Chapter 3
Current Issues in Ventilator-Associated Pneumonia

3.1 Background

Infections in critically ill patients account for a major proportion of the mortality, morbidity, and cost associated with their care. Infection rate in critically ill patients are about 40% and may be 50–60% in those remaining in the intensive care unit (ICU) for more then 5 days.[1,2] Pneumonia acquired in the ICU (after 48 h intubation) ranges from 10% to 65%,[3,4] and respiratory infections account for 30–60% of all infections acquired in the ICU.[5,6] Mortality rates of ventilator-associated pneumonia (VAP) have been very high (30–70%) and may account for 15% of all deaths in the ICU. [7–9] When controlled for severity of underlying disease and other factors the attributable mortality of VAP range from 0% to 50% absolute increase, and prolonged length of ICU stay (range 5–13 days).[10] In a recent review of the clinical and economic consequences of VAP from analysis of studies published after 1990, the findings were: 10–20% of ICU-ventilated patients will develop VAP, and are twice as likely to die compared to patients without VAP, with 6 extra days in the ICU and an additional US$10019 hospital cost per case.[11]

Empiric broad-spectrum antimicrobials in the ICU for presumed pneumonia has contributed substantially to the worldwide increase in antibiotic-resistant bacteria in hospitals. This has compounded the problem of increasing morbidity, mortality, and cost because of the challenge posed by these difficult-to-treat microorganisms, particularly the use of expensive drugs and need for isolation.

This chapter will address emerging issues in VAP such as diagnosis, appropriate management, and prevention.

3.2 Issues in the Diagnosis of VAP

Confirming a diagnosis of VAP is a most challenging and difficult task, but is crucial for appropriate management. The criteria used for diagnosing VAP are controversial with some studies relying on clinical and radiological findings and

I.W. Fong (ed.), *Emerging Issues and Controversies in Infectious Disease*.
DOI: 10.1007/978-0-387-84840-2_3,

others on microbiological specimens. Differing criteria may largely account for the variable rates of VAP reported from different centers – 5–85%. The standard clinical criteria such as new or progressive infiltrates on chest radiographs, together with fever, leukocytosis or leucopenia, and purulent tracheobronchial secretion are of limited diagnostic accuracy. In studies using histologic analysis and culture of lung samples immediately after death for confirmation of the diagnosis, the presence of new or progressing chest infiltrate with two of three clinical criteria had a sensitivity of 69% and a specificity of 75% for the diagnosis of VAP.[12] This is quite understandable considering that there are several common causes of pulmonary infiltrates in critically ill patients (i.e., pulmonary edema, ARDS, atelectasis, and pulmonary hemorrhage) that can mimic pneumonia; and many intubated patients have tracheobronchitis with purulent respiratory secretions, and may develop fever and leucocytosis from a number of sources (such as urinary tract infection, venous, or arterial catheter infections, *Clostridium difficile* colitis, drugs, blood products, etc.).

Alternative clinical criteria such as the "clinical pulmonary infection score (CPIS)" (a composite of clinical, microbiologic, and oxygenation-related criteria) have not been consistently superior, even with addition of analysis of tracheobronchial secretion.[12,13] The use of CPIS or Pugin score of >6 as recommended by Pugin et al.[14] resulted in a sensitivity of 77% and a specificity of 42%. Although analysis of qualitative culture of tracheobronchial secretion is helpful in identification of the underlying pathogen, it is not specific for the diagnosis of VAP. A common abuse and overuse of antibiotics that we have observed in the ICU by physicians is treatment of potential pathogens from purulent respiratory secretions (tracheobronchitis), with no evidence of pneumonia (personal observation). There is no evidence that antibiotics in these situations are of value and treatment of tracheobronchitis in the ICU is not justified. On the other hand prompt and appropriate treatment of VAP is beneficial and may have a major impact on mortality and morbidity. Although appropriate antibiotics may improve survival in VAP, empiric broad-spectrum antibiotics without clinical infection is potentially harmful, increasing the risk for colonization and superinfection with multiresistant bacteria, fungi (candidiasis), *C. difficile* colitis, and potential adverse events. Numerous studies have documented the increase in multiresistant gram-negative bacilli and gram-positive bacteria in hospital-acquired infection worldwide,[5,15] and the ICU have been deemed "factories for creating, disseminating and amplifying resistance to antibiotics."[16] The presence of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), multiresistant *Pseudomonas aeruginosa*, multiresistant *Acinetobacter baumannii*, extended-spectrum beta lactamase (ESBL) producing coliforms (*Escherichia coli*, *Klebsiella* species, *Enterobacter* species, *Serratia marcescens*, etc.) have become common isolates in many tertiary ICUs.[16] In the United States data from the National Nosomial Infection Surveillance (NNIS) System from 2003 found that *S. aureas* was the most common pathogen in VAP (27.8%), followed by *P. aeruginosa* (18.1%), *Enterobacter* species (10%), *Klebsiella pneumoniae* (7.2%), and *Acinetobacter* species (6.9%).[17]

3.2.1 Microbiological Techniques for Diagnosis

While qualitative cultures of endobronchial aspirates yield a higher rate of false-positive results (from tracheobronchial colonization), efforts were made to study the role of quantitative analysis of cultures of respiratory secretions to aid in the diagnosis of VAP in the past two decades. These techniques include simple endobronchial aspiration (EA), use of bronchoscopic techniques with or without protected devices, such as protected specimen brush (PSB), or protected catheter to retrieve distal respiratory secretions by lavage (BAL).

Quantitative cultures of EAs with use of cutoff points between $>10^5$ and $>10^7$ CFU/ml have been used, and is simple and practical to perform at anytime in any ICU without fiberoptic bronchoscopy. Although some studies showed favorable results with PBB cultures, with slightly higher sensitivity (82% vs 64%) and lower specificity (83% vs 96%)[17]; others found this technique was only modestly accurate with sensitivity of 70% and relative specificity of <72% in diagnosing pneumonia.[18,19] Most of the studies also used a standard clinical or microbiological criteria as the reference for diagnosing VAP, which as mentioned before lacks accuracy. In one study which compared results of EA quantitative cultures (using $>10^7$ CFU/ml) with those of postmortem lung biopsy quantitative cultures, only 53% of the microorganism isolated in EA samples were also found in lung tissue cultures,[20] Thus indicating poor specificity.

Some investigators have found that quantitative cultures of BAL correlate well with VAP diagnosis, but others have found mixed results and poor specificity especially in patients with tracheobronchial colonization.[7]

Also there is a lack of consensus on the cutoff point for diagnosis; some investigators use 10^4 and others 10^5 CFU/ml of at least one microorganism for interpretative threshold. An International Consensus Conference in 1992 had recommended $\geq 10^4$ CFU/ml as the best threshold.[21] To overcome the problem of contamination present in the proximal airways, use of a protected transbronchoscopic balloon-tipped catheter to obtain BAL for quantitative culture has been used. One study of 13 patients with pneumonia and 33 controls, with a threshold of 10^4 CFU/ml, yielded a diagnostic sensitivity of 97% and a specificity of 92%.[22] Samples obtained by the protected BAL can also be examined directly by Giemsa stain or the gram stain immediately after the procedure to enable intervention with antimicrobial therapy before obtaining culture results. Several studies found that if the Giemsa or gram stain was positive, where >3% or 5% BAL cells contained intracellular bacteria, this correlated with most patients with pneumonia and negative for patients without pneumonia.[13,23,24] Furthermore, the morphological findings on the stained specimens closely correlated with the bacterial cultures.

Other studies used the combination of the BAL procedures sampling and PSB technique to try and improve the diagnostic accuracy. But the PSB by itself has been extensively studied for quantitative cultures (using a special double-catheter brush system with a distal occluding plug to reduce contamination). The PSB is done with a fiberoptic bronchoscope, with cutoff threshold set at 10^3 CFU. Since

0.01–0.001 ml of secretion is collected with PSB technique, $>10^3$ CFU of bacteria represents 10^5–10^6 CFU/ml of secretion.

Comparison of quantitative BAL and PSB microbiological findings has been noted to have high correlation. In one study[25] the quantitative agreement was 83% of the organisms isolated, and the qualitative results were significantly correlated (rho = 0.46, $p < 0.0001$). Numerous studies have been done in patients with VAP to assess quantitative BAL and PSB. Most of these studies were limited by small sample size and use of clinical or microbiological criteria as the "gold standard" for diagnosis. In studies evaluating both techniques a meta-analysis of 11 studies in 435 ICU patients found the overall accuracy BAL to be close to that of PSB.[26]

Blind-protected telescoping catheter (PTC) (or blind-protected brush PTB) without bronchoscopy has been compared to quantitative BAL via bronchoscope to diagnose VAP. Although blind PTC and PTB specimens have been reported to show very good correlation with BAL in some studies,[27,28,29] provided the sample containing visible secretions expelled from the catheter and both lungs are sampled, other studies showed low concordance between blind and directed PSB samples (53%).[30]

Although there are numerous studies assessing quantitative cultures of various respiratory samples (EA, BAL, blind, and directed PSB or PTC) for diagnosis of VAP they have several shortcomings. Most of the studies involved small sample size with pneumonia; there were frequent flaws and design-related biases,[31] and most important, the "gold standard" for diagnosis of VAP used is controversial and not well-established. The "gold standard" for diagnosis of VAP in several studies included autopsy or histopathology and cultures from open or percutaneous biopsies of lungs immediately after death. The correlation of the various sampling techniques with histology and biopsy culture results is summarized in Table 3.1. Eleven studies performed between 1984 and 2001, were reviewed,[12,32–41] involving 378 subjects from the ICU with 209 (55%) with confirmed VAP. Seventy-two percent of the cases received antibiotics within 48 h of the postmortem studies, thus potentially affecting the accuracy of quantitative cultures in the majority of studies. The sensitivity of quantitative PSB ranged from 15% to 100% (mean 54.6%) and the specificity ranged from 50% to 100% (mean 74.6%), similar to the results of BAL (bronchoscopic and mini-BAL combined) with mean sensitivity and specificity of 51.3% and 79.8%, respectively. Unfortunately only five of the studies assessed the clinical criteria for pneumonia compared to the gold standard, and the mean sensitivity was 81% (range 69–100%) and the mean specificity 62.8% (range 42–85%). Thus, the clinical criteria for pneumonia were not inferior to more invasive investigations and may be somewhat more sensitive. However, it is very likely that prior antibiotics treatment before the quantitative cultures (within 48 h) was responsible for the low sensitivity of these techniques.

There were a few studies assessing the accuracy of these invasive techniques for diagnosis of VAP in animal models. In a canine model of *S. pneumoniae* infection of 18 ventilated dogs quantitative cultures 24 h after infection from transbronchial biopsy, protected-catheter brush, and percutaneous needle aspiration yielded sensitivity of 100%, and specificity of 88% for needle aspiration, and 72% for both catheter brush and transbronchial aspirations specimens.[42] Fiberoptic bronchial

Table 3.1 Diagnosis techniques for VAP:Histology as "Gold Standard" Sensitivity/ Specifity (%) of quantitative

Source	Year	Total no. patients	No. (%) with pneumonia	No. (%) receiving antibiotics	PSB	BAL	Clinical criteria	Method of Validation	Shortcomings
Chastre et al.[33]	1984	26	6(23)	14(54)	100/42–87	–	–	Open lung (L) biopsy 1 cm^3 immediately after death.	Pneumonia sample size small.
Rouby et al.[34]	1992	83(33 had quantitative cultures)	43(52)	67(81)	–	70/69 (Protected mini-BAL)	–	Pneumonectomy 30 min after death.	Most patients received antibiotic.
Torres et al.[35]	1994	30	18(60)	30(100)	36/50	50/45	70/45	Lung Biopsies <1 h after death.	All received antibiotics.
Chastre et al.[36]	1995	20	11(55)	18(90)	82/89	91/78	–	Open lung biopsy PM 2 × 5 cm^3 <1 h after death.	Used bacterial burden in lung tissue, not histology as gold standard.
Papazian et al.[37]	1995	38	18(47)	16(43) <48 hr	33/95	50/95	72/85(CPIS)	Pneumonectomy 30 min after death	–
Marquette et al.[38]	1995	28	19(68)	15(54)	57/88	77/58	–	Lungs at autopsy	Clinical criteria for VAP not analyzed.
Kirtland et al.[39]	1997	39	9(23)	38(97)	15–50/50–77	11–14/80	–	Open lung biopsy <1 h after death	Most patients received antibiotics.
Fabregas et al.[12]	1999	25	23(92)	17(68)	62/75	77/58	69/75 77/42 (CPIS)	Multiple lung biopsies (2 cm^3) immediately after death.	Most patients received antibiotics.

(*continued*)

Table 3.1 (continued)

Source	Year	Total no. patients	No. (%) with pneumonia	No. (%) receiving antibiotics	PSB	BAL	Clinical criteria	Method of Validation	Shortcomings
Bregeon et al.[40]	2000	27	14(52) by histology 9, (33) by culture + histology	13(48)	(PDA) Histo-criteria-57/100 Combined-criteria 67–71/75–87	(Mini BAL) 50/86 78/86	100/61 100/69 (CPIS)	Pneumonectomy within 30 min of death.	Two different criteria for pneumonia: lower cut off threshold than others.
Torres et al.[41]	2000	25	23(92)	17(68)	Histo-criteria 24–28/50–54 Combined-criteria 67–71/75–87	PBAL 16–19/75–77 43–63/83–91	80/–	Bilateral open lung biopsies (2 cm^3) <90 min after death	Clinical criteria not assessed for specificity; criteria for pneumonia.
Balthazar et al.[42]	2001	37	20(54)	Not given	–	90/94	–	Open lung biopsy <1 h after death	Antibiotic treatment not mentioned clinical criteria not assessed.
Total 11 studies:	1984–2001	378	209(55)	245/341(72)	54.6/74.6 (mean)	51.3/79.8 (mean)	81/62.8 (mean)	–	–

aspirations specimens were found to be unreliable, and unfortunately quantitative cultures were not performed.

In a baboon model of VAP (ventilated for 7–10 days), BAL recovered 74% of all species present in lung tissue compared to 41% by PSB and 56% for needle aspirates.[43] Although false-positive rates for the three techniques were similar, the specificity was not provided. Tracheal aspirations revealed 78% of the organism but 40% of the species were not present in lung tissue.

In summary, quantitative cultures from BAL (with or without protected catheter) or PSB have not been proven superior to clinical criteria for diagnosis of VAP. This is reflected in the most recent consensus conference on VAP in 2001,[44] when it was acknowledged that there is no accepted "gold standard" for diagnosis, and no superiority of any specific diagnostic method. The diagnosis of VAP was still defined as the presence of new, persistent pulmonary infiltrates not otherwise explained, appearing on chest radiograph (not present before intubation); and the presence of at least two of the following criteria: (1) temperature $>38°C$, (2) leukocytosis $>10{,}000$ cells/mm^3, and (3) purulent respiratory secretions.[44] A recent multicenter randomized trial of 740 patients in 28 ICUs in Canada and the United States have confirmed these opinions.[46] There were no differences in outcome and overall use of antibiotics when two diagnostic strategies for VAP were compared, BAL with quantitative culture and EA with nonquantitative culture.[46]

3.2.2 New Diagnostic Methods for VAP

Several biological markers have been studied to improve the diagnostic accuracy of VAP but with disappointing results. These include serum and bronchial procalcitonin levels,[47,48] C-reactive protein,[48] tumor necrosis factor alpha (TNFα),[49] and other proinflammatory cytokines concentrations.[49,50] The most promising investigative tool to date appears to be the measurement of soluble triggering receptor expressed on myeloid cells (sTREM-1) from BAL fluid.

TREM-1 is a member of the immunoglobulin super family[51] that is important in the acute inflammatory response to infections,[52] and the expression is up-regulated on phagocytes on exposure to bacterial and fungal products. Neutrophils and monocytes in tissues infected with bacteria express high levels of TREM-1, whereas noninfectious inflammatory disorders weakly express TREM-1 on those calls.[52] TREM-1 can be measured in body fluids in the soluble form as it is shed by the membrane of activated phagocytes.

In a study of 76 patients admitted to the ICU with suspected infection and fulfilling at least two criteria for the systemic inflammatory response syndrome (SIRS) sTREM-1 plasma levels were measured.[53] Sepsis or septic shock was diagnosed in 47 (62%) patients, and a plasma level of >60 ng/ml of sTREM-1 was more accurate than any other clinical or laboratory findings for indicating infection (sensitivity 96%, specifically, 89%).[53] The same investigators also assessed sTREM-1 in BAL fluid in patients admitted to the ICU with and without

pneumonia.[35] In a prospective study of 148 patients receiving mechanical ventilation a rapid immunoblot technique (also available from R & D systems, with the entire procedure taking less than 3 h), was used to measure sTREM-1 in BAL fluid (sensitivity 5 pg/ml),[54] obtained by mini-BAL technique. Forty-six patients were diagnosed with VAP (clinical criteria similar to the consensus conference in 2001),[44] 38 patients had community-acquired pneumonia, and 68 patients had no pneumonia. A sTREM-1 cutoff value of 5 pg/ml had a sensitivity of 98% and specificity of 90% for presence of any pneumonia; and was the strongest predictor of pneumonia, with an odds ratio of 41.5.[55] The best clinical predictor of pneumonia was a CPIS of >6 (odds ratio, 3.0).

In a more recent study from the Netherlands, BAL fluid and plasma were collected sequentially on alternate days (from start of ventilatory support until complete weaning) for measurement of sTREM-1 levels by enzyme-linked immunosorbent assay (ELISA) in 9 patients who developed VAP and 19 controls without pneumonia.[55] Plasma levels of sTREM-1 did not change significantly in either patient group, while BAL fluid levels increased towards significance with the diagnosis of VAP but not in controls.[55] A cutoff value of 200 pg/ml in BAL fluid for sTREM-1 on the day of pneumonia diagnosis had a sensitivity of 75% and specificity of 84%.

3.3 Microbial Etiology of VAP

The causes of VAP can vary considerably by geographic location, local epidemiology, patient characteristics, length of hospital stay, and duration of mechanical ventilation. Most studies of VAP, however, find a predominance of gram-negative bacilli and staphylococci that normally colonize the oropharynx and gut. The most common pathogens include *S. aureus*, *P. aeruginosa*, *Klebsiella* species, *Enterobacter* species, *Acinetobacter* species, and *S. marcescens*, but the relative frequency will vary from center to center. In early-onset VAP, soon after admission and <7 days on mechanical ventilation, *S. pneumoniae*, *Haemophilus influenzae*, and more susceptible gram-negative bacilli, maybe the etiological agents.[44] Polymicrobial infections with mixed bacteria have also been reported in up to 48% of all cases of VAP.[57] The importance of anaerobes is unknown due to inadequate studies and is likely underestimated. The rates of isolation of anaerobes in VAP have been low in most studies (1–3.5%),[44] but has been higher (23%) in one study.[58] This suggests that other studies may be using inadequate techniques for obtaining (oxygen administration), transporting, and culturing respiratory secretions for anaerobes. Atypical bacteria (*Legionella pneumophila*, *Chlamydia pneumoniae*, viruses (i.e., respiratory syncytial virus), and fungi have also been implicated at times, but these pathogens have not been studied systematically and their role is presently unclear.[58]

The method of obtaining specimen to confirm the etiology has been contentious, with, advocates of deep endotracheal aspirates citing simplicity, easy to perform by any ICU nurses, versus advocates of more invasive bronchoscopy techniques.

However, recent studies have found similarities in obtaining clinically significant pathogens from four procedures used (blind endotracheal aspiration, PSB, bronchoscopic BAL, or directed brushings).[59,60] Although, initial prospective studies showed improved outcomes (mortality) with invasive versus noninvasive diagnostic management for suspected VAP,[61,62] more recent studies have not.[63,64] In the most recent review and meta-analysis of this topic it was concluded that the invasive strategies do not alter mortality in VAP, but affect antibiotic use and prescribing.[65,66] Although most investigators favored a more invasive approach,[44] others recommended initial endotracheal aspiration for diagnosis, and reserve invasive methods for patients not responding to initial empirical antibiotic treatment.[64,67] The latter course is reasonable and may allow more rapid intervention, as a precise bacteriologic diagnosis is of paramount importance for therapeutic success and cultures should be obtained before initiating therapy. Other areas where initial invasive diagnostic procedures are warranted include immunocompromised hosts (i.e., acquired immune deficiency syndrome [AIDS]), and BAL samples should be sent for viral studies, mycobacterial and fungal smears and cultures, cytology, and stain for *Pneumocystis carinii*.

3.4 Issues in Treatment of VAP

Treatment of VAP should be started in a timely manner with appropriate antibiotics once the diagnosis is made. The results of cultures should not delay starting empirical therapy, usually a broad-spectrum agent (or combination) to cover *S. aureus* and gram-negative bacilli. There is some data to indicate that starting therapy early in VAP lowers the mortality (trend) than delaying therapy for >48 h after the diagnosis was considered.[67,68] Treatment may be guided by gram stain of respiratory samples to assist in choice of antimicrobial agents, as the overall accuracy in diagnosing VAP for any organism was 88% in one retrospective study.[69] A combination of gram stain and bacterial adenosine triphosphate (ATP) assay have also been used for rapid diagnosis of BAL samples, with sensitivity of 95.3%, specificity of 54.9%, and negative predictive value of 97.6%.[70] Thus a negative result may allow use of narrow spectrum antimicrobial agents or withholding empiric therapy for suspected VAP.[70] Assaying for endotoxin from BAL samples have also been used to diagnose gram-negative bacterial VAP as a rapid test, but this is not generally available in most centers and appears to provide the same accuracy as a gram stain (which is cheaper and easier to perform in any clinical laboratory).[71]

There is no consensus as to the initial empiric therapy for VAP, as this should depend on the individual center's experience with the prevalence and pattern of antimicrobial-resistant bacteria. Factors that should be taken into consideration in selecting an antibiotic include onset of pneumonia after ventilation, duration of hospitalization, previous antimicrobial therapy, and underlying disease. Early onset of VAP (<7 days of ventilation) in patients not previously treated with antibiotics

may be due to more sensitive bacteria, such as in *S. pneumoniae, H. influenzae*, methicillin-susceptible *S. aureus*, and enteric gram-negative bacilli. In this situation it is recommended to use a single agent that has no anti-pseudomonal activity such as ampicillin-sulbactam, -ceftriaxone, or -cefotaxime, newer fluoroquinolones, or ertapenem.[44]

In cases of VAP occurring >7 days after ventilation, or previously treated with antibiotics or hospitalized for prolonged periods, more resistant bacteria may be responsible for pneumonia such as MRSA, *P. aeruginosa*, *Acinetobacter* species, and multiresistant organisms. However, it would appear that the duration of ventilation before development of pneumonia is less important than the duration of hospitalization and previous antibiotic therapy in predisposing to *Pseudomonas* or more resistant bacterial infection.[72] Initial therapy under these circumstances may include a broad-spectrum coverage (such as imipenem or meropenem, piperacillin-tazobacterum, or combination of agents) to cover the most prevalent bacteria circulating in the ICU. Empiric therapy for MRSA is usually not necessary unless the patient is known to be colonized or in close contact with a subject with MRSA, and the respiratory sample shows gram-positive cocci in clusters. In a consensus conference most investigators preferred to use a combination of an aminoglycoside or a fluoroquinolone with an anti-pseudomonal, extended-spectrum β-lactam or a carbapenem plus an aminoglycoside in late onset VAP, until cultures and susceptibility are available, but there are no clinical trials available to support these guidelines.[44] Intuitively it seems rational that selection of an antimicrobial regimen should be effective against recent pathogens that colonize the patient's respiratory tract. However, serial routine microbial cultures result in the initial management of VAP has been found to be of limited value.[73]

Does *P. aeruginosa* pneumonia require a combination therapy? It has been standard practice in many centers and recommendation by most investigators to use a combination of anti-pseudomonal, extended-spectrum β-lactam with an aminoglycoside or with a fluoroquinolone (i.e., ciprofloxacin) for *P. aeruginosa* pneumonia.[74] However, the concept that dual therapy is superior to monotherapy or less likely to develop antibacterial resistance is unproven. Despite this, since *P. aeruginosa* pneumonia carries a poor prognosis with mortality rate that exceeds 40%[8] and the variable resistance pattern to extended-spectrum β-lactam agents and ciprofloxacin (which is increasing in many centers)[75] it is a reasonable recommendation to use a combination of two agents.

The most common advocated practice for VAP is to maximize empirical antimicrobial coverage with subsequent streamlining of therapy once culture and sensitivity data are available.[76,77] This appears to be a successful strategy but studies using historical controls may suffer from significant bias. It has been suggested that computer-assisted antibiotic prescription in ICUs may supplement or replace such strategies in the future.[76]

Duration of therapy for VAP was often variable and empirical with a tendency for overtreatment. A recent randomized multicenter study of 402 patients with VAP showed no difference in outcome between 8-day versus 15-day course of antibiotic therapy and the recurrence rate was similar (28.9% and 26.0%), except

P. aeruginosa was associated with higher recurrence in the shorter course group (40.6% vs 25.4%).[78] Thus shorter course of therapy may lead to less antibiotic exposure and possible help reduce antimicrobial resistance in the ICU. Another approach to limit antibiotic overuse in the ICU for low-risk patients with pulmonary infiltrates with suspected pneumonia is to initiate monotherapy then stop antibiotic therapy at 3 days for those with a CPIS < 6.[79] In this randomized, unblinded, controlled study of 81 patients, the outcome was similar but patients receiving earlier discontinuation of antibiotics had lower incidence of antimicrobial resistance or superinfection, and lower mean antibiotic costs.[79]

In the past when less active anti-pseudomonal β-lactam (carbenicillin) was available and aminoglycosides were used by multiple dosing, there was concern about inadequate endobronchial concentration of aminoglycoside for severe *Pseudomonas* or gram-negative pneumonia. Interest was generated by a few studies to administer the aminoglycoside endobronchially via endotracheal tube or tracheostomy to complement combined systemic therapy. In a double-blind randomized study of gram-negative VAP, all patients received systemic tobramycin plus piperacillin or cefazolin and half the patients were randomized to receive 40 mg tobramycin every 8 h or placebo instilled enotracheally.[80] *P. aeruginosa* was the main pathogen in 41% of 41 assessable cases. Although the causative pathogens were eradicated from respiratory tract more frequently in those receiving endotracheal tobramycin, there was no difference in the clinical outcome of the two groups.[80] In a more recent study of 38 VAP patients with a similar design half the patients were randomized to receive either additional nebulized tobramycin (6 mg/kg/day) or placebo, once daily for 5 days.[81] Extubation by day 10 was achieved in 35% of patients receiving nebulized tobramycin and 18.5% of those in the placebo group but the difference was not statistically significant.

Of growing concern in the past three decades is the emergence of *Acinetobacter* nosocomial infection worldwide, especially in ICUs. This is alarming in view of the ability of this gram-negative bacteria to accommodate diverse mechanisms of resistance, with multiresistant strains to all available antibiotics occurring in local outbreaks.[82] *A. baumannii*, the most important of the three commonly isolated species (including *A. calcoaceticus*, and *A. lwoffi*), has shown dramatic increased resistance to carbapenem from 9% in 1995 to 40% in 2004 in surveillance of 300 US hospitals.[83] These nosocomial strains of *Acinetobacter* commonly demonstrate extended-spectrum beta-lactamases (ESBL), alterations in cell-wall channels (porins), antibiotic efflux pumps, aminoglycoside-modifying enzymes, mutations in the genes gyrA and par C (conferring quinolone resistance), and serine or metallo-β-lactamases conferring resistance to carbapenems.[82] The most frequent clinical manifestation of *Acinetobacter* infection are VAPs and bacteremias (often from vascular catheters).

VAP due to *Acinetobacter* occurs later in the ICU stay in patients on prolonged ventilation, often previously treated with broad-spectrum β-lactams (third-generation cephalosporins and quinolones). The clinical effect of *Acinetobacter* VAP on outcome has been variable. The major impact has been on longer ICU stays and hospitalization when matched for severity of underlying illness, suggesting that

coexisting conditions were the major predictors of outcome.[82] Treatment of multi-drug-resistant *Acinetobacter* VAP is a challenge with limited options. Recent reports have been mostly small retrospective case series on the use of colistin alone or in combination with rifampin (with success of 25–50%).[81] Tigecycline, a new glycylcycline antibiotic, has in vitro activity against some *A. baumannii* resistant strains but there is evidence of increased resistance.[81] Susceptible strains can be treated with sulbactam, imipenem, third-generation cephalosporins, or aminoglycosides depending on in vitro susceptibility.

3.5 Prevention of VAP

There are several issues and areas of contention in the approach to prevent pneumonia in the mechanically ventilated patients. Obviously this would be worthwhile as it should save lives, reduce mortality, decrease duration of ventilation and hospitalization, and reduce costs. It would appear evident that the best way to prevent VAP is to avoid intubation and mechanical ventilation but this is not feasible in most instances. There has been much interest in the use of noninvasive positive-pressure ventilation (NPPV) to prevent intubation and manage patients with respiratory failure. In a recent review and meta-analysis of 12 studies, NPPV showed a strong benefit in reducing pneumonia compared to standard ventilation (relative risk 0.31, 95% CI 0.16 to 0.57, $p = 0.0002$).[84] However, the strongest evidence to support use of NPPV in patients with acute respiratory failure is in patients with exacerbation of underlying chronic obstructive pulmonary disease.[85] Patients with cardiogenic pulmonary edema and pulmonary contusion have also been found to require lower intubation rates, whereas patients with a higher severity score, an older age, ARDS or pneumonia, or fail to improve after 1 h of treatment, the risk of failure with NPPV is higher.[86] Thus in hypoxic acute respiratory failure management with NPPV can be successful in selected patients.

Rotational beds, prone position and semi-recumbent position have been proposed and investigated as simple measures to prevent VAP. These measures as preventative techniques have recently been reviewed by Hess.[87] Rotational therapy uses a special kinetic bed designed to turn continuously, or nearly continuously, the patient from side to side. A meta-analysis of studies evaluating the effect of rotational bed therapy shows a decrease in risk of pneumonia but no effect on mortality.[88] Considering increased cost of these kinetic beds ($200/day), potential for an advertent disconnection of intravenous catheters, they are not routinely recommended but may be useful in select patients with neurologic problems or surgical patients.[88]

Prone positioning has been shown to increase alveolar oxygenation (PaO_2) in patients with ARDS and lung injury but no survival benefit.[87] Two randomized studies on prone positioning (4–8 h/day) compared to supine position has been performed. One small study showed reduction in VAP (not statistically significant), and a larger study in 21 ICUs found just significant lower VAP with prone

positioning (20.6% vs 24.1%) but no improvement in mortality in both studies.[89,90] Thus prone positioning is not recommended as technical considerations preclude its use and it is associated with increased complications such as pressure ulcers and obstruction of the endotracheal tube.[89]

Studies have shown that radiolabeled enteral feeding in mechanically ventilated patients are more likely to be aspirated in the supine position compared to the semi-recumbent position (head elevated at a 45 degree angle).[87] One randomized study have found that semi-recumbent position was associated with lower VAP compared to the supine position (RRO.22, 95%, CI 0.05–0.92, $p = 0.04$).[91] Since semi-recumbent positioning is a low-cost, low-risk approach to preventing VAP it has been recommended for routine positioning in the ICU by the Centers for Disease Control and Prevention[92] and the Canadian Critical Care Society,[10] despite the fact that mortality was not improved in the randomized study.[89] However, in a more recent randomized, prospective study 109 patients were assigned supine position (with backrest elevation of 10 degrees), and 112 to the semi-recumbent position (target backrest elevation of 45 degrees) was not achieved 85% of the study time. The achieved difference in the treatment position (28 degrees vs 10 degrees) did not prevent the development of VAP.[93]

In a small pilot study 35 patients on mechanical ventilation received continuous lateral rotational therapy (CLRT) for 5 days, compared to 35 control patients matched for age, gender, cause of respiratory failure, admission APACHE score, received routine positional change.[94] The patients receiving CLRT had improved oxygenation and reduced incidence of VAP compared to controls. Thus a large, randomized, prospective study is warranted to confirm this observation. In another small study 60 ventilated patients were randomized to receive chest physiotherapy or sham physiotherapy, VAP occurred in 39% of the controls and 8% of the treated group, $p = 0.02$.[95] However, there were no differences in duration of stay or ICU mortality. It is surprising that larger randomized control trials have not been reported since this report in 2002 to confirm these results.

3.5.1 Antibiotic Prophylaxis for Prevention of VAP

Interest in the use of antibiotic prophylaxis for prevention of nosocomial pneumonia has existed from the early 1970s. Although a randomized study in 1974 had shown that gentamicin administered endotracheally could prevent gram-negative pneumonia in patients with tracheotomies,[96] this method was not widely adopted due to fears of antimicrobial-resistant bacteria developing.

The gastrointestinal tract is believed to play an important role in the pathogenesis of VAP, and gram-negative enteric bacteria colonizing the stomach and oropharynx are the same bacteria isolated from respiratory secretions in VAP. Interventions used to reduce the bacterial colonization and hence VAP include selective decontamination of the digestive tract (SDD) with antimicrobials (topical with or without systemic therapy), use of sucralfate for stress ulcer prophylaxis, and

external feeding strategies that preserve gastric acidity, or lessen pooling of oropharyngeal secretions.

Numerous studies have been published on antibiotic prophylaxis or SDD to prevent VAP in the past two decades. In the most recent Cochrane Review of 36 trials involving 6,922 patients, 17 trials ($N = 4,295$ patients) tested a combination of topical and systemic antibiotics, the average rate of respiratory tract infections and mortality in the control group were 36% and 29%, respectively.[97] There was a significant reduction of both VAP (OR 0.35, 95% CI 0.29–0.41) and mortality (OR 0.78, 95% CI 0.68–0.89) and on average required 5 patients to be treated to prevent one VAP, and 21 patients to prevent one death. In 17 trials ($N = 2,664$) that tested topical antimicrobial alone, there was a significant reduction in VAP (OR 0.52, 95% CI, 0.43–0.63) but not in total mortality in the treated group.[97] However, only one of the trials explored the consequences of antibiotic resistance and superinfection as a result of prophylaxis. With accumulating evidence of increasing antimicrobial resistance in the ICU, and evidence that SDD promotes gram-positive bacterial infections, most guidelines do not recommend routine antibiotic prophylaxis in the ICU.[10,92,97–100]

Efforts to reduce heavy colonization of oropharyngeal bacteria by improving oral hygiene and use of topical antiseptics have received little attention in the scientific literature as a means of prevention of VAP. Oral hygiene is compromised in ICU patients by the presence of intubations tube, nasogastric catheter, heavy sedation, anticholinergic drugs, and mouth breathing all impair salivation and normal swallowing mechanism and allow bacterial overgrowth. Unfortunately, little is known about the efforts of oral care interventions in ICU patients on mechanical ventilation and development of VAP.[101]

Chlorhexidine is a broad-spectrum antibacterial agent (bactericidal for both gram-negative and gram-positive bacteria), that is not absorbed through mucosa or skin, and is the recommended antiseptic of choice for preoperative preparations. It is also available as an oral rinse to prevent and treat gingivitis. An advantage of chlorhexidine is the absence of any significant bacterial resistance and good safety profile when used topically. Two previous randomized, placebo-controlled studies were performed before intubating and continued therapy throughout the ICU stay in patients undergoing elective cardiac surgery.[102,103] Both studies showed a reduction in nosocomial pneumonia, but was significant only for one study,[102] and for a subgroup of those at highest risk of pneumonia in the other.[103]

In a prospective, nonrandomized, controlled study in a surgical ICU patient's intubated for mechanical ventilation for the 5 months were given standard care with ventilator weaning protocol (controls).[104] During the following 5 months 0.12% chlorhexidine gluconate oral rinse was added twice daily to all intubated patients ($N = 95$ for both groups). The addition of chlorhexidine led to a significant reduction and delay in the occurrence of VAP (37% overall, 75% for late VAP, $p < 0.05$). The median duration of mechanical ventilation and length of stay in the ICU or hospital, between the groups were no different.[104] This type of design, however, may lead to biases that could influence results.

A recent randomized, placebo-controlled multicenter trial on the value of antiseptic oral decontamination in 228 nonedentulous patients on mechanical

ventilation has been reported.[105] A 0.2% chlorhexidine gel or placebo gel on gingival and dental surfaces was applied three times daily during the entire ICU stay. No difference was observed in the incidence of VAP, duration of ventilation, mortality, or length of stay, but the number of positive dental plaque cultures was significantly lower in the treated group (29% vs 66%, $p < 0.05$).[105]

3.5.2 Maintaining Gastric Acidity to Prevent VAP

It is a routine practice in ICUs to give stress ulcer prophylaxis to prevent upper gastrointestinal hemorrhage. However, gastric colonization with potentially pathogenic bacteria increases with decreasing acidity, and these enteric pathogens are the potential causes of VAP from aspiration. Medications used for stress ulcer prophylaxis that alter gastric pH include antacids, H2 antagonists, and proton pump inhibitors, which increase bacterial colonization of the stomach and may increase the risk for VAP. Sucralfate, which is a gastric cytoprotective agent that enhances natural mucosal barrier, is an alternative prophylactic agent that may reduce VAP. Seven meta-analysis of 20 randomized trials on the benefit of sucralfate therapy compared to H2 antagonists have been reported.[10] Four of the seven meta-analysis found a significant decrease in VAP with sucralfate, and three also found a reduction of mortality with sucralfate.[93] Three other meta-analyses found similar but insignificant trends in reduction of VAP with use of sucralfate. Thus sucralfate has been recommended for stress ulcer prophylaxis in patients with low to moderate risk for gastrointestinal bleeding (absence of bleeding tendency or need for prolong mechanical ventilation).[10,92]

In patients at high risk for gastrointestinal bleeding H2 antagonists or a proton pump inhibitor are preferred for stress ulcer prophylaxis. In these circumstances other methods to reduce gastric enteric bacterial overgrowth are needed. A recent pilot study has examined the benefit of acidifying feeding formula using potassium sorbate to reduce bacterial burden.[106] Sixteen patients on mechanical ventilation were randomized to receive acidified formula (PH 4.25) and 14 controls received standard formula. The number of organisms isolated in each patient per week and the quantity of bacteria (colony forming units/ml) of gastric aspirates were significantly higher in the controls.[106]

There was no difference in gastrointestinal bleeding between the two groups. Thus large, randomized clinical trials to assess prevention of VAP and bleeding risk in patients requiring H2 antagonists or proton pump inhibitor are warranted with this acidified feeding formula. A previous randomized study of acidified feeding formula used hydrochloric acid added to the formula in critically ill patients, all on sucralfate with 120 enrolled but 95 analyzed with primary outcome measure being bacterial colonization of gastric contents, and secondary outcome VAP.[107] Bacterial colonization was significantly less in the acidified treatment group 2% versus 43%; VAP was less than half in the acid feeds (6.1%) versus control group (15%) but sample size was too small to show any significant difference.

3.5.3 Methods to reduce Aspiration

Pooling of oropharyngeal secretions above the endotracheal tube cuff may play a role in aspiration of bacteria-laden fluid and subsequent VAP. Thus methods to reduce or drain subglottic secretions require use of specially designed endotracheal tube with a separate dorsal lumen that opens into the subglottic region.

In a recent meta-analysis of five randomized studies with 896 patients enrolled, subglottic secretions drainage reduced the incidence of VAP by nearly half (*RR* = 0.51, 95% CI 0.37–0.71), mainly within 7 days of intubation.[108] Secretion drainage shortened the duration of mechanical ventilation by 2 days and the length of ICU stay by 3 days and delayed the onset of pneumonia by almost 7 days. Thus subglottic secretion appears effective in preventing early-onset VAP in patients requiring mechanical ventilation for >3 days. Although no beneficial effect on mortality was reported, it would be cost-effective even though the specialized endotracheal tubes cost about 25% more than standard endotracheal tubes, and there is no significant harm reported with this technique. This method for prevention of VAP has been recommended by the CDC and other guidelines.[10,89,92]

Few other methods to reduce oropharyngeal or gastric content aspiration have been examined in randomized studies. One approach is to use gel lubrication of the tracheal tube cuff to reduce pulmonary aspiration. In a small pilot study of 36 anesthetized patients and 9 ICU patients with tracheostomies, lubricated cuffs were compared to non-lubricated cuffs leakage of dye placed in the subglottic space[109]. Dye leakage was 11% in the lubrication group and 83% in the non-lubrication group of anesthetized patients, $p < 0.001$. In the ICU patients with lubricated cuff tracheostomy tubes leakage first occurred after a mean of 48 h (range 24–120 h). Thus for patients with prolonged intubation/ventilation changing or reinserting the tube with fresh lubrication every 48 h would be a practical limitation.

Use of large-bore nasogastric tube may promote gastroesophageal reflux and pulmonary aspiration in ICU patients. In a pilot study of 30 patients on mechanical ventilation 16 received external feeding through a small-bore tube and 14 received no tube feeding, all in the semi-recumbent position, and aspiration of gastric contents was assessed by radioisotope technique.[110] There were no gastric contents aspirations in both groups, but patients with large-bore nasogastric tubes should have been assessed as well. This hypothesis has not been tested in any large, randomized clinical trials.

The mere presence of a nasogastric tube is considered a risk factor for development of VAP. Alternatively, gastrostomy can be used for administration of external feedings. A previous randomized study had found no benefit of small-bowel feeding versus gastric feeding, when the nasoenteric tube was placed in the duodenum versus the stomach.[111] Two recent meta-analysis reviewed the evidence from randomized control trials comparing gastric with post-pyloric feeding (3 studies). Heyland et al.[112] found a significant reduction in VAP with post-pyloric feeding (OR 0.76, 95% CI 0.59–0.99), while Marick and Zaloga[113] found a nonsignificant trend in reduction of VAP with post-pyloric feeding.

In a recent small, randomized study in patients mechanically ventilated for stroke or head injury, 20 subjects were allocated for gastrostomy and 21 for nasogastric tube (controls) for 3 weeks.[114] VAP developed in 12.5% of patients with gastrostomy and 44.4% with nasogastric tube, but the overall duration of hospitalization and mortality were no different. This study needs to be confirmed by larger studies, and the result is suggestive that for patients with central nervous system deficit on ventilation, gastrostomy feeding is preferable to nasogastric feeding when prolong ventilatory support is needed.

3.5.4 Ventilator Circuit and VAP

In recent years, the relationship of respiratory care equipment and VAP has been undergoing scrutiny by several studies. Several randomized, controlled studies have examined the effect of antibacterial humidification strategies, such as the replacement of heated humidifiers by heat and moisture exchangers, in preventing VAP. In a meta-analysis of eight studies conducted between 1990 and 2003 revealed a reduction in a relative risk of VAP (0.7) with heat and moisture exchanges particularly in patients on mechanical ventilation for 7 days (RR0.57).[115] Also, those heat and moisture exchangers do not need to be changed more than every 5 days. However, for wider applicability further studies were recommended because of patient selection and exclusion for patients with high risk of airway occlusion.

There is potential for cross-infection in the ICU of multiresistant bacteria, or contamination of the patients' airway by extrinsic microorganism during the traditional suction of the airway by disconnection from the ventilator (open system). In the past several years there have been several randomized, prospective studies of VAP pneumonia in patients using closed versus open suction system. Most of the studies enrolled insufficient number of patients to demonstrate a significant difference (<100 patients), and as yet no meta-analysis have been published. However, two large studies are worthwhile reviewing. Combes et al.[116] enrolled 54 patients to closed suction and 50 to open suction, and the rate of VAP was lower with the closed suction group, 7.32 versus 15.89/1,000 patient days, $p = 0.07$. A much larger randomized study of 443 patients, recently found no difference in mortality or VAP between open or closed suctioning, 17.59 versus 15.94/1,000 ventilation-days but the cost per day for the closed suction was more expensive.[117]

3.5.5 Summary of Prevention

Several methods are available that have been shown by randomized, controlled studies to reduce the incidence of VAP. Surprisingly, most of these techniques have not resulted in improved survival.

Before intubation and mechanical ventilation attempts should be made to give a trial of NPPV for at least an hour in selected patients (exacerbation of COPD, cardiogenic pulmonary edema, and pulmonary contusion). The available evidence

suggests that semi-recumbent position should be used routinely, rotational therapy should be considered in selected patients, and prone position should not be used as a technique to reduce VAP. Sucralfate rather than H2 antagonists in patients at low to moderate risk for gastrointestinal tract bleeding should be used for prophylaxis. Aspiration of subglottic secretions should be routinely practiced to decrease VAP, but closed tracheal suctioning is not superior to an open system. Small bowel feeding rather than gastric feeding for patients requiring prolonged mechanical ventilation (>7 days) may be considered but the value is still controversial.

Selected patients with low risk of airway occlusion (tenacious secretions etc.), intubation for >7 days can benefit from heat and moisture exchangers, which may not be changed more than every 5 days. Although selective decontamination of the upper digestive tract is of proven value, it is not routinely recommended as the risk of widespread antimicrobial resistance is a major concern.

3.6 Future Directions

A noninvasive method of confirming VAP or a clinical "gold standard" for the diagnosis is still elusive. The most promising technique to date is to measure BAL fluid s-TREM-1 concentration. Further large prospective studies are needed to confirm its utility with autopsy/open lung biopsies as "gold standard" for VAP. Moreover, controls without VAP should include septic patients from other sources; patients with lung cancers and tracheobronchitis without pneumonia to confirm the specificity.

New innovative methods to prevent VAP should be investigated. Development of substances to block adhesion of bacteria to oropharyngeal and gastric mucosa may be of benefit to prevent VAP, rather than antimicrobial prophylaxis. For example, cranberry juice (or its metabolite) can prevent adhesion of enteric coliform bacteria to the uroepithelium and has been shown to decrease recurrent urinary tract infections.

A recent study on the long-term prognosis of VAP has shown that the in-hospital mortality was 42.3%, but also the estimated after discharge mortality was substantial at 1, 3, and 5 years, 25.9%, 33.6%, and 44.7%, resperctively.[118] The 5-year estimated mortality of the survivors is just less than 50%. Thus, there should be great impetus for clinicians and intensivists to try and prevent VAP.

Rapid methods to identify and determine antibiotic susceptibility to the organisms causing VAP are needed and should be studied. A recent prospective, randomized study over 2 years in Spain demonstrated the utility of direct E-test (AB Biodisk) of respiratory samples in VAP.[119] In 250 patients with VAP, 167 were enrolled in the direct E-test and 83 in the standard methods of susceptibility, results were available to the clinicians with a mean of 1.4 days by direct E-test versus 4.2 days by the standard method. This method of rapid antimicrobial susceptibility resulted in decreased antibiotic consumption, *C. difficile* colitis, and fewer days on mechanical ventilation with significant cost savings.[119] One of the limitations of

this method is the unreliability of direct E-test with polymicrobial infection.[120] Novel molecular technologies, using real-time PCR and peptide nucleic acid fluorescent in situ hybridization (PNA-FISH), are now available that can provide rapid identification of resistant bacteria such as MRSA in 1 h.[121] These techniques need to be studied in respiratory secretions of VAP and would facilitate more targeted therapy, less utilization of unnecessary agents such as vancomycin. This would likely improve outcome with less superinfection and predisposition to proliferation of resistant bacteria.

Should a newer macrobide be used in combination with other antimicrobials for VAP with sepsis? Atypical microorganisms are rare causes of VAP or nosocomial pneumonia, except for the occasional case and local mini-outbreaks of legionella pneumonia and, thus, macrolides are not routinely used for VAP. However, there is evidence that some macrolides (e.g., clarithromycin) have anti-inflammatory properties by inhibiting the biosynthesis of proinflammatory cytokines in mononuclear cells in vitro an in vivo. In a recent randomized, blinded, multicenter trial clarithromycin 1 g/day for 3 days was compared to placebo in 200 patients with VAP.[122] Clarithromycin accelerated the resolution of VAP (5.5 days earlier, $p = 0.011$) and weaning from mechanical ventilation (6.5 days earlier, $p = 0.049$) but did not improve survival. Thus larger RCTs are warranted to confirm these results.

New endotracheal tubes silver coated internally and externally may be of value to prevent VAP, as the silver ion microdispersed in the proprietary polymer exert sustained antimicrobial effect that can block biofilm formation at the surface. In a recent prospective, randomized, single-blind controlled study of 9417 adults intubated for 24 h the prevalence of VAP declined from 7.5% in controls versus 4.8% in the silver-coated endotracheal tube group, $p = 0.005$.[123] There were a few limitations of this trial including not blinding the investigators, and imbalance of patients with chronic obstructive lung disease favoring the study group.[124] Thus further blinded larger studies with cost-effective analysis are needed; moreover, this trial did not demonstrate decrease in mortality, ICU or hospital stay and duration of intubation.

References

1. Bueno-Cavanillas, A., Delgado- Rodriguez, M., Lopez-Luque, A., Schaffinocano, S., Galvez-Vargas, R., (1994), Influence of nosocomial infection on mortality rate in intensive care unit. Unit Core Med. 22:55–60.
2. Ginou, E., Stephen, F., Novara, A., Safor, M., Fagon, J.Y., (1998), Risk factors and outcome of nosocomial infections: results of a matched case-control study of ICU patients. Am. J. Respir. Crit. Care. Med. 157:1151–1158.
3. Rello, J., Quintana, E., Ausina, V., Castella, J., Luquin, M., Net., A., Prats, G., (1991), Incidence, etiology and outcome of nosocomial pneumonia in mechanically ventilated patients. Chest 100:439–444.
4. Fagon, J.Y., Chastre, J., Vuagnat, A., Trouillet, J.L., Novora, A., Gilbert, C., (1996), Nosocomial pneumonia and mortality among patients in intensive care unit. JAMA 275:866–869.

5. Vincent, J.L., Bihari, D.J., Suter, P.M., Bruining, H.A., White, J., Nicholas-Chanoin, M.H., Wolff, M., Spencer, R.C., Hemmer, M., (1995), The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee.JAMA 274:639–644.
6. Potgieter, P.D., Linton, D.M., Oliver, S., Forder, A.N., (1987), Nosocomial infections in a respiratory intensive care unit. Crit. Care. Med. 15:495–498.
7. Chastre, J., Fagon, J.Y., Trouillet, J.L., (1995) Diagnosis and treatment of nosocomial pneumonia in patients in intensive care units. Clin. Infect. Dis. 21(Suppl. 3):S226–S237
8. Fagon, J.Y., Chastre, J., Hance, A.J., Montravers, P., Novara, A., Gilbert, C., (1993), Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. Am. J. Med. 94:281–288.
9. Crouch, B.S., Wunderink, R.G., Jones, C.B., Leeper, K.V.J., (1996) Ventilator associated pneumonia due to *Pseudomonas aeruginosa*. Chest 109:1019–1029.
10. Dodek, P., Keenan, S., Cook, D., Heyland, D., Jacka, M., Hand, L., Muscedere, J., Foster, D., Mehta, N., Hall, R., Bun-Buisson, C., For the Canadian Critical Care Trials Group and The Canadian Critical Care Society, (2004), Evidence based clinical practice guideline for the prevention of ventilator associated pneumonia. Ann. Intern. Med 141:305–313.
11. Safdar, N., Dezfulian, C., Collard, H.R., Saint, S., (2005), Clinical and economic consequences of ventilator associated pneumonia: a systematic review. Crit. Care. Med. 33:2184–2193.
12. Fabregas, N., Ewig, S., Torres, A., El-Ebiary, M., Ranirez, J., dela Bellacusa, J.P., Bauer, T., Cabello, H., (1999), Clinical diagnosis of ventilator associated pneumonia revisited: comparative validation using immediate post-mortem lung biopsies. Thorax 54:867–873.
13. Torres, A., Ewig, S., (2004), Diagnosing ventilator associated pneumonia. N. Engl. J. Med. 350:433–435.
14. Pugin, J., Anckenthaler, R., Mili, N., Janssens, J.P., Lew, P.D., Suter, P.M, (1991), Diagnosis of ventilator associated pneumonia by bacteriologic analysis of bronchoscopic and non-bronchoscopic "blind" bronchoalveolar lavage fluid. Am. Rev. Respir. Dis. 143:1121–1129.
15. Richards, M.J., Edwards, J.R., Culver, D.H., David, H., Gaynes, R., (1999), Nosocomial infection in medical intensive care unit in the United States. National Nosocomial Infections Surveillance System. Crit. Care Med. 27:887–892.
16. Carlet, J., Ben Ali, A., Chalfine, A., (2004), Epidemiology and control of antibiotic resistance in the intensive care unit. Curr. Opin. Infect. Dis. 17:309–316.
17. Gaynes, R., Edwards, J.R., (2005), Overview of nosocomial infections caused by gram-negative bacilli. Clin. Infect. Dis. 41:848–854.
18. Marquette, C., Georges, H., Wallet, F., Ramon, P., Saulnier, F., Neviere, R., Mathieu, D., Rime, A., Tonnel, A.B., (1993), Diagnostic efficiency of endotracheal aspirates with quantitative bacterial cultures in intubated patients with suspected pneumonia. Am. Rev. Respir. Dis. 148:138–144.
19. el-Ebiary, M., Torre, A., Gonzales, J., dela Bellacasa, J.P., Garcia, C., Jimenez de Anta, M.T., Ferrer, M., Rodriguez-Roisin, R., (1993), Quantitative cultures of endobronchial aspirates for the diagnosing of ventilator associated pneumonia. Am. Rev. Respir. Dis. 148:1552–1557.
20. Mondi, M.M., Chang, M.C., Bowton, C.L., Kiglo, P.D., Meredith, J.W., Miller, P.R., (2005), Prospective comparison of bronchial-alveolar lavage quantitative deep –tracheal aspirate in the diagnosis of ventilator associated pneumonia. J. Trauma-Injury Infect. Crit. Care. 59:891–895.
21. Borderon, E., Leprince, A., Guevelier, C., Borderon, J., (1981), Valeirs des examenes barteriologiques des secretions tracheales. Rev. Fr. Mal. Resp. 9:229–239.
22. Meduri, G.U., Chastre, J., (1992), The standardization of bronchoscopic techniques for ventilator-associated pneumonia. Chest 102(Suppl. 1):5575–5645.
23. Meduri, G.U., Beals, D.H., Maijub, A.G., Baselski, V.L., (1991), Protested bronchoalveolar lavage: a new bronchoscopic technique to retrieve uncontaminated distal airway secretions. Am. Rev. Respir. Dis. 143:855–864.

24. Chastre, J., Fagon, J.Y., Soler, P., Bornet, M., Domart, Y., Trouillet, J.L., Gibert, C., Hance, A. J., (1988), Diagnosis of nosocomial bacterial pneumonia in intubated paitents undergoing ventilation: comparison of the usefulness of bronchoalveolor lavage and the protected specimen brush. Am. J. Med. 85:499–506.
25. Chastre, J., Fagon, J.Y., Soler, P., Domart, Y., Pierre, J., Dombret, M.C., Gibert, C., Hance, A. J., (1989), Quantitation of BAL cells containing intracellular bacteria rapidly identifies ventilated patients with nosocomial pneumonia. Chest 95(Suppl.):1905–1925.
26. Jourdain, B., Jolly-Guillou, M.L., Dombret, M.C., Calvat, S., Trouillet, J.L., Gibert, C., Chastre, J., (1993), Usefullness of quantitative cultures of BAL fluid for diagnosing nosocomial pneumonia in ventilated patients. Chest 103:1017–1022.
27. de Jaeger, A., Litalien, C., Lacroix, J., Guertin, M.C., Infante-Rivard, C., (1999), Protected specimen brush or bronchoalveolar lavage to diagnose nosocomial pneumonia in ventilated adults: a meta-analysis, Crit. Care Med. 27:2548–2560.
28. Brun-Buisson, C., Fartoukh, M., Lechapt, E., Honore, S., Zahar, J.R., Cerf, C., Maitre, B., (2005), Contribution of blinded, protected quantitative specimens to the diagnosis and therapeutic management of ventilator associated pneumonia. Chest 128:533–544.
29. Mentec, H., May-Michelangeli, L., Rabbat, A., Varon, E., Le Turdu, F., Bleichner, G., (2004), Blind and bronchoscopic sampling methods on suspected ventilator associated pneumonia. A multicentre prospective study. Inten. Care Med. 30:1319–1326.
30. Wood, A.Y., Dovit, A.J. 2nd, Ciraulo, D.L., Ays, N.W., Richart, O.M., Maxwell, R.A., Baxer, D.E., (2003), A prospective assessment of diagnostic efficacy of blind protective bronchial brushings compared to bronchoscope-assisted lavage, bronchoscope-directed brushing, and blind and endotracheal aspirates in ventilator associated pneumonia. J. Trauma-Injury Infect. Crit. Care: 55:825–834.
31. Butler, K.L., Best, I.M., Oster, R.A., Katon-Benitez I., Lyn Weaver, W., Bumpers, H.L., (2004), Is bilateral protected specimen brush sampling necessary for the accurate diagnosis of ventilation-associated pneumonia. J. Trauma-Injury Infect. Crit. Care: 57:316–322.
32. Michaud, S., Suzuki, S., Harlarth, S., (2002), Effect of design-related bias in studies of diagnostic tests for ventilated pneumonia. Am. J. Respir. Crit. Care Med. 166:1320–1325.
33. Chastre, J., Viau, F., Brum, P., Pierre, J., Dauge, M.C., 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.
34. Rouby, J.J., De Lassale, E.M., Poete, P., Nicolas, M.H., Bodin, L., Jarlier, V., Le Carpentier, Y., Grosset, J., Viars, P., (1992), Nosocomial bronchopneumonia in the critically ill. Histologic and bacteriologic aspects. Am. Rev. Respir. Dis. 146:1059–1066.
35. Torres, A., el-Ebiary, M., Padro, L., Gonzalez, J., De La Bellacasa, J.P., Ramirez, J., Xaubet, A., Ferrer, M., Rodriguez-Roisin, R., (1994), Validation of different techniques for the diagnosis of ventilator-associated pneumonia. Am. J. Respir. Crit. Care Med. 149:324–331.
36. Chastre, J., Fagon, J.Y., Barnet-Lecso, M., Calvat, S., Dombret, M.C., Al Khani, R., Basset, f., Gibert, C., (1995), Evaluation of broncoscopic techniques for the diagnosis of nosocomial pneumonia. Am. J. Respir. Crit. Care Med. 152:231–240.
37. 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.
38. Marquette, C.H., Copin, M. C., Wallet, F., Neviere, R., Saulnier, F., Mathieu, D., Dirocher, A., Ramon, P., Tonnel, A.B., (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.
39. Kirtland, S.H., Corley, D.E., Winterbauer, R.H., Springmeyer, S.C., Casey, K.R., Hampson, N.B., Dreis, D.E., (1997), The diagnosis of ventilator associated pneumonia: a comparison of histologic, microbiologic, and clinical criteria. Chest 112:445–457.

40. Bregeon, F., Papazian, L., Thomas, P., Corret, V., Garbe, L., Saux, P., Drancourt, M., Auffray, J.P., (2000), Diagnostic accuracy of protected catheter sampling in ventilator associated bacterial pneumonia. Eur. Respir. J. 16:969–975.
41. Torres, A., Fabregas, N., Ewig, S., de la Bellacasa, J.P., Bauer, T.T., Ramirez, J., (2000), Sampling methods for ventilator associated pneumonia: validation using different histologic and microbiological references. Crit. Care Med. 28:2799–2804.
42. Balthazor, A.B., Von Nowakonski, A., De Copitani, E.M., Bottini, P.V., Terzi, R.G.G, Araujo, S., (2001), Diagnostic investigation of ventilator associated pneumonia using bronchoalveolar lavage: comparative study with a postmortem lung biopsy. Brazilian J. Med. Biolog. Res. 34:993–1001.
43. Moser, K.M., Maurer, J., Jassy, L., Kremsdorf., R., Konopka, R., Share, D., Hurrell, J.H., (1982), Sensitivity, specificity, and risk of diagnostic procedures in a canine model of *Sreptococusl pneumoniae* pneumonia. Am. Rev. Respir. Dis. 125:436–442.
44. Johanson, W.G.Jr, Seidenfeld, J.R., Gomez, P., De Los Santos, R., Coalson, J.J., (1988), Bacteriologic diagnosis of nosocomial pneumonia following prolonged mechanical ventilation. Am. Rev. Respir. Dis. 137:259–264.
45. Rello, J., Paiva, J.A., Baraibor, J., Barcenilla, F., Bodi, M., Castander, D., Correa, H., Diaz, E., Garnacho, J., Llorio, M., Rios, M., Rodriguez, A., Sol-Violan, J., (2001), International Conference for the Development of Consensus on the Diagnosis and Treatment of Ventilator associated pneumonia. Chest 120:955–970.
46. The Canadian Critical Care Trials Group, (2006), A randomized trial of diagnostic techniques for ventilator-associated pneumonia. N, Engl. J. Med. 335:2619– 2630.
47. Duflo, E., Debon, R., Monneret, G, Bienvenu, J., Chassard, D., Allaouchiche, B., (2002), Alveolar and serum procalcitonin: diagnostic and prognostic value in ventilator-associated pneumonia. Anesthesiology 96:74–79.
48. Brunkhorst, F.M., Al-Nawas, B., Krummenauer, F., Forycki, Z.F., Shah, P.M., (2002), Procalcitonin, C – reactive protein, APACHE II Score for risk evaluation in patients with severe pneumonia. Clin. Microbiol. Infect. 8:93–100.
49. Fukushuma, R., Alexander, J.W., Gianotti, L., Ogle, C.K., (1994), Isolated pulmonary infection acts as a source of systemic tumor necrosis factor. Crit. Care Med. 22:114–120.
50. Wu, C.L., Lee, L.Y., Chang, K.M., King, S.L., Chiang, C.D., Niederman, M.S., (2003), Bronchoalveolar interleukin I β: a marker of bacterial burden in mechanically ventilated paitents with community acquired pneumonia. Crit. Care Med. 31:812–817.
51. Bonten, M.J., Froon, A.H., Gaillard, C.A., Greve, J.W., Drent, M., Stobberingh, E.E., Buurman, W.A., (1997), The systemic inflammatory response in the development of ventilator associated pneumonia. Am. J. Respir. Crit. Care Med. 156:1105–1113.
52. Bouchon, A., Dietrich, J., Colonna, M., (2000), Inflammatory responses can be triggered by TREM-1, a novel receptor expressed in neutrophils and monocytes. J. Immunol. 164:4991–4995.
53. Bouchon, A., Facchetti, F., Weigand, M.A., Colonna, M., (2001), TREM-1 amplifies inflammation and is a critical mediator of septic shock. Nature 410:1103–1107.
54. Gibot, S., Kolopp-Sarda, M.N., Béné, M.C., Cravoisy, A., Levy, B., Faure, G.C., Bollaert, P. E., (2004), Plasma level of a triggering receptor expressed on myeloid cells-1: Its diagnostic accuracy in patients with suspected sepsis. Ann. Intern. Med. 141:9–15.
55. Gibot, S., Cravoisy, A., Levy, B., Béné, M.C., Faure, G., Bollaert, P.E., (2004), Soluble triggering receptor expressed on myeloid cells and the diagnosis of pneumonia. N. Engl. J. Med. 350:451–458.
56. Determann, R.M., Miller, J.L., Gibot, S., Korevaar, J.C., Vroom, M.B., van der Poll, T., Garrard, C.S., Schultz, M.J., (2005), Serial changes in soluble triggering receptor expressed on myeloid cells in the development of ventilator-associated pneumonia. Intern. Care Med. 31:1495–1500.

57. Combes, A., Figliolini, C., Trouillet, J.L., Kasis, N., Wolff, M., Gibert, C., Chastre, J., (2002), Incidence and outcome of polymicrobial ventilator-associated pneumonia. Chest 121:1390–1391.
58. Dor, P., Robert, R., Grollier, G., Rouffineau, J., Languetot, H., Charries, J.M., Fauchere, J.L., (1996), Incidence of anaerobes in ventilator-associated pneumonia with use of a protected specimen brush. Am. J. Respir. Crit. Care Med. 153:1292–1298.
59. Park, D.R., (2005), Microbiology of ventilator-associated pneumonia. Respir. Care 50: 742–763.
60. Woody, A.Y., Davit, A.J. 2nd, Ciraulo, D.L., Arp, N.W., Richart, C.M., Maxwell, R.A., Barker, D.E., (2003), A prospective assessment of diagnostic efficacy of blind protective bronchial brushings compared to bronchoscope assisted lavage, bronchoscope-directed brushings, and blind endotracheal aspirates in ventilator-associated pneumonia. J. Trauma-Injury Infect. Crit. Care 55:825–834.
61. Elatrous, S., Boukef, R., Ouanes Besbes, L., Marghli, S., Noonan, S., Nouira, S., Abroug, F., (2004), Diagnosis of ventilator-associated pneumonia: agreement between cultures of endotracheal aspiration and plugged telescoping catheter. Intern. Care Med. 30:853–858.
62. Heyland, D.K., Cook, D.J., Marshall, J., Heule, M., Guslits, B., Lang, J., Jaeschke, R., (1999), The clinical utility of invasive diagnostic techniques in the setting of ventilator associated pneumonia. Canadian Critical Care Trial Groups. Chest 115:1076–1084.
63. Fagon, J.Y., Chastre, J., Wolff, M., Gervais, C., Parer-Aubas, S., Stephan, F., Similowski, T., Mercat, A., Diehl, J.L., Sollet, J.P., Tenaillon, A., (2000), Invasive and non-invasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. Ann Interm. Med. 132:621–630.
64. Ruiz, M., Torres, Ewig, S., Marcos, M.A., Alcon, A., Lledo, R., Asenjo, M.A., Maldonaldo, A., (2000), Non-invasive versus invasive microbial investigation in ventilator-associated pneumonia. Am. J. Respir. Crit. Care Med. 162:119–125.
65. Ioanas, M., Ferrer, R., Angrill, J., Ferrer, M., Torres, A., (2001), Microbial investigation in ventilator-associated pneumonia. Europ. Respir. 17:791–801.
66. Shorr, A.F., Sherner, J.H., Jackson, W.1., Kollef, M.H., (2005), Invasive approaches to the diagnosis of ventilator-associated pneumonia: a meta-analysis. Crit. Care Med. 33:46–53.
67. Luna, C.M., Vujacich, P., Niederman, M.S., Vay, C., Gherardi, C., Matera, J., Jolly, E.C., (1997), Impact of BAL data on therapy and outcome of ventilator-associated pneumonia. Chest 111:676–685.
68. Ibrahim, E.H., Sherman, G., Ward, S., Fraser, V.J., Kollef, M.H., (2000), The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest 118:146–155.
69. Davis, K.A., Eckert, M.J., Reed, R.L., 2nd, Esposito, T.J., Santaniello, J.M., Poulakidas, S., Luchette, F.A., (2005), Ventilator-associated pneumonia in injured patients: do you trust your Gram's-stain? J. Trauma-Injury Infect. Crit. Care 58:462–466.
70. Laupland, K.B., Church, D.L., Gregson, D.B., (2005), Validation of a rapid diagnostic strategy for determination of significant bacterial counts in bronchoalveolar lavage samples. Arch. Pathol. Lab. Med. 129:78–81.
71. Flanagan, P.G., Jackson, S.K., Findlay, G, (2001), Diagnosis of gram negative, ventilator-associated pneumonia by assaying endotoxin in bronchial lavage fluid. J. Clin. Pathol. 54:107–110.
72. Ibrahim, E.H., Ward, S., Sherman, G., Kollef, M.H., (2000), A comparative analysis of patients with early-onset vs late onset nosocomial pneumonia in the ICU setting. Chest 117:1434–1442.
73. Hayon, J., Figliolini, C., Combes, A., Trouillet, T.L., Kassis, N., Dombret, M.C., Gibert, C., Chastre, J., (2002), Role of serial routine microbiologic culture results in the initial management of ventilator-associated pneumonia. Am, J. Respir. Crit. Care Med. 165:41–46.

74. American Thoracic Society, Infectious Disease Society of America, (2005), ATS/IDSA: guidelines for the management of hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am. J. Respir. Crit. Care Med. 171:388–416
75. National Nosocomial Infection Surveillance, (2004), System report: data summary from January 1992 thorough June 2004, issue October 2004. Am. J. Infect. Control 41:848–854
76. Beardsley, J.R., Williamson, J.G., Johnson, J.W., Ohl, C.A., Karehmer, TB, Bowton, D.L., (2006), Using local microbiologic data to develop institution-specific guidelines for the treatment of hospital-acquired pneumonias. Chest 130:787–793.
77. Peterson, D.L., Rice, L.B., (2003), Empirical antibiotic choice for the seriously ill patient: are minimization of selection of resistant organisms and maximization of individual outcome mutually exclusive? Clin Infect. Dis. 36:1006–1012.
78. Chastre, J., Wolff, M., Fagon, J.Y., Chevret, S., Thomas, F., Wermert, D., Clementi, E., Gonzalez, J., Jusserand, D., Asfar, P., Perrin, D., Fieux, F., Aubas, S., (2003), Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA 290:2588–2598.
79. Singh, N., Rogers, P., Atwood, C.W., Wagener, M.M., Yu, V.L., (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: 205–211.
80. Brown, R.B., Kruse, J.A., Counts, G.W., Russell, J.A., Christou, N.V., Sards, M.L, and The Endobronchial Tobramycin Study Group. (1990), Double-blind study of endobronchial tobramycin in the treatment of gram-negative bacterial pneumonia. Antimicrob. Agents Chermother. 34:269–272.
81. Le Conte, P., Potel, G., Clementi, E., Legras, A., Villars, D., Bironneau, E., Cousson, J., Baron, D., (2000), Administration d'aerosols de tobramycine chez des patients ayant une pnemopathie nosocomiable: etcide preliminaire. RESSE Med. 29:76–78.
82. Munoz-Price, L.S., Weinstein, R.A., (2008), Acinetobacter infection. N. Engl. J. Med. 358: 1271–1281.
83. Carey, R.B., Banerjee, S.N., Srinivasan, A., (2006), Multidrug-resistant acinetobacter infection. 1995–2004. 46th Intersc. Conf. Antimicrob. Agents Chemother, San Francisco Calif. Sept. 27–30, Abstract.
84. Hess, D.R., (2005), Noninvasive positive-pressure ventilation and ventilator-associated pneumonia. Respir. Care; 50:924–929.
85. Sinciff, T., Cook, D.J., (2003), Health technology assessment in the ICU: noninvasive positive pressure ventilation for acute respiratory failure. J. Crit. Care 18:59–67.
86. Antonelli, M., Conti, G., Moro, M.L., Esquinas, A., Gonzalez-Diaz, G., Confalonieri, M., Proietti, R., Passariello, M., Meduri, G.U., (2001), Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxic respiratory failure: a multi-centre study. Intern. Care Med. 27:1718–1728.
87. Hess, D.R., (2005), Patient positioning and ventilator-associated pneumonia. Respir. Care 50:892–898.
88. Choi, S.C., Nelson, LD., (1992), Kinetic therapy in critically ill patients: combined results based on meta-analysis. J. Crit. Care 7:57–62.
89. Collard, H.R., Saint, S., Matthay, M.A., (2003), Prevention of ventilator-associated pneumonia: an evidence-based systemic review. Ann. Intern. Med. 138:494–501.
90. Guerin, C., Gaillard, S., Lemasson, S., Ayzac, L., Girord, R., Beuret, P., Palmier, B., Le, Q.U., Sirodot, M., Rosselli, S., Cadiergue, V., Sainty, J.M., Barbe, P., Combourieu, E.O., Renault, A., Sibille, J.P., Kaidomar, M., (2004), Effects of systematic prone positioning in hypoxic acute respiratory failure: a randomized controlled trial. JAMA 292:2379–2387.
91. Drakulovic, M.B., Torres, A., Bauer, T.T., Nicolas, J.M., Nogue, S., Ferrer, M., (1999), Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomized trial. Lancet 354:1851–1858.

92. Tablan, O.C., Anderson, L.J., Bescer, R., Bridges, C., Hajjeh, R., CDC. Healthcare Infection Control Practices Advisory Committee, (2003), Guidelines for preventing health-care-associated pneumonia: recommendations of CDL and the Healthcare Infection Control Proactive Advisory Committee. M.M.W.R 53:1–36.
93. van Nieuwenhoven, C.A., Vandenbroucke-Grauls, C., van Tiel, F.H., Joone, H.C., van Schijndel, R.J., van der Tweel, I., Ramsay, G., Bonten, M.J., (2006), Feasibility and effects of the semirecumbent position to prevent ventilator-associated pneumonia: a randomized study. Crit. Care Med. 34:559–561.
94. Wang, J.Y., Chuang, P.Y., Lin, C.J., Yu, C.J., Yang, P.C., (2003), Continuous lateral rotational therapy in the medical intensive care unit. J. Formosan Med. Assoc. 102:788–792.
95. Ntoumenopoulos, G., Presneill, J.J., McElholum, M., Code, J.F., (2002), Chest physiotherapy for the prevention of ventilator-associated pneumonia. Intern. Care Med. 28:850–856.
96. Klastersky, J., Huysmans, E., Weerts, D., Hensgens, C., Daneau, D., (1974), Endotracheally administered gentamicin for the prevention of infections of the respiratory tract in patients with tracheotomy: a double blind study. Chest 65:650–654.
97. Libérati, A., D'Amico, R., Pifferi, Torri, V., Brazzi, L., (2004), Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. Cochrane Database Systemic Reviews CD000022: PMID 14973945.
98. Bonten, M.J., Kullberg, B.J., van Dalen, R., Girbes, A.R., Hoepelman, I.M., Hustrix, W., van der Meer, J.W., Speelman, P., Stobberingh, E.E., Verbrugh, H.A., Verhoef, J., Zwaveling, J. H., (2000), Selective digestive decontamination in patients in intensive care. The Dutch Working Group on Antibiotic Policy. J. Antimicrob. Chemother 43:351–362.
99. Kollef, M.H., (2003), Selective digestive decontamination should not be routinely employed. Chest 123(Suppl. 5):4645–4685.
100. Kallet, R.H., Quinn, T.E., (2005), The gastrointestinal tract and ventilator-associated pneumonia. Respir. Care 50:910–921.
101. Munro, C.L., Grap, M.L., (2004), Oral health and care in the intensive care unit: state of the science. Am. J. Crit. Care 13:25–33.
102. DeRiso, A.J., Jr, Ladowski, J.S., Dillon, T.A., Justice, J.W., Peterson, A.C., (1996), Chlorhexidine gluconate 0.12% oral rinse reduces the incidence of total nosocominal respiratory infection and nonprophylactic systematic antibiotic use in patients undergoing heart surgery. Chest 109:1556–1561.
103. Houston, S., Hougland, P., Anderson, J.J., LaRocco,M., Kennedy, V., Gentry, L.O., (2002), Effectiveness of 0.12% chlorhexidine gluconate oral rinse in reducing prevalence of nosocominal pneumonia in patients undergoing heart surgery. Am. J. Crit. Care 11:567–570.
104. Genuit, T., Bochicchio, G., Napolitano, L.M., McCarter, R.J., Roghman, M.C., (2001), Prophylactic chlorhexidine oral rinse decreases ventilator-associated pneumonia in surgical ICU patients. Surg. Infect. 2:5–18.
105. Fourrier, F., Dubios, D., Pronnier, P., Herberg, P., Leroy, O., Desmettre, T., Potier-Cau, E., Boutigny, H., Di Pompeo, C., Durocher, A., Roussel-Delvallez, M., PIRAD Study Group, (2005), Effect of gingival and dental plague antiseptic decontamination on nosocomial infections acquired in the intensive care unit: a double-blind placebo-controlled multicentre study. Crit. Care Med. 33:1867–1868.
106. Tulamait, A., Laghi, F., Mikrut, K., Carey, R.B., Budinger, G.R., (2005), Potassium sorbate reduces gastric colonization in patients receiving mechanical ventilation. J. Crit. Care 20:281–287.
107. Heyland, D.K., Cook, D.J., Schoenfeld, P.S., Frietag, A., Varon, J., Wood, G., (1999), The effect of acidified enteral feeds on gastric colonization in critically ill patients: results of a multicentre randomized trial. Canadian Critical Care Trials Group. Crit. Care Med. 27: 2399–2406.
108. Dezfulian, C., Shojania, K., Collard, H.R., Kim, H.M., Matthay, M.A., Saint, S., (2005), Subglottic secretion drainage for preventing ventilator-associated pneumonia: a meta-analysis. Am. J. Med. 118:11–18.

109. Blunt, M.C., Young, P.J., Patil, A., Haddock, A., (2001), Gel lubrication of the tracheal cuff reduces pulmonary aspiration. Anesthesiology 92:377–381.
110. Ibanez, J., Penafiel, A., Morse, P., Jorcla, R., Raurich J.M., Mata, F., (2000), Incidence of gastroesophageal reflux and aspiration in mechanically ventilated patients using small-bore nasogastric trials. J. Parenteral Enteral Nutr. 24:103–106.
111. Kearns, P.J., Chin, D., Mueller, L., Wallace, K., Jensen, W.A., Krisch, C.M., (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.
112. Heyland, D.K., Drover, J.W., Dhaliwad, R., Greenwood, J., (2002), Optimizing the benefits and minimizing the risks of enteral nutrition in the critically ill: role of small bowel feeding. J. Parenter. Enteral. Nutr. 26:551–555.
113. Marik, P.E., Zaloga, G.P., (2003), Gastric versus post-pyloric feeding: a systematic review. Crit. Care Med. 7:46–51.
114. Kostadima, E., Kaditis, A.G., Alexopoulos, E.I., Zakynthinos, E., Sfyras, D., (2005), Early gastrostomy reduces the rate of ventilator-associated pneumonia in stroke or head injury patients. Eur. Respir. J. 26:106–111.
115. Kola, A., Eckmanns, T., Gastmeier, P., (2005), Efficacy of heat and moisture exchangers in preventing ventilator-associated pneumonia: meta-analysis of randomized controlled studies. Intern. Care Med. 31:5–11.
116. Combes, P., Fauvage, B., Oleyer, C., (2000), Nosocominal pneumonia in mechanically ventilated patients, a prospective randomized evaluation of the stericath closed suctioning system. Intern. Care Med. 26:878–882.
117. Lorente, L., Lecuona, M., Martin, M.M., Garcia, C., Mora, M.L., Siera, A., (2005), Ventilator-associated pneumonia using closed versus an open tracheal suction system. Crit. Care Med. 33:115–119.
118. Ranes, J.L., Gordon, S.M., Chen, P., Fatica, C. Hammel, J., Gonzales, J.P., Arroliga, A.C., (2006), Predictors of long-term mortality in patients with ventilator-associated pneumonia. Am. J. Med. 119:897.e13–19.
119. Bouza, E., Torres, M.V., Radice, C., Cercenado, E., deDiego, R., Sánchez-Carrillo, C., Munoz, P., (2007), Direct e-test (AB Biodisk) of respiratory samples improves antimicrobial use in ventilator-associated pneumonia. Clin. Infect. Dis. 44:382–387.
120. Kollef, M.H., (2007), Moving towards real-time antimicrobial management of ventilator associated pneumonia. Clin. Infect. Dis. 44:388–390.
121. Tenover, F.C., (2007), Rapid detection and identification of bacterial pathogens using novel molecular technologies, Infection control and beyond. Clin. Infect. Dis. 44:418–423.
122. Giamarellos-Bourboulis, EJ, Pechére. J-C, Routsi, C, Plachouras, T, Kollias, S, Raftogiannis, M, Zeruakis, D, Baziaka, F, Koronaios, A, Antonopoulou, A, Markaki, V, Koutoukas, P, Papadomichelakis, E, Tsaganos,T, Armaganidis, A, Koussoulas, V, Kotanidou, A, Roussos, C, Giamarellou, H, (2008), Effect of clarithromycin in patients with sepsis and ventilator-associated pneumonia. Clin. Infect. Dis. 46:1157–1164.
123. Kollef, A.H., Afessa, B., Anzueto, A., Veremakis, C., Kerr, K.M., Margolis, B.D., Craven, D.E., Roberts, P.R., Arroliga, A.C., Hubmayr, R.D., Restrepo, M.I., Auger, W.R., Schinner, R., for the NASCENT Investigation Group, (2008), Silver-coated endotracheal tubes and incidence of ventilator-associated pneumonia. JAMA: 300:805–813.
124. Chastre, J., (2008), Preventing ventilator-associtaed pneumonia. Could silver-coated endotracheal tube be the answer? JAMA; 300:842–844.