Chapter 11
Ventilator-Associated Pneumonia

The area of the alveolar epithelium of the lung is approximately 70 m². This area is constantly in contact with the ambient air and is therefore vulnerable to contamination with airborne microbes and particles of respirable size. Due to the configuration of the respiratory tract, airborne particles having diameters in the range of 0.5–2.0 μ can reach and deposit in the terminal part of the tracheobronchial tree – most bacteria are of this size. In reality, very few bacteria cause infections by spreading via the airborne route (e.g., mycobacteria, viruses, and legionella). Most bacteria cause pneumonia by first colonizing the upper respiratory tract and later descending into the tracheobronchial tree.

In contrast to the lower airways, the upper airways are literally teeming with microorganisms, and a multitude of these flourish here even in good health. The majority of them are anaerobes, and these outnumber the aerobes by approximately 3–5 times.

Colonization of the oropharynx begins soon after birth, initially by *E. coli* and other transient contaminants. After a few days, the flora begins to resemble the adult commensal flora, with disappearance of gram-negative rods and appearance of *Streptococcus salivarius*, the lactobacilli, and other anaerobic bacteria. Distinct ecological niches exist within the oral cavity – in areas that are otherwise in anatomical continuity – and in each of these, the dominant organism may differ. A small percentage of normal adults, persistently harbor gram-negative rods in their oropharynxes (see below).
In healthy adults, the upper respiratory secretions generally contain ten to 100 million organisms per mL of secretion. The number sharply rises in gingivodental disease, when the levels may increase almost 1,000-fold. During sleep, even in healthy individuals, small quantities of upper airway secretions are aspirated into the tracheobronchial tree. About 45% of normal subjects aspirate small quantities during sleep. A much greater proportion of individuals aspirate pharyngeal secretions during sickness. In sick persons, not only is aspiration more frequent but the aspirated flora is different.

Airway mucosa is histologically quite similar, from the nasopharynx through the trachea down to the conducting airways, and is composed of ciliated epithelial cells. Receptors present on epithelial cells allow bacteria to bind to the mucosa via protrusions from bacterial cells called adhesions. In health, the adherence of normal oropharyngeal bacteria to the epithelial cells of the pharynx prevents gram negative aerobes from gaining a foothold on the pharyngeal mucosa, as does the phenomenon of interbacterial inhibition. In less than 1–6% cases, the upper airways of normal subjects are colonized by gram-negative bacteria.

In hospitalized patients, particularly those admitted to intensive care units, proteases eliminate the fibronectins from the epithelial cell surfaces, and a significant change occurs within the oropharyngeal flora. Fibronectins normally prevent bacterial adherence to epithelial surfaces and when the fibronectin film is removed, the adherence of pathogenic bacteria to the oropharyngeal epithelium is facilitated. Increased bacterial adherence leads to colonization of the upper respiratory tract by enteric gram-negative bacteria, and this predisposes to the later development of nosocomial pneumonia (NP). The incidence of colonization with gram-negative rods mounts with the gravity of the illness as well as with the degree of supportive care required by the patient.

Once gram negative aerobes colonize the oropharynx, the stage is set for the aspiration of these noxious organisms into the lower respiratory tract, with the potential peril of NP. The link between NP and oropharyngeal colonization has been established by several studies. In one study, NP occurred in 23%
of patients in whom prior oropharyngeal colonization was documented, but in only 3.3% of noncolonized patients.75

11.1 Incidence

Ventilator-associated pneumonia (VAP) is a form of NP, and several mechanisms of pathogenesis are common to the two. NP is the most common infection in the ICU and the most deadly of all nosocomial infections. It is the second most common nosocomial infection overall, second only to urinary tract infection.64 Although prevalence has been shown to vary between 12 and 29% in different studies,89 the mortality rate of NP has been uniformly high (20–50%).1,37 The case fatality ranges between 25 and 33% in most studies,50 though pneumonia is not necessarily the cause of death in these patients.35

Mechanically ventilated patients have extremely high infection rates – the incidence of NP may be 17–23% higher in intubated patients. This means that approximately one of every four mechanically-ventilated patients will get NP at some stage during the course of mechanical ventilation.

The crucial distinction of the ventilated patient is the presence of an endotracheal tube. This by itself (along with certain other factors associated with the care of a mechanically-ventilated patient) predisposes the patient to pneumonia. Ventilated patients may be at 6-20-fold greater risk of contracting pneumonia than are other hospitalized patients.66 VAP has an even greater mortality rate than NP: the attributable mortality rate of VAP can be as high as 30–50%.48

Patients with other comorbidities are prone to NP: smoking, COPD, ARDS, organ failure, major surgery, trauma, burns, and hypoalbuminemia.

11.2 Microbiology

The responsible flora in NP is polymicrobial in many cases, but the dominant organism usually varies from center to center. Aerobic gram-negative bacilli are frequently isolated.
Together with *Staphylococcus aureus*, they may account for as many as 50–70% cases of VAP.\(^3,95\)

The poor outcome in patients with VAP has been strongly linked to the inappropriateness of initial antibiotic therapy. Since initial antibiotic strategy assumes such profound importance, it is essential to realize that initial antibiotic treatment will almost always be empirical – as no test is likely to reveal the etiological agent at a time when initiation of antimicrobials is a medical urgency. It is therefore vital to include under the antibiotic umbrella the most likely etiological agents. Since different organisms prevail in different clinical circumstances – and indeed in different medical units – attempts have been made to formulate guidelines for initial antibiotic therapy depending on the clinical scenario.

Pneumonia developing in less than 5 days from the time of admission (early NP) is likely to be caused by organisms colonizing the patient’s upper respiratory tract at the time of intubation\(^13\) – viz., microorganisms that were acquired in the community: this flora is generally drug sensitive – except if antibiotics have been administered recently, or if hospitalization has occurred in the last 90 days. The most common community-acquired pathogens include *Streptococcus pneumoniae, Hemophilus influenzae*, and Methicillin-sensitive *Staphylococcus aureus* (MSSA); so antibiotic therapy is directed against these (Fig. 11.1).

**Microbiology of early ventilator-associated pneumonia**
- *Streptococcus pneumoniae*
- *Hemophilus influenzae*
- Methicillin-sensitive *Staphylococcus aureus* (MSSA)

**Microbiology of late ventilator-associated pneumonia**
- *Streptococcus pneumoniae*
- *Hemophilus influenzae*
- Methicillin-sensitive *Staphylococcus aureus* (MSSA)
- *Pseudomonas aeruginosa*
- *Acinetobacter*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)

**Figure 11.1.** Microbiology of ventilator-associated pneumonia.
The flora in late NP is different: it includes bacteria that are not part of the usual group of community-acquired pathogens – the *Pseudomonas aeruginosa*, Acinetobacter species and Methicillin-resistant *Staphylococcus aureus* (MRSA). Not only is the pattern of antibiotic susceptibility different, but these organisms tend to be multidrug resistant, having thrived on the antibiotic-rich milieu of the intensive care units wherein they proliferate. Predictably, the outcome in this group is palpably worse: not only is this related to the problem of drug resistance, but also to the inadequacy of initial antibiotic prescription which does not always cover these organisms within its ambit.

Different authors have proposed different time-frames for distinguishing between early from late VAPs: a cutoff period of 3 days appears to work just as well as one of 7 days, though a 4 day cutoff (4 days or less, vs. 5 days or more) is the most usually used to set the two apart.

Viral and fungal NPs rarely occur in immunocompetent hosts.

### 11.3 Risk Factors

Risk factors specific to certain clinical circumstances have been set out in Table 11.1 below.

#### 11.3.1 The Physical Effect of the Endotracheal Tube

As mentioned earlier, the endotracheal tube increases the risk of pneumonia by severalfold. It provides a direct conduit for bacteria to the tracheobronchial tree, bypassing the defenses of the upper respiratory tract. It also interferes with the cough reflex which is an important protective mechanism for the airway. During breathing, the endotracheal tube moves upon the tracheal mucosa (which is especially susceptible to damage in the vicinity of its tip and also in the region
24 The denudation of the airway epithelium encourages bacterial adherence with subsequent airway colonization. By a foreign-body effect, it also promotes reflex mucus secretion.

11.3.2 Alteration of Mucus Properties

Apart from the overt tracheobronchitis that may be induced by endotracheal or tracheostomy tubes, a chronic low-grade inflammatory state may exist in the intubated patient that may promote the binding of gram-negative bacteria to the airway epithelium; this may be more important in the distal airways than in the proximal.

One of the important functions of respiratory tract secretions is to trap and neutralize bacteria. To facilitate such an action, airway secretions contain IgA, lactoferrin, and certain bactericidal enzymes. The bacteria and particulate matter trapped in the blanket of mucus that covers the respiratory mucosa are propelled out of the tracheobronchial tree by the coordinated beating of the cilia.

The role of the mucus itself may be quite complex. It is believed that to trap germs, the mucus itself must have

| Specific risk factor         | Pathogen                                |
|------------------------------|-----------------------------------------|
| Aspiration                   | Anaerobes                               |
| Diabetes mellitus            | Methicillin-sensitive *Staphylococcus aureus* |
| Chronic renal failure        | Methicillin-sensitive *Staphylococcus aureus* |
| Steroid therapy              | *Legionella, Aspergillus*               |
| Prior antibiotic therapy     | *Pseudomonas, Acinetobacter, Enterobacter* |
| Structural lung disease      | *Pseudomonas*                           |
| Abdominal surgery            | *Anaerobes, Enterococcus*               |
| Coma                         | Methicillin-sensitive *Staphylococcus aureus* |
| Prolonged hospitalization    | *Pseudomonas, Acinetobacter, Enterobacter* |
| Intravenous drug abuse       | Methicillin-sensitive *Staphylococcus aureus* |
| COPD                         | *S. pneumonia, H. influenzae, M. catarrhalis* |
| Trauma                       | Methicillin-sensitive *Staphylococcus aureus* |
receptors for bacteria. If there is reflex mucus hypersecretion as a result of presence of an endotracheal tube, this may mean that more mucus receptors are present for bacterial adherence. The receptors might then serve as a bridge between the bacteria and respiratory epithelium. On the other hand, respiratory mucins may inhibit bacterial binding to the tracheal epithelium by themselves preferentially binding to the bacteria. Either or both the above may be true – the complex interactions between bacteria, mucins and respiratory epithelium are as yet far from clear.\textsuperscript{59}

11.3.3 Microaspiration

Pooling of throat secretions frequently occurs above the cuff of the endotracheal tube, and microaspiration between the cuff and the tracheal mucosa is always possible; this could potentially transmit microbes (that have multiplied in the sump created by the pooling of secretions above the endotracheal tube cuff) down into the tracheobronchial tree.\textsuperscript{66} The low-pressure high-volume cuff in contemporary use is more effective at preventing aspiration than is the high-pressure low-volume cuff. This is because the low-pressure high-volume cuff lies more closely in apposition with the tracheal wall and assumes the shape of the tracheal lumen with which it is in contact, thereby more reliably preventing aspiration. The possibility of epithelial injury is understandably higher with the low-volume \textit{high-pressure} cuffs,\textsuperscript{62} but inadvertent overinflation of a \textit{low-pressure} high-volume cuff may prove just as detrimental.\textsuperscript{104}

11.3.4 Biofilms

The luminal surface of the endotracheal tube is invariably contaminated by bacteria-laden secretions coughed out by the patient: it has been shown that within 2 days, the endotracheal tubes of three-fourths of all severely ill patients do get colonized.\textsuperscript{138} These bacteria become embedded in a
biofilm (glycocalyx) which thinly coats the inner surface of the endotracheal tube. Here, sheltered from the host defenses and antibiotics, these bacteria multiply to enormous numbers.\textsuperscript{148} If for some reason, the glycocalyx with its high population of bacteria is dislodged from the wall of the endotracheal tube and enters the tracheobronchial tree, it carries down with it a high burden of infection which can overwhelm host defenses. Such dislodgement is possible when the biofilm is stripped off the tube wall by suction catheters or bronchoscopes, or washed down by liquids deliberately instilled down the endotracheal tube.

**Box 11.1 The Endotracheal Tube and Lower Respiratory Tract Infection**

- Direct conduit for microorganisms by bypassing the upper respiratory tract
- Interference with the cough reflex
- Denudation of the tracheal mucosa by fricative movement
- Alteration of airway mucus properties
- Microaspiration of pooled secretions above the cuff
- Mucosal injury by overinflated cuff
- Biofilm formation

### 11.3.5 Ventilator Tubings

Like the endotracheal tubes, ventilator tubings can get colonized by bacteria that originate in the patient’s secretions. Understandably, colonization is heaviest in the part of the ventilator tubing closest to the patient.\textsuperscript{31} The expiratory limb of the ventilator circuit has been found to become colonized approximately after 2–4 days of initiation of mechanical ventilation.\textsuperscript{35} Eighty per cent of ventilator condensates are contaminated by bacteria, presumably from the patient’s own
respiratory tract. The accumulation of pooled condensate in the ventilator tubings provides a haven for bacteria to multiply, sheltered from host defenses and from the effects of antibiotics. When parts of the ventilator tubing are elevated as in the act of raising the bedrail, or when the position of the patient is changed, this condensate may find its way down the endotracheal tube, carrying with it a large “amplified” population of bacteria.

11.3.6 Gastric Feeds

The normally acidic gastric juice discourages the survival of microbiological flora within the stomach, which is therefore sterile. With advancing age and malnutrition, or in achlorhydric states, or indeed with the use of certain drugs that increase the gastric pH, the stomach is liable to get populated with bacteria. Gram-negative bacteria proliferate exponentially with rising in gastric pH: the use of antacids and H₂ blocking agents in the ICU has been shown to be associated with increased gastric colonization.

It appears that the gastric contents can reach the lungs in a number of ways. Recumbency encourages retrograde movement of the gastric contents up the esophagus, facilitating oropharyngeal colonization. Large volume gastric feeds that overwhelm the limited emptying time of the stomach in critically ill patients further encourage reflux. Nasogastric tubes, especially of wide bore interfere with the functioning of the gastroesophageal sphincter, and so promote regurgitation.

The presence of a nasogastric tube can encourage oropharyngeal colonization by various mechanisms. The nasogastric tube may provide a conduit whereby bacteria are transmitted upon its surface in a retrograde fashion from the stomach to the oropharynx, in a manner analogous to the urinary infection that occurs in catheterized patients. Gastric colonization might also be facilitated by the erosion of the oropharyngeal mucosa by the nasogastric tube, in the same manner that endotracheal-induced erosion of tracheal mucosa encourages tracheal colonization with bacteria. Although
this sequence of events is certainly plausible, even one study could not prove that nasogastric tubes could indeed predispose to NP.\textsuperscript{15}

At this time it is unclear whether initial gastric colonization – with subsequent oropharyngeal colonization, and then aspiration of the contaminated secretions – could be one of the key mechanisms in the genesis of NP. Bacteria isolated from gastric juice have frequently – but not always – been shown to be identical to the bacteria isolated from the lung, and this may imply a causal relationship between the two.\textsuperscript{47,77}

\subsection*{11.3.7 Sinusitis}

Sinusitis has emerged as an important cause of VAP. As many as 10\% of orally intubated patients have been found to have evidence of sinusitis by culture of maxillary sinus secretions,\textsuperscript{20} and the incidence may be much higher in nasally intubated patients.\textsuperscript{133} The evidence that bacterial sinusitis can lead to VAP is as yet circumstantial, but the flora isolated from the sinuses has been identical to the flora isolated from the lungs in a high proportion of cases of VAP.\textsuperscript{133} Indeed, the flora in nosocomial sinus infections tends to be polymicrobial or predominantly gram negative as does the flora in NPs.\textsuperscript{147} Anaerobic organisms are also common.\textsuperscript{90}

The occurrence of sinusitis in the ICU patient can be related to a variety of mechanisms that are unique to the critically ill patient. Nasogastric\textsuperscript{153} and nasotracheal tubes\textsuperscript{125} act as foreign bodies, and these elicit a local mucosal reaction. The ensuing mucus hypersecretion and mucosal edema is liable to block sinus ostia, permitting pooling of secretions within the blocked sinuses. Stagnated secretions within the sinuses act as culture media for bacteria; once contaminated, the sinuses act as foci of sepsis, with the potential for dissemination into other areas. It appears that biofilms can form upon plastic nasogastric tubes, much in the same manner as they can within endotracheal tubes.\textsuperscript{128}
In the recumbent and immobile ICU patient, the gravitational advantage for natural sinus drainage is lost.\textsuperscript{5} Furthermore, in a patient on positive pressure ventilation, the raised intrathoracic pressure diminishes the venous return from the head and neck contributing to nasal mucosal congestion and sinus ostial occlusion.\textsuperscript{5} It is also possible that the absence of the normal airflow through the nose in an intubated patient, as also the absence of sneezing and coughing reflexes, may make the patient susceptible to infection.

The paranasal sinuses are the site of production of large quantities of nitric oxide (NO), which is continuously released into the airways through sinus ostia. In quantities as small as 1 part per million, NO can exert substantive antibacterial effects.\textsuperscript{100,103} NO is also an important regulating agent for mucociliary activity.\textsuperscript{43,102} Ostial blockage can diminish NO production as can sepsis itself.

Box 11.2 Pathologic Mechanisms in Sinusitis

- Mucus hypersecretion
- Mucosal edema with blockage of sinus ostia
- Decreased mucociliary clearance
- Biofilm formation
- Increased gravitational mucosal congestion
- Decreased NO production
- Absence of coughing and sneezing

Nosocomial sinusitis usually originates in the maxillary sinuses before spreading to the sphenoid and ethmoid sinuses. Signs of sinusitis in the ICU can be notoriously difficult to appreciate. A high index of suspicion in a febrile patient may unearth sinusitis as the cause of the intercurrent infection. Due to gravitational influences, purulent secretions often trickle down posteriorly, and are aspirated, mimicking symptoms of tracheobronchitis rather than the symptoms of sinusitis.
The radiographic visualization of sinuses is best achieved with CT scans; sinus opacification and air fluid levels are consistent with sinusitis. Transport of the ventilated patient is itself a risk factor for VAP. Bedside sinus ultrasound, which has a high sensitivity and specificity for maxillary sinusitis\textsuperscript{67} – though not for the other sinuses – may obviate the need to transport the patient to the imageology suite.\textsuperscript{67}

Attempts should be made at microbiological diagnosis, not merely to identify the organism and its antibiotic sensitivity, but also because the tomographic features of infection are nonspecific and may sometimes be misleading.

11.3.8 Respiratory Therapy Equipment

Respiratory therapy equipment such as mainstream nebulizers can generate contaminated aerosols that can infect the ventilator tubing: contaminated medication nebulizers are capable of inciting infection.\textsuperscript{32} Airway interventions like fiberoptic bronchoscopy can also contaminate the airway in much the same way as suction catheters.

11.4 Position

Transportation of the patient out of the ICU appears to be an important risk factor for NP. Positioning the patient supine
will not only promote the aspiration of gastric contents or contaminated oropharyngeal secretions, but may cause the condensate in the ventilator tubing to enter the endotracheal tube and so find its way into the lower respiratory tract. In one study, as many as a quarter of all patients transported within the hospital developed NP.  

11.5 Diagnosis of VAP

Once introduced into the respiratory tract, the onset of infection and its spread are the factors of the virulence of the organism vis-a-vis the host defenses. The defenses of the critically ill and possibly malnourished host can be further impaired by alveolar hypoxia or neutropenia.

Early and appropriate antibiotic therapy is often crucial to the outcome in NP and VAP. The difficulties of choosing the right regimen are obvious, since it is neither easy to diagnose VAP nor to differentiate it from other confounding conditions that frequently coexist in the ventilated patient. With the insertion of an endotracheal or tracheostomy tube, the normally sterile lower airways become colonized within hours of “tubing” the patient: thus, recovery of at least one bacterial species from the lower airways is frequent, even in the absence of a frank infective process. Also, purulent tracheobronchial secretions are common and do not equate with disease. The occurrence of fever may represent disease elsewhere (e.g., sinusitis, cystitis, or catheter-induced sepsis) and not necessarily infection within the respiratory tract. Pulmonary fibroproliferation occurring later during the course of ARDS may be another noninfectious cause of fever.

Radiological shadows can be cast by a variety of cardiopulmonary conditions in the ventilated patient. Pulmonary infarction, pulmonary edema and areas of atelectasis or alveolar hemorrhage may cause confusion. Importantly, blood cultures, otherwise the sine qua non of infection, are frequently positive in ventilated patients even in the absence of pneumonia (Fig. 11.2).
When the lower respiratory tract is actually infected, two kinds of infection may occur: infectious tracheobronchitis and pneumonia. When fever and leucocytosis develop along with purulent sputum – but with no new radiological infiltrate – infectious tracheobronchitis is likely.\textsuperscript{115} When a new and persistent radiological infiltrate occurs in the setting of leucocytosis and purulent sputum, this indicates that the infection has now involved the pulmonary parenchyma, and a provisional diagnosis of pneumonia should be made.

When purely clinico-radiological criteria are used to identify NP or VAP, over-diagnosis can occur due to the fact that a wide variety of noninfectious clinical conditions can cast radiological shadows (see Fig…). Using bacterial criteria alone to diagnose nosocomial or VAP will result in a large false positive rate, owing to the inadvertent sampling of those organisms causing tracheobronchitis or those merely colonizing the respiratory tract.

Obviously therefore, the diagnosis is more reliable when bacterial criteria are considered in conjunction with clinical criteria. When the patient fulfills all the clinical criteria and the sampling method yields a “representative sample” (see below), pneumonia can be diagnosed with greater assurance.
Since the price to pay for an undiagnosed VAP is heavy, a high index of suspicion must be maintained especially in the situation of a new radiological infiltrate. Although the diagnosis of NP or VAP is untenable without a radiological infiltrate, a new radiological shadow, especially with fresh clinical signs such as fever, increased quantity or purulence of tracheobronchial secretions, or leucocytosis, may be taken to represent VAP unless proven otherwise. Thus, it has proven easier and possibly quite effective to employ a clinical definition for VAP: in epidemiologic studies at least, this has been shown to be quite sensitive – though not quite as specific – for ventilator-induced pulmonary infection.

Once NP or VAP is suspected, every effort should be made to identify the pathogen responsible. Various methods have been developed to sample the proximal and distal airways. Sampling of proximal airways is liable to turn up microbes colonizing the airways rather than true pathogens. Since the trachea may be colonized within a few hours of intubation, sampling by bronchial suction can be expected to yield false positive results.

Interestingly, in the presence of VAP/NP, tracheal suction does frequently yield the pathogen responsible, but will frequently contain as well, bacteria which have merely colonized the respiratory tract and are not responsible for pneumonia. Further confusion is engendered on account of the fact that in a little less than half of all cases, pneumonias may be polymicrobial.

### 11.5.1 Sampling Methods

Bronchoscopic (protected specimen brushing, bronchoalveolar lavage, protected bronchoalveolar lavage etc.) and non-bronchoscopic methods (telescoping and nontelescoping catheters) of sampling are available and these have varying sensitivities and specificities. The protected bronchoscopic brush is being increasingly favored as the modality least
likely to yield contaminated samples and most likely to yield a positive microbiological diagnosis,\textsuperscript{24} but much disagreement still remains regarding its sensitivity and specificity.\textsuperscript{48} Bronchial washings may be as reliable as protected brush sampling when clinical parameters as suggested above are applied.\textsuperscript{150} In difficult situations, open lung biopsy may need to be resorted to.

\subsection*{11.5.2 Interpretation of the Sample}

Having isolated a microorganism, it is helpful to ascertain the reliability of the sampling process before treating the microbe as a pathogen – this is because many of the sampling techniques possess less than ideal specificity. To this end, it is desirable to have objective indices wherever possible, but this is easier said than done. Qualitative techniques are generally nonspecific and can lead to unnecessary or inappropriate antibiotic therapy.\textsuperscript{52} Quantitative cultures are more representative, but colony counts above the generally accepted levels may not by themselves be diagnostic of pneumonia. Nevertheless, when 1,000 or more colony forming units are grown per milliliter, this means that 1,000–1,000,000 bacteria are present in every mL of the recovered lavage fluid, and this is usually considered significant.\textsuperscript{154}

These numbers emerge from the observation that pathogens in distal lung secretions prevail at concentrations of at least $10^5$–$10^6$ colony forming units per milliliter (cfu/mL).\textsuperscript{8} Only 1 mL or so of the >100 mL returned is truly representative of one million-odd alveoli sampled during a typical broncho-alveolar lavage (BAL): the number of pathogens in 100 mL of the returning fluid will be about one million cfu. In contrast, colonizing organisms prevail at much lower concentrations (<$10^4$cfu/mL). As can be expected, the microbial yield will increase in direct proportion to the quantity of returning lavage fluid.
Bronchoalveolar lavage samples are probably representative if 5% or more lavaged cells show intracellular organisms. In such cases, the likelihood of the sample being representative may be...
as high as 89–100%, though prior or ongoing antibiotic therapy can substantially reduce the sensitivity of the sampling technique.

When epithelial cells are seen in large numbers, it means that their site of origin is generally the buccal or pharyngeal mucosa. Epithelial cells comprising more than 1% of the total cellular component in bronchoscopic samples imply substantial contamination by oropharyngeal secretions and the samples should not be taken to represent secretions from distal airways or lung parenchyma.

Conversely, the presence of a large number of alveolar macrophages or polymorphs signifies that the sample originated in the terminal air units. When polymorphs are scant, pneumonia is unlikely, or the sample may simply not be adequate. The opposite cannot be said of a high polymorph count, as this may be a nonspecific finding. The presence of elastin fibers in the lavaged fluid may be indicative of gram negative pneumonia.

With both bronchoscopic and nonbronchoscopic techniques, contamination from the upper airways can confound interpretation. For example, Candida colonizing the upper airways can find their way into most samples recovered from the lower respiratory tract: demonstration of the fungus intracellularly within lung biopsy specimens is the only reliable means of confirming the diagnosis.

In spite of the poor sensitivity and specificity of most of these procedures, an attempt should be made to recover a microbiological pathogen, principally because appropriate antimicrobial therapy in the initial stages of NP is so crucial. Recovery of a pathogen may result in retailoring of the antibiotic regimen, with an improvement in outcome.

11.6 Prevention of NP/VAP

11.6.1 Hand-Washing

The old medical adage “prevention is better than cure” holds admirably in the case of NP or VAP, because the outcome of
these is often adverse. Vigilance and effective prophylaxis hold the key to successful outcome in a mechanically ventilated patient.

It is surprising to what extent scrupulous hand-washing before and between examining patients can help to reduce the incidence of nosocomially-transmitted infection. Provided it is correctly done, hand-washing remains an extremely important technique for the prevention of nosocomial infection.

11.6.2 Feeding and Nutrition

As discussed earlier, the colonization of the gastrointestinal tract and the subsequent aspiration of its contents may constitute a risk factor for the development of NP/VAP. To reduce the risk of aspiration, the patient must be nursed in a semi-recumbent position wherever possible. Supine head position is an independent risk factor for VAP. Large volume gastric feeds should be avoided.

Adequate nutritional support is important: malnutrition is an independent risk factor for VAP. Septic complications are more frequent with parenteral feeding; carefully regulated enteral feeds are of utmost importance. In the nonintubated patient, all agents which depress the sensorium – and thereby increase the risk of aspiration – must be avoided. Prokinetic agents, by decreasing gastric transit time may reduce the residual gastric volume and prevent aspiration. Large bore feeding tubes by their mechanical effect can promote gastrointestinal sphincter dysfunction and predispose to aspiration; smaller bore feeding tubes may be safer. In theory, enteral placement of the feeding tube could help by introducing the food bolus beyond two valves (gastroesophageal and gastroduodenal), rather than one, but it is uncertain that the risk of pneumonia can be brought down by replacing a gastroduodenal with a gastrojejunal tube.

Before every feed, the gastric residual volumes should be checked: the feed should be delayed or withheld if an excessive volume is aspirated at the time of the scheduled feed. It may be
safer to administer enteral nutrition using continuous infusion rather than bolus feeds, using feeding tubes of small bore.

### 11.6.3 Stress Ulcer Prophylaxis

Mechanical ventilation is intensely stressful for the patient. The risk of stress ulceration in the ICU is extremely high. Stress ulcer prophylaxis is common in ICUs and there may be a tendency to overprescribe these medications. The demerits of pH lowering agents such as H₂ receptor antagonists have been discussed earlier. Sucralfate may offer some advantage over the former in the sense that it does not lower the pH, but rather achieves gastroprotection by acting as a physical barrier between the gastric mucosa and the acidic gastric contents; also, it may have an intrinsic antibacterial activity of its own, theoretically reducing gastric colonization. However, recent studies have, by and large, vindicated the H₂ receptor antagonists, although the last word on the matter has not yet been said.

### 11.6.4 Topical Antibiotics

Topical antibiotics may be efficacious in treating tracheobronchitis in intubated patients. The rationale behind appears to be that in the absence of florid infection, a topical antibiotic may be able to contain the local tracheobronchial contaminants. Topical antibiotic therapy has been used in the form of drugs delivered to the lower respiratory tract in high concentrations, through a tracheostomy or endotracheal tube. The method of introduction of the antibiotic is usually by nebulization or by direct instillation, but it is not clear which of the two approaches is superior. Aminoglycosides are used in this fashion, usually after pretreatment with a bronchodilator. Although the efficacy of the antibiotics administered by the endotracheal route in preventing VAP has been proven in several studies, their potential for producing bacterial resistance is as yet not ruled out, and as such, the use of
topical antibiotics for the prophylaxis of infection is presently discouraged.

*Selective digestive decontamination:* Application of antibiotic paste to the oropharynx to reduce oropharyngeal colonization, and instillation of antibiotics into the stomach to prevent gastric colonization can possibly prevent bacterial transmission from these sites into the lungs. Used widely in Europe, a mixture of antibiotics like an aminoglycoside or a fluoroquinolone plus a nonabsorbable antibiotic (e.g., polymyxin) and an antifungal agent (either amphotericin B or nystatin) were found to reduce the incidence of pneumonia, but not so much as to favorably alter the outcome. Methodological issues confound the interpretation of a large number of these studies.

In theory, this method of prophylaxis relies on the prevention of colonization of the oropharynx and the stomach for the prevention of the subsequent NP. Therefore it does not prevent the onset of pneumonias that are caused by direct bacterial inoculation into the endotracheal or tracheostomy tubes. Pseudomonas, in particular, has been known to directly colonize the tracheobronchial tree without previously colonizing the gastrointestinal tract or the oropharynx. Again, concerns regarding the emergence of bacterial resistance limit the usage of selective digestive decontamination until more data are available.

*Chlorhexidine mouth wash:* The use of chlorhexidine – which is an antiseptic – as a mouth wash was found to significantly decrease the incidence of NP in a group of patients undergoing cardiac bypass surgery.

11.7 Interventions Related to the Endotracheal Tube and Ventilator Circuit

Changing of the endotracheal tube with the intent of preventing infection has not been shown to help; indeed, it may actually be harmful, presumably because of the risk of aspiration
during such a process, of the pooled pharyngeal secretions collected in the sump above the tube cuff. Also, the act of introducing a new endotracheal tube may itself cause more bacteria to be carried down into the tracheobronchial tree. The answer may lie in the development of new biomaterials for the endotracheal tube that might prevent the development of biofilms. Coating the inside of the endotracheal tube with a silver material appears to reduce biofilm formation and inhibit bacterial colonization, but more trials are necessary.\textsuperscript{132} Continuous subglottic suctioning has been shown to be effective: a metaanalysis revealed an almost 50% reduction in the rate of VAP.\textsuperscript{42}

Changing the ventilator circuits frequently has also not been shown to have any positive impact in preventing VAP. In fact, one study showed no increase in the rates of VAP if the circuitry was never changed,\textsuperscript{46} and patients in whom ventilator circuitry was changed more frequently than every 48 h were shown to actually run a higher risk of VAP.\textsuperscript{33} It seems sensible to change tubings only if the circuit appears to be overtly soiled.\textsuperscript{152}

Condensate that accumulates in ventilator tubings should be emptied regularly and treated as infectious waste. When airway humidification is required, heat-moisture exchangers (HMEs) are probably safer than heated humidifiers (see section 15.5).

11.8 Treatment of Nosocomial Sinusitis

The treatment of nosocomial sinusitis not only involves the institution of appropriate antibiotic therapy, but also requires the removal of all nasal tubes in order to decrease nasal irritation and mucosal edema. Drainage of stagnant secretions from the sinuses can be aided by opening up the sinus ostia by topical nasal vasoconstrictor drops, and by elevating the head-end of the bed. When maxillary puncture is performed for diagnostic purposes, an antral wash carried out at the same time may prove therapeutic.
11.9 Treatment

In NP, early and aggressive antibiotic therapy strongly correlates with survival. Although attempts to procure respiratory specimens for culture should be swiftly undertaken, antibiotic therapy should never be delayed merely for the purpose of collecting samples.

11.9.1 Antibiotic Resistance

Antibiotic resistance issues have now become the bane of ICUs the world over. Indiscriminate antibiotic usage has resulted in the emergence of resistance, and multidrug resistant bacteria now abound. Indeed, it is true to say that only in the past couple of decades has the gravity of the problem really begun to sink in.

Half of all ICU usage of antibiotics is for lung infections. It is now universally appreciated that indiscriminate antibiotic usage can exert a selective pressure on bacteria, eradicating sensitive organisms and enabling the intrinsically resistant strains to survive and proliferate.

The principles of microbiological resistance (as proposed by Levy) postulate that:

- Given sufficient time and drug use, antibiotic resistance will emerge.
- Antibiotic resistance is progressive, evolving from low levels through intermediate to high levels.
- Organisms that are resistant to one drug are likely to be resistant to other antibiotics.
- Once resistance appears, it is likely to decline slowly, if at all.
- The use of antibiotics by any one person affects others in the extended and immediate environment.

Bacteria can develop antibiotic resistance by several mechanisms: gram-negative bacteria contain a three-layered cell wall. Aqueous porin channels contained within the outer
wall allow solutes including antibiotics to diffuse into the bacterial cell. Alteration of porin channels within gram negative bacteria can impede the penetration of the antibiotic into the bacterial cell. The production and concentration of beta-lactamases and other antibiotic-inactivating enzymes within the periplasmic space by gram-negative bacteria has become a cause of troublesome bacterial resistance the world over. In addition, both gram-negative and gram-positive bacteria can have intracellular inactivating enzymes. Bacteria can also alter antibiotic target sites within themselves, or even develop an efflux mechanism to actively pump antibiotics outside the bacterial cell, thereby limiting intracellular antibiotic concentrations. Resistance in gram negative bacteria most frequently is mediated by their production of (beta-lactamase) enzymes that rapidly inactivate the beta-lactam antibiotics. Over 500 beta-lactamases have been identified now; 5 times the number that microbiologists were aware of, 30 years ago.

Beta-lactamase production can result in bacterial resistance to a large spectrum of powerful beta-lactam agents. The enormity of the problem can be appreciated by the fact that it took just 2 years after the introduction of ceftazidime and ceftriaxone for the first extended-spectrum beta-lactamase (ESBL) to be recognized. Since then, there has been a tremendous surge in the frequency with which ESBLs are encountered worldwide. The local prevalence of ESBLs has been shown to vary greatly, and pockets of local dissemination rather than wide-range spread are usual. ESBLs have mostly been encountered in Klebsiella isolates and their incidence worldwide appears to be on the increase. Importantly, once established within the ICU or the hospital, ESBLs can be extremely difficult to eradicate. For the treatment of severe infection by ESBL producing strains, carbapenems like imipenem may be most appropriate.

Certain bacteria, in particular, Pseudomonas and Acinetobacter, are especially adept at developing drug resistance and may do so through several highly specialized and innovative mechanisms. The major mechanism of resistance
36711.9 Treatment

is chromosomal or plasmid-mediated beta-lactamase production, but Pseudomonas, for instance, can also modify pencillin binding proteins and prevent aminoglycoside binding to ribosomes. Further, Pseudomonas can develop multi-drug resistance (MDR) by decreasing cellular permeability to beta-lactams and four quinolones, in addition to actively pumping these drugs outside the bacterial cell. Resistance to four-quinolones can also develop by mutations at chromosomal loci encoding binding sites on DNA-gyrase.

MDR in gram-negative bacilli has been defined as resistance to at least two – and sometimes as many as eight – key gram-negative antibiotics. When the organisms are resistant to all the antibiotics regarded as effective for gram-negative infections (e.g., cefepime, ceftazidime, imipenem, meropenem, piperacillin-tazobactam, ciprofloxacin, and levofloxacin), they are termed panresistant.

Box 11.5 Primary Host-Related Risk Factors for MDR Infection

Antibiotic use in the preceding 90 days
- Current hospitalization of 5 days
- Admission in a healthcare facility such as a nursing home or a dialysis unit
- High incidence of antibiotic resistance in the hospital unit, hospital, or community

Pseudomonas with its advanced mechanisms of developing drug resistance has for some years been recognized as a grave threat, but the recent emergence of multidrug resistant Acinetobacter has been a cause of considerable dismay in certain regions. The revival of the once-redundant colistin is a testament to the desperate need for more antibiotics.

In terms of bacterial resistance, certain gram-positive organisms – such as S. aureus – are proving as problematic as aerobic gram-negative bacilli. Pencillin-resistant staphylococci
were described shortly after the advent of penicillin, and in just two decades the rates of penicillin resistant strains had spiraled to 90% in some health facilities in England. Currently, nearly all isolates of S. aureus from hospitals, and most community acquired strains are anticipated to be penicillin resistant.

The introduction of methicillin in 1961 did succeed to an extent in overcoming penicillin-resistant strains, but only at the cost of the creation of a new menace, the methicillin-resistant *Staphylococcus aureus* (MRSA). By 1989, MRSA strains comprised 50% of all isolates of *S. aureus* in most major hospitals in the USA. Vancomycin and linezolid are considered the cornerstones for MRSA therapy. Vancomycin-resistant strains of enterococci have now been identified, as have strains of *S. aureus* showing intermediate sensitivity to vancomycin. The vancomycin-intermediate *S. aureus* or glycopeptide-resistant *S. aureus* (VISA, GISA) strains have surfaced under conditions of prolonged exposure to vancomycin, or in situations where dialysis or intravascular device placement was required. Vancomycin-resistant enterococci are capable of spreading vancomycin resistance to other organisms, since the mode of spread is plasmid transmission to other microbes by conjugation.

### 11.9.2 Pharmacokinetics

An exhaustive discussion on antibiotic pharmacokinetics and pharmacodynamics and indeed of the antibiotic strategy in NP/VAP is beyond the scope of this book.

The efficacy of an antibiotic against a pathogen can be quantified in several ways. These have been summarized in Fig. 11.3.

**Choice of antibiotic:** The choice of the initial antibiotic for NP is determined not only by the organism likely to be present, the pharmacokinetic profiles of the various antibiotics and their potential toxicity, but also by local resistance issues. As discussed above, organisms that are found in early NP are comparable to those that cause community-acquired pneumonias, and the treatment of the two is generally very
similar – that is, except, if the patient has been a resident of a nursing home or has other risk factors for antibiotic resistance (see Fig...). For late NP therapeutic decisions are predictably more complex. In general, antibiotic therapy should primarily target gram-negative organisms; in particular the possibility of Pseudomonal infection should be kept in mind. As mentioned above, polymicrobial infections are common and coverage with multiple antibiotics may be needed until microbiological reports are available.

Wherever possible, antibiotic therapy should be guided by microbiology, and the regimen should be restructured in the light of the lab reports. This is essential if the responsible microbe is to be covered with as narrow spectrum antibiotic as possible: the emergence of antibiotic resistance is always a greater concern with broad-spectrum therapy.
Monotherapy may be acceptable in nonbacteremic cases and a carbapenem could be used. A beta-lactam antibiotic with antipseudomonal action plus either an aminoglycoside or ciprofloxacin is a commonly used regimen. Because of resistance issues, dual antibiotic coverage for *Pseudomonas aeruginosa* may be important, especially in bacteremic cases.\(^7^0\)

Cephalosporins as first-line agents are generally not preferred because of their propensity to select out resistant pseudomonas, and the combination of a broader spectrum penicillin (such as piperacillin with or without tazobactam) along with an aminoglycoside may be more suitable. Indeed, empiric usage of ceftazidime has been incriminated in the emergence of extended spectrum beta-lactamase producing bacteria. It is equally likely that if other antibiotics are used regularly as monotherapy, similar patterns of resistance could emerge. The pharmacokinetics of aminoglycosides preclude their role as sole agents for pneumonia. Since the lungs are, in effect, large capillary beds, penetration of most antibiotics into the lungs is adequate; aminoglycosides act poorly in the acidic milieu that is present locally in the pneumonic lung. When the targeted organism is pseudomonas, owing to its sophisticated methods of developing drug resistance, it is necessary to administer at least two antibiotics to which the organism is sensitive.

As regards the specific antibiotics that should be used, there exist no hard and fast rules – except to hit hard (that is, use the antibiotic considered most appropriate up front) – and hit “fast” (that is, to administer the appropriate drug as quickly as possible). It bears emphasis that the choice of an antibiotic for empiric therapy should be based on regional patterns of antibiotic sensitivity, which are generally dynamic and should be continually updated.

*Aerosolized antibiotics*: The direct delivery of antibiotics into the lungs may provide an alternative to systemic administration.\(^1^6^4\) Higher drug concentrations are achievable by nebulizing or instilling antibiotics directly into the lower respiratory tract. Peak drug concentrations in respiratory secretions have been shown to be 200 times those achievable with systemic administration,\(^1^2^1\) with sputum trough levels over 20 times those considered adequate.
Reservations about antibiotic resistance have inevitably been voiced, but it may well be that earlier studies relied upon drug delivery systems which did not achieve a satisfactory lung deposition of the aerosolized antibiotic. On the other hand, several investigators have found a much lower incidence of resistance.

At the present time, nebulized antibiotics such as tobramycin may be viewed as being adjunctive treatments to systemic antibiotics in the treatment of VAP: most authorities would strenuously discourage their use as prophylactics. There is less clarity as regards their role in the treatment of ventilator-associated tracheobronchitis. Indeed, if tracheobronchitis be viewed as part of a continuum – of which VAP forms one extreme – aerosolized antibiotics may well have a vital role to play in the future.

All nebulizers do not have similar aerosol outputs in relation to specific drugs: this has been considered in Chap... (Figs. 11.4 and 11.5).

### 11.9.3 Duration of Therapy

It may be possible to use shorter courses of antibiotics than previously considered necessary. The duration of antibiotic therapy should be individualized to the patient and to the microbe. The speed of resolution of the pneumonia as well as the pathogen incriminated will often help in deciding this. In general, a multilobar or necrotizing pneumonia often presages a delayed response to therapy, as does a poor nutritional status of the host. It is generally possible to eliminate relatively rapidly, the organisms that cause early NP – *H. influenzae* and *S. pneumoniae*. On the other hand, the Enterobacteriaceae, *S. aureus* need more prolonged courses of antibiotic. Certain microbes, particularly *Pseudomonas* or *Acinetobacter* show high rates of treatment failure and relapse. In such cases antibiotic therapy may be extended to a minimum of 2–3 weeks. Unnecessarily prolonged antibiotic therapy often results in bacterial colonization, and this then presages recurrent VAP.
| **Pseudomonas aeruginosa** | **Acinetobacter species** | **ESBL producing Enterobacteriaceae** | **MRSA** |
|---------------------------|--------------------------|--------------------------------------|---------|
| Combination therapy has not been shown to alter the rates of resistance, but seem to show a survival benefit. | Combination therapy is generally considered unnecessary. | Monotherapy with third generation (Paterson DL, 2001) – and possible also fourth generation–cephalosporins should be avoided. | Both vancomycin or linezolid can be considered effective. |
| The ATS/IDSA nevertheless recommends combination therapy in proven pseudomonas pneumonia, because the incidence of resistance to monotherapy is so high, and combination therapy is less likely to result in inadequate coverage. | The choice of antibiotics is relatively limited because of the organism’s innate resistance to multiple classes of drugs. | A carbapenem is presently considered effective. | Vancomycin drug failures may be related to inadequate dosing underdosing in renal failure is one example. |
| A beta lactam antibiotic could be used with either a quinolone or an aminoglycoside. | Appropriate antibiotics: carbapenems, sulbactam (ampicillin-sulbactam), the polymyxins and colistin. | Resistance is common to aminoglycosides and 4-quinolones, and so combination therapy is not considered important. | Vancomycin in combination with rifampin or aminoglycosides has not been shown to be clearly superior to vancomycin as monotherapy. |
| As a companion antibiotic, an aminoglycoside may result in a trend towards an increased survival than a 4-quinolone. | When used carbapenems should be used in appropriately high doses to avoid the development of resistance. | The efficacy of piperacillin-tazobactam is uncertain, and the combination should be used with due care when choices are severely limited. | Linezolid penetrates better into the epithelial lining fluid than vancomycin and has been shown to be at least as effective as vancomycin in some clinical trials; it may actually be preferable to vancomycin especially if there are nephrotoxic drugs in the prescription or if there is a coexistent renal failure. |
| A quinolone as a companion antibiotic is appropriate if local data support its usage: antibiotic resistance is common with overuse. Data are scant. | Aerosolized antibiotics may be used as adjuncts especially in patients who have shown an unsatisfactory initial response. | Aerosolized antibiotics may be used as adjuncts especially in patients who have shown an unsatisfactory initial response. | |
| Levofloxacin at higher doses (eg 750 mg once daily) may be superior, though at present, there is no evidence to support this presumption. | | Levofloxacin at higher doses (eg 750 mg once daily) may be superior, though at present, there is no evidence to support this presumption. | |
| Aerosolized antibiotics may be used as adjuncts. | | Aerosolized antibiotics may be used as adjuncts especially in patients who have shown an unsatisfactory initial response. | |

**Figure 11.4. Empiric choice of antibiotic.**
In responders, an initial course of about 8 days may be as effective as a 14 day course.\textsuperscript{23}

\textit{11.9.4 Lack of Response to Therapy}

An early response – by day 3–5 or so – is a marker of survival.\textsuperscript{101} Clinical worsening or a lack of response to what is considered appropriate therapy, often requires a reappraisal of the situation: bacterial causes for the lack of response must of course be considered. The initial pathogens causing NP can persist despite what can be construed as appropriate antibiotic therapy, and such a bacterial persistence has been particularly linked to necrotizing pneumonia and gram-negative bacteremia.\textsuperscript{133} The reason for bacterial persistence appears to be drug resistance: the responsible pathogen may have been resistant from the very beginning, or have acquired resistance...
during the course of therapy. In the case of beta-lactam antibiotics, typically, bacterial isolates show initial susceptibility. However the pathogen at a culture repeated a few days later may be demonstrably resistant to the same antibiotic(s), illustrating the phenomenon of inducible drug resistance.

Clinical lack of response could also mean that the pathogen, by its very generic disposition, is unresponsive to antibiotics as a class: it may be a virus, a fungus or a mycobacterium.

Superinfection pneumonia can emerge when treatment of the dominant organisms allows the other aspirated components of a polymicrobial flora to proliferate,\textsuperscript{113} or when reinoculation of infected secretions occurs. The new pathogens generally prove to be much more drug resistant and destructive than their predecessors.\textsuperscript{113}

The problem of recurrent pneumonia has been described with regard to Pseudomonas; in practice it may be extremely difficult to differentiate recurrence from superinfection pneumonia.\textsuperscript{144} The options in nonresponding patients are not easy and initial broadening of the antibiotic umbrella followed by renewed attempts at directed microbiological sampling may help in clinical problem-solving.

That the pathology is noninfective must also be considered. Congestive cardiac failure, pulmonary infarction, segmental atelectasis, and alveolar hemorrhage are all capable of radiologically mimicking pneumonia. Extrapulmonary sources of infection such as complicated pleural collections may be overlooked, as could catheter induced infection, urinary sepsis, or drug-fever (Fig. 11.6).

\subsection*{11.9.5 Drug Cycling}

Drug cycling – in which different antibiotics are deliberately rotated after a period of use – has been proposed as a means to restrict the emergence of antibiotic resistant organisms.

This policy seems to be effective in that resistance to the withdrawn antibiotic can been seen to fall, as reported by some researchers,\textsuperscript{56} but the danger inherent in such an approach seems to be that resistance to the antibiotic
substituted in its place may subsequently rise. John Burke described this phenomenon as “squeezing the balloon of resistance,” implying that bacterial resistance may shift its focus to the newly substituted antibiotics when the usage of other antibiotics is restricted. There also remains considerable concern that rotation strategies may expose bacteria sequentially to different classes of antibiotics and thereby lead to a proliferation of multidrug-resistant microbes. Nevertheless, gratifying and sustainable results have been noted by several investigators, and in the dynamic scenario that prevails in most ICUs, the subject continues to evoke considerable interest.
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