unexplained change in clinical status, including fever, drop in oxygenation, increased

Infections with Gram-positive organisms, especially *Staphylococcus aureus* and coagulase-negative staphylococci, are the second most common bacterial cause of NP and have a better outcome than those with Gram-negative organisms, with associated mortality ranging from 5 to 24%.^[3] *Staphylococcus epidermidis* is a prominent cause of NP in NICUs, particularly in infants with umbilical or central venous catheters.^[40] *S. aureus* is an important cause of NP in both intensive care units (ICUs) and general wards.^[11,33,41] The prevalence of methicillin-resistant *S. aureus* (MRSA) and *S. epidermidis* has increased rapidly in the past 20 years.^[42,43] A recent study in a Polish PICU reported that *S. epidermidis* was

oxygen or ventilation requirements, new chest signs, metabolic acidosis, or alteration in the type or quantity of respiratory secretions. Chest x-ray findings are usually nonspecific but the development of new or progressive pulmonary infiltrates, consolidation or pleural effusion may provide radiological evidence of NP.^[58] *S. aureus*, *P. aeruginosa* and *K. pneumoniae* may produce a rapidly progressive necrotizing pneumonia. The epidemiological circumstances of the patient and nursing environment may also suggest NP; for example, recent in-hospital exposure to RSV. The resident bacterial flora in the ward should also be considered.

The efficacy of invasive diagnostic techniques remains controversial as they have not reduced morbidity or mortality, nor has the most reliable method for microbiologic confirmation of NP been defined.^[59,60] Transbronchial, percutaneous, and open lung biopsies are definitive diagnostic procedures but are rarely done in children as they are invasive, may be complicated by bleeding or pneumothorax, and can be especially risky in patients who are very ill or unstable. A variety of methods have been developed to obtain cultures from the lower respiratory tract, including sputum induction,^[61] endotracheal aspiration,^[62] bronchoalveolar lavage (BAL),^[63] and protected bronchial specimen brushings (PSB).^[64] Sputum induction can be effectively and safely performed, even in infants.^[61] In intubated children, nonbronchoscopic BAL or aspiration of peripheral bronchial secretions by briefly inserting a catheter through the endotracheal tube may provide specimens from the distal airways;^[63-65] however, qualitative cultures of tracheobronchial secretions are a sensitive but not specific method for evaluating the lower respiratory tract flora as these sampling procedures do not distinguish between colonizing organisms and those causing pulmonary infection. Nevertheless, tracheobronchial cultures do have a high negative predictive value, as a negative culture in the absence of antimicrobial pretreatment may exclude NP. Similarly, they may be useful for excluding specific pathogens.^[59]

To improve diagnostic sensitivity, techniques such as Gram stain of specimens, microscopic examination for pus cells, and semiquantitative culture have been used. The role of quantitative invasive diagnostic testing for NP is also controversial. Moreover, the results may be influenced by the stage of pneumonia, antimicrobial use, differences in diagnostic technique, variability of the sampling methods, and the ability of laboratories to do quantitative culturing. Gram stain of BAL fluid has been reported to be useful for the early diagnosis of VAP, with a sensitivity of 90% and specificity of 74%.^[66] In adults, the presence of bacteria, especially if intracellular, has been reported to correlate with histologically confirmed pneumonia.^[67] The presence of white cells, particularly polymorphonuclear cells, in high numbers (>25 per

low-power field) with low numbers of squamous epithelial cells (<10 per low-power field) is indicative of lower respiratory tract secretions;^[68] however, few studies have validated the different techniques with biopsy confirmation of pneumonia. Chastre and colleagues^[69] reported a good correlation between quantitative bacterial culture of >10⁴ colony forming units (CFU)/ml for BAL, and postmortem histology and microbiology lung features in ventilated patients who died. BAL fluid cultures were also found to be a sensitive and specific method for diagnosing NP compared with PSB in adult ventilated patients using a threshold for bacterial growth of 10⁴ CFU/ml for BAL and 10³ CFU/ml for PSB;^[70] however, BAL, fiberoptic bronchial aspirates, and percutaneous lung needle aspiration had poor sensitivity (50, 44 and 25% respectively) compared with histopathology for diagnosis of NP in ventilated adults on antibacterials.^[71]

Pleural effusions, if present, should be aspirated and investigated for infectious agents. Percutaneous fine needle aspiration may be useful for culture of pulmonary pathogens. An analysis of 59 studies of the etiology of childhood pneumonia found that aspiration yielded a bacterial cause in approximately 50% of patients, and was associated with few complications.^[72] In immunocompromised children with NP unresponsive to broad-spectrum antibacterials, open lung biopsy for histology and culture may confirm fungal pneumonia.

Nasal washings are useful for viral isolates. Respiratory secretions should be obtained for culture and antigen detection. The use of new rapid diagnostic testing for RSV and other respiratory viruses is important for early identification, and institution of appropriate infection control precautions. Fluorescent microscopy of respiratory secretions may aid in the identification of *P. carinii* and *L. pneumophila*.

Blood culture, when positive, may be useful for identifying bacterial pathogens and their antimicrobial sensitivity;^[73] however, only about 10 to 31% of blood cultures are positive in NP.^[74] Moreover, data from adults with VAP suggest that blood cultures have a low sensitivity for detecting the same pathogen as BAL.^[75] Nevertheless, blood cultures are minimally invasive, relatively inexpensive and indicative of severe, life-threatening infection.^[76] Urine antigen detection may be useful for detection of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *L. pneumophila*. Serologic studies are unhelpful for the diagnosis of NP except for retrospective confirmation of viral or *Legionella* infections; however, they may have epidemiologic value.^[59]

5. Treatment

Early initiation of appropriate empiric therapy is essential to reduce morbidity and mortality from NP.^[77] Empiric therapy

should cover the likely pathogens, with particular attention to the local flora, and therefore several patient and hospital factors must be considered in the selection of an empiric antibacterial regimen. Important patient factors include the severity of illness, time of onset of NP, use of mechanical ventilation, underlying illness, and recent use of antibacterials that could select resistant organisms or promote fungal infection.

General principles for empiric treatment of NP include the use of antibacterials directed against the common nosocomial pathogens, and modification once a specific organism is identified (table II). Although a number of empiric regimens that provide coverage of Gram-negative and Gram-positive organisms have been proposed (table III), there are few data on the efficacy of empiric regimens in children. In general, for children in an ICU or immunosuppressed patients, empiric therapy should provide good coverage against *P. aeruginosa* as this is a common cause of NP and associated with a high mortality. Anti-pseudomonal coverage is also effective against most other aerobic Gram-negative pathogens responsible for NP. When staphylococcal infection is suspected, the local rate of methicillin resistance should be considered. Similarly, for Gram-negative infections, the prevalence of ESBL-secreting organisms is important. We consider that antibacterials such as vancomycin, carbapenems and ureidopenicillin/ β -lactamase inhibitor combinations should be used when the prevalence of resistant organisms is >5%. For patients in general wards who are not immunocompromised and where multiresis-

tant organisms are not prevalent, a β -lactam such as ampicillin, together with an aminoglycoside or cefuroxime, which has the advantage of activity against *S. aureus* and β -lactamase-producing *H. influenzae*, may be used. The disadvantage, however, is the promotion of ESBL-secreting organisms. Hospital factors influencing the choice of an empiric treatment regimen include the antimicrobial susceptibility patterns of resident microbial flora and potential nosocomial pathogens, seasonality (for example RSV and influenza virus in winter), and recent illness of any staff.

ATS guidelines for the management of adults with NP distinguish between patients with clinically mild-to-moderate pneumonia, and those with severe pneumonia.^[59] For patients with mild-to-moderate pneumonia, infection should be considered to be most likely due to enteric (nonpseudomonal) Gram-negative bacilli, methicillin-sensitive *S. aureus*, or *S. pneumoniae*. In these patients a second-generation cephalosporin or β -lactam/ β -lactamase inhibitor is advised. The presence of specific risk factors such as prior antibacterial treatment, immunosuppression, and aspiration predispose to infection with additional pathogens. Under these circumstances a broader range of antimicrobial agents should be considered, including clindamycin, vancomycin or rifampin (rifampicin). The length of hospital stay prior to the onset of NP may also influence the pathogenesis; adults who develop NP after a prolonged hospital stay are more likely to be infected with MRSA and resistant Gram-negative bacteria, including *P. aeruginosa*, *Enterobacter* spp. and *Acinetobacter* spp.^[59,78] Combination antibacterial therapy would be indicated for late onset NP; possible combinations include an aminoglycoside plus one of the following: an antipseudomonal penicillin, β -lactam/ β -lactamase inhibitor, some third- or fourth-generation cephalosporins, imipenem, or aztreonam. Vancomycin should be added if MRSA is suspected. Severe NP usually results from the presence of multiple risk factors or a highly virulent organism. In early onset severe NP (within 5 days of admission) in a patient without risk factors, infection with *H. influenzae* and methicillin-sensitive *S. aureus* are of particular concern; however, when severe NP occurs after 5 days of hospitalization, highly resistant Gram-negative bacteria and MRSA should be considered, and combination therapy is indicated.

The role of monotherapy compared with combination therapy has not been well defined. Monotherapy is cheaper and associated with less toxicity than combination therapy. Broad spectrum antibacterials available for monotherapy include third-generation and newer cephalosporins, penicillin/ β -lactamase inhibitor combinations, and carbapenems.^[79] The clinical efficacy of single-drug empiric treatment of NP in adults is comparable to that of multidrug regimens; however, emergence of resistance and superinfection

Table II. General principles of antibacterial use for nosocomial pneumonia

Culture available sources before commencing empiric therapy: blood culture, tracheal aspirate (immediately after intubation), induced sputum, pus, urine. Samples (tracheal aspirate, stool, nasal washings and urine) should also be sent for virological investigations

Step down therapy as soon as the causative organism and its sensitivity are known, i.e. stop all unnecessary antibacterials, using the agent with the narrowest spectrum that has good activity against the isolate

Limit the use of specific antibacterials:

- discontinue antibacterials for Gram-positive bacteria if a Gram-negative organism is cultured from a sterile or representative sample, and vice versa
- if methicillin-sensitive *Staphylococcus* is cultured, substitute cloxacillin for vancomycin
- if *Escherichia coli* or *Klebsiella* spp. is cultured that does not produce extended spectrum β -lactamase, use the narrowest spectrum antibacterial
- for *Enterobacter* spp. (possible resistance due to derepressed mutants), use a carbapenem or cefepime
- for *Pseudomonas*, *Citrobacter* and *Enterobacter* spp., use an aminoglycoside with an appropriate β -lactam such as piperacillin, ceftazidime or cefepime

Consult with a medical microbiologist and/or infectious diseases specialist when uncertain about antibacterial choices or modifications

Table III. Empiric selection of antibacterials for nosocomial pneumonia in a tertiary care hospital where MRSA and ESBL-producing Enterobacteriaceae are endemic

Empiric therapy

Piperacillin-tazobactam + aminoglycoside *or*

Carbapenem + aminoglycoside. Change aminoglycoside according to sensitivity pattern, or stop if organism is resistant to all aminoglycosides

Add clindamycin *or* vancomycin if no response to initial treatment within 48 hours or if MRSA suspected, based on:

- radiological evidence of necrotizing pneumonia, empyema or lung abscess
- presence of thrombophlebitis
- presence of an indwelling central line for longer than 48 hours

Immunocompromised child

Add trimethoprim-sulfamethoxazole (cotrimoxazole) for suspected *Pneumocystis carinii* if not on chemoprophylaxis

If no response after 48-72 hours, consider adding amphotericin B

ESBL = extended spectrum β -lactamase; **MRSA** = methicillin-resistant *Staphylococcus aureus*.

have been noted during carbapenem monotherapy, especially where *P. aeruginosa* is implicated.^[80] Both meropenem and piperacillin-tazobactam have been successfully used as single agents in adults with NP and/or peritonitis, although the latter was associated with a better outcome when *P. aeruginosa* was implicated.^[81,82]

In general, antibacterials should be given intravenously and oral therapy instituted once clinical improvement has occurred. There are few data on inhaled antibacterials for NP in children. In cystic fibrosis, regular administration of aerosolized tobramycin reduces sputum volume and *P. aeruginosa* organism density with concomitant improvement in lung function.^[83] A recent report described three patients with multiresistant *P. aeruginosa* NP for whom supplemental therapy with aerosolized colistin was beneficial.^[84] Currently there are insufficient data to support the routine use of inhaled antibacterials for NP.^[85]

Therapy should be modified when a specific pathogen and its antimicrobial susceptibility are identified. Most clinicians will commence with a combination of a β -lactam plus aminoglycoside to ensure adequate Gram-positive, Gram-negative and anaerobic cover. To achieve bactericidal activity in bronchial secretions and associated good clinical outcome, adequate concentrations of antibacterial must penetrate into these secretions.^[86] Penetration into bronchial secretions is high for trimethoprim, macrolides, quinolones, and tetracyclines, moderate for aminoglycosides, and low for β -lactams.^[87] Guidelines for antibacterial use and dosage, and a strategy for institutions where MRSA and ESBL-secreting Gram-negative infections are endemic, are presented in table II, table III and table IV. Supportive therapy should be provided for children with viral NP.

6. Prevention

Antiviral agents may have a role in the treatment of influenza A, herpes simplex virus, cytomegalovirus, varicella zoster virus pneumonitis in selected immunosuppressed children. Effective prevention of NP requires infection control measures that affect the environment, personnel and patients. For the environment, the appropriate design and staffing of critical care areas is important to prevent NP. Measures to prevent NP are aimed at preventing colonization and increasing host defenses.^[21]

6.1 Prevention of Colonization

A number of measures may be useful to prevent colonization of the upper respiratory tract with exogenous and endogenous flora. These include attention to hygiene, care of medical equipment, optimal nursing, selective gut decontamination, avoidance of H₂ antagonists, and judicious use of antibacterials.

Transmission of infectious agents by hand carriage is important and preventable, but hand washing is frequently underperformed.^[21] Recent data suggest better compliance for hand disinfection than hand washing, probably because the former is far less time-consuming. Pittet and colleagues^[90] recently documented an improvement from 48% of opportunities for compliance with hand cleansing to 66% between 1994 and 1997 after introduction of a hand disinfection program. At the same time, the prevalence of nosocomial events decreased from 16.9 to 9.9%. Gloves should be worn when touching bloody secretions and open wounds.

Appropriate infection control and isolation policies for specific viruses and multiresistant bacteria are fundamental to the prevention of NP.^[3] Patients infected or colonized with resistant organisms should be cohorted. In circumstances where cohorting is not possible, hand hygiene should be re-emphasized and non-sterile gloves should be worn for each patient contact. Signposting is important to reinforce infection control measures and to identify patients and areas that may be a source of nosocomial infection. Outbreaks of *S. aureus* in newborn nurseries require unique control measures, including application of antiseptics to the umbilical stump to prevent colonization, cohorting of infants and staff, and attention to hand washing using antimicrobial soap. Nasal carriers should be identified and treated with mupirocin.^[91] Attempts to eradicate nasal carriage of *S. aureus* by the use of mupirocin, rifampin, trimethoprim-sulfamethoxazole (cotrimoxazole), ciprofloxacin and novobiocin have only been partially successful, as emerging resistance to these agents, recolonization, and partial eradication have been problematic.^[92]

RSV infection may be transmitted by patients, staff, or visitors. Control measures include segregation of, and contact precautions

Table IV. Recommended dosages of commonly used antibacterials for treatment of nosocomial pneumonia in children^[88,89]

Agent	Dose (mg/kg/dose)	Administration
Broad-spectrum penicillin (with β-lactamase inhibitor)		
Amoxicillin-clavulanic acid	25 (amoxicillin)	q6h
Cephalosporins		
Cefepime	25	q12h (q8-12h) over 5 min
Cefepime (severe infection)	50	q8-12h
Cefotaxime	30	q8h
Cefotaxime (severe infection)	50	q4-6h
Cefuroxime	25	q8h
Cefuroxime (severe infection)	60-75	q8h
Aminoglycosides		
Amikacin	5-7.5	q8h
Gentamicin	2.5	q8h
Ureidopenicillin (with β-lactamase inhibitor)		
Piperacillin-tazobactam	100 (piperacillin)	q4-6h
Carbapenems		
Imipenem-cilastin	15 (imipenem)	q8h
Imipenem (severe infection)-cilastin	25	q6h over 1h
Meropenem	10-20	q8h over 5-30 min
Meropenem (severe infection)	20-40	q8h over 5-30 min
Other		
Dicloxacillin	5-10	q6h
Dicloxacillin (severe infection)	25-50	q4-6h
Trimethoprim-sulfamethoxazole (cotrimoxazole) ^a	Loading 10 (trimethoprim) then 5	q6h over 1h
Vancomycin	10	q6h over 1h

a For *Pneumocystis carinii* pneumonia.

q $\times$ h = every x hours.

for, RSV-infected children, and exclusion from susceptible children, particularly those with underlying cardiac, pulmonary, or immune problems, of visitors and staff with respiratory tract or documented RSV infection.^[93] Such a targeted intervention program can reduce the incidence of RSV NP by 39%.^[52] HIV-infected children with RSV infections have prolonged shedding of RSV and may be an important source of nosocomial spread.^[94]

Both RSV immunoglobulin intravenous (RSV-IGIV) and the humanised monoclonal antibody against RSV F protein are effective in preventing RSV infection in high risk infants, especially premature infants <32 weeks gestation, and any infant <2 years of age in the presence of chronic lung disease. Because of the ease of administration (intramuscular rather than intravenous), and the low volume of fluid required, palivizumab is far more widely used than RSV-IGIV. Both products are extremely expensive. The guidelines of the American Academy of Pediatrics published in

1998 recommended that primary emphasis should be on proper infection control practices rather than passive immunization for prevention of nosocomial infection.^[95] In a recent review of nosocomial RSV infection, Hall^[96] endorsed this viewpoint. Palivizumab has been associated with the control of NP due to RSV in a special care baby unit in the UK where conventional infection control practices were reportedly ineffective. Seven infants developed RSV infection. Palivizumab was then given to the eight 'at risk' infants, all of whom remained uninfected.^[97]

Care of equipment, particularly ventilator apparatus, and use of sterile medications and materials for respiratory support have reduced the incidence of bacterial colonization of equipment. Infrequent changes of the ventilator circuitry reduce the risk of VAP.^[17,18] A heavy nursing workload has been correlated with increased risk for patients to be colonized with multiresistant organisms.^[98] Improvements in the design, amount of space, and nursing staff-to-infant ratio were reported to substantially reduce the rate of major nosocomial infection from 5.2 to 0.9% in a NICU in the USA.^[99] Optimal nursing care may reduce the risk of VAP. Placing adult patients who are receiving mechanical ventilation in a semi-recumbent position may help to reduce aspiration of upper airways secretions.^[100] The use of an endotracheal tube designed with a suction port above the endotracheal tube cuff to allow continuous suctioning of subglottic secretions, so removing contaminated secretions before they reach the lung, has been reported to decrease the incidence of VAP in adult patients at high risk and to be cost-effective;^[101,102] however, this approach will not prevent VAP from organisms that may colonize the lung after direct inoculation, such as *P. aeruginosa*.^[59]

Selective gut decontamination may reduce the incidence of NP and mortality in critically ill adult patients.^[103] By applying a paste of nonabsorbable antimicrobials (usually 2% tobramycin, 2% amphotericin B, 2% polymyxin E) to the oropharynx and stomach, the number of potential Gram-negative pathogens may be reduced. Lack of data in children, concern about the emergence of resistant bacterial strains, and failure to improve outcome has limited its use.^[104] Nevertheless, selective gut decontamination may be useful in particular situations, such as patients undergoing liver transplantation.^[21]

6.2 Altering Host Defenses

Local and systemic host defense mechanisms are frequently impaired in severe illness. Minimizing factors that impair host defense and administering agents that improve host response may prevent or reduce the severity of NP. Immunosuppressive agents should be avoided where possible.^[11] As malnutrition is an important risk factor for NP, maintenance of adequate nutrition is essential. Enteral feeding has fewer complications than the par-

enteral route but may raise the gastric pH, thus enhancing bacterial colonization. Jejunal feeding tubes may overcome this problem but increase the complexity of management.^[105] Further work is needed to determine the optimal nutritional supplementation for enhancing gut immunological function.

Although there is conflicting evidence on the effects of H₂ antagonists on NP, meta-analyses have concluded that there is a trend towards a decreased risk of NP in patients treated with sucralfate rather than H₂ antagonists or antacids.^[22-24] The available evidence therefore suggests that routine use of antacids and H₂ antagonists should be discouraged as they may increase the risk of NP.

6.3 Appropriate Use of Antibacterials

Restricted and controlled use of antibacterials is critical to prevent the development of resistant bacteria. De Man et al.^[106] demonstrated that by avoiding broad spectrum antibacterials such as amoxicillin and cefotaxime, they were able to significantly reduce the colonization of neonates in an ICU with *Enterobacter cloacae* resistant to their empirical therapy for nosocomial sepsis (flucloxacillin and tobramycin). A study in a PICU reported that antibacterial treatment for suspected VAP far exceeded the rate of confirmed infections, and concluded that the largest reduction in antibacterial usage would result from improved diagnostic strategies for NP and guidelines to limit the use of antibacterials.^[107] Ongoing epidemiological surveillance of resident flora at individual institutions is important for monitoring, and as a guide for empiric therapy.

7. Conclusions

NP is a common infection, particularly in neonates and children who require intubation or intensive care support, and those with underlying chronic illnesses. Viruses are the most common cause of NP. Gram-negative bacteria are the major bacterial pathogens and are associated with a poor prognosis. Amongst the Gram-positive bacteria, *S. aureus* and *S. epidermidis* predominate as a cause of NP. Increasingly multiresistant pathogens have been reported.

Diagnosis of NP in children is difficult and relies on clinical, radiological and microbiological findings. Broad spectrum antimicrobials effective against Gram-negative and Gram-positive bacteria should be used empirically. A carbapenem or ureidopenicillin derivative plus β -lactamase inhibitor should be used where extended spectrum β -lactamase-producing *Enterobacteriaceae* are endemic. Vancomycin is indicated when infection with methicillin-resistant *S. aureus* is suspected. Therapy should be

modified according to the type and susceptibility of a pathogen once identified. Prevention of NP requires infection control measures that affect the environment, personnel and patients. Of these, hand hygiene, appropriate infection control policies, and selective use of antibacterials can effectively reduce the incidence of NP.

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