PULMONARY INFECTION IN INTENSIVE CARE UNITS

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Since the earliest days of organized intensive care, pulmonary infection has been a problem in patients undergoing artificial ventilation of the lungs [43]. Hospital-acquired pneumonia is an important cause of morbidity and mortality among Intensive Care Unit (ICU) patients, and its incidence has not been reduced by developments in medical technology.

Pneumonia in artificially ventilated patients can be clinically indistinguishable from non-infective conditions commonly encountered in intensive care, such as atelectasis and pulmonary oedema, and the patient's condition may fail to improve even when antimicrobial therapy is commenced early in the course of the condition.

The practical difficulties of diagnosing and treating pneumonia in patients undergoing artificial ventilation have encouraged a more detailed investigation of the determinants of nosocomial pneumonia in the hope of developing more successful preventive strategies. The outcome of this research has been the recognition of the importance of bacterial colonization of the ventilated lung, which in turn has become the basis for preventive strategies, including selective decontamination and preservation of the “gastric acid barrier”.

EPIDEMIOLOGY

Hospital-acquired (nosocomial) pneumonia is the third most common category of nosocomial infection, after urinary tract and wound infections, and is more common in the ICU [18]. However, nosocomial pneumonia is claimed to cause more deaths than any other type of nosocomial infection [47]. It is more common in patients requiring mechanical ventilation, which one large study found increased the risk of developing pneumonia by a factor of 21 [29].

There is some confusion as to the terminology used to describe nosocomial pneumonia in intensive care patients. Some authorities have used the terms “primary” and “secondary” synonymously with community- and hospital-acquired in this context, with primary taken to mean pneumonias occurring within 24–48 h after admission to intensive care, and secondary pneumonias occurring thereafter. It should be apparent that a patient could be admitted to intensive care with a pneumonia that developed after hospital admission. To avoid the problem of wrongly categorizing this type of patient, it is better to use the terms “community-acquired” and “hospital-acquired” (nosocomial) pneumonia. In the case of a patient developing pneumonia more than 24 h after commencing mechanical ventilation, it is best to use the term “ventilator-associated pneumonia”.

Aspiration pneumonia, or pneumonia developing as part of an aspiration syndrome, may fall into any of the above categories and has its own distinct microbiological features.

The problem of agreeing on common diagnostic criteria for nosocomial pneumonia, and local variations in intensive care admission patterns, means that there is considerable between-centre variation in the stated incidence of ventilator-associated pneumonia. In the United States, baseline epidemiological data have been collected from a representative cross section of hospitals since 1970 in the National Nosocomial Infection Survey (NNIS). An agreed definition has been used for clinical diagnosis of nosocomial pneumonia [47] (in patients without prior pulmonary disease the production of newly purulent sputum more than 48 h after hospital admission, and in patients with prior pulmonary disease increased sputum production and a new onset of pyrexia), but information on subgroups such as ventilator-associated pneumonia has not been collected. The

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KEY WORDS

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overall incidence of nosocomial pneumonia found by the NNIS was 5 per 1000 patients discharged (including deaths). Further epidemiological analysis of these patients since 1974 in the Study on Efficacy of Nosocomial Infection Control (SENIC) found an incidence of 6 per 1000 admissions [28].

The data available on the epidemiology of nosocomial pneumonia in the United Kingdom are limited. A large-scale point prevalence survey was conducted in 1981 by the Hospital Infection Society [39]. An agreed definition of nosocomial pneumonia was used (onset after hospital admission, clinically evident reaction or subclinical reaction; and new purulent sputum or increased sputum; and chest signs or changes in chest x-ray) which differed from the criteria used in the American survey, and did not differentiate ICU patients. Hospital-acquired pneumonia developed in 4.7 patients per 1000 and in only 25% of these patients was a potential bacterial pathogen isolated. While there are many reasons why a bacterial pathogen might not have been implicated, the authors of the above report drew particular attention to the poor correlation between clinical and microbiological diagnosis in nosocomial pneumonia.

The mortality rate in patients with nosocomial pneumonia is high, but there are wide variations in the figures reported. In one study, a mortality rate of 55% was recorded in ventilated patients acquiring pneumonia. However, the same study failed to implicate pneumonia as a significant independent risk factor for ICU mortality after stepwise logistic regression analysis [16]. Another study found a mortality rate of 33% in patients with Gram-negative pneumonia, compared with 3.8% in a control group [51]. Nosocomial pneumonia is thought to be the direct cause of death in 19000 American patients each year, and a contributory factor in a further 58000 [26].

Nosocomial pneumonia adds to the cost of inpatient care by prolonging the period during which ventilatory support is required, generating a series of additional diagnostic procedures and increasing consumption of expensive therapeutic agents—in particular, i.v. antibiotics. The additional expenditure attributed to the estimated 1.3 million nosocomial pneumonias in the United States each year is about $1 billion at 1985 rates. If the SENIC estimate that 17% of all nosocomial pneumonias are ventilator-associated is correct [29], the annual estimated attributable cost of ventilator-associated pneumonia in the U.S.A. alone would be greater than $170 million. The true figure is likely to be higher than this, because of the rising cost of health care and the increasing incidence of nosocomial pneumonia (thought to be the result of increasingly ambitious medical intervention).

The data required to produce detailed costings for the consumption of resources attributable to pneumonia in intensive care patients are not available in the U.K., but since the cost of treatment with a single injectable antibiotic for one patient may be several hundred pounds, and every day spent in an ICU costs approximately £500 [49], it is certain that pneumonia represents a considerable drain on health care resources, probably running to an annual total of many millions of pounds.

**Diagnosis**

An aetiological diagnosis may already be available in cases of pneumonia acquired before admission to the ICU. When this information is not available, a full diagnostic investigation (including sputum and blood culture) should be completed before commencing antimicrobial therapy. Where viral, mycobacterial or atypical pneumonia is suspected, it is advisable to take the appropriate specimens as soon as possible after the patient's admission to the unit, since diagnostically useful information may not be available for several weeks. When pneumocystis pneumonia is suspected, specimens should be obtained at bronchoscopy, preferably by broncho–alveolar lavage [23].

The diagnosis of ventilator-associated pneumonia is complicated by the insidious and non-specific nature of its clinical presentation, and by the common finding of a colonizing bacterial flora in the trachea and upper bronchi. These diagnostic problems mean that a close collaboration between clinical and laboratory staff is required. Bacteria isolated from the smaller airways are presumed to be of greater aetiological relevance to current pulmonary infection than isolates from the trachea and main bronchi. While the presence of a tracheal tube bypasses the principal source of contamination of sputum specimens, bacterial colonization of the trachea will confound attempts to obtain specimens when a standard bronchoscopy specimen brush is used. To overcome this problem, a protected specimen brush was
developed, with a double-lumen catheter. The sensitivity was found to be high when a threshold of \(> 10^3\) bacteria per 1 ml of secretions was used as a cut-off point for bacterial counts in specimens recovered using this device in animals [40]. However, a study using the protected specimen brush in ventilated human subjects and the same quantitative threshold showed that false positive results were common, and found a selectivity of 42\% [13]. The sample brush used for specimen collection has been improved by the addition of a small agar plug, which can be dislodged after placement of the device.

Quantitative bacteriological analysis of secretions obtained with the protected specimen brush does not provide clinically useful information in time to affect initial therapeutic decisions, as it depends on the results of culture. Moreover, the technique also relies on accurate placement of the bronchoscopy catheter. Another approach relies on Gram staining of cytocentrifuged bronchoalveolar lavage fluid to demonstrate intracellular bacteria, and has the advantage of producing results in time to influence therapeutic decisions. One study comparing the protected specimen brush technique with bronchoalveolar lavage found similar degrees of accuracy [12]. Alternative, more invasive techniques, such as percutaneous needle aspiration and transbronchial biopsy, may have a role in diagnosis of pulmonary infections in ICU patients, but the potential for serious complications such as pneumothorax means that this is strictly limited. Open lung biopsy has been recommended for diagnosis of pulmonary infections in immunocompromised patients, and the available data suggest that there is a higher diagnostic yield than with transtracheal biopsy. However, the results of biopsy often do not warrant a change in treatment, and mortality rates do not appear to be altered by the information generated.

The diagnostic techniques used in most centres do not produce results quickly enough to influence the choice of antibiotics when treatment is urgent. Until diagnostic methods allow more accurate diagnosis, particularly a confident negative diagnosis, of pneumonia in the patient with ventilated lungs, the appropriateness of antibiotic therapy will remain a largely retrospective judgement.

A practical approach to the intensive care patient with suspected pneumonia would be:

1. Spontaneously ventilating, with productive cough: microscopy and culture of sputum.
2. Spontaneously ventilating, without productive cough: chest physiotherapy, and consider transtracheal aspiration if this fails to produce a sputum specimen.
3. Mechanically ventilated, onset within 48 h of admission: check for recent sputum and blood culture reports. Obtain sputum and blood culture specimens, and request urgent Gram stain on sputum.
4. Mechanically ventilated, onset 48 h after admission to ICU or later: preferred method of diagnosis is quantitative culture and cytological examination of broncho-alveolar fluid specimens if the laboratory has experience of these techniques. Culture of sputum obtained by tracheal suction may establish bacterial colonization of larger airways, but will not distinguish between colonization and infection. If clinical picture unresolved when results available, discuss interpretation and therapeutic strategy with microbiologist.
5. Clinical picture suggests atypical pneumonia: collect 10 ml of blood as first in pair of specimens for serological analysis.
6. Patient with AIDS or otherwise immunocompromised: discuss possibility of *Pneumocystis carinii* with microbiologist and obtain specimen for immunofluorescent stain by broncho-alveolar lavage or, preferably, bronchoscopic biopsy. Consider possibility of tuberculosis or cytomegalovirus pneumonia in AIDS patient. Discuss with microbiologist if special diagnostic procedures are required, for example for atypical mycobacteria.

**AETIOLOGY**

It is rarely possible to predict the bacterial pathogen responsible for pneumonia in the intensive care patient because any one of a wide range of species may be involved. In patients admitted to ICU with community-acquired pneumonia, common respiratory pathogens such as *Streptococcus pneumoniae* and *Haemophilus influenzae* are often isolated. The results of a large scale survey of community-acquired pneumonias are listed in table I. *Mycoplasma pneumoniae*, *Legionella* sp., and the recently identified TWAR strain (so-called after the first strain isolated: Taiwan, adult respiratory) of *Chlamydia* [25] may also be implicated if the appropriate investigations are carried out. As yet, the necessary diagnostic
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Table I. Agents of community-acquired pneumonia. (Taken from a prospective survey [2])

<table>
<thead>
<tr>
<th>Microbial agent</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pneumonia</td>
<td>154</td>
<td>34</td>
</tr>
<tr>
<td>Mycoplasma pneumonia</td>
<td>81</td>
<td>18</td>
</tr>
<tr>
<td>Influenza A virus</td>
<td>32</td>
<td>7</td>
</tr>
<tr>
<td>Haemophilus influenza</td>
<td>26</td>
<td>6</td>
</tr>
<tr>
<td>Chlamydia psittaci</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Legionella pneumophila</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Streptococcus, other species</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Coxiella burnetii</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Others</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Microbiologically negative</td>
<td>150</td>
<td>33</td>
</tr>
</tbody>
</table>

Table II. Bacterial species isolated in association with nosocomial pneumonia. (From the National Nosocomial Infection Survey, 1980-1982 [47])

<table>
<thead>
<tr>
<th>Bacterial species</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas spp.</td>
<td>15</td>
</tr>
<tr>
<td>Klebsiella spp.</td>
<td>14</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>14</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>10</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>8</td>
</tr>
<tr>
<td>Haemophilus influenza</td>
<td>8</td>
</tr>
<tr>
<td>Proteus spp.</td>
<td></td>
</tr>
<tr>
<td>Morganella morganii</td>
<td>7</td>
</tr>
<tr>
<td>Providencia stuartii</td>
<td></td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>6</td>
</tr>
<tr>
<td>Streptococcus pneumonia</td>
<td>4</td>
</tr>
<tr>
<td>Streptococcus faecalis</td>
<td>2</td>
</tr>
<tr>
<td>Other Gram-positive spp.</td>
<td>5</td>
</tr>
<tr>
<td>Anaerobic spp.</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Miscellaneous spp.</td>
<td>3</td>
</tr>
</tbody>
</table>

tests are available in only a few centres. Tuberculosis is seen rarely outside the major at-risk groups, but is commonly found in patients with AIDS, from whom atypical mycobacteria, such as the avium-intracellulare group, may be isolated. Patients whose immune system is compromised by AIDS or other factors are at risk from pneumonias caused by opportunistic organisms such as *Pneumocystis carinii*, and cytomegalovirus, in addition to more common bacterial respiratory pathogens.

After aspiration of gastric contents, bacteria may play a secondary role in causing pulmonary damage, or may cause an invasive infection where pulmonary tissues have already been disrupted by prior chemical or mechanical damage. The bacterial species commonly associated with aspiration pneumonia are similar to those normally found in the bacterial flora of the oro- and nasopharynx, including penicillin-sensitive anaerobic species [5]. In our centre, *Staphylococcus aureus* has been isolated in a number of severe pulmonary infections following aspiration.

The microbial species associated with hospital-acquired pneumonia (table II) differ from those associated with community-acquired pneumonias in several respects. Viral and anaerobic bacterial species are rarely implicated, and common bacterial respiratory pathogens are isolated less frequently than Gram-negative species, which explains why some authors refer to nosocomial pneumonia as “Gram-negative pneumonia”.

The Gram-negative species isolated from patients with nosocomial pneumonia are divided by some authorities into “endogenous” and “exogenous” groups, according to the presumed source of the organism. Typical exogenous species include *Pseudomonas aeruginosa* which is a common contaminant of the hospital environment, and not a major component of the normal human microbial flora. Representative endogenous species would include *Escherichia coli*, which is commonly found in the human intestinal flora.

The rigid subdivision into exogenous and endogenous groups is probably no longer appropriate, because of changing views on the principal mechanisms of respiratory colonization and the observation that even species classically regarded as exogenous in origin, such as *Pseudomonas aeruginosa*, may become transient members of the gastrointestinal flora in some ICU patients [1].

There is some evidence that the newly recognized *Chlamydia TWAR* strain has been a cause of nosocomial pneumonia in a number of patients [24], but too little is known about this organism at present to permit comment on its importance in ICU patients.

There have been a number of outbreaks of nosocomial legionnaire’s disease documented since the species was first recognized in the late 1970s. One outbreak affected patients in the high-dependency peripheral vascular and cardiothoracic unit of the Glasgow Royal Infirmary and was caused by spray from a wet cooling tower entering the closed ventilation system to the unit [55]. This particular outbreak might have been prevented had the first case, which was 6 weeks earlier than the others and proved fatal, prompted an investigation of the air conditioning system.
Respiratory colonization

The presence of bacteria in the lower respiratory tract is an abnormal finding which, in spontaneously ventilating patients, would normally be associated with a pathological process such as chronic bronchitis or cystic fibrosis [35]. In artificially ventilated patients, the architecture of the respiratory tract is altered by the presence of the tracheal tube so that bacteria are commonly found in the larger airways. Although it may be possible theoretically to distinguish between bacteria that are merely colonizing the lower respiratory tract and those causing infection, this is rarely possible in clinical practice.

In the patient with the trachea intubated, colonization is important as a necessary precursor to pneumonia, and implies a more than transient association between a given bacterial species and the lower respiratory tract mucosa. The species in question must therefore have found a means of adhesion to host cell surface structures, and a source of substrates for microbial metabolism, whilst avoiding the antibacterial effects of IgA, lysozyme, and bacteriocidins produced by other bacterial species.

The procedures used in most diagnostic laboratories do not attempt to recognize this complex relationship, and can only achieve a crude approximation by demonstrating the presence of bacteriologically identical isolates over a period of time, in the absence of the clinical features of infection.

The interrelationship between colonizing bacteria and respiratory mucosa is further complicated by the mediating influence of respiratory mucus. This viscoelastic liquid is a complex milieu in which a lattice of negatively charged mucopolysaccharide fibrils is surrounded by cations and water molecules. In the presence of inflammation, increased local concentration of cations may change the stereochemical arrangement of mucopolysaccharide fibrils, thus altering the viscoelastic properties of respiratory mucus to make it more tenacious [22]. DNA fibres released into respiratory secretions upon the death of granulocytes also contribute to the increased viscosity of purulent sputum.

The aerobic Gram-negative bacilli most commonly associated with pneumonia in ICU patients are rarely found amongst the bacterial flora of the buccal cavity or pharynx in healthy adults. The frequency with which Pseudomonas aeruginosa, a common hospital environment organism, was isolated from ICU patients with pneumonia, and the concurrent isolation of the same species from respiratory support equipment gave credibility to the view that bacteria gained access to the lower respiratory tract via the ventilator circuit. Common-source outbreaks of nosocomial pneumonia as a result of contamination of ventilators and other respiratory support equipment were reported [44]. Despite improvements in equipment design and the introduction of infection control procedures, common-source incidents involving Klebsiella sp., Acinetobacter sp. and other bacterial species continue to be reported from ICUs [8, 10].

It was first proposed that bacteria colonized the lower respiratory tract of ventilated patients from a source within the patient when a correlation was recognized between bacterial isolates from tracheal secretions and isolates from oropharyngeal specimens. This study also noted that prior treatment with antibiotics increased the risk of development of a Gram-negative lower respiratory flora, as a result of selection pressure on antibiotic-sensitive species [54]. Another factor found to correlate with the acquisition of Gram-negative species in the oropharynx was the severity of illness, irrespective of prior antibiotic treatment [34].

It is now recognized that the systemic effects of severe illness can cause molecular changes in the cells on mucosal surfaces, which in the mouth results in cleavage of fibronectin, causing an increase in available binding sites for Gram-negative bacteria [58]. Surface structures on Gram-negative bacteria, termed pili, adhere to receptor sites on mucosal epithelial cells. Mucosal binding of *E. coli* for example, can be inhibited by prior treatment of the surface with concanavalin A, which binds to mannose [42].

A study in adult volunteers showed that nine of 20 subjects aspirated small quantities of fluid into the trachea during deep sleep [31]. In the same study, aspiration of fluid into the trachea occurred in seven of 10 patients with a reduced level of consciousness. Aspiration occurs frequently in patients with head injury, patients undergoing controlled ventilation and patients treated with sedative drugs.

It is possible that the tracheal tube may, by interfering with deglutition, add to the pooling of secretions in the lower pharynx and upper oesophagus. The inflatable tracheal tube cuff was
designed to prevent aspiration of a large fluid bolus into the trachea providing the cuff remained inflated, and modern high volume–low pressure cuffs do not often deflate spontaneously. However, the intentional cuff deflation practised in some ICUs in order to prevent mucosal damage will allow contaminated secretions that have pooled above the cuff to gain access to the lower respiratory tract. Furthermore, bacteria can still gain access to the lower trachea from the reservoir above the cuff by passing between the cuff and the tracheal mucosa when the tube moves in relation to the trachea. This may occur during respiratory care procedures or even in the course of the normal ventilatory cycle.

While this phenomenon is easily demonstrated in vitro, it is not possible to demonstrate it directly in patients with the trachea intubated. However, there is indirect bacteriological evidence to support the above sequence of events. In one study of 10 mechanically ventilated patients, gastric bacterial overgrowth was observed in nine, and evidence for a sequence of colonization from stomach to trachea was found in three [4].

**Effect of gastric pH on colonization**

In a later study of patients undergoing mechanical ventilation, those with a gastric pH greater than 4.0 were found to be at higher risk of gastric bacterial overgrowth, bacterial counts reaching $10^8$ ml$^{-1}$ in some patients. Gastric bacterial overgrowth was unusual in patients with a gastric pH less than 3.5. Histamine blockers and antacids were observed to be associated with a greater risk of gastric bacterial overgrowth [41].

The same group isolated Gram-negative bacilli from either or both stomach and trachea in 52 of 58 postoperative patients, claiming a sequence of isolation in 17 of the 52 patients (in 11 of 17 patients with this apparent sequence, gastric colonization occurred before tracheal colonization). Bacterial translocation from the stomach to the trachea of mechanically ventilated patients has been termed "retrograde colonization".

Other studies of gastric bacterial overgrowth in artificially ventilated patients have confirmed these observations, but have not established a direct relationship between gastric colonization and subsequent pneumonia in ICU patients. Indirect evidence to support this relationship came from a study of risk factors for ventilator-associated pneumonia in 233 patients, in which it was shown that the use of histamine type 2 blockers was a significant risk factor for pneumonia [16].

Other explanations are possible for some of the above bacteriological findings. Changes on mucosal surfaces might occur which allow previously suppressed Gram-negative species to grow above the lower limit of detection, or bacteria might gain access to the lower respiratory tract via the circulation following translocation across the intestinal mucosa. While these remain theoretically possible, the observations made in recent clinical studies concur with the "retrograde colonization" model.

The increased risk of respiratory colonization following use of histamine antagonists is thought to be a pH-mediated effect, in which stress ulcer prophylaxis blocks gastric acid secretion, removing the "gastric acid barrier" and thereby promoting the overgrowth of aerobic Gram-negative bacteria in the stomach.

Little information is available on gastrointestinal physiology in patients undergoing mechanical ventilation of the lungs, but clinical experience suggests that a large proportion of patients ventilated for a prolonged period have delayed or absent gastric emptying, whether caused by postoperative ileus or other factors, such as administration of opioids. A static small intestine is likely to assist bacterial overgrowth in the jejunum and duodenum, to produce the contaminated small bowel syndrome [6].

It is assumed that bacteria in the gastric contents gain access to the trachea either by active regurgitation or by passive flow along the oesophagus. The reason why thoracic and upper abdominal operations put patients at greater risk of pneumonia [30] may be a decreased efficiency of anti-reflux mechanisms and, in the case of oesophagectomy, a shortened distance between pooled gastric contents and epiglottis. Reflux of gastric contents is also assisted in artificially ventilated patients by the presence of the nasogastric tube, which keeps the oesophagus open, allowing fluid to pass along its outer surface, and by the near-horizontal positioning of most ICU patients.

**Mucociliary clearance**

Under normal physiological circumstances, micro-organisms that impinge on mucosal surfaces in the lower respiratory tract are trapped in respiratory mucus and cleared by the continuous upward movement of the mucus layer caused by
cilia on the epithelial surface. Larger particles and boluses are cleared by the cough reflex. In artificially ventilated patients the tracheal tube presents an anatomical barrier to upward mucociliary movement at the level of the inflatable cuff. Respiratory secretions build up in the region of the tube tip. The tracheal mucosa may be damaged by contact with the tracheal tube or the suction catheter tip, even at low suction pressures [46]. There is experimental evidence from work on ferrets that mechanically induced damage to the tracheal mucosa assists the adherence of Pseudomonas aeruginosa by exposing areas of basement membrane [45]. It is possible, therefore, that the local inflammatory reaction seen in the intubated trachea during prolonged ventilation may begin with mechanical damage and proceed to a low grade bacterial insult.

Colonization from tracheal tube biofilm: two phase flow

Spread of bacteria into the lungs of ventilated patients cannot be explained by retrograde colonization alone, for this model of bacterial spread only provides for the carriage of bacteria as far as the trachea. It has been observed that a film of bacteria and respiratory secretions form on the inner surface of tracheal tubes during prolonged use [50]. It was proposed that fragments of this biofilm could be dislodged during insertion of the suction catheter, and carried further into the lung.

Further investigation of this tracheal tube biofilm, including flow studies with tubes removed from patients undergoing artificial ventilation, has shown that small fragments of biofilm can be disseminated by ventilator gas flow. Scanning electron microscopy and bacteriological studies of filters used in ICU ventilator circuits revealed particles consistent with dissemination of tracheal tube biofilm during the expiratory phase of ventilation in vivo [33]. Particles produced in this system have been found to be as small as 25 μm [32], and have been shown to travel up to 90 cm. Additional gas–liquid interaction with the layer of respiratory mucus lining the lower trachea is possible, but since the tracheal tube has a narrower diameter, it is probably the zone of maximal gas–liquid interaction and biofilm fragmentation. Furthermore, it is known that gas–liquid interaction may occur at relatively low Reynolds numbers, although this may be sufficient only to cause flow of the biofilm layer, without fragmentation and subsequent particle dissemination [14].

The local inflammatory reaction discussed above ensures that activated neutrophils are present in the material on the inner surface of the tracheal tube. Gas–liquid interaction may therefore disseminate into the lung host-derived inflammatory mediators such as myeloperoxidase and neutrophil elastase.

The probable explanation for the formation of a biofilm on the inner surface of tracheal tubes is that respiratory secretions are propelled into the mouth of the tracheal tube after accumulating below its tip. This material is probably carried further into the tracheal tube, and smeared over the inner surface by passage of the suction catheter.

Hypothesis for bacterial colonization of the ventilated lung

The patient has an abnormal gastrointestinal flora at or shortly after admission to the ICU, and diagnostic and therapeutic procedures used during admission may cause further alterations in that flora. Overgrowth of Gram-negative species in the stomach contents is the result of increased gastric pH. Reflux of gastric contents carries bacteria into the respiratory tract. Bacteria from the stomach and oropharynx accumulate above the inflatable tracheal tube cuff and pass in small quantities to contaminate the respiratory secretions accumulating below the cuff. Mucociliary clearance and passage of the suction catheter through these secretions leads to the development of a biofilm on the inner surface of the tracheal tube and the larger airways. When the biofilm reaches sufficient thickness, gas–liquid interaction causes fragmentation of the biofilm surface and dissemination of bacteria-laden particles deep into the lung. Bacterial components and host-derived inflammatory mediators then initiate the damage that produces the clinical features recognized as ventilator-associated pneumonia (VAP).

Bacteria–host interaction

Bacteria–host interaction is of the utmost importance in the foregoing hypothesis, and the aerobiology of inhaled micro-organisms appears to be a major factor in the development of disease. It was not recognized until recently that the method of administration of bacteria to experimental
animals was an important factor in determining the host response.

Experiments on mice have shown that the response to inhaled *Streptococcus pneumoniae* depends on whether they are delivered as an aerosol of monodispersed organisms, or as a cloud of aggregated bacteria [3]. When bacteria are inhaled in the aggregated form, a smaller inoculum was observed to cause saturation of the pulmonary macrophage system and induction of a neutrophil response. These observations have been repeated with a variety of bacterial species relevant to pulmonary infection in humans, including *Pseudomonas aeruginosa* [9]. It appears that aggregated bacteria are more resistant to phagocytosis than are monodispersed organisms. It has been claimed that the biofilm also gives bacteria some resistance to phagocytosis [48]. The size of biofilm particles produced by gas–liquid interaction means that only a small percentage may reach the smallest airways compared with an aerosol of monodispersed bacteria, yet their resistance to phagocytosis may render such particles more pathogenic.

Although the “retrograde” route from the patient’s own gastrointestinal tract is currently favoured as the principal means of respiratory colonization, the more direct route from external sources in respiratory support devices is still believed to account for a proportion of pneumonias in ICU patients.

Role of host factors

Host factors that increase the risk of pneumonia, such as pre-existing pulmonary disease, operative procedures and smoking, have already been mentioned. In the immunocompromised patient, host factors are an even more important determinant of pneumonia, increasing the susceptibility of the lower respiratory tract to infection by common respiratory pathogens and opportunistic organisms. The pulmonary infections to which an immunocompromised patient is more susceptible differ with the nature of the compromise. For example, a patient with deficient cell-mediated immunity as a result of AIDS, a lymphoma, an organ transplant or steroid treatment is at increased risk of cytomegalovirus, pneumocystis, cryptococcal, and nocardial infections, while a neutropenic patient is at increased risk of Gram-negative, staphylococcal and fungal infections.

Once the presumed cause of bacterial pneumonia has been identified, the appropriate antimicrobial agent may become clear before antimicrobial susceptibility results have become available. In many cases, susceptibility data will be obtained too late to influence urgent therapeutic decisions. We have found that a planned progressive antimicrobial prescribing policy can be applied to the majority of intensive care patients with pneumonia.

Ampicillin is used to treat community-acquired bronchopneumonia, with erythromycin in reserve for patients with a documented penicillin allergy. Erythromycin is used for patients with a suspected community-acquired atypical pneumonia caused by either *Legionella pneumophila* or *Mycoplasma pneumoniae*. When a patient has a lobar pneumonia, or when *Streptococcus pneumoniae* has been isolated, i.v. benzyl penicillin should be used in preference to other penicillins. We use i.v. cloxacillin to treat patients with staphylococcal pneumonia following influenza and often, in our experience, aspiration of gastric contents. The more severe cases of staphylococcal pneumonia usually require the addition of fucidic acid.

In cases of aspiration pneumonia we use ampicillin, although there is no convincing evidence that antibiotics significantly alter the course of the disease. In our experience, the most problematic agent of secondary infection following aspiration has been *Staphylococcus aureus*, for which the appropriate antibiotic is cloxacillin, with the possible addition of fucidic acid, as described above. Some centres use metronidazole, although most oral anaerobic bacteria are penicillin-sensitive.

Our first choice for a patient with VAP occurring more than 48 h after admission to the ICU is cefotaxime. When gentamicin is used to treat Gram-negative pneumonia, it should be accompanied by another agent because of its poor bioavailability in respiratory secretions. When the patient is known to have a *Pseudomonas aeruginosa* pneumonia we use either a combination of gentamicin and pipercillin, or ciprofloxacin alone. Changes to the type and duration of antimicrobial chemotherapy are normally made after discussion with a microbiologist and consideration of current microbiological data.

In many ICUs, a large proportion of patients have already been given antibiotic treatment before their admission to the unit. To prevent the
accumulation of antimicrobial resistance and to reduce selection pressure caused by widespread use of systemic antimicrobial agents, it is wise to review all surgical antibiotic prophylaxis regimens on admission of the patient to the ICU, aiming to discontinue such prophylaxis after a maximum of 48 h. If antibiotics are required for therapeutic purposes, different agents should be used.

In most ICUs the i.v. route of antibiotic administration is used for treatment of patients with pneumonia. Therapeutic concentrations are obtained rapidly and the widespread use of intravascular lines makes this route convenient. Despite promising early claims [37], intrabronchial administration of antibiotics in the treatment of VAP has not been shown to be superior to more conventional routes of administration. Moreover, problems of early antimicrobial resistance have been reported in patients treated with intrabronchial antibiotics [21].

Other therapeutic measures

Maintenance of adequate oxygenation and physiotherapy are a common adjunct to antibiotic treatment of pneumonia in ICU patients. Physiotherapy in VAP has been poorly researched and there is limited evidence for a specific beneficial effect.

The suction catheterization that accompanies chest physiotherapy or is carried out independently may be administered as frequently as every 30 min, with the possible consequences of mucosal damage, bacterial colonization, tracheal tube biofilm formation and bacterial contamination of the lung.

PREVENTION

A number of preventive strategies have been designed to deal with the problem of VAP.

Equipment

The earliest attempts to prevent pneumonia in ICU patients involved the disinfection and sterilization of respiratory support equipment such as ventilators and ventilator tubing. Further measures included the use of sterile water in humidifier reservoirs and sterile charging solutions in nebulizers. Recent developments in the “device hygiene” approach have been the introduction of disposable core-heated humidifiers with disposable sterile water reservoirs, and low resistance microbial ventilator filters.

The transmission of bacteria between patients on the hands of staff is facilitated by the need for rapid access in resuscitation procedures and by inadequate staffing levels or high levels of bed occupancy [27]. Infection control in intensive care is assisted by a high staff:patient ratio, in-service training on infection control practice and collaboration with the hospital infection control team.

There is disagreement over the usefulness of microbial ventilator filters. There have been reports of sudden increases in resistance as a result of the accumulation of condensate [7]. Moreover, one study comparing the incidence of pulmonary infection in patients with and without filters as part of their ventilating apparatus, failed to show a significant difference between the two groups [17]. These results possibly reflect the relative importance of the endogenous route of colonization over the exogenous route. The issue of whether or not to use microbial ventilator filters remains unresolved, as the evidence for any measurable benefit is scanty, while the claimed risks of use have not been substantiated in clinical trials.

Where pulmonary infections by Legionella pneumophila have been a problem, specific measures have had to be taken by hospital engineers, with particular emphasis on air-conditioning systems and cooling towers.

Bacteriological examination of ventilator tubing to assess the adequacy of policies for replacement or sterilization has shown that the greatest contamination occurs at the patient’s end of the tubing, and that the organisms isolated are normally those found in the patient’s respiratory tract [15]. These observations are not conclusive evidence for an endogenous source of contamination of ventilator tubing, but they do support the view that the respiratory support equipment is a less importance source of bacterial contamination than the patient. It is therefore possible that microbial filters may have a role in intensive care practice, but as a means of preventing the contamination of tubing rather than in the prevention of pulmonary colonization.

Selective decontamination of the gut

The first major strategy designed to interrupt pathways of endogenous bacterial colonization was selective decontamination of the digestive tract (SDD).

Selective decontamination relies on the concept
of "colonization resistance". This concept was developed from work on the intestinal bacterial flora of mice, following problems with unwanted gastrointestinal colonization in gnotobiotic animals. These studies were the foundation for the current belief that the majority anaerobic gut flora hold the minority aerobic Gram-negative species in check, preventing overgrowth of commensal Gram-negative bacteria or colonization by exogenous Gram-negative aerobes [57].

Antibiotic regimens were screened in mice for their effect on the colonization resistance provided by the anaerobic flora, and agents chosen if the anaerobic flora were preserved while the aerobic Gram-negative bacterial and yeast flora were suppressed. From this work a combination of tobramycin, polymyxin E and amphotericin B was chosen. Preliminary trials of these three agents in paste given orally and down the nasogastric tube, combined with cefotaxime given for the first 4 days of the decontamination regimen, in patients who had experienced multiple trauma, were claimed to show a reduction in the incidence of pneumonia from 59% to 8% [52]. In a later study, no significant selection of antimicrobial resistance was found [53].

A number of SDD trials have been conducted, with varying degrees of success and with differing criteria for the diagnosis of VAP.

A detailed study of SDD was conducted over two non-consecutive 6-month periods by a group in Glasgow, using a strict definition of pulmonary infection [36]. The incidence of respiratory colonization and secondary pneumonia decreased in the SDD treated group, although there was no significant reduction in mortality rate in this group. After post-hoc stratification, however, a significant reduction in the mortality rate of the multiple trauma subgroup was noted. These results led to the recommendation that SDD should be used only in those ICUs where thorough microbiological surveillance was possible.

Despite the absence of acquired antimicrobial resistance in this and other studies of SDD, misgivings have been expressed concerning the use of prolonged, broad spectrum prophylactic regimens in a group of patients at high risk of carrying a preselected resistant bacterial flora [20]. There is particular concern about cefotaxime, which has been used as a supplementary prophylactic agent in most of the SDD trials to date. Cefotaxime is said to be required as treatment for primary infections established before admission to the ICU, yet the use of SDD regimens without such pre-emptive treatment has not yet been evaluated properly. It is therefore not possible to separate the effects of the SDD agents and cefotaxime on bacterial isolates from clinical samples during the first 4 days of admission to the ICU—the key period during which initial respiratory colonization takes place. Moreover, Gram-negative species producing enzymes capable of inactivating cefotaxime have been reported recently [11]. Extensive use of SDD in ICUs could provide suitable conditions for the selection of resistance and reduce the clinical effectiveness of a hitherto useful agent.

In every SDD trial so far, there has been a proportion of patients who develop secondary or ventilator-associated pneumonia despite rigorous application of the regimen. A possible reason for respiratory colonization during the use of SDD could be a reduced antimicrobial effect in patients with slowed or absent gastrointestinal motility. A large bacterial biomass in the stomach and upper small intestine may reduce the effectiveness of intragastric antibiotics. There is, therefore, a possibility that SDD is more effective at preventing colonization in patients who already have a lower risk of developing pneumonia.

A further point raised by work on SDD is the relationship between VAP and ICU mortality. A significant decrease in mortality should be expected in SDD-treated patients if there is a substantial decrease in the incidence of VAP. The absence of such a relationship in general intensive care patients raises important questions about VAP and whether it is a true pulmonary infection. When day-by-day microbiological support is available, SDD may have a place in the management of patients requiring ventilatory support for more than 48 h, but only if it is recognized that the benefits may be more subtle than a reduction in mortality. A careful cost–benefit analysis of SDD may clarify this matter.

**Sucralfate**

Many of the theoretical and practical weaknesses of SDD do not apply to another preventive strategy recently proposed for patients undergoing artificial ventilation. This is preservation of the "gastric acid barrier" by substitution of histamine blocker stress ulcer prophylaxis with sucrose aluminium sulphate (sucralfate). This novel anti-ulcer agent works by coating damaged
gastric mucosa, and does not significantly reduce gastric pH [56]. By avoiding the additional risk of respiratory colonization resulting from the gastric bacterial overgrowth caused by reduced gastric acid secretion, it was thought that use of sucralfate would cause a decrease in the incidence of VAP.

In a study of sucralfate compared with antacids or cimetidine in 130 general ICU patients, gastric colonization with Gram-negative species and gastric pH were higher in the group receiving antacids or cimetidine [19]. VAP was reduced from 23% to 12% in the sucralfate group, but the difference was not significant unless patients withdrawn from the sucralfate group and given cimetidine by their attending physician were removed from the study. The marginal statistical significance of this study detracts from the apparent trends of reduced colonization and reduced VAP when the gastric acid barrier had been preserved with sucralfate.

The attractions of a sucralfate-based strategy are that it should not select antimicrobial resistance or require microbiological surveillance. It is also simpler to administer. This strategy, like SDD, has a measurable failure rate which is probably attributable to the proportion of intensive care patients who have a high resting gastric pH. There may be reasons for this other than the administration of antacids or histamine blockers for prophylaxis of stress ulcer, which contribute to gastric bacterial overgrowth and will confound attempts to prevent subsequent respiratory colonization by using sucralfate. An antibacterial effect has been claimed for sucralfate [39], but it is unlikely that this has a significant effect on the high concentrations of Gram-negative bacilli found in the stomachs of some patients being ventilated artificially.

CONCLUSIONS

Pneumonia remains an important problem in ICU patients, despite advances in respiratory support and other aspects of intensive care. While the management of community-acquired pneumonia and postoperative pneumonia is often straightforward, management strategies for VAP are still far from satisfactory.

Difficulties with diagnosis and conventional antimicrobial therapy in VAP have led to the development of new diagnostic techniques such as broncho–alveolar lavage and the bronchoscopic protected specimen brush, and preventive strategies such as selective decontamination and sucralfate-based preservation of the gastric acid barrier. Many improvements could be made to the management of pulmonary infections in the ICU, but a number of issues, such as the contribution of altered gastrointestinal physiology, tracheal suction procedures and bacterial–mucosal interaction, still require resolution.

REFERENCES


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PULMONARY INFECTION IN INTENSIVE CARE UNITS


