Control of Bacterial Pneumonia during Mechanical Ventilation

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Abstract

Pneumonia complicates the course of 50% of patients on mechanical ventilation, requiring three or more days of mechanical ventilation and potentially increasing the relative risk of mortality by 20-40%. The predominant potentially pathogenic micro-organisms are Streptococcus pneumoniae, Staphylococcus aureus (sensitive to methicillin in the previously healthy host), Pseudomonas aeruginosa (aerobic gram-negative bacilli), and methicillin-resistant Staphylococcus aureus in the host with underlying disease. Approximately 85% of pneumonias are endogenous, caused by bacteria present in the patient’s oropharyngeal flora. Bacteria present on admission cause primary endogenous pneumonia (55%), whereas bacteria acquired in the unit lead to supercarriage or secondary carriage and subsequently secondary endogenous pneumonia (30%). The remaining 15% are exogenous, i.e., the bacteria causing pneumonia are not carried by the patient. The diagnosis is usually based on clinical, radiological, and microbiological criteria, using the non-invasive method of tracheal aspirate, which yields ≥10⁵ micro-organisms. Seven randomized trials have evaluated three non-antibiotic prophylactic maneuvers: hygiene (1 trial), subglottic drainage (4 trials), and semirecumbent position (2 trials). The impact on pneumonia was mixed, whereas mortality was unchanged. Selective digestive decontamination, using parenteral and enteral antimicrobials to control the three types of pneumonia, has been evaluated in 54 trials and showed an absolute mortality reduction of 8%. The therapy of pneumonia relies on six basic principles: (a) surveillance and diagnostic cultures to identify micro-organisms; (b) immediate and adequate antibiotic treatment to sterilize the lower airways, (c) the source of potential pathogens requires elimination for recovery of the original infection and prevention of relapses and/or superinfections; (d) aerosolized antimicrobials; (e) removal or replacement of the endotracheal tube; and (f) surveillance samples are indispensable to monitor efficacy of treatment. The aim of our review was to evaluate up to date facts regarding control of bacterial pneumonias during mechanical ventilation in intensive care unit settings.

This review aims to summarize the present knowledge of pneumonia in patients requiring mechanical ventilation, using evidence from randomized controlled trials (RCT) where possible. The scope of the article includes incidence, causative micro-organisms, pathogenesis, diagnosis, prevention, and treatment. We include pneumonias presenting as the prime indication for ventilation and those developing during treatment in the intensive care unit (ICU). Terminology such as “ventilator associated” or “nosocomial” pneumonia can cause confusion. We propose definitions of pneumonia, presenting in the ICU based on the origin of causative micro-organisms, using surveillance cultures to detect microbial carrier states.
Magnitude of the Problem

Epidemiological investigations have shown cumulative incidence rates of pneumonia in ventilated patients in the range 10-50%, depending on the method of diagnosis and underlying illness severity (1). Pneumonia can increase the relative risk of mortality by 20-40% (2). The length of the stay is increased by 4.3 days (95% CI=1.5-7.0 days) in patients acquiring pneumonia in ICU (3). The attributable additional cost has been estimated to be approximately €10,000 euros per case (4).

Potentially Pathogenic Microorganisms Causing Pneumonia

There are fourteen common potentially pathogenic micro-organisms (PPMs) that cause most pneumonias (5) (Table 1). PPMs causing pneumonia can be classified into two groups: “normal,” usually carried by previously healthy people and “abnormal,” usually harbored by individuals with chronic or acute underlying condition. “Normal” PPMs include *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Escherichia coli,* and *Staphylococcus aureus.* More than 60% of healthy people carry *S. pneumoniae* and *H. influenzae* in the oropharynx (7,8). The carriage rate of *M. catarrhalis* is 5% (9). Everybody carries an indigenous E. coli in the gut (10). One third of healthy individuals carry methicillin-sensitive *S. aureus* (MSSA), usually simultaneously in the throat and the rectum (11). *Candida* species do not usually cause pneumonia although yeasts belong to the normal flora in one third of the healthy population (12). The lower airways do not possess receptor sites for yeasts migrating from the oropharynx into the lower airways (13).

The group of “abnormal” bacteria causing pneumonia comprises eight aerobic Gram-negative bacilli (AGNB) and methicillin-resistant *S. aureus* (MRSA). The AGNB are *Klebsiella, Enterobacter, Citrobacter, Proteus, Morganella, Acinetobacter, Serratia,* and *Pseudomonas* species. The carriage of AGNB and MRSA in the oropharynx and gastro-intestinal tract of healthy individuals is uncommon.

The acquisition and subsequent carriage of PPMs in throat and gut is promoted by disease states. For example, one third of treated diabetic patients and a similar proportion of alcoholics harbor *Klebsiella* species in their oropharynx and gut (14,15). One third of patients with chronic obstructive pulmonary disease (COPD), with forced expiratory volume in 1 second less than 50%, carry *Enterobacter* (16). Forty percent of a group of malnourished children carried *Klebsiella* in throat and gut (17).

Two studies in ICU patients showed a correlation between abnormal AGNB and illness severity (18,19). This may be, in part, due to the increased availability of AGNB-receptor sites on the digestive tract mucosa during illness. One third of ICU patients with an Acute Physiology and Chronic Health Evaluation (APACHE) II score ≥15 were carriers of abnormal AGNB. This increased to 50% in a population with an APACHE score ≥27. Another study (20) evaluated the acquisition and subsequent carriage rate of abnormal AGNB in patients who had been free from AGNB on admission to the ICU, apart from indigenous *E. coli* in their gut. The presence of multi-resistant *Klebsiella* or *Acinetobacter* species, or both, was used as a marker of abnormal AGNB. One third of the patients developed abnormal carriage with a high illness severity score as an independent risk factor.

MRSA belongs to the category of abnormal flora. People in good health clear MRSA from throat and gut following exposure. There is no difference in mortality between MSSA and MRSA pneumonias, if prompt adequate treatment is given (21).

In general, abnormal carriage develops early, within the first week of admission to the ICU, when the patient’s illness is most severe and the associated immunodepression is maximal. The severity of illness is the most important factor in the conversion of “normal” into “abnormal” carrier state.

### Table 1. Potentially pathogenic microorganisms (PPM) causing pneumonia during mechanical ventilation

<table>
<thead>
<tr>
<th>Normal PPM carried by previously healthy individuals (%)</th>
<th>Abnormal PPM carried by individuals with underlying disease*</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em> (60)</td>
<td><em>Klebsiella</em> sp.</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> (25-80)</td>
<td><em>Enterobacter</em> sp.</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em> (5)</td>
<td><em>Citrobacter</em> sp.</td>
</tr>
<tr>
<td><em>Escherichia coli</em> (99)</td>
<td><em>Proteus</em> sp.</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> sensitive to methicillin (MSSA) (30)</td>
<td><em>Morganella</em> sp.</td>
</tr>
<tr>
<td></td>
<td><em>Serratia</em> sp.</td>
</tr>
<tr>
<td></td>
<td><em>Acinetobacter</em> sp.</td>
</tr>
<tr>
<td></td>
<td><em>Pseudomonas</em> sp.</td>
</tr>
<tr>
<td></td>
<td><em>Staphylococcus aureus</em> resistant to methicillin (MRSA)</td>
</tr>
</tbody>
</table>

*One-third of the patients when APACHE II (Acute Physiology and Chronic Health Evaluation score) ≥15 (8).
Pathogenesis

Up to 85% of pneumonias that occur during mechanical ventilation are due to PPMs present in the patients’ own oropharyngeal flora, termed as endogenous pathogenesis. The oropharynx is the internal source of PPMs that colonize and infect the lower airways following micro-aspiration of saliva or migration of bacteria (22). It is highly likely that PPMs present in the throat on admission will cause primary endogenous pneumonia (23,24). If the patient was previously healthy, the causative bacteria are usually the five “normal” PPMs, S. pneumoniae, H. influenzae, M. catarrhalis, E. coli, and S. aureus. “Abnormal” MRSA and AGNB may cause primary endogenous pneumonia, if the patient’s defenses are impaired by underlying disease. For example, a patient with chronic illnesses such as diabetes, alcoholism, or COPD may carry “abnormal” bacteria in the admission flora. Patients with debilitating conditions, transferred from other hospitals, wards, or nursing homes, also have high abnormal carriage rates. Primary endogenous pneumonias due to both “normal” and “abnormal” PPM in general develop within the first week of admission to the ICU.

Critically ill patients requiring ventilation for a week or more usually develop an abnormal carrier state with MRSA and AGNB, which have been acquired on the unit. This condition of oropharyngeal supercarriage (or secondary carriage) may lead to secondary endogenous pneumonia (23,24).

About 15% of all pneumonias during mechanical ventilation are of exogenous pathogenesis. The source of the PPM causing this type of pneumonia is external (23-25). For example, in long-stay patients, particularly those who receive a tracheostomy, are at high risk of exogenous pneumonias (26). Purulent lower airway secretions yield a PPM which has never been previously carried by the patients in the digestive tract flora or indeed in their oropharynx but has probably gained access via the tracheostomy. Causative bacteria are almost always “abnormal” AGNB such as Acinetobacter and Pseudomonas species and MRSA. Exogenous infection can occur at any time throughout the patient’s stay in the ICU.

The origin of PPM, including AGNB, causing secondary endogenous and exogenous pneumonias is, by definition, outside the patient, i.e., they are not present in the patient’s admission flora (Fig. 1). In secondary endogenous pneumonia, the causative PPM multiply in the oropharynx of the patient (internal source), whereas in an exogenous infection, multiplication occurs outside the patient (external source), omitting the first stage of oropharyngeal carriage (27).

Diagnosis

There is no current “gold standard” for the diagnosis of pneumonia in the critically ill patient requiring mechanical ventilation (30). The diagnosis is usually based on clinical, radiological, and microbiological criteria, using the non-invasive method of tracheal aspirate yielding ≥10³ colony forming units (CFU) of a PPM/ml of lower airway secretion (Table 2). Combining these criteria has a sensitivity of 65-70% and a specificity of 75-80% for the diagnosis of pneumonia during mechanical ventilation in post mortem studies (1). Some investigators have promoted invasive tech-
niques requiring bronchoscopy, including the protected specimen brush and broncho-alveolar lavage yielding $\geq 10^3$ and $\geq 10^4$ CFU of PPM/ml, respectively, to increase the specificity of the diagnosis of pneumonia during mechanical ventilation (31,32). The “pneumonia” rate is halved by invasive strategies, compared with non invasive methods (33). Two randomized trials have demonstrated that diagnosing pneumonia less frequently in this fashion is not associated with a mortality reduction (31,32). A French randomized trial of 413 patients compared 204 patients managed invasively with protected brush specimens with 209 patients managed non-invasively with tracheal aspirates (31). They failed to show any survival benefit at 28 days (30.9% vs 38.8%, $P=0.10$) using restrictive antibiotic prescribing policies. A Spanish randomized trial of 77 patients, comparing an invasive diagnostic approach ($n=39$) with a non-invasive tracheal aspirate method ($n=38$) found that the 30-day outcome of pneumonia was not influenced (38% vs 46%, $P=0.48$) by the techniques used for microbial investigation (32). Additionally, both trials evaluated the emergence of antimicrobial resistance as a secondary endpoint. In the French trial, the proportions of resistant isolates obtained from lower airway secretions were similar in both invasive (61.3%) and non-invasive (59.8%) groups, despite significantly less use of antibiotics in the invasive group (31). The Spanish trial reported identically high isolation rates of 58.3% of resistant bacteria (MRSA and P. aeruginosa in both groups) (32).

Recently, a new approach to diagnosis has been reported, using measurements of triggering receptor expressed on myeloid cells (TREM-1) in samples of broncho-alveolar lavage fluid (34). However, further studies are required to evaluate this technique.

**Defining Pneumonia during Ventilation Using the Criterion of Carriage**

Recent studies (23,24,35-38), using surveillance cultures from the throat and rectum to detect carrier states, revealed that pneumonias due to microbial sources external to the patient rarely occur in the first week of treatment in ICU. The incidence of these types of pneumonia, termed secondary endogenous and exogenous, varies between 15 and 40% (Table 3).

In the case of secondary endogenous pneumonias, PPMs that are within the ICU environment but are not present in the patient’s admission flora, are first acquired in the oropharynx due to transmission via hands of health care workers. In the critically ill patient, oropharyngeal acquisitions invariably lead to abnormal microbial carrier states (termed secondary or super carriage). The subsequent build-up to overgrowth, defined as $\geq 10^2$ PPMs per ml of saliva, can then result in colonization of the normally sterile lower airways. This may take a few days. The degree of immunosuppression of the ICU patient determines the day on which tracheal colonization leads to established secondary endogenous pneumonia of the lower airways.

The other type of ICU pneumonia is exogenous pneumonia due to the breaches of hygiene. Exogenous pneumonias may occur at any time during the patient’s stay in ICU. The causative bacteria are also acquired in the unit but are never present in the throat of the patient (Fig. 1). Long-stay patients, particularly those who receive a tracheostomy, are at high risk of exogenous pneumonias. Purulent lower airway secretions yield a PPM never previously carried by the patient in the oropharynx. Although a tracheostomy and the oropharynx are both vulnerable to bacterial entry, the tracheostomy tends to be the entry site for bacteria that colonize and infect the lower airways.

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>PPM Carriage</th>
<th>Time cut-off</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endogenous normal/abnormal</td>
<td>present in admission flora</td>
<td>&lt;one week</td>
<td>55</td>
</tr>
<tr>
<td>Secondary endogenous abnormal</td>
<td>not present in admission flora, but acquired and carried later</td>
<td>&lt;one week</td>
<td>30</td>
</tr>
<tr>
<td>Exogenous abnormal</td>
<td>no carriage at all</td>
<td>anytime throughout ICU stay</td>
<td>15</td>
</tr>
</tbody>
</table>

**Table 2.** Clinical, radiological, and microbiological criteria for the diagnosis of pneumonia during mechanical ventilation, using non-invasive strategy of tracheal aspirate

1. New, persistent, or progressive infiltrate on chest X-ray
2. Purulent tracheal aspirate
3. Temperature $>38.2^\circ$ C or $<35.5^\circ$ C
4. Leukocytes $>10^3$$X10^9$/L or $<4$$X10^9$/L
5. Tracheal aspirate culture $\geq 10^5$ potential pathogens/mL

**Table 3.** Three different types of pneumonia due to 14 potentially pathogenic microorganisms (PPM)

- **Primary endogenous normal/abnormal**
  - Carriage: present in admission flora
  - Time cut-off: <one week
  - Incidence (%): 55
- **Secondary endogenous abnormal**
  - Carriage: not present in admission flora, but acquired and carried later
  - Time cut-off: <one week
  - Incidence (%): 30
- **Exogenous abnormal**
  - Carriage: no carriage at all
  - Time cut-off: anytime throughout ICU stay
  - Incidence (%): 15
most frequent problem is primary endogenous pneumonia. These pneumonias are due to PPMs that the patient carries at the time of ICU admission. The proportion of primary endogenous pneumonias varies between 55 and 85%, typically occurring within the first week of the ICU stay. The PPMs involved do not bear any direct relation to the ICU-ecology (23,24,35-38) (Table 3).

The conventional approach to pneumonia in the intensive care is to classify episodes of pneumonia occurring after 48 hours as “nosocomial” infections. This definition implies that the PPMs responsible for pneumonia on the day three and subsequently are acquired in the ICU from sources external to the patient. The 48-hour cut-off would classify 70% of all pneumonias as “nosocomial”, implying a major problem of microbial transmission between patients. Most importantly, the time classification does not identify exogenous infections. In contrast, using the carriage criterion, approximately 60% of the ICU patients develop pneumonias with PPMs imported with the patient into the ICU.

Prevention
Non-antibiotic Interventions
There are 7 RCTs that evaluated non-antibiotic maneuvers to control pneumonia. Only a single RCT evaluated hygiene (39). Four RCTs were undertaken to study the impact of subglottic drainage on pneumonia over the past ten years, in approximately 800 patients (40-43). The semi-recumbent position (45°) was studied in 2 RCTs over the last five years, including 300 patients (45,46).

Hygiene
There is a single RCT that evaluated hygiene including personal protective equipment such as gloves, gowns, and hand hygiene in two surgical ICUs (39). Standard care was administered in the same way in the two units. The same medical staff always administered care but did not mix between units. In one unit, all personnel and visitors donned gowns and gloves before entering the ventilated patient’s room; hand washing was required before entry and on leaving the room (test unit). In the control unit, all health care workers utilized standard precautions including hand washing and gloves. Remarkably, the incidence of pneumonia was significantly higher in the test group compared with the control group (36.4% vs 19.5%, P = 0.02). There was no difference in mortality.

Subglottic drainage. The accumulation of saliva contaminated with PPMs above the balloon of the endotracheal ventilation tube is thought to increase the risk of aspiration and pneumonia. Removal of pooled salivary secretions, through suctioning of the subglottic region, is thought to reduce the risk of aspiration and subsequent pneumonia during ventilation, a practice termed subglottic drainage. This requires the use of a specially designed endotracheal tube with a separate dorsal lumen that opens into the subglottic region. Three of the 4 RCTs have examined subglottic drainage in a mixed ICU-population (surgical and medical patients) requiring three or more days of mechanical ventilation (40,41,43). The fourth RCT (42) was limited to post-cardiac surgery patients (Table 4). The results of these trials are mixed. Two RCTs (40,43) reported a statistically significant reduction in pneumonia in the treatment group. This reduction was due to a significant decrease in the number of primary endogenous pneumonias, caused by “normal” PPMs S. pneumoniae and H. influenzae. The two other RCTs failed to show a difference (41,42). A meta-analysis of these trials shows a relative risk reduction of 0.49 (95% CI = 0.39-0.71) in pneumonia. No difference in mortality was observed. A recent RCT reports tracheal injury as a serious side-effect of subglottic drainage (44).

Semi-recumbent position (45°). Although the oropharynx is generally considered to be the internal source of PPMs causing pneumonia, some investigators believe that PPMs carried in the stomach may also contribute. The concept

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient type</th>
<th>Sample size</th>
<th>Pneumonia RR (95% CI)</th>
<th>Mortality RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mahul et al (40)</td>
<td>mixed</td>
<td>145</td>
<td>0.46 (0.23 to 0.93)</td>
<td>1.14 (0.62 to 2.07)</td>
</tr>
<tr>
<td>Valles et al (41)</td>
<td>mixed</td>
<td>190</td>
<td>0.56 (0.31 to 1.01)</td>
<td>1.07 (0.70 to 1.65)</td>
</tr>
<tr>
<td>Kollef et al (42)</td>
<td>cardiac</td>
<td>343</td>
<td>0.61 (0.27 to 1.40)</td>
<td>0.86 (0.30 to 2.42)</td>
</tr>
<tr>
<td>Smulders et al (43)</td>
<td>mixed</td>
<td>150</td>
<td>0.25 (0.07 to 0.85)</td>
<td>1.20 (0.55 to 2.61)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>828</td>
<td>0.49 (0.39 to 0.71)</td>
<td>1.10 (0.84 to 1.46)</td>
</tr>
</tbody>
</table>

*Abbreviations: RR – relative risk; CI – confidence interval.
of the gastro-pulmonary route implies that positioning patients supine increases the risk of gastric reflux, aspiration, and pneumonia. This hypothesis suggests that semi-recumbent positioning, defined as the elevation of the bed head to 45°, decreases the risk of developing pneumonia during ventilation.

Two RCTs have evaluated the efficacy of semi-recumbent positioning in preventing pneumonia. The first RCT (n = 86) found that ventilating patients in semi-recumbent position significantly reduced pneumonia (45). There was no difference in mortality. Patients were excluded if they had undergone abdominal or neurological surgery within 7 days, had shock refractory to vasoactive therapy or had required readmission to ICU within one month. The second larger multicenter RCT (n = 221) failed to confirm the positive results of the first RCT (46). Table 5 shows that there was no difference in pneumonia or mortality rates.

Antibiotic intervention, selective decontamination of the digestive tract (SDD). SDD is a prophylactic protocol comprising four components. It is designed to control the three types of pneumonia due to the 14 PPMs, comprising 5 “normal” and 9 “abnormal” species of bacteria (Table 6) (47).

Adequate prompt parenteral antimicrobial therapy is aimed at the prevention and treatment of primary endogenous pneumonia, the most common type of lower airway infection on the ICU. Cefotaxime, active against both “normal” and “abnormal” PPM (except Pseudomonas species), was used in most RCTs that evaluate SDD. Parenteral cefotaxime was discontinued as soon as the oropharynx and lower airways are negative for PPM, usually after 3 days. The choice of the parenteral antimicrobial is crucial because the immediate administration of adequate systemic antibiotics has been shown to significantly reduce mortality in a large multicenter study (48).

The second component of SDD is the administration of high doses of non-absorbable antimicrobials into the throat and gut to prevent the acquisition, carriage, and overgrowth of PPMs. The usual combination is polymyxin E, tobramycin, and amphotericin B (PTA). About one third of patients with pneumonia in ICUs not using SDD have a secondary endogenous infection, due to PPMs acquired during their ICU treatment. The origin of the causative PPMs is outside the patient (usually the other long-term ventilated patients). PPMs are transmitted via the hands of carriers. The patient acquires the PPM in the oropharynx, becoming the internal source. Acquisition leads to carriage and overgrowth in the throat and gut of the critically ill. The next stage in the pathogenesis of secondary endogenous pneumonia is colonization of the lower airways following aspiration or migration into the lungs.

Table 5. Results of two randomized controlled trials on reduction the risk of pneumonias during ventilation using semi-recumbent positioning of 45°*

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient type</th>
<th>Sample size</th>
<th>Pneumonia RR (95% CI)</th>
<th>Mortality RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drakulovic et al (45)</td>
<td>mixed</td>
<td>86</td>
<td>0.22 (0.05-0.93)</td>
<td>0.65 (0.29-1.47)</td>
</tr>
<tr>
<td>van Nieuwenhoven et al (46)</td>
<td>mixed</td>
<td>221</td>
<td>1.58 (0.68-3.86)</td>
<td>0.94 (0.63-1.42)</td>
</tr>
</tbody>
</table>

*Abbreviations: RR – relative risk; CI – confidence interval.

Table 6. Full four-component protocol of selective digestive decontamination (SDD) of potentially pathogenic microorganisms (PPM)*

<table>
<thead>
<tr>
<th>Total daily dose (4×daily)</th>
<th>age &lt; or = 5 years</th>
<th>age 5-12 years</th>
<th>age &gt;12 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enteral antimicrobials:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>oropharynx:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AGNB: polymyxin E with tobramycin</td>
<td>2 g of 2% paste or gel</td>
<td>2 g of 2% paste or gel</td>
<td>2 g of 2% paste or gel</td>
</tr>
<tr>
<td>yeasts: amphotericin B or nystatin</td>
<td>2 g of 2% paste or gel</td>
<td>2 g of 2% paste or gel</td>
<td>2 g of 2% paste or gel</td>
</tr>
<tr>
<td>MRSA: vancomycin</td>
<td>2 g of 2% paste or gel</td>
<td>2 g of 2% paste or gel</td>
<td>2 g of 2% paste or gel</td>
</tr>
<tr>
<td>gut:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AGNB: polymyxin E (mg) with tobramycin (mg)</td>
<td>100, 80</td>
<td>200, 160</td>
<td>400, 320</td>
</tr>
<tr>
<td>yeasts: amphotericin B (mg) or nystatin (units)</td>
<td>500, 2×10⁶</td>
<td>1,000, 4×10⁹</td>
<td>2,000, 8×10⁹</td>
</tr>
<tr>
<td>MRSA: vancomycin (mg)</td>
<td>20-40/kg</td>
<td>20-40/kg</td>
<td>500-2,000</td>
</tr>
<tr>
<td>Parenteral antimicrobials:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cefotaxime (mg)</td>
<td>150/kg</td>
<td>200/kg</td>
<td>4,000</td>
</tr>
<tr>
<td>hygiene:</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>surveillance culture of the throat and rectum:</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*Abbreviations: AGNB – aerobic Gram-negative bacilli; MRSA – methicillin resistant Staphylococcus aureus.
The third component is a high standard of hygiene. Pneumonia during mechanical ventilation can be exogenous, due to PPMs from an external source. The PPMs causing exogenous pneumonias are introduced into the lower airways, following transmission via the hands of carriers but bypassing oropharyngeal carriage. Only high standards of hygiene can prevent this type of pneumonia.

The fourth component of SDD is surveillance cultures of the throat and rectum, which monitor the efficacy, safety of, and compliance with this protocol (Fig. 1 and Fig. 2).

Figure 2. The “full” selective decontamination of the digestive tract (SDD) protocol and the type of infection prevented/controlled by each component. PPM – potentially pathogenic micro-organisms; PTA – polymyxin E, tobramycin and amphotericin B; ICU – intensive care unit.

Fifty-four RCTs were designed to evaluate SDD in a total of 8,715 patients between 1987-2004 (49). Thirty-eight RCTs showed a significant reduction in pneumonia and 4 individual trials demonstrated a mortality reduction (50-53). There are 7 meta-analyses (54-60) of the RCTs assessing SDD and all show a significant reduction in pneumonia. Five out of seven meta-analyses report a mortality reduction. The most recent meta-analysis included 36 RCTs in 6,922 patients, and showed that SDD, including enteral and parenteral antimicrobials, reduced the odds ratio for pneumonia to 0.35 (95% CI = 0.29-0.41) and mortality to 0.80 (95% CI = 0.68-0.89) (60). The absolute mortality reduction was 4.8%. This information implies that 5 ICU-patients need to be treated with SDD to prevent one case of pneumonia, and 21 ICU-patients need to be treated to prevent one death (60). Two recent large RCTs (51,52) reported absolute mortality reduction of 8%, corresponding to the treatment of 12 patients with SDD to save one life.

The primary theoretical risk associated with SDD is the emergence of antibiotic resistance (47). In the latest meta-analysis of SDD, covering trials over a 17 year period, antibiotic resistance was not a clinical problem (60). However, antibiotic resistance is a long-term evolutionary issue. Five SDD trials prospectively evaluated resistance for 2, 2.5, 5, 6, and 7 years (61-65). No increase in the rate of superinfections due to resistant bacteria could be demonstrated. The latest trial, evaluating SDD in about 1,000 patients, had significantly fewer carriers of multi-resistant AGNB in the patients receiving SDD than in the control group (51).

There is no relevant data about cost-benefit analysis of SDD.

SDD, by design, is not active against MRSA. Six RCTs, conducted in ICUs where MRSA was endemic at the time of the study, showed a trend towards higher MRSA infection rates in patients receiving SDD (66-71). These observations suggest that the parenteral and enteral antimicrobials of the SDD protocol, ie, cefotaxime and polymyxin E, tobramycin and amphotericin B, may cause selection and overgrowth of MRSA in the throat and gut. Under these circumstances, SDD requires the addition of oropharyngeal and enteral vancomycin (72-75). Two studies, using 2 g of a 4% vancomycin gel or paste and 2 g of vancomycin solution added to the non-absorbable PTA component of SDD, demonstrated the prevention and the eradication of carriage and overgrowth of “abnormal” MRSA (72,73). Subsequent MRSA infection, transmission, and outbreaks were controlled. Using this protocol, the ICU becomes free from MRSA. Severe infections, including MRSA pneumonia and septicemia, were significantly reduced using enteral vancomycin in two RCTs (74,75).

The concern that SDD promotes vancomycin resistant enterococcus (VRE) carriage and infection has been investigated in 4 studies, 3 in liver transplant recipients (76-78) and 1 in patients requiring mechanical ventilation (79). The incidence of both carriage and infection due to VRE was low and similar in test and control groups in the two American RCTs evaluating SDD in liver transplant recipients (76,77). The Dutch RCT was
conducted in a unit without VRE history (78). An American study, conducted in an ICU with a low incidence of VRE infection, reported that oral SDD did not increase the incidence of VRE carriage and infection (79). SDD, combined with enteral vancomycin throughout the treatment in ICU, was evaluated in 4 European studies, 2 Spanish studies (73,74), and 2 Italian (72,75). Despite VRE being imported into one of the Spanish units, no change in the use of non-absorbable vancomycin and SDD was required, as rapid and extensive spread did not occur over a four year period (73). VRE was not isolated in any of the other three studies (72,74,75). Recent literature shows that parenteral antibiotics that do not respect the patient’s gut ecology, rather than high doses of enteral vancomycin, promote the emergence of vancomycin-resistant enterococci in the gut (80,81).

The most recent data showing a survival benefit without emerging bacterial resistance, support level I evidence for SDD, allowing a grade A recommendation. Table 7 shows the five evidence-based medicine maneuvers showing survival benefit in the critically ill (51,52,82-85). Only SDD is supported by at least 2 level I investigations (51,52), the other 4 are supported by only a single trial, providing a grade B recommendation. Additionally, SDD can be administered to all patients at risk of infection, whereas the other 4 only in specific subsets of critically ill patients (47, 82-85).

Surveillance cultures of the throat and rectum are not popular amongst many microbiologists in the UK. Although the rationale for SDD is based on the detection of abnormal carrier states using surveillance cultures, SDD can still be used in their absence. The treatment effect on pneumonia and mortality by SDD was independent of the use of surveillance cultures in the most recent meta-analysis (60). In 7 trials, surveillance cultures were not obtained. If the microbiology department is unable to provide a service based on surveillance cultures, SDD infection prophylaxis is still feasible and supported by evidence.

Withholding SDD from critically ill populations can result in harm to a significant proportion of long term ventilated patients. New prevention methods against pneumonia should be compared with the effect of SDD. This is the only prevention method supported by a large body of level I evidence.

### Therapy

The difficulties in pneumonia diagnosis have yet to be resolved, despite two decades of evaluation of various diagnostic techniques. Four trials provide evidence that the non-invasive clinical approach using quantitative culturing of endotracheal aspirate is as good as the invasive methods for diagnosing pneumonia (31,32,86, 87). A recent editorial advocates a strategy in which treatment is started immediately, on the basis of sufficient suspicion of pneumonia, using classical criteria (30) (Table 2). The response to treatment should be closely evaluated over the first 2-3 days. In the event of a poor response, the diagnosis should be re-considered, including a search for non-respiratory sites of infection and non-infectious causes of pulmonary infiltrates. If the initial cultures are sterile but a high clinical suspicion of pulmonary infection persists, broncho-alveolar lavage should be performed to investigate viral and atypical causes, particularly in the immunocompromised host (30).

### Table 7. Interventions that reduce mortality in critically ill patients in intensive care unit

<table>
<thead>
<tr>
<th>Intervention (ref.)</th>
<th>RR (95% CI)*</th>
<th>Absolute mortality reduction (%)</th>
<th>Number needed to treat</th>
<th>Grade of recommendation†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low tidal volume (82)</td>
<td>0.78 (0.65 to 0.93)</td>
<td>8.8 (2.4 to 15.3)</td>
<td>11</td>
<td>B</td>
</tr>
<tr>
<td>Activated protein C (83)</td>
<td>0.80 (0.69 to 0.94)</td>
<td>6.1 (1.9 to 10.4)</td>
<td>16</td>
<td>B</td>
</tr>
<tr>
<td>Intensive insulin (84)</td>
<td>&lt;5 days</td>
<td>0.44 (0.36 to 0.81)</td>
<td>3.7 (1.3 to 6.1)</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>&gt;5 days</td>
<td>0.52 (0.33 to 0.84)</td>
<td>9.6 (3.0 to 16.1)</td>
<td>10</td>
</tr>
<tr>
<td>Steroids (85):</td>
<td>responders</td>
<td>0.90 (0.74 to 1.09)</td>
<td>6.4 (4.8 to 17.6)</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>non-responders to 0.25 mg of tetracosactrin</td>
<td>0.83 (0.66 to 1.04)</td>
<td>10.8 (1.9 to 23.6)</td>
<td>9</td>
</tr>
<tr>
<td>Selective digestive decontamination</td>
<td>0.65 (0.49 to 0.85)</td>
<td>8.1 (3.1 to 13.0)</td>
<td>12</td>
<td>A</td>
</tr>
</tbody>
</table>

*Abbreviations: RR – relative risk; CI – confidence interval; SDD – selective digestive decontamination.
†Grade A – supported by Level I evidence; Grade B – supported by Level II evidence; Level I evidence – data from randomized trials with low false-positive (a) and low false-negative (b) errors; Level II evidence – data from randomized trials with high false-positive (a) and high false-negative (b) errors.
The six basic principles (88) behind the concept of the treatment of pneumonia are summarized in Table 8.

Table 9 shows our management of suspected pneumonia, based on the knowledge of the oropharyngeal microbial carrier state, at the time of admission to the ICU. Parenteral antibiotics should be started immediately after obtaining surveillance and diagnostic samples (48,89). If the patient was previously in reasonably good health, monotherapy with cefotaxime is sufficient, as the patient carries normal flora in the oropharynx. Patients who are admitted with a chronic underlying condition or who are transferred from another hospital or ward are usually the carriers of abnormal flora and hence require parenteral administration of cefotaxime with gentamicin. On the next day, clinical microbiologist is able to distinguish "normal" from "abnormal" potential pathogens isolated from the lower airways. In the case of "normal" PPMs causing pneumonia, gentamicin can be discontinued, as monotherapy with cefotaxime is adequate. If S. aureus is isolated from the lower airways, monotherapy with cephradine or cefazolin is the first choice. If the clinical microbiologist reports that P. aeruginosa is involved in the pneumonia, the combination of cefotaxime and gentamicin is replaced by an antipseudomonal combination of ceftazidime and gentamicin (tobramycin). Remarkably, there is no convincing RCT evidence that combination therapy is superior to monotherapy in patients with pneumonia (90-92). Monotherapy of pneumonia, due to abnormal flora including AGNB and MRSA, is contraindicated as it is thought to be a risk factor for the selection of resistant PPM (93-95). If a patient admitted with a primary endogenous pneumonia does not improve on this antibacterial therapy within 24-48 hours and all cultures remain sterile, the possibility of an atypical pneumonia due to an agent such as Legionella pneumophila should be considered and sought (96). Serological and urine tests have to be done, and the empirical therapy should be discontinued and replaced by a macrolide. There is no evidence to support an antibiotic course exceeding one week (97).

Eradication of the source of PPM is an important component of an effective treatment of pneumonia. The cure rate of pneumonia in patients receiving parenteral and enteral antimicrobials is inferior to that of patients receiving only parenteral antibiotics (98). If the patient does not improve on the antibacterial therapy within 48 hours of admission, the possibilities of an atypical pneumonia due to an agent such as Legionella pneumophila should be considered and sought (96). Seriological and urine tests have to be done, and the empirical therapy should be discontinued and replaced by a macrolide. There is no evidence to support an antibiotic course exceeding one week (97).

Table 8. Six principles behind the concept of the treatment of pneumonia

1. Surveillance and diagnostic cultures to ensure identification of the microorganisms so that modification of the otherwise “empirical” treatment can be undertaken.
2. Immediate and adequate antibiotic treatment in order to sterilize the lower airways.
3. The source of potential pathogens causing the infection – whether endogenous or exogenous – requires elimination for both the recovery of the original infection and the prevention of relapses and/or superinfection. Selective digestive decontamination (SDD) aims at the eradication of internal sources of the oropharynx (and gut) in patients, whilst identification and eradication of the external sources outside the patients, using disposables and/or hygiene, are in integral part of the therapy of pneumonia.
4. Aerosolized antimicrobials for delivering high antibiotic concentrations directly to the site of infection.
5. Removal or replacement of invasive airway devices, often contaminated with potential pathogens, is thought to contribute to recovery from pneumonia in curtailing the supply of microorganisms.
6. Surveillance samples are indispensable in evaluating the efficacy of this protocol.

Table 9. Proposed strategy for management of suspected pneumonia during mechanical ventilation in the intensive care unit (ICU)*

<table>
<thead>
<tr>
<th>ICU pneumonia</th>
<th>PPM antimicrobials</th>
<th>Elements of strategy of pneumonia management</th>
<th>Duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endogenous pneumonia</td>
<td>imported in patient’s flora:</td>
<td></td>
<td>7 days (or 5 days if selective digestive decontamination is used simultaneously)</td>
</tr>
<tr>
<td>Secondary endogenous and exogenous pneumonia</td>
<td>acquired in ICU (abnormal only):</td>
<td></td>
<td>7 days (or 5 days if selective digestive decontamination is used simultaneously)</td>
</tr>
</tbody>
</table>

*Abbreviations: PPMs - potentially pathogenic microorganisms; AGNB - aerobic Gram negative bacilli; MRSA - methicillin resistant Staphylococcus aureus.
crobials of SDD was 96% (98,99). There were no superinfections. Contaminated ventilators, humidifiers, and sinks are potential external sources. Breaches of hygiene by care givers, particularly during periods of high workload, may lead to increased transmission of PPM and a higher exogenous pneumonia rate.

The topical application of antimicrobials by nebulization as part of pneumonia therapy is safe (90) and contributes to a more rapid killing of PPM resulting in cultures of the lower airway secretions becoming sterile earlier (100). A placebo controlled trial showed that nebulized delivery of aerosolized antibiotics in combination with systemic antibiotics resulted in a significantly more rapid eradication of AGNB from the lower airways (101). The doses of the different aerosolized antimicrobials are shown in Table 10. Relatively high doses are applied to the lower airways as only less than 5% of the aerosolized drug reaches the terminal airways. In the case of P. aeruginosa and S. aureus being the causative PPMs of the pneumonia, antimicrobials are nebulized via the endotracheal tube. Besides parenteral and topical antimicrobials, the patient with pneumonia during ventilation always receives enteral antibiotics as part of SDD, to prevent relapses and/or superinfections. Contaminated ventilators, humidifiers, and sinks are potential external sources.

This management strategy is based on our experience in a pediatric ICU. There are low carriage and infection rates due to resistant micro-organisms. Surveillance cultures and SDD are used for normal carrier states (107). Most units use neither surveillance cultures nor SDD (108), and experience considerable problems with multi-resistant AGNB such as Klebsiella and Pseudomonas spp and MRSA. These particular resistant micro-organisms determine the empirical initial antibiotic therapy of primary endogenous pneumonia. The local resistance pattern will dictate the appropriate antibiotic therapy for the secondary endogenous and exogenous pneumonias (Table 9). We believe that surveillance cultures of the throat and rectum are crucial in establishing the epidemiology of pulmonary infections due to resistant micro-organisms (109,110).

Acknowledgements

We are grateful to Mrs Lynda Jones for meticulously typing the manuscript.

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Bacterial Pneumonia and Mechanical Ventilation


Received: January 17, 2005
Accepted: March 2, 2005

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