Intensive Care Med (2002) 28:1521–1536
DOI 10.1007/s00134-002-1514-0

CONSENSUS CONFERENCE

R. D. Hubmayr

Statement of the 4th International Consensus Conference in Critical Care on ICU-Acquired Pneumonia – Chicago, Illinois, May 2002

Published online: 8 October 2002

Sponsored by the American Thoracic Society Assembly on Critical Care (ATS), the European Respiratory Society (ERS), the European Society of Intensive Care Medicine (ESICM), and the Société de Réanimation de Langue Française (SRLF)

Jurors and co-authors: Hilmar Burchardi (Goettingen, Germany), Mark Elliott (Leeds, UK), Henry Fessler (Baltimore, USA), Dimitrios Georgopoulos (Crete, Greece), Amal Jubran (Chicago, USA), Andrew Limper (Rochester, Minn., USA), Antonio Pesenti (Monza, Italy) Gordon Rubenfeld (Seattle, USA), Thomas Stewart (Toronto, Canada), Jesus Villar (Santa Cruz de Tenerife, Spain)

Consensus Conference Organization: Scientific Advisors: Christian Brun Bruisson (Paris, France), Waldemar Johanson (New Jersey, USA)

International Consensus Conference Committee. ATS: Catherine Sassoon (Long Beach, Calif., USA), Brian Kavanagh (Toronto, Canada); ERS: Marc Elliott (Leeds, UK); ESICM: Graham Ramsay (Maastricht, Netherlands), Marco Ranieri (Turino, Italy); SRLF: Didier Dreyfuss (Paris, France), Jordi Mancebo (Barcelona, Spain) Scientific Experts: Edward Abraham (Denver, USA), Massimo Antonelli (Roma, Italy), Robert P. Baughman (Cincinnati, USA), Marc Bonten (Utrecht, Netherland), Lucca Brazzi (Italy), Jean Chastre (Paris, France), Deborah Cook (Hamilton, Canada), Donald E. Craven (Boston, USA), Lisa L. Dever (New Jersey, USA), Didier Dreyfuss (Colombes, France), Mahmoud Eltorky, (Memphis, USA), Jean-Yves Fagon (Paris, France), Jesse Hall (Chicago, USA), Alan M. Fein (Manhasset, USA), Dean Hess (Boston, USA), Steven H. Kirtland (Seattle, USA), Marin H. Kollef (St. Louis, USA), Lionel A. Mandell (Hamilton, Canada), Charles H. Marquette (Lille, France), Thomas R. Martin (Seattle, USA), C. Glen Mayhall (Galveston, USA), G. Umberto Meduri (Memphis, USA), Dominique L. Monnet (Copenhagen, Denmark), Michael S. Niederman (Mineola, USA), Jerome Pugin (Geneva, Switzerland), Theodore J. Standiford (Michigan, USA), Jordi Rello (Tarragona, Spain), Jean-François Timsit (Paris, France), Antonio Torres (Barcelona, Spain), Robert Weinstein (Chicago, USA), Richard Wunderink (Memphis, USA)

R.D. Hubmayr (✉)
Stabile 8–62, Mayo Clinic, 200 First Street SW, Rochester, MN, 55905, USA
e-mail: rhubmayr@mayo.edu
Tel.: +1-507-2669722, Fax: +1-507-2844521

Introduction

On 23–24 May 2002, in Chicago, Illinois, USA, a jury of 11 intensivists heard expert testimony that was intended to answer five specific questions: 1) What is the epidemiology of ICU-acquired pneumonia? 2) What are the pathophysiological characteristics and pathogenesis of ICU-acquired pneumonia? 3) What are the risk factors and effective preventive measures for ICU-acquired pneumonia? 4) What is the best means to establish a diagnosis of ICU-acquired pneumonia? 5) What are the optimal therapeutic approaches to ICU-acquired pneumonia. The following is a synopsis of the expert testimony, the jury's interpretation of the testimony and their recommendations.

Question 1: what is the epidemiology of ICU-acquired pneumonias?

General methodological limitations

There are major limitations to the existing studies of the epidemiology of ICU-acquired pneumonias. The entity under review varies, and often fails to distinguish between nosocomial pneumonia and ventilator-associated pneumonia (VAP). The criteria used for the diagnosis of VAP also varies between studies. Terminology and definitions may significantly affect the epidemiology of VAP [1]. Associations between variables and development of VAP (risk factors for incidence) or patient-outcome VAP (risk factors for mortality and morbidity) may not be causal or may be due to confounding factors. Optimal epidemiology studies of VAP would repeat the analyses using various pneumonia definitions, in different patient populations, and use several different techniques to adjust for confounding factors. In the absence of such studies, we will use the generic term ICU-acquired pneumonia to refer to the topic of this consensus statement, acknowledging that most studies have examined VAP.

Incidence

Incidence rates for VAP (clinically defined) average seven cases per 1,000 ventilator days with a range of 1 to >20 [2, 3]. In one cross-sectional study, VAP was reported in 47% of ICU patients with infections [4]. There are no accurate estimates of the population incidence of VAP or its overall burden of illness. A number of patient factors are associated with VAP including: age, male gender, coma, burn, trauma, acute lung injury, and severity of illness [5, 6]. Perhaps the most important factors in the incidence, microbiology, and severity of VAP is the duration of mechanical ventilation and antibiotic exposure prior to its onset. The risk of VAP peaks around day 5 of mechanical ventilation [6]. After 15 days the incidence plateaus and then declines, such that pneumonia rates are quite low in chronically ventilated patients.

Nosocomial bacterial pneumonia is under-recognized in ARDS, with one study finding histologically proven pneumonia at autopsy in 58% of patients, in 36% of whom it was unsuspected [7]. Premortem diagnosis is difficult because clinical criteria are non-specific and bilateral pulmonary infiltrates are present as a consequence of ARDS. Studies suggest a VAP rate between 37% and 60% [8, 9]. This exceeds the rate in intubated patients without ARDS (23–28%) in two comparative studies [8, 9].

Microbiology

Organisms that are seen early (<72 h) in a patient's stay in the ICU vary markedly from those seen later. "Early" organisms are largely *Staphylococcus aureus*, *S. pneumoniae*, other Streptococci and *H. influenzae*, while "late" pathogens reflect resistant nosocomial pathogens, particularly *Pseudomonas aeruginosa*, methicillin-resistant *S. aureus* (MRSA), and *Acinetobacter baumannii*. Approximately 50% of isolates comprise "normal" respiratory tract flora. However, such a finding cannot be dismissed considering that the lower respiratory tract is usually sterile. Multiple organisms may be involved in over half of all pneumonias [10, 11]. Anaerobes are often co-pathogens in early pneumonia, but do not adversely affect outcome [12]. MRSA has a higher mortality and is more common in patients who have received steroids, prior antibiotics, and who have been ventilated for more than 6 days [13, 14].

Attributable mortality and morbidity

The case fatality rate in VAP ranges from 20% to over 50% [15, 16] and is increased by age, late onset, resistant pathogens, medical (as opposed to surgical) diagnosis, and severity of illness. Studies of the independent attributable mortality and morbidity of VAP are difficult to compare, not only because of the varied definitions and patient populations, but also because of the different methods employed to control for confounding factors. Estimates of attributable mortality range from none to a relative risk of 3.6. Many observational studies do not show any attributable mortality from VAP after matching of age, diagnosis, duration of mechanical ventilation, severity of illness, and careful exclusion of control patients with undiagnosed VAP [16, 17]. The optimal study design to assess attributable mortality is a randomized controlled trial of an effective prevention for VAP [18]. Such studies have not consistently decreased mortality, despite reduction of pneumonia rates [19]. It is therefore not clear from the available data that VAP independently causes mortality in heterogeneous ICU patient populations. Meta-analyses of the selective digestive tract decontamination literature [19, 20] argue that the attributable mortality is low (1–5%), that it varies with the type of patient, (i.e., medical vs surgical vs trauma), and that it also depends on host response factors [21, 22].

The effect of VAP on length of stay is difficult to isolate, since the incidence of pneumonia is so strongly associated with duration of ventilation, and because patients who die of pneumonia have their length of stay reduced. Nevertheless, the effect of VAP on length of stay is more consistently seen than is the effect on mortality. Estimates range from no statistically significant increase in length of stay to 8 days [16].

The relationship between ARDS and VAP has been extensively studied to explore whether patients with injured lungs are at greater risk of infection, death from infection, or whether infection worsens lung injury. Studies have shown a wide range of incidence of VAP in patients with ARDS, but this may be due to differences in diagnostic approach or case definition [9, 23]. One multicenter study found similar death rates in patients with ARDS with and without VAP (57% vs 59%) but the high baseline mortality may obscure the effect of VAP in patients with ARDS [9].

Current state of knowledge and unresolved controversies

- Incidence rates for VAP using a clinical definition average seven cases per 1,000 ventilator days.
- VAP is the most common ICU acquired infection reported in up to 60% of ICU patients.
- Organisms that are seen early (<72 h) in a patient's ICU course vary markedly from those seen later.
- Case fatality rates in VAP ranges from 20% to over 50%.
- Estimates of attributable mortality range from no statistically significant attributable mortality to a relative risk of 3.6.
- Data that clearly separate the epidemiology and outcomes of overlapping entities such as hospital acquired pneumonia, nosocomial pneumonia cared for

in the ICU, ICU-acquired pneumonia, and VAP are not available.
- Whether VAP really leads to an increased mortality can only be established by a prospective interventional study to prevent VAP.

Question 2: what are the pathophysiological characteristics and pathogenesis of ICU-acquired pneumonia?

It was apparent at the Consensus Conference that pathologists, microbiologists, epidemiologists, and clinicians will rarely agree on what is pneumonia. We will define pneumonia as distal airspace inflammation caused by microbes or microbial products. Normally, the lower respiratory tract is sterile. In a patient with lung inflammation, the presence of microbes in the lower respiratory tract is therefore highly suggestive of pneumonia.

Pathology of ICU-acquired pneumonia

The histopathological examination of lung tissue has been traditionally regarded as the gold standard of diagnosis. However, even with histology, pneumonia is difficult to diagnose because the presence of inflammation does not establish infection as the specific cause [13, 24, 25, 26]. Moreover, the inflammatory response may persist in the lung long after bacteria have been cleared from the tissue [27].

Rouby defined the histological progression of bacterial lung infections from bronchiolitis to focal bronchopneumonia to confluent bronchopneumonia [28]. In some patients, tissue destruction may cause lung abscess. In the early phase of infection (up to 24 h), neutrophils invade interstitial and air spaces. In patients with underlying diffuse alveolar damage, this results in multifocal lung consolidation with poorly delimited hemorrhagic lesions as well as acute necrotizing and non-necrotizing bronchiolitis. In intermediate phases, fibrin is deposited and polymorphonuclear leukocytes and hemolyzed red blood cells accumulate in air spaces, resulting in focal necrotic lesions. Finally, the advanced phase of VAP is characterized by macrophages in the interstitium and the air spaces. If the infection is controlled, restructuring of the damaged tissue occurs, with or without resulting fibrosis. If the infection is not controlled, complications include lung abscess, empyema, and bacteremia with metastatic abscess formation, and multiorgan failure.

Lessons from animal model

Lung damage may result as much from the host inflammatory responses as from direct bacterial toxicity. The bacterial burden depends on the equilibrium between bacterial virulence and the host immune response. Experimental animal models of pneumonia demonstrate that quantitative cultures of lung parenchyma may not confidently differentiate the presence or absence of pneumonia as verified by histological examination [24, 29, 30, 31]. This may explain why even techniques such as protected specimen brush and bronchoalveolar lavage can be unreliable. On the other hand, there is no straightforward relationship between the intensity of lung damage and the local microbial burden. Thus, a purely histological definition of pneumonia is difficult to formulate and is of doubtful clinical benefit.

The lung's response to bacterial challenge and its alterations in critically ill patients

Pulmonary response to acute bacterial challenge

The lung is defended by alveolar macrophages, which ingest the inhaled particles and eliminate them either up the mucociliary escalator or to the regional lymphoid tissue. Alveolar macrophages phagocytose and digest bacteria and release peptide and lipid mediators. These initiate and amplify inflammatory responses and recruit neutrophils, monocytes, and lymphocytes into the alveolar spaces [32, 33]. Alveolar macrophages also stimulate repair processes and contribute to the resolution of inflammation [34, 35, 36].

Bacteria and their products (such as lipopolysaccharide, LPS) are recognized by receptors [including toll-like receptors (TLRs), CD14, and others] present on the surface of leukocytes and non-myeloid cells which activate them [37, 38, 39, 40]. The alveolar lining fluid contains lipopolysaccharide-binding protein (LBP) and soluble CD14 (sCD14) that potentiate cell activation related to LPS. However, in normal airspaces, the effects of LPS are also dampened by surfactant lipids and associated proteins, particularly SP-A, and soluble factors [41, 42, 43, 44]. With small bacterial inocula, macrophages and PMNs clear the microbes, and cytokine expression is compartmentalized to the site of infection. As the bacterial inoculum increases, organisms proliferate despite local cellular and cytokine responses [45]. With still larger bacterial challenges, cytokines are expressed in the systemic circulation [46]. In addition, mechanical ventilation may promote the spill-over of microbes and cytokines into the systemic circulation [47, 48].

The systemic response to lung infection

Cytokine-mediated lung host defense

Numerous cytokines play an essential protective role during bacterial pneumonia. The magnitude of these re-

sponses is usually controlled and compartmentalized to prevent excessive tissue injury [49, 50]. However, in severe infection accompanying lung injury, inflammatory cytokines may penetrate the damaged alveolar epithelia and activate the systemic immune responses [51, 52]. TNF-α is required for an effective local pulmonary host response, yet it may trigger shock and organ failure when it escapes into the systemic circulation [53, 54, 55, 56, 57]. In contrast, interleukin-10 (IL-10), interleukin-1 receptor antagonist, TNF soluble receptors, and selected surfactant proteins dampen and compartmentalize lung inflammation in pneumonia [58, 59, 60].

There is emerging evidence that systemic responses to sepsis can result in a state of monocyte/macrophage immunoparalysis or "deactivation" [61, 62, 63]. This has been demonstrated in patients with severe sepsis trauma, burn injury, and after large surgical interventions [64, 65, 66]. The mechanisms for this have not been fully defined, but appear to involve IL-10 and peroxisome proliferator-activated receptor-gamma (PPARγ), a transcriptional signaling pathway [67, 68, 69, 70, 71].

The relationship between upper-airway colonization and ICU-acquired lung infection

The normal microflora of the oropharynx does not contain enteric gram-negative bacteria (EGNB), but they can be detected in the oropharynx in 73% of critically ill individuals [72]. Tracheobronchial colonization by EGNB is present in 45–100% of intubated patients. Following one week of mechanical ventilation, *Pseudomonal* species become the predominant pathogens [73]. The source of colonization may be either endogenous flora [74] or, in as many as half of cases, cross-contamination from other patients in the ICU [75].

Bacterial adherence to epithelium and matrix is essential for EGNB colonization. Sites of colonization can include the sinuses, oropharynx, dental plaque, the endotracheal tube, and trachea [76]. Bacteria bind to mucosal receptors through adhesion molecules. Such binding is both specific and of high affinity, if receptors for the organism are present, the bacteria express the appropriate adhesins, and host defenses allow prolonged contact between bacteria and cells [42, 77].

Another important site for bacterial adherence is the endotracheal tube itself, which provides a sequestered nidus of bacteria within biofilms coating the tube surface [6, 38, 78]. Furthermore, the endotracheal tube and suctioning can traumatize the tracheobronchial surface, facilitating bacterial adherence, and can promote mucus stagnation, which also favors bacterial proliferation.

The sequence of airway colonization is still controversial. The leading hypothesis proposes that the oropharynx becomes overgrown by EGNB, which are aspirated into the lung and colonize the airways. However, the stomach [79] and the tracheobronchial tree [80] may instead be the primary sites of colonization. Primary tracheal colonization, mainly by *Pseudomonas aeruginosa* which exhibits a particular ability to adhere to tracheal epithelial cells, may explain in part the observation that subglottis secretion drainage does not generally prevent late onset VAP or VAP caused by *P. aeruginosa* [80, 81]. Pneumonia often follows airway colonization [82, 83]. This association may indicate causality, or may only indicate that colonization is a marker for defective host defenses.

The relationship between gastro-intestinal colonization and ICU-acquired lung infection

A number of investigations have indicated that the stomach is a reservoir of bacteria that may infect the lung [84, 85, 86, 87]. The "gastropulmonary hypothesis" of VAP proposes that such overgrowth moves retrograde to the oral pharynx and then may be aspirated into the lower respiratory tract [21, 84, 85, 86, 87, 88].

Current state of knowledge and unresolved controversies

- Intrusion of bacteria into the lower respiratory tract is usually the result of the aspiration of organism from the upper respiratory or gastrointestinal tract.
- Pneumonia can result when the inoculum is large, the microbes are virulent, or host defenses are impaired.
- The histopathological examination of lung tissue has been traditionally regarded as the gold standard of diagnosis. However, even with histology, pneumonia is frequently difficult to define.
- Alveolar macrophages play a central role in the initial defense against pathogens and amplify inflammatory responses and recruit neutrophils, monocytes, and lymphocytes into the alveolar spaces.
- Bacteria and their products (such as lipopolysaccharide, LPS) are recognized by a series of innate immune molecules.
- With small bacterial inocula, macrophages and PMNs clear the microbes, and cytokine expression is compartmentalized to the site of infection. "Spill-over" of cytokines into the systemic circulation is observed in severe and invasive infections.
- Systemic responses to sepsis can result in a state of monocyte/macrophage immunoparalysis or "deactivation."

There are still important controversies remaining:

- What are the effects of the host inflammatory response on lung structure?
- Are alveolar defenses enhanced or impaired during bacterial infections?

- How do bacterial defense systems in the lung change in patients with acute lung injury or sepsis?
- Should therapeutic attempts be directed at enhancing or suppressing inflammation in the lung?

Question 3: what are the risk factors and effective preventive measures for ICU-acquired pneumonia?

Instrumentation

Presence of endotracheal tube (ETT)

Although mechanical ventilation appears to be an independent risk factor for ICU-AP [3, 4, 89, 90] it is difficult to separate the risk imposed by the ventilator and its circuitry from that imposed by the ETT. Endotracheal tubes bypass normal upper airway reflexes and prevent effective coughing. Oral secretions pool above the tube cuff and tend to "trickle" down the airway. The independent risk of the ETT might be inferred from studies of non-invasive ventilation (NIV). In prospective observational studies, the incidence of ICU-AP was lower in patients who received NIV compared to invasive ventilation [91, 92]. In a matched case-control study, Girou and colleagues found that NIV reduced nosocomial infections and pneumonia [93]. Similarly in a large survey of 42 ICUs, patients receiving NIV were less likely to develop pneumonia even after adjustment for severity of illness [94]. NIV has been compared to "standard" therapy in several Randomized Controlled Trials (RCTs). There is a consistent trend suggesting NIV reduces ICU-AP [95, 96]. However, these studies are small and not blinded. Moreover, since purulent tracheal secretions contribute to the diagnosis of ICU-AP, the diagnosis may be less common in the NIV patients because secretions are less accessible. In the absence of large trials, the current data is encouraging but not definitive. Since invasive mechanical ventilation is a risk factor for ICU-AP [97, 98], strategies that reduce its duration (i.e., weaning protocols) might reduce its incidence [96].

Reintubation

Reintubation secondary to unplanned or failed extubation is an independent risk factor for ICU-AP [89, 100]. This may occur because such patients frequently have their upper airways colonized with pathogens [101] and aspirate during the reintubation procedure. Avoiding reintubation (for example with NIV) may prevent pneumonia [100].

Route of ETT (i.e., nasal or oral)

Nasal intubation is associated with a higher incidence of sinusitis [102]. However, it is unclear if sinusitis or nasal intubation predisposes to and/or is associated with ventilator-associated pneumonia [20, 103]. Indeed, in fewer than 10% of patients with opacified sinuses can bacterial pathogens be recovered from the site [104].

Oro-/naso-gastric feeding tubes

Enteral feeding via nasogastric tubes may promote reflux and aspiration of stomach contents, especially when patients are lying supine [105]. The risk of aspiration is unaltered by the size of the feeding tube [106], and inconsistently affected by pro-motility agents and different feeding regimes [107, 108]. Post-pyloric placement of feeding tubes decreases neither the risk of aspiration nor of ICU-AP [101, 109]. There is not enough data to conclude that timing of feeding, position of feeding tubes, type of tube or type of feeding formula can be used as preventive measure for ICU-AP.

Body position

Patients receiving mechanical ventilation should be in a semi-recumbent position (30–45°), especially when enterally fed, to decrease the occurrence of aspiration of gastric contents [110, 111]. At least three prospective studies, one a RCT, have identified supine positioning to be associated with pneumonia [112, 113, 114]. Kollef and colleagues [115] demonstrated that transportation out of the intensive care unit is also independently associated with pneumonia development, possibly related to supine positioning during the transport [115].

Pharmacologic agents

Use of sedation/paralysis

Since mechanical ventilation is a risk for ICU-AP [6] and sedation and paralysis can prolong mechanical ventilation [116, 117] it is possible that they may be a risk factor for the development of pneumonia.

Systemic antibiotic use

Antibiotics may eradicate susceptible organisms early in a patient's stay or encourage the emergence of resistant organisms later in the patient's stay. Accordingly, epidemiological studies have found that systemic antibiotics can either reduce or increase the risk of ICU-AP [6]. Antibiotics could prevent ICU-AP by eradicating bacteria colonizing the lower respiratory tract (by aerosol or direct endotracheal instillation of antibiotics), the pharynx, and the gastrointestinal tract (by topical pastes and enter-

al instillations). Currently: (i) there are insufficient data to support tracheal instillation of antibiotics; and (ii) meta-analysis of reports on selective decontamination of the digestive tract (defined by regimes using a combination of topical and intravenous antibiotics and regimes using topical antibiotics alone) demonstrated that both approaches decreased the rate of ICU-AP, but only strategies including intravenous antibiotics showed a beneficial effect on survival when analyzed in systematic reviews [19, 20]. Data on the use of systemic antibiotics alone to prevent ICU-AP are conflicting [118, 119].

Prior administration of broad spectrum antibiotics, length of mechanical ventilation, and pre-existing lung disease are the strongest risks for infection with resistant strains [10, 11]. However, because these factors co-relate it is difficult to disentangle the relative contribution of each. Trouillet and colleagues estimated the odds ratio for length of ventilation >7 days to be 6 and that associated with prior antibiotic use to be 13. Some studies in which antibiotic usage was controlled by clinical scoring systems have shown a reduction in the numbers of resistant bacteria [120, 121].

Gastric pH-raising drugs

It is hypothesized that drugs which raise the stomach pH such as H2-receptor antagonists encourage bacterial overgrowth and predispose to pneumonia. While this was the conclusion of a meta-analysis [122], the largest RCT comparing ranitidine to sucralfate showed ranitidine was superior in preventing GI bleeding and did not increase the risk for ICU-AP [1]. It is unknown if the risk of ICU-AP with H_2-receptor antagonists is modified by feeding or mitigated when other preventative measures are used. Most experts believe that in high risk populations (mechanically ventilated patients or those with bleeding disorders) the benefit of H2 blockers in preventing stress ulcers outweighs any added risk of VAP, and that GI-bleeding prophylaxis is unnecessary in low-risk patients.

Ventilator management

Circuit, humidifier, and suctioning management

The condensate in the ventilator tubing can become contaminated with bacteria and could thereby lead to VAP. However, the frequency of ventilator tubing changes does not alter the risk of VAP [123, 124, 125, 126]. There is no evidence that active (wick or cascade) humidifiers increase the risk of ICU-AP [127]. Heated wire humidification may result in a higher incidence of ICU-AP than Heat Moisture Exchangers (HME) [128]. However, some HMEs can increase deadspace and work of breathing [129].

There is little evidence to suggest that closed suction systems lower the risk of VAP [130] even though open systems are associated with increased environmental contamination [131]. When closed systems are used, infrequent changes do not appear to increase the risk for ICU-AP [132]. There is no data to suggest that frequency of suctioning impacts on ICU-AP.

Other factors

General preventive measures: hand washing and oral antiseptics

Hand washing is an important, often overlooked, measure to prevent nosocomial infections. Strict hand-washing techniques by the ICU personnel, combined with other measures to control infection, including the use of gloves when dealing with specific antibiotic-resistant pathogens, reduce the rate of acquired nosocomial infections [133]. The specific impact on ICU-AP is unknown.

Accumulated bacteria in the dental plaque of intubated patients have been implicated as a source of pathogens in ICU-AP [134]. Oropharyngeal decontamination with chlorhexidine solution has been shown to reduce the occurrence of ICU-AP in patients undergoing cardiac surgery [134]. However, overuse may result in superinfection with chlorhexidine-resistant pathogens [135].

Physiotherapy

In one small prospective controlled systematic allocation trial chest physiotherapy was independently associated with a reduction in VAP [136]. The suggested benefit of physiotherapy in prevention of VAP requires confirmation with a larger randomized controlled trial.

Subglottic secretion drainage

Secretions that accumulate above an inflated ETT cuff may be a source of aspirated material [137]. These secretions may be removed by irrigation and drainage or by continuous suctioning above the cuff of the ETT, using a specially designed ETT. Others have questioned whether drainage of subglottic secretions are likely to have a major impact on VAP, since in most cases, the pathogens have already adhered to the lower airway mucosa before suctioning begins [122, 138].

Current state of knowledge and unresolved controversies

- Coma, prolonged mechanical ventilation through an endotracheal tube, repeated intubations, the supine

posture, and long-term antibiotic use increase the risk of ICU-AP.
- The only *established* preventive measure is avoidance of the supine posture.
- Safe, inexpensive, logical, but unproven interventions include routine handwashing, avoidance of indiscriminate antibiotic use, limiting stress ulcer prophylaxis to high-risk patients, and the use of non-invasive mechanical ventilation whenever feasible.
- More data are needed concerning the potential benefit from postpyloric placement of feeding tubes, kinetic/physiotherapy, subglottic drainage, the use of oral and digestive tract decontamination in specific patient populations, early tracheostomy, the placement of oral as opposed to nasotracheal tubes, and the use of endotracheal tube material that inhibits biofilms.

Question 4: diagnosis of ICU-acquired pneumonia

Sensitivity and specificity of clinical assessment

Clinical signs such as fevers (core temperature >38.3°C), leukocytosis (>10,000/mm^3) or leukopenia (<5,000/mm^3), purulent secretions, and the presence of a new and persistent radiographic infiltrate taken separately have limited value for the diagnosis of VAP [34, 43]. While chest radiographic findings are traditionally considered the cornerstone for diagnosing pneumonia, many patients have abnormal chest radiographs from causes other than pneumonia [139]. Moreover, there is poor interobserver agreement on the presence or absence of specific radiologic findings [140]. While CT scans detect infiltrates not seen on chest radiographs in one-third of the cases [23], the clinical importance of these small infiltrates is unknown.

In an attempt to simulate "clinical judgment," Pugin and colleagues combined information on body temperature, white blood cell count, volume and appearance of tracheal secretions, oxygenation, chest X-ray, and tracheal aspirate culture into a clinical pulmonary infection score (CPIS) (Table 1) [141]. A high CPIS value was predictive of a large number of bacteria in BAL fluid and diagnosed ventilator-associated pneumonia with a sensitivity and specificity of 72–85% and 85–91%, respectively [25, 142]. When this scoring system was incorporated in a clinical management algorithm, overall antibiotic use was substantially reduced [120]. The use of the CPIS is attractive because it is quantitative, and can define the pre-test probability of pneumonia. However, it, too, has several drawbacks. Its use is validated in only a small number of studies and relatively small numbers of patients [25, 141, 143], and its validity in ARDS patients is questionable. In the CPIS, several factors are subjective, so that the same patient might be judged to require or not need antibiotics by different observers. The application of the CPIS does not follow the pattern of clinical logical reasoning. For example, all of the elements of the CPIS are given equal weighting. In practice, most clinicians would probably attribute greater importance to some features such as a new lobar infiltrate, while others, such as leukocytosis, would be considered non-specific. Finally, formal calculation of the CPIS is not widely used and could become complex if weighting factors are used.

Mechanically ventilated patients with clinical signs of pneumonia often have alternative diagnoses. Therefore, the suspicion of pneumonia should not preclude a search for other sources of infection or other causes of fever. Meduri and colleagues were able to establish a definitive diagnosis in 45 of 50 patients with a clinical suspicion for ventilator-associated pneumonia [144]. While 37 patients turned out to have an infection, only 19 had pneu-

Table 1 Clinical pulmonary infection score calculation. (*ARDS* acute respiratory distress syndrome, *CHF* congestive heart failure, PaO_2/FiO_2 ratio of arterial oxygen pressure to fraction of inspired oxygen)

Temperature (°C)
>or equal to 36.5 and < or equal to 38.4 = 0 point >or equal to 38.5 and < or equal to 38.9 = 1 point >or equal to 39 and < or equal to 36 = 2 points
Blood leukocytes, mm^3
>or equal to 4,000 and < or equal to 11,000 = 0 point <4, 000 or >11,000 = 1 point + band forms > equal to 50% = add 1 point
Tracheal secretions
Absence of tracheal secretions = 0 point Presence of nonpurulent tracheal secretions = 1 point Presence of purulent tracheal secretions = 2 points
Oxygenation: PaO_2/FiO_2, mmHg
>240 or ARDS (ARDS defined as PaO_2/FiO_2, or equal to 200, pulmonary arterial wedge pressure <or equal to 18 mmHg and acute bilateral infiltrates) = 0 point <or equal to 240 and no ARDS = 2 points
Pulmonary radiography
No infiltrate = 0 point Diffuse (or patchy) infiltrate = 1 point Localized infiltrate = 2 points
Progression of pulmonary infiltrate
No radiographic progression = 0 point Radiographic progression (after CHF and ARDS excluded) = 2 points
Culture of tracheal aspirate
Pathogenic bacteria cultured in rare or light quantity or no growth = 0 point Pathogenic bacteria cultured in moderate or heavy quantity = 1 point Same pathogenic bacteria seen on Gram stain, add 1 point

monia, some of whom also harbored another site of infection.

Interpretation of microbiologic data

Technical considerations

Ideally, microbiologic data should define the need for antimicrobial treatment, not just define the presence of pneumonia. The diagnostic/predictive value of microbiologic data varies with technique and clinical context. Positive or negative culture results may or may not alter the pretest probability that a pneumonia is present. A diagnosis of pneumonia may be difficult to establish even when lung tissue is examined post-mortem [13, 24, 25, 26]. Therefore, much controversy surrounds the use of different culture techniques. The debate centers on cost and efficacy of invasive sampling of lower airway secretions and of quantitative culture. Studies of patient outcomes in which management is based on microbiologic data obtained with different techniques may hold greater promise in resolving this controversy than do attempts to diagnose pneumonia using imperfect reference standards.

- Non-invasive, semiquantitative techniques (tracheal aspirate). Using post-mortem lung pathology as the gold standard, qualitative cultures of tracheal aspirates yield a high percentage of false positive results [145]. The diagnostic value of quantitative cultures of endotracheal aspirates varies with the bacterial load and prior use of antimicrobial agents [43]. Marquette and coworkers report that sensitivity of quantitative endotracheal aspirates is 55% while specificity is 85%, using histology as the reference [146]. The accuracy of endotracheal aspirates, however, is dependent on the threshold cut-off employed. Reducing the diagnostic threshold from 10^6 to 10^5 cfu/ml resulted in a sensitivity of 63% and specificity of 75% [146].
- Invasive and quantitative culture techniques (BAL and PSB). Quantitative cultures of lower respiratory tract secretions may be obtained with or without fiberoptic bronchoscopy. Several studies have demonstrated that the overall diagnostic accuracy of bronchoscopy-guided protected specimen brush (PSB) and broncho-alveolar lavage (BAL) has a sensitivity and specificity >80% [10, 146, 147]. The various comparisons suggest that PSB may be more specific and BAL more sensitive in diagnosing VAP [148]. Marquette demonstrated that results from repeated same site samples were within one log of each other, and the classification of the presence or absence of pneumonia was altered in only 13% of patients [149].

Non-bronchoscopic techniques such as blinded sampling with a PSB or mini-BAL have been developed [150, 151, 152]. These techniques have similar diagnostic accuracy as bronchoscopic techniques, but carry a slightly lower specificity [145]. The sensitivity of the mini-BAL is 63–100% and 58–86% for the blinded PSB; the specificity for the mini-BAL is 66–96% and 71–100% for the blinded PSB [13, 28, 141, 153]. Non- bronchoscopic techniques, however, can miss pneumonia when it is localized to the left lung [154, 155].

- Laboratory processing of culture material. Samples recovered from invasive procedures should be rapidly cultured on solid media according to standard procedures. Fagon's study suggesting improved survival from such an invasive sampling approach utilized the plate dilution methods to quantify the numbers of organism obtained per ml of sample [98]. Such an approach, although accurate, is time consuming, labor intensive, expensive, and may not be practical for many laboratories where large numbers of samples will be processed for quantitative cultures. Some laboratories have instead implemented a calibrated loop method for performing quantitative cultures, entirely analogous to that used for routine quantitative urine cultures. To date, in only one small study has the less cumbersome calibrated loop method been compared to the plate dilution method in the diagnosis of VAP [99].

Effect of prior antibiotic therapy

The effect of antibiotic therapy on the diagnostic value of bacteriological samples depends on when the antibiotics were started relative to microbiologic sampling. In experimental models, recent antimicrobial therapy (defined as therapy initiated within 24 h) decreased the accuracy of lung culture, PSB, BAL, and endotracheal aspiration in diagnosing histologically-proven pneumonia [24, 29, 31]. Studies have shown that the administration of antibiotics to treat patients with suspected VAP decreased the number of microorganisms recovered by follow-up PSB [61]. Therefore, performing quantitative bacteriological samplings of respiratory tract secretions after the initiation of antibiotic therapy can lead to false negative results. In contrast, ongoing current antibiotic treatment (defined as therapy initiated >72 h prior), appears to have less effect on the accuracy of PSB and BAL in diagnosing VAP. In general BAL seems less affected than other quantitative techniques [57, 89].

Current state of knowledge and unresolved controversies

- Microbiological samples should be collected before initiation of antimicrobial agents.
- Reliance on endotracheal aspirates leads to both over- and under-diagnosis of pneumonia.

- Available evidence favors the use of invasive quantitative culture techniques over tracheal aspirates when establishing an indication for antimicrobial therapy.
- Available data suggest that the accuracy of non-bronchoscopic techniques for obtaining quantitative cultures of lower respiratory tract samples is comparable to that of bronchoscopic techniques. The choice depends on local resources and expertise.
- The cost-effectiveness of invasive vs non-invasive diagnostic strategies has not been established.
- The precision of the calibrated loop method to measure bacterial burden has yet to be compared to that of the plate dilution method.
- The predictive value of non-quantitative BAL cultures in the diagnosis of VAP remains to be established.

Question 5: optimal therapeutic approaches to ICU-acquired pneumonia

On which grounds should empiric therapy for ICU-acquired pneumonia be initiated?

Several observational studies have shown that immediate initiation of appropriate antibiotics is associated with a reduced mortality in patients suspected of pneumonia [16, 34, 156, 157]. At the same time, there is evidence suggesting that excess mortality of inappropriate antibiotics is not reduced by correction of regimens when culture results are available 24–48 h later [34, 157, 158, 159]. Thus, it follows that it is imperative to initiate antibiotics as soon as a threshold for suspicion of pneumonia is exceeded.

The varied criteria which have been used to diagnose pneumonia in ICU patients have been discussed. We conclude that microbiological specimens must be obtained and antibiotics begun promptly if there is sufficient clinical suspicion of ICU-AP. However, the benefits of such an approach requires discontinuation of antibiotics if culture results are negative and the patient has not deteriorated in the ensuing 48–72 h [120]. Clinical suspicion is usually derived from observations and variables included in the CPIS (see Table 1). However most clinicians do not formally calculate the CPIS and depending on personal bias they may assign different weights to different components of the CPIS.

In some studies the presence of phagocytes containing bacteria in cytospin preparations of BAL fluid predicted bacterial growth in subsequent culture [10, 98]. Therefore, the number of patients requiring empiric antibiotics might be reduced by immediate direct examination of cytospun BAL fluid. However, the cost and invasive nature of the procedure, the importance of rigorous adherence to technique and expertise in performing the bronchoscopy and processing the sample, and the need for 24-h laboratory support has limited the general acceptance of this method.

Which factors should be taken into account for the choice of empiric antimicrobial therapy in patients with ICU-acquired pneumonia?

The choice of empiric therapy is guided by four factors: 1) the local antibiogram and patterns of antimicrobial resistance; 2) patient characteristics; 3) data from direct examination of pulmonary secretions; and 4) drug characteristics. The data that drives the choice of antibiotics are complex, dynamic, and local. It is a challenge for intensivists to remain current in this area, and this decision is ideally suited for computer-assisted antimicrobial management. These algorithms can be designed to incorporate clinical data, local microbial epidemiology, the local hospital formulary, and cost considerations. Limited studies have shown that such systems improve the quality of patient care and reduce costs [160]. However, these require considerable technical support, which is not currently available in most ICUs. Recent studies also indicate that targeting the drug dose to an individual patient, taking into consideration the pharmacokinetic and pharmacodynamic parameters as well as the putative pathogens' susceptibilities may be more appropriate than using the recommended standard dose [161, 162].

Recent data suggests that consistent use of a few, broad-spectrum antibiotics in rotation reduces the prevalence of resistant strains [145, 163, 164]. In these protocols, a group of antibiotics are chosen for empiric treatment of all suspected infections, based on the unit-specific antibiogram. Each is used exclusively for a several-month period, and then avoided for the remainder of the year. In some studies, even if a highly sensitive organism is recovered from culture, the course of therapy is completed with the broad-spectrum agent. This approach is antithetical to traditional infectious disease practice. It is based on the observation that the prevalence of resistant isolates in the face of new selection pressure increases linearly with time, while the loss of prevalence after the pressure is removed occurs by exponential decay. The rotation takes advantage of the rapid early exponential loss to reduce overall prevalence. If the effectiveness of this approach to empiric therapy is confirmed, it will greatly revise these recommendations for the definitive treatment of ICU-acquired pneumonia. The antibiotics for rotation can be chosen based only upon the local ICU epidemiology. Modification of empiric therapy would occur only if cultures revealed pathogens resistant to the currently assigned choice. The simplicity of this approach is appealing, but awaits further confirmation.

When can empiric therapy for ICU-acquired pneumonia be withheld or withdrawn?

When neither the criteria for pneumonia discussed under the heading 'On which grounds should empiric therapy for ICU-acquired pneumonia be initiated?' nor generalized signs of sepsis are present, antibiotics can be withheld. One study also safely withheld antibiotics in patients without sepsis with clinical signs of pneumonia if direct examination of BAL lacked neutrophils with intracellular bacteria [98]. This approach has not been widely confirmed and requires expertise unavailable in many hospitals.

Once treatment has been started, prompt discontinuation of antibiotics if pneumonia is not confirmed has several advantages. Emergence of resistant organisms may be less likely. Pharmacy costs are reduced. Antibiotic side-effects or drug interactions are minimized. Other sites of infection requiring definitive therapy may be more likely to be discovered because their signs are not suppressed and clinicians are not lulled into complacency [98, 144].

Several studies have shown that it may be safe to withdraw the empiric therapy when quantitative cultures of the lower respiratory tract secretions are sterile or show a bacterial concentration which is lower than the threshold used to define infection [21, 98, 165]. However, these thresholds must not be used in patients who had recent changes or new antibiotics before the diagnostic specimen was obtained [28, 57]. It must be emphasized that these studies were not designed to specifically address the issue of withdrawing therapy, and the decision to stop antibiotics was made by the physician based on *both* the culture results and clinical status of the patient [21, 98, 165]. Only one study used pre-defined criteria for withdrawing therapy by calculating CPIS 3 days after the initiation of therapy in patients with pulmonary infiltrates and CPIS 3–6 and showed that it is safe to withdraw antibiotics after 3 days of therapy in patients in whom CPIS remains less than 6 [120]. Collectively, these studies indicate that the decision to withdraw empiric therapy should be based both on culture results and patient's serial clinical evaluation. Those with a low initial likelihood of pneumonia (e.g., low CPIS) whose likelihood does not increase with a few days of treatment or is not supported by quantitative cultures can have therapy stopped. The level of clinical suspicion defines the context in which microbiologic data should be interpreted. Only a test with a high likelihood ratio (for example a positive blood culture) should make the clinician continue antibiotics in the face of a low clinical suspicion. On the other hand, a test with a lower likelihood ratio such as a positive tracheal aspirate culture might be dismissed as contaminant. These guidelines leave out large numbers of patients in whom this question has not been addressed: for example, those with more convincing early signs of pneumonia which rapidly clear, or who have negative cultures despite persistent clinical signs of pneumonia.

How should definitive therapy for ICU-acquired pneumonia be conducted? For how long?

The traditional approach to infectious disease has been to narrow the antibiotic spectrum to the most specific, safest, and least costly drug based on definitive culture results. This dogma is complicated in the setting of ICU-acquired pneumonia because of concerns about sensitivity and specificity of virtually all culture techniques.

The most unambiguous situation is one in which bacteria are cultured from blood, open lung biopsy, or pleural fluid. In those rare cases, treatment can be confidently based on the culture findings. With somewhat less confidence, treatment can be focused or altered based on the results of bronchoscopic (PSB or BAL) cultures. In patients whose bronchoscopy was performed prior to any antibiotic changes, narrowing the antibiotic spectrum based on the quantitative cultures is logical. The side effects and the drug interaction of the regimen should be also taken into consideration. However, in patients who had antibiotic changes before bronchoscopy, patients who are clinically deteriorating despite "subthreshold" or negative cultures, or patients who are found to be on effective empiric therapy but are worsening nonetheless, the results of bronchoscopic cultures should be viewed skeptically. These situations should prompt investigation for alternative sites of infection or broadened empiric coverage.

For many or most patients, empiric therapy will have been begun after obtaining only expectorated or suctioned sputum for culture, with only fair sensitivity and poor specificity [146, 166, 167]. If pathologic organisms are recovered, it is logical to use antibiotics to which they are sensitive. However, there are many occasions in which the patient's clinical course and the microbiologic data are discordant. If patients are improving on antibiotics that do not cover some of the cultured pathogens, it is also rational to retain the current regimen and monitor the clinical progress. If patients are not improving on antibiotics that appear adequate for the organisms recovered in suctioned specimens, more invasive (bronchoscopic) methods may be necessary, and alternative sites of infection should be sought. However, it can take as long as 6 days for fever and other clinical signs of pneumonia to begin improving, even with appropriate antibiotic treatment [168]. For patients who are not deteriorating, premature changes in therapy are unwarranted.

There are no studies that specifically address the duration of therapy of ICU-acquired pneumonia. The length of typical courses is based arbitrarily on the decimal system or length of the week. Until these data be-

come available, the duration of therapy should be individualized based on the clinical response and the causative pathogen. As a general statement, patients infected with sensitive organisms may be treated for 7–10 days [169, 170]. Patients infected with multiresistant pathogens may require 14–21 days of treatment, because infections with these microorganisms have been associated with high rates of relapse and treatment failure. It has also been suggested, based on little data, that multilobar, necrotizing, or cavitary pneumonia have extended (2–3 weeks) treatment [169]. There is also no data to indicate if therapy can be discontinued a certain time after defervescence has occurred.

Current state of knowledge and unresolved controversies

The decision to start antibiotics:

- Should include an assessment of the clinical probability that the patient has a pulmonary infection.
- Should be preceded by sampling of blood and respiratory secretions for culture.

The decision to discontinue antibiotics 48–72 h later.

- Should be based on a low pretest probability that the patient is infected and a clinical course that is consistent with the low pretest probability of ICU-AP.
- May be based on negative culture results in the absence of signs of sepsis.

Other unresolved controversies:

- Should hospitals invest in computer-based decision support to improve antibiotic utilization?
- Do rotating antibiotics decrease pneumonias with resistant organisms or improve outcomes?
- What is the best diagnostic and therapeutic approach to patients who fail to improve despite negative culture results or appropriate antibiotics?
- What is the optimal duration of therapy to reduce costs and emergence of resistant organisms while still curing the pneumonia?

References

1. Cook D, Guyatt G, Marshall J, Leasa D, Fuller H, Hall R, Peters S, Rutledge F, Griffith L, McLellan A, Wood G, Kirby A (1998) A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. N Engl J Med 338:791–797
2. Richards MJ, Edwards JR, Culver DH, Gaynes RP (1999) Nosocomial infections in medical intensive care units in the United States. National Nosocomial Infections Surveillance System. Crit Care Med 27:887–892
3. Fagon JY, Chastre J, Domart Y, Trouillet JL, Pierre J, Darne C, Gibert C (1989) Nosocomial pneumonia in patients receiving continuous mechanical ventilation. Am Rev Respir Dis 139:877–884
4. Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH, Wolff M, Spencer RC, Hemmer M (1995) The prevalence of nosocomial infection in intensive care units in Europe: results of the European Prevalence of nosocomial infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. JAMA 274:639–644
5. Cook DJ, Reeve BK, Guyatt GH, Heyland DK, Griffith LE, Buckingham L, Tryba M (1996) Stress ulcer prophylaxis in critically ill patients: resolving discordant meta-analyses. JAMA 275:308–314
6. Cook DJ, Walter SD, Cook RJ, Griffith LE, Guyatt GH, Leasa D, Jaeschke RZ, Brun-Buisson C (1998) Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. Ann Intern Med 129:433–440
7. Andrews CP, Coalson JJ, Smith JD, Johanson WG Jr (1981) Diagnosis of nosocomial bacterial pneumonia in acute, diffuse lung injury. Chest 80:254–258
8. Chastre J, Trouillet JL, Vuagnat A, Joly-Guillou ML, Clavier H, Dombret MC, Gibert C (1998) Nosocomial pneumonia in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 157:1165–1172
9. Markowicz P, Wolff M, Djedaini K, Cohen Y, Chastre J, Delclaux C, Merrer J, Herman B, Veber B, Fontaine A, Dreyfuss D and the ARDS study group (2000) Multicenter prospective study of ventilator-associated pneumonia during acute respiratory distress syndrome. Am J Respir Crit Care Med 161:1942–1948
10. Chastre J, Fagon JY, Bornet-Lecso M, Calvat S, Dombret MC, al Khani R, Basset F, Gibert C (1995) Evaluation of bronchoscopic techniques for the diagnosis of nosocomial pneumonia. Am J Respir Crit Care Med 152:231–240
11. Chastre J, Trouillet JL, Vuagnat A, Joly-Guillou ML, Clavier H, Dombret MC, Gibert C (1998) Nosocomial pneumonia in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 157:1165–1172
12. Dore P, Robert R, Grollier G, Rouffineau J, Lanquetot H, Charrière JM, Fauchère JL (1996) Incidence of anaerobes in ventilator-associated pneumonia with use of a protected specimen brush. Am J Respir Crit Care Med 153:1292–1298
13. Chastre, J, Viau F, Brun P, Pierre J, Dauge MC, Bouchama A, Akesbi A, Gibert C (1984) Prospective evaluation of the protected specimen brush for the diagnosis of pulmonary infections in ventilated patients. Am Rev Respir Dis 130:924–929
14. Rello J, Torres A, Ricart M, Valles J, Gonzales J, Artigas A, Rodriguez-Roisin R (1994) Ventilator-associated pneumonia by Staphylococcus aureus: comparison of methicillin-sensitive and methicillin-resistant episodes. Am J Respir Crit Care Med 150:1545–1549

15. Cook D, De Jonghe B, Brochard L, Brun-Buisson C (1998) Influence of airway management on ventilator-associated pneumonia: evidence from randomized trials. JAMA 279:781–787
16. Heyland DK, Cook DJ, Griffith L, Keenan SP, Brun-Buisson C (1999) The attributable morbidity and mortality of ventilator-associated pneumonia in the critically ill patient. The Canadian Critical Trials Group. Am J Respir Crit Care Med 159:1249–1256
17. Craig CP, Connelly S (1984) Effect of intensive care unit nosocomial pneumonia on duration of stay and mortality. Am J Infect Control 12:233–238
18. Hulley SB, Cummings SR (eds) (1998) Designing clinical research: an epidemiologic approach. Williams & Wilkins, Baltimore
19. D'Amico R, Pifferi S, Leonetti C, Torri V, Tinazzi A, Liberati A (1998) Effectiveness of antibiotic prophylaxis in critically ill adult patients: systematic review of randomised controlled trials. BMJ 316:1275–1285
20. Nathens AB, Marshall JC (1999) Selective decontamination of the digestive tract in surgical patients: a systematic review of the evidence. Arch Surg 134:170–176
21. Bonten MJ, Bergmans DC, Stobberingh EE, van der Geest S, De Leeuw PW, van Tiel FH, Gaillard CA (1997) Implementation of bronchoscopic techniques in the diagnosis of ventilator-associated pneumonia to reduce antibiotic use. Am J Respir Crit Care Med 156:1820–1824
22. Froon AH, Bonten MJ, Gaillard CA, Greve JW, Dentener MA, de Leeuw PW, Drent M, Stobberingh EE, Buurman WA (1998) Prediction of clinical severity and outcome of ventilator-associated pneumonia: comparison of simplified acute physiology score with systemic inflammatory mediators. Am J Respir Crit Care Med 158:1026–1031
23. Winer-Muram HT, Rubin SA, Ellis JV, Jenning SG, Arheart KL, Wunderink RG, Leeper KV, Meduri GU (1993) Pneumonia and ARDS in patients receiving mechanical ventilation: diagnostic accuracy of chest radiography. Radiology 188:479–485
24. Marquette CH, Wallet F, Copin MC, Wermert D, Desmidt A, Ramon P, Courcol R, Tonnel AB (1996) Relationship between microbiologic and histologic features in bacterial pneumonia. Am J Respir Crit Care Med 154:1784–1787
25. Papazian L, Thomas P, Garbe L, Guignon I, Thirion X, Charrel J, Bollet C, Fuentes P, Gouin F (1995) Bronchoscopic or blind sampling techniques for the diagnosis of ventilator-associated pneumonia. Am J Respir Crit Care Med 152:1982–1991
26. Rouby JJ, Rossignon MD, Nicolas MH, Martin de Lassale E, Cristin S, Grosset J, Viars P (1989) A prospective study of protected bronchoalveolar lavage in the diagnosis of nosocomial pneumonia. Anesthesiology 71:679–685
27. Kirtland SH, Corley DE, Winterbauer RH, Springmeyer SC, Casey KR, Hampson NB, Dreis DF (1997) The diagnosis of ventilator-associated pneumonia. Chest 112:445–457
28. Rouby, JJ, Martin De Lassale E, Poete P, Nicolas MH, Bodin L, Jarlier V, Le Charpentier Y, Grosset J, Viars P (1992) Nosocomial bronchopneumonia in the critically ill: histologic and bacteriologic aspects. Am Rev Respir Dis 146:1059–1066
29. Johanson WG Jr, Seidenfeld JJ, Gomez P, de los SR, Coalson JJ (1988) Bacteriologic diagnosis of nosocomial pneumonia following prolonged mechanical ventilation. Am Rev Respir Dis 137:259–264
30. Marquette CH, Wermert D, Wallet F, Copin MC, Tonnel AB (1999) Characterization of an animal model of ventilator-acquired pneumonia. Chest 115:200–209
31. Wermert D, Marquette CH, Copin MC, Wallet F, Fraticelli A, Ramon P, Tonnel AB (1998) Influence of pulmonary bacteriology and histology on the yield of diagnostic procedures in ventilator-acquired pneumonia. Am J Respir Crit Care Med 158:139–147
32. Martin TR, Raugi G, Merritt TL, Henderson WR Jr (1987) Relative contribution of leukotriene B4 to the neutrophil chemotactic activity produced by the resident human alveolar macrophage. J Clin Invest 80:1114–1124
33. Rankin JA, Sylvester I, Smith S, Yoshimura T, Leonard EJ (1990) Macrophages cultured in vitro release leukotriene B4 and neutrophil attractant/activation protein (interleukin 8) sequentially in response to stimulation with lipopolysaccharide and zymosan. J Clin Invest 86:1556–1564
34. Luna CM, Vujacich P, Niederman MS, Vay C, Gherardi C, Matera J, Jolly EC (1997) Impact of BAL data on the therapy and outcome of ventilator-associated pneumonia. Chest 111:676–685
35. Madtes DK, Raines EW, Sakariassen KS, Assoian RK, Sporn MB, Bell GI, Ross R (1988) Induction of transforming growth factor-alpha in activated human alveolar macrophages. Cell 53:385–293
36. Shapiro SD, Kobayashi DK, Welgus HG (1992) Identification of TIMP-2 in human alveolar macrophages. Regulation of biosynthesis is opposite to that of metalloproteinases and TIMP-1. J Biol Chem 267:13890–13894
37. Bowie A, O'Neill LA (2000) The interleukin-1 receptor/Toll-like receptor superfamily: signal generators for pro-inflammatory interleukins and microbial products. J Leukoc Biol 67:508–514
38. Ehlers MR (2000) CR3: a general purpose adhesion-recognition receptor essential for innate immunity. Microbes Infect 2:289–294
39. Gough PJ, Gordon S (2000) The role of scavenger receptors in the innate immune system. Microbes Infect 2:305–311
40. Martin TR, Mathison JC, Tobias PS, Leturcq DJ, Moriarty AM, Maunder RJ, Ulevitch RJ (1992) Lipopolysaccharide binding protein enhances the responsiveness of alveolar macrophages to bacterial lipopolysaccharide: implications for cytokine production in normal and injured lungs. J Clin Invest 90:2209–2219
41. Sano H, Sohma H, Muta T, Nomura S, Voelker DR, Kuroki Y (1999) Pulmonary surfactant protein A modulates the cellular response to smooth and rough lipopolysaccharides by interaction with CD14. J Immunol 163:387–395
42. Sano H, Chiba H, Iwaki D, Sohma H, Voelker DR, Kuroki Y (2000) Surfactant proteins A and D bind CD14 by different mechanisms. J Biol Chem 275:22442–22451
43. Torres A, el-Ebiary M, Padro L, Gonzalez J, de la Bellacasa JP, Ramirez J, Xaubet A, Ferrer M, Rodriquez-Roisin R (1994) Validation of different techniques for the diagnosis of ventilator-associated pneumonia: comparison with immediate postmortem pulmonary biopsy. Am J Respir Crit Care Med 149:324–331
44. Martin TR, Mathison JC, Tobias PS, Leturcq DJ, Moriarty AM, Maunder RJ, Ulevitch RJ (1992) Lipopolysaccharide binding protein enhances the responsiveness of alveolar macrophages to bacterial lipopolysaccharide: implications for cytokine production in normal and injured lungs. J Clin Invest 90:2209–2219
45. Fox-Dewhurst R, Alberts MK, Kajikawa O, Caldwell E, Johnson MC, Skerrett SJ, Goodman RB, Ruzinski JT, Wong VA, Chi EY, Martin TR (1997) Pulmonary and systemic inflammatory responses in rabbits with gram-negative pneumonia. Am J Respir Crit Care Med 155:2030–2040

46. Kurahashi K, Kajikawa O, Sawa T, Ohara M, Gropper MA, Frank DW, Martin TR, Wiener-Kronish JP (1999) Pathogenesis of septic shock in Pseudomonas aeruginosa pneumonia. J Clin Invest 104:743–750
47. Nahum A, Hoyt J, Schmitz L, Moody J, Shapiro R, Marini JJ (1997) Effect of mechanical ventilation strategy on dissemination of intratracheally instilled Escherichia coli in dogs. Crit Care Med 25:1733–1743
48. Murphy DB, Cregg N, Tremblay L, Engelberts D, Laffey JG, Slutsky AS, Romaschin A, Kavanagh BP (2000) Adverse ventilatory strategy causes pulmonary-to-systemic translocation of endotoxin. Am J Respir Crit Care Med 162:27–33
49. Boutten A, Dehoux MS, Seta N, Ostinelli J, Venembre P, Crestani B, Dombret MC, Durand G, Aubier M (1996) Compartmentalized IL-8 and elastase release within the human lung in unilateral pneumonia. Am J Respir Crit Care Med 153:336–342
50. Dehoux MS, Boutten A, Ostinelli J, Seta N, Dombret MC, Crestani B, Deschenes M, Trouillet JL, Aubier M (1994) Compartmentalized cytokine production within the human lung in unilateral pneumonia. Am J Respir Crit Care Med 150:710–716
51. Kragsbjerg P, Jones I, Vikerfors T, Holmberg H (1995) Diagnostic value of blood cytokine concentrations in acute pneumonia. Thorax 50:1253–1257
52. Lieberman D, Livnat S, Schlaeffer F, Porath A, Horowitz S, Levy R (1997) IL-1beta and IL-6 in community-acquired pneumonia: bacteremic pneumococcal pneumonia versus Mycoplasma pneumoniae pneumonia. Infection 25:90–94
53. Gosselin D, DeSanctis J, Boule M, Skamene E, Matouk C, Radzioch D (1995) Role of tumor necrosis factor alpha in innate resistance to mouse pulmonary infection with Pseudomonas aeruginosa. Infect Immun 63:3272–3278
54. Kolls JK, Lei D, Nelson S, Summer WR, Greenberg S, Beutler B (1995) Adenovirus-mediated blockade of tumor necrosis factor in mice protects against endotoxic shock yet impairs pulmonary host defense. J Infect Dis 171:570–575
55. Laichalk LL, Kunkel SL, Strieter RM, Danforth JM, Bailie MB, Standiford TJ (1996) Tumor necrosis factor mediates lung antibacterial host defense in murine Klebsiella pneumonia. Infect Immun 64:5211–5218
56. Takashima K, Tateda K, Matsumoto T, Iizawa Y, Nakao M, Yamaguchi K (1997) Role of tumor necrosis factor alpha in pathogenesis of pneumococcal pneumonia in mice. Infect Immun 65:257–260
57. Torres A, Fabregas N, Ewig S, de la Bellacasa JP, Bauer TT, Ramirez J (2000) Sampling methods for ventilator-associated pneumonia: validation using different histologic and microbiological references. Crit Care Med 28:2799–2804
58. Standiford TJ (2000) Anti-inflammatory cytokines and cytokine antagonists. Curr Pharm Des 6:633–649
59. Howard M, O'Garra A, Ishida H, de Waal MR, de Vries J (1992) Biological properties of interleukin 10. J Clin Immunol 12:239–247
60. LeVine AM, Whitsett JA, Gwozdz JA, Richardson TR, Fisher JH, Burhans MS, Korfhagen TR (2000) Distinct effects of surfactant protein A or D deficiency during bacterial infection on the lung. J Immunol 165:3934–3940
61. Montravers PH, Fagon JY, Chastre J, Lesco M, Dombret MC, Trouillet JL, Gibert C (1993) Follow-up protected specimen brushes to assess treatment in nosocomial pneumonia. Am Rev Respir Dis 147:38–44
62. Munoz C, Carlet J, Fitting C, Misset B, Bleriot JP, Cavaillon JM (1991) Dysregulation of in vitro cytokine production by monocytes during sepsis. J Clin Invest 88:1747–1754
63. Volk HD, Reinke P, Krausch D, Zuckermann H, Asadullah K, Muller JM, Docke WD, Kox WJ (1996) Monocyte deactivation: rationale for a new therapeutic strategy in sepsis. Int Care Med 22:S474–S481
64. Christou NV (1985) Host-defence mechanisms in surgical patients: a correlative study of the delayed hypersensitivity skin-test response, granulocyte function and sepsis. Can J Surg 28:39–46, 49
65. Wakefield CH, Carey PD, Foulds S, Monson JR, Guillou PJ (1993) Changes in major histocompatibility complex class II expression in monocytes and T cells of patients developing infection after surgery. Br J Surg 80:205–209
66. Mustard RA, Bohnen JM, Rosati C, Schouten BD (1991) Pneumonia complicating abdominal sepsis: an independent risk factor for mortality. Arch Surg 126:170–175
67. Chinetti G, Griglio S, Antonucci M, Torra IP, Delerive P, Majd Z, Fruchart JC, Chapman J, Najib J, Staels B (1998) Activation of proliferator-activated receptors alpha and gamma induces apoptosis of human monocyte-derived macrophages. J Biol Chem 273:25573–25580
68. Clark RB, Bishop-Bailey D, Estrada-Hernandez T, Hla T, Puddington L, Padula SJ (2000) The nuclear receptor PPAR gamma and immunoregulation: PPAR gamma mediates inhibition of helper T cell responses. J Immunol 164:1364–1371
69. Faveeuw C, Fougeray S, Angeli V, Fontaine J, Chinetti G, Gosset P, Delerive P, Maliszewski C, Capron M, Staels B, Moser M, Trottein F (2000) Peroxisome proliferator-activated receptor gamma activators inhibit interleukin-12 production in murine dendritic cells. FEBS Lett 486:261–266
70. Jiang C, Ting AT, Seed B (1998) PPAR-gamma agonists inhibit production of monocyte inflammatory cytokines. Nature 391:82–86
71. Ricote M, Li AC, Willson TM, Kelly CJ, Glass CK (1998) The peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation. Nature 391:79–82
72. Johanson WG, Pierce AK, Sanford JP (1969) Changing pharyngeal bacterial flora of hospitalized patients: emergence of gram-negative bacilli. N Engl J Med 281:1137–1140
73. Niederman MS (1994) The pathogenesis of airway colonization: lessons learned from the study of bacterial adherence. Eur Respir J 7:1737–1740
74. Bonten MJM, Bergmans DCJJ, Speijer H, Stobberingh EE (1999) Characteristics of polyclonal endemicity of Pseudomonas aeruginosa colonization in intensive care units. Implications for infection control. Am J Respir Crit Care Med 160:1212–1219
75. Bertrand X, Thouverez M, Talon D, Boillot A, Capellier G, Floriot C, Helias JP (2001) Endemicity, molecular diversity and colonisation routes of Pseudomonas aeruginosa in intensive care units. Intensive Care Med 27:1263–1268
76. Fourrier F, Duvivier B, Boutigny H, Roussel-Delvallez M, Chopin C (1998) Colonization of dental plaque: a source of nosocomial infections in intensive care unit patients. Crit Care Med 26:301–308
77. Grant MM, Niederman MS, Poehlman MA, Fein AM (1991) Characterization of Pseudomonas aeruginosa adherence to cultured hamster tracheal epithelial cells. Am J Respir Cell Mol Biol 5:563–570
78. Plotkowski MC, Costa AO, Morandi V, Barbosa HS, Nader HB, de Bentzmann S, Puchelle E (2001) Role of heparin sulphate proteoglycans as potential receptors for non-piliated Pseudomonas aeruginosa adherence to non-polarised airway epithelial cells. J Med Micro 50:183–190

79. Niederman MS, Craven DE (1997) Devising strategies for preventing nosocomial pneumonia: should we ignore the stomach? Clin Infect Dis 24:320–323
80. Niederman MS, Mantovani R, Schoch P, Papas J, Fein AM (1989) Patterns and routes of tracheobronchial colonization in mechanically ventilated patients: the role of nutritional status in colonization of the lower airway by Pseudomonas species. Chest 95:155–161
81. Valles J, Artigas A, Rello J, Bonsoms N, Fontanals D, Blanch L, Fernandez R, Baigorri F, Mestre J (1995) Continuous aspiration of subglottic secretions in preventing ventilator-associated pneumonia. Ann Intern Med 122:179–186
82. Johanson WG Jr, Pierce AK, Sanford JP, Thomas GD (1972) Nosocomial respiratory infections with gram-negative bacilli: the significance of colonization of the respiratory tract. Ann Intern Med 77:701–706
83. Rello J, Mariscal D, March F, Jubert P, Sanchez F, Valles J, Coll P (1998) Recurrent Pseudomonas aeruginosa pneumonia in ventilated patients: relapse or reinfection? Am J Respir Crit Care Med 157:912–916
84. Prod'hom G, Leuenberger P, Koerfer J, Blum A, Chiolero R, Schaller MD, Perret C, Spinnler O, Blondel J, Siegrist H (1994) Nosocomial pneumonia in mechanically ventilated patients receiving antacid, ranitidine, or sucralfate as prophylaxis for stress ulcer: a randomized controlled trial. Ann Intern Med 120:653–662
85. Driks MR, Craven DE, Celli BR, Manning M, Burke RA, Garvin GM, Kunches LM, Farber HW, Wedel SA, McCabe WR (1987) Nosocomial pneumonia in intubated patients given sucralfate as compared with antacids or histamine type 2 blockers: the role of gastric colonization. N Engl J Med 317:1376–1382
86. du Moulin GC, Paterson DG, Hedley-Whyte J, Lisbon A (1982) Aspiration of gastric bacteria in antacid-treated patients: a frequent cause of postoperative colonisation of the airway. Lancet 1:242–245
87. Tryba M (1991) The gastropulmonary route of infection: fact or fiction? Am J Med 91:135S-146S
88. Bonten MJ, Gaillard CA, de Leeuw PW, Stobberingh EE (1997) Role of colonization of the upper intestinal tract in the pathogenesis of ventilator-associated pneumonia. Clin Infect Dis 24:309–319
89. Timsit JF, Misset B, Renaud B, Goldstein FW, Carlet J (1995) Effect of previous antimicrobial therapy on the accuracy of the main procedures used to diagnose nosocomial pneumonia in patients who are using ventilation. Chest 108:1036–1040
90. Chevret S, Hemmer M, Carlet J, Langer M (1993) Incidence and risk factors of pneumonia acquired in intensive care units: results from a multicenter prospective study on 996 patients. European Cooperative Group on Nosocomial Pneumonia. Intensive Care Med 19:256–264
91. Guerin C, Girard R, Chemorin C, De Varax R, Fournier G (1997) Facial mask noninvasive mechanical ventilation reduces the incidence of nosocomial pneumonia: a prospective epidemiological survey from a single ICU. Intensive Care Med 23:1024–1032
92. Nourdine K, Combes P, Carton MJ, Beuret P, Cannamela A, Ducreux JC (1999) Does noninvasive ventilation reduce the ICU nosocomial infection risk? A prospective clinical survey. Intensive Care Med 25:567–573
93. Girou E, Schortgen F, Delclaux C, Brun-Buisson C, Blot F, Lefort Y, Lemaire F, Brochard L (2000) Association of noninvasive ventilation with nosocomial infections and survival in critically ill patients. JAMA 284:2361–2367
94. Carlucci A, Richard JC, Wysocki M, Lepage E, Brochard L (2001) Noninvasive versus conventional mechanical ventilartion: an epidemiologic survey. Am J Respir Crit Care Med 163:874–880
95. Keenan SP (2000) Noninvasive positive pressure ventilation in acute respiratory failure. JAMA 284:2376–2378
96. Nava S, Ambrosino N, Clini E, Prato M, Orlando G, Vitacca M, Brigada P, Fracchia C, Rubini F (1998) Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease: a randomized, controlled trial. Ann Intern Med 128:721–728
97. Hess D, Burns E, Romagnoli D, Kacmarek RM (1995) Weekly ventilator circuit changes: a strategy to reduce costs without affecting pneumonia rates. Anesthesiology 82:903–911
98. Fagon JY, Chastre J, Wolff M, Gervais C, Parer-Aubas S, Stephan F, Similowski T, Mercat A, Diehl JL, Sollet JP, Tenaillon A (2000) Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia: a randomized trial. Ann Intern Med 132:621–630
99. Middleton RM 3rd, Huff W, Brickey DA, Kirkpatrick MB (1996) Comparison of quantitative cultures to semi-quantitative loop cultures of bronchoscopic protected specimen brush samples. Chest 109:1204–1209
100. Torres A, Gatell JM, Aznar E, El-Ebiary M, Puig De La Bellacasa J, Gonzalez J, Ferrer M, Rodriguez-Roisin R (1995) Re-intubation increases the risk of nosocomial pneumonia in patients needing mechanical ventilation. Am J Respir Crit Care Med 152:137–141
101. Heyland DK, Drover JW, MacDonald S, Novack F, Lam M (2001) Effect of postpyloric feeding on gastroesophageal regurgitation and pulmonary microaspiration: results of a randomized controlled trial. Crit Care Med 29:1495–1501
102. Rouby JJ, Laurent P, Gosnach M, Cambau E, Lamas G, Zouaoui A, Leguillou JL, Bodin L, Khac TD, Marsault C, Poete P, Nicolas MH, Jarlier V, Viars P (1994) Risk factors and clinical relevance of nosocomial maxillary sinusitis in the critically ill. Am J Respir Crit Care Med 150:776–783
103. Holzapfel L, Chastang C, Demingeon G, Bohe J, Piralla B, Coupry A (1999) A randomized study assessing the systematic search for maxillary sinusitis in nasotracheally mechanically ventilated patients. Am J Respir Crit Care Med 159:695–701
104. George DL, Falk PS, Umberto Meduri G, Leeper KV Jr, Wunderink RG, Steere EL, Nunnally FK, Beckford N, Mayhall CG (1998) Nosocomial sinusitis in patients in the medical intensive care unit: a prospective epidemiological study. Clin Infect Dis 27:463–70
105. Joshi N, Localio R, Hamory BH (1992) A predictive risk index for nosocomial pneumonia in the intensive care unit. Am J Med 93:135–142
106. Ferrer M, Bauer TT, Torres A, Hernandez C, Piera C (1999) Effect of nasogastric tube size on gastroesophageal reflux and microaspiration in intubated patients. Ann Intern Med 130:991–994
107. Heyland DK, Cook DJ, Schoenfeld PS, Frietag A, Varon J, Wood G (1999) The effect of acidified enteral feeds on gastric colonization in the critically ill patient: results of a multicenter randomized trial. Canadian Critical Care Trials Group. Crit Care Med 27:2399–2406
108. Spilker CA, Hinthorn DR, Pingleton SK (1996) Intermittent enteral feeding in mechanically ventilated patients: the effect on gastric pH and gastric cultures. Chest 110:243–248
109. Kearns PJ, Chin D, Mueller L, Wallace K, Jensen WA, Kirsch CM (2000) The incidence of ventilator-associated pneumonia and success in nutrient delivery with gastric versus small intestinal feeding: a randomized clinical trial. Crit Care Med 28:1742–1746

110. Torres A, Serra-Batlles J, Ros E, Piera C, Puig de la Bellacasa J, Cobos A, Lomena F, Rodriguez-Roison R (1992) Pulmonary aspiration of gastric contents in patients receiving mechanical ventilation: the effect of body position. Ann Intern Med 116:540–543
111. Orozco-Levi M, Torres A, Ferrer M, Piera C, el-Ebiary M, de la Bellacasa JP, Rodriguez-Roisin R (1995) Semirecumbent position protects from pulmonary aspiration but not completely from gastroesophageal reflux in mechanically ventilated patients. Am J Respir Crit Care Med 152:1387–1390
112. Fernandez-Crehuet R, Diaz-Molina C, de Irala J, Martinez-Concha D, Salcedo-Leal I, Masa-Calles J (1997) Nosocomial infection in an intensive-care unit: identification of risk factors. Infect Control Hosp Epidemiol 18:825–830
113. Kollef MH (1993) Ventilator-associated pneumonia, a multivariate analysis. JAMA 270:1965–1970
114. Drakulovic MB, Torres A, Bauer TT, Nicolas JM, Nogue S, Ferrer M (1999) Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. Lancet 354:1851–1858
115. Kollef M, Von Harz B, Prentice D, Shapiro S, Silver P, St. John R, Trovillion E (1997) Patient transport from intensive care increases risk of developing ventilator-associated pneumonia. Chest 112:765–773
116. Brook AD, Ahrens TS, Schaiff R, Prentice D, Sherman G, Shannon W, Kollef MH (1999) Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. Crit Care Med 27:2609–2615
117. Kress JP, Pohlman AS, O'Connor MF, Hall JB (2000) Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Eng J Med 342:1471–1477
118. Mendelli M, Mosconi P, Langer M, Cigada M (1989) Prevention of pneumonia in an intensive care unit: a randomized multicenter clinical trial. Crit Care Med 17:501–505
119. Sirvent JM, Torres A, El-Ebiary M, Castro P, de Battlle J, Bonet A (1997) Protective effect of intravenously administered cefuroxime against nosocomial pneumonia in patients with structural coma. Am J Respir Crit Care Med 155:1729–1734
120. Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL (2000) Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit: a proposed solution for indiscriminate antibiotic prescription. Am J Respir Crit Care Med 162:505–511
121. Ibrahim EH, Ward S, Sherman G, Schaiff R, Fraser VJ, Kollef MH (2001) Experience with a clinical guideline for the treatment of ventilator-associated pneumonia. Crit Care Med 29:1109–1115
122. Van Saene HKF, de la Cal MA, Petros AJ (2000) To suction or not to suction, above the cuff. Crit Care Med 28:596–598
123. Craven DE, Connolly MG, Lichtenberg DA, Primeau PJ, McCabe WR (1982) Contamination of mechanical ventilators with tubing changes every 24 h or 48 h. N Engl J Med 306:1505–1509
124. Dreyfuss D, Djedaini K, Weber P, Brun P, Lanore JJ, Rahmani J, Boussougant Y, Coste F (1991) Prospective study of nosocomial pneumonia and of patient and circuit colonization during mechanical ventilation with circuit changes every 48 h versus no change. Am Rev Respir Dis 143:738–743
125. Kollef MH, Shaprio SD, Fraser VJ, Silver P, Murphy DM, Trovillion E, Hearns ML, Richards RD, Cracchilo L, Hossin L (1995) Mechanical ventilation with or without 7-day circuit changes. Ann Intern Med 123:168–174
126. Long MN, Wickstrom G, Grimes A, Benton CF, Belcher B, Stamm AM (1996) Prospective, randomised study of ventilator-associated pneumonia in patients with one versus three ventilator circuit changes per week. Infect Control Hosp Epidemiol 17:14–19
127. Dreyfuss D, Djedaini K, Gros I, Mier L, Le Bourdelles G, Cohen Y, Estagnasie P, Coste F, Boussougant Y (1995) Mechanical ventilation with heated humidifiers or heat moisture exchangers: effects on patient colonization and incidence of nosocomial pneumonia. Am J Respir Crit Care Med 151:986–992
128. Kirton O, DeHaven B, Morgan J, Morejon O, Civetta J (1997) A prospective randomized comparison of an in-line heat moisture exchange filter and heated wire humidifiers: rates of ventilator-associated early-onset (community-acquired) or late-onset (hospital-acquired) pneumonia and incidence of endotracheal tube occlusion. Chest 112:1055–1059
129. Pelosi P, Solca M, Ravagnan I, Tubiolo D, Ferrario L, Gattinoni L (1996) Effects of heat and moisture exchangers on minute ventilation, ventilatory drive, and work of breathing during pressure-support ventilation in acute respiratory failure. Crit Care Med 24:1184–1188
130. Combes P, Fauvage B, Oleyer C (2000) Nosocomial pneumonia in mechanically ventilated patients, a prospective randomised evaluation of the Stericath closed suctioning system. Intensive Care Med 26:878–882
131. Cobley M, Atkins M, Jones PL (1991) Environmental contamination during tracheal suction: a comparison of disposable conventional catheters with a multiple-use closed system device. Anaesthesia 46:957–961
132. Kollef MH, Prentice D, Shapiro SD, Fraser VJ, Silver P, Trovillion E, Weilitz P, Von Harz B, St John R (1997) Mechanical ventilation with or without daily changes of in-line suction catherters. Am J Respir Crit Care Med 156:466–472
133. Doebbeling BN, Stanley GL, Sheetz CT, Pfaller MA, Houston AK, Annis L, Li N, Wenzel RP (1992) Comparative efficacy of alternative hand-washing agents in reducing nosocomial infections in intensive care units. N Engl J Med 327:88–93
134. DeRiso AJ II, Ladowski JS, Dillon TA, Justice JW, Peterson AC (1996) Chlorhexidine gluconate 0.12% oral rinse reduces the incidence of total nosocomial respiratory infection and nonprophylactic systemic antibiotic use in patients undergoing heart surgery. Chest 109:1556–1561
135. Russell AD (1997) Plasmids and bacterial resistance to biocides. J Appl Microbiol 83:155–165
136. Ntoumenopoulos G, Presneill JJ, McElholum M, Cade JF (2002) Chest physiotherapy for the prevention of ventilator-associated pneumonia. Intensive Care Med 28:850–856
137. Craven DE, Steger KA (1995) Epidemiology of nosocomial pneumonia: new perspectives on an old disease. Chest 108:1S-16S
138. Cook DJ, Hébert PC, Heyland DK, Guyatt GH, Brun-Buisson C, Marshall JC, Russell J, Vincent JL, Sprung CL, Rutledge F (1997) How to use an article on therapy or prevention: pneumonia prevention using subglottic secretion drainage. Crit Care Med 25:1502–1513
139. Wundernik RG, Woldenberg LS, Zeiss J, Day CM, Ciemins J, Lacher DA (1992) The radiologic diagnosis of autopsy-proven ventilator-associated pneumonia. Chest 101:458–463
140. Wunderink RG (2000) Radiologic diagnosis of ventilator-associated pneumonia. Chest 117:188S-190S
141. Pugin J, Auckenthaler R, Mili N, Janssens JP, Lew PD, Suter PM (1991) Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. Am Rev Respir Dis 143:1121–1129

142. Flanagan PG, Findlay GP, Magee JT, Ionescu A, Barnes RA, Smithies M (2000) The diagnosis of ventilator-associated pneumonia using non-bronchoscopic, non-directed lung lavages. Intensive Care Med 26:20–30
143. Fabregas N, Ewig S, Torres A, El-Ebiary M, Ramirez J, de La Bellacasa JP, Bauer T, Cabello H (1999) Clinical diagnosis of ventilator-associated pneumonia revisited: comparative validation using immediate post-mortem lung biopsies Thorax 54:867–873
144. Meduri GU, Mauldin GL, Wunderink RG, Leeper KV, Jones CB, Tolley E, Mayhall G (1994) Causes of fever and pulmonary densities in patients with clinical manifestations of ventilator-associated pneumonia. Chest 106:221–235
145. Grossman RF, Fein A (2000) Evidence-based assessment of diagnostic tests for ventilator-associated pneumonia: executive summary. Chest 117:177S-181S
146. Marquette CH, Copin MC, Wallet F, Neviere R, Saulnier F, Mathieu D, Durocher A, Ramon P, Tonnel AB (1995) Diagnostic tests for pneumonia in ventilated patients: prospective evaluation of diagnostic accuracy using histology as a diagnostic gold standard. Am J Respir Crit Care Med 151:1878–1888
147. Chastre J, Fagon JY, Soler P Bornet M, Domart Y, Trouillet JL, Gibert C, Hance AJ (1988) Diagnosis of nosocomial bacterial pneumonia in intubated patients undergoing ventilation: comparison of the usefulness of bronchoalveolar lavage and the protected specimen brush. Am J Med 85:499–506
148. Baughman RP (2000) Protected-specimen brush technique in the diagnosis of ventilator-associated pneumonia. 117:203S-206S
149. Marquette CH, Herengt F, Mathieu D, Saulnier F, Courcol R, Ramon P (1993) Diagnosis of pneumonia in mechanically ventilated patients: repeatability of the protected specimen brush. Am Rev Respir Dis 147:211–214
150. Bregeon F, Papazian L, Thomas P, Carret V, Garbe L, Saux P, Drancourt M, Auffray JP (2000) Diagnostic accuracy of protected catheter sampling in ventilator-associated bacterial pneumonia. Eur Respir J 16:969–575
151. Pham LH, Brun-Buisson C, Legrand P, Rauss A, Verra F, Brochard L, Lamaire F (1991) Diagnosis of nosocomial pneumonia in mechanically ventilated patients: comparison of a plugged telescoping catheter with the protected specimen brush. Am Rev Respir Dis 143:1055–1061
152. Kollef MH, Bock KR, Richards RD, Hearns ML (1995) The safety and diagnostic accuracy of minibronchoalveolar lavage in patients with suspected ventilator-associated pneumonia. Ann Intern Med 122:743–748
153. Marik PE, Brown WJ (1995) A comparison of bronchoscopic vs blind protected specimen brush sampling in patients with suspected ventilator-associated pneumonia. Chest 108:203–207
154. Jorda R, Parras F, Ibanez J, Reina J, Bergada J, Raurich JM (1993) Diagnosis of nosocomial pneumonia in mechanically ventilated patients by the blind protected telescoping catheter. Intensive Care Med 19:377–382
155. Leal-Noval SR, Alfaro-Rodriguez E, Murillo-Cabeza F, Garnacho-Montero J, Rey-Perez J, Munoz-Sanchez MA (1992) Diagnostic value of the blind brush in mechanically ventilated patients with nosocomial pneumonia. Intensive Care Med 18:410–414
156. Kollef MH (2000) Inadequate antimicrobial treatment: an important determinant of outcome for hospitalized patients. Clin Infect Dis 31:S131-S138
157. Kollef MH, Ward S (1998) The influence of mini-BAL cultures on patient outcomes: implications for the antibiotic management of ventilator-associated pneumonia. Chest 113:412–420
158. Rello J, Gallego M, Mariscal D, Sonora R, Vallés J (1997) The value of routine microbial investigation in ventilator-associated pneumonia. Am J Respir Crit Care Med 156:196–200
159. Kollef MH, Sherman G, Ward S, Fraser VJ (1999) Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 115:462–474
160. Evans RS, Pestotnik SL, Classen DC, Clemmer TP, Weaver LK, Orme JF JR, Lloyd JF, Burke JP (1998) A computer-assisted management program for antibiotics and other antiinfective agents. N Engl J Med 338:232–238
161. Forrest A, Nix DE, Ballow CH, Goss TF, Birmingham MC, Schentag JJ (1993) Pharmacodynamics of intravenous ciprofloxacin in seriously ill patient. Antimicrob Agents Chemother 37:1073–1081
162. Peloquin CA, Cumbo TJ, Nix DE, Sands MF, Schentag JJ (1989) Evaluation of intravenous ciprofloxacin in patients with nosocomial lower respiratory tract infections: impact of plasma concentrations, organism, minimum inhibitory concentration, and clinical condition on bacterial eradication. Arch Intern Med 149:2269–2273
163. Kollef MH, Vlasnik J, Sharpless L, Pasque C, Murphy D, Fraser V (1997) Scheduled change of antibiotic classes: a strategy to decrease the incidence of ventilator-associated pneumonia. Am J Respir Crit Care Med 156:1040–1048
164. Raymond DP, Pelletier SJ, Crabtree TD, Gleason TG, Hamm LL, Pruett TL, Sawyer RG (2001) Impact of a rotating empiric antibiotic schedule on infectious mortality in an intensive care unit. Crit Care Med 29:1101–1108
165. Croce MA, Fabian TC, Waddle-Smith L, Melton SM, Minard G, Kudsk KA, Pritchard FE (1998) Utility of Gram's stain and efficacy of quantitative cultures for posttraumatic pneumonia: a prospective study. Ann Surg 227:743–751
166. Villers D, Derriennic M, Raffi F, Germaud P, Baron D, Nicolas F, Courteau AL (1985) Reliability of the bronchoscopic protected catheter brush in intubated and ventilated patients. Chest 88:527–530
167. Lamber RS, Vereen LE, George RB (1989) Comparison of tracheal aspirates and protected specimen brush for identifying pathogenic bacteria in mechanically ventilated patients. Am J Med Sci 297:377–382
168. Dennesen PJ, van der Ven AJ, Kessels AG, Ramsay G, Bonten MJ (2001) Resolution of infectious parameters after antimicrobial therapy in patients with ventilator-associated pneumonia. Am J Respir Crit Care Med 163:1371–1375
169. ATS Statement (1996) Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy, and preventive strategies. A consensus statement, American Thoracic Society. Am J Respir Crit Care Med 153:1711–1725
170. Mandell LA, Marrie TJ, Grossman RF, Chow AW, Hyland RH (2000) Canadian guidelines for the initial management of community-acquired pneumonia: an evidence-based update by the Canadian Infectious Diseases Society and the Canadian Thoracic Society. The Canadian Community-Acquired Pneumonia Working Group. Clin Infect Dis 31:383–421