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## Defining, treating and preventing hospital acquired pneumonia: European perspective

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**Abstract** *Introduction:* Many controversies still remain in the management of hospital acquired pneumonia (HAP), and ventilation-acquired pneumonia (VAP). Three European Societies, European Respiratory Society (ERS), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and European Society of Intensive Care Medicine (ESICM), were interested in producing a document on HAP and VAP with European perspective. *Materials and methods:* The scientific committees from each Society designated one chairman; Antoni Torres (ERS), Harmut Lode (ESCMID) and Jean Carlet (ESICM). The chairmen of this Task Force suggested names from each Society to be a member of the panel. They also choose controversial topics on the field and others that were not covered by the last IDSA/ATS guidelines. Each topic was assigned to a pair of members to be reviewed and written. Finally, the panel defined 20 consensual points that were circulated several times among the members of the panel until total agreement was reached. A combination of evidences and clinical-based medicine was used to reach these consensus. *Conclusion:* This manuscript reviews in depth several controversial or new topics in HAP and VAP. In addition 20 consensual points are presented. This manuscript may be useful for the

development of future guidelines and to stimulate clinical research by lying out what is currently accepted and what is unknown or controversial.

**Keywords** Hospital acquired pneumonia · Ventilator-associated pneumonia · Ventilation-acquired pneumonia · Nosocomial pneumonia

### Abbreviations

CDC	Centre for diseases control
HAP	Hospital acquired pneumonia
IAP	ICU acquired pneumonia
VAP	Ventilation-acquired pneumonia
ARDS	Acute respiratory distress syndrome
ERS	European Respiratory Society
ESICM	European Society of Intensive Care Medicine
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
ATS	American Thoracic Society
HELICS	Hospital in Europe link for infection control through surveillance
BAL	Broncho alveolar lavage
PSB	Protected specimen brush
TBA	Tracheo bronchial aspirates
CRP	C Reative protein

PCT	Procalcitonin	NH	Nursing homes	RR	Risk ratio
CPIS	Clinical pulmonary infection score	LOS	Length of stay	RCT	Randomized clinical trials
SDD	Selective digestive decontamination	MRSA	Methicillin resistant <i>Staphylococcus aureus</i>		
ICU	Intensive care unit	ESBL	Extended spectrum $\beta$ lactamases		
LTCF	Long term care facilities	OR	Odd ratio		

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## Introduction

Although thousands of papers have been devoted to hospital-acquired pneumonia (HAP), many controversies remain, and management of HAP is probably often sub-optimal. Several reviews or guidelines have been published recently, mostly by North American initiatives (CDC, ATS) [1–4].

Three European Societies (ERS, ESCMID and ESCIM) were interested in producing a document that could complement in some way the last IDSA/ATS guidelines published 3 years ago. In addition, the Helics working group supported this initiative.

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## Process of the manuscript

The three societies through their respective scientific committees designated one responsible from each society: Antoni Torres (ERS), Hartmut LODE (ESCMID) and Jean Carlet (ESCIM). This committee suggested names from each society to be a member of the panel. These members were re-appointed by the scientific committees. The chairmen of this Task-Force reviewed the last IDSA/ATS guidelines published in 2005 [1] and thought that there were some issues not covered by the guidelines, and some other issues considered important, had to be included. The chairmen proposed the topics and the panel agreed and suggested additional ones.

The following topics were chosen:

1. Definitions and semantic issues
2. HAP and VAP as quality indicators (not covered in the IDSA/ATS guidelines)
3. Microbiology
4. Tracheostomy and VAP (not covered in the IDSA/ATS guidelines)
5. Tracheobronchitis (not covered)
6. Postoperative pneumonia (partially covered in the IDSA/ATS guidelines)
7. Diagnostic strategies
8. Empirical antibiotic treatment
9. Prevention.

Each Topic was assigned to a pair of members to be reviewed and written. Once all sections were available the

document was distributed and the panel met again to define consensual points based on the document. These consensual points (Table 1) were circulated several times among the members of the panel until total agreement was reached.

The rule of Intensive Care Medicine is that a document of this type has to be previously approved by the scientific Committees of the other societies. Thus, the document was sent to ERS and ESCMID for peer review.

We had two revisions from the ERS and one from the ESCMID. Finally, the document was approved by the two societies and sent to Intensive Care Medicine for peer review.

A combination of evidence and clinical-based medicine was used to reach this consensus in a group of 11 experts. Thus, this work is not a guideline or a metaanalysis, but intends to stimulate research by laying out what is currently accepted and what is unknown or controversial.

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## Twenty points which are highly consensual between the 11 European experts

The chairmen of this Task force (Torres, Carlet and Lode) proposed a series of points for consensus. The remaining authors added some others. All these points were circulated two times among experts and finally all of them agreed on them. Points not consented by all experts were not included in these documents (see Table 1).

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## Definition and semantic issues

Pneumonia in ICU patients is mostly due to the aspiration of microorganisms from the nasal, oro-pharyngeal, or gastric flora [5]. These events can occur either before ICU admission, mostly when patients have abnormal upper airway functions due to coma, trauma, or surgery, or after intubation and ICU admission. Therefore, the term ventilator-associated pneumonia (VAP) is not appropriate and should be abandoned. The terms intubation-associated pneumonia for early onset and tube-associated pneumonia for late onset VAP would be more precise. For reasons of simplicity and in order to conserve the

**Table 1** 20 Points which are highly consensual between the eleven European experts

1. Ventilation-acquired pneumonia (VAP) is not due to the ventilator but to the coincidence of several factors (tubes, high likelihood of aspiration of the nasal and oropharyngeal secretions, presence of an underlying morbidity and impairment of the local and systemic host defenses). Thus, the wording VAP is not scientifically logical and should be avoided, and we would like to insist on the change of the term into “ventilation-acquired pneumonia”
2. HAP can happen in patients either not ventilated (under non-invasive ventilation), or intubated or tracheotomized (ventilated or not)
3. Risk factors include intubation, invasive mechanical ventilation, sedation, curarization, coma, trauma, the presence of enteral nutrition, and surgery. All those factors increase the risk for silent aspiration and can reduce lung and host defences
4. Mortality associated with HAP is high, but is mostly related to the underlying condition of the patients. Lung infection often represents the terminal event prior to end of life. In the past, when patients died at home, this event was community-acquired. Nowadays it is frequently hospital-acquired because many patients die in the hospital or in the ICU, often mechanically ventilated. Many HAP events can be regarded as “end of life pneumonia”. Mortality is limited in patients with a reasonably good underlying condition, when an appropriate therapy is started immediately, but can be very high if initial antibiotic therapy is inappropriate
5. Both under- and overtreatment of HAP in particular VAP have detrimental consequences in terms of mortality and microbial selection pressure
6. In most instances, HAP can be diagnosed with reasonable accuracy using clinical, radiological, and bacteriological criteria
7. For diagnosis of VAP in mechanically ventilated patients, both noninvasive tracheobronchial aspirates (TBA) and invasive (protected specimen brush (PSB), bronchoalveolar lavage (BAL) and its modifications) issues work, provided that the samples are quantitatively evaluated. Quantitative cultures are orientative to guide antibiotic therapy. No advantage in terms of length of ICU stay and survival could be consistently shown for an invasive diagnostic strategy
8. Culture procedures must be performed before starting or modifying a previous antimicrobial treatment
9. Samples are preferably analysed within 2–4 h, but can be kept at 4°C up to 24 h if needed
10. Antimicrobial treatment should be started immediately, particularly if the patient is haemodynamically compromised
11. Antimicrobials can be stopped if the samples are negative (provided they were performed before starting antimicrobial treatment), unless the clinical likelihood of VAP is high
12. In VAP, sampling should be performed during therapy (after 72 h) to assess efficacy of antimicrobial treatment and detect resistant strains
13. CPIS is not superior to classical clinical criteria to define suspicion of VAP. However, it is useful to follow the evolution under therapy
14. Biological markers (CRP, PCT) are useful to follow evolution under therapy
15. Subglottic aspiration is effective in preventing VAP, but patients should not be re-intubated just for this purpose
16. Semi-recumbent position is an effective preventive measure, but data are still limited, and 45° inclination is often not realistic. It is likely that a 30° inclination is equally effective
17. SDD alone in surgical patients works in reducing the risk of HAP, but does not reduce mortality. The preventive approach using SDD plus short-term systemic intravenous antimicrobial treatment should not be called SDD
18. SDD reduces the incidence of VAP, but the effects on mortality are still controversial. There are indications that there is a lower mortality in surgical patients without increasing antimicrobial resistance (or even decreasing it) in countries with a low resistance level to antimicrobial agents. It should be tested in patients with high resistance level and high risk of exogenous infection
19. A short course of intravenous antimicrobial treatment without SDD could work as well. It was studied only once in comatose patients and this should be confirmed
20. When assessing quality of care, early HAP (less than 4 days after admission in the hospital) should not be taken into account, unless pre-emptive antimicrobial treatment becomes a recommendation, in particular in patients with a high risk of very early, or even pre-hospital aspiration

acronym, ventilation-acquired pneumonia (VAP) may be the best term.

Pneumonia which occurs early in the course of ICU stay is addressed as “early onset pneumonia” [6]. However, it is unknown what is the best cut off to separate early from late onset pneumonia, since we do not know how long it takes to develop pneumonia after aspiration of micro-organisms. The cut off of 4 days has been used by several authors [6]; others have used 7 days [7].

When the concept of early and late onset pneumonia is applied, it is essential to rely on hospital admission (and not intubation) as day one. Otherwise, when intubation occurs after hospital admission, nosocomial colonization of the upper airways may have already occurred and consequently pneumonia may be caused by pathogens typically associated with late onset pneumonia.

A new category of infections has been defined recently by the ATS guidelines, belonging to the broad category of

health care associated infections, but happening outside the hospital itself (in particular in long term care facilities), mostly in patients recently discharged from the hospital [8–10]. These infections can be due to “community” micro-organisms, but also to hospital and resistant strains. The antimicrobial strategy must keep this confounder into account. However, a redefinition of health-care associated pneumonia (HCAP) is needed, particularly in terms of risk factors and microbial etiology.

In most reports, it is not known if ICU-acquired pneumonia happens in patients coming from home, from another ward in the hospital, another hospital or long-term care facilities. From an ecological standpoint, only pneumonia occurring shortly after hospital admission should be called early onset pneumonia. In fact, the micro-organisms responsible will also depend on the contacts the individual patient had with the health care network (and not only the hospital).

By opposition, pneumonia happening later in the course of ICU stay is called “late onset pneumonia”. Late onset pneumonia is probably more closely related to quality of care although it is difficult to prevent in the most severely compromised patients. Some pneumonia events occur as a terminal event of a finally fatal disease [11]. Many of these cases are not preventable and should be called end of life nosocomial pneumonia.

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### **Challenges in the definitions and rates of nosocomial infections: can we use them as quality indicators?**

Hospital acquired pneumonia (HAP) and VAP are often considered as events that could have been prevented if the quality of care had been optimal. The rates of nosocomial infections, when available, are sometimes immediately used to compare units or countries in a benchmarking philosophy [12]. Although using nosocomial infections rates to assess a quality improvement program in a given unit is possible [13, 14], comparing unit or countries is still very problematic [12].

Definitions of HAP and VAP have not been initially designed for quality assessment purposes [15, 16]. An extensive tailoring of definitions is absolutely mandatory if we want to use rates for quality purposes with some level of credibility [17–19]. In particular, early onset VAP is mostly due to aspiration of commensal micro-organisms, happening most often before ICU admission and intubation [6, 20]. Thus, most of those events are not related with poor quality of care. Some cases HAP happen in very old patients in nursing home or long term care facilities and are due to aspirations that are difficult to prevent. Those HAP are end of life events. Similarly, we do not know which postoperative HAP is really correlated with quality issues. Therefore it is better to use process indicators to measure the quality of care.

Lung and general defences of the host play a dramatic role in the development of HAP. For a given inoculum of bacteria or viruses in the distal lung, the risk for developing pneumonia is certainly heavily influenced by local and general defences. Again, those factors are not related to quality of care and create a dramatic noise when analysing and comparing HAP rates.

The risk of late onset VAP is very high in the most severely disabled patients staying in the ICU, and attributable mortality is likely to be overestimated, as demonstrated for catheter-related bacteremias [21] since adjustment is usually done only with admission parameters and does not take in to account the trends towards severity during the stay.

When trying to compare units using any quality indicator as standardized mortality ratio (SMR), nosocomial or iatrogenic events rates, a very careful adjustment for case mix is needed [22–24]. Unfortunately, this is rarely done in available studies or network results. For example, rates of nosocomial infections were compared between countries within the EPIC study without any adjustment for case mix [12]. As an example, length of stay (LOS) in the ICU is a strong risk factor for VAP [20] and there is a logical and clear-cut relationship between nosocomial infection rates and LOS. However, LOS is surprisingly dramatically different between units or even countries [12].

In order to compare VAP rates and try to relate this to quality issues, a very sophisticated adjustment for many different risk factors is needed. The number of ventilator days which has been proposed as the reference method to calculate and publish rates (VAP densities) is far from being enough and many additional risk factors are mandatory [22]. Those models are efficient but extremely time consuming and cannot be implemented in each ICU, although they would be absolutely mandatory to address the issue of quality and benchmarking. Those risk-adjusted rates have been accepted as the gold standard in the European Helics program [25].

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### **Microbiology**

In general, there are significant geographical differences in the rates of resistance between some European areas and even within countries, from one hospital to another. Therefore, pathogen and susceptibility patterns should be regarded primarily as potential indicators of general trends and lead to increased attention to the local epidemiology.

#### **Gram negative pathogens**

Gram-negative pathogens are the most frequent cause of HAP [26–29]. The most frequent Gram-negative pathogens involved include the following: *Pseudomonas*

*aeruginosa*, *A. baumannii*, microorganisms belonging to the family Enterobacteriaceae (*Klebsiella* spp., *Enterobacter* spp., *Serratia* spp., etc.) and, under certain conditions, microorganisms such as *Haemophilus influenzae*.

### *Pseudomonas aeruginosa*

Antimicrobial susceptibility of *P. aeruginosa* isolated in Europe varies considerably. Nevertheless, in general it is different from that reported in the USA. Data from the SENTRY study showed that during the study period (1997–1999), Europe was the only region to show a significant decline in  $\beta$ -lactam and aminoglycoside susceptibility rates against *P. aeruginosa*. Isolates from 1999 are given in Table 2 [30]. The MYSTIC study, another multicenter, multinational European study, shows that a multiresistant phenotype (resistance at least to ciprofloxacin, ceftazidime and gentamicin) occurred at least in 12% of the isolates from ICU [31]. In case of multiresistant *P. aeruginosa*, colistin may be the last available treatment option. Preliminary reports have confirmed it as a relatively effective and safe choice [32–37].

### *Acinetobacter baumannii*

Nosocomial isolates of *Acinetobacter* may exhibit high rates of resistance to antimicrobials (see Table 2). Carbapenems are one of the groups with better activity against *Acinetobacter*, but these agents can also be inactivated by various mechanisms [38, 39]. Sulbactam by itself is active against a large majority of strains of *Acinetobacter* and the combination of ampicillin and sulbactam is a good alternative [40]. Colistin is universally active against *A. baumannii*. It is occasionally the only drug available for treatment in multi-resistant strains [33–37, 41, 42]. Other drugs potentially active on multi-resistant strains are tetracycline, tigecycline, doxycycline and rifampin [43–45]. However, experience with

**Table 2** Resistance rates of *P. aeruginosa* and *Acinetobacter baumannii* in European surveys

Antimicrobial agent	<i>P. aeruginosa</i> [31]	<i>Acinetobacter baumannii</i> [33]
Piperacillin	26	80
Piperacillin–tazobactam	26	63
Ceftriaxone	–	85
Ceftazidime	28	71
Imipenem	28	23
Amikacin	21	58
Gentamicin		70
Fluoroquinolones (ciprofloxacin and levofloxacin)	32	40

Numbers display percentages of isolates

tigecyclin is limited and a previous report has confirmed treatment failures and evolution of resistance during treatment in originally susceptible strains [46].

### *Klebsiella* spp., *Enterobacter* spp., and other enterobacteriaceae

Although almost all isolates of *K. pneumoniae* and *K. oxytoca* were initially considered susceptible to third and fourth generation cephalosporins, many studies have shown that this figure has notably decreased in Europe. This increase in resistance is due to the spread of plasmid-mediated extended-spectrum beta-lactamases (ESBLs). *Klebsiella* and *Enterobacter* are producers of ESBLs in at least 5% of the isolates in the USA and in higher proportions in Europe [47]. Since resistance varies both from hospital to hospital and regionally within countries, each institution must establish and monitor the incidence of ESBL.

Although carbapenem-resistance has been described in *K. pneumoniae*, the carbapenems (imipenem and meropenem) are the most active agents in vitro against ESBL-producing strains [30, 47].

Microorganisms of the genus *Enterobacter*, are intrinsically resistant to ampicillin, amoxicillin, cephalothin, cefazolin and cefoxitin. This is due to the induction of the production of constitutive chromosomal AmpC beta-lactamase by these microorganisms. Third-generation cephalosporins, ureidopenicillins (piperacillin), and carboxypenicillins (ticarcillin) also are labile to hydrolysis. Consequently,  $\beta$ -lactamase-inducible strains appear susceptible to these antimicrobials whereas derepressed organisms are resistant. Clavulanate, sulbactam, and tazobactam do not inhibit this  $\beta$ -lactamase.

Fourth generation cephalosporins (cefepime and ceftipime), which are rapid permeants and are more stable than other extended-spectrum cephalosporins, retain reasonable activity against derepressed strains. Carbapenems have better activity than cephalosporins and are active against more than 95% of the isolates. Imipenem and meropenem have similar activity against *Enterobacter* species. Most *Enterobacter* spp. are also susceptible to aminoglycosides, quinolones, and trimethoprim-sulfamethoxazole.

### *Haemophilus influenzae*

Regarding antimicrobial resistance, the European isolates of *H. influenzae* show the following resistance rates: Ampicillin 16%, Amoxicillin-Clavulanate <1%, third generation cephalosporins <1%, Clarithromycin 10%, Ciprofloxacin <1%, Chloramphenicol 2%, Rifampin <1% and tetracycline 3% [55], but there is considerable variation among different European countries [48–50].

## Gram-positive pathogens

The Gram-positive pathogens commonly isolated in HAP include *Staphylococcus aureus*, *Streptococcus* spp. and *Streptococcus pneumoniae*, accounting for 35–39% of all cases [51, 52].

### *Staphylococcus aureus*

*Staphylococcus aureus* showed an increasing resistance to methicillin/oxacillin over the past four decades, approaching 55% in United States [53] and 59.6% in Europe [54]. However, there is a large variability of MRSA prevalence among the European countries, regions and even hospitals. Generally, the lowest MRSA proportion is seen in the Nordic countries and the Netherlands (0–2%), while much higher MRSA incidence has been reported in most southern European countries, even exceeding 40% in France, Italy and United Kingdom. Interestingly, a rapid increase in the prevalence of methicillin-resistance over the last decade has been reported in Germany, United Kingdom and Spain [55, 56].

Methicillin resistance is carried by a mobile genetic element called SSCmec (staphylococcal cassette chromosome mec) and there are three different types identified in MRSA isolates from hospitals worldwide [57].

MRSA strains have the particularity to add multiple antimicrobial resistance, such as up to 80% macrolide resistance and 90% quinolone resistance. Furthermore, the intensive use of glycopeptides as the only therapeutic option for MRSA during the past years led to the emergence of isolates with reduced susceptibility to glycopeptides (GISA/GRSA). Since the first strain has been reported in Japan in 1996, a limited number of *S. aureus* isolates with reduced susceptibility to glycopeptide have been identified worldwide, the majority of these being actually glycopeptide-intermediate *S. aureus* isolates (GISA), with a MIC below 3 mg/mL [58]. In Europe, vancomycin-intermediate *S. aureus* (VISA) isolates have been reported in France, UK, Germany and Belgium [59].

The first documented case of vancomycin-resistant *S. aureus* (VRSA) (vancomycin MIC 32 µg/mL), containing the vanA vancomycin resistance gene from enterococci, was described in 2002 in the United States [58]. GISA are selected by long-term glycopeptide usage but also by β-lactams and fluoroquinolones [59]; there has been also mentioned an in vivo selection independent of any antimicrobial selective pressure [60].

Of concern, standard clinical laboratory testing does not detect *S. aureus* with vancomycin heteroresistance (hVISA), which was found to be present in 2.16% of 16000 MRSA isolates. The gradual reduction in susceptibility of *S. aureus* to vancomycin and the poor response to treatment in patients infected with *S. aureus* isolates

whose MICs lie at the higher end of the range of susceptibility (MIC 2 mg/mL) make the continued use of vancomycin increasingly problematic [59, 60].

## Other bacteria

There is still controversy regarding the role and the clinical significance of anaerobic bacteria in HAP. Many of the series of recent years do not try to recover anaerobic bacteria from lower respiratory tract secretions in patients with HAP. They may have a role in patients developing HAP within 5 days of hospital admission but doubtfully after that time. The microorganisms most frequently recovered are *Prevotella* spp., *Fusobacterium* spp. and *Veillonella* spp. and the need to administer drugs with antianaerobic activity has not been clearly established [61–64].

## Nonbacterial pathogens

*Candida* spp. in respiratory specimen should not be treated unless there is clear histological evidence for such an infection. However, the findings of a very recent study from Canada showed the incidence of 17.8% initial colonization by *Candida* in patients with VAP. This colonization was associated with worse clinical outcomes and independently associated with increased hospital mortality [65].

In contrast, *Aspergillus* spp. has been increasingly recognized in VAP. Disseminated aspergillosis in intensive care patients was diagnosed by autopsy in 6 (2.7%) of 222 fatal cases [101]. Of these, five patients were receiving corticosteroid treatment for underlying pulmonary diseases [66]. In a study by Maertens et al., *Aspergillus* pneumonia was identified in patients with COPD, renal disease, liver cirrhosis, and in patients with iatrogenic immunosuppression. *Aspergillus* pneumonia is associated with an extremely high mortality [67].

Viruses are rarely associated with HAP in immunocompetent patients. However, Papazian et al. identified *cytomegalovirus* in lung biopsy in 25 of 85 patients with VAP [68]. The significance of this finding remained undetermined.

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## The relationship between tracheostomy and VAP

### Incidence of VAP after tracheostomy

In a recent meta-analysis, comparing percutaneous with surgical tracheostomy, ventilator-associated pneumonia (VAP) rates of 13.1 per 1,000 surgical procedures have been reported. The authors found no pneumonia reported

as a complication of percutaneous tracheostomy [69]. However, two recent studies reported higher VAP rates after surgical and percutaneous tracheostomy (25.9 and 18%, respectively) [70, 71]. Unfortunately, the incidence of VAP after tracheostomy was not compared with VAP incidence in patients without tracheostomy. In these studies, most VAP episodes occurred in the week after the procedure, and *Pseudomonas aeruginosa* was the most frequently isolated organism.

### Tracheostomy as a risk factor for VAP

Several recent studies identified tracheostomy as an independent risk factor for VAP [72–76]. However, only two studies have excluded tracheostomy from risk factor analysis when it was performed after VAP occurrence [72, 76]. In addition, none of these studies has adjusted for the duration of mechanical ventilation. These data suggest that tracheostomy is rather a marker of longer duration of mechanical ventilation than a risk factor for VAP.

Based on pathophysiology of VAP in intubated patients, tracheotomized patients are probably at decreased risk for the development of VAP as compared to patients with translaryngeal intubation. Several factors support this hypothesis. In intubated patients, endotracheal tube allows inhalation of contaminated oropharyngeal secretions into the lung, and contributes to tracheal colonization and subsequent VAP development [77]. Liberation of vocal cords in tracheotomized patients results in normal closure and reduces the risk of inhalation of secretions from the oropharyngeal cavity. In addition, endotracheal tube provides a surface for the formation of a bacterial biofilm along the inside of the endotracheal tube which plays an important role as a reservoir for infecting microorganisms [78]. Tracheostomy facilitates weaning from mechanical ventilation resulting in shorter duration of mechanical ventilation and probably a reduced risk for VAP [79–81].

### Risk factors for VAP after tracheostomy

Positive tracheobronchial aspirate culture at  $\geq 10^5$  CFU/mL, hyperthermia (temperature  $\geq 38.3^\circ\text{C}$ ) on the day of tracheostomy and the continuation of sedation  $>24$  h after surgical tracheostomy were identified as independent risk factors for VAP following surgical tracheostomy [71]. In another study, nearly 90% of patients had tracheal colonization prior to the procedure; no or very weak relationship was found between pretracheostomy culture results and bacteriology of subsequent pneumonias [70]. To our knowledge, no study has identified independent risk factors for VAP following percutaneous tracheostomy.

### Antimicrobial prophylaxis in patients who undergo tracheostomy

Although some physicians use antimicrobial treatment to prevent VAP following tracheostomy, this prophylaxis has not been evaluated. In addition, antimicrobial treatment is associated with subsequent emergence of multidrug-resistant bacteria. Therefore, no recommendation can be made to use prophylactic antimicrobials in patients undergoing tracheostomy.

### VAP and timing of tracheostomy

Several studies have compared the risks of prolonged intubation to early tracheostomy but lacked good study design and appropriate controls, had selection bias, and involved small sample sizes [79–82]. A recent prospective randomized study has compared early percutaneous tracheostomy within 48 h with delayed tracheostomy on days 14–16 [82]. Early group showed significantly less mortality (31 vs. 61%,  $P < 0.005$ ), and pneumonia (5 vs. 25%,  $P < 0.001$ ). However, 8 of the 60 (13%) patients randomized to the delayed group were extubated before day 14 according to the weaning protocol. Therefore, further studies are needed to determine markers of prolonged mechanical ventilation. Another limitation of this study is the use of APACHE  $>25$  as an inclusion criteria. This limits the application of its results to patients with a high risk of death.

### Tracheobronchitis in ventilated patients

Nosocomial tracheobronchitis is difficult to define. A definition may include the following criteria: occurrence of purulent tracheal secretion after  $\geq 48$  h of hospitalisation or mechanical ventilation plus  $\geq 2$  of the following: fever ( $\geq 38.5^\circ\text{C}$ ) or hypothermia ( $< 36^\circ\text{C}$ ), leukocytosis ( $\geq 12 \times 10^9/\text{L}$ ), significant bacteriologic counts in respiratory secretions ( $\geq 10^3$  cfu/mL for protected brush specimen (PBS) and  $\geq 10^5$  cfu/mL for endotracheal aspirates); absence of new pulmonary infiltrates compatible with pneumonia and absence of other causes of fever are mandatory [83–87].

A recent study of Bouza et al. [83] on the frequency of lower respiratory tract infection in patients after heart surgery found an incidence of nosocomial tracheobronchitis of 29/356 (15%) and an incidence rate of 31.13 per 1,000 days of mechanical ventilation. No difference in length of hospital stay was noted between patients with tracheobronchitis and patients without respiratory infection; mortality rate was 20.7% in the tracheobronchitis group being significantly higher in comparison to patients with no evidence of bacterial colonisation (1.6%). Finally,

5/29 of tracheobronchitis cases subsequently developed ventilator-associated pneumonia. Mortality rate was similar in patients with and without nosocomial tracheobronchitis (38.7 vs. 32.1%,  $P = \text{NS}$ ), but the presence of nosocomial tracheobronchitis prolonged significantly the length of hospital stay [ $39.2 \pm 32$  vs.  $18.1 \pm 15.1$  days,  $P = 0.05$  (surgical patients)] as well as the duration of mechanical ventilation [ $32.2 \pm 31.1$  vs.  $13.6 \pm 12.5$  days,  $P < 0.001$  (surgical patients)] even after exclusion of patients that subsequently developed a nosocomial pneumonia. This finding was confirmed in a subsequent study by Nseir et al. [84].

The impact of antimicrobial treatment of tracheobronchitis has been addressed by Nseir et al. [85] in a large prospective study over 6.5 years on 2,128 mechanically ventilated patients. Of them, 201 (10.6%) patients (36 surgical and 165 medical) developed a nosocomial tracheobronchitis. In this study, antimicrobial treatment in patients with tracheobronchitis did not significantly influence the length of ICU stay, duration of mechanical ventilation or overall mortality when compared to those not treated; furthermore, the rate of subsequent nosocomial pneumonia was also similar in patients with tracheobronchitis, irrespective of antimicrobial treatment. Thus, adequate antimicrobial treatment did not improve significantly the outcome suggesting that antimicrobial treatment may not be necessary in nosocomial bronchitis.

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## Postoperative pneumonia

### Incidence and prediction

According to a retrospective study using 7 years' National Healthcare Cost and Utilization Project data, the rate of postoperative pneumonia was 0.97% in major teaching hospitals [86, 87].

The largest study assessing postoperative pneumonia published included 155,266 patients after major noncardiac surgery. Overall, 2466 patients (1.5%) had postoperative pneumonia. The 30-day postoperative mortality rate was 21% in patients with postoperative pneumonia and 2% in patients without postoperative pneumonia [88].

The accuracy of preoperative assessment in predicting postoperative pulmonary risk was examined in a prospective cohort of 272 consecutive patients before nonthoracic surgery. Among 22 (8%) postoperative pulmonary complications, nine patients had postoperative pneumonia. Multiple regression analyses revealed three preoperative clinical predictors that were independently associated with pulmonary complications: age above 65 years or more (odds ratio, 1.8), smoking 40 packets per year or more (odds ratio, 1.9), and maximal laryngeal height of 4 cm or less (odds ratio, 2.0) [89].

### Treatment of postoperative pneumonia

In the Eole study, appropriateness of initial antimicrobial therapy was not associated with mortality in patients developing postoperative pneumonia, whereas the time to onset of pneumonia was a significant determinant [90]. Among 322 patients with microbiologically proven postoperative pneumonia, 92 (28%) patients received an inappropriate antimicrobial therapy, which was defined by the isolation of at least one pathogen with a significant threshold in the bronchial sampling, either resistant or with intermediate susceptibility to the antimicrobial prescribed. Early and appropriate antimicrobial therapy reduced hospital-acquired mortality rates in clinical studies [91, 92]. Importantly, the benefit of an appropriate initial antimicrobial therapy was demonstrated when antimicrobial therapy was started before bronchial sampling.

Only one prospective randomized study was published in nonneutropenic cancer patients with postoperative pneumonia, who were randomized to receive either piperacillin/tazobactam (4.5 g/6 h) or clindamycin 900 mg plus aztreonam (2 g/8 h). Amikacin (500 mg/12 h) was given to all patients for the first 48 h. Patients were intubated for a median duration of 6 (3–36) and 5 (1–45) days. Response rates were 83% for patients receiving piperacillin/tazobactam and 86% for those who received clindamycin plus aztreonam. The cost of piperacillin/tazobactam regimen was lower than that of clindamycin plus aztreonam regimen [93].

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## Diagnostic strategies

### Identifying patients with pneumonia and starting immediate therapy with an effective regimen

The presence of new chest X-ray infiltrates plus one of the three clinical variables (fever  $>38^{\circ}\text{C}$ , leucocytosis or leucopenia and purulent secretions) is useful for the clinical screening of HAP (high sensitivity). For patients suffering from ARDS and for whom it is difficult to demonstrate deterioration of radiological images, at least one of the three preceding may suffice to activate initial screening. However, in a recent study from the Canadian critical care group pretest probability and a modified clinical pulmonary infection score (CPIS), which excludes culture results, were of limited utility in the diagnosis of late-onset VAP [94].

The combination of the presence of pulmonary infiltrates plus two of the three clinical signs is enough accurate to start antimicrobial treatment [95]. In any addition, further diagnostic evaluation is mandatory, such as cultures of lower respiratory tract secretions. Samples of respiratory secretions for culture have to be obtained



before the initiation or change of antimicrobial treatment [96]. Available evidence favours the use of quantitative culture techniques over qualitative culture of respiratory secretions when establishing an indication for antimicrobial therapy [97]. The accuracy of non-bronchoscopic techniques for obtaining quantitative cultures of lower respiratory tract samples is comparable to that of bronchoscopic techniques [98]. The choice depends on local resources and expertise.

In patients with clinical evidence of severe sepsis, or patients with a very high pretest probability of the disease, the initiation of antimicrobial therapy must not be delayed and patients should be treated immediately with broad-spectrum antimicrobials, even when no bacteria are detected using microscopic examination of pulmonary secretions [99]. Because delays in the administration of effective antimicrobial therapy may impact on HAP outcome, antimicrobial treatment should not be postponed pending performance of diagnostic procedures, even when the patient is clinically stable [92].

#### Avoiding overtreatment

Because clinical signs of infection are non-specific and can be caused by any condition associated with an inflammatory response, many more patients than necessary initially receive antimicrobial treatment. Thus, all diagnostic strategies for managing suspicion of HAP should include a statement indicating that treatment will be re-evaluated after 48–72 h and therapy be stopped if infection appears unlikely [1, 98].

Using a “clinical strategy” in which all patients with clinically suspected pulmonary infection are treated with new antimicrobials, even when the likelihood of infection is low, the decision whether to continue antimicrobials on day 3 will be based essentially on a combination of clinical signs [1]. Antimicrobial treatment is discontinued if and only if the following three criteria are fulfilled: (1) clinical diagnosis of HAP is unlikely (there are no definite infiltrates found on chest radiography at follow-up and no more than one of the three following findings: temperature  $>38.3^{\circ}\text{C}$ , leukocytosis or leukopenia, and purulent tracheobronchial secretions) or an alternative noninfectious diagnosis is confirmed, (2) tracheobronchial aspirate culture results are non-significant, and (3) there is no severe sepsis or shock.

An attracting, albeit not yet validated approach relies on the clinical probability of VAP at repeated assessment on day 3. Using the clinical pulmonary infection score (CPIS), patients with CPIS  $>6$  are treated as having HAP with a full course of antimicrobial treatment; therapy is discontinued when CPIS is  $\leq 6$  at day 3 [99].

The decision algorithm for withholding or withdrawing antimicrobials using the “invasive strategy” is based on results of direct examination of distal pulmonary

samples obtained by bronchoscopic or nonbronchoscopic BAL and results of quantitative cultures. Antimicrobial treatment is withheld in patients with no bacteria on Gram-stained cytocentrifuged preparations and no signs of severe sepsis or septic shock; and discontinued when quantitative culture results are below the cut-off defining a positive result, except in patients with proven extrapulmonary infection and/or severe sepsis [98]. As demonstrated by several studies, patients managed with such a bacteriological strategy receive fewer antimicrobials, and more patients have all their antimicrobials discontinued compared to the clinical strategy group, thereby confirming that the two strategies actually differed [97, 100–103]. However, a recent large multicentre trial comparing an invasive and a noninvasive strategy (even using qualitative TBAS) did not find a difference in days on antimicrobial treatment, rate of targeted treatment, length of stay and ICU-mortality [104].

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### Empirical antimicrobial treatment in hospital-acquired pneumonia (HAP)

#### General considerations

The ambiguous implications of any antimicrobial treatment have clearly been settled. The immediate administration of appropriate antimicrobial treatment is crucial in order to achieve an optimal outcome, and inappropriate antimicrobial treatment is associated with an excess mortality from pneumonia [105–107]. Moreover, it could be shown that even if the initially inappropriate, antimicrobial treatment is corrected according to diagnostic results; there still remains an excess mortality as compared to the group treated appropriately from the beginning [91].

On the other hand, antimicrobial treatment is not without risk. This is particularly true for the patient receiving prolonged broad-spectrum antimicrobial treatment. Antimicrobial pretreatment exhibits a considerable microbial selection pressure and is associated with an excess mortality due to pneumonia through the selection of potentially drug resistant microorganisms [108].

It has increasingly become clear that each antimicrobial treatment policy exhibits a specific selection pressure. Therefore, the microbial and resistance patterns of each local setting can to some extent be regarded as footprints of past antimicrobial treatment policies. Recognizing these relationships, it is evident that recommendations for initial empiric antimicrobial treatment must be flexible enough to get modified according to local peculiarities [109].

An adequate dosage of antimicrobial treatment is crucial for a favourable outcome. Accordingly, suboptimal dosage constitutes a prominent risk factor for

development of resistance during antimicrobial treatment. Therefore, it is referred to the current dosing guidelines given in ATS guideline update [1].

However, the most adequate methodology to assess the optimal dosage remains a matter of debate. Factors such as differences in pharmacodynamics (time-dependent or concentration-dependent microbial killing) and pharmacokinetics of antimicrobial agents, microbiological characteristics of underlying pathogens, methods applied to determine microbial resistance levels, as well as immunological host factors all may influence the final antimicrobial effect of a given dosage [110].

Penetration into lung tissue is a particularly important pharmacokinetic issue which should be considered when selecting an antimicrobial treatment regimen. In this regard, aminoglycosides are not ideal drugs because their lung tissue penetration reaches only 30–40% of the serum-level.  $\beta$ -lactams also exert a penetration of <50%. In contrast, quinolones achieve a cellular and lung tissue penetration 1,000% higher than the serum-level. When using vancomycin, recent data suggest that continuous IV infusion targeting a serum level 20–30 mg/ml is superior to discontinuous IV [111]. However, these data must be regarded with caution. In contrast to the data presented in that study, the parameter that seems to correlate with efficacy in the case of vancomycin is AUC/MIC and not time above MIC [112].

### Selection of initial antimicrobial treatment

The outcome of nosocomial pneumonia clearly depends on the adequacy of initial antimicrobial treatment. In fact, initial antimicrobial treatment almost always has to be started empirically. Therefore, the definition of adequate initial empiric antimicrobial treatment regimes crucially depends on the identification of essential risk factors for distinct pathogen and resistance patterns.

Three fundamental determinants for particular pathogen-spectrums have been recognized:

- pneumonia of the spontaneously breathing or the ventilated patient. The differences between these two groups are not firmly settled but available data indicate that in spontaneously breathing patients potentially drug resistant microorganisms may play a minor role. Instead, Gram-negative enterobacteriaceae (GNEB), *Staphylococcus aureus* and *Streptococcus pneumoniae* have been described as leading pathogens [113, 114].
- Time course of development of pneumonia (early vs. late) [7, 113].

Early onset pneumonia (onset within  $\leq 4$  days of hospital admission): principal pathogens include *S. aureus*, *S. pneumoniae* and *H. influenzae* as well as non-drug resistant GNEB;

Late onset pneumonia (onset  $>4$  days of hospital admission): principal pathogens include MRSA, drug-resistant GNEB, *P. aeruginosa*, *A. baumannii*, among other potentially drug resistant microorganisms).

- Presence of defined risk factors [7, 113].

These include age, structural lung disease, previous antimicrobial treatment, prior tracheobronchial colonization (mainly as a result of comorbidity and previous antimicrobial treatment) as well as pneumonia severity.

The specific pathogen pattern will depend on local peculiarities of the particular hospital which in turn are mainly the result of the structures of ICU care, prevention and antimicrobial treatment policies, and patient populations treated.

A controversial issue of debate is to use or not previous cultures for empiric initial antibiotic. A recent study has confirmed a poor agreement between prior cultures and cultures performed at time of suspicion of VAP indicating that prior cultures should not be used to narrow the spectrum of empiric antibiotics [115].

Recent data force to reconsider to role of aminoglycosides in the treatment of HAP. Several studies and metaanalyses have proven that the combination treatment of  $\beta$ -lactam and aminoglycoside for immunocompetent patients with sepsis [116], cancer, neutropenia [117–119], for Gram-negative bloodstream infections [120, 121] as well as *P. aeruginosa* infections (including pneumonia) [122, 123] is not superior to monotherapy. In a large Cochrane analysis comparing clinical outcomes for  $\beta$ -lactam-aminoglycoside combination therapy versus  $\beta$ -lactam monotherapy for sepsis, 64 trials (7,586 patients) were included. In studies comparing the same  $\beta$ -lactam, there was no difference between study groups with regard to all-cause fatality, RR 1.01 (95% CI 0.75–1.35) and clinical failure, RR 1.11 (95% CI 0.95–1.29). In studies comparing different  $\beta$ -lactams, there was an advantage to monotherapy: all cause fatality RR 0.85 (95% CI 0.71–1.01), clinical failure RR 0.77 (95% CI 0.69–0.86). No significant disparities emerged from subgroup and sensitivity analyses, including the assessment of patients with Gram-negative and *P. aeruginosa* infections. Also no differences in the rate of resistance development were found. Adverse events rates did not differ significantly between the study groups overall, although nephrotoxicity was significantly more frequent with combination therapy, RR 0.30 (95% CI 0.23–0.39) [124].

Another argument frequently made in favour of a combination treatment is the control of emerging resistance. A recent metaanalysis including a total of eight randomised controlled trials addressed this issue [125].  $\beta$ -Lactam monotherapy was not associated with a greater emergence of resistance than was the aminoglycoside/ $\beta$ -lactam combination (OR 0.90; 95% CI 0.56–1.47). Actually,  $\beta$ -lactam monotherapy was associated with

fewer superinfections (OR, 0.62; 95% CI, 0.42–0.93) and fewer treatment failures (OR, 0.62; 95% CI, 0.38–1.01). Rates of treatment failure attributable to emergence of resistance (OR, 3.09; 95% CI, 0.75–12.82), treatment failure attributable to superinfection (OR, 0.60; 95% CI, 0.33–1.10), all-cause mortality during treatment (OR, 0.70; 95% CI, 0.40–1.25), and mortality due to infection (OR, 0.74; 95% CI, 0.46–1.21) did not differ significantly between the two regimens [125].

Nevertheless, combination treatment may still be advisable as initial treatment (e.g. for the first 48 h) for the reason that it decreases the probability of inadequate treatment, a failure that is known to be associated with an excess mortality, regardless whether active agents are introduced after cultures become available [126]. The findings of a recent study comparing combination therapy and monotherapy of VAP due to *P. aeruginosa* support this concept. Initial use of combination therapy significantly reduced the likelihood of inappropriate therapy, which was associated with higher risk of death. However, administration of only one effective agent provided similar outcomes to combination therapy, suggesting that switching to monotherapy once the susceptibility is documented is feasible and safe [127]. This strategy is a formidable example for a de-escalation strategy of antimicrobial treatment.

Thus, we advocate that in patients at risk for *P. aeruginosa*, initial treatment may preferably be a combination treatment predominantly of  $\beta$ -lactams and an antipseudomonal quinolone. In the absence of other alternatives, increased resistance rates to quinolones and concerns about the adverse effects of increased quinolone use still force to consider aminoglycosides as additional still suitable choice.

Antimicrobial treatment recommendations are summarized in Table 3.

#### Focusing therapy once the agent of infection is identified

Once the results of respiratory tract and blood cultures become available, therapy should be focused or narrowed, based on the identity of specific pathogens and their susceptibility to specific antimicrobials, in order to avoid prolonged use of a broader spectrum of antimicrobial treatment than is justified by the available information.

Vancomycin and linezolid should be stopped if no MRSA is identified, unless the patient is allergic to  $\beta$ -lactams and has developed an infection caused by a Gram-positive pathogen. Very broad-spectrum agents, such as carbapenems, piperacillin–tazobactam, and/or cefepime should also be restricted to patients with infection caused by pathogens only susceptible to these agents. Targeted antibiotic therapy is associated with less antibiotic use and no harm in the management of patients with VAP [128].

#### Optimizing antimicrobial therapy

Clinical and bacteriologic outcomes can be improved by optimizing the therapeutic regimen according to the pharmacokinetic properties of the agent(s) selected for treatment [129–135].

Development of a priori dosing algorithms based on MIC, patient creatinine clearance and weight, and the clinician-specified AUC target might be a valid way to improve treatment of these patients, leading to a more precise approach than current guidelines for use of antimicrobial agents.

#### Switching to monotherapy at days 3–5

Therapy could be switched to monotherapy in most patients after 3–5 days, provided that initial therapy was appropriate, clinical course appears favourable, and that microbiological data do not suggest a very difficult-to-treat microorganism, with a very high in vitro minimal inhibitory concentration, as it can be observed with some nonfermenting-GNB.

#### Shortening duration of therapy

Prolonged therapy in patients with HAP simply leads to colonization with resistant bacteria, which may precede a recurrent episode of VAP [136]. Reducing duration of therapy in patients with VAP has led to good outcomes with less antimicrobial use with a variety of different strategies [137, 138]. Based on these data, an 8-day regimen can probably be standard for patients with HAP. Exceptions to this recommendation include pneumonia due to *S. aureus*, immunosuppressed patients, those whose initial antimicrobial treatment was not appropriate for the causative microorganism(s), and patients whose infection was caused by very difficult-to-treat microorganisms and had no improvement in clinical signs of infection. In the latter patients in need of a prolonged treatment, it may be prudent to change antimicrobial agents after 8 days if possible.

Most recent exciting data indicating that protocol based serial PCT measurement allows reducing antibiotic treatment duration and exposure in patients with severe sepsis and septic shock without apparent harm await further validation [139].

#### Assessment of treatment response

Both a clinical score and inflammatory markers have been described as adjunct to assess the response to initial antimicrobial treatment. The CPIS score may form the basis of objective evaluation [140–142], and both serial

**Table 3** Antimicrobial treatment of nosocomial pneumonia

<b>Antimicrobial treatment of early onset pneumonia without any additional risk factors<sup>a</sup></b>	
Aminopenicillin plus $\beta$ -lactamase-inhibitor	Amoxicillin–clavulanic acid 3 $\times$ 2.2 g Ampicillin–Sulbactam 3 $\times$ 3 g
Or	
Second	Cefuroxime 3 $\times$ 1.5 g
Or	
Third generation cephalosporin	Cefotaxime 3 $\times$ 2 g Ceftriaxone 1 $\times$ 2 g
Or	
“Respiratory” quinolone (not ciprofloxacin)	Levofloxacin 1 $\times$ 750 mg Moxifloxacin 1 $\times$ 400 mg
<b>Antimicrobial treatment of late onset pneumonia<sup>b</sup></b>	
Piperacillin/tazobactam	3 $\times$ 4.5 g
Or	
Ceftazidime	3 $\times$ 2 g
Or	
Imipenem/cilistatin	3 $\times$ 1 g
Or	
Meropenem	3 $\times$ 1 g
Plus	
Ciprofloxacin	3 $\times$ 400 mg
Or	
Levofloxacin	1 $\times$ 750 mg
<i>Addition of coverage for MRSA if suspected</i>	
Vancomycin	2 $\times$ 1 g
Or	
Linezolid	2 $\times$ 600 mg
<b>Antimicrobial treatment of pneumonia with risk factors, any onset</b>	
MRSA	Vancomycin 2 $\times$ 1 g Linezolid 2 $\times$ 600 mg
<i>P. aeruginosa</i>	Antipseudomonal combination treatment (see late onset pneumonia treatment)
<i>Acinetobacter spp.</i>	Imipenem/cilastatin 3 $\times$ 1 g Or Meropenem 3 $\times$ 1 g Or Ampicillin/sulbactam 3 $\times$ 3 g (tigecycline 1 $\times$ 100 mg loading dose, then 2 $\times$ 50 mg <sup>c</sup> )
Legionellosis	Respiratory quinolone (see early onset pneumonia treatment)
Fungi	Fluconazole 2 $\times$ 800 mg Or Caspofungin 1 $\times$ 70 mg loading dose, then 1 $\times$ 50 mg Or Voriconazole 2 $\times$ 4 mg/kg If aspergillus spp is suspected

<sup>a</sup> Ertapenem should not be used on a regular basis because this would imply considerable overtreatment

<sup>b</sup> Combination treatment only until results of susceptibility testing are available

<sup>c</sup> Very limited experience

CRP [142–144] and PCT [140, 145, 146] measurements may be of help in increasing the validity of decisions to stop antimicrobial treatment.

#### Failure of response to initial antimicrobial treatment

A failure to respond to initial antimicrobial treatment is a serious event associated with excess adverse outcome rates. It must be expected in around 20–40% of cases, depending on the severity of underlying illnesses and pneumonia. Therefore, any treatment failure should prompt an extensive diagnostic reevaluation of the patient.

This should always include bronchoscopic respiratory secretion sampling by PSB and/or BAL and blood cultures [147–149].

In mechanically ventilated patients with nosocomial pneumonia who do not respond to the primary treatment, *Pseudomonas aeruginosa*, MRSA, *Acinetobacter spp.*, *Klebsiella spp.* or *Enterobacter spp.* are the most likely underlying pathogens [148–150]. A recent study in patients with VAP found that the risk factors associated with clinical failure were older age, duration of mechanical ventilation before enrolment, presence of neurologic disease at admission and failure to improve PaO<sub>2</sub>/FIO<sub>2</sub> ratio to improve by day 3 [151].

## Antimicrobial inhalation treatment

There are limited data about the administration of antimicrobial agents via the respiratory tract for treating nosocomial pneumonia, either by inhalation or endotracheally instilled, with or without concomitant systemic antimicrobial treatment. Although promising in general, inhaled antimicrobial treatment should be reserved as last line therapeutic alternative, e.g. in VAP due to GNEB and multiresistant *P. aeruginosa* [152–156].

## Clinical practice strategies for the prevention of VAP

General measures for infection control include alcohol-based hand disinfection, use of microbiologic surveillance, monitoring and early removal of invasive devices, and programs to reduce antimicrobial prescriptions [157–160]. Only recently, it has been impressively reinforced that increased antimicrobial usage heavily predisposes to VAP due to *P. aeruginosa* or multidrug-resistant pathogens [161]. Specific measures for the prevention of VAP are addressed towards different modifiable risk factors.

Endotracheal intubation and reintubation increase the incidence of VAP. If needed, orotracheal intubation and orogastric tubes should be preferred to nasotracheal intubation and nasogastric tubes in order to prevent nosocomial sinusitis and to reduce the risk of VAP [162].

The accumulation of contaminated oropharyngeal secretions above the ET cuff contributes to the risk for aspiration. Removal of these pooled secretion may reduce the risk for aspiration and the early-onset VAP, as reported by two different randomized clinical trials [163, 164]. Moreover, maintenance of the ET cuff pressure at approximately 20 cm H<sub>2</sub>O may prevent leakage of bacterial pathogens around the cuff into the lower respiratory tract [163, 165]. A recent experimental study has shown the possibility to reduce the bacterial colonization of the endotracheal tube, of the ventilator circuits, and lungs, by using endotracheal tubes coated with antiseptics [166]. More recently, a very important study showed that patients receiving a silver-coated endotracheal tube had a statistically significant reduction in the incidence of VAP and delayed time to VAP occurrence [167].

Ventilator circuits are rapidly colonized with bacteria, and the condensate within these circuits can have very high bacterial counts. A large number of prospective, randomized trials have demonstrated that the frequency of ventilator circuit change does not affect the incidence of nosocomial pneumonia [168, 169], while flushing the condensate into the lower airway or to in-line medication nebulizers may increase the risk of VAP [170].

Five randomized, controlled trials have investigated the use of both heat-moisture exchangers (HMEs) and heater humidifiers (HH) as risk factors of VAP, and have

been summarized by Cook et al. [165]. The largest of these five trials showed a significant reduction in the incidence of VAP ( $P < 0.05$ ) in patients randomized to receive HME compared with those receiving HH [171].

Oropharyngeal colonization, either present on admission or acquired during ICU stay, has been recognized as an independent risk factor for the development of VAP. Modulation of oropharyngeal colonization by combinations of oral antimicrobial agents, with or without systemic therapy, and by selective decontamination of the digestive tract (SDD) has been proposed with the goal of decreasing the pathogenicity of aspirated secretions and reducing the incidence of VAP.

Seven meta-analyses of more than 40 randomized controlled trials (most in surgical patients) have reported a significant reduction in the risk of VAP with the use of SDD [172–179]. Four of these seven meta-analyses also reported a significant reduction in mortality but only when a systemic antimicrobial was added (SPAPS) [173–177]. The use of SPAPS should be discussed at a local level. The routine prophylactic use of SDD should be discouraged, particularly in hospital settings with high levels of antimicrobial-resistant microorganisms.

Short course systemic antimicrobial treatment immediately after intubation has been described to reduce the incidence of early onset VAP in comatose patients [180]. However, another study could show that while decreasing the risk for early onset tracheobronchial colonization and subsequent early onset pneumonia, it increased the risk for colonization with more difficult-to-treat pathogens and subsequent late onset pneumonia [113]. Since only the latter is associated with excess mortality, short course systemic antimicrobial treatment appears as a two-sided sword. Clearly, more research is necessary in this field.

Recently, a large body of evidence has shown that patient positioning is crucial in the development of VAP [181, 182]. The semirecumbent position may reduce the volume of aspirated secretions when compared with the supine position. A clinical trial [172] reported results for 86 intubated and mechanically ventilated patients who were randomly assigned to the semirecumbent or the supine body position. The trial was stopped when the planned interim analysis showed that supine body position and enteral nutrition were independent risk factors for nosocomial pneumonia and the frequency was highest for patients receiving enteral nutrition in the supine body position. It is unlikely that the 45° angle, initially targeted can be reached in real life, and 20°–30° is probably sufficient.

One randomized trial comparing antiacids, H<sub>2</sub> blockers and sucralfate reported no differences in rates of early-onset VAP, while rates of late-onset VAP were reduced in patients treated with sucralfate [183]. However, another large, double-blind, randomized study comparing ranitidine with sucralfate reported a clinically significant increase in gastrointestinal bleeding among patients receiving sucralfate [184]. Consequently, if stress ulcer

**Table 4** Recommended measures for prevention of VAP**Generally recommended general measures:**

Alcohol-based hand disinfection  
 Use of microbiologic surveillance  
 Monitoring and early removal of invasive devices  
 Programs to reduce antimicrobial prescriptions  
 Generally recommended specific measures  
 Avoidance of endotracheal intubation  
 Avoidance of reintubation  
 Preference of noninvasive ventilation (NIV)  
 Preference of orotracheal intubation and orogastric tubes  
 Maintenance of the ET cuff pressure at approximately 20 cmH<sub>2</sub>O  
 Avoidance of flushing the condensate into the lower airway or to in-line medication nebulizers  
 Patient positioning (semirecumbent position)

**Additional measures which might be helpful in distinct settings and populations:**

Continuous aspiration of subglottic secretions  
 Endotracheal tubes coated with antiseptics or silver  
 Preference of heat-moisture exchangers (HMEs) over heater humidifiers (HH)  
 Oral decontamination  
 Selective decontamination of the digestive tract (SDD)

prophylaxis is indicated, the risk and benefits of each therapeutic strategy should be carefully considered.

Several authors have demonstrated that NIV may represent a valid, complementary or alternative approach to conventional ventilation with ET in selected groups of ARF patients [185–188]. This approach may have several advantages in terms of prevention of infections, mainly reducing the rate of ETI. Factors involved in reducing the incidence of VAP may include the maintenance of natural barriers provided by the glottis and the upper respiratory tract, the reduction in need of sedation and the shortening of MV duration. Randomized and non-randomized studies on the application of NIMV in patients with acute respiratory failure have showed promising results, with reduction of complications, including sinusitis and VAP, and duration of ICU stay [185–199]. The VAP Guidelines Committee and the Canadian Critical Care Trials group have recommended the following measures for VAP prevention: (1) Use orotracheal route for intubation; (2) A new ventilator circuit for each patients; (3) Not scheduled changes of the ventilator circuits; (4) Change of heat or moisture exchangers every 5–7 days or when clinically indicated; (5) the use of a closed endotracheal suctioning system changed for each patients and as clinically indicated; (6) subglottic secretion drainage in patients expected to be mechanically ventilated for more than 72 h and 6-head of the bed elevated to 45° if possible. [200]

Our recommendations are summarized in Table 4.

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## Appendix

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