Witness Statement Ref. No. 281/3

NAME OF CHILD: RAYCHEL FERGUSON (LUCY CRAWFORD)

Name: CAROLINE GANNON

Title: Doctor

Present position and institution:
Consultant paediatric pathologist
Northern Ireland Regional Paediatric Pathology Service
Royal Victoria Hospital, Belfast

Previous position and institution:
[As at the time of the child's death]

April 2000: Specialist registrar in paediatric pathology, Hammersmith and Queen Charlotte's Hospital, London

Membership of Advisory Panels and Committees:
[Identify by date and title all of those between January 2000 – August 2012]

Group B Strepococcus working group, 2011-2012

Previous Statements, Depositions and Reports:
[Identify by date and title all those made in relation to the child's death]

OFFICIAL USE:
List of previous statements, depositions and reports attached:

Ref:	**Date:**	
WS-281/1	11-10-2012	Statement to the Inquiry
WS-282/2	28.12.2012	Statement to the Inquiry

Supplementary Response to 'Additional Questions to Professor Sebastian Lucas'

I would first state that Professor Lucas is not known to me to be a practicing paediatric pathologist. To the best of my knowledge, he has never held a substantive post as a paediatric or perinatal pathologist. I do not believe he holds any specialist qualification in paediatric pathology. I therefore do not consider that he can be properly regarded as an expert in paediatric pathology.

Professor Lucas has clearly stated (page 252-003-006) that he has not seen the histological sections of the tissues sampled from Lucy Crawford. However, despite NOT seeing the sections, he still feels able to draw a conclusion about the pathological findings present. As a practicing paediatric pathologist, I believe that not only I but many of my colleagues in this specialty would regard this as amounting to unprofessional behaviour and to such an extent as to invalidate his conclusions. Professor Lucas has stated that Dr O'Hara's report is 'imprecise', 'basic', and 'includes non-specific pathology'. If he is so critical about the quality of the reporting, why then is he using the written description of the case to base his conclusions on? The presence of bronchopneumonia was commented on by Dr O'Hara, and was confirmed by me when I examined the sections prior to attending the inquest.

Dr O'Hara was an experienced perinatal and paediatric pathologist, and was involved in a considerable body of research looking at lung disease in infants (for example, he was the guarantor of a paper published in the journal Paediatric Pathology, reference: 1994 Nov-Dec;14(6):945-53, entitled 'Surfactant replacement therapy in preterm neonates: a comparison of postmortem pulmonary histology in treated and untreated infants'). This means he would have been fully cognisant with the range of ventilator associated lung changes that can occur, and he would have reasonably been expected to use this term to describe the changes seen in the lungs had this been what he thought it was: the fact that he used the term bronchopneumonia indicates that this was his preferred diagnosis. I am of the opinion that for Professor Lucas to make a diagnosis of ventilatory changes based solely on a brief written description without actually seeing the sections for himself could be considered, at best, unwise and, at worst, unprofessional.

I accept that the clinicians didn't consider bronchopneumonia as a diagnosis but it is not uncommon for a small infant to present with non specific symptoms. Every year in Northern Ireland, we have approximately 20 'cot deaths'. In 2-3 of these deaths, babies who were apparently reasonably well with only very minimal symptoms such as not feeding too well, die unexpectedly, and at autopsy these turn out to have bronchopneumonia. The lack of symptoms does not necessarily correlate with the lack of disease. Dr O'Hara would have known this, and that is why he was considering the lung pathology as important. I believe that Professor Lucas is dismissing the presence of bronchopneumonia, as did Dr Sumner before him, because this does not fit with his preconceived idea of the cause of death of this infant. My understanding from Dr O'Hara's report is that he was genuinely in doubt as to the extent of the contribution of dilutional hyponatraemia in the causation of cerebral oedema, and that the hypoxia occasioned by the child's bronchopneumonia could also have been a contributory factor.

In histopathology practice, personal confirmation of the histological diagnosis is extremely important. For example, for patients who are sent to Belfast for their cancer treatment, all of their cancer diagnoses are reviewed by the pathologists in Belfast: if you are a pathologist

being asked to comment on a tissue diagnosis, confirming the diagnosis by looking at the sections is essential. To refute a diagnosis when you haven't even seen the sections is reprehensible.

The only way a fair, unbiased and independent opinion could be obtained about the standard of the autopsy and the interpretation of the sections would be to approach a paediatric pathologist and provide them with just the information that Dr O'Hara had at the time of the autopsy, and a copy of his autopsy findings but redacting his commentary and conclusions to allow them to reach their own conclusion. I doubt that any paediatric pathologist would reach a firm conclusion that the cerebral oedema was wholly due only to the presence of hyponatraemia and I would think that they would be as circumspect as Dr O'Hara was in the formulation of his conclusions.

On page 252-003-006 Professor Lucas makes a personally disparaging comment about Dr O'Hara 'not liking difficult brain histology'. This is a comment which I believe is uncalled for and unprofessional: as above, Dr O'Hara was an experienced paediatric and perinatal pathologist and Professor Lucas should confine himself to the facts, not suppositions.

On page 252-003-007, Professor Lucas comments that I was incorrect to come to the same conclusion that Dr O'Hara had. May I point out that at the time I was asked to present myself to the Inquest, HM Coroner did not see fit to give me any of the background of the case: I was unaware of the reason why the case had been retrospectively turned into a coronial investigation. The Coroner did not share with me any of his correspondence with Dr O'Hara, or any expert report he had commissioned. I was not informed that this was now considered one case in a series of similar cases and that there were concerns about the clinical management because of this. The only documentation available to me was the copy of Dr O'Hara's original report, and his subsequent commentary for the Coroner. As I was not called to give evidence at the Inquest, to the best of my knowledge the pathological findings in this case have never been discussed.

Professor Lucas has stated 'there is some confusion as to whether she was merely asked to familiarise herself with the report, so as to read it out to the Court; or she was to re-examine the original histology material and the report'. Again, this raises the serious concern that Professor Lucas appears to think it is acceptable to discuss histopathological findings without actually seeing the histological sections. I would never, in any situation, profess an opinion on a case when I haven't seen the histology sections myself. To do so would be anathema to me: this is unprofessional and frankly dangerous.

In section O (page 252-003-010), Professor Lucas states assertively that the HM Coroner has only two options when a case is referred to him: he can take the case on, or he can tell the clinicians to complete a natural cause of death certificate.

This statement is incorrect and reflects Professor Lucas' ignorance of the system in Northern Ireland. In Northern Ireland we have a third way: the coroner can direct the doctor to complete a 'proforma letter'. This tends to be used where the doctor thinks the death is probably natural, but that they aren't sure of the exact sequence of events or the contribution from different disease processes in the causation of death. The proforma letter is a statement that the clinician makes outlining the circumstances of death and then the coroner makes a decision on how to certify the death without going as far as an autopsy examination. Professor Lucas appears to be unfamiliar with this. This is an option which

was available to the coroner at the time of Lucy Crawford's death but he chose not to exercise this option.

On page 252-003-011 to 012, Professor Lucas makes a serious allegation which I believe he should withdraw forthwith. He appears to be accusing Dr O'Hara (and the clinicians) of collusion in a conspiracy to cover up the cause of death, and he seems to have reached this conclusion because of the way in which the medical certificate of the cause of death (MCCD) was completed after the autopsy.

In this case, the doctors apparently had the option to certify death as due to gastroenteritis (as suggested by the coroner at the time and the forensic pathologist), but it appears that they wanted to know more about the cerebral oedema. On the MCCD, there is a 'tick box' on the back of the form to indicate that more information may be forthcoming about the cause of death at a later date. If there had been a long delay between the death and the autopsy, the death could have been certified as gastroenteritis, and this box ticked. However, in Northern Ireland, the autopsy is carried out within a short time after death, and so I submit that it may not be unreasonable to delay completing the MCCD for a few hours until the autopsy is completed and more information may be available to be added to the MCCD. The MCCD could have been completed prior to the autopsy being carried out, but to delay it very slightly to see if more detailed information could be added is not unreasonable in my opinion. The cause of death is not been 'covered up'. I think to call this a perversion and suggest that there is a conspiracy to hide the cause of death this way is unfair and uncalled for: in my opinion, delaying the completion of the MCCD until after the PM is more likely to have been a genuine attempt to complete the MCCD with as much information as possible. Certainly, if there was going to be several days delay between death and completion of the autopsy, the MCCD should have been completed shortly after death to allow for registration of the death, but in Northern Ireland, with an autopsy being completed so quickly, there is minimal delay.

Page 252-003-012: Professor Lucas asserts that it is usual UK practice for the relevant doctors to see the autopsy and discuss the findings: I agree with this statement and in my experience, most clinicians are very keen to attend the autopsy and do so. However, I would suggest that in this case, as the autopsy was carried out so very quickly after death, it may have been too short notice for the clinicians to rearrange clinical commitments.

He also states that clinico-pathological correlation is essential and should be carried out in all cases: this is another statement with which I agree. As a trainee in this hospital in 1993-1998 I recall attending morbidity and mortality meetings in Royal Belfast Hospital for Sick Children to discuss cases, so this forum did exist.

In his appendix (252-003-016), Professor Lucas seems to find something sinister in the fact that the autopsy was carried out very quickly after death, stating that only homicides would be carried out as quickly as this. This is frankly bizarre wording, and appears to insinuate that this was a potential homicide that was being covered up. Again, this reflects a deep ignorance about the system in Northern Ireland. In this region, we have a cultural tradition of being buried very quickly after death, usually within 2 or 3 days. As a result, any autopsies are carried out as quickly as possible. My paediatric pathologist colleague and I are essentially on stand-by: if a case is transferred to us from the more distant hospitals such as Erne or Altnagelvin, we will ask the funeral director bringing the body to us to wait for a couple of hours while the autopsy takes place so that he can return the baby to the

family as quickly as possible. In the rest of the country, there is often a considerable delay between death and the autopsy, and between the autopsy and the funeral. This doesn't generally happen in Northern Ireland. The fact that the autopsy on Lucy was carried out so quickly does not suggest that anything untoward was occurring; it merely reflects cultural practice in attempting to return the child to her family as quickly as possible so as not to delay the funeral.

Dr O'Hara was a pathologist who worked to the highest standards, and was internationally recognised as a paediatric and perinatal pathologist: my personal opinion is that he behaved professionally and ethically at all times, and I believe that if he had any concerns about the care of an infant he would have reported these as necessary. I think for Professor Lucas to insinuate that Dr O'Hara was involved in a conspiracy is offensive, uncalled for and unprofessional.

We occasionally have cases where a consented autopsy has been carried out, and we discover that the death was due to a complication of medical or surgical treatment which had not been diagnosed at the time of death (e.g. perforation of the small bowel due to a feeding tube insertion), and these cases are reported to the coroner retrospectively for investigation. I have had two cases like this in the last 10 years, and in each case, the clinician has reported the death to the coroner after the consented autopsy has been carried out, and I then send the report to the coroner. This is the system that was taught to me by Dr O'Hara as a trainee pathologist, and I have no doubt that he worked this way himself.

The impression I get is that Professor Lucas has been asked to review all of the deaths. When he was appointed to provide an opinion, he was presumably given the whole background to each case, including the fact that these were deaths in which there was a considerable degree of public interest, and with the whole background of this being one of a series of similar cases. Essentially, he was told 'this child died of hyponatraemia' and considered the autopsy report with this in mind.

In pathology, we have to be extremely cautious of bias. If I have a complex case, for example, a difficult tumour, and I ask my colleague for her opinion on it, I would give it to her with the history with which I was provided. So, I would say, for example, 'This is a tumour from a 2 year old child's kidney.' If I give it to her with 'This is a tumour from a 2 year old child's kidney and I think it is an X tumour', she is far more likely to agree with me, as I would with her. Bias is inevitable, and so we try and approach cases like this 'blind' i.e. without being coloured by someone else's opinion.

My impression from Professor Lucas's report is that he approached the case with a mindset of 'this baby died of hyponatraemia: how did the pathologist miss that diagnosis?' rather than a mindset of 'with the amount of information available to the pathologist at the time of the PM, and no knowledge of the surrounding events, what diagnosis would I have reached on this case? '

I think it is evident that Professor Lucas is reviewing the case with the benefit of hindsight and is not considering what the general awareness of hyponatraemia was at that time.

There is a prevailing attitude among some pathologists that the autopsy is the be-all and end-all, and that it is the so-called 'gold standard'. It is not: it is a clinical tool for the

investigation of disease processes and needs to be considered within the whole gamut of clinical investigations. It is an important investigation certainly, but it is not the responsibility of the pathologist to determine the cause of death on his or her own, without considering clinical input. I would suggest that Dr O'Hara's 'failure' to consider hyponatraemia as the cause of the cerebral oedema is indicative of his genuine uncertainty as to the role of hyponatraemia in the causation of this, and that his report instead defers to the clinicians in the final determination of the cause of death. This is not a failing on his part and should not be regarded as such.

The care of a living patient is very much a team approach: if the case is complex, the consultant clinician will obtain the opinion and advice of other specialists as needed, for example, other doctors, nurses and associated personnel, each with their own area of expertise. Why then, after the death of a patient, is the pathologist expected to reach an opinion entirely on their own with no input from any other specialist? As paediatric pathologists, we discuss cases with others who may have had a role in caring for the mother and baby such as midwifery staff, obstetricians and neonatologists in order to formulate an overall impression as to the mechanism and cause of death. We do not operate in the manner of 'I am the pathologist; this is the cause of death'. This is a behaviour perpetuated by the media such that the pathologist can say with absolute certainty that the death was caused by X, and the patient died at such and such a time. This is far from the truth: the autopsy findings may be equivocal and non-diagnostic, and it is then up to the pathologist and the clinicians to work together to see what diagnosis best fits the clinical presentation and the autopsy findings. I think Dr O'Hara's report was more diffident or empirical rather than dogmatic and reflected his thought processes accurately about the causation of cerebral oedema.

Caroline Gannon MA, FRCPath

Consultant paediatric pathologist
Northern Ireland Paediatric Pathology Service

HSC Business Services Organisation

Directorate of Legal Services
PRACTITIONERS IN LAW TO THE HEALTH & SOCIAL CARE SECTOR

2 Franklin Street, Belfast, BT2 8DQ
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Your Ref:

Our Ref:
HYP B04/05

Date:
20th June 2013

Ms Anne Dillon
Solicitor to the Inquiry
Arthur House
41 Arthur Street
Belfast
BT1 4GB

Dear Madam,

RE: INQUIRY INTO HYPONATRAEMIA RELATED DEATHS – RAYCHEL FERGUSON

I refer to the above and now enclose documentation prepared by Dr Gannon for your consideration. Dr Gannon will refer to the various guidelines referred to therein which define VAP in her evidence.

I trust that this is in order, however, should you wish to discuss this matter please do not hesitate to contact me.

Yours faithfully

JR Bolton

Joanna Bolton
Solicitor Consultant

Ventilator Associated Pneumonia

References

Ventilator-associated Pneumonia
Chastre J, Jean-Yves Fagon J-Y

Am J Respir Crit Care Med Vol 165. pp 867–903, 2002

This paper is a 'State of the Art' review on the subject in the American Journal of Respiratory and Critical Care Medicine, and has been cited over 1800 times in other papers.

From this document:

'Ventilator-associated pneumonia (VAP) continues to complicate the course of 8 to 28% of the patients receiving mechanical ventilation…'

'VAP, defined as pneumonia occurring more than 48 hours after endotracheal intubation and initiation of MV (mechanical ventilation)'

'Conceptually, VAP is defined as an inflammation of the lung parenchyma caused by infectious agents not present or incubating at the time MV was started. Despite the clarity of this conception, the past three decades have witnessed the appearance of numerous operational definitions, none of which is universally accepted. Even definitions based on histopathologic findings at autopsy may fail to find consensus or provide certainty. Pneumonia in focal areas of a lobe may be missed, microbiologic studies may be negative despite the presence of inflammation in the lung, and pathologists may disagree about the findings'

'Prolonged (more than 48 hours) MV is the most important factor associated with nosocomial pneumonia. However, VAP may occur within the first 48 hours after intubation. Since the princeps study by Langer and co-workers, it is usual to distinguish early-onset VAP, which occurs during the first 4 days of MV, from late-onset VAP, which develops five or more days after initiation of MV. Not only are the causative pathogens commonly different but the disease is usually less severe and the prognosis better in early-onset than late-onset VAP'

The American Thoracic Society has produced a guidance document for the diagnosis and management of hospital acquired respiratory infections:

American Thoracic Society Documents

Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia

This official statement of the American Thoracic Society and the Infectious Diseases Society of America was approved by the ATS Board of Directors, December 2004 and the IDSA Guideline Committee, October 2004

" VAP refers to pneumonia that arises more than 48–72 hours after endotracheal intubation."

NICE, the National Institute for Health and Clinical Excellence (NICE) in the UK, along with the National Patient Safety Agency, has issued guidance on safety solutions to reduce the incidence of VAP, and in that document has stated:

"There is no generally accepted definition of VAP in mechanically ventilated patients, but it is often defined as pneumonia that develops 48 hours or more after intubation with an endotracheal or tracheostomy tube and that was not present before intubation"

Ventilator associated pneumonia (Published 29 May 2012), accessible online at:

BMJ 2012;344:e3325

"a hospital acquired pneumonia that occurs 48 hours or more after tracheal intubation. It can usefully be classified as early onset or late onset pneumonia. Early onset pneumonia occurs within four days of intubation and mechanical ventilation, and it is generally caused by antibiotic sensitive bacteria. Late onset pneumonia develops after four days."

Ventilator Associated Pneumonia in Neonatal and Pediatric Intensive Care Unit Patients

Clin. Microbiol. Rev. 2007, 20(3):409.
Elizabeth Foglia, Mary Dawn Meier and Alexis Elward

'Ventilator-associated pneumonia (VAP) is pneumonia in mechanically ventilated patients that develops later than or at 48 h after the patient has been placed on mechanical ventilation'

From: Gannon, Caroline
Sent: 28/06/2013 12:49
To: [redacted]
Subject: Professor Lucas report

Dear Amanda,

I think Professor Lucas and I will have to disagree on some aspects of interpretation.

My comment about his paediatric experience was based on the fact that the report which was originally sent to me was entitled 'File 252-Expert paediatric pathology opinion'. He is not a paediatric pathologist and therefore this report cannot be entitled 'expert paediatric pathology report'. Had this been entitled 'expert histopathology report', or 'expert autopsy pathology report' I would have had no issue with the title. However, I think the title of the report as it stands is misleading.

I continue to disagree with his interpretation of bronchopneumonia. Whilst I agree that the histological appearance of ventilator associated pneumonia and community acquired pneumonia is the same, the criteria to meet the clinical definition of VAP have not been met in this case, and therefore community acquired bronchopneumonia is far more likely. As Professor Lucas states, it is the chronology of the case that is important, and VAP is generally defined as pneumonia appearing after 48 hours of ventilation (see my previous emails providing data and definitions from CDC in USA, the American College of Respiratory Physicians and NICE in UK): this child was ventilated for 18 hours as far as I am aware.

In section 5, I continue to disagree with Professor Lucas, and in my opinion, many pathologists would. I do not think it is appropriate to pass comment on the histological interpretation of a case without having seen the histological sections for myself, regardless of the type of case, regardless of whether this is a surgical biopsy, a surgical resection, or an autopsy case .

The interpretation of the histological findings required significant clinical input. Many patients are hyponatraemic before death to varying degrees. I understand that Dr Stewart, who completed the clinical request form for the autopsy, did not place much emphasis on hyponatraemia, simply listing it as one of the clinical features present. I do not know if Dr O'Hara had been given the exact levels, or if he had access to the full clinical notes. Whilst I agree that it is important that the pathologist has access to the medical notes, particularly in complex cases, this does not always happen.

I think the fundamental issue here is the communication between the pathologist and the clinician: I do not know how much communication took place between Dr O'Hara and his clinical colleagues, or what format this was i.e. was the case presented at a mortality meeting, were there phone calls or informal discussions? Whilst I agree that Dr O'Hara could have been more effusive in his clinical commentary, I think his approach reflects his position in that he was uncertain as to the cause of the cerebral oedema: whilst he may have known that the infant had

hyponatraemia, he may not have had the information of how severely hyponatraemic. I agree with Professor Lucas that a complex case like this should have had clinical discussion afterwards in order to reach a consensus diagnosis-I do not necessarily think that it is the pathologist's role to lead this however, unlike Professor Lucas.

I'm glad that Professor Lucas has had the courtesy to modify his language regarding the accusations of collusion, and the insinuation of 'homicide'. Whilst I fully accept that criticism of individual pathologists *work* as evidenced by their autopsy reporting may take place during an inquiry of this kind, to call into question an individual's *motivation* at the time of the autopsy should be no part of this.

Best wishes,

Caroline

Clinical Microbiology Reviews

Ventilator-Associated Pneumonia in Neonatal and Pediatric Intensive Care Unit Patients

Elizabeth Foglia, Mary Dawn Meier and Alexis Elward
Clin. Microbiol. Rev. 2007, 20(3):409. DOI: 10.1128/CMR.00041-06.

CLINICAL MICROBIOLOGY REVIEWS, July 2007, p. 409–425 Vol. 20, No. 3
0893-8512/07/$08.00+0 doi:10.1128/CMR.00041-06

Ventilator-Associated Pneumonia in Neonatal and Pediatric Intensive Care Unit Patients

Elizabeth Foglia, Mary Dawn Meier, and Alexis Elward*

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INTRODUCTION

Ventilator-associated pneumonia (VAP) is pneumonia in mechanically ventilated patients that develops later than or at 48 h after the patient has been placed on mechanical ventilation. VAP is the second most common hospital-acquired infection among pediatric and neonatal intensive care unit (ICU) (NICU) patients (41, 43). Overall, VAP occurs in 3 to 10% of ventilated pediatric ICU (PICU) patients (1, 28). Surveillance studies of nosocomial infections in NICU patients indicate that pneumonia comprises 6.8 to 32.3% of nosocomial infections in this setting (26, 39, 48). The incidence of VAP is higher in adult ICU patients, ranging from 15 to 30% (8, 31, 50, 70, 90).

NICU VAP rates vary by birth weight category as well as by institution. Two large studies are summarized in Table 1. The most recent National Nosocomial Infection Surveillance (NNIS) data from 2002 to 2004 show NICU VAP rates ranging from 1.4 to 3.5 per 1,000 ventilator days (68). In 1998, a cross-sectional study of hospital-acquired infections in 50 children's hospitals was performed by the Pediatric Prevention Network (88). Of 43 children's hospitals that returned questionnaires reporting NICU and PICU surveillance data, the VAP rate by device days was reported by 19 hospitals, and 12 hospitals provided VAP rates stratified by birth weight groups (Table 1). In this cross-sectional survey, VAP rates were highest for the 1,001- to 1,500-g and <1,000-g birth weight categories.

Differences in study methodology and case mix can influence the reported incidence of VAP (6). Surveillance methods differ across study institutions, introducing variability into the reported incidence of VAP. The influence of surveillance intensity on the reported prevalence of nosocomial infections is illustrated by a 41-month surveillance study in a children's hospital. Infection control surveillance was conducted twice a week for the first 2 years of the study and then daily for the second 2 years of the study through a nursing sentinel sheet. Those investigators found a 50% increase in the incidence of

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TABLE 1. VAP rates stratified by birth weight[a]

Study	Source	Range (median) of VAP rates by birth weight (g) of:			
		≤1,000	1,001–1,500	1,501–2,500	>2,500
NNIS[b]	86–102 high-risk nurseries	0.0–8.5 (2.4)	0.0–8.0 (0.0)	0.0–6.1 (0.0)	0.0–3.2 (0.0)
Stover[c]	12 NICUs	0.0–21.2 (3.5)	0.0–34.5 (4.9)	0.0–13.7 (1.1)	0.0–6.0 (0.9)

[a] Range given is the 10th to 90th percentile for NNIS data.
[b] See reference 68.
[c] See reference 88.

reported nosocomial infections following the introduction of daily surveillance (39).

NNIS definitions for VAP were revised in 2002, resulting in a more stringent definition of VAP. Studies of VAP incorporating these revised definitions reported lower rates of VAP, making it difficult to know if VAP was previously overdiagnosed or is now underdiagnosed. The revised definitions must also be considered when VAP rates are compared over time. Applying the Centers for Disease Control and Prevention (CDC) definitions for VAP in low-birth-weight infants introduces additional complexity in defining the incidence of VAP. CDC definitions for VAP exist for infants <1 year of age, but there are no specific definitions for low- or very-low-birth-weight infants. These patients often have comorbidities such as bronchopulmonary dysplasia, hyaline membrane disease, bloodstream infections (BSIs), and necrotizing enterocolitis that obscure clinical, laboratory, and radiographic evidence of VAP.

OUTCOMES

VAP is associated with increased morbidity in PICU patients, specifically, a longer duration of mechanical ventilation. Fischer et al. (34) performed a prospective cohort study to determine the delay of extubation attributable to VAP among neonates and children undergoing repair of congenital heart disease. Twenty-six of the 272 patients enrolled over a 22-month period developed VAP (9.6%). VAP diagnosis was made when the following criteria were met: fever exceeding 38.5°C, tachypnea and/or otherwise unexplained increased oxygen requirement, elevated white blood cell count ($>15 \times 10^9$ cells/liter), a cultured pathogen from tracheal aspirate together with a positive gram stain, and increased leukocyte contents, plus an infiltrate on chest radiographs persisting for 48 h or more (29). Using a Cox proportional hazards model to control for complexity of surgery, other respiratory complications, and secondary surgeries, those investigators found that the median delay of extubation attributable to VAP was 3.7 days (average of 5.2 versus 1.5 for patients with and without VAP, respectively). VAP rates increased dramatically for patients intubated for long periods of time. Among patients extubated within the first 3 days of surgery, only 4% developed VAP, compared to 40% of postoperative cardiothoracic surgery patients intubated longer than 30 days (34). Of the 26 VAP cases, 19 occurred within the first 3 to 6 days after surgery.

Presumed VAP is also associated with additional resource utilization with respect to antibiotic administration. VAP is the most common reason for the initiation of empirical antibiotics among PICU patients. A prospective cohort study at an academic tertiary care center performed in a PICU ($n = 456$) found that over half (56.6%) of all patients ($n = 258$) received antibiotics (33). Treatment for suspected VAP comprised 616 of 1,303 (47%) of the antibiotic treatment days. Those authors reviewed medical records to determine whether patients had evidence of an alternative explanation for the symptoms attributed to VAP, such as a viral infection. For 40% of the antibiotic days (552/1,303 treatment days), patients were classified as having no infection (i.e., did not meet clinical criteria as defined by the CDC) or as having a viral infection. Those authors concluded that an intervention targeted at decreasing antibiotic use for VAP would have the greatest impact on antibiotic use.

In pediatric populations, the published data are unmatched for severity of illness and univariate but suggest that pediatric patients with VAP may have excess mortality and length of PICU and NICU stay. The European Multicenter Trial examined the epidemiology of hospital-acquired infections in 20 units (5 PICUs, 7 neonatal units, 2 hematology-oncology units, and 8 general pediatric units) in eight countries, with a total of 14,675 admissions (710 admission in PICUs) (77). Those investigators found the infected patients had a longer mean length of stay in the PICU (26.1 ± 17.3 versus 10.6 ± 6 days; $P < 0.001$) than uninfected patients. The mortality rate was 10% for PICU patients with nosocomial infections. The mortality and length of stay associated specifically with VAP were not reported, although VAP accounted for 53% of the nosocomial infections in PICU patients. Mortality among uninfected PICU patients was not reported. Similarly, PICU length of stay in a 9-month prospective cohort study in an academic tertiary care center revealed that patients with VAP ($n = 30$) had a mean PICU length of stay of 27 days versus 6 days for uninfected patients ($n = 595$) ($P = 0.001$) (28). In that same study, the mortality rates with and without VAP were 20% and 7%, respectively ($P = 0.065$). Outcomes between patients on mechanical ventilation for more than 8 days with VAP ($n = 30$) and those without VAP ($n = 62$) were also compared. PICU length of stay was longer for VAP patients (27.53 ± 20.09 versus 18.72 ± 35 days), as was hospital length of stay (52.63 ± 37.43 versus 33.77 ± 49.51 days), but no differences in mortality rates for VAP (20%) or uninfected patients (21%) were found. Almuneef et al. (1) determined in a prospective cohort study ($n = 361$) that PICU lengths of stay with ($n = 37$) and without ($n = 324$) VAP were longer for patients with VAP (33.70 ± 30.28 versus 14.66 ± 17.34 days; $P = 0.001$). Statistically significant differences in mortality rates between patients with VAP and those without VAP were not found ($P = 0.362$). Both of those studies performed only univariate analyses to compare mortality rates among patients with and with-

out VAP. Multivariate analysis of predictors of mortality among PICU patients with sufficient numbers of VAP controlling for severity of illness both at admission and at the time of VAP as well as other potential predictors of death is necessary to determine the true attributable mortality of VAP in pediatric patients.

VAP has also been shown to increase hospital costs. The cost of VAP was analyzed in a 2-year study of PICU patients (n = 1919) with a single admission (38). The direct cost for patients with VAP (n = 56) was $38,614, and that for patients without VAP was $7,682. In a multivariate analysis controlling for other predictors of cost including age, severity of illness, underlying disease, and ventilator days, VAP was independently associated with a direct cost of $30,931 (95% confidence interval [CI], $18,349 to $82,638) (38). This is a single study from an academic tertiary care center; further studies are needed to determine whether the results from this single center are generalizable.

Recommendations for Current Practice and Future Research

Differences in the incidence of VAP occur as a result of the definitions used, persons doing surveillance, and frequency of surveillance. Standardization of surveillance methodology and validation of current definitions against a histopathologic or microbiologic "gold standard" would make interinstitutional comparisons meaningful, particularly in light of mandatory reporting of health care-associated infections. Recent literature suggests that pediatric VAP is associated with increased morbidity, antibiotic use, PICU cost, and PICU and hospital length of stay. Prospective studies using consistent definitions of VAP and controlling for severity of illness both at admission and at the time of VAP as well as other possible predictors of death and length of stay are necessary to define the true attributable mortality and cost associated with VAP in pediatric patients.

DIAGNOSIS

Clinical Criteria

The lack of a gold standard for the diagnosis of VAP in both adults and children makes an interpretation of the literature complex. The clinical criteria for the diagnosis of VAP have been established by the NNIS and the CDC (22). Patients who are mechanically ventilated for more than or equal to 48 h must have two or more abnormal chest radiographs with at least one of the following symptoms: new or progressive and persistent infiltrate, consolidation, cavitation, and/or pneumatoceles (in infants ≤1 year of age). However, in patients without underlying pulmonary or cardiac disease (respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary edema, or chronic obstructive pulmonary disease), one definitive chest radiograph is acceptable. In addition to abnormal chest radiographs, a patient must have at least one of the following symptoms: fever (>38°C) with no other recognized cause, leukopenia (<4,000 white blood cells [WBC]/mm^3) or leukocytosis (≥12,000 WBC/mm^3), and at least two of the following criteria: new onset of purulent sputum, change in character of sputum, increased respiratory secretions, or increased suctioning requirements; new onset of or worsening cough, dyspnea, or tachypnea; rales or bronchial breath sounds; and worsening gas exchange (e.g., O_2 desaturations [e.g., PaO_2/FiO_2 levels of ≤240], increased oxygen requirements, or increased ventilation demand). The criteria described above may be used to diagnose VAP in children; however, specific diagnostic criteria for VAP have been developed for infants ≤1 year of age and children >1 and ≤12 years of age. Infants that are ≤1 year old must have worsening gas exchange (oxygen desaturations, increased oxygen requirements, or increased ventilator demand) and at least three of the following criteria: temperature instability with no other recognized cause; new onset of purulent sputum, change in character of sputum, increased respiratory secretions, or increased suctioning requirements; apnea, tachypnea, nasal flaring with retraction of chest wall, or grunting; wheezing, rales, or rhonchi; cough; and bradycardia (<100 beats/min) or tachycardia (>170 beats/min). Children >1 and ≤12 years of age must meet at least three of the following criteria: fever (>38.4°C or >101.1°F) or hypothermia (<37°C or 97.7°F) with no other recognized cause; leukopenia (<4,000 WBC/mm^3) or leukocytosis (≥15,000 WBC/mm^3); new onset of purulent sputum, change in character of sputum, increased respiratory secretions, or increased suctioning requirements; rales or bronchial breath sounds; and worsening gas exchange (O_2 desaturations [pulse oximetry of <94%], increased oxygen requirements, or increased ventilation demand). NNIS/CDC criteria do not require microbiologic confirmation to diagnose pneumonia.

In summary, many of the diagnostic criteria are similar for the ≤1-year-old and >1- or ≤12-year-old age groups. Temperature instability is a diagnostic criterion for the ≤1-year-old age group; either temperature elevation or hypothermia is a criterion for the >1- and ≤12-year-old age group. For the <1-year-old group, cough, bradycardia, tachycardia, nasal flaring, grunting, and wheezing are diagnostic criteria not listed for the >1- or ≤12-year-old age groups, although for the older age group, dyspnea without further specific definition is a diagnostic criterion. Worsening gas exchange, change in character or amount of sputum, cough, rales, or bronchial breath sounds are criteria for diagnosis in all three age groups. We suggest that a consistent use of the age-specific definitions are preferred, although we were unable to find any published studies directly comparing the sensitivity and specificity of the age-specific definitions to those for any age group.

Clinical definitions for VAP may be applied inconsistently, and the lack of specific definitions of components of the clinical definition such as worsening gas exchange, oxygen desaturations, increased oxygen requirements, and increased ventilator demand may exacerbate this. Cordero et al. (19) determined differences in the application of the CDC definitions using NICU patients (n = 37) diagnosed with VAP by interpretation of CDC definitions by infection control practitioners (ICPs) and a positive tracheal aspirate culture. A panel of neonatologists reviewed the clinical and laboratory evidence as well as the radiographs. The neonatologists diagnosed VAP in only seven patients. The neonatologists categorized the other patients as having asymptomatic airway colonization (n = 12), BSI (n = 7), and airway colonization with equivocal signs of infection (n = 11). Among 8 of the 11 patients with equivocal signs of infection, the general radiologist report

TABLE 2. Accuracy of invasive diagnostic techniques for the diagnosis of VAP in adults and children[a]

Age group and source (reference)	No. of patients	Diagnostic technique	Gold standard(s)	SE (%)	SP (%)
Adults					
Rouby et al. (80)	26	Protected mini-BAL	Histopathology, lung tissue culture	70	69
Chastre et al. (13)	26	PSB	Histopathology, lung tissue culture	100	60
Fabregas et al. (30)	25	TBA	Histopathology, lung tissue culture	69	92
		Protected BAL		39	100
		BAL		77	58
		PSB		62	75
		Any invasive diagnostic technique		85	50
Children					
Gauvin et al. (42)	10	BAL (10^4 CFU/ml)	Expert opinion; 2/3 blinded to BAL and PSB results	50	80
		Bacterial index >5		78	86
		ICB		30	95
		Endotracheal cultures		90	40
Labenne et al. (60)	29	BAL (10^4 CFU/ml)	(i) Positive pleural fluid culture, (ii) computed tomography scan with abscess, (iii) histopathology, (iv) lung tissue culture, (v) blood and tracheal aspirate positive for same organism without other source, (vi) expert opinion; 2/3 blinded to BAL/PSB	72	88
		PSB		69	95
		ICB on gram stain and + BAL		79	88
		ICB on gram stain and + BAL and + PSB		90	88

[a] SE, sensitivity; SP, specificity; TBA, tracheobronchial aspirates; ICB, intracellular bacteria.

stated that the radiographic changes were suggestive of VAP; the neonatologist panel, reviewing the same radiographs, concluded that VAP was unlikely in these patients. Those authors concluded that an isolated positive tracheal aspirate does not distinguish between airway colonization and VAP and that routine radiology reports without definitive clinical and laboratory evidence may be misleading.

Invasive Testing in Adults

NNIS/CDC criteria for VAP do not require microbiologic confirmation. A brief review of invasive testing to confirm the diagnosis of VAP in adults will be performed, given the paucity of literature regarding invasive testing in children. It is unclear whether the adult experience can be extrapolated to children. Several studies have examined the accuracy of invasive testing for the diagnosis of VAP in critically ill adults (Table 2). Microbiologic examination of specimens obtained from bronchoalveolar lavage (BAL) or protected specimen brush (PSB) have an estimated 70% sensitivity and 77% specificity compared to histopathology and/or lung tissue culture (13, 30, 80).

In one of the most comprehensive studies of VAP in mechanically ventilated adults, Rouby et al. (80) sought to describe the histologic and bacteriologic characteristics of human nosocomial pneumonia and to evaluate the accuracy of protected mini-BAL for the diagnosis of VAP compared to lung tissue cultures and lung histology in patients who died while on mechanical ventilation. Twenty-six patients had both positive pathology and lung tissue culture; in 20 of these patients, the BAL and lung tissue culture results were concordant (Fig. 1).

Chastre (13) compared the accuracy of the bronchoscopic PSB to that of histologic and bacteriologic examinations of pulmonary specimens in adults ($n = 26$). PSB and lung cultures were highly correlated ($r = 0.65$; $n = 28$; $P < 0.001$) and higher in patients not on antibiotics within 1 week before death than in patients on antibiotics before death ($r = 0.55$; $n = 33$; $P < 0.001$). Pneumonia was not found by histology or lung tissue culture when PSB culture organisms were $<10^3$ CFU per ml. PSB cultures with $\geq 10^3$ CFU/ml identified all patients with histologically proven pneumonia. In patients treated with antibiotics, four patients had microorganisms isolated by PSB with concentrations of $>10^3$ CFU/ml not found in the lung tissue cultures.

Fabregas and colleagues (30) sought to determine the accu-

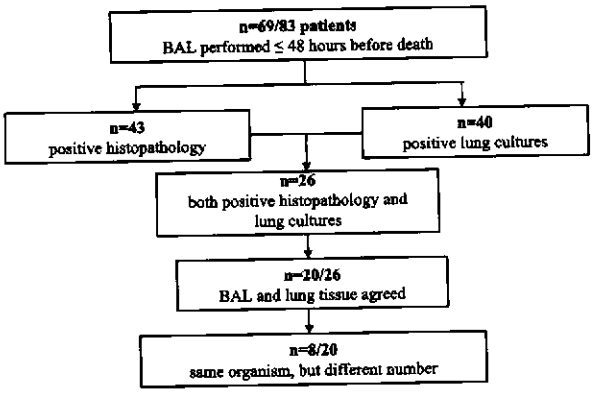

FIG. 1. Comparison of protected minibronchoalveolar lavage with histopathology and bacteriology for diagnosing VAP.

racy of clinical criteria and microbiologic testing for the diagnosis of VAP. The clinical pulmonary infection score (CPIS) was used to compare microbiological criteria, clinical criteria, and sampling techniques. Lung biopsies were performed for 25 mechanically ventilated patients immediately after death. The reference standard was the presence of positive histology for pneumonia or positive lung cultures. Chest X-ray infiltrates and at least two of three clinical criteria achieved sensitivity and specificity of 69% and 75%, respectively. The CPIS sensitivity and specificity were 77% and 42%, respectively. Noninvasive and invasive techniques achieved similar results. All diagnostic techniques combined (PSB, BAL fluid, and protected BAL fluid) achieved sensitivity and specificity of 85% and 50%, respectively.

A meta-analysis done in 2005 (n = 628) determined whether invasive testing altered the management and mortality of VAP in critically ill adults (84). VAP was confirmed bronchoscopically in 44 to 69% of the patients. Overall, antibiotics were almost three times as likely to be changed if a bronchoscopy was performed. In a separate pooled analysis of prospective uncontrolled trials, alteration in antibiotic prescription occurred 50% (36 to 65%) of the time. To our knowledge, no similar meta-analyses exist for pediatric populations.

Invasive Testing in Children

A few studies have examined the sensitivity and specificity of lower airway sampling in PICU patients and found the sensitivity and specificity of BAL (10^4 CFU/ml) to be 50 to 72% and 80 to 88%, respectively (42, 60) (Table 2). The nonbronchosopic BAL (NB-BAL) has been used in children as an alternative to fiberoptic BAL to diagnose pneumonia. This procedure is performed by placing a suction catheter into the endotracheal tube until resistance is met and then placing and suctioning back a small amount of sterile normal saline from the lower airway. The presence of bubbles in the returned fluid is suggestive that a lower airway sample containing surfactant has been obtained. Quantitative cultures of the fluid are then performed by the microbiology laboratory. This procedure may be advantageous compared to fiberoptic bronchoscopic techniques because bronchoscopic equipment is not required, a trained bronchoscopist is not necessary, and the diagnostic accuracy is comparable to that of fiberoptic techniques (36, 37, 71).

Gauvin et al. (42) performed a 27-month prospective cohort study of PICU patients suspected of having VAP in a tertiary academic care center. Of 30 patients, 10 were diagnosed with VAP and 9 were diagnosed with ventilator-associated tracheitis by an expert panel. The expert panel was used as the reference standard; they were given clinical, radiographic, and microbiologic data but were blinded to the BAL results. A bacterial index (sum of the log of all species obtained from BAL) of >5 had the highest correlation with the reference standard (concordance, 83%; kappa = 0.61), a sensitivity of 78%, a specificity of 86%, a positive predictive value of 70%, and a negative predictive value of 90% (42). Intracellular bacteria and gram stain from BAL were specific (95% and 81%, respectively) but not sensitive (30% and 50%, respectively) for the diagnosis of pediatric VAP, whereas clinical criteria and endotracheal cultures were sensitive (100% and 90%, respectively) but not specific (15% and 40%, respectively). That study concluded that blind BALs with a bacterial index of >5 are the most reliable method for diagnosing VAP in mechanically ventilated children. The study did not describe what proportion of patients were on antibiotics or the duration of antibiotic exposure prior to BAL.

Labenne et al. (60) also investigated the sensitivity and specificity of PSB and BAL in PICU patients with suspected VAP. The gold standards used by those investigators were a positive pleural fluid culture, computed tomography scan with pulmonary abscesses, histopathological evidence, positive lung biopsy (>10^4 CFU/gram), the same bacteria isolated in blood and endotracheal aspirate without another source, or clinical diagnosis using CDC guidelines established independently by two investigators blinded to PSB/BAL culture results. Of 103 patients, 29 were diagnosed with VAP, 10 were labeled as "uncertain," and 64 were classified as not having VAP. Thirteen of 64 patients with negative PSB and BAL cultures had antibiotics stopped after 48 h, 25 of 64 had negative cultures, and antibiotics were not used at all, and 28 of 38 had a positive tracheal aspirate culture but negative PSB and BAL, so antibiotics were discontinued prior to the standard 7-day treatment in that center. The sensitivity and specificity for BAL fluid culture were 72% and 88%, respectively. The intracellular bacteria and the BAL combined had sensitivity and specificity of 79% and 88%, respectively. Use of PSB culture results in combination with intracellular bacteria and BAL further increased the sensitivity and specificity to 90% and 88%, respectively. The PSB and BAL are effective methods of collecting distal samples and were helpful in diagnosing VAP. However, a combined diagnostic approach was superior to either one alone.

The safety of the NB-BAL in children has also been determined by several studies; few adverse experiences (n = 18) have been reported (12, 42, 60, 66, 79). The types of adverse events were sustained oxygen desaturation requiring increased ventilatory support (n = 11), pneumothorax (n = 4), hypotension (n = 2), and significant increase in intracranial pressure (n = 1). Of the 11 patients who experienced sustained oxygen desaturations, 7 patients were diagnosed with acute respiratory distress syndrome and saturations in the low 80s before the procedure was performed. Pneumothorax occurred in patients less than 1 month of age (n = 4). Hypotension occurred in patients requiring dopamine before the NB-BAL procedure began.

The safety of NB-BAL and BAL have been examined in a study evaluating the diagnosis of infectious and interstitial lung disease in children (n = 32) (79). That study found that both NB-BAL and the BAL were safe, as respiratory rate, heart rate, and oxygen saturation were monitored during the procedure and a minimum of 6 h afterwards. Patients did not require increased supplemental oxygen after the procedure, and no major airway bleeding occurred.

Computerized Surveillance

Recently, a retrospective study was performed to determine the accuracy of computerized surveillance to detect nosocomial pneumonia in two NICUs over a 2-year period (n = 2,932 patients) (46). The automated monitoring system was a natural language processor, referred to as the Medical Language Ex-

traction and Encoding system, that converted the electronic narrative reports to coded descriptions to identify patients with pneumonia. The automated monitoring system was compared to diagnosis of VAP by an ICP who performed prospective surveillance for pneumonia using NNIS definitions. A total of 1,277 patients had chest radiographs. In NICU 1, seven cases of VAP were identified by the ICP prospective surveillance; five of the seven cases found by the ICP were also identified by automated computer surveillance, which flagged an additional 61 patients with possible nosocomial pneumonia. Nine were considered to be inappropriately flagged by a second independent ICP review. The sensitivity and specificity of the computerized surveillance were 71% and 99.8%, respectively. The positive predictive value was 7.9%, and the negative predictive value was >99%. In NICU 2, 10 cases of VAP were identified by the ICP; only 2 of these were flagged by the computer. Further investigation revealed that 7 of the original 10 cases were not flagged by the computer because the original chest radiograph reports could not be found. Eight hundred thirty-six patients had chest radiographs performed; 84 were flagged by the computer as VAP. The sensitivity and specificity for NICU 2 could not be calculated. The findings of that study indicate that computerized surveillance may be useful in streamlining the identification of patients with possible VAP who require a more time-consuming chart review by an ICP. This system was not linked with microbiology reports. An unstudied area is computerized surveillance linking both radiology and microbiology reports.

Recommendations for Current Practice and Future Research

The lack of a gold standard plagues all literature regarding VAP in both adults and children. The current literature suggests that NB-BAL, BAL, and PSB are safe in older children who do not have severe hypoxemia, increased intracranial pressure, hemodynamic instability, or bleeding problems and that invasive testing is sensitive and specific compared to a reference of expert opinion. Comparison of the clinical definitions, including the age-specific definitions, with and without invasive testing against histopathology and/or lung tissue culture would be a valuable addition to the literature. The feasibility of using NB-BAL in a general patient population and the effect on antibiotic use remain to be determined.

Computerized surveillance has the potential for considerable time savings, particularly if electronic surveillance of the radiographic reports could be combined with that of microbiology and vital signs and validated against the current practical gold standard of application of CDC/NNIS definitions by an experienced clinician who has reviewed the complete medical record. Additional computerized surveillance studies are necessary to help further understand the impact that computerized surveillance may have on diagnosing pneumonia.

MICROBIOLOGY

Understanding the microbiology of VAP is critical for guiding decisions regarding empirical antibiotic therapy. A retrospective cohort study of the microbiologic etiology of VAP in the ICU setting was performed in three hospital settings: a large teaching hospital, a community hospital, and a children's hospital (5). The most commonly isolated organisms were similar across adult and pediatric hospitals: *Staphylococcus aureus* (28.4%), *Pseudomonas aeruginosa* (25.2%), and other gram-negative bacilli (26.6%). The microbiologies of early-onset and late-onset infections differed in the adult populations, but this was not the case in the children's hospital. *Pseudomonas aeruginosa* and *Staphylococcus aureus* were the most commonly isolated organisms in the children's hospital. *Pseudomonas aeruginosa* was more common in the PICU than in the NICU (33.3% versus 17%; $P = 0.01$), while *Staphylococcus aureus* was more common in the NICU than in the PICU (38% versus 17.6%; $P < 0.001$). A prospective cohort study of VAP in the same NICU was performed. Most of the tracheal isolates from patients with VAP grew polymicrobial cultures; the organisms most commonly isolated included *Staphylococcus aureus* (23%), *Pseudomonas aeruginosa* (38.4%), *Enterobacter* spp. (38.4%), and *Klebsiella* spp. (23%) (3). A limitation of these studies is that the vast majority of isolates were from endotracheal aspirates rather than from invasive sampling of the lower airway, and thus, the results may represent oropharyngeal flora.

Two studies reported differences in the microbiologies of early-onset and late-onset nosocomial pneumonia among children. Group B streptococci were most commonly isolated from infants with maternally acquired pneumonia (31.8%), while these organisms were rarely isolated in cases of late-onset pneumonia (1.3%). The frequency of *Staphylococcus aureus* increased from 2.4% of maternally acquired cases to 18.7% of non-maternally-acquired cases of pneumonia, and *Pseudomonas aeruginosa* frequency increased from 2.9% of maternally acquired cases to 12.9% of non-maternally-acquired cases of pneumonia (43).

A 41-month prospective surveillance study of nosocomial infections in a NICU divided pneumonia into early-onset (onset of symptoms within first 48 h of life) and late-onset (onset of symptoms more than 48 h after birth) infections (98). There were 35 cases of definite or probable early-onset pneumonia. In 26 of these cases, potential pathogens were identified: 18 (76.9%) group B streptococci, 1 (3.8%) group F streptococcus, 3 (11.5%) *Streptococcus pneumoniae* isolates, and 2 (7.7%) nontypeable *Haemophilus influenzae* infections. Late-onset pneumonia occurred in 36 of 358 (10%) neonates who were ventilated for over 24 h. Cultures were taken from endotracheal tubes or nasopharyngeal secretions for 41 episodes of late-onset nosocomial pneumonia. The most commonly isolated organisms were coliform spp. ($n = 18$; 43.9%), *Pseudomonas aeruginosa* ($n = 14$; 34.1%), and *Staphylococcus aureus* ($n = 6$; 14.6%).

RISK FACTORS FOR VAP IN NICU PATIENTS

In pediatric populations, the pathogenesis of VAP is not well studied. In adult patients, aspiration of oropharyngeal secretions, inhalation of aerosols containing bacteria, hematogenous spread, and bacterial translocation from the gastrointestinal tract are all considered to be mechanisms of the development of VAP (89).

Neonates have unique characteristics predisposing them to nosocomial infections. These patients' immature immune sys-

tems place them at increased risk for infection (24). Skin and mucous membranes are more permeable and are less effective barriers to infection (47). Abnormal granulocyte migration and bacterial digestion in these patients have been demonstrated. Additionally, decreased activity of complement, particularly complement opsonization, occurs in newborns (40). Lastly, hypogammaglobulinemia occurs in premature newborns. Maternal immunoglobulin G (IgG) is transported to the fetus in the second and last trimesters of pregnancy, and fetal IgG levels reach maternal levels by term (58). Levels of IgG are lower in premature newborns, as maternal levels have not yet been attained. In the initial months following birth, maternal IgG levels drop, and it takes the infant months to produce ample levels of IgG and other immunoglobulins.

Low birth weight has been shown to be a risk factor for the development of nosocomial pneumonia. A 41-month surveillance study demonstrated a significant association between a birth weight of <1,500 g and a higher rate of nosocomial pneumonia (48). However, low birth weight may be a marker for an increased duration of mechanical ventilation. That study was limited by the lack of a specific control for the duration of mechanical ventilation. Apisarnthanarak et al. (3) focused on estimated gestational age (EGA) rather than birth weight in their 10-month-long case control study of 211 intubated NICU patients. VAP rates were much higher in babies with an EGA of <28 weeks (19 VAP cases) than in babies with an EGA of ≥28 weeks (5 VAP cases) ($P < 0.001$) (3). The VAP rate per 1,000 ventilator days was also higher in babies with an EGA of <28 weeks (6.5/1,000 ventilator days) than in babies with an EGA of ≥28 weeks (4.0/1,000 ventilator days) but was not statistically significant ($P = 0.34$) (3). Not all investigators found an inverse relationship between birth weight and frequency of nosocomial pneumonia. A prospective surveillance study of nosocomial infections in seven Brazilian NICUs found that the rate of nosocomial pneumonia was actually higher in neonates with birth weights of >1,500 g than in babies with birth weights of ≤1,500 g (4.4/1,000 patient days versus 2.8/1,000 patient days) (72).

Prior BSIs have been identified as a being a risk factor for VAP in NICU patients. In babies with an EGA of <28 weeks, history of a prior BSI was the only significant risk factor for the development of VAP in multivariate analyses after controlling for the duration of mechanical ventilation ($P = 0.03$). Although none of the cases of VAP were caused by the same organism as that which caused the BSI, those authors suggested that prior BSI may serve as a surrogate for severity of illness rather than actually contributing to VAP (3).

The design of the NICU may also have an effect on the incidence of nosocomial infections and specifically VAP. A 5-year prospective study of nosocomial infections in a NICU was performed (44). Midway through that study, the NICU location was moved from cramped quarters adjacent to a busy medical ward to a new facility. The new nursery had a 50% increase in staffing and improved infection control features. In the old nursery, 16 of 492 patients had pneumonia, whereas in the new nursery, only 1 patient of 419 had pneumonia. While the new nursery had improved structural infection control measures such as more space per patient, a large number of sinks, and a separate isolation room, it is not clear if other practices of care, such as head-of-bed elevation or suctioning, changed after the move to the new unit. Those authors did not report any changes in infection control surveillance or diagnosis in the new nursery.

RISK FACTORS FOR VAP IN PICU PATIENTS

Several prospective cohort studies described risk factors for pediatric VAP. In a prospective cohort study at a tertiary care center, genetic syndrome (odds ratio [OR], 2.37; 95% CI, 1.01 to 5.46), transport out of the PICU (OR, 8.90; 95% CI, 3.82 to 20.74), and reintubation (OR, 2.71; 95% CI, 1.18 to 6.21) were all independent predictors of pediatric VAP (28). That study also found that primary BSIs were associated with the development of VAP, as five of the nine patients with primary BSIs and VAP had the BSI first. Another prospective cohort study identified prior antibiotic use (OR, 2.45; 95% CI, 1.112 to 5.405), continuous enteral feeding (OR, 2.29; 95% CI, 1.093 to 4.798), and bronchoscopy (OR, 5.04; 95% CI, 1.665 to 15.266) as being independent predictors of pediatric VAP (1). Immunosuppressant drugs (OR, 4.8; $P = 0.04$), immunodeficiency (OR, 6.9; $P = 0.06$), and neuromuscular blockade (OR, 11.4; $P = 0.002$) were also found to be independent predictors in another prospective cohort study (32). Torres et al. (94) identified several factors associated with increased risk of developing VAP: reintubation (OR, 4.95; 95% CI, 3.48 to 7.04; $P = 0.000012$), gastric aspiration (OR, 5.05; 95% CI, 3.28 to 7.77; $P = 0.00018$), mechanical ventilation for >3 days (OR, 1.17; 95% CI, 1.15 to 1.19; $P = 0.015$), chronic obstructive pulmonary disease (OR, 1.89; 95% CI, 1.38 to 2.59; $P = 0.048$), and positive end-expiratory pressure (OR, 1.85; 95% CI, 1.30 to 2.64; $P = 0.092$). In nosocomial pneumonia patients, factors associated with increased mortality risk were a rapidly fatal underlying condition (OR, 8.84; 95% CI, 3.52 to 22.22; $P = 0.0018$), worsening acute respiratory failure from developing pneumonia (OR, 11.94; 95% CI, 4.75 to 30; $P = 0.0096$), septic shock (OR, 2.83; 95% CI, 1.41 to 5.78; $P = 0.016$), inappropriate antibiotic treatment (OR, 5.81; 95% CI, 2.70 to 12.48; $P = 0.02$), and non-cardiac-surgery ICU patients (OR, 3.38; 95% CI, 1.70 to 6.71; $P = 0.08$) (78). Medications associated with the development of VAP are NADP, steroids, and histamine type 2 receptor blockers (28).

Recommendations for Current Practice and Future Research

Several factors have been identified as being risk factors for VAP in NICU and PICU patients. Many of these factors reflect a risk for aspiration such as that which may occur during reintubation, physical movement out of the ICU, and bronchoscopy. In addition, neuromuscular weakness and immunodeficiency may predispose a patient to VAP, as does prolonged mechanical ventilation. A risk stratification system incorporating preventable and nonpreventable risk factors for pediatric VAP might assist intensivists in the development of pediatric VAP prevention bundles and methods for identifying meaningful indicators as a measure of an institution's success at VAP prevention. Larger, multicenter, randomized controlled trials using a standard reference definition of VAP to test interventions to prevent aspiration in children would be useful. Testing the efficacy of a standardized assessment of readiness

to wean mechanical ventilatory support would also be useful in this patient population, as would a standardized assessment of pain and the need for sedation and neuromuscular blockade.

PREVENTION

Several recommendations have been given to decrease VAP. The CDC and Healthcare Infection Control Practices Advisory Committee suggest using orotracheal tubes (instead of nasotracheal tubes) when patients require mechanical ventilation, changing breathing circuits of ventilators only if they malfunction or if they are visibly contaminated, and using endotracheal tubes with dorsal lumens to allow respiratory secretions to drain (89). There are no recommendations for the preferential use of sucralfate, histamine 2 receptor antagonists, or antacids for stress bleeding prophylaxis (89).

Head-of-Bed Elevation

Supine position has been associated with VAP in adult patients, which is thought to be related to an increase in gastroesophageal reflux and aspiration. Semirecumbent positioning has been demonstrated to decrease surrogate outcomes such as aspiration and gastroesophageal reflux in adults (16), and one clinical trial demonstrated a dramatic decrease in the incidence of confirmed VAP in patients with head-of-bed elevation (5% versus 23%; OR, 6.8; 95% CI, 1.7 to 26.7) (25). The efficacy of semirecumbent positioning in preventing VAP in children has not been established. One age- and sex-matched case control study of nosocomial pneumonia in children found that head-of-bed elevation did not differ between cases and controls. That study was limited by small numbers of cases and controls (n = 9 for each group) (10). Additionally, size-related factors must be considered in the utility of semirecumbent positioning in children. For instance, elevating the head >30° is logistically challenging for small pediatric patients such as infants and toddlers.

In-Line Suctioning

Endotracheal suctioning is used for eliminating bronchopulmonary secretions from the airway. Traditional open endotracheal suction requires disconnection from the ventilator. This process has been shown to result in increased intracranial pressure, increased mean blood pressure, and hypoxia in mechanically ventilated children (27, 57). The introduction of a closed multiuse suction catheter in the 1980s allowed endotracheal suctioning without disconnection from the ventilator. In critically ill adult populations, closed suction systems have been shown to result in fewer physiologic disruptions such as arterial and venous desaturations and arrhythmias (54).

Closed endotracheal suction systems present the potential for bacterially contaminated secretions to pool in the lumen of the tube, with reinoculation of the respiratory tract with each repeated suctioning. On the other hand, a closed system could potentially decrease environmental contamination of the respiratory device. Many studies of critically ill adults have compared the incidence of airway colonization and nosocomial pneumonia in patients on a closed multiuse system to that in patients on a single-use open suction system. The frequency of airway colonization has been shown to be significantly more frequent in patients on the closed suction system (23). However, studies have not demonstrated an increased frequency of nosocomial pneumonia in patients on the closed suction system (23, 54). Indeed, a more recent prospective randomized study of 102 ventilated adults demonstrated an increased risk of VAP for patients with an open suction system compared to a closed suction system (adjusted risk, 3.5; 95% CI, 1.0 to 12.33) (17). There are currently no CDC recommendations regarding the preferential use of closed or open suction systems, nor are there recommendations regarding the frequency of change for multiuse closed suctioning systems in a single patient (89).

A single study has compared open and closed suction systems in critically ill children. Cordero et al. (20) monitored 133 ventilated NICU patients who were alternately assigned to a closed or open suction system for bacterial airway colonization, nosocomial pneumonia, BSI, and bronchopulmonary dysplasia. A definition of nosocomial pneumonia required radiographic evidence of "probable" pneumonia (new airspace disease or a parenchymal process) and positive blood cultures and tracheal culture for a respiratory pathogen. Colonization patterns from tracheal cultures were comparable between groups, with gram-positive colonization occurring by the second week of intubation and gram-negative colonization occurring after the third week of ventilation. There were no significant differences in the incidences of VAP or BSIs or mortality between patient groups. Additionally, the numbers of endotracheal suctions per day, the numbers of reintubations, the incidences and severities of bronchopulmonary dysplasia, and the numbers of infants discharged on supplemental oxygen were similar between groups. Finally, 40 of 44 (91%) NICU nurses judged the closed suction system to be easier to use, less time-consuming, and better tolerated by NICU patients.

H_2 Blockers/Sucralfate

The acidification of gastric contents is thought to decrease colonization with potentially pathogenic bacteria. Stress ulcer prophylactic medications that increase gastric pH, like H_2-antagonists and antacids, may increase colonization with pathogenic organisms and increase the risk of VAP (18). Sucralfate is an alternative stress ulcer prophylactic agent that does not alter gastric pH, and this medication may lower the risk of VAP while maintaining stress ulcer prophylaxis. Over 20 clinical trials with adults have investigated the risk of VAP associated with these medications. Of seven meta-analyses of these clinical trials, four found a significant reduction in the incidence of VAP in patients treated with sucralfate compared to patients receiving H_2 antagonists. The same effect occurred in the other three analyses but did not reach statistical significance. Three of these meta-analyses demonstrated a significant reduction in mortality associated with sucralfate therapy (16).

Two clinical trials compared the risk of VAP with various methods of stress ulcer prophylaxis in pediatric patients. A retrospective study included 155 PICU patients who had a nasogastric tube in place and were mechanically ventilated for >48 h: 54 were given ranitidine, 53 were give sucralfate, and 48 were not on stress ulcer prophylaxis (62). There was no signif-

icant difference in the incidences of VAP between patients treated with ranitidine and patients treated with sucralfate (11.1% versus 7.5%; $\chi^2 = 0.40$; $P = 0.52$). That study had several limitations. Patients were not randomized into study groups, and patient characteristics differed between patients given stress ulcer prophylaxis and those who were not given prophylaxis. The retrospective nature of the study may have resulted in errors in diagnosing VAP.

A prospective study was performed to study the incidence of VAP and associated mortality among patients randomized to one of four groups for stress ulcer prophylaxis in Turkey (101). That study included 160 PICU patients: 38 received sucralfate, 42 received ranitidine, 38 received omeprazole, and 42 did not receive prophylaxis. VAP occurred in 70 of 160 (44%) patients, ranging from 41 to 48% in individual treatment groups. There was no difference in the incidence of VAP across treatment groups. The overall mortality rate was 35 of 160 (22%) and did not differ significantly among treatment groups, ranging from 21 to 23% across groups. The overall incidence of VAP (44%) in this study was much higher than that reported in other pediatric studies from referral hospitals (5.1% to 10.2%) (1, 28). It is possible that VAP was overdiagnosed in that study, although diagnostic criteria used in that study were similar to criteria used in this country. If VAP was overdiagnosed, this effect would likely be distributed throughout all study groups. That study may also have been underpowered to detect differences in the incidences of VAP among these patient groups.

Both of those studies failed to demonstrate a difference in the incidence of VAP in patients treated with sucralfate compared to those treated with agents that alter gastric pH. Additionally, neither study demonstrated an increased risk of VAP in patients treated with agents that alter gastric pH compared to that in patients with no treatment. The microbiologies of infections were similar across treatment groups, and many infections were caused by organisms that are not likely to be affected by stress ulcer prophylaxis. It is possible that the study sizes presented were simply too small to appreciate a significant difference in the incidence of VAP, or it is possible that stress ulcer prophylaxis is not associated with VAP in the pediatric population. Larger prospective randomized studies of children are needed to asses the impact of stress ulcer prophylaxis on VAP and whether sucralfate has a protective effect compared to medications that decrease gastric acidity.

Hand Hygiene

Efforts at reducing person-to-person transmission of bacteria are crucial for preventing nosocomial infections. Significant bacterial contamination of hospital employees' hands during routine patient care has been demonstrated (75). The concept that routine hand washing by health care workers reduces nosocomial infections is not new, but the first study investigating the impact of hand hygiene on the rate of hospital-acquired infections in NICU patients was recently performed (99). A 2-year-long multimodal intervention was instigated, which consisted of formal lectures, written and posted instruction regarding proper hand hygiene technique, covert observation, financial incentives, and regular feedback of observed hand hygiene rates. Surveillance of hand washing compliance and nosocomial infections from the pre- and postintervention periods were compared. The rate of hand hygiene compliance increased from 43% at baseline to 80% during the intervention, and the rate of respiratory infections decreased from 3.35 to 1.06 per 1,000 patient days ($P = 0.002$) in the pre- and postintervention periods. The two parameters were statistically correlated ($r = -0.385$; $P = 0.014$). That study is helpful in demonstrating an association of hand hygiene and prevention of nosocomial pneumonia, but it has limitations. The before-after design of the study makes it difficult to assess if a reduction in the rate of pneumonia is attributable exclusively to the increase in hand hygiene. An intervention of this magnitude may have altered other clinical practices related to the spread of bacterial contamination, as employees' awareness of preventing nosocomial infections was increased. Those authors did point out that no changes in the use of surfactant or suction procedures occurred during the study period but did not comment on other procedural changes that may have occurred such as head-of-bed elevation, stress ulcer prophylaxis, or oral hygiene changes. Additionally, while rates of hand hygiene compliance remained at 81% during the 16-month postintervention period, it is unclear how sustainable this effect was after observations were discontinued.

A prospective study of a 3-month-long implementation of an intervention to decrease rates of nosocomial infection in NICU patients was undertaken (69). The intervention consisted of three parts: (i) grouping of all blood-taking tasks to reduce the number of daily blood draws, (ii) reducing the frequency of blood investigations after stabilization of acute illness, and (iii) using an aseptic delivery system of drugs though a central venous catheter to reduce peripheral intravenous access. The incidences of nosocomial infection in the NICU between the 1-year preintervention period and the 1-year postintervention period were compared. VAP rates declined from 3.3/1,000 ventilator days to 1.0/1,000 ventilator days after the intervention. Again, that study was limited by the before-after nature of the design. Those authors acknowledged that practices regarding mechanical ventilation also changed during the study period, as patients were weaned from the ventilator more aggressively and as soon as possible. Earlier weaning may have contributed to lowering the VAP rates, as prolonged intubation is a risk factor for VAP in children (62).

The importance of hand hygiene in preventing horizontal transmission of pathogens among mechanically ventilated patients was highlighted by a study performed by Sole et al. (86) to evaluate the proportion of suctioning devices colonized with pathogenic bacteria and to correlate the bacteria found on respiratory equipment with those found in patients' mouths and sputum. Those investigators found that within 24 h of changing to new suctioning equipment, 94% of tonsil suction tubing, 83% of in-line suction tubing, and 61% of distal suction connectors were colonized with pathogenic bacteria similar to those found in the patients' oropharynx and sputum (86).

Selective Decontamination

The impact of using topical antibiotics on tracheostomy sites on exogenous colonization or infection of the lower airways has been studied. A 2-year-long prospective observational cohort study was performed with 23 children who were treated with 2% paste of polymyxin E and tobramycin on the trache-

ostoma four times a day for the first two postoperative weeks (65). Only 1 of 23 (4%) patients developed exogenous colonization or infection of the lower respiratory tract, which was lower than that in historical controls (6/22 [27%]). While topical antibiotics may be useful in preventing exogenous colonization or infection of the lower airways in children with tracheostoma, the risk of endogenous colonization remains high. Endogenous colonization or infection occurred in 15 episodes in 14 of 23 (61%) patients during the 2-week postoperative period.

Many investigators have studied the efficacy of selective digestive tract decontamination (SDD) in preventing VAP. SDD traditionally consists of a regimen of topical antimicrobials applied to the oropharynx and through a nasogastric tube, with the aim of reducing the burden of pathogenic bacteria in aspirated secretions. While the majority of trials have focused exclusively on the use of topical antimicrobials, many have also used a short course of intravenous antimicrobial therapy. Seven meta-analyses of randomized, controlled trials of SDD in adults all showed a significant reduction in the risk of VAP, and four of those analyses also demonstrated a significant reduction in mortality in patients treated with SDD (16). One recent meta-analysis divided trials into those that used topical antibiotics alone and those that used a combination of topical and systemic antimicrobials for the prevention of nosocomial respiratory infections (61). That analysis included 32 randomized, controlled trials including a total of 5,185 adult patients. A protective effect was demonstrated in trials comparing patients on a combination of systemic and topical antibiotics with controls (OR, 0.35; 95% CI, 0.29 to 0.41) and in trials comparing patients on topical antibiotics alone with controls (OR, 0.52; 95% CI, 0.43 to 0.63). A significant reduction in mortality was seen only in trials that used a combination of topical and systemic therapy (OR, 0.78; 95% CI, 0.68 to 0.89). Mortality from VAP was not reduced when topical therapy alone was used (OR, 0.97; 95% CI, 0.81 to 1.16).

Recent evidence suggests that results from some of those trials may be overly optimistic. A meta-analysis of 32 primary trials of SDD was performed to assess the impact of study methodology on results (97). Study methodology was evaluated based on allocation and concealment, patient selection, patient characteristics, blinding, and definition of nosocomial pneumonia. That analysis found an inverse relationship between the methodologic quality and benefit of SDD on the incidence of pneumonia, suggesting that the benefit of SDD for the prevention of VAP may be overestimated by many clinical trials (97).

Studies focusing on the use of SDD to prevent VAP in children have conflicting results. A prospective study of SDD in 226 PICU patients randomized study subjects into a treatment (n = 116) or control (n = 110) group (81). The treatment group received colistin, tobramycin, and nystatin orally or through a nasogastric tube every 6 h, and patients were monitored for the development of nosocomial infection in any body site. There were 87 episodes of any nosocomial infection in 65 of 226 (28.8%) patients. The most common nosocomial infections were catheter-related bacteremia, sepsis, pneumonia, and urinary tract infection. The overall incidence of nosocomial infection across all sites did not differ between treatment and control groups. However, when infections were studied by body site, patients in the treatment group had a significantly lower frequency of pneumonia (2.6% versus 7.2%). In multivariate analyses, SDD retained a protective effect against pneumonia (OR, 0.21; 95% CI, 0.06 to 0.8). There was no significant difference in overall mortality between the treatment and control groups (six versus five patients). Patients in that study were randomized and were well matched for most variables with the exception of severity of illness; the treatment group had more severely ill patients. This difference in severity of illness would be expected to skew the results toward the null hypothesis, but there were actually fewer cases of pneumonia in the more severely ill group who were treated with SDD.

A prospective, randomized, double-blinded study was performed to determine the efficacy of SDD in preventing nosocomial infections in severely burned (>30% total body surface area) PICU patients (7). Patients were randomized to the treatment group (n = 11) or control group (n = 12). The treatment group was given a mixture of polymyxin E, tobramycin, and amphotericin B four times daily by nasogastric tube. No significant differences regarding demographics, underlying conditions, inhalation, injury, or percent of surface area burned between patient and control groups existed. There was no difference in the proportion of patients with colonization of wounds, feces, nasogastric aspirates, or sputum between groups at the start of the study or throughout the study. No significant differences between groups were noted with regard to the serious complications measured: sepsis, pneumonia, gastrointestinal bleeding, respiratory distress syndrome, and mortality. The group treated with SDD had a higher incidence of diarrhea than the control group (82% versus 17%; P = 0.003). Results from that study suggest that SDD may not prevent nosocomial infections in pediatric patients. However, that study was limited by a small sample size (n = 23). Additionally, results of that study may not be generalizable to all PICU patients, as that study was restricted to burn patients.

A prospective nonrandomized cohort study was performed to determine the impact of SDD on nosocomial infections in NICU patients (49). The decision to administer decolonization was left to attending physicians. Investigators later determined if patients had received well-performed decolonization (decolonization within the first 5 days with oral polymyxin E, tobramycin, and nystatin), incorrect decolonization (started after 5 days or less than three drugs used), or no decolonization. The incidence of nosocomial respiratory infection was lower in patients given well-performed (2.5%) or incorrect (7%) decolonization (P value not given). Interestingly, the incidence of nosocomial respiratory infection was lowest in patients who were not decolonized (1%). However, because patients were not randomized into treatment groups, significant underlying differences between groups, including gestational age, birth weight, NICU length of stay, exposure to central catheters, and respiratory support, existed. To control for these differences, investigators performed logistic regression and found that well-performed selective intestinal decolonization exerted a protective effect toward nosocomial infections of intestinal origin (OR, 0.17; 95% CI, 0.03 to 0.83). This group of infections included respiratory tract infections, sepsis, surgical wound infections, and urinary tract infections. The investigators did not supply a separate analysis of the impact of SDD on respiratory infections alone.

Oral Hygiene

The CDC suggests that health care facilities develop and implement a comprehensive oral hygiene program for patients in acute-care settings or residents in long-term care facilities who are at high risk for health care-associated pneumonia (89).

Fitch et al. (35) demonstrated that an oral care protocol and scores developed by a dental hygienist could be used by ICU nurses to improve oral health in critically ill adult patients. Mean oral inflammation scores were significantly lower after the implementation of a standard oral care protocol using toothpaste, antibacterial mouthwash, and oral gel (3.9 [standard error of the mean, 3.0] versus 12.4 [standard error of the mean, 2.2]; $P = 0.03$). Those investigators also noted lower mean scores for oral candidiasis, purulence, bleeding, and plaque, but the differences were not statistically significant. The dental hygienist and nurses' assessments had a high degree of interrater reliability (kappa = 0.64). The scores used in that study were developed by one of the investigators and reviewed by other dental faculty members but were not validated in other patient populations. In addition, those investigators did not examine the effect of the standard oral care protocol on the incidence of VAP or bacterial oropharyngeal colonization.

Bergmans et al. (9) performed a prospective, randomized, placebo-controlled, double-blind study in adult ICU patients to determine if VAP was preventable by the modulation of bacterial flora in the oropharynx. Those investigators compared topical prophylaxis to the buccal cavities with 2% each gentamicin, colistin, and vancomycin ($n = 87$) to an Orabase placebo group ($n = 78$) (group A) and a second control group of patients admitted to an ICU where no topical preparation was used ($n = 61$) (group B). Topical prophylaxis eradicated a significantly higher proportion of organisms present on admission in the oropharynx in the treatment group than in either control group (75% of the treatment group versus 0% in the placebo group and 9% in the no-preparation ICU group; $P < 0.00001$). Topical prophylaxis was also effective in eradicating organisms from the trachea (treatment group, 52%; group A, 22%; group B, 7% [$P \leq 0.03$]). The incidence of VAP was also lower in the treatment group (10%) than in the controls (group A, 31% [$P = 0.001$]; group B, 23% [$P = 0.04$]). That study concluded that preventing oropharyngeal colonization is protective against VAP, with an absolute risk reduction of 0.21 (95% CI, 0.09 to 0.33); treating five patients with topical antibiotics would prevent one case of VAP. VAP was defined prospectively using CDC definitions and confirmed with BAL or PSB. However, it is unclear whether the person who determined whether the patients had VAP was blinded to the treatment group. In addition, the treatment group received enteral feeds more frequently than controls, which could alter oropharyngeal flora. The placebo group (group A) was significantly more likely than the treatment group to receive sucralfate, another potential confounder of oropharyngeal colonization.

Pineda et al. (73) performed a meta-analysis to determine if oral chlorhexidine treatment reduced the incidence of VAP. Four randomized controlled trials including 1,202 patients met inclusion criteria for the meta-analysis. Patients in the chlorhexidine treatment group were less likely to develop VAP than those in the control group (4% [24 of 587] versus 7% [41 of 615]), although the difference did not reach statistical significance (OR, 0.42; 95% CI, 0.16 to 1.06; $P = 0.07$). ICU length of stay and duration of mechanical ventilation did not differ between the groups. Mortality was not significantly different between the two groups (OR, 0.77; 95% CI, 0.28 to 2.11; $P = 0.6$). The magnitude of the protective OR is striking, as is the proximity of the CIs to statistical significance, suggesting that additional studies with larger sample sizes might demonstrate a significant protective effect from oral chlorhexidine rinses. Of note, patients in those studies received either a 0.12% chlorhexidine rinse twice a day ($n = 914$) or 0.2% chlorhexidine gel three times a day ($n = 288$).

A meta-analysis of seven randomized controlled trials ($n = 1,650$ patients) performed by Chlebicki and Safdar (15) revealed a similar protective effect with a relative risk (RR) of 0.74 (95% CI, 0.56 to 0.96; $P = 0.02$) using a fixed-effects model and a RR of 0.70 (95% CI, 0.47 to 1.04; $P = 0.07$) using a random-effects model for patients treated orally with chlorhexidine. The risk reduction was even higher in cardiac surgery patients (RR, 0.41; 95% CI, 0.17 to 0.98; $P = 0.04$) (15).

The Bundle Approach

In December 2004, the Institute for Healthcare Improvement (IHI) challenged hospitals to save 100,000 lives by June 2006 (21). One of the six evidence-based guidelines to be implemented was the prevention of VAP. The VAP bundle for adults is to (i) avoid/decrease endotracheal intubation and duration of mechanical ventilation whenever possible, (ii) use orotracheal and orogastric tubes to decrease the risk of hospital-acquired sinusitis, (iii) avoid heavy sedation and neuromuscular blockade with depression of cough reflexes, (iv) maintain endotracheal cuff pressures to greater than 20 cm water, (v) prevent condensate in tubing from entering the lower respiratory tract, (vi) maintain head-of-bed elevation at 30° to 45°, (vii) maintain oral care, and (viii) maintain hand hygiene (21, 67).

The team approach using the IHI bundle has been shown to be successful in reducing VAP (21). The bundle approach has been used at the Children's Hospital in Boston and at Vanderbilt Children's Hospital. In the latter, an education and intervention termed "ZAP VAP" was put into practice, with their efforts emphasizing the IHI bundle (21). Prevention included hand washing, elevating the head of the bed 30° to 45°, monitoring gastric residuals every 4 h to prevent aspiration, providing aggressive oral care (and documentation) every 2 h, managing hypopharyngeal secretions, providing in-line endotracheal suction, and providing equipment care. During the first 6 months of implementation, the time between VAP occurrences has nearly tripled.

Educational Interventions

Identifying effective measures for preventing VAP is only as useful as the proper implementation of these measures in the clinical setting. Many studies have shown a reduction in rates of VAP following initiatives to educate health care workers about the epidemiology of VAP and infection control measures used to prevent VAP (89). Most of those studies were performed in the adult ICU setting. A recent educational intervention was performed in an integrated health system, with

results compared across a large adult teaching hospital, two community hospitals, and a pediatric teaching hospital (4). The targeted health care workers were respiratory care practitioners and nursing staff working in the ICU setting. This intervention centered on a 10-page self-study module that focused on multiple aspects of VAP and also included posters, fact sheets, and in-services for nursing staff and respiratory therapists. VAP rates between the 12-month preintervention period and the 18-month postintervention period were compared. Nursing compliance rates were highest among nurses at the pediatric hospital (100%) and one of the community hospitals (98.9%). The adult teaching hospital and the other community hospital had significantly lower compliance rates among nurses (64.9% and 44.2%; $P < 0.001$). Three hospitals had a significant drop in the VAP rates from the preintervention period to the postintervention period. The VAP rate at the pediatric hospital fell 38%, from 7.9 episodes to 4.9 episodes per 1,000 ventilator days ($P < 0.001$). The community hospital with no change in the rate of VAP had the lowest compliance of respiratory therapists compared to the other three hospital combined (56.3% versus 95.2%; $P < 0.001$).

Not all lapses in infection control measures result from a lack of knowledge. A survey of NICU health care workers was performed to investigate the knowledge, beliefs, and practices regarding nosocomial infections and infection control measures (56). The survey revealed some areas in which health care workers' actions arose from unawareness of data related to infection control. For instance, few participants believed that nosocomial infections were related to health care workers' rings (40%), artificial fingernails (61%), or long fingernails (48%). However, that study also revealed some disconnects between knowledge and practice. Although 96% of respondents believed that using sterile techniques for catheter insertion and care reduces a patient's risk for BSI, only 67% reported using full sterile barriers at least 76% of the time when participating in inserting a line. Likewise, 91% of participants believed gloves are important for preventing the spread of nosocomial infections, but only 53% reported changing their gloves in all indicated situations. That study demonstrated the need for increased educational efforts to bridge the gaps in knowledge of infection control recommendations. Additionally, the study demonstrated that a lack of knowledge alone does not account for the lapses in infection control practices in the NICU studied. The most common barriers to infection control perceived by respondents included logistics (54%), time (48%), and lack of supplies (47%).

Interventions that lower rates of VAP may have temporary effects, with VAP rates eventually rising following the conclusion of the intervention, indicating the need for continuous reinforcement of interventional measures (55). Factors associated with noncompliance with hand hygiene exist at the individual, group, and institutional levels (74). A proposed framework for the promotion of hand hygiene includes 12 factors: (i) education, (ii) routine observation and feedback, (iii) engineering controls, (iv) patient education, (v) reminders in the workplace, (vi) administrative sanctions and rewards, (vii) change in hand hygiene agents, (viii) promotion of workers' skin care, (ix) active participation at the individual and institutional level, (x) maintenance of an institutional safety climate, (xi) enhancement of individual and institutional self-efficacy, and (xii) avoidance of overcrowding, understaffing, and excessive workload (74). The diversity of these factors emphasizes the need for a multipronged and continuous approach necessary to maintain high levels of compliance with infection control measures.

A summary of interventional measures to decrease the incidence of VAP in children is provided in Table 3.

Recommendations for Current Practice and Future Research

There is scant literature regarding testing the efficacy of head-of-bed elevation, in-line suctioning, and preferential use of sucralfate over histamine type 2 receptor antagonists in pediatric VAP prevention. However, head-of-bed elevation and other measures to prevent aspiration, a consistent approach to oral hygiene, meticulous hand hygiene, and regular assessment of readiness to wean are biologically plausible as effective VAP prevention measures in children. Further studies documenting that head-of-bed elevation in children decreases aspiration and risk of pneumonia as well as determining the natural history of aerodigestive tract colonization and its relationship to gastric acidity in children may shed light on the risk/benefit ratio of sucralfate and/or H_2 blockers and the number needed to treat to prevent pediatric VAP.

VAP TREATMENT

Treatment of suspected VAP is centered on an approach of initial empirical therapy with broad-spectrum antibiotics followed by de-escalation to specific antimicrobial therapy once culture results are known or discontinuation of antibiotics if VAP is no longer suspected. The American Thoracic Society and Infectious Disease Society of America have recently published an updated version of their evidence-based guidelines for the management of VAP in adults (2). Key recommendations in the new document include the use of early, appropriate, and broad-spectrum antibiotics for empirical therapy; utilization of empirical antibiotics from a different class than antibiotics that the patient has recently received; judicious use of combination therapy in hospital-acquired pneumonia; the potential use of linezolid as an alternative to vancomycin for VAP caused by methicillin-resistant *Staphylococcus aureus* (MRSA); the use of colistin for patients with VAP caused by carbapenem-resistant *Acinetobacter* species; the potential use of aerosolized antibiotics as adjunctive therapy for patients with VAP caused by certain antibiotic-resistant organisms; de-escalation of antibiotics based on patients' culture results and clinical improvement; and a shorter duration of antibiotics for patients with uncomplicated health care-associated pneumonia from bacteria other than nonfermenting gram-negative bacilli. These guidelines are based on data from clinical trials of hospital-acquired pneumonia in adult patients. There have been few clinical studies regarding the optimal treatment for VAP in children.

Empirical Therapy

The importance of prompt initiation of appropriate empirical therapy for suspected VAP has been demonstrated in

TABLE 3. Summary of interventions to prevent VAP[a]

Intervention and source (reference)	Design	Patient description	Outcome
Enteral feeds			
Almuneef et al. (1)	Prospective active surveillance	361 PICU patients(37 with VAP, 324 without VAP)	Cases had higher frequency of enteral feeds (48.6% vs 26.8%; OR, 2.58; $P = 0.006$)
Lopriore et al. (62)	Retrospective case control	155 PICU patients (13 with VAP, 142 without VAP)	No significant difference between cases and controls (53.8% vs 43.6%)
Motility agents			
Lopriore et al (62)	Retrospective case control	155 PICU patients (13 with VAP, 142 without VAP)	Cases had higher frequency of motility agent use ($P < 0.05$) (association not significant in logistic regression)
Head-of-bed elevation			
Black et al. (10)	Matched case control study	18 PICU patients (9 with VAP, 9 without VAP)	No significant difference between cases and controls in head-of-bed elevation
Closed vs open suctioning			
Cordero et al. (20)	Prospective, randomized	133 NICU patients (67 closed, 66 open)	No difference in diagnosis of nosocomial pneumonia between groups ($n = 5$ patients each)
SDD			
Barret et al. (7)	Prospective, randomized, double-blinded	23 burn patients (11 SDD, 12 placebo)	No difference in rates of pneumonia (1 case in SDD group, 0 in placebo group)
Ruza et al. (81)	Prospective, randomized, nonblinded	226 PICU patients (116 with SDD, 110 without SDD)	SDD protective toward respiratory infection in logistic regression (OR, 0.21; 95% CI, 0.06–0.8)
Herruzo-Cabrera et al. (49)	Prospective cohort, nonrandomized	536 neonates (58 WP SID, 88 IP SID, 392 no SID)	WP SID protective toward NI of intestinal origin in logistic regression (OR, 0.17; 95% CI, 0.03–0.83).
Stress ulcer prophylaxis			
Lopriore et al. (62)	Retrospective case control	155 PICU patients (54 ranitidine, 53 sucralfate, 48 no prophylaxis)	No significant difference in upper airway colonization with GNB, no significant difference in incidence of VAP
Yildizdas et al. (101)	Prospective, randomized, nonblinded	160 PICU patients (38 sucralfate, 42 ranitidine, 38 omeprazole, 42 no prophylaxis)	No significant difference in VAP between patient groups
Infection control interventions			
Won et al. (99)	Prospective study of hand hygiene campaign	NICU patients admitted during hand hygiene campaign	Rate of respiratory infections dropped from 3.35 to 1.06 per 1,000 patient days ($P = 0.002$)
Babcock et al. (4)	Prospective study of educational intervention	PICU patients at pediatric teaching hospital	38% reduction in VAP rate from 7.9 to 4.9 episodes per 1,000 ventilator days ($P < 0.001$)
Nursing practice (decreasing peripheral intravenous access)			
Ng et al. (69)	Prospective surveillance	493 NICU patients (227 before period, 266 after period)	Non-statistically-significant decrease in VAP rate from 3.3 to 1.0 per 1,000 ventilator days ($P = 0.22$)
Oral hygiene			
Chlebicki and Safdar (15)	Meta-analysis, seven randomized controlled trials	1,650 patients total ($n = 812$ [topical chlorhexidine]; $n = 838$ [comparator])	Topical chlorhexidine reduced VAP incidence (RR, 0.74; $P = 0.02$); risk reduction was even higher in cardiac surgery patients (RR, 0.41; $P = 0.04$).
Pineda et al. (73)	Meta-analysis, four randomized controlled trials	1202 patients total ($n = 587$ [chlorhexidine group]; $n = 615$ [control group])	Chlorhexidine group less likely to develop VAP (4%) compared to control group (7%)($P = 0.07$); ICU length of stay, duration of mechanical ventilation, and mortality not significantly different
Bergmans et al. (9)	Prospective, randomized, double-blinded, placebo controlled	87 patients (treatment group), 78 patients, (control group A), and 61 patients (control group B)	VAP incidences were less in treatment group (10%) than in groups A (31%; $P = 0.001$) and B (23%; $P = 0.04$)
Fitch et al. (35)	Longitudinal design, repeated measures	ICU nurses and dental hygienist	Nurses following oral care protocols can help improve ICU patient oral health

[a] WP, well performed; IP, incorrectly performed; GNB, gram-negative bacilli; NI, nosocomial infection.

adults, with many studies describing higher mortality in patients who received delayed appropriate treatment for VAP (51, 59, 63). However, inappropriate use and overuse of antibiotics can lead to increased hospital expenditures and could potentially promote antibiotic resistance (33, 83). Empirical antibiotic therapy for suspected VAP accounts for a major proportion of inappropriate antibiotic use in pediatric patients, with up to 33% of patients receiving unwarranted antimicro-

bial therapy for suspected VAP (33). Prescribing patterns have also shifted toward more expensive and broader-spectrum antibiotics in hospitalized children in recent years, with the proportion of total antibiotic expenditure used for vancomycin increasing from 0.2% in 1984 to 17.2% in 1994. Additionally, broad-spectrum cephalosporins accounted for 17.7% of antibiotic expenditures in 1984 and 49.6% in 1994 (96). Thus, prescribing patterns for empirical therapy for suspected VAP should maintain a balance between adequately covering patients who are potentially infected and minimizing unnecessary and prolonged exposure to antimicrobials.

Infection with potentially antibiotic-resistant organisms accounts for a large proportion of VAP in adults (95). When selecting empirical therapy, physicians should be aware of the patient's risk factors for infection with multidrug-resistant (MDR) bacteria, the antibiotics that the patient has recently received, and the local antibiotic resistance patterns. Risk factors for VAP with MDR pathogens in adults include mechanical ventilation for at least 7 days, prior antibiotic use, and prior exposure to broad-spectrum antibiotics (imipenem, broad-spectrum cephalosporins, or fluoroquinolones) (95). In children, it has been postulated that patients may be colonized with organisms from their own preexisting endogenous flora in response to antibiotic pressure (92). Risk factors for colonization with antibiotic-resistant gram-negative organisms in PICU patients include younger age, increasing PRISM (pediatric risk of mortality) score, previous PICU admissions, intravenous antibiotic use in the past 12 months, and exposure to chronic care facilities (91, 93). Additional special considerations for the pediatric population include premature infants with an increased risk of *Staphylococcus epidermidis* infections and immunocompromised patients with an additional need for empirical antifungal therapy (52).

Monotherapy for empirical coverage is recommended for adult patients with early-onset VAP without risk factors for infection with MDR pathogens, while combination therapy should be used for coverage of potential infection with MDR organisms or late-onset VAP based on a local antibiogram. Additionally, patients should be treated with antibiotics differing in class from those that they have recently received in case colonizing bacteria have developed antibiotic resistance from previous exposures (2). No consensus guidelines for empirical coverage of suspected VAP in children exist.

Empirical therapy should be discontinued or altered based on culture results and clinical status. The fear that negative culture results may have missed an infection in critically ill children often leads to prolonged empirical antimicrobial therapy in neonates (87). A study of late-onset sepsis evaluations in neonates was undertaken to determine a sufficient time point for the discontinuation of empirical therapy. Those investigators found that 99% of blood cultures were positive within 48 h, and investigators used this finding as a basis for decreasing empirical coverage from 72 h to 48 h for suspected late-onset sepsis in neonates. That study examined cultures from sterile body sites only. Cultures from the respiratory tract and the vagaries of diagnosing VAP may not lend themselves to an easily defined time point for the discontinuation of empirical therapy in suspected VAP.

Singh et al. (85) used the CPIS to guide the duration of empirical therapy in adults. Intensive care patients with new-onset pulmonary infiltrate who were suspected of having pneumonia were evaluated at baseline with five of the seven CPIS items on a scale of 0 to 2 each (temperature, blood leukocytes, tracheal secretions, oxygenation, and pulmonary radiography). Patients with a total CPIS of ≤ 6 were considered to have a low likelihood of pneumonia and were randomized to receive standard care as determined by their attending physician or experimental therapy with ciprofloxacin monotherapy. All patients were reevaluated at 3 days, and of those with CPIS remaining at ≤ 6, 100% of patients in the experimental arm had a cessation of antimicrobial therapy, compared to 4% of patients in the standard therapy arm. There was no difference in mortality or length of stay between treatment groups; antibiotic resistance, superinfections, or both occurred more frequently in patients receiving standard therapy than patients receiving experimental therapy (35% versus 15%; $P = 0.017$). Replication of these results in children could offer clinical guidelines for the rapid cessation of empirical antimicrobial therapy for suspected VAP.

Specific Treatment

Combination therapy exposes patients to multiple antibiotics and is more expensive; a prompt de-escalation of empirical therapy to more specific antimicrobial therapy should occur once culture results and susceptibilities are known. Monotherapy is recommended for patients who are not at risk for infection with MDR pathogens and for patients infected with gram-positive pathogens including MRSA. Additionally, patients with severe VAP should initially be treated with combination therapy but may be changed to monotherapy if lower respiratory tract cultures do not identify an antibiotic-resistant pathogen (2). Agents that have demonstrated efficacy for monotherapy in adult patients infected with susceptible organisms include fluoroquinolones, carbapenems, cefepime, and piperacillin-tazobactam (2).

Recent interest surrounding the substitution of linezolid for vancomycin in the treatment of VAP caused by MRSA has emerged. A meta-analysis of two prospective, randomized, double-blind, multicenter, multinational trials in adults with nosocomial pneumonia comparing clinical cure from linezolid to vancomycin was performed (100). Patients with MRSA pneumonia who were treated with linezolid had survival that was significantly higher than that of patients treated with vancomycin (80.0% versus 63.5%; $P = 0.03$). Clinical cure rates were also higher for patients treated with linezolid than those treated with vancomycin (59.0% versus 35.5%; $P < 0.01$). Both of these effects remained significant in logistic regression models.

A prospective, randomized, open-label, multicenter, multinational trial was performed to compare the efficacy and safety of linezolid and vancomycin for antibiotic-resistant gram-positive bacteremia and nosocomial pneumonia in hospitalized children (53). Among patients with nosocomial pneumonia, patients randomized to the linezolid group were more often mechanically ventilated (63.6% versus 10.0%; $P = 0.011$) and had more multiple-lobe involvement (90.9% versus 50.0%; $P = 0.038$). No significant difference in clinical cure was seen between patients treated with linezolid and those treated with vancomycin. However, patients treated with linezolid appeared to experience a faster resolution of dyspnea/tachypnea/grunting than patients with vancomycin, with fewer than 40% of patients receiving linezolid and more than 80% of patients receiving vancomycin demonstrating these symptoms of VAP

on day 3 of treatment (P value not given). Additionally, patients treated with linezolid experienced a shorter mean duration of total therapy (10.5 days versus 12.8 days; $P = 0.03$) and intravenous therapy (8.5 days versus 11.3 days; $P = 0.004$). The frequency of drug-related adverse events was similar between groups. That analysis was a subset of a larger study, and it analysis was not powered for nosocomial pneumonia or bacteremia. Other subanalyses of this same patient population have demonstrated the safety of linezolid compared to vancomycin in children (64, 82).

Aerosolized antibiotics have been studied most extensively in children in the setting of cystic fibrosis. The FDA approval of tobramycin solution for inhalation is only for maintenance therapy in patients with cystic fibrosis known to be colonized with *Pseudomonas aeruginosa* (76). In two randomized controlled trials, a modest improvement in the forced expiratory volume in 1 min occurred after 24 weeks of therapy with tobramycin solution for inhalation; there were significant decreases in CFU/ml of *Pseudomonas aeruginosa* in sputum, decreases in hospital admission days, and decreases in numbers of parenteral antibiotic days for treatment of *Pseudomonas aeruginosa* infections. To our knowledge, there are no data showing that treatment of acute pulmonary infections with aerosolized antibiotics is beneficial in children. Inhaled aminoglycosides do produce low but measurable serum concentrations (1 to 4 μg/ml). Sputum concentrations vary. No ototoxicity or nephrotoxicity has been associated with the use of inhaled aminoglycosides, although many of those studies excluded children with serum creatinine levels greater than 2. The potential disadvantages of use include bronchospasm, increased MICs of the targeted organism, increased isolation of *Candida* and *Aspergillus* species from sputum, nebulization of microorganisms, and antibiotic contamination of the environment (76).

Finally, subpopulations of pediatric patients deserve special consideration. Neurologically impaired children are at increased risk for aspiration or tracheostomy-associated pneumonia. The mixed microbiology of these infections, often including anaerobic organisms, warrants specific antimicrobial therapy against likely pathogens. A retrospective study of 57 neurologically impaired children with aspiration or tracheostomy-related pneumonia was performed to evaluate the efficacy of various antimicrobial therapies (11). Children with either type of pneumonia had better clinical improvement and microbiological response when treated with agents effective against penicillin-resistant anaerobic bacteria (ticarcillin-clavulanate or clindamycin) than patients treated with ceftriaxone ($P < 0.05$ for both tracheostomy-related pneumonia and aspiration pneumonia groups). Although this was a small study within a focused population, it underscores the need to account for unique underlying conditions in children that may predispose them to infections with specific pathogens.

Duration of Therapy

No consensus exists regarding the appropriate duration of antimicrobial therapy for VAP in adults, and the appropriate duration for proven infections in critically ill children has not been established (45). A multicenter, randomized, controlled trial was performed using adults with VAP to compare patients treated with appropriate empirical therapy for 8 days to patients treated for 15 days (14). There was no difference in mortality or recurrent infections between groups. Among patients infected with nonfermenting gram-negative bacilli, patients treated for 8 days did have a higher relapse rate (32.8% versus 19.0%; 13.8% risk difference; 90% CI, 7.8% to 19.7%). However, among patients who experienced recurrent infections, patients treated for 8 days were less likely to become infected with MDR pathogens (42.1% versus 62.0%; $P = 0.04$). These data suggest that limiting treatment of VAP in patients infected with pathogens other than nonfermenting gram-negative bacilli is safe and may decrease the incidence of reinfection with MDR pathogens.

Recommendations for Current Practice and Future Research

No consensus guidelines exist for empirical coverage of suspected VAP in children.

Empirical therapy should be discontinued or altered based on clinical status and culture results, preferably from lower airway samples. Patients who are severely ill and/or with previous exposure to the health care system should be treated with combination therapy. Areas for future research in children include the efficacy of linezolid compared to vancomycin for VAP treatment, the duration of optimal antibiotic therapy for VAP, and validation of the CPIS in children as well as its use in treatment decisions.

CONCLUSION

VAP is the second most common hospital-acquired infection among PICU patients. Empirical therapy for VAP accounts for approximately 50% of antibiotic use in PICUs. VAP is associated with an excess of 3 days of mechanical ventilation among pediatric cardiothoracic surgery patients. The attributable mortality and excess length of ICU stay of VAP have not been defined in matched case control studies. VAP is associated with an estimated $30,000 in attributable cost. Surveillance for VAP is complex and usually performed using clinical definitions established by the CDC. Invasive testing via BAL increases the sensitivity and specificity of the diagnosis. The pathogenesis is poorly understood in children, but several prospective cohort studies suggest that aspiration and immunodeficiency are risk factors. In children, educational interventions and efforts to improve adherence to hand hygiene have been associated with decreased VAP rates. More consistent and precise approaches to the diagnosis of pediatric VAP are needed to better define the attributable morbidity and mortality, pathophysiology, and appropriate interventions to prevent this disease.

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Action deadlines for the Safety Alert Broadcast System (SABS)

Category: ACTION

For action by: clinical leads for critical care units in acute and foundation trusts

Deadline: (actions 1.1 and 1.2 underway) 26 September 2008

Deadline: (actions 1.1 and 1.2 completed) 27 November 2008

NHS
National Institute for Health and Clinical Excellence

National Patient Safety Agency

Issue date: August 2008
Alert reference: NICE/NPSA/2008/PSG002

Technical patient safety solutions for ventilator-associated pneumonia in adults

1 Action

1.1 Mechanically ventilated patients who are intubated should be positioned with their upper body elevated (in a semi-recumbent or seated position) for as much of the time as possible. For some patients this will not be appropriate (for example, those with spinal injuries).

1.2 Oral antiseptics (for example, chlorhexidine) should be included as part of the oral hygiene regimen for all patients who are intubated and receiving mechanical ventilation.

2 Other interventions evaluated

2.1 This guidance is not intended as a comprehensive overview of interventions aimed at preventing ventilator-associated pneumonia (VAP); (see section 4 for information on current practice, including guidelines from other organisations). The interventions in section 1 are those for which the evidence was considered adequate to recommend them as actions to the NHS in England and Wales. The Patient Safety Advisory Committee also examined evidence on other interventions, which may have benefits in the prevention of VAP, and reached the following conclusions.

2.2 The Committee examined evidence which suggested that selective decontamination of the digestive tract (SDD) using topical antibiotics may reduce the incidence of VAP and that SDD regimes that include systemic antibiotics may also reduce mortality. However, Specialist Advisers stated that UK intensive care specialists had particular concerns about the risk of infection with *Clostridium difficile* and the induction and/or selection of resistant, including multiresistant, microorganisms as a result of SDD. Therefore the Committee recommended further research into SDD in a UK setting (see section 7.2).

2.3 A lack of robust evidence meant the Committee was unable to make recommendations for action on the use of kinetic beds.

2.4 Although the evidence supported the use of elements of care bundles, there was insufficient evidence to recommend a care bundle of any specific design.

2.5 Further information is given in section 5.

3 The patient safety problem or harm

3.1 Pneumonia is an inflammatory condition of the lungs caused by bacterial, viral or fungal infection. VAP can occur as a complication of mechanical ventilation, particularly when ventilation is required for a prolonged period of time and in patients who are critically ill. VAP can be caused by a range of microorganisms, some of which are resistant to many antimicrobials. These microorganisms are normally found in the throat (specifically, the

NICE patient safety guidance 2

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

NICE patient safety guidance advises on how to improve the safety of patients in the NHS in England and Wales.

oropharynx) and the gut. Mechanical ventilation allows the microorganisms to move to the lungs, despite the best standards of ventilator use.

3.2 There is no generally accepted definition of VAP in mechanically ventilated patients, but it is often defined as pneumonia that develops 48 hours or more after intubation with an endotracheal or tracheostomy tube, and that was not present before intubation. Definite diagnosis may not be straightforward because there are no firm diagnostic criteria for VAP; it is generally diagnosed on the basis of clinical signs and symptoms and chest X-rays and is confirmed microbiologically.

3.3 VAP is recognised as a significant problem in the USA, where data suggest that it represents 31% of all intensive care unit (ICU)-acquired infections, and that it occurs in 9–27% of all intubated patients. There are no data on the incidence of VAP in the UK. The lack of an accepted definition and firm diagnostic criteria contribute to the difficulty in collecting this information.

3.4 Patients who develop VAP are at risk of serious complications (for example, acute respiratory distress syndrome) and have a significantly longer duration of mechanical ventilation and ICU stay. Data from the USA indicate that the mortality rate of patients who have developed VAP is between 38% and 50%. However, many patients with VAP have other serious comorbidities which make it difficult to establish any direct causal link between VAP and mortality. It should be noted that the comorbidity profiles of patients receiving mechanical ventilation in the USA and UK may be different.

4 Current practice

4.1 Anecdotal evidence suggests that in the UK there is substantial variation in VAP prevention strategies.

4.2 The Health Act 2006 Code of Practice requires NHS organisations to audit policies and procedures to prevent infection. To support this requirement, the Department of Health (DH) published a high impact intervention for ventilated patients in June 2007. This uses a care bundle approach with an accompanying tool to enable organisations to demonstrate compliance with the Code of Practice. The interventions specified in the high impact intervention are as follows, and include the two recommended technical patient safety solutions:

- elevation of the head of the bed to 30–45 degrees
- sedation holding/review
- deep vein thrombosis prophylaxis
- gastric ulcer prophylaxis
- appropriate humidification of inspired gas
- appropriate ventilator tubing management
- suctioning of respiratory secretions (including use of gloves and decontaminating hands before and after the procedure)
- routine oral hygiene as per local policy.

4.3 The British Society for Antimicrobial Chemotherapy has developed guidelines on the diagnosis, prevention and treatment of VAP[1].

5 Basis for guidance

5.1 Summary

5.1.1 Children under the age of 16 years were outside the scope of this guidance.

5.1.2 The published scientific evidence evaluated on all of the potential patient safety solutions was relatively poor. However, the actions in section 1 were considered by the Committee to have low potential for harm and were supported by credible efficacy data and expert advice. The actions were considered to be relatively easy to implement and associated with little or no additional resource.

5.2 Body position

5.2.1 Two randomised controlled trials (RCTs) compared the incidence of VAP in mechanically ventilated patients positioned in either a semi-recumbent position (45 degrees) or a supine position. One well-conducted RCT of 86 patients found that the semi-recumbent position significantly reduced the frequency of clinically suspected and microbiologically confirmed pneumonia. The incidence of VAP was 3/39 (8%) in the semi-recumbent group compared with 16/47 (34%) in the supine group (relative risk [RR] 0.23, 95% confidence interval [CI] 0.07 to 0.72). A second RCT reported that the incidence of VAP was 12/112 (11%) in the semi-recumbent group compared with 8/109 (7%) in the supine position (RR 1.46; 95% CI 0.62 to 3.43). However, the intended angle of 45 degrees was only achieved in the semi-recumbent patients for 15% of the time; the average angle attained was 28 degrees. A third RCT found that the incidence of VAP in the prone position was 5/25 (20%) compared with 10/26 (38%) in the supine position (RR 0.52; 95% CI 0.21 to 1.31).

5.2.2 The cost effectiveness of placing the patient in a semi-recumbent position was not evaluated as it was not associated with any readily identifiable costs. It is one element of the advanced nursing care required by ventilated patients.

5.2.3 It was noted that placing the patient in a semi-recumbent position was a component of all the care bundles identified.

5.2.4 All the Specialist Advisers considered that placing the patient in a semi-recumbent position was efficacious in reducing the risk of VAP. They thought that it should be routine practice and saw few obstacles to implementation. However, it was clear that it would not be appropriate to place some patients in a semi-recumbent position (for example, those with spinal injuries).

[1] Masterton RG, Galloway A, French G et al. (2008) Guidelines for the management of hospital-acquired pneumonia in the UK: Report of the Working Party on Hospital-Acquired Pneumonia of the British Society for Antimicrobial Chemotherapy. *The Journal of Antimicrobial Chemotherapy* 62: 5–34.

5.2.5 Concerns were raised in the Assessment Report about body elevation causing skin shearing and pressure sores, but the Committee was advised that patients would routinely be receiving appropriate preventative care.

5.3 Prophylactic antimicrobials

Antiseptics

5.3.1 The published systematic reviews considered by the Committee included a total of nine RCTs. The RCTs investigated oral decontamination of mechanically ventilated patients using a range of chlorhexidine antiseptic regimens (0.12–2%). One RCT investigated the use of povidone iodine (10%). The systematic review authors concluded that oral decontamination using antiseptics is associated with a lower risk of VAP but noted that the meta-analysis did not show any significant reduction in mortality, duration of mechanical ventilation or duration of ICU stay.

5.3.2 The Committee sought evidence on complications associated with chlorhexidine. It noted that anaphylaxis and serious respiratory complications associated with chlorhexidine are extremely rare.

Antibiotics

5.3.3 One published systematic review included four RCTs which examined topical application of antibiotics to the mouth. The authors concluded that oral decontamination using topical application of antibiotics did not significantly reduce the incidence of VAP, mortality, duration of mechanical ventilation or duration of ICU stay.

5.3.4 The Committee considered nine systematic reviews on SDD. The academic group undertook a new systematic review that included a meta-analysis of data from 27 RCTs. Data from this meta-analysis suggested that SDD using non-absorbable antimicrobials applied to the oropharynx and through a nasogastric tube may reduce the incidence of VAP. In addition, the new meta-analysis indicated that SDD regimes that include systemic antibiotics may also reduce mortality. These findings were consistent with those in the nine published systematic reviews. There was limited reporting of safety data; none of the RCTs indicated that serious adverse effects were associated with SDD. There were some reports that oropharyngeal paste formulations were not acceptable to some patients and that the enteral antibiotics could cause gastrointestinal problems.

5.3.5 The results of the economic evaluation indicated that SDD is very likely to be a cost-effective intervention if it is assumed that SDD reduces the incidence of VAP, and that VAP increases mortality and length of stay (either ICU or hospital), and reduces quality of life. However, the Committee was concerned about the reliability of the final estimates because the economic evaluation was primarily based on RCTs that had been undertaken over 10 years ago in non-UK populations. The RCTs also did not take account of the potential impact of *Clostridium difficile* and resistant and multiresistant microorganisms.

5.3.6 The Specialist Advisers stated that there was concern about *Clostridium difficile* and the risk of increasing antibiotic resistance through the use of antibiotics in SDD. They pointed out that few of the studies had been undertaken in the UK, and therefore they did not reflect current NHS practice or, potentially, the range of infecting microorganisms encountered in the UK. In particular, many of the trials were carried out in countries with low incidences of meticillin-resistant *Staphylococcus aureus* (MRSA).

5.4 Use of kinetic bed therapy

5.4.1 The review group identified two meta-analyses on kinetic bed therapy (which is known by a number of names including oscillatory therapy). Only one of the meta-analyses was judged to be methodologically robust, however, the authors reported that the methodological quality of all 15 of the RCTs included in the meta-analysis was poor and none met all of their validity criteria. The authors pooled the data available from 10 of the RCTs. The pooled data indicated that kinetic bed therapy reduced the incidence of VAP compared with manual turning (odds ratio [OR] 0.38; 95% CI 0.28 to 0.53, $p < 0.001$) but did not reduce mortality, duration of mechanical ventilation, or duration of ICU or hospital stay. Kinetic beds were poorly tolerated by conscious patients, resulting in a high withdrawal rate from the studies. Only one RCT undertook an intention-to-treat analysis. The authors of the meta-analysis expressed concern that the lack of allocation concealment and blinding could introduce bias into the diagnosis of pneumonia. The authors also expressed concern that the potential complications of kinetic bed therapy, including those arising from increased sedation, had not been systematically addressed. One of the RCTs identified a number of serious complications, including disconnection of intravascular catheters. In addition, there was no information available to determine the effectiveness of the different rotation parameters of the kinetic beds.

5.4.2 The results of the cost-effectiveness evaluation, based on data from the RCTs, indicated that, although there is uncertainty around the mean incremental cost-effectiveness ratio (ICER), kinetic bed therapy would be associated with lower overall costs (costs associated with bed hire and costs arising from acquiring VAP) than not undertaking any intervention to prevent VAP.

5.4.3 In considering the use of kinetic beds, the Committee noted that the trials were of poor methodological quality and that potentially serious complications had not been systematically evaluated. It also noted that many conscious patients find kinetic beds unacceptable. The Committee considered that there may be some subgroups of ventilated patients for whom kinetic beds are appropriate, but no good evidence was identified.

5.4.4 The Committee also took account of the views of the Specialist Advisers who stated that kinetic beds may interfere with other aspects of nursing care. The Advisers noted that there is limited experience with kinetic beds in the UK and that they are used infrequently. They also pointed out that there are concerns about decontamination of kinetic beds.

5.5 Care bundles

5.5.1 A number of different care bundles have been produced for patients receiving mechanical ventilation. They include some measures relating directly to the prevention of VAP and others relating to the overall management of ventilated patients. There have been no RCT evaluations of care bundles. Two before-and-after studies conducted in the USA reported reduced incidences of VAP following the introduction of two different care bundles, from 22–33 cases per 1000 bed days to 0–13 cases per 1000 bed days in one study, and a reduction from 8 cases per 1000 bed days to 3 cases per 1000 bed days in the second study. The components of the care bundles differed between the studies, and it was not possible to determine the benefit of individual components. The authors of the second study, however, believed that elevating the head of the bed and oral care had a major impact in reducing the incidence of VAP.

5.5.2 The results of the economic evaluation indicated that the care bundle with the most components (the first of those described in section 5.5.1) was likely to be cost effective.

5.5.3 All the Specialist Advisers considered care bundles to be a good approach to the management of ventilated patients and likely to improve outcomes and reduce the incidence of VAP. However, it was noted that there was insufficient evidence for the recommendation of any particular care bundle. The Specialist Advisers stated that there is a lack of awareness and understanding among ICU staff about the care bundle approach and there would be a need for training to support implementation. There was support for a number of the individual components of care bundles, and the Specialist Advisers thought that these should be part of routine clinical practice. It was noted that the DH had recently published a UK care bundle (see section 4.2).

For further information please see the systematic review for the prevention of ventilator-assisted pneumonia (www.nice.org.uk/patientsafety/index.jsp?action=pilot&o=11770).

6 Implementation

The Healthcare Commission assesses the performance of NHS organisations in meeting core standards set by the Department of Health in 'Standards for better health' issued in July 2004. Core standard C1(b) states that healthcare organisations should ensure that patient safety notices, alerts and other communications concerning patient safety which require action are acted upon when required.

'Healthcare standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12b requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE guidance.

6.1 Assessing the impact of the guidance

The impact of the action alert will be tracked in England through the safety alert broadcast system (SABS; www.info.doh.gov.uk/sar/cmopatie.nsf) and in Wales through the regional offices of the Welsh Assembly Government. In addition, healthcare organisations are expected to use indicators, audit tools and patient safety incident reports to monitor the continued implementation of the patient safety recommendations. Clinical governance groups in organisations should review these data annually and take appropriate action to ensure patient safety. Healthcare commissioners and performance management groups should also review these data and any resulting actions taken by the organisation annually. The NPSA will also review these data to gain feedback on the impact of the patient safety guidance.

6.2 Implementation tools

NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website: www.nice.org.uk/PSG002

- Slides highlighting key messages for local discussion.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

7 Research recommendations

7.1 A national data collection initiative is required to provide epidemiological data on the incidence of VAP in the UK. This could involve the Intensive Care National Audit and Research Centre (ICNARC) and/or the Health Protection Agency. This initiative should include agreement of a case definition to overcome the variation in diagnostic criteria.

7.2 Research into SDD as a means of preventing VAP is required in a UK setting. This should investigate microbiological outcomes including infection with *Clostridium difficile* and resistant microorganisms in the context of well-defined policies of antibiotic use. Studies should define clearly what other prophylactic methods (such as elevation of the upper body) are used. Information about barriers to implementation of SDD regimes would also be helpful.

7.3 Further research into different antiseptics for oral decontamination is required, including type of antiseptic, the optimal concentration and frequency of application in different groups of patients.

8 Further information

8.1 Ordering information

You can download the following documents from www.nice.org.uk/PSG002

- Patient safety guidance – this document.
- 'Understanding NICE guidance' – information for patients and carers.
- Details of all the evidence that was looked at and other background information.

For printed copies of the patient safety guidance or 'Understanding NICE guidance', phone NICE publications on 0845 003 7783 or email publications@nice.org.uk and quote:

- N1656 (patient safety guidance)
- N1657 ('Understanding NICE guidance').

8.2 Related NICE/NPSA guidance

- Acutely ill patients in hospital: recognition of and response to acute illness in adults in hospital. NICE clinical guideline 50 (2007). Available from: www.nice.org.uk/CG050
- Clean hands help to save lives. NPSA patient safety alert 04 (2004). Available from: www.npsa.nhs.uk/patientsafety/alerts-and-directives/alerts/clean-hands
- Infection control: prevention of healthcare-associated infection in primary and community care. NICE clinical guideline 2 (2003). Available from: www.nice.org.uk/CG002

9 Review of guidance

9.1 The decision to review this patient safety guidance will be taken in consultation with stakeholders and in the light of information gathered by NICE and the NPSA, and research findings.

9.2 This patient safety guidance will be considered for review by the NPSA in August 2011.

Andrew Dillon NICE

Chief Executive

August 2008

Sources of evidence

The following documents, which contain the evidence, were considered by the Patient Safety Advisory Committee when making its recommendations. They are available from www.nice.org.uk/PSG002

- Systematic review of selective decontamination of the digestive tract for the prevention of ventilator-associated pneumonia (2008).
- Economic model of selective decontamination of the digestive tract for the prevention of ventilator-associated pneumonia (2008).
- Specialist adviser comments on selective decontamination of the digestive tract for the prevention of ventilator-associated pneumonia (2008).
- Systematic review for the prevention of ventilator-associated pneumonia (2007).
- Economic model for the prevention of ventilator-associated pneumonia (2007).
- Specialist adviser comments on the prevention of ventilator-associated pneumonia (2007).
- Patient group feedback on the prevention of ventilator-associated pneumonia (2007).

This guidance represents the view of the Institute and the NPSA, which was arrived at after careful consideration of the available evidence. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of healthcare professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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DH Gateway number: 10271
ISBN 1-84629-775-3
N1656 1P 10k Aug 08

State of the Art

Ventilator-associated Pneumonia

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CONTENTS

Ventilator-associated pneumonia (VAP) continues to complicate the course of 8 to 28% of patients receiving mechanical ventilation (MV). In contrast to infections of more frequently involved organs (e.g., urinary tract and skin), for which mortality is low, ranging from 1 to 4%, the mortality rate for VAP ranges from 24 to 50% and can reach 76% in some specific settings or when lung infection is caused by high-risk pathogens. The predominant organisms responsible for infection are *Staphylococcus aureus, Pseudomonas aeruginosa,* and Enterobacteriaceae, but etiologic agents widely differ according to the population of patients in an intensive care unit, duration of hospital stay, and prior antimicrobial therapy. Because appropriate antimicrobial treatment of patients with VAP significantly improves outcome, more rapid identification of infected patients and accurate selection of antimicrobial agents represent important clinical goals. Our personal bias is that using bronchoscopic techniques to obtain protected brush and bronchoalveolar lavage specimens from the affected area in the lung permits physicians to devise a therapeutic strategy that is superior to one based only on clinical evaluation. When fiberoptic bronchoscopy is not available to physicians treating patients clinically suspected of having VAP, we recommend using either a simplified nonbronchoscopic diagnostic procedure or following a strategy in which decisions regarding antibiotic therapy are based on a clinical score constructed from seven variables. Selection of the initial antimicrobial therapy should be based on predominant flora responsible for VAP at each institution, clinical setting, information provided by direct examination of pulmonary secretions, and intrinsic antibacterial activities of antimicrobial agents and their pharmacokinetic characteristics. Further trials will be needed to clarify the optimal duration of treatment and the circumstances in which monotherapy can be safely used.

Keywords: antimicrobial therapy; bronchoscopy; epidemiology; nosocomial infection; ventilator-associated pneumonia

Despite major advances in techniques for the management of ventilator-dependent patients and the routine use of effective procedures to disinfect respiratory equipment, ventilator-associated pneumonia (VAP) continues to complicate the course of 8 to 28% of the patients receiving mechanical ventilation (MV) (1–5). Rates of pneumonia are considerably higher among patients hospitalized in intensive care units (ICUs) compared with those in hospital wards, and the risk of pneumonia is increased 3- to 10-fold for the intubated patient receiving MV (1, 3, 6–13). In contrast to infections of more frequently involved organs (e.g., urinary tract and skin), for which mortality is low, ranging from 1 to 4%, the mortality rate for VAP, defined as pneumonia occurring more than 48 hours after endotracheal intubation and initiation of MV, ranges from 24 to 50% and can reach 76% in some specific settings or when lung infection is caused by high-risk pathogens (2, 11–20). Because several studies have shown that appropriate antimicrobial treatment of patients with VAP significantly improves outcome, more rapid identification of infected patients and accurate selection of antimicrobial agents represent important clinical goals (14, 21, 22). However, consensus on appropriate diagnostic, therapeutic, and preventive strategies for VAP has yet to be reached.

The present review is based on an evaluation of the literature, selected using a computerized MEDLINE search from 1980 through March 2001. Review articles, consensus statements, and the references cited therein were also considered in this endeavor to update our current knowledge on the epidemiology, diagnosis, and treatment of VAP. Because the Hospital Infection Control Practice Advisory Committee of the Centers for Disease Control and Prevention (CDC, Atlanta, GA) published extensive and up-to-date recommendations for the prevention of nosocomial pneumonia in 1997 (23), and other comprehensive reviews are also available (24–26), this topic is not covered herein.

(Received in original form May 17, 2001; accepted in final form January 17, 2002)

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Am J Respir Crit Care Med Vol 165. pp 867–903, 2002
DOI: 10.1164/rccm.2105078
Internet address: www.atsjournals.org

EPIDEMIOLOGY

Accurate data on the epidemiology of VAP are limited by the lack of standardized criteria for its diagnosis. Conceptually, VAP is defined as an inflammation of the lung parenchyma caused by infectious agents not present or incubating at the time MV was started (27). Despite the clarity of this conception, the past three decades have witnessed the appearance of numerous operational definitions, none of which is universally accepted. Even definitions based on histopathologic findings at autopsy may fail to find consensus or provide certainty. Pneumonia in focal areas of a lobe may be missed, microbiologic studies may be negative despite the presence of inflammation in the lung, and pathologists may disagree about the findings (28–31). The absence of a "gold standard" continues to fuel controversy about the adequacy and relevance of many studies in this field.

Prolonged (more than 48 hours) MV is the most important factor associated with nosocomial pneumonia. However, VAP may occur within the first 48 hours after intubation. Since the princeps study by Langer and coworkers (32), it is usual to distinguish early-onset VAP, which occurs during the first 4 days of MV, from late-onset VAP, which develops five or more days after initiation of MV. Not only are the causative pathogens commonly different but the disease is usually less severe and the prognosis better in early-onset than late-onset VAP (27, 33).

Incidence of Ventilator-associated Pneumonia

A large-scale 1-day point prevalence study of pneumonia arising in the ICU was conducted on April 29, 1992, in 1,417 ICUs (6). A total of 10,038 patients was evaluated: 2,064 (21%) had ICU-acquired infections, including pneumonia in 967 (47%) patients, for an overall nosocomial pneumonia prevalence of 10%. In that study, logistic regression analysis identified MV as one of the seven risk factors for ICU-acquired infections. Another large-scale study, conducted in 107 European ICUs, demonstrated a crude pneumonia rate of 9% (7). In that study, MV was associated with a 3-fold higher risk of developing VAP than that observed for nonventilated patients. On the basis of their analyses of overall rates of nosocomial pneumonia, Cross and Roup reported 10-fold higher frequencies for ventilated patients than for those without respiratory assistance (8). Similarly, in a nationwide American study, the pneumonia rate was 21-fold higher for patients receiving continuous ventilatory support than for those not requiring MV (34), in agreement with a multivariate analysis of 120 consecutive VAP episodes and 120 control subjects that had shown intubation to independently increase the risk of nosocomial pneumonia ~ 7-fold (11). A large prospective cohort study was conducted in 16 Canadian ICUs: of the 1,014 mechanically ventilated patients included, 177 (18%) developed VAP, as assessed by bronchoscopic sampling with bronchoalveolar lavage (BAL) or protected specimen brush (PSB) in 131 (35). These data confirmed the considerably higher risk of VAP observed in the subset of ICU patients treated with MV.

In the majority of reports, VAP frequencies varied between 8 and 28% (9, 11, 12, 14, 15, 32, 35–51) (Table 1). A prospective investigation of VAP in 23 Italian ICUs that included 724 critically ill patients who had received prolonged (more than 24 hours) ventilatory assistance after admission found a mean rate of 23%; the frequency rose from 5% for patients receiving MV for 1 day to 69% for those receiving MV for more than 30 days (9, 32). Concerning a subset of 124 trauma patients, 67% of whom were ventilated, early-onset pneumonia, defined as pneumonia occurring within the first 96 hours after admission, represented 63% of the 41 pulmonary infections complicating the course of these patients (44). In another study of 244 medical, surgical, or trauma patients treated with MV, Prod'hom and coworkers defined early-onset pneumonia as occurring during the first 4 days of MV; overall, 53 (22%) VAP episodes were observed, with early-onset pneumonia representing 45% of all pneumonia episodes (52). When quantitative cultures of specimens obtained with a PSB during fiberoptic bronchoscopy (FOB) were used to define pneumonia in 567 ventilated patients, the VAP rate was 9% (12). According to an actuarial method, the cumulative risk of pneumonia in that context was estimated to be 7% at 10 days and 19% at 20 days after the onset of MV. Furthermore, in that study, the incremental risk of pneumonia was virtually constant throughout the entire ventilation period, with a mean rate of ~ 1% per day. In contrast, Cook and coworkers demonstrated

TABLE 1. INCIDENCE AND CRUDE MORTALITY RATES OF VENTILATOR-ASSOCIATED PNEUMONIA

First Author	Ref.	Year of Publication	No. of Patients	Incidence (%)	Diagnostic Criteria	Mortality Rate (%)
Patients in ICU						
Salata	41	1987	51	41	Clinical–autopsy	76
Craven	15	1986	233	21	Clinical	55
Langer	9	1989	724	23	Clinical	44
Fagon	12	1989	567	9	PSB	71
Kerver	43	1987	39	67	Clinical	30
Driks	40	1987	130	18	Clinical	56
Torres	14	1990	322	24	Clinical–PSB	33
Baker	44	1996	514	5	PSB/BAL	24
Kollef	45	1993	277	16	Clinical	37
Fagon	51	1996	1,118	28	PSB/BAL	53
Timsit	46	1996	387	15	PSB/BAL	57
Cook	35	1998	1,014	18	Clinical–PSB/BAL	24
Tejada Artigas	47	2001	103	22	PSB	44
Patients with ARDS						
Sutherland	49	1995	105	15	PSB/BAL	38
Delclaux	17	1997	30	60	PTC/BAL	63
Chastre	16	1998	56	55	PSB/BAL	78
Meduri	50	1998	94	43	PSB/BAL	52
Markowicz	18	2000	134	37	PSB/BAL	57

Definition of abbreviations: ARDS = acute respiratory distress syndrome; BAL = bronchoalveolar lavage; ICU = intensive care unit; PSB = protected specimen brush; PTC = plugged telescoping catheter.

in a large series of 1,014 mechanically ventilated patients that, although the cumulative risk for developing VAP increased over time, the daily hazard rate decreased after Day 5 (35). The risk per day was evaluated at 3% on Day 5, 2% on Day 10, and 1% on Day 15. Independent predictors of VAP retained by multivariable analysis were a primary admitting diagnosis of burns (risk ratio [RR], 5.1; 95% confidence interval [CI], 1.5 to 17.0), trauma (RR, 5.0; 95% CI, 1.9 to 13.1), central nervous system disease (RR, 3.4; 95% CI, 1.3 to 8.8), respiratory disease (RR, 2.8; 95% CI, 1.1 to 7.5), cardiac disease (RR, 2.7; 95% CI, 1.1 to 7.0), MV during the previous 24 hours (RR, 2.3; 95% CI, 1.1 to 4.7), witnessed aspiration (RR, 3.2; 95% CI, 1.6 to 6.5), and paralytic agents (RR, 1.6; 95% CI, 1.1 to 2.4). Exposure to antibiotics conferred protection (RR, 0.4; 95% CI, 0.3 to 0.5), but this effect was attenuated over time. Thus, the daily risk for developing VAP is highly dependent on the population being studied and also on many other factors, particularly the number of patients in the given population who received antibiotics immediately after their admission to the ICU.

VAP is thought to be a common complication of the acute respiratory distress syndrome (ARDS) (Table 1). Most clinical studies have found that pulmonary infection affects between 34 and more than 70% of patients with ARDS, often leading to the development of sepsis, multiple organ failure, and death. When the lungs of patients who died of ARDS were examined histologically at autopsy, pneumonia could be demonstrated in as many as 73% (13, 53). The diagnosis of pulmonary infection in patients with ARDS, however, is often difficult. Several studies have clearly demonstrated the inability of physicians to accurately diagnose nosocomial pneumonia in this setting on the basis of clinical criteria alone (53). Using PSB and/or BAL techniques at predetermined times from Day 3 to 21 after the onset of the syndrome in a series of 105 patients with ARDS, Sutherland and coworkers concluded that VAP may indeed occur far less frequently than expected in this group of patients (49). Only 16 (15.2%) of their 105 patients met the quantitative criteria for pneumonia (PSB > 10^3 cfu/ml or BAL > 10^4 cfu/ml), and no correlations were found between total colony counts in BAL fluid or PSB cultures and severity of ARDS, as judged by Pa_{O_2}/FI_{O_2} (fraction of inspired oxygen) ratios, days receiving MV, static lung compliance, and/or survival. Unfortunately, these results are probably not of general value, because most patients included in the study were lavaged while receiving antibiotics and at predetermined times during the course of ARDS, rather than at the time of clinically suspected infection. According to four other studies, the VAP rate was higher in patients with ARDS than in other mechanically ventilated patients (16–18, 50). In one study of 56 patients with ARDS, PSB and BAL were used to define pneumonia and the VAP rate was 55% (16), whereas it was only 28% for 187 non-ARDS patients diagnosed according to the same criteria during the same period. It was specified that early-onset VAP (occurring before Day 7) was relatively rare in patients with ARDS: only 10% of the first VAP episodes, as opposed to 40% among non-ARDS patients. Those observations were confirmed in 30 patients with ARDS for whom repeated quantitative culture results of specimens obtained with a plugged catheter were available and in 94 ARDS patients with suspected VAP who underwent 172 bronchoscopies, with VAP rates of 60% (incidence density, 4.2/100 ventilator days) and 43%, respectively (17, 50). In another prospective multicenter study, VAP was bacteriologically confirmed in 49 (37%) of 134 patients with ARDS, versus 23% of ventilated non-ARDS patients ($p < 0.002$) (18).

The finding of a higher incidence of microbiologically provable VAP in patients with ARDS than in other populations of mechanically ventilated patients was not unexpected. Several studies have clearly shown that alveolar macrophages and neutrophils retrieved from the lungs of patients with ARDS have impaired phagocytic function and/or lower maximal activity after *ex vivo* stimulation by bacterial products than do corresponding cells from normal subjects, which could explain why these patients are at high risk of developing pulmonary infection (54, 55). However, the actuarial risk of pneumonia after 30 days of MV does not differ significantly between patients with and without ARDS (16). Therefore, the higher incidence of VAP observed in patients with ARDS is probably essentially the result of their need for a much longer duration of MV than that of other patients, thereby increasing the time during which they are at risk for developing VAP.

These findings emphasize (*1*) the major influence of underlying medical conditions on the epidemiologic characteristics of VAP, and (*2*) the critical role of the diagnostic techniques used to identify patients with VAP and to provide accurate epidemiologic data. As the data presented in Table 2 suggest, for the same patients, VAP was clinically diagnosed almost twice as often as it could be bacteriologically confirmed (12, 47, 56–63). Understanding this difference is crucial for the implementation of a rational and pertinent surveillance program in the ICU, with possible intra- and interunit comparisons, to evaluate new therapeutic strategies, particularly prophylactic measures, and to improve antibiotic use in this setting with accurate identification of infected patients and appropriate selection of antimicrobial agent(s). This distinction between clinically suspected versus bacteriologically confirmed VAP has now been integrated into the most recent CDC guidelines (23).

Mortality

Crude ICU mortality rates of 24 to 76% have been reported for VAP at a variety of institutions (*see* Table 1) (9, 12, 14, 15, 35, 40, 41, 43–47, 51, 57). ICU ventilated patients with VAP appear to have a 2- to 10-fold higher risk of death compared with patients without pneumonia. In 1974, fatality rates of 50% for ICU patients with pneumonia versus 4% for patients without pneumonia were reported (64). The results of several studies conducted between 1986 and 2001 have confirmed that observation: Despite variations among studies that partly reflect the populations considered, overall mortality rates for patients with or without VAP were, respectively: 55 versus 25% (15), 71 versus 28% (12), 33 versus 19% (14), 37 versus 9% (45), and 44 versus 19% (47). These rates correspond to increased risk ratios of mortality of VAP patients of 2.2, 2.5, 1.7, 4.4, and 2.3, respectively.

TABLE 2. BACTERIOLOGICAL CONFIRMATION OF CLINICALLY SUSPECTED VENTILATOR-ASSOCIATED PNEUMONIA

First Author	Ref.	Clinically Suspected VAP (*n*)	Bacteriological Confirmation	
			n	%
Fagon	12	84	27	32
Croce	56	136	46	34
Rodriguez de Castro	57	110	45	41
Luna	58	132	65	49
Bonten	59	138	72	52
Kollef	60	130	60	46
Sanchez-Nieto	61	51	36	71
Ruiz	62	76	42	55
Fagon	63	204	90	44
Tejada Artigas	47	103	23	22

Definition of abbreviation: VAP = ventilator-associated pneumonia.

Although these statistics indicate that VAP is a severe disease, previous studies have not clearly demonstrated that pneumonia is indeed responsible for the higher mortality rate of these patients. Two independent factors make it difficult to assign responsibility unambiguously. The first is, once again, the difficulty in establishing a firm diagnosis, that is, to clearly identify patients with VAP; thus, the widely diverging VAP mortality rates reported might reflect not only differences in the populations studied but also differences in the diagnostic criteria used. Second, numerous studies have demonstrated that severe underlying illness predisposes patients in the ICU to the development of pneumonia, and their mortality rates are, consequently, high (6, 7, 11, 36, 37, 42, 45). Therefore, it is difficult to determine whether such patients would have survived if VAP had not occurred. However, nosocomial pneumonia has been recognized in several studies as an important prognostic factor for different groups of critically ill patients, including cardiac surgery patients (48, 65) or those with acute lung injury (66), and immunocompromised patients, for example those with acute leukemia (67), lung transplantation (68), or bone-marrow transplantation (69). In contrast, in patients with extremely severe medical conditions, such as those surviving cardiac arrest (70), or young patients with no underlying disease, such as those admitted after trauma (44, 71, 72), nosocomial pneumonia does not seem to significantly affect prognosis. Similarly, VAP does not appear to markedly influence overall survival of patients with ARDS, as documented by several studies (13, 16–18, 50). However, studies evaluating excess mortality attributed to VAP in patients with ARDS are difficult to interpret, because most VAP in this subset of patients occurs late in the course of the disease, whereas patients with ARDS who do not develop VAP, but who nevertheless die, do so earlier than other patients with ARDS, thus having little opportunity to develop nosocomial infection (16).

Despite these difficulties and limitations, several arguments support the notion that the presence of VAP is an important determinant of the poor prognosis of patients treated with MV. Risk factors for death of ventilated patients who developed pneumonia have been systematically investigated only by two groups (11, 14). Using multiple logistic regression analysis, Torres and coworkers demonstrated that the worsening of respiratory failure, the presence of an ultimately or rapidly fatal underlying condition, the presence of shock, inappropriate antibiotic therapy, and/or type of ICU were factors that negatively affected the prognosis of VAP. Thus, those authors emphasized the complex relationships among the severity of underlying disease leading to ICU admission and treatment with MV, the severity of pneumonia itself, and the adequacy of initial antibiotic treatment. The important prognostic role played by the adequacy of the initial empiric antimicrobial therapy was also analyzed by several other investigators and is summarized in Table 3 (19, 58, 61, 62, 73–76).

The prognosis for aerobic, gram-negative bacilli (GNB) VAP is considerably worse than that for infection with gram-positive pathogens, when these organisms are fully susceptible to antibiotics. Death rates associated with *Pseudomonas* pneumonia are particularly high, ranging from 70 to more than 80% in several studies (12, 64, 77–81). According to one study, mortality associated with *Pseudomonas* or *Acinetobacter* pneumonia was 87% compared with 55% for pneumonias due to other organisms (12). Similarly, Kollef and coworkers demonstrated that patients with VAP due to high-risk pathogens (*Pseudomonas aeruginosa*, *Acinetobacter* spp., and *Stenotrophomonas maltophilia*) had a significantly higher hospital mortality rate (65%) than patients with late-onset VAP due to other microbes (31%) or patients without late-onset pneumonia (37%) (65). Concerning gram-positive pathogens, in a study comparing VAP due to methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillin-sensitive *S. aureus* (MSSA), mortality was found to be directly attributable to pneumonia for 86% of the former cases versus 12% of the latter, with a relative risk of death equal to 20.7 for MRSA pneumonia (82).

Multivariate analyses conducted to evaluate the independent role played by VAP in inducing death failed to identify VAP as a variable independently associated with mortality in two studies (15, 45). In contrast, the EPIC (European Prevalence of Infection in Intensive Care) Study's stepwise logistic regression analyses demonstrated that ICU-acquired pneumonia increased the risk of death with an odds ratio of 1.91 (95% CI, 1.6 to 2.3), independently of clinical sepsis and bloodstream infection (6). Another study based on 1,978 patients in the ICU, including 1,118 patients receiving MV, demonstrated that, in addition to the severity of illness, the presence of dysfunctional organ(s); stratification according to the McCabe and Jackson criteria of underlying disease as fatal, ultimately fatal, or not fatal; and nosocomial bacteremia and nosocomial pneumonia independently contributed to the deaths of ventilated patients (51). Using the Cox model in a series of 387 patients, it was demonstrated that patients with clinically suspected pneumonia had an increased risk of mortality; however, confirmation of the diagnosis by invasive techniques added no prognostic information (respective relative risk of 2.1 and 1.7) (46).

Case–control studies have been used to assess mortality attributable to nosocomial pneumonia, that is, the difference between the mortality rates observed for case patients (patients with pneumonia) and control subjects (patients without pneumonia). The results of matched cohort studies evaluating mortality and relative risk attributable to nosocomial pneumonia are given in Table 4 (44, 81, 83–87). Of these seven studies, five concluded that VAP was associated with a significant attributable mortality. For example, it was reported that the mortality rate attributable to VAP exceeded 25%, corresponding to a relative risk of death of 2.0 (with respective values of 40% and 2.5 for cases of pneumonia caused by *Pseudomonas* or *Acinetobacter* spp.) (81). These results were supported by those of other authors who reported that the risk of mortality was almost three

TABLE 3. MORTALITY RATES ACCORDING TO INITIAL EMPIRIC ANTIBIOTIC THERAPY

First Author	Ref.	Crude Mortality Rates of Patients Receiving		p Value
		Inadequate Antibiotic Therapy	Adequate Antibiotic Therapy	
Luna	58	92.2% (n = 34)	37.5% (n = 15)	< 0.001
Alvarez-Lerma	74	34.9% (n = 146)	32.5% (n = 284)	NS
Rello	21	63.0% (n = 27)	41.5% (n = 58)	0.06
Kollef	60	60.8% (n = 51)	26.6% (n = 79)	0.001
Sanchez-Nieto	61	42.9% (n = 14)	25.0% (n = 24)	NS
Ruiz	62	50.0% (n = 18)	39.3% (n = 28)	NS
Dupont	76	60.7% (n = 56)	47.3% (n = 55)	NS

Definition of abbreviation: NS = not significant.

TABLE 4. MORTALITY RATES AND RISK RATIOS FOR DEATH ATTRIBUTABLE TO NOSOCOMIAL PNEUMONIA IN MATCHED CASE–CONTROL STUDIES

First Author	Ref.	Diagnostic Criteria	Type of Patient	No. of Cases	Crude Mortality		Attributable Mortality (%)	Risk Ratio	p Value
					Cases (%)	Controls (%)			
Craig	83	Clinical	ICU	54	20.4	5.6	14.8	3.6	< 0.01
Fagon	81	PSB + BAL	Ventilated	48	54.2	27.1	27.1	2.0	< 0.01
Cunnion	84	Clinical	Surgical	20	55.0	5.0	50.0	23.2*	< 0.002
			ICU	20	55.0	7.5	47.5	15.1*	< 0.002
Baker	44	PSB/BAL	Medical	62	24.0	24.0	0	1	NS
Papazian	85	PSB	ICU	85	40.0	38.8	1.2	1.3	NS
Heyland	86	PSB/BAL	Trauma	177	23.7	17.9	5.8	1.3	NS
Bercault	87	PSB	Ventilated	135	41.0	14.0	27.0	2.7*	0.03

Definition of abbreviations: BAL = bronchoalveolar lavage; ICU = intensive care unit; NS = not significant; PSB = protected specimen brush.

* Odds ratio.

times higher in patients with pneumonia (RR, 2.95; 95% CI, 1.73 to 5.03) than in those without, with a major impact being observed for patients with intermediate-grade severity (88).

Finally, only a few reports have been published on mortality as a result of nosocomial pneumonia for which autopsy material from patients who died during their hospital stay was analyzed. On the basis of the analysis of 200 consecutive hospital deaths, it was concluded that nosocomial pneumonia contributed to 60% of the fatal infections and was the leading cause of death from hospital-acquired infections (89). By matching control subjects with half of these patients who died in the hospital, the same authors found that nosocomial lower respiratory tract infection occurred in 18% of the patients but in only 4% of the control subjects. Among patients who did not have a terminal condition on admission, nosocomial infections were three times more frequent among those who died (46%) than among survivors (11%) (89). A clinical investigation to determine whether VAP is an independent risk factor for death matched 108 nonsurvivors with 108 survivors for their underlying diseases, age, admission date, severity of illness, and duration of MV (90); 39 patients in each group developed VAP. This finding contrasts with those of other investigations, which identified the occurrence of VAP as an independent determinant of hospital mortality. Other factors beyond the simple development of VAP, such as the severity of the disease or the responsible pathogens, may be more important determinants of outcome for patients in whom VAP as well as other nosocomial infections develop. Indeed, it may well be that VAP increases mortality only in the subset of patients with intermediate severity (88) and/or in patients with VAP caused by high-risk pathogens, as indicated above (12, 65, 82). It is probable that several case–control studies were confounded by the fact that patients with low-severity and early-onset pneumonia due to organisms such as *Haemophilus influenzae* or *Streptococcus pneumoniae* have excellent prognoses with or without VAP, whereas very ill patients with late-onset VAP occurring while they are in a quasi-terminal state would die anyway.

Thus, considering many different kinds of evidence, VAP seems indeed associated with a 20 to 30% higher risk of death than that due to the underlying disease alone, at least in several subgroups of patients requiring MV, which pleads for new approaches to improve the management of ventilator-dependent patients, including more effective prophylactic measures, and earlier diagnosis and treatment.

Morbidity and Cost

It is impossible to evaluate precisely the morbidity and excess costs associated with VAP. However, with respect to morbidity measures, the prolonged hospital stay as a direct consequence of VAP has been estimated in several studies (46, 51, 81, 83, 84, 91). In one study, VAP prolonged the duration of MV from 10 to 32 days (42). In another, the median length of stay in the ICU for the patients who developed VAP was 21 days versus a median of 15 days for paired control subjects (81). Furthermore, a mean prolongation of ICU stay of 20 days was noted for patients with VAP when surviving pairs were compared. Reported mean durations of MV, ICU stay, and hospital stay were, respectively, 12.0, 20.5, and 43.0 days for trauma patients with pneumonia compared with 8.0, 15.0, and 34.0 days for their matched control subjects (44). Analyzing the same variables, others found, respectively, 27.3, 32.9, and 52.5 days for case patients versus 19.7, 24.5, and 43.2 days for patients without VAP (85). Similarly, it was demonstrated that the mean hospital stay after ICU admission was longer for surgical ICU patients (30.0 versus 22.3 days for control subjects) and medical and respiratory ICU patients who developed nosocomial pneumonia (40.9 versus 23.1 days for control subjects) (84). Heyland and coworkers compared 177 VAP patients with matched patients who did not develop VAP, and showed that VAP patients stayed in the ICU 4.3 days longer than did control subjects; the attributable ICU length of stay was longer for medical than surgical patients (6.5 versus 0.7 days), and for patients infected with "high-risk" as opposed to "low-risk" organisms (9.1 versus 2.9 days) (86). In patients with ARDS, all studies clearly identified prolonged duration of MV and lengthened ICU and hospital stays for patients with VAP compared with those without (16–18, 50). Thus, summarizing available data, VAP likely extended the ICU stay by at least 4 days.

These prolonged hospitalizations underscore the considerable financial burden imposed by the development of VAP. However, a precise and universal evaluation of such overcosts is difficult. Cost analysis is, indeed, dependent on a wide variety of factors that differ from one country to another, including health care system, organization of the hospital and the ICU, the possibility of patients being treated by private practitioners, cost of antibiotics, and so on. Only a few, and frequently discrepant, data are available: The average excess cost of nosocomial pneumonia was estimated to be US$1,255 in 1982 (92). In a similar study in 1985, the average extra cost was US$2,863 (93). More recently, the extra hospital charges attributed to nosocomial pneumonia occurring in trauma patients were evaluated to be US$40,000 (44).

Etiologic Agents

Microorganisms responsible for VAP may differ according to the population of patients in the ICU, the durations of hospital and ICU stays, and the specific diagnostic method(s) used.

The high rate of respiratory infections due to GNB in this setting has been repeatedly documented (12, 14, 19, 34, 94–97). Several studies have reported that more than 60% of VAP is caused by aerobic GNB. More recently, however, some investigators have reported that gram-positive bacteria have become increasingly more common in this setting, with *S. aureus* being the predominant gram-positive isolate. For example, *S. aureus* was responsible for most episodes of nosocomial pneumonia in the EPIC Study, accounting for 31% of the 836 cases with identified responsible pathogens (97). The data from 24 investigations conducted with ventilated patients, for whom bacteriologic studies were restricted to uncontaminated specimens, confirmed those results: GNB represented 58% of recovered organisms (12, 14, 16, 18–21, 44, 46, 48, 50, 62, 63, 70, 98–107) (Table 5). The predominant GNB were *P. aeruginosa* and *Acinetobacter* spp., followed by *Proteus* spp., *Escherichia coli*, *Klebsiella* spp., and *H. influenzae*. A relatively high rate of gram-positive pneumonias was also reported in those studies, with *S. aureus* involved in 20% of the cases (Table 5).

The high rate of polymicrobial infection in VAP has been emphasized repeatedly. In a study of 172 episodes of bacteremic nosocomial pneumonia, 13% of lung infections were caused by multiple pathogens (77). Similarly, when the PSB technique was used to identify the causative agents in 52 consecutive cases of VAP, a 40% polymicrobial infection rate was found (12), a value similar to that observed in another study conducted at the same time on a comparable population of ventilated patients (96). Findings were also similar for patients with ARDS: 58% of the 106 VAP episodes were polymicrobial, of which 55 and 60%, respectively, occurred in patients with and without ARDS (16).

Underlying diseases may predispose patients to infection with specific organisms. Patients with chronic obstructive pulmonary disease (COPD) are, for example, at increased risk for *H. influenzae*, *Moraxella catarrhalis* or *S. pneumoniae* infections; cystic fibrosis increases the risk of *P. aeruginosa* and/or *S. aureus* infections, whereas trauma and neurologic patients are at increased risk for *S. aureus* infection (33, 44, 72, 82). Furthermore, the causative agent for pneumonia differs among ICU surgical populations (108), with 18% of the nosocomial pneumonias being due to *Haemophilus* or pneumococci, particularly in trauma patients, but not in patients with malignancy, transplantation, or abdominal or cardiovascular surgery.

Several studies tried to identify specific risk factors for infection by a given pathogen; for example, logistic regression analysis identified neurosurgery, head trauma, and large-volume aspiration as risk factors for VAP due to *Acinetobacter baumannii* (109). In studies of patients with ARDS compared with non-ARDS patients, there were no major differences in the distributions of pathogens responsible for VAP, with, however, a predominance of nonfermenting GNB and MRSA among the latter (16–18). Rather, the differences observed seemed primarily to reflect the duration of MV before VAP onset (16).

Despite somewhat different definitions of early-onset pneumonia, varying from < 3 to < 7 days (33, 107), high rates of *H. influenzae*, *S. pneumoniae*, MSSA, or susceptible Enterobacteriaceae were constantly found in early-onset VAP, whereas *P. aeruginosa*, *Acinetobacter* spp., MRSA, and multiresistant GNB were significantly more frequent in late-onset VAP (33, 106, 107). This different distribution pattern of etiologic agents between early- and late-onset VAP is also linked to the frequent administration of prior antimicrobial therapy in many patients with late-onset VAP. In a prospective study that included 129 episodes of nosocomial pneumonia documented by PSB specimens, the distributions of responsible pathogens were compared according to whether the patients had received antimicrobial therapy before pneumonia onset (19). The most striking finding was that the rate of pneumonia caused by gram-positive cocci or *H. influenzae* was significantly lower ($p < 0.05$) in patients who had received antibiotics, whereas the rate of pneumonia caused by *P. aeruginosa* was significantly higher ($p < 0.01$). A stepwise logistic regression analysis retained only prior antibiotic use (odds ratio [OR] = 9.2, $p < 0.0001$) as significantly influencing the risk of death from pneumonia (19). Similar results were obtained when multivariate analysis was used to determine risk factors for VAP caused by potentially drug-resistant bacteria such as MRSA, *P. aeruginosa*, *A. baumannii*, and/or *S. maltophilia* in 135 consecutive episodes of VAP (107). Only three variables remained significant: duration of MV before VAP onset ≥ 7 days (OR = 6.0), prior antibiotic use (OR = 13.5), and prior use of broad-spectrum drugs (third-generation cephalosporin, fluoroquinolone, and/or imipenem) (OR = 4.1) (107). Not all studies, however, have confirmed this distribution pattern. For example, one study found that the most common pathogens associated with early-onset VAP were *P. aeruginosa* (25%), MRSA (18%), and *Enterobacter* spp. (10%), with similar pathogens being associated with late-onset VAP (110). Their finding may, in part, be due to the prior hospitalization and use of antibiotics in many patients developing early-onset VAP before their transfer to the ICU.

The incidence of multiresistant pathogens is also closely linked to local factors and varies widely from one institution to another. Consequently, each ICU must continuously collect meticulous epidemiologic data. With these aims, variations of VAP etiology among three Spanish ICUs were analyzed (106) and compared with data collected in Paris (107). The authors concluded that VAP pathogens varied widely among these four treatment centers, with marked differences in all of the microorganisms isolated from VAP episodes in Spanish centers as compared with the French site. Clinicians must clearly be aware of the common microorganisms associated with both early-onset and late-onset VAP in their own hospitals to avoid the administration of initial inadequate antimicrobial therapy.

Legionella species (111, 112), anaerobes (100), fungi (113), viruses (114), and even *Pneumocystis carinii* should be mentioned as potential causative agents but are not considered to

TABLE 5. ETIOLOGY OF VENTILATOR-ASSOCIATED PNEUMONIA AS DOCUMENTED BY BRONCHOSCOPIC TECHNIQUES IN 24 STUDIES FOR A TOTAL OF 1,689 EPISODES AND 2,490 PATHOGENS

Pathogen	Frequency (%)
Pseudomonas aeruginosa	24.4
Acinetobacter spp.	7.9
Stenotrophomonas maltophilia	1.7
Enterobacteriaceae*	14.1
Haemophilus spp.	9.8
Staphylococcus aureus†	20.4
Streptococcus spp.	8.0
Streptococcus pneumoniae	4.1
Coagulase-negative staphylococci	1.4
Neisseria spp.	2.6
Anaerobes	0.9
Fungi	0.9
Others (< 1% each)‡	3.8

* Distribution when specified: *Klebsiella* spp., 15.6%; *Escherichia coli*, 24.1%; *Proteus* spp., 22.3%; *Enterobacter* spp., 18.8%; *Serratia* spp., 12.1%; *Citrobacter* spp., 5.0%; *Hafnia alvei*, 2.1%.

† Distribution when specified: methicillin-resistant *S. aureus*, 55.7%; methicillin-sensitive *S. aureus*, 44.3%.

‡ Including *Corynebacterium* spp., *Moraxella* spp., and *Enterococcus* spp.

be common in the context of pneumonia acquired during MV. However, several of these causative agents may be more common and potentially underreported because of difficulties involved with the diagnostic techniques used to identify them, including anaerobic bacteria and viruses (100, 114). In a study conducted to determine the frequency of anaerobes in 130 patients with a first episode of bacteriologically documented VAP, with special precautions taken to preserve anaerobic conditions during PSB transport and microbiologic procedures (100), anaerobes were involved in 23% of the total number of episodes and the main strains isolated were as follows: *Prevotella melaninogenica* (36%), *Fusobacterium nucleatum* (17%), and *Veillonella parvula* (12%). The probability of recovering anaerobic bacteria was particularly high in orotracheally intubated patients and patients in whom pneumonia occurred during the 5 days after ICU admission. However, in a study conducted among 143 patients who developed 185 episodes of suspected VAP and 25 patients with aspiration pneumonia, only 1 anaerobic organism (*V. parvula*) was isolated from 1 patient with aspiration pneumonia, and none from patients with VAP (99).

Thus, examining currently available data, the clinical significance of anaerobes in the pathogenesis and outcome of VAP remains unclear, except as etiologic agents in patients with necrotizing pneumonitis, lung abscess, or pleuropulmonary infections. Anaerobic infection and coverage with antibiotics, such as clindamycin or metronidazole, should probably also be considered for patients with gram-positive respiratory secretions documenting numerous extra- and intracellular microorganisms in the absence of positive cultures for aerobic pathogens.

Isolation of fungi, most frequently *Candida* species, at significant concentrations poses interpretative problems. Invasive disease has been reported in VAP but, more frequently, yeasts are isolated from respiratory tract specimens in the apparent absence of disease. One prospective study examined the relevance of isolating *Candida* spp. from 25 non-neutropenic patients who had been mechanically ventilated for at least 72 hours (113). Just after death, multiple culture and biopsy specimens were obtained by bronchoscopic techniques. Although 10 patients had at least one biopsy specimen positive for *Candida* spp., only two had evidence of invasive pneumonia as demonstrated by histologic examination. Many of the endotracheal aspirates, PSB specimens, and BAL specimens also yielded positive cultures for *Candida* spp., sometimes in high concentrations, but they did not contribute to diagnosing invasive disease. On the basis of these data, the use of the commonly available respiratory sampling methods (bronchoscopic or nonbronchoscopic) in mechanically ventilated patients appears insufficient for the diagnosis of *Candida* pneumonia. At present, the only sure method to establish that *Candida* is the primary lung pathogen is to demonstrate yeast or pseudohyphae in a lung biopsy. However, the significance of *Candida* isolation from the respiratory samples of mechanically ventilated patients merits being investigated in greater depth (115).

In another study conducted over a 5-year period, cytomegalovirus (CMV) was identified as a possible cause of VAP in 25 of 86 patients on the basis of histologic examination of lung tissues obtained at autopsy or open-lung biopsy (114). The authors concluded that CMV should not be excluded as a pathogen potentially responsible for VAP in patients in the ICU, even those without acquired immunodeficiency syndrome, hematologic malignancy, or immunosuppressive therapy.

Pathogenesis

Pneumonia results from microbial invasion of the normally sterile lower respiratory tract and lung parenchyma caused by either a defect in host defenses, challenge by a particularly virulent microorganism, or an overwhelming inoculum. The normal human respiratory tract possesses a variety of defense mechanisms that protect the lung from infection, for example: anatomic barriers, such as the glottis and larynx; cough reflexes; tracheobronchial secretions; mucociliary lining; cell-mediated and humoral immunity; and a dual phagocytic system that involves both alveolar macrophages and neutrophils (27). When these coordinated components function properly, invading microbes are eliminated and clinical disease is avoided, but when these defenses are impaired or if they are overcome by virtue of a high inoculum of organisms or organisms of unusual virulence, pneumonitis results.

As suggested by the infrequent association of VAP with bacteremia, the majority of these infections appear to result from aspiration of potential pathogens that have colonized the mucosal surfaces of the oropharyngeal airways. Intubation of the patient not only compromises the natural barrier between the oropharynx and trachea, but may also facilitate the entry of bacteria into the lung by pooling and leakage of contaminated secretions around the endotracheal tube cuff (10, 33). This phenomenon occurs in most intubated patients, whose supine position may facilitate its occurrence. In previously healthy, newly hospitalized patients, normal mouth flora or pathogens associated with community-acquired pneumonia may predominate. In sicker patients who have been hospitalized more than 5 days, GNB and *S. aureus* frequently colonize the upper airway (33).

Uncommonly, VAP may arise in other ways (116). Observed "macroaspirations" of gastric material initiate the process in some patients. Allowing condensates in ventilator tubing to drain into the patient's airway may have the same effect (25). FOB, tracheal suctioning, or manual ventilation with contaminated equipment may also bring pathogens to the lower respiratory tract. More recently, concerns have focused on the potential role of contaminated in-line medication nebulizers, but these devices are infrequently associated with VAP (116).

Although tracheal colonization by potentially pathogenic microorganisms occurs before lung infection in a majority of ventilated patients, its relationship with VAP development remains controversial. In 1972, Johanson and coworkers established that upper airway colonization is a frequent occurrence in ventilated patients and that it can act as a harbinger of nosocomial pneumonia in this setting (117). Those authors demonstrated that 45% of 213 patients admitted to a medical ICU became colonized with aerobic GNB by the end of 1 week in the hospital. Among the 95 colonized patients, 22 (23%) subsequently developed nosocomial pneumonia. By comparison, only four of the 118 (3.4%) noncolonized patients developed pneumonia. As determined in that study and several others, the tracheobronchial tree as well as the oropharynx of mechanically ventilated patients are frequently colonized by enteric GNB (118–121). In a study of 130 intubated patients, GNB were found in the trachea of 58% of those who had received antacids and/or H_2 blockers to prevent bleeding and in 30% of those receiving sucralfate for this purpose (40). Risk factors for tracheobronchial colonization with GNB appear to be the same as those that favor pneumonia and include more severe illness, longer hospitalization, prior or concomitant use of antibiotics, malnutrition, intubation, azotemia, and underlying pulmonary disease (119). Experimental investigations have linked some of these risk factors to changes in adherence of GNB to respiratory epithelial cells. Although formerly attributed to losses of cell surface fibronectin, these changes in adherence more likely reflect alterations of cell surface carbohydrates (27). Bacterial adhesins and prior antimicrobial ther-

apy appear to facilitate the process. Interestingly, Enterobacteriaceae usually appear in the oropharynx first, whereas *P. aeruginosa* more often appears first in the trachea (122, 123).

Other sources of pathogens causing VAP include the paranasal sinuses, dental plaque, and the subglottic area between the true vocal cords and the endotracheal tube cuff. The role of the gastrointestinal tract as a source of oropharyngeal and tracheal colonization by GNB is more controversial (118–120). A sequence of events leading to colonization from the stomach to the trachea, with increasing frequency in direct correlation to the gastric pH, was reported by several investigators, with 27 to 45% of patients having primary colonization of the gastric juice and subsequent colonization of the tracheobronchial tree ~ 2 days later (124–127). In addition to those microbiologic studies, other studies have clearly proven, by means of radiolabeled gastric juice or other techniques, that the gastric juice of intubated patients is aspirated into the tracheobronchial tract within a few hours (128–131). Those investigations convincingly corroborate the microbiologic studies demonstrating that tracheobronchial colonization originates in the stomach in at least 25 to 40% of patients and, therefore, lend support to the role of the gastric barrier in the pathogenesis of nosocomial pneumonia. Whether bacteria ascend from the intestines or descend from the oropharynx, the stomach may act as a reservoir in which pathogens can multiply and attain high concentrations. Alkalinization of the normally acid gastric environment seems to be a prerequisite for this mechanism to be operational.

However, not all authors agree that the gastropulmonary route of infection is truly operative in ICU patients (120, 132). Colonization from the stomach to the upper respiratory tract, eventually leading to 14 VAP episodes, could not be clearly demonstrated in one study (132). The same group, in another study conducted with 141 patients (117), reported that intragastric acidity influenced gastric colonization but not colonization of the upper respiratory tract or the incidence of VAP, suggesting therefore that it is unlikely that the gastropulmonary route contributes importantly to VAP development. Similarly, de Latorre and coworkers demonstrated that only 19 of 72 patients developed tracheal colonization after pharyngeal or gastric colonization by the same organisms; moreover, among the 12 patients who developed VAP, the microorganism(s) responsible had already colonized the trachea in 10 of them, but only 10 of the 21 responsible microorganisms isolated from VAP had previously colonized the pharynx or stomach (133). Last, efforts to eliminate the gastric reservoir by antimicrobial therapy without decontaminating the oropharyngeal cavity have generally failed to prevent VAP (134, 135). In fact, there is more than one potential pathway for colonization of the oropharynx and trachea in such a setting, including fecal–oral cross-infection on the hands of health care personnel, and contaminated respiratory therapy equipment. Patient care activities, such as bathing, oral care, tracheal suctioning, enteral feeding, and tube manipulations, provide ample opportunities for transmission of pathogens when infection control practices are substandard (136).

In summary, the relationship between VAP and tracheal, pharyngeal, and/or gastric colonizations remains to be elucidated for patients with an endotracheal tube. To date, these findings lead to the following conclusions: (*1*) tracheal colonization precedes VAP in most, but not all, patients; (*2*) only a minority of patients with tracheal colonization develop VAP; (*3*) the stomach can be a reservoir for pneumonia pathogens, although this is not the case in many ICU patients requiring MV.

Risk Factors

Risk factors provide information about the probability of lung infection developing in individuals and populations. Thus, they may contribute to the elaboration of effective preventive strategies by indicating which patients might be most likely to benefit from prophylaxis against pneumonia. Independent factors for VAP that were identified by multivariate analyses in selected studies are summarized in Table 6 (7, 11, 14, 15, 19, 35, 36, 45, 72, 84, 137).

Surgery. Postsurgical patients are at high risk for VAP, which accounts for nearly one-third of the pulmonary infiltrates in these ICU patients (11, 45, 108, 138). In a 1981 report, the pneumonia rate during the postoperative period was 17% (37). Those authors stated that the development of pneumonia was closely associated with preoperative markers of severity of the underlying disease, such as low serum albumin concentration and high American Society of Anesthesiologists preanesthesia physical status classification score (37). A history of smoking, longer preoperative stays, longer surgical procedures, and thoracic or upper abdominal surgery were also significant risk factors for postsurgical pneumonia. Another study comparing adult ICU populations demonstrated that postoperative patients had consistently higher rates of nosocomial pneumonia than did medical ICU patients, with a RR of 2.2 (84). Multiple regression analysis was performed to identify independent predictors of nosocomial pneumonia in the two groups; for surgical ICU patients, MV (> 2 days) and

TABLE 6. INDEPENDENT FACTORS FOR VENTILATOR-ASSOCIATED PNEUMONIA IDENTIFIED BY MULTIVARIATE ANALYSIS IN SELECTED STUDIES*

Host Factors	Intervention Factors	Other Factors
Serum albumin, < 2.2 g/dl	H_2 blockers ± antacids	Season: fall, winter
Age, ≥ 60 yr	Paralytic agents, continuous intravenous sedation	
ARDS	> 4 units of blood products	
COPD, pulmonary disease	Intracranial pressure monitoring	
Coma or impaired consciousness	MV > 2 d	
Burns, trauma	Positive end-expiratory pressure	
Organ failure	Frequent ventilator circuit changes	
Severity of illness	Reintubation	
Large-volume gastric aspiration	Nasogastric tube	
Gastric colonization and pH	Supine head position	
Upper respiratory tract colonization	Transport out of the ICU	
Sinusitis	Prior antibiotic or no antibiotic therapy†	

Definition of abbreviations: ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; MV = mechanical ventilation.

* *See* references 7, 11, 14, 15, 19, 35, 36, 45, 72, 84, and 137.

† *See* text.

acute physiology and chronic health evaluation score were retained by the model; for the medical ICU population, only MV (> 2 days) remained significant. It has been suggested that different surgical ICU patient populations may have different risks for nosocomial pneumonia: cardiothoracic surgery (139) and trauma (particularly the head) patients were more likely to develop VAP than medical or other types of surgical patients (35).

Antimicrobial agents. The use of antibiotics in the hospital setting has been associated with an increased risk of nosocomial pneumonia and selection of resistant pathogens (19, 45, 72, 80, 97, 107, 117, 140, 141). In a cohort study of 320 patients, prior antibiotic administration was identified by logistic regression analysis to be one of the four variables independently associated with VAP along with organ failure, age > 60 years, and the patient's head positioning (i.e., flat on his back or supine versus head and thorax raised 30 to 40° or semirecumbent) (45). However, other investigators found that antibiotic administration during the first 8 days was associated with a lower risk of early-onset VAP (142, 143). For example, Sirvent and coworkers showed that a single dose of a first-generation cephalosporin given prophylactically was associated with a lower rate of early-onset VAP in patients with structural coma (144). Moreover, multiple logistic regression analysis of risk factors for VAP in 358 medical ICU patients identified the absence of antimicrobial therapy as one of the factors independently associated with VAP onset (105). The same result was obtained for a particular subset of 250 patients with very early-onset VAP, occurring within 48 hours of intubation, that was investigated to identify potential risk factors for developing VAP (145). Multivariate analysis selected cardiopulmonary resuscitation (OR = 5.13) and continuous sedation (OR = 4.40) as significant risk factors for pneumonia, whereas antibiotic use (OR = 0.29) had a protective effect. Finally, the results of the multicentric Canadian study on the incidence of and risk factors for VAP indicated that antibiotic treatment conferred protection against VAP (35). This apparent protective effect of antibiotics disappears after 2 to 3 weeks, suggesting that a higher risk of VAP cannot be excluded beyond this point. Thus, risk factors for VAP change over time, thereby explaining why they differ from one series to another.

In contrast, prolonged antibiotic administration to ICU patients for primary infection is thought to favor selection and subsequent colonization with resistant pathogens responsible for superinfections (12, 107, 140, 146–148). According to our data on 567 ventilated patients, those who had received antimicrobial therapy within the 15 days preceding lung infection were not at higher risk for development of VAP (12), but 65% of the lung infections that occurred in patients who had received broad-spectrum antimicrobial drugs versus only 19% of those developing in patients who had not received antibiotics were caused by *Pseudomonas* or *Acinetobacter* spp. In a 1988 investigation of mechanically ventilated baboons treated with a variety of regimens of intravenous and topical antibiotics or no antibiotics at all (146), polymicrobial pneumonia occurred in almost all untreated animals. However, baboons that had received prophylactic topical polymycin had only a slightly lower incidence of pneumonia and the prevalence of drug-resistant microorganisms in the tracheal secretions was high: 60 and 78% after 4 and 8 days of MV, respectively. Therefore, strong arguments suggest that the prophylactic use of antibiotics in the ICU increases the risk of superinfection with multiresistant pathogens, while only delaying the occurrence of nosocomial infection.

Stress ulcer prophylaxis. In theory, patients receiving stress ulcer prophylaxis that does not change gastric acidity should have lower rates of gastric bacterial colonization and, consequently, a lower risk for nosocomial pneumonia. A direct relationship between alkaline gastric pH and gastric bacterial colonization has been demonstrated in several studies (124–127). For example, 86% of 28 postoperative patients had sterile gastric juice at ICU admission; 2 days later, the gastric secretions were colonized in 61% of the patients and the pH was more than 4 in 43% of them (125). These findings were fully confirmed by an analysis of 153 ICU patients receiving antacid or cimetidine: Total gastric colonization, particularly with GNB, was highly significantly increased ($p < 0.001$) (127). When the pH was less than 2, the gastric juice was sterile in 65% of the cases, but when it rose above 4, gastric juice GNB colonization was documented in at least 60% of the patients.

The results of several studies have indicated lower rates of pneumonia for patients given a gastroprotective agent (sucralfate) rather than agents that neutralize gastric secretions (antacids) or block gastric acid secretion (H_2 blockers) (40, 52, 137, 149, 150). In a well-designed, randomized study of 244 mechanically ventilated patients that compared stress ulcer prophylaxis with antacids, ranitidine, or sucralfate, the potential benefit of using sucralfate was confirmed (52). Although no differences in the incidence of macroscopic gastric bleeding and early-onset (within 4 days of ICU entry) VAP were found among the three groups, late-onset VAP was observed in only 5% of the patients who had received sucralfate compared with 16 and 21% of the patients who had received antacids or ranitidine, respectively ($p < 0.02$). Sucralfate-treated patients also had a lower median gastric pH and less frequent gastric colonization compared with the other groups. Molecular typing showed that 84% of the patients with late-onset GNB pneumonia had gastric colonization with the same strain before pneumonia developed.

According to meta-analyses of the efficacy of stress ulcer prophylaxis in ICU patients, respiratory tract infections were significantly less frequent in patients treated with sucralfate than in those receiving antacids or H_2 blockers (150–159). However, this conclusion was not fully confirmed in a large, multicenter, randomized, blinded, placebo-controlled trial that compared sucralfate suspension (1 g every 6 hours) with the H_2 receptor antagonist ranitidine (50 mg every 8 hours) for the prevention of upper gastrointestinal bleeding in 1,200 patients who required MV (160). Clinically relevant gastrointestinal bleeding developed in 10 of the 596 (1.7%) patients receiving ranitidine, as compared with 23 of the 604 (3.8%) receiving sucralfate (RR, 0.44; 95% CI, 0.21 to 0.92; $p = 0.02$). In the ranitidine group, 114 of 596 (19.1%) patients had VAP, as diagnosed by an adjudication committee using a modified version of the CDC criteria, versus 98 of 604 (16.2%) in the sucralfate group (RR, 1.18; 95% CI, 0.92 to 1.51; $p = 0.19$). Thus, although pneumonia rates were similar for the two groups, the relative risks suggest a trend toward a lower pneumonia rate for patients receiving sucralfate. Furthermore, VAP occurred significantly less frequently in patients receiving sucralfate when the diagnosis of pneumonia was based on Memphis VAP Consensus Conference criteria (if there was radiographic evidence of abscess and a positive needle aspirate, or histologic proof of pneumonia at biopsy or autopsy) ($p = 0.03$) (160).

Sucralfate appears to have a small protective effect against VAP because stress ulcer prophylactic medications that raise the gastric pH might themselves increase the incidence of pneumonia. This contention is supported by direct comparisons of trials of H_2 receptor antagonists versus no prophylaxis, which showed a trend toward higher pneumonia rates among the patients receiving H_2 receptor antagonists (OR, 1.25; 95% CI, 0.78 to 2.00) (158). Furthermore, the comparative effects of

sucralfate and no prophylaxis are unclear. Among 226 patients enrolled in two randomized trials, those receiving sucralfate tended to develop pneumonia more frequently than those given no prophylaxis (OR, 2.11; 95% CI, 0.82 to 5.44) (161, 162).

Endotracheal tube, reintubation, and tracheotomy. The presence of an endotracheal tube by itself circumvents host defenses, causes local trauma and inflammation, and increases the probability of aspiration of nosocomial pathogens from the oropharynx around the cuff. Scanning electron microscopy of 25 endotracheal tubes revealed that 96% had partial bacterial colonization and 84% were completely coated with bacteria in a biofilm or glycocalyx (163). The authors hypothesized that bacterial aggregates in biofilm dislodged during suctioning might not be killed by antibiotics or effectively cleared by host immune defenses (163, 164). Clearly, the type of endotracheal tube may also influence the likelihood of aspiration. Use of low-volume, high-pressure endotracheal cuffs reduced the rate to 56% and the advent of high-volume, low-pressure cuffs further lowered it to 20% (131). Leakage around the cuff allows secretions pooled above the cuff to enter the trachea; this mechanism, recently confirmed, underlines the importance of maintaining adequate intracuff pressure for preventing VAP (145). The relationship between tracheal colonization and VAP occurrence was confirmed in a study of 100 patients with head trauma and Glasgow Coma Scale scores less than 12 (165): within 24 hours of intubation, 68% of the patients who required intubation and MV for coma had tracheal *S. aureus*, *H. influenzae*, or *S. pneumoniae* colonization, which was identified as an independent risk factor for developing early-onset (less than 5 days) VAP.

Continuous or intermittent suction of oropharyngeal secretions has been proposed to avoid chronic aspiration of secretions through the tracheal cuff of intubated patients (Table 7) (166–169). Among 145 ventilated patients, pneumonia occurred less frequently (13%) in those whose endotracheal tube had a separate dorsal lumen for hourly suctioning of stagnant secretions above the cuff than the others (29%; $p < 0.05$) and VAP developed later (16.2 versus 8.3 days for the control group) (166). Similarly, in a 3-year prospective, randomized, controlled study, a lower VAP rate was documented when continuous subglottic suction was applied (18 versus 33% of the control subjects, NS; corresponding to an incidence density of 19.9 versus 39.6 episodes per 1,000 ventilator days, $p < 0.03$) (168). However, this difference was fully explained by the VAP occurring during the first week (3 of 76 versus 21 of 77, $p < 0.009$), whereas late-onset pneumonias were more frequent in the continuous subglottic-suctioning group (11 of 76 versus only 4 of 77) than the control group. Furthermore, detailed microbiologic analysis demonstrated that this reduction concerned only pneumonia due to *H. influenzae* or gram-positive cocci. The incidence of VAP due to *P. aeruginosa* or Enterobacteriaceae and mortality rates did not differ between the two groups (168). On the basis of 343 patients who had undergone cardiac surgery, continuous subglottic suction significantly delayed VAP occurrence but did not modify the overall VAP frequency (5 versus 8%; $p = 0.24$) (169).

In addition to the presence of endotracheal tubes, reintubation is, per se, a risk factor for VAP (170). This finding probably reflects an increased risk of aspiration of colonized oropharyngeal secretions into the lower airways by patients with subglottic dysfunction or impaired consciousness after several days of intubation. Another explanation is direct aspiration of gastric contents into the lower airways, particularly when a nasogastric tube is kept in place after extubation. According to a case–control study, the pneumonia rate was 47% for reintubated patients compared with 4% for control subjects matched for the duration of prior MV. In another study evaluating the risk of VAP after intrahospital patient transport, reintubation was identified as one of the independent risk factors for VAP (OR, 3.05; $p < 0.001$) (171). A recent case–control study of 135 patients following heart surgery also found reintubation to be a major risk factor, since VAP occurred in 92% of the reintubated patients versus 12% of the control subjects (48). Multivariate analysis associated reintubation with a greater risk for the development of pneumonia.

The role of early tracheotomy in VAP prevention remains controversial, with only a few studies that examined this issue (122, 172–177). Whereas some studies found a reduction in the rate of VAP in patients with early tracheotomy (173–175), others could not demonstrate any benefit (122, 172, 177). For example, in a randomized, prospective, multicenter trial including 112 patients who were thought to need prolonged MV, there were no differences, at least until Day 14, between ICU length of stay, pneumonia rate, or mortality between the 53 patients who underwent early (Day 3 to 5) tracheotomy and the 59 who were managed by translaryngeal intubation (177). The major problem that doomed that study was the overwhelming physician bias, which led to limited patient entry

TABLE 7. RESULTS OF RANDOMIZED TRIALS EVALUATING THE IMPACT OF DIFFERENT RESPIRATORY EQUIPMENT ON INCIDENCE OF VENTILATOR-ASSOCIATED PNEUMONIA

First Author	Ref.	No. of Patients	Incidence of VAP (%)		p Value
			Intervention	Control	
Continuous or intermittent aspiration of oropharyngeal secretions versus standard care					
Mahul	166	145	13	29	< 0.05
Valles	168	153	18	33	NS
Kollef	169	343	5	8	NS
Open versus closed endotracheal suction					
Deppe	194	84	26	29	NS
Johnson	195	35	50	53	NS
Combes	196	104	17	8	NS
Heat and moisture exchangers versus heated humidifiers					
Martin	200	73	6	19	NS
Roustan	201	112	10	15	NS
Dreyfuss	202	131	10	11	NS
Hurni	203	115	8	13	NS
Kirton	204	280	6	16	< 0.05

Definition of abbreviations: NS = not significant; VAP = ventilator-associated pneumonia.

and premature arrest of the study. In the absence of any meaningful data, practice patterns are influenced and guided by strong assumptions and quasi-religious dogma. Until a properly constructed randomized trial is performed to define the timing and utility of tracheotomy in the ICU, its true impact on decreasing VAP will remain merely speculative (178).

Nasogastric tube, enteral feeding, and position of the patient. Almost all patients receiving MV have a nasogastric tube inserted to evacuate gastric and enteral secretions, prevent gastric distention, and/or provide nutritional support. The nasogastric tube is not generally considered to be a potential risk factor for VAP, but it may increase oropharyngeal colonization, cause stagnation of oropharyngeal secretions, and increase reflux and the risk of aspiration. A multivariate analysis retained the presence of a nasogastric tube as one of the three independent risk factors for nosocomial pneumonia based on a series of 203 patients admitted to the ICU for 72 hours or more (36). The case–control study cited above also identified a nasogastric tube as one of the four independent risk factors for VAP in postcardiac surgery patients (48).

Early initiation of enteral feeding is generally regarded as beneficial in critically ill patients, but it may increase the risk of gastric colonization, gastroesophageal reflux, aspiration, and pneumonia (179, 180). Cultures of simultaneously sampled daily gastric, tracheal, and oropharyngeal specimens from 18 MV-dependent patients not receiving antacids or H_2 antagonists (181) showed that, after enteral feeding was started, the number of gram-negative isolates increased significantly, and 5 (28%) patients had gram-negative rods that were first recovered in the stomach and subsequently isolated from the trachea. The mechanism of transfer of gastric organisms into the trachea appears to have been aspiration. Among enterally fed, critically ill patients with small-bore nasogastric tubes, aspiration was reported in 38%, even though the bolus technique was used to feed all patients (130). Other observations suggested that aspiration is infrequent when small-bore feeding tubes and continuous infusion are used (182–186), but the real benefit of using small-bore tube is still unclear. To determine whether gastroesophageal reflux and microaspiration in intubated patients can be reduced by the use of a small-bore nasogastric tube, 17 patients intubated for more than 72 hours were assigned, after instillation of radioactive technetium colloid in each patient's stomach, to receive in randomized order one of two different types of nasogastric tubes (one with a 6.0-mm external bore and the other with a 2.85-mm external bore) (187). No differences were found between tube types when the time course and cumulative counts of pharyngeal and tracheal samples were compared, suggesting that small-bore nasogastric tubes do not reduce gastroesophageal reflux or microaspiration in intubated patients.

The aspiration rate generally varies as a function of differences in the patient population, neurologic function, type of feeding tube, location of the feeding port, and method of evaluating aspiration (182, 188). Clinical impressions and preliminary data suggest that postpyloric or jejunal feeding entails less risk of aspiration and may therefore be associated with fewer infectious complications than gastric feeding, although this point remains controversial (129, 189). Nonetheless, aspiration can easily occur should the feeding tube be inadvertently dislodged. A retrospective study of noncritically ill adult patients showed a 40% rate of accidental feeding-tube dislodgment, but all the patients whose tube was dislodged were confused, disoriented, or had altered awareness, as is frequently observed in patients in ICUs (190).

Maintaining mechanically ventilated patients with a nasogastric tube in place in a supine position is also a risk factor for aspiration of gastric contents into the lower airways. When radioactive material was injected through a nasogastric tube directly into the stomach of 19 mechanically ventilated patients, the mean radioactive counts in endobronchial secretions were higher in a time-dependent fashion in samples obtained from patients in a supine position than in those obtained from patients in a semirecumbent position (128). The same microorganisms were isolated from the stomach, pharynx, and endobronchial samples of 32% of the specimens taken while patients were lying supine. However, the results of a subsequent study published by the same group from Barcelona were disappointing, as they demonstrated that gastroesophageal reflux in mechanically ventilated patients with a nasogastric tube occurs irrespective of body position (191). The same investigators then conducted a randomized trial comparing semirecumbent and supine positions (192). The trial, which included 86 intubated and mechanically ventilated patients, was stopped after the planned interim analysis because the frequency and the risk of VAP were significantly lower for the semirecumbent group. These findings were indirectly confirmed by the demonstration that the head position of the supine patient during the first 24 hours of MV was an independent risk factor for acquiring VAP (45).

Respiratory equipment. Respiratory equipment itself may be a source of bacteria responsible for VAP. In the 1980s, the major risk of infection was associated with contaminated reservoir nebulizers, designed to deliver small-sized particles suspended in the effluent gas (15). Those observations led to the current practices in respiratory therapy, for example, the use of cascade humidifiers, which do not generate microaerosols. Nevertheless, respiratory equipment continues to be a source of bacterial contamination. For example, medication nebulizers inserted into the inspiratory-phase tube of the mechanical ventilator circuit may inadvertently be responsible for bacterial aerosols after a single use (193).

To avoid hypoxia, hypotension, and contamination of suction catheters entering the tracheal tube, investigators have examined closed suctioning systems (Table 7) (194–196). Closed versus open suctioning systems were compared for 104 mechanically ventilated patients and a nonsignificantly lower prevalence rate of VAP was found for patients managed with the closed system compared with those with the open system (7.3 versus 15.9 per 1,000 patient-days; $p = 0.07$) without demonstrating any adverse effect (196). In an earlier study, not only did the investigators not show a statistically significant protective effect of the closed system on the incidence of VAP (26 versus 29%), they observed a higher frequency of endotracheal colonization associated with the closed device (67 versus 39%; $p < 0.02$) (194).

Mechanical ventilators with humidifying cascades often have high levels of tubing colonization and condensate formation that may also be risk factors for pneumonia. The rate of condensate formation in the ventilator circuit is linked to the temperature difference between the inspiratory-phase gas and the ambient temperature and may be as high as 20 to 40 ml/h (197–199). Examination of condensate colonization in 20 circuits detected a median level of 2.0×10^5 organisms/ml, and 73% of the 52 gram-negative isolates present in the patients' sputum samples were subsequently isolated from condensates (198). Because most of the tubing colonization was derived from the patients' secretions, the highest bacterial counts were present near the endotracheal tube. Simple procedures, such as turning the patient or raising the bed rail, may accidentally spill contaminated condensate directly into the patient's tracheobronchial tree. Inoculation of large amounts of fluid with high bacterial concentrations is an excellent way to overwhelm pulmonary defense mechanisms and cause pneumonia. Heating ventilator tub-

ing markedly lowers the rate of condensate formation, but heated circuits are often nondisposable and are expensive. In-line devices with one-way valves to collect the condensate are probably the easiest way to handle this problem; they must be correctly positioned into disposable circuits and emptied regularly. Furthermore, to date, no scientific evidence has confirmed that heated circuits reduce the rate of VAP (199).

To decrease condensation and moisture accumulation in ventilator circuits, several studies have investigated the use of heat–moisture exchangers (HMEs) in place of conventional heated-water humidification systems. Slightly lower VAP rates were observed in four studies and a significant difference was observed in a fifth study, suggesting that HMEs are at least comparable to heated humidifiers and may be associated with lower VAP rates than heated humidifiers (Table 7) (200–204). Changing the HME every 48 hours did not affect ventilator circuit colonization, and the authors concluded that the cost of MV might be substantially reduced without any detriment to the patient by prolonging the time between HME changes from 24 to 48 hours (205). Furthermore, using HMEs may decrease the nurses' workload (no need to refill cascades, to void water traps on circuits, etc.), decrease the number of septic procedures (it was clearly shown that respiratory tubing condensates must be handled as an infectious waste), and reduce the cost of MV, especially when used for prolonged periods without change. However, because some observational studies have documented an increased resistive load and a larger dead space associated with exchangers (206, 207), their use should be discouraged in patients with ARDS ventilated with a low tidal volume and in patients with COPD during the weaning period, when pressure support, and not T-piece trials, are used.

There is no apparent advantage to changing ventilator circuits frequently for VAP prevention. This holds true whether circuits are changed every 2 days or every 7 days compared with no change at all and whether they are changed weekly as opposed to three times per week (208–210). A policy of no circuit changes or infrequent circuit changes is simple to implement and the costs are likely lower than those generated by regular, frequent circuit changes; thus, such a policy is strongly recommended by the 1997 CDC guidelines (23).

Sinusitis. Whereas many studies have compared the risk of nosocomial sinusitis as a function of the intubation method used and the associated risk of VAP (211–227), only a few were adequately powered to give a clear answer. In 1 study of 300 patients who required MV for at least 7 days and were randomly assigned to undergo nasotracheal or orotracheal intubation, computed tomographic evidence of sinusitis was observed slightly more frequently in the nasotracheal group than in the oral endotracheal group ($p = 0.08$), but this difference disappeared when only bacteriologically confirmed sinusitis was considered (223). The rate of infectious maxillary sinusitis and its clinical relevance were also prospectively studied in 162 consecutive critically ill patients, who had been intubated and mechanically ventilated for 1 hour to 12 days before enrollment (221). All had a paranasal computed tomography scan within 48 hours of admission, which was used to divide them into three groups (no, moderate, or severe sinusitis), according to the radiologic appearance of the maxillary sinuses. Patients who had no sinusitis at admission ($n = 40$) were randomized to receive endotracheal and gastric tubes via the nasal or oral route and, on the basis of radiologic images, respective sinusitis rates were 96 and 23% ($p < 0.03$); yet, no differences in the rates of infectious sinusitis were documented according to the intubation route. However, VAP was more common in patients with infectious sinusitis, with 67% of them developing lung infection in the days following the diagnosis of sinusitis (221). Therefore, whereas it seems clear that infectious sinusitis is a risk factor for VAP, no studies have yet been able to definitively demonstrate that orotracheal intubation decreases the infectious sinusitis rate compared with nasotracheal intubation, and thus no firm recommendations on the best route of intubation to prevent VAP can be advanced.

Intrahospital patient transport. A prospective cohort study conducted with 531 mechanically ventilated patients evaluated the impact of transporting the patient out of the ICU to other sites within the hospital (171). Results showed that 52% of the patients had to be moved at least once for a total of 993 transports and that 24% of the transported patients developed VAP compared with 4% of the patients confined to the ICU ($p < 0.001$). Multiple logistic regression analysis confirmed that transport out of the ICU was independently associated with VAP (OR = 3.8; $p < 0.001$).

DIAGNOSIS

Unlike community-acquired pneumonia, it may be difficult to determine whether pneumonia has developed in a hospitalized ventilator-dependent patient.

Clinical Evaluation Combined with Microscope Examination and Culture of Tracheal Secretions

The diagnosis of VAP is usually based on three components: systemic signs of infection, new or worsening infiltrates seen on the chest roentgenogram, and bacteriologic evidence of pulmonary parenchymal infection (53). The systemic signs of infection, such as fever, tachycardia, and leukocytosis, are nonspecific findings and can be caused by any condition that releases cytokines (228). In trauma and other surgical patients, fever and leukocytosis should prompt the physician to suspect infection, but during the early posttraumatic or postoperative period (i.e., during the first 72 hours), these findings usually are not conclusive. However, later, fever and leukocytosis are more likely to be caused by infection, but even then, other events associated with an inflammatory response (e.g., devascularized tissue, open wounds, pulmonary edema, and/or infarction) can be responsible for these findings.

Although the plain (usually portable) chest roentgenogram remains an important component in the evaluation of hospitalized patients with suspected pneumonia, it is most helpful when it is normal and rules out pneumonia. When infiltrates are evident, the particular pattern is of limited value for differentiating among cardiogenic pulmonary edema, noncardiogenic pulmonary edema, pulmonary contusion, atelectasis (or collapse), and pneumonia. Because atelectasis is common among patients in the ICU, the contribution of repeating the chest X-ray after vigorous pulmonary physiotherapy was emphasized to differentiate infiltrates caused by atelectasis from those due to infection (229). Few studies have examined the accuracy of the portable chest radiograph in the ICU (53, 230–235). In a review of 24 patients with autopsy-proven pneumonia who were receiving MV, no single radiographic sign had a diagnostic accuracy greater than 68% (230). The presence of air bronchograms was the only sign that corresponded well with pneumonia, correctly predicting 64% of pneumonias in the entire group. When the group was divided into patients with and without ARDS, however, a significant difference was noted. The presence of air bronchograms or alveolar opacities in patients without ARDS correlated with pneumonia, whereas no such correlation was found for patients with ARDS. A variety of causes other than pneumonia can explain asymmetric consolidation in patients with ARDS, for example, atelectasis,

emphysema, pulmonary edema, and thromboembolic disease. Marked asymmetry of radiographic abnormalities has also been reported in patients with uncomplicated ARDS (236).

Microscopy evaluation and culture of tracheal secretions and/or expectorated sputum are also frequently inconclusive for patients clinically suspected of having pneumonia, because the upper respiratory tract of most patients in the ICU is colonized with potential pulmonary pathogens, whether or not parenchymal pulmonary infection is present (96, 117, 237–239). On the basis of specimens simultaneously obtained from the deep trachea and lung for culture from 48 patients with respiratory failure undergoing open-lung biopsy, culture results agreed for only 40% of these paired samples (240). For patients with histologically documented pneumonia, endotracheal aspirate sensitivity was 82%, but its specificity was only 27%. Microscope examination of tracheal aspirates may, however, be of some potential value in the diagnosis of patients with VAP. Indeed, specimens from intubated patients with pneumonia showed higher semiquantitative grading of neutrophils and bacteria including intracellular organisms than did those from patients without pneumonia (41). Nine of the 11 patients with pneumonia experienced rapid rises in bacterial counts at an average of 5 days before the appearance of a new or progressive pulmonary infiltrate. In the same study, elastin fibers seen on KOH-treated preparations of endotracheal aspirates had a sensitivity of 52% and a specificity of 100% for detecting pneumonia. However, in patients with ARDS, elastin fibers have only a 50% positive-predictive value for pneumonia because noninfectious lung necrosis is common in this context (41, 241, 242).

A study conducted with 84 ventilated patients suspected of having lung infection prospectively compared the diagnostic predictions independently formulated by each member of a team of physicians aware of all clinical, radiologic, and laboratory data, including the results of gram-stained bronchial aspirates, with those resulting from a complete work-up including quantitative culture results of PSB specimens (243). Only 27 of the 84 clinically suspected pneumonias were indeed present and only 62% of the predictions accurately diagnosed lung infection. The mean values of temperature; blood leukocytes and blood lymphocytes; Pa_{O_2}/FI_{O_2} and radiologic scores; and changes in temperature, blood leukocytes, and radiologic score during the 3 days preceding suspicion of pneumonia did not differ between patients who had pneumonia and those who did not, thereby confirming previous conclusions that no objective clinical criteria exist for differentiating patients who have pneumonia from those who do not. A postmortem study established 69% sensitivity and 75% specificity for a diagnostic rule consisting of new and persistent infiltrates on chest radiographs and two of the following three criteria: (*1*) fever > 38.3° C; (*2*) leukocytosis > 12×10^9/ml, and/or (*3*) purulent tracheobronchial secretions (235). Thus, available evidence indicates that clinical diagnosis of VAP is associated with about 30 to 35% false-negative and 20 to 25% false-positive results (244). Even when the clinical diagnosis of pneumonia is accurate, results of gram staining and culture of tracheal aspirates can be misleading for the choice of the appropriate antibiotics. In the prospective study comparing predicted with PSB-documented VAP (243), only 33% of the treatments prescribed for patients subsequently diagnosed as having pneumonia proved to be effective, despite the fact that the physicians who contributed their predictions usually used combination antibiotic regimens, which are currently considered to be standard therapy for nosocomial pneumonia.

In 1991, a composite clinical score was proposed, based on seven variables (temperature, blood leukocyte count, volume and purulence of tracheal secretions, oxygenation, pulmonary radiography, and semiquantitative culture of tracheal aspirate) accorded zero, one, or two points (245). That study of 28 patients requiring prolonged MV showed a good correlation ($r = 0.84$, $p < 0.0001$) between this clinical score and quantitative bacteriology of BAL samples, with a threshold value of 6 enabling identification of patients with infection. However, this scoring system is tedious to calculate and difficult to use in clinical practice, because several variables, such as progression of pulmonary infiltrates and results of semiquantitative cultures of tracheal secretions, can lead to different calculations depending on the observer. Furthermore, its value remains to be validated in a large prospective study, especially in patients with bilateral pulmonary infiltrates.

The potential usefulness of routine culture of endotracheal aspirates for monitoring the response to antibiotic treatment in patients with VAP is also questionable, because the upper respiratory tract of most patients with pneumonia remains colonized with multiple potential pathogens, even when the clinical course is favorable. These cultures contribute indisputably to the diagnosis of VAP only when they are completely negative for a patient with no modification of prior antimicrobial treatment. In such a case, the negative-predictive value is high and the probability of the patient having pneumonia is close to null (31).

Microbiologic Diagnosis of Ventilator-associated Pneumonia Using Nonbronchoscopic Techniques

Bacteremia and positive pleural effusion cultures are generally considered to be able to identify the organisms causing the pneumonia, if no other source of infection is found. Therefore, most experts recommend that investigation of suspected VAP should include taking two sets of blood samples for culture and tapping pleural effusions > 10 mm, even though spread to the blood or pleural space occurs in < 10% of VAP (2, 33, 39, 246).

Quantitative cultures of endotracheal aspirates. While the simple qualitative culture of endotracheal aspirates is a technique with a high percentage of false-positive results due to bacterial colonization of the proximal airways observed in most patients in the ICU, some studies using quantitative culture techniques suggest that endotracheal aspirate cultures may have an acceptable overall diagnostic accuracy, similar to that of several other more invasive techniques (29, 241, 247–251). In one study, the operating characteristics of endotracheal aspirate quantitative cultures, using 10^6 cfu/ml of respiratory secretions as the interpretative cutoff point, compared favorably with those of the PSB technique, with slightly higher sensitivity (82 versus 64%) and lower specificity (83 versus 96%) (247). To assess the reliability of that method, FOB with PSB and BAL was used to study 57 episodes of suspected lung infection in 39 ventilator-dependent patients with no recent changes of antimicrobial therapy (250). The operating characteristics of endotracheal aspirate cultures were calculated over a range of cutoff values (from 10^3 to 10^7 cfu/ml) and the threshold of 10^6 cfu/ml appeared to be the most accurate, with a sensitivity of 68% and a specificity of 84%. However, when this threshold was applied to the study population, almost one-third of the patients with pneumonia were not identified. Furthermore, only 40% of microorganisms cultured in endotracheal aspirate samples coincided with those obtained from PSB specimens. Other authors have emphasized that, although quantitative endotracheal aspirate cultures can correctly identify patients with pneumonia, microbiologic results cannot be used to infer which microorganisms present in the trachea are really present in the lungs. In a study comparing quantitative endotracheal aspirate culture results with postmortem quantitative lung bi-

opsy cultures, only 53% of the microorganisms isolated from the former samples at concentrations greater than 10^7 cfu/ml were also found in the latter cultures (252).

Therefore, quantitative endotracheal aspirate cultures may be an adequate tool for diagnosing pneumonia when no fiberoptic techniques are available. But it must be kept in mind that this technique has several potential pitfalls. First, many patients may not be identified by using the cutoff value of 10^6 cfu/ml. Second, as soon as a lower threshold is used, specificity declines sharply and overtreatment becomes a problem. Finally, selecting antimicrobial therapy solely on the basis of endotracheal aspirate culture results can lead to either unnecessary antibiotic therapy or overtreatment with broad-spectrum antimicrobial agents.

Sampling of distal airways. Secretions in the distal airways can be collected through a bronchoscope or blindly, using an endobronchial catheter that is wedged in the tracheobronchial tree. The nonbronchoscopic techniques are used in mechanically ventilated patients essentially because the endotracheal tube, which bypasses the proximal airways, permits easy access to the lower airways. At least 15 studies have described a variety of nonbronchoscopic techniques for sampling lower respiratory tract secretions (30, 60, 121, 245, 253–265). Inherent advantages of these techniques are less invasiveness, availability to nonbronchoscopists, lower initial cost than FOB, the lack of potential contamination by the bronchoscopic channel, less compromise of patient gas exchange during the procedure, and availability to patients with small endotracheal tubes. Disadvantages include the potential sampling errors inherent in a blind technique and the lack of airway visualization.

Apparently acceptable results were, however, obtained by several investigators using nonbronchoscopic methods (30, 60, 245, 254, 256–258, 261–265). For example, a study of 78 suspected episodes of nosocomial pneumonia in 55 patients found that a protected telescoping catheter gave results similar to those obtained with the PSB technique for 74% of the cases (254). To assess the accuracy of a protected telescoping catheter inserted blindly into the respiratory tract, 27 patients who died after receiving MV for at least 72 hours were included in a comparative prospective postmortem study (266). Microbiologic sampling procedures were performed immediately after death, using either simple distal protected suction or instillation of sterile saline, that is, protected mini-BAL, and the results were compared with histologic postmortem lung examination or biopsies. When bacterial VAP was defined by the association of histologic signs and positive lung tissue culture, both techniques provided good specificity (86 and 100% for mini-BAL and protected distal suction, respectively) with an acceptable sensitivity (78%) for the diagnosis of bacterial VAP.

Although autopsy studies indicate that pneumonia in ventilator-dependent patients has often spread into every pulmonary lobe and predominantly involves the posterior portion of the lower lobes (30, 267–269), two clinical studies of ventilated patients with pneumonia contradict those findings, as some patients had sterile cultures of PSB specimens from the noninvolved lung (50, 270). Furthermore, although the authors of most studies concluded that the sensitivities of nonbronchoscopic and bronchoscopic techniques were comparable, the overall concordance was only $\sim$ 80%, emphasizing that, in some patients, the diagnosis could be missed by this technique, especially in the case of pneumonia involving the left lung, as demonstrated by Jorda and coworkers (256) and Meduri and coworkers (50).

Microbiologic Diagnosis of Ventilator-associated Pneumonia Using Bronchoscopic Techniques

Procedure. FOB provides direct access to the lower airways for sampling bronchial and parenchymal tissues at the site of lung inflammation. To reach the bronchial tree, however, the bronchoscope must traverse the endotracheal tube and proximal airways, where contamination is likely to occur. Therefore, distal secretions directly aspirated through the bronchoscope suction channel are frequently contaminated, thereby limiting their clinical specificity (271). Modifications of specimen retrieval, discussed below, and quantitative cultures are used to control for this contamination. However, poor technique during FOB can negate the benefit of these modifications. Therefore, to obtain meaningful results with FOB, it is extremely important to follow a precise methodology, as summarized in the Memphis International Consensus Conference report (272).

One major technical problem with all bronchoscopic techniques is proper selection of the sampling area in the tracheobronchial tree. Almost all intubated patients have purulent-looking secretions and the first secretions seen may represent those aspirated from another site in gravity-dependent airways or upper airway secretions aspirated around the endotracheal tube. Usually, the sampling area is selected on the basis of the location of the infiltrate on the chest radiograph or the segment visualized during FOB as having purulent secretions (272). In patients with diffuse pulmonary infiltrates or minimal changes in a previously abnormal chest film, determining the correct airway to sample may be difficult. In these cases, sampling should be directed to the area where endobronchial abnormalities are maximal. However, when in doubt, and because autopsy studies indicate that VAP frequently involves the posterior portion of the right lower lobe, this area should probably be sampled as a first priority (29, 30, 267, 269). While bilateral sampling has been advocated in the immunosuppressed host with diffuse infiltrates, there is no convincing evidence that multiple specimens are more accurate than single specimens for diagnosing VAP (236).

Complications. The risk inherent in FOB appears slight, even for critically ill patients requiring MV, although the associated occurrence of cardiac arrhythmias, hypoxemia, or bronchospasm is not unusual (60, 273–275). Careful methodical attention to the anesthesia protocol, with addition of a short-acting neuromuscular blocking agent, and monitoring of patients during FOB should permit rapid correction and more frequent prevention of hypoxemia in this setting, and therefore should further decrease the morbidity associated with this procedure. In a study that was conducted with 110 patients with ARDS, only 5% of them had arterial oxygen saturation less than 90% during FOB, although many suffered severe prebronchoscopy hypoxemia (274).

Although bacteremia does not appear to occur after PSB (276), release of tumor necrosis factor-α has been documented in patients undergoing BAL (277, 278). Transbronchial spread of infection is also an extremely remote possibility (272, 278, 279).

Specimen types and laboratory methods. A variety of bronchoscopic techniques can be used to diagnose bacterial pneumonia but, among them, two have been considered to be of particular value in establishing a specific diagnosis of VAP: (*1*) the use of a double-lumen catheter with a PSB to collect and calibrate uncontaminated specimens directly from the affected area in the lower respiratory tract (280); and (*2*) BAL, because this technique is a safe and practical method for obtaining cells and secretions from a large area of the lung that can be examined microscopically immediately after the procedure and are also suitable for culture by quantitative techniques (281).

Using BAL, infusion of at least 120 ml of saline in several (3 to 6) aliquots is needed to sample secretions in the distal respiratory bronchioles and alveoli (239, 272). It is estimated that the alveolar surface area distal to the wedged bronchoscope is 100 times greater than that of the peripheral airway

and that ~ 1 million alveoli (1% of the lung surface) are sampled, with ~ 1 ml of actual lung secretions retrieved in the total lavage fluid (281). The fluid return on BAL varies greatly and may affect the validity of results. In patients with emphysema, collapse of airways with the negative pressure needed to aspirate fluid may limit the amount of fluid retrieved. A small return may contain only diluted material from the bronchial rather than alveolar level and thus give rise to false-negative results (281).

Specimen handling. Regardless of the bronchoscopic technique used, rapid processing of specimens for culture is desirable to prevent loss of viability of pathogens or overgrowth of contaminants in these unfixed specimens (239, 280, 282). Although no absolute guideline exists, it is generally accepted that a delay of more than 30 minutes should not elapse before specimens are processed for microbiologic analysis (272, 279, 282). According to some investigators, refrigeration may be used to prolong transport time, and thus may permit the procedure to be performed even when the microbiology laboratory cannot immediately handle the specimens, for instance, during the weekend or night shift (279, 283).

Once bronchoscopic specimens are received in the laboratory, they should be processed according to clearly defined procedures (see Baselski [239] and Baselski and Wunderink [279] for complete description). Because of the inevitable oropharyngeal bacterial contamination that occurs in the collection of all bronchoscopic samples, quantitative culture techniques are always needed to differentiate oropharyngeal contaminants present at low concentration from higher concentration infecting organisms. Several investigators have confirmed that, in pneumonia, pathogens are present in lower respiratory tract inflammatory secretions at concentrations of at least 10^5 to 10^6 cfu/ml, and contaminants are generally present at less than 10^4 cfu/ml (267, 284–288). The diagnostic thresholds proposed for PSB and BAL are a confirmation of this concept. Because PSB collects between 0.001 and 0.01 ml of secretions, the presence of more than 10^3 bacteria in the originally diluted sample (1 ml) actually represents 10^5 to 10^6 cfu/ml of pulmonary secretions. Similarly, 10^4 cfu/ml for BAL, which collects 1 ml of secretions in 10 to 100 ml of effluent, represents 10^5 to 10^6 cfu/ml (239, 282).

Although PSB samples can be subjected to direct microscopy, the optimal method for smear preparation has not yet been established. Methods used include direct smearing of the secretions retrieved by the brush and cytocentrifugation of the material suspended in the diluent used for quantitative cultures. Although more sensitive, the former method has the disadvantages of decreasing the amount of secretions available for quantitative cultures and possibly contaminating the specimen. Reported sensitivities and specificities for PSB gram staining range from 20 to 100% and from 95 to 100%, respectively (239, 282, 289–291).

For BAL, it is recommended that a total cell count be performed to assess adequacy and a differential count be performed to assess cellularity. For quality assessment, the percentages of squamous and bronchial epithelial cells may be used to predict heavy upper respiratory contamination, with more than 1% of the total cells being proposed as a rejection criterion, even if only a few studies have directly assessed this point (292). Modified Giemsa staining (e.g., Diff-Quik; Baxter Scientific Products, McGaw Park, IL) is recommended, as it offers a number of advantages over Gram staining, including better visualization of host cell morphology, improved detection of bacteria, particularly intracellular bacteria, and detection of some protozoan and fungal pathogens (e.g., *Histoplasma*, *Pneumocystis*, *Toxoplasma*, and *Candida* spp.) (239, 293).

Usefulness of the protected specimen brush technique. The potential contribution of the PSB technique to evaluate ventilated patients suspected of having developed VAP has been extensively investigated in both human and animal studies, including eight investigations in which the accuracy of this culture technique was determined by comparison of both histologic features and quantitative cultures from the same area of the lung (29, 30, 267, 286–288, 294, 295). Despite the need for cautious interpretation, the results of those studies indicated that the PSB technique offers a sensitive and specific approach to identifying the microorganisms involved in pneumonia in critically ill patients, and to differentiate between colonization of the upper respiratory tract and distal lung infection. Pooling the results of 18 studies evaluating the PSB technique in a total of 795 critically ill patients showed the overall accuracy of this technique for diagnosing nosocomial pneumonia to be high, with a sensitivity of 89% (95% CI, 87 to 93%) and a specificity of 94% (95% CI, 92 to 97%) (29, 235, 238, 241, 257, 263, 266, 270, 288, 293, 294, 296–305).

Nevertheless, some controversy persists in the literature concerning the sensitivity of this technique, especially for detecting some pneumonias in patients already receiving antimicrobial treatment (269, 306). Although several studies have shown that, once bacterial infection of the lung is clinically apparent, there are at least 10^4 microorganisms/g of tissue, this assumption is valid only when patients have not received appropriate antimicrobial treatment after the onset of lung infection but before obtaining lung specimens (98, 307–309). Furthermore, the relationships between histology and quantitative cultures are highly complex, and investigation in this field is hampered by several unresolved methodologic problems. Thus, the reference standard shifts from one study to another and there is certainly no "gold standard." Even diagnosis based on histologic examination of open-lung biopsies has been called into question lately by studies such as the one showing that VAP diagnosis ranged from 18 to 38% among four different pathologists (28).

For 30 patients who died while receiving MV after having received prior antibiotic treatment, quantitative bacterial cultures of lung biopsies using 10^3 cfu/g of tissue as the cutoff point had low sensitivity (40%) and low specificity (45%), and could not differentiate between the histologic absence and presence of pneumonia (235). Pertinently, however, the operating characteristics of the PSB technique were similar to those obtained with lung cultures. Studies of experimental VAP in miniature pigs have also raised some concerns about the validity of the quantitative culture technique. Whereas higher lung tissue bacterial counts were found in the presence of pneumonia as compared with mere bronchial infection or absence of infection, it was not possible to define a threshold that would identify the presence or absence of pneumonia (268, 310). However, it remains unclear to what extent these findings obtained in experimental VAP and/or autopsied patients can be extended to patients in the ICU. From a practical point of view, it should be kept in mind that a diagnostic method based on microbiologic culture techniques only documents, qualitatively and quantitatively, the bacterial burden present in the lung tissue that was sampled. In no way can these bronchoscopic techniques retrospectively identify resolving pneumonia, or when antimicrobial treatment and lung antibacterial defenses might have been successful in suppressing microbial growth in lung tissue.

Even when PSB is performed before any antimicrobial treatment is given for suspected pneumonia, three major drawbacks are still inherent in this technique. First, even using the most accurate threshold of 10^3 cfu/ml to distinguish patients

with airway colonization from those with deep lung infection, a small number of false-positive results may be observed (249). Second, results of such cultures require 24 to 48 hours, and, therefore, no information is available to guide initial decisions concerning the appropriateness of antimicrobial therapy and which antibiotics should be prescribed. Finally, the PSB technique can yield negative results in patients with pneumonia in the following situations: (*1*) FOB performed at an early stage of infection when the bacterial burden is below the concentration necessary to reach diagnostic significance; (*2*) specimens obtained from an unaffected segment (which is probably crucial in patients with diffuse lung injury, in whom it is sometimes difficult to be sure to have selected the proper site for sampling); (*3*) incorrectly processed specimens; and/or (*4*) specimens obtained after initiation of a new class of antimicrobial agents.

Many technical factors, including the medium, adequacy of incubation and antibiotic or other toxic components, may influence microbiologic test results. Two groups evaluated the reproducibility of PSB sampling (299, 301) and concluded that, although *in vitro* repeatability is excellent and *in vivo* qualitative recovery is 100%, quantitative results are more variable. For 14 to 17% of patients, results of replicate samples fell on both sides of the 10^3 cfu/ml threshold and cfu counts varied by more than 10-fold for 59 to 67% of samples. This variability presumably reflects both the irregular distribution of organisms in secretions and the small volume actually sampled by PSB. It was concluded that, as with all diagnostic tests, borderline PSB quantitative culture results should be interpreted with caution and the clinical circumstances considered before any therapeutic decision can be made. FOB should be repeated in persistently symptomatic patients with an initially negative (less than 10^3 cfu/ml) concentration (311).

Usefulness of bronchoalveolar lavage. Although providing a broader image of lung content than PSB, BAL is subject to the same risk of contamination as bronchoscopic aspirates. Many groups have now investigated the value of quantitative BAL culture for the diagnosis of pneumonia in mechanically ventilated patients (29, 58, 96, 235, 241, 245, 248, 249, 257, 262, 272, 292–296, 300, 302, 303, 312–322). Although some investigators have concluded that BAL provides the best reflection of the lung's bacterial burden, both quantitatively and qualitatively, others have reported mixed results with poor specificity of BAL fluid cultures for patients with high tracheobronchial colonization. Analysis of postmortem lung biopsy samples showed quantitative cultures of BAL fluid to be as useful as those of PSB cultures (294). Although a few more microorganisms not detected in lung tissue were grown from BAL specimens than PSB specimens, the concentrations of organisms grown in cultures of BAL fluid and lung tissue specimens were strongly correlated ($\rho = 0.75$, $p < 0.0001$). Using more than 10^4 bacteria/ml of BAL fluid as the discriminative value for differentiating between infected lung segments with at least 10^4 cfu/g of tissue ($n = 11$) and noninfected lung segments ($n = 9$), only one false-negative and two false-positive results were observed, giving a sensitivity of 91% and a specificity of 78%. When the results of the 11 studies evaluating BAL fluids from a total of 435 ICU patients suspected of having developed VAP were pooled, the overall accuracy of this technique was close to that of the PSB, with a Q value of 0.84 (Q represents the intersection between the summary receiver operating characteristics [ROC] curve and a diagonal from the upper left corner to the lower right corner of the ROC space) (296). Similar conclusions were drawn in another meta-analysis when the results of 23 studies were pooled, with a sensitivity of 73 ± 18% and a specificity of 82 ± 19% (312).

The repeatability of BAL was assessed in 44 mechanically ventilated patients with suspected VAP (323). Two BALs were performed by the same physician in the same lung area during two FOB within a 30-minute interval. For the 44 patients studied, the qualitative repeatability (i.e., presence or absence of bacteria) was excellent (95%). For the 16 patients who had at least one positive culture, however, the results were more controversial. The quantitative repeatability for bacteria (same $\log_{10}$ for both BALs from the same patient) was lower (53%). The authors of that study concluded that BAL seems to have excellent repeatability when sterile, but that its repeatability when positive needs further assessment (323).

Because BAL harvests of cells and secretions from a large area of the lung and specimens can be microscopically examined immediately after the procedure to detect the presence or absence of intracellular or extracellular bacteria in the lower respiratory tract, it is particularly well adapted to provide rapid identification of patients with pneumonia. Several studies have confirmed the diagnostic value of this approach (56, 103, 245, 291, 293, 294, 320, 324–330). In each study, either the Giemsa or Gram staining was positive (more than 1 or 5% of BAL cells containing intracellular bacteria) for most patients with pneumonia and negative for those without pneumonia. Furthermore, in patients with pneumonia, the morphology and Gram staining of these bacteria were closely correlated with bacterial culture results, enabling early formulation of a specific antimicrobial therapy before the culture results became available. In one study in which the diagnostic accuracy of direct microscope examination of BAL cells could be directly assessed with both histologic and microbiologic postmortem lung features in the same segment, a high correlation could be established among the percentage of BAL cells containing intracellular bacteria, the total number of bacteria recovered from the corresponding lung samples, and the histologic grades of pneumonia ($\rho < 0.001$) (294). However, assessment of the degree of qualitative agreement between BAL Gram staining and PSB quantitative cultures for a series of 51 patients with VAP showed the correspondence to be complete for 51%, partial for 39%, and nonexistent for 10% of the cases (326).

Because measurement of endotoxin in BAL fluid may permit the rapid diagnosis of GNB pneumonia, the potential value of this technique was evaluated by several investigators (331–334). On the basis of 170 patients clinically suspected of having VAP and considering that an endotoxin level equal to or greater than 4 endotoxin units/ml distinguished patients with a significant GNB count from colonized patients, a sensitivity of 82 to 93%, a specificity of 81 to 95%, and a correct classification rate of 85 to 90% were found. Gram staining of BAL fluid for the presence of GNB, although much less expensive, yielded slightly inferior operating characteristics (334). These findings suggest that determination of endotoxin in BAL fluid could become an acceptable adjunct for the rapid diagnosis of GNB pneumonia in the near future.

Arguments for Bronchoscopy for the Diagnosis of Ventilator-associated Pneumonia

The use of invasive techniques, such as FOB, coupled with quantitative cultures of PSB or BAL specimens help guide the choice of antibiotic therapy in addition to confirming the actual diagnosis of VAP, while culture results precisely identify the offending organisms and their susceptibility patterns (Figure 1). Such data are invaluable for optimal antibiotic selection. They also increase the confidence and comfort level of health care workers in managing patients with suspected noso-

comial pneumonia (335). Antibiotic therapy that is selected on the basis of quantitative culture results may be more effective than empiric treatment. It is clear that the inappropriate initial management of VAP is associated with higher mortality (Table 3) and evidence suggests that the clinical recognition of treatment failure may be delayed. Indeed, initial, empiric antibiotic treatment often requires modification when quantitative culture results become available (21, 59, 61, 62, 74, 243). What is less clear is whether this delayed modification of initial treatment affects outcome (58, 98). The results of gram-stained bronchoscopic specimens, especially of BAL fluid, may provide an earlier guide to antibiotic management, but the impact of this information on physician practice and patient outcomes has not been fully investigated (103).

The second most compelling argument for invasive bronchoscopic techniques is that they can reduce excessive antibiotic use. There is little disagreement that the clinical strategy too readily opts for a diagnosis of VAP and leads to the unnecessary administration of broad-spectrum antibiotics. Because of their potentially greater specificity, bronchoscopic techniques should reduce antibiotic selection pressure in the ICU, thereby limiting the emergence of drug-resistant strains and the resulting higher risks of superinfection (45, 336–340). Indeed, most epidemiologic investigations have clearly demonstrated that the indiscriminate administration of antimicrobial agents to patients in the ICU have immediate as well as long-term consequences, which contribute to the emergence of multiresistant pathogens and increase the risk of severe superinfections (336, 340). This enhanced risk is not limited to one patient but may raise the risk of colonization or infection by multidrug-resistant bacterial strains in patients throughout the ICU and even the entire hospital (148). Therefore, policies regarding the empiric use of antibiotics do matter in the control of antimicrobial resistance. Virtually all reports emphasize that better antibiotic control programs to limit bacterial resistance are urgently needed in the ICU and that patients without true infection should not receive antimicrobial agents (339–344).

The more targeted use of antibiotics could also reduce overall costs, despite the expense of FOB and quantitative cultures, and minimize antibiotic-related toxicity (298). This possibility is particularly true for patients who develop late-onset VAP, in whom expensive combination therapy is recommended by most experts in the field. A conservative cost analysis performed in a trauma ICU suggested that the discontinuation of antibiotics on the return of negative bronchoscopic quantitative culture results could lead to a savings of more than US$1,700 per patient suspected of having VAP (345).

Finally, and probably the most important risk of not performing FOB for the patient, is that another site of infection may be missed. The major benefit of negative FOB findings may indeed be to direct attention away from the lungs as the source of fever. Many hospitalized patients with negative bronchoscopic cultures have other potential sites of infection that can be identified via a simple diagnostic protocol. A study of 50 patients with suspected VAP who were subjected to a systematic diagnostic protocol, designed to identify all potential causes of fever and pulmonary densities, confirmed the presence of lung infection in only 42% of them, and that the frequent occurrence of multiple infectious and noninfectious processes justifies a systematic search for the source of fever in this setting (231). This search is in general greatly facilitated by the absence of an empiric antimicrobial therapy that can mask the true diagnosis (346).

Other than decision analysis studies (347, 348), only five trials have assessed the impact of a diagnostic strategy on antibiotic use and outcome of patients suspected of having VAP (Table 8) (61–63, 104, 335). No differences in mortality and

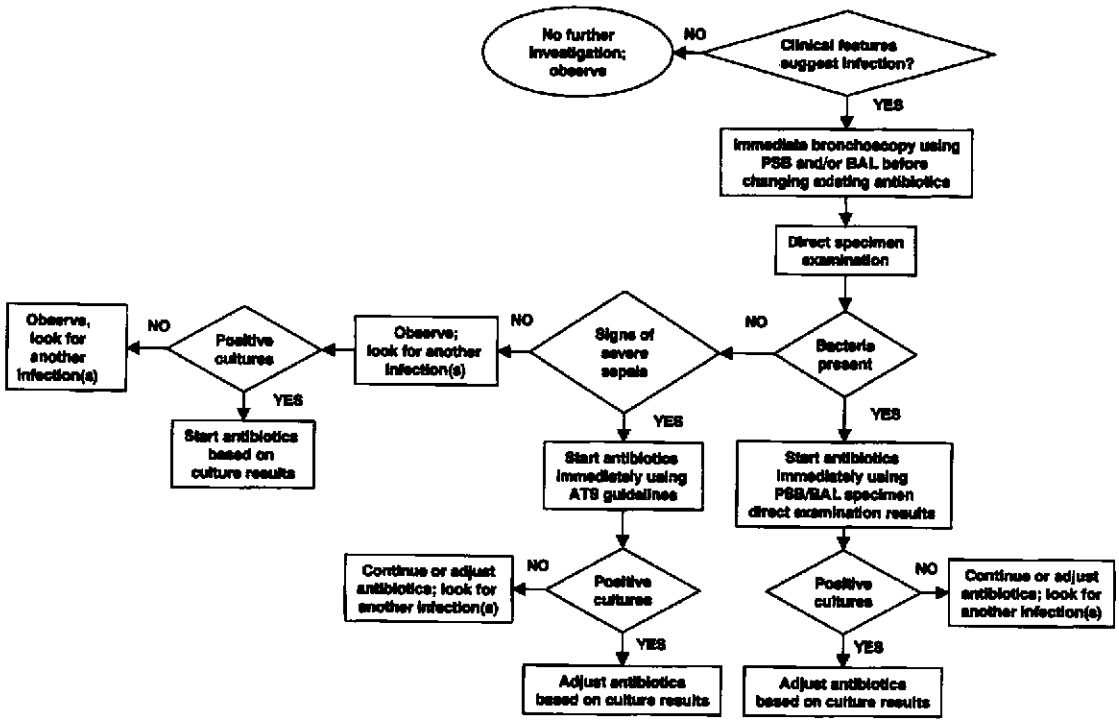

Figure 1. Diagnostic and therapeutic strategy applied to patients managed according to the "invasive" strategy.

morbidity were found when either invasive (PSB and/or BAL) or noninvasive (quantitative endotracheal aspirate cultures) techniques were used to diagnose VAP in three Spanish randomized studies (61, 62, 104). However, those studies were based on relatively few patients (51, 76, and 88, respectively) and antibiotics were continued in all patients despite negative cultures, thereby neutralizing one of the major potential advantages of any diagnostic test in patients clinically suspected of having VAP. Concerning the latter, it was shown, on the basis of 138 patients investigated by bronchoscopic specimen collection, that antibiotics can indeed be stopped in patients with negative quantitative cultures with no adverse effects on the recurrence of VAP and mortality (59). Authors of other studies have also concluded that antibiotics can be safely stopped in patients with negative quantitative cultures (21, 102, 298, 311, 335).

One of the first studies to clearly demonstrate a benefit in favor of invasive techniques was a prospective cohort study conducted in 10 Canadian tertiary care ICUs (335). The investigators compared antibiotic use, duration of MV, duration of ICU stay, and mortality for 92 mechanically ventilated patients clinically suspected of having VAP who underwent FOB and 49 patients who did not. Although mortality among patients undergoing FOB was lower than for control subjects (19 versus 35%, $p = 0.03$), the strength of that observation is somewhat diluted because control patients were those suspected of having VAP who did not undergo the intended FOB. The reasons that led their physicians to forego FOB may explain the higher mortality rate of these patients. However, once FOB results had become available to the physicians treating the study patients, the diagnosis of VAP was deemed much less likely ($p < 0.001$), confidence in the diagnosis increased ($p = 0.03$), and the level of comfort with the management plan rose ($p = 0.02$). Furthermore, patients in the FOB group received fewer antibiotics (31of 92 versus 9 of 49; $p = 0.05$) and more patients had all their antibiotics discontinued (18 of 92 versus 3 of 49; $p = 0.04$) compared with the no-FOB group. Invasive diagnostic testing may thus increase physician confidence in the diagnosis and management of VAP, and allows for greater flexibility to limit or discontinue antibiotic treatment.

A large, prospective, randomized trial compared noninvasive versus invasive diagnostic management of 413 patients suspected of having VAP (63). For the noninvasive group ($n = 209$), empiric antimicrobial therapy was based on the presence of bacteria in the gram-stained endotracheal aspirates, and therapy could be adjusted or discontinued according to the results of endotracheal aspirate qualitative cultures. In the case of severe sepsis, empiric therapy was started without the laboratory result. With this schedule, which resembles clinical practice in most ICUs, 91% of the patients (191 of 209) received empiric therapy for suspected VAP and only 9% did not. The invasive work-up ($n = 204$) consisted of FOB with direct microscope examination of BAL and/or PSB specimens and empiric therapy was started only when results were positive. A definitive diagnosis based on quantitative culture results of specimens obtained with a PSB or by BAL was awaited before starting, adjusting, or discontinuing therapy (Figure 1). This strategy resulted in treatment of 52% (107 of 204) of the patients with suspected VAP, whereas 47% (97 of 204) did not immediately receive antibiotics. Compared with patients managed clinically, those receiving invasive management had a lower mortality rate on Day 14 (16 and 25%; $p = 0.02$), lower mean sepsis-related organ failure assessment scores on Days 3 and 7 ($p = 0.04$), and less antibiotic use (mean number of antibiotic-free days, 5 ± 5 and 2 ± 3; $p < 0.001$). At 28 days, the invasive management group had significantly more antibiotic-free days (11 ± 9 versus 7 ± 7; $p < 0.001$), and only multivariate analysis showed a significant difference in mortality (hazards ratio, 1.54 [CI, 1.10 to 2.16]; $p = 0.01$) (63).

Thus, implementation of bronchoscopic techniques for the diagnosis of VAP may reduce antibiotic use and improve patient outcome. Pertinently, in that study, invasive group patients had 22 infections at other sites that required specific therapeutic measures versus only five in the clinical group (63). This difference suggests that reliance on noninvasive techniques and the consequent overestimation of VAP may mean that diagnoses of nonpulmonary infections are missed. Many hospitalized patients with negative bronchoscopic specimen cultures have other potential sites of infection that can more readily be identified in the absence of antibiotic interference (13, 231, 349, 350). Delaying diagnosis or definitive treatment of the true infection site may lead to prolonged antibiotic therapy, more antibiotic-associated complications, and induction of additional organ dysfunctions (102, 345, 351–353).

Arguments against Bronchoscopy for the Diagnosis of Ventilator-associated Pneumonia

Reasons not to use invasive diagnostic techniques include the following: (*1*) their accuracy is questionable for patients who received prior antibiotics, especially when new antibiotics have been introduced after the onset of the symptoms suggestive of

TABLE 8. RESULTS OF TRIALS COMPARING A FIBEROPTIC BRONCHOSCOPY–BASED "INVASIVE" STRATEGY WITH A CLINICAL EVALUATION-BASED STRATEGY FOR PATIENTS CLINICALLY SUSPECTED OF HAVING VENTILATOR-ASSOCIATED PNEUMONIA

First Author	Ref.	Year of Publication	Total No. of Patients	Study Design	Mortality: No. of Patients Who Died/Total No. (%) "Invasive" Strategy	Mortality: No. of Patients Who Died/Total No. (%) "Clinical" Strategy	p Value
Sanchez-Nieto	61	1998	51	Monocenter, randomized	11/24 (46)	7/27 (26)	NS
Ruiz	62	2000	76	Monocenter, randomized	14/37 (38)	18/39 (46)	NS
Sole Violan	104	2000	88	Monocenter, randomized	10/45 (22)	9/43 (21)	NS
Heyland	335	1999	141	Multicenter, nonrandomized, prospective cohort	17/92 (18)	17/49 (35)	0.03
Fagon	63	2000	413	Multicenter, randomized	63/204 (31)	81/209 (39)	0.07*

Definition of abbreviation: NS = not significant.
* $p = 0.01$, using multivariate analysis.

nosocomial pneumonia but before collection of pulmonary secretions; (2) FOB may transiently worsen the patient's status, although the results of several studies indicate that the frequency of such complications is low; (3) an invasive approach to diagnosing nosocomial pneumonia may increase the costs of caring for critically ill patients, at least at some institutions where fees for FOB are high; and (4) although patient management may change on the basis of results of invasive tests, data suggesting that these changes lead to an improvement of patient outcome are limited (306).

The appropriateness of diagnostic tools may also differ depending on whether the goal is to prevent the spread of resistant organisms, compare the rates of pneumonia, or prescribe treatment for a patient. For example, to calculate the frequency, a definition that is applicable to all patients over prolonged time periods should be used. Infection control personnel should be able to make the diagnosis on the basis of common clinical and laboratory findings. Definitions that require the performance of specialized diagnostic tests are not sufficiently universal to provide comparable rates in most health care settings.

The presence of prior antimicrobial treatment in patients clinically suspected of nosocomial pneumonia is frequently cited as a major limitation to accurate diagnosis, because it may lead to a high number of false-negative results. In fact, as demonstrated by several investigative teams, the results of respiratory secretion cultures are usually not modified when pneumonia develops as a superinfection in patients who have been receiving systemic antibiotics for several days before the appearance of the new pulmonary infiltrates, because the bacteria responsible for the new infection have become resistant to the antibiotics being given (98, 267). To evaluate further the effects of antibiotic treatment received before the suspicion of pneumonia on the diagnostic yield of PSB and direct examination and culture of BAL fluid, two groups of ventilated patients with suspected nosocomial pneumonia were studied: 65 patients who had received antibiotics for an earlier septic episode and 96 patients who had not (308). FOB was always performed before any treatment for suspected pneumonia was given. The sensitivity and specificity of each test did not differ between the two groups, thereby confirming that the antibiotics used to treat an earlier septic episode unrelated to suspected pneumonia do not affect the diagnostic yield of PSB and BAL.

On the other hand, cultures of pulmonary secretions for diagnostic purposes after initiation of new antibiotic therapy in patients suspected of having developed VAP can clearly lead to a high number of false-negative results, regardless of the way in which these secretions are obtained. In one study, in which follow-up cultures of PSB samples were obtained 24 and 48 hours after the onset of antimicrobial treatment for 43 cases of proven VAP, nearly 40% of the cultures were negative after only 24 hours of treatment and 65% were negative after 48 hours (354). Similar results were obtained for a series of 76 consecutive patients with VAP evaluated by FOB after 3 days of treatment (98). In a series of 63 episodes of suspected VAP (307), when therapy had recently been initiated, the sensitivities of the invasive diagnostic methods, using traditional thresholds, were only 38% for BAL and 40% for PSB (307). Using a lower threshold to define a positive PSB or BAL result in such a setting may be inaccurate, because follow-up cultures can be completely negative in at least 40% of true cases of VAP (98, 354). Pulmonary secretions therefore need to be obtained before new antibiotics are administered, as is the case for all microbiologic samples.

Several investigators argue that the use of FOB to evaluate VAP is limited by the lack of standardized, reproducible methods and diagnostic criteria (306, 355). There is no doubt that the literature is replete with variations on this theme: BAL versus PSB; whether to collect secretions with the PSB under direct observation or wedge it distally; what volume of saline to use for BAL; which transport medium to use; whether to set up cultures using quantitative loops or serial dilutions; and whether to express the results in colony-forming units per milliliter or construct a bacterial index composed of the sum of the exponents from each quantitated isolate. Although a general consensus has emerged on the use of 10^3 cfu/ml as the cutoff for a PSB culture, and 10^4 cfu/ml for BAL specimens, concern has been raised about their reproducibility, particularly near the diagnostic thresholds (299, 301, 323). Whether the clinical suspicion of VAP should influence the interpretation of quantitative culture results also has not been entirely resolved (347). It is likely that no single method will emerge as superior to others. What is most important is that physicians using these techniques establish a protocol that is supported by the literature and within the capabilities of the local microbiology laboratory. Many microbiology laboratories may not be able to promptly and accurately process quantitative cultures, even though the techniques used can be similar to those applied routinely to urine cultures (279).

Others have suggested that any potential value of FOB in the management of nosocomial pneumonia would be limited to late-onset infections, as infections that occur within 4 days of admission often are caused by community-acquired pathogens, and are easier to diagnose and manage than pneumonia occurring later in the hospital stay (355, 356). Although it is true that community-acquired pathogens are often identified in early-onset pneumonia, hospital-acquired pathogens cannot be excluded during the early time frame (106, 107, 110). Furthermore, early-onset pneumonia may be a less common problem than late-onset infection in many medical ICUs, as the cumulative risk of pneumonia (and the risk of infection with hospital-acquired pathogens) increases with the duration of hospitalization.

Some experts also doubt the willingness of physicians to stop antibiotic therapy when confronted with a negative bronchoscopic culture. Indeed, as cited above, there is evidence that physicians are reluctant to discontinue antibiotics for suspected VAP solely because of a negative culture (356). The development of algorithms incorporating clinical suspicion into the interpretation of culture results may improve the acceptability of and responsiveness to negative results. However, the potential benefit of an invasive strategy can be obtained only when physicians accept the basing of their antibiotic prescription on the results of bronchoscopic specimen cultures and, thus, to withdraw antimicrobial therapy from patients with negative results (347, 348).

Because VAP in the ICU has substantial attributable mortality, there is justification, albeit unwarranted at times, to use antibiotics for patients with pulmonary infiltrates, despite a low likelihood of infection. A randomized study proposed to minimize excessive use of antibacterial agents, but still allow clinicians flexibility in managing patients with a perceived treatable infection (Figure 2) (357). Patients with a Clinical Pulmonary Infection Score (CPIS) ≤ 6 (implying low likelihood of pneumonia) were randomized to receive either standard therapy (choice and duration of antibiotics at the discretion of physicians) or ciprofloxacin monotherapy with reevaluation on Day 3; ciprofloxacin was discontinued when the CPIS remained ≤ 6. Antibiotics were continued beyond 3 days for 90% (38 of 42) of the patients receiving standard therapy compared with 28% (11 of 39) in the ciprofloxacin group ($p = 0.0001$). Mortality and length of ICU stay did not differ de-

spite the shorter duration ($p = 0.0001$) and lower cost ($p = 0.003$) of antimicrobial therapy in the monotherapy arm than in the standard-therapy arm. Antimicrobial resistance, superinfections, or both developed in 15% of the patients in the ciprofloxacin group versus 35% of the patients in the standard therapy group ($p = 0.017$). Such an approach may thus lead to significantly lower antimicrobial therapy costs, antimicrobial resistance, and superinfections without adversely affecting the length of stay or mortality and merits prospective analysis in a large study sample. However, it should be emphasized that this strategy was tested in relatively few patients ($n = 81$) and that only 42% of patients included in the study did not require MV. Thus, it remains to be precisely determined whether this strategy can perform as well when it is applied to mechanically ventilated patients.

Recommendations

The diagnosis of bacterial pneumonia in the severely ill, mechanically ventilated patient remains a difficult dilemma for the clinician. Our personal bias is that the use of bronchoscopic techniques to obtain PSB and/or BAL specimens from the affected area in the lung of ventilated patients with signs suggestive of pneumonia allows definition of a therapeutic strategy superior to that based exclusively on clinical evaluation (Figure 1). When performed before introduction of new antibiotics, these bronchoscopic techniques enable physicians to identify most patients who need immediate treatment and help to select optimal therapy, in a manner that is safe and well tolerated by patients. Furthermore, these techniques prevent resorting to broad-spectrum drug coverage in all patients who develop a clinically suspected infection. Although the true impact of this decision tree on patient outcome remains controversial, available data clearly suggest that being able to withhold antimicrobial treatment from some patients without infection may constitute a distinct advantage in the long term, by minimizing the emergence of resistant microorganisms in the ICU and redirecting the search for another (the true) infection site.

Despite broad clinical experience with the PSB and BAL techniques, it remains, nonetheless, unclear which one should be used in clinical practice. As discussed above, their operating characteristics for diagnosing VAP are probably similar, with only small differences in their sensitivities and specificities. Most investigators prefer to use BAL rather than PSB to diagnose bacterial pneumonia, because BAL (*1*) has a slightly higher sensitivity to identify VAP-causative microorganisms, (*2*) enables better selection of an empiric antimicrobial treatment before culture results are available, (*3*) is less dangerous for many critically ill patients, (*4*) is less costly, and (*5*) may provide useful clues for the diagnosis of other types of infections. However, it must be acknowledged that a small return on BAL may contain only diluted material from the bronchial rather than the alveolar level and thus give rise to false-negative results, particularly for patients with severe COPD. In these patients, the diagnostic value of BAL techniques is greatly diminished and the PSB technique should be preferred. Therefore, the choice of procedure(s) may eventually depend on the preferences and experiences of individual physicians and the patient's underlying disease(s).

In patients with clinical evidence of severe sepsis with rapidly deteriorating organ dysfunction, hypoperfusion, or hypotension, the initiation of antibiotic therapy should not be delayed while awaiting FOB and patients should be treated immediately with antibiotics. It is probably in this latter situation that simplified nonbronchoscopic diagnostic procedures could be most justified, because distal pulmonary secretions can be obtained on a 24-hour basis, just before starting new antimicrobial therapy. Because several studies have indicated that delays in the administration of effective antibiotic therapy may impact on VAP outcome, antibiotic therapy should not be postponed for more than a few hours (less than 6 hours) pending performance of FOB, even when the patient is clinically stable.

When FOB is not available to physicians treating patients clinically suspected of having VAP, we recommend using either a simplified nonbronchoscopic diagnostic procedure, replacing FOB in the algorithm depicted in Figure 1 by one of these techniques, or following the strategy described by Singh and coworkers (357), in which decisions regarding antibiotic therapy are based on a clinical score constructed from seven variables, the CPIS. Using this algorithm (Figure 2), patients with CPIS > 6 are treated as having VAP with antibiotics for 10 to 21 days, whereas antibiotics are discontinued when the

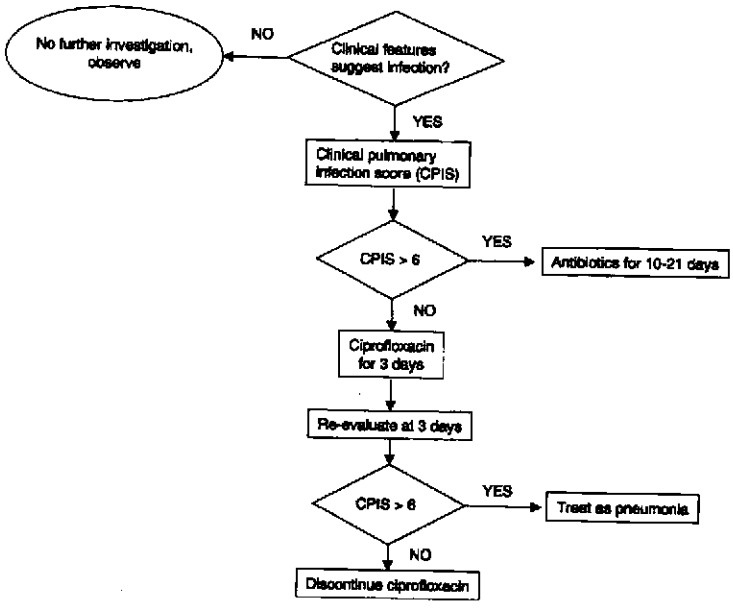

Figure 2. Diagnostic and therapeutic strategy applied to patients managed according to the strategy proposed by Singh and coworkers (357).

CPIS remains ≤ 6 at 3 days. Such an approach avoids prolonged treatment of patients with a low likelihood of infection, while allowing immediate treatment of patients with VAP. However, two conditions must rigorously be respected when implementing this strategy. First, selection of the initial antimicrobial therapy should be based on predominant flora responsible for VAP at each institution. It is highly probable that ciprofloxacin would not be the right choice in numerous institutions because of the high prevalence of MRSA infections in many of them (358). Second, it should be made clear to physicians that antimicrobial treatment should be reevaluated on Day 3, when susceptibility patterns of the microorganism(s) considered to be VAP causative are available, to select treatment with a narrower spectrum.

TREATMENT

Evaluation of Current Antimicrobial Strategies

Successful treatment of patients with VAP remains a difficult and complex undertaking. Despite broad clinical experience with this disease, no consensus has been reached concerning issues as basic as the optimal antimicrobial regimen or its duration. In fact, to date, evaluation of various antimicrobial strategies for the treatment of bacterial VAP has been difficult for several reasons.

First, as indicated above, the criteria for a definitive diagnosis of VAP in critically ill patients remain to be established. Although it is difficult to clinically distinguish between bacterial colonization of the tracheobronchial tree and true nosocomial pneumonia, nearly all previous therapeutic investigations have relied solely on clinical diagnostic criteria and, therefore, have probably included patients who did not have pneumonia. Second, most of those studies used tracheal secretions as the major source of specimens for microbiologic cultures, despite the fact that the upper respiratory tract of most ventilated patients is usually colonized with multiple potential pathogens. Finally, the lack of an adequate technique to directly sample the infection site in the lung has hampered the study of the ability or inability of antibiotics to eradicate the causative pathogens from the lower respiratory tract and, therefore, to predict their bacteriologic efficacy.

Newer methods for a more precise microbiologic diagnosis of pneumonia, such as the use of quantitative cultures of protected endoscopic brushings, appear promising in this context. Follow-up PSB sample cultures were used to assess directly the infection site in the lung in 76 patients with bacteriologically proven VAP and results demonstrated that the administration of antimicrobial therapy combining, in most cases, two effective agents was able to sterilize or contain the lower respiratory tract infection, after only 3 days of treatment, in 67 (88%) of the patients (98). The only two bacteriologic failures were observed in patients who did not receive appropriate treatment due to errors in the selection of antimicrobial drugs. Early superinfection due to bacteria resistant to the initial antibiotics was, however, documented in seven (9%) patients, thus emphasizing the need to carefully monitor the impact of treatment on the initial microbial flora for optimal management of such patients, when the clinical response is suboptimal. Furthermore, results of cultures of follow-up PSB samples correlated well with the clinical outcome noted during the 15-day observation period, making this test a good prognostic indicator for patients with VAP (98).

Antibiotic Treatment: General Considerations

Whereas VAP carries significant added mortality and morbidity, as previously demonstrated (6, 51, 81, 89, 359), tracheobronchitis alone does not seem to be associated with a poor prognosis and, therefore, antimicrobial treatment of mechanically ventilated patients with only tracheobronchitis is probably not justified (41, 81, 311, 360). Several investigative teams analyzed the outcome of patients who were clinically suspected of having VAP but in whom this diagnosis was finally excluded and found that the mortality rate was lower for these patients than for those with documented pneumonia, and that their death rate was the same as that observed for patients not suspected of having pneumonia (81, 311, 360). These findings support the conclusion that it is pneumonia per se that is associated with poorer survival, not the presence of acute tracheobronchitis with purulent tracheal secretions. Not all studies, however, have generated the same results. For example, the prognostic multivariate analysis based on 387 patients who required MV for more than 48 hours indicated that confirmation of VAP using PSB and/or BAL in patients clinically suspected of having lung infection added no prognostic information (46).

Patient survival may improve if pneumonia is correctly diagnosed and treated (Table 3) (11, 14, 21, 22, 74, 361). Using multiple logistic regression analysis to study risk factors for death of ventilated patients who developed pneumonia, it was demonstrated that inappropriate therapy was strongly associated with fatality, with a relative OR of 5.8 (14). Similar results were obtained by logistic regression analysis, which selected six independent risk factors for death: advanced age, ultimately or rapidly fatal underlying disease, high-risk microorganisms, bilateral infiltrates on the chest radiograph, presence of respiratory failure, and inappropriate antibiotic therapy, with this last factor having the most impact on prognosis (11).

Two other Spanish studies (Table 3) examined the influence of the adequacy of initial empiric antibiotic therapy on the outcomes of patients with VAP (21, 74). The first monitored 530 patients who developed 565 episodes of pneumonia (92% during MV in the ICU setting) (74). Attributable mortality and numbers of patients who developed shock after the onset of pneumonia were significantly higher for patients with inappropriate initial antimicrobial therapy than for other patients. The second study included 113 ventilated patients judged to have VAP on the basis of clinical criteria and cultures of either blood, pleural fluid, or lower airway secretions obtained bronchoscopically by BAL or PSB (21). The crude and VAP-associated mortality rates for the patients with inappropriate therapy were found to be significantly higher than the respective mortality rates for patients receiving adequate initial empiric antibiotics. Similar results were obtained for a series of 130 mechanically ventilated patients with clinically identified VAP in a medical ICU (361). The hospital mortality rate for the 51 patients who required new or modified antibiotic therapy after identification of causative pathogens by mini-BAL cultures was significantly higher than those for patients requiring no change of their antibiotic management (n = 51) and patients whose antibiotics were discontinued (n = 28). Multiple logistic regression analysis demonstrated that being immunocompromised and receiving inadequate antibiotic therapy (i.e., the presence of a microorganism in the mini-BAL culture resistant to the initially prescribed empiric antibiotic regimen) were independently associated with the likelihood of hospital mortality.

Two factors appear to render the choice of antibiotics particularly difficult in critically ill patients. First, VAPs are likely to result from highly resistant organisms, especially in patients who were previously treated with antibiotics (5, 107, 362–364). Second, multiple organisms are frequently cultured from the pulmonary secretions of patients considered to have pneumonia (12, 16, 18, 19, 77, 96, 106). Because of the emergence of

multiresistant, extended spectrum β-lactamase-producing GNB in many institutions and the increasing role played by gram-positive bacteria, such as MRSA, even a protocol combining ceftazidime or imipenem and amikacin would not ensure adequate coverage of all cases of VAP in these ICUs. Therefore, no "magic bullet" exists to cover all the microorganisms potentially responsible for VAP.

Finally, although appropriate antibiotics may improve survival of patients with VAP, use of empiric broad-spectrum antibiotics in patients without infection is potentially harmful, as it facilitates colonization and superinfection with multiresistant microorganisms. The results of many epidemiologic investigations have clearly demonstrated a direct relationship between the use of antimicrobial agents and increased resistance of Enterobacteriaceae and other pathogens (336, 338, 340, 365). The indiscriminate administration of antimicrobial agents to patients in the ICU may have immediate but also long-term consequences, contributing to the emergence of multiresistant pathogens and increasing the risk of severe superinfections (336, 339). Therefore, it should be made clear to physicians confronted with ICU patients clinically suspected of having VAP that prescribing new antimicrobial agents to all these patients may lead to overtreatment of many of them and, thus, possibly to the rapid emergence of multiresistant pathogens, not only in the treated patients but also in other patients hospitalized in the same unit or elsewhere in the same hospital.

Factors Contributing to Selection of Treatment

Important factors to be considered for the optimal selection of initial antibiotic therapy include the following: (*1*) putative etiologic agents and their antibiotic susceptibility patterns, as observed in previous cases of VAP, based on local epidemiologic studies and data obtained by surveillance cultures from the same patient; (*2*) the clinical setting and, in particular, the prior duration of hospitalization and/or MV before the onset of pneumonia, and the absence or presence of prior antibiotic use; (*3*) information obtained by direct microscope examination of pulmonary secretions; (*4*) intrinsic antibacterial activities of antimicrobial agents; and (*5*) other pharmacokinetic considerations.

Etiologic agents. Even though the exact prevalence of each infecting microorganism may vary as a function of country, hospital, and ward concerned, precise knowledge of the distribution of pathogens most frequently reported to be associated with VAP greatly facilitates the selection of appropriate therapy, as does information about their antibiotic susceptibility patterns, as determined by continuous collection of surveillance data. The authors of several epidemiologic studies of nosocomial pneumonia in patients receiving MV have reported increased rates of multiresistant bacteria (5, 106, 107). Many *P. aeruginosa* and *A. baumannii* strains have become class I cephalosporinase producers and are resistant to piperacillin, aztreonam, and ceftazidime. *Klebsiella pneumoniae* and other Enterobacteriaceae strains are also increasingly being recognized as producers of transferable extended spectrum β-lactamases, which confer resistance to third-generation cephalosporins (42, 362, 363, 366). Other multiresistant, aerobic GNB include *Xanthomonas* (*Stenotrophomonas*) *maltophilia* and *Alcaligenes* spp. Unfortunately, MRSA is also being implicated more and more frequently as a causative pathogen in ICU patients who required MV for a prolonged period (107, 142). Therefore, the microbiologic trends of VAP are evolving toward more resistant and more difficult-to-treat pathogens (5, 142, 367).

Several investigators have recommended routine surveillance cultures of patients in the ICU because they may be predictive of patients who are at high risk of invasive disease and, furthermore, should invasive disease develop, empiric therapy can be selected on the basis of the predominant pathogens identified in these cultures (33, 121, 368). However, the accuracy of this approach for selecting initial antimicrobial treatment for ICU patients requiring new antibiotics for VAP has not yet been established (121, 369, 370). This hypothesis was retested in a prospective study conducted with 125 patients, who required MV for more than 48 hours, and for whom strict bronchoscopic criteria were applied to diagnose pneumonia and identify the causative pathogens (371). Although a large number of various prior microbiologic specimen culture results (mean, 45 ± 43 per episode) were obtained before FOB for each VAP episode, only 73 (33%) of the 220 VAP-causative microorganisms were isolated by these routine analyses and their susceptibility patterns made available to guide initial antimicrobial treatment. When the analysis focused on VAP episodes for which prior (within 72 hours) respiratory secretion culture results were available, on the hypothesis that this microbiologic information might be particularly useful for identifying the responsible organisms in the case of subsequent pneumonia, results were still disappointing because all causative pathogens were recovered for less than 60% of them (371).

Several factors may explain the lack of accuracy of routine microbiologic specimen culture results for predicting the causative microorganisms of pneumonia in ICU patients requiring MV. First, the role played by colonization of some of the sites sampled before VAP onset, such as the nares, skin, and/or urine, in the pathogenesis of nosocomial lung infection is probably limited, thus explaining the absence of concordance between these microorganisms and those responsible for VAP. Second, a large number of different bacterial species are recovered from specimens obtained before VAP onset, whereas only a much smaller number of microorganisms is responsible for the infection, making identification of the "true" VAP pathogen(s) difficult. Finally, even when bacteria are isolated from a site likely to play a role in lung infection, such as the tracheobronchial tree, the interval between prior specimen culture results and VAP onset is frequently long enough to permit the development of lung infection caused by microorganism(s) other than the one(s) previously isolated (17, 133, 372).

Although tracheal colonization by potentially pathogenic microorganisms precedes lung infection in a majority of, but not all, ventilated patients (117, 133, 373), data have also emphasized that the pattern of tracheobronchial colonization, and especially the types of microorganisms involved, reflect a dynamic process that is rapidly modified by the flora present at that level and influenced by factors such as prior duration of MV and prior antibiotics (372, 374). In one study in which lower respiratory tract colonization and infection were prospectively evaluated in 30 patients with severe ARDS, using repeated quantitative cultures of plugged telescopic catheter specimens taken blindly via the endotracheal tube every 48 to 72 hours after ARDS onset, colonization preceded BAL-microbiologically confirmed VAP, and VAP was microbiologically confirmed in only 67% of the VAP episodes (17). Therefore, careful evaluation of distal airway colonization can fail to document at least one-third of VAP episodes. Such a strategy may also considerably increase the workload of the microbiology laboratory without having any positive impact on patient management.

Colonization with potentially drug-resistant pathogens, such as MRSA or extended spectrum β-lactamase-producing strains of *K. pneumoniae* or other Enterobacteriaceae, is associated with an increased risk of infection caused by the corresponding

microorganism (368, 375–377). These results were confirmed in the study by Hayon and coworkers (371), with positive-predictive values of recovering such a microorganism from a specimen of 62, 52, or 24% for VAP caused by MRSA, *P. aeruginosa*, or *A. baumannii*, respectively. However, because the sensitivity of prior microbiologic culture results for identifying bacteria causing VAP does not exceed 70%, selection of initial antimicrobial therapy for patients with VAP can hardly be based only on these results, especially for deciding to use (or not use) vancomycin and/or a broad-spectrum β-lactam effective against *P. aeruginosa* and/or *A. baumannii*. However, when one of the three microorganisms (or any pathogen) is isolated from respiratory secretions within 72 hours of VAP, it should probably be covered by the antimicrobial regimen selected, even though predictive values do not exceed 50 to 60% (371).

Clinical setting. As indicated in the section EPIDEMIOLOGY (above), underlying diseases may predispose patients to infection with specific organisms (33). In a study that prospectively included only VAP episodes documented by positive PSB samples, the risk factors for patients who developed nosocomial MRSA or MSSA infection in the lower respiratory tract were compared (82). The former were more likely to have received corticosteroids before developing infection (RR = 3.45), to have been ventilated for > 6 days (RR = 2.03), to be > 25 years old (RR = 1.50), or to have COPD (RR = 2.76). On the other hand, head trauma was more frequent among MSSA-infected persons (RR = 1.94). The most striking finding was that all patients with MRSA infections had previously received antibiotics, compared with only 21% of those with MSSA infections. These observations are consistent with earlier reports on VAP due to multiresistant pathogens and strongly support the notion that duration of MV and prior antibiotic use are two key factors selecting for such microorganisms (107).

Taking into account these epidemiologic characteristics allows the definition of a more rational decision tree for selecting initial treatment in this setting. In 1996, the American Thoracic Society published a Consensus Statement that provides guidelines based on assessments of disease severity, the presence of risk factors for specific organisms, and time of onset of pneumonia to guide initial antibiotic selection (33). Once these determinations are made, patients suspected of having nosocomial pneumonia fall into one of three groups, each with its own set of likely pathogens: (*1*) patients without unusual risk factors who present with mild-to-moderate pneumonia with onset at any time during hospitalization or severe pneumonia of early onset; (*2*) patients with specific risk factors who present with mild-to-moderate pneumonia occurring any time during hospitalization; and (*3*) patients with severe pneumonia, either of early onset with specific risk factors or of late onset. Recommended therapeutic regimens for ICU ventilated patients or patients with risk factors for pneumonia due to *P. aeruginosa* are given in Table 9. Because the guidelines have not been updated since their publication in 1996, they do not include newer therapies (e.g., cefepime, meropenem, and newer fluoroquinolones) that may be effective and/or associated with less resistance. Furthermore, they fail to distinguish among some compounds with different antibacterial activities or to recommend specific antibiotics.

On the basis of the results of a French prospective study in which the responsible microorganisms for infection in 135 consecutive episodes of VAP observed in the ICU were documented with bronchoscopic specimens, the distribution of infecting pathogens was markedly influenced by prior duration of MV and prior antibiotic use (107). Whereas early-onset pneumonias in patients who had not received prior antimicrobial treatment were mainly caused by susceptible Enterobacteriaceae, *Haemophilus* spp., MSSA, or *S. pneumoniae*, early-onset pneumonias in patients who had received prior antibiotics were commonly caused by nonfermenting GNB, such as *P. aeruginosa*, in addition to streptococci and *Haemophilus* spp. On the other hand, late-onset pneumonias that occurred without antibiotics during the 15 days preceding the onset of infection were essentially caused by streptococci, MSSA, or Enterobacteriaceae; however, some of these GNB were class I cephalosporinase producers, which may require treatment with a new cephalosporin, such as cefepime or cefpirome, for optimal therapy. Late-onset pneumonias in patients having recently received antibiotics were caused by multiresistant patho-

TABLE 9. CORE ORGANISMS RESPONSIBLE FOR VENTILATOR-ASSOCIATED PNEUMONIA AND RECOMMENDED ANTIMICROBIAL THERAPY

Core Organisms	Core Antibiotics
Early-onset VAP, no specific risk factor	
Enteric gram negative (nonpseudomonal)	Cephalosporin
Enterobacter spp.	Second generation
Escherichia coli	Nonpseudomonal third generation
Klebsiella spp.	or
Proteus spp.	β-Lactam–β-lactamase inhibitor combination
Serratia marcescens	
Haemophilus influenzae	If allergic to penicillin:
MSSA	Fluoroquinolone
	or
Streptococcus pneumoniae	Clindamycin + aztreonam
Late-onset VAP	
Core organisms *plus*	Aminoglycoside or ciprofloxacin *plus* one of the following:
Pseudomonas aeruginosa	Antipseudomonal penicillin
Acinetobacter baumannii	β-Lactam–β-lactamase inhibitor combination
	Ceftazidime or cefoperazone
	Imipenem
	Aztreonam
Consider MRSA	± Vancomycin

Definition of abbreviations: MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-sensitive *S. aureus*; VAP = ventilator-associated pneumonia.
Adapted from the American Thoracic Society (33).

gens, such as *P. aeruginosa*, *A. baumannii*, or MRSA in more than 40% of cases. Taking these epidemiologic characteristics into account allowed the authors to devise a rational decision tree for selecting initial treatment in this setting that prevents resorting to broad-spectrum drug coverage in all patients. For example, monotherapy with a second-generation cephalosporin (cefuroxime, cefamandole, or cefotetan), or a third-generation cephalosporin with no antipseudomonal activity (cefotaxime or ceftriaxone), or therapy combining the β-lactamase inhibitor clavulanic acid with amoxicillin would generally be an appropriate choice for most patients with early-onset VAP who have not received prior antimicrobial treatment. In contrast, for patients who have required prolonged MV and antimicrobial treatment, three-antibiotic therapy with a combination of aminoglycoside or ciprofloxacin plus a broad-spectrum anti-*Pseudomonas* β-lactam, such as piperacillin–tazobactam or imipenem, plus vancomycin should be started, keeping in mind that even such a regimen will not ensure complete coverage of all putative pathogens. For the two intermediate groups, early-onset episodes with previous antibiotic therapy and late-onset episodes without previous antibiotic therapy, in which a mixed distribution of pathogens is frequently observed, including some nonfermenting GNB, such as *P. aeruginosa*, but practically no MRSA and no multiresistant *A. baumannii*, treatment should be based on a combination of aminoglycoside or ciprofloxacin and an anti-*Pseudomonas* β-lactam, but without vancomycin.

However, because the range of bacteria that cause VAP and their susceptibility patterns vary widely among hospitals in the same or different countries, selection of initial antimicrobial therapy needs to be tailored to each institution's local patterns of antimicrobial resistance (106, 358). A computerized decision support program linked to computer-based patient records can facilitate the dissemination of such information to physicians for immediate use in therapy decision-making and improve the quality of care (378–381). Use of such a program for 545 patients in the ICU led to significantly fewer orders for drugs to which the patients had reported allergies (35 versus 146 during the preintervention period; $p < 0.01$), fewer excess drug doses (87 versus 405; $p < 0.01$), and fewer antibiotic-susceptibility mismatches (12 versus 206; $p < 0.01$) than for the 1,136 patients admitted to the same unit during the 2 years before the intervention period (379). In comparison with patients who did not always receive the recommended regimens ($n = 195$) and those in the preintervention cohort ($n = 766$), patients who always received the regimens recommended by the computer program ($n = 203$) had significantly lower costs for anti-infective agents (adjusted means, US$427 and US$340 versus US$102, respectively; $p < 0.001$), total hospital costs (adjusted means, US$44,865 and US$35,283 versus US$26,315; $p < 0.001$), and fewer hospital-stay days (adjusted means, 16.7 and 12.9 versus 10.0; $p < 0.001$) (379).

Information provided by direct examination of pulmonary secretions. Direct microscopy of pulmonary secretions is extremely important not only to identify patients with true VAP but also to select appropriate treatment, especially when BAL specimens are used to prepare cytocentrifuged gram-stained smears. In patients with pneumonia, the morphology and Gram staining of bacteria are closely correlated to the results of bacterial cultures, enabling early formulation of a specific antimicrobial regimen before the culture results are available. In a study assessing the potential value of bronchoscopic techniques, only 1 patient, among the 204 who underwent the invasive-sampling procedure and (of these) the 107 treated, received inappropriate initial empiric therapy, compared with 24 of the 191 patients in the clinical group, probably because of the additional information obtained by direct specimen examination (63). Similar results were obtained in a study of 94 mechanically ventilated patients with suspected VAP who underwent FOB with BAL and PSB (103). Direct BAL fluid examination results were available within 2 hours, BAL and PSB culture results after 24 hours, and antibiotic susceptibility after 48 hours. At each step in the strategy, the senior physician and the resident in charge of the patient were asked their diagnoses and their therapeutic plans based on the available data. Using a threshold of 1% infected cells, direct BAL examination discriminated well between patients with VAP and those without VAP (sensitivity, 94%; specificity, 92%; area under the ROC curve, 0.95). In contrast, the senior clinical judgment before FOB was correct for only 71% of the cases, compared with the definitive diagnosis and final antibiotic susceptibility test results. In addition, the therapeutic prediction was correct for 65% using clinical judgment (15 untreated patients, 3 ineffective treatments, 15 unnecessary treatments), 66% using airway visualization (14 untreated VAP, 4 ineffective treatments, 14 unnecessary treatments), and 88% using direct BAL examination results (1 untreated patient, 6 ineffective treatments, 4 unnecessary treatments) (103). Therefore, a strategy based on bronchoscopy and direct examination of BAL fluid may lead to more rapid and appropriate treatment of VAP than a strategy based only on clinical evaluation.

Intrinsic antibacterial activities of antimicrobial agents. The interactions between bacteria and antimicrobial agents, as tested *in vitro* by means of standard techniques, are highly contributive to therapeutic decision-making, even if a wide variety of local factors at the pulmonary site of infection may affect the antibacterial activities of most antibiotics.

The role of aminoglycosides in treating VAP deserves further comment because of conflicting data. Evidence exists that aminoglycosides are more active than β-lactams against certain resistant GNB (2, 157, 364). Their bactericidal mode of action, concentration-dependent killing rate, and postantibiotic effect, and their synergism with β-lactam compounds, are clear advantages. However, because the therapeutic activity ratios for aminoglycosides in serum are low, the penetration of circulating aminoglycosides into the infected lung tissues may be insufficient to eradicate infecting organisms and the low pH of infected airways has the potential to inactivate them (382, 383). Consequently, aminoglycosides are now used essentially in combination with β-lactam antibiotics (33).

To improve antibiotic concentrations in respiratory secretions and tissues without increasing toxicity, alternative administration routes have also been investigated, such as direct instillation of aminoglycosides in the bronchial tree or use of a single, high daily dose. Direct aminoglycoside instillation in the respiratory tract via the endotracheal tube or tracheostomy enables high drug concentrations to be attained directly at the site of infection, while possibly avoiding systemic toxicity. In a prospective, randomized study comparing systemic treatment alone versus systemic treatment plus sisomicin deposition in the respiratory tract, more patients receiving local aminoglycoside treatment improved (384). In a subsequent, double-blind, randomized trial (385), patients with endobronchial tubes or tracheostomies in place and documented GNB pneumonia were assigned to receive conventional parenteral antibiotics (β-lactam plus aminoglycoside) and intratracheal instillation of tobramycin (40 mg) in solution every 8 hours versus the same parenteral regimen with intratracheal saline instillation every 8 hours. Among the 85 patients enrolled, only 41 could be evaluated. GNB were eradicated from sputum more frequently in the group receiving endobronchial tobramycin (68 versus 31% of control subjects). However, clini-

cal improvement was virtually identical for the endobronchial tobramycin group (80%) and the placebo group (81%). Further investigation of local aminoglycoside therapy for VAP is therefore required before the relative risks and benefits of this approach can be definitively defined or approved.

Third- and fourth-generation cephalosporins can be divided into two groups depending on their activity against *P. aeruginosa*. For example, ceftazidime, cefoperazone, and cefsulodin exhibit excellent *in vitro* anti-*P. aeruginosa* activity but, unfortunately, are considerably less active against *S. aureus* than other cephalosporins. Conversely, cefotaxime, ceftriaxone, and cefpirome exhibit acceptable or good *in vitro* anti-*S. aureus* activity but relatively weak *in vitro* activity against *P. aeruginosa*. Thus, if one is hoping to achieve monotherapy coverage of the appropriate gram-positive and gram-negative bacterial spectrum for VAP, not all cephalosporins fit the bill.

The *in vitro* spectrum of imipenem exceeds that of any other single agent. It provides bactericidal activity against most gram-positive cocci (except MRSA and enterococci), most GNB, including *P. aeruginosa*, and also most pathogenic anaerobes. Drawbacks for this agent, however, include reports of the emergence of resistant organisms during therapy and seizures when high doses are given to patients with renal dysfunction. Furthermore, the frequency of *Pseudomonas* strains resistant to imipenem is increasing (362, 367, 386).

Meropenem is a new carbapenem already available in some, but not all, countries. Its spectrum of antibacterial activity is similar to that of imipenem, with potent activity against a variety of gram-positive species, gram-negative aerobes, and anaerobic strains. It is slightly less active against gram-positive bacteria, but more active against GNB, including some imipenem-resistant strains of *P. aeruginosa*. The toxicity profile of meropenem is similar to that of imipenem, except that data from animal experiments suggest that meropenem is less epileptogenic and less nephrotoxic. Clinical experience with meropenem is, however, limited and single-drug therapy of severe *P. aeruginosa* infections has been accompanied by the emergence of resistance (387).

Three randomized trials evaluated piperacillin–tazobactam, a new combination of ureidopenicillin plus a β-lactamase inhibitor with excellent activity against *P. aeruginosa* (with or without an aminoglycoside) as therapy for VAP (388–390). One study from 27 French ICUs randomized 127 patients with VAP to be treated with amikacin plus either piperacillin–tazobactam, 4.5 g four times daily, or ceftazidime, 1 g four times daily (388). Bacteriologic failures were more common in the ceftazidime-treated patients (51%) compared with those treated with piperacillin–tazobactam (33%). However, 28-day mortality rates were similar (16 and 20%, respectively). When *P. aeruginosa* was isolated, success rates were 40 or 39% with piperacillin–tazobactam or ceftazidime, respectively. Lower respiratory tract superinfections were significantly more common with ceftazidime (21%) than with the piperacillin–tazobactam plus amikacin combination (9%).

A multicenter American trial randomized 300 patients with VAP to combination therapy with tobramycin plus either piperacillin–tazobactam, 3.375 g every 4 hours, or ceftazidime, 2 g every 8 hours (389). The aminoglycoside could be discontinued at the discretion of the investigator once the pathogen was identified. Among assessable patients, final clinical responses, overall microbiologic response rates, and *P. aeruginosa* eradication were higher with piperacillin–tazobactam than ceftazidime. Mortality was 7.7% in the former group compared with 17% in the latter ($p = 0.03$). A Swiss trial randomized patients with hospital-acquired pneumonia to receive monotherapy with piperacillin–tazobactam, 4.5 g four times daily, or imipenem–cilastatin, 0.5 g four times daily (390). Among 154 assessable patients, clinical success rates were similar for both groups. However, among 45 patients with pseudomonal VAP, a higher percentage of patients responded to piperacillin–tazobactam than to imipenem–cilastatin (90 versus 50%; $p = 0.004$). Antimicrobial resistance developed in six patients treated with imipenem–cilastatin but in only one patient treated with piperacillin–tazobactam. Taken together, all these results suggest that piperacillin–tazobactam is at least as effective as (and possibly more effective than) ceftazidime or imipenem–cilastatin for VAP, particularly when *P. aeruginosa* is isolated.

Among available fluoroquinolones, ciprofloxacin is the most active against GNB, including *P. aeruginosa*. MSSA is also susceptible to these agents; however, resistance has developed rapidly in MRSA and now most of these strains are no longer susceptible to fluoroquinolones (364). Concerning norfloxacin, ciprofloxacin, ofloxacin, lomefloxacin, and enoxacin, activity against *S. pneumoniae*, enterococci, streptococci, and many anaerobes is limited, even though these agents are concentrated intracellularly in most tissues including bronchial mucosa, neutrophils, and alveolar macrophages, which may enhance their effectiveness against pathogens with intermediate susceptibility. Some newer quinolones, such as trovafloxacin, levofloxacin, sparfloxacin, clinafloxacin, gatifloxacin, tosufloxacin, and moxifloxacin, have excellent *in vitro* activities against streptococci and anaerobic species, but only trovafloxacin and sparfloxacin have been released in the United States.

A randomized, double-blind, multicenter study compared monotherapy with ciprofloxacin or imipenem for severe pneumonia in a series of 405 patients (391). Bacteriologic eradication rates were higher for ciprofloxacin-treated than imipenem-treated patients (69 versus 59%; $p = 0.07$) as were clinical response rates (69 versus 56%; $p = 0.02$). However, when *P. aeruginosa* was recovered from initial respiratory tract cultures, failure to achieve bacteriologic eradication and development of resistance during therapy were common in both treatment groups (respectively, 67 and 33% for ciprofloxacin, and 59 and 53% for imipenem), emphasizing that monotherapy, even with a potent antibiotic, can lead to more failures when *P. aeruginosa* is present.

Pharmacokinetic considerations. Effective antibiotic treatment of bacterial pneumonia depends on adequate delivery of antibacterial agents to the infection site and, therefore, scrupulous attention must be given to optimal doses, routes of administration, and pharmacodynamic characteristics of each agent used to treat this infection. Antibiotic levels in infected tissues are considered to be therapeutic when free drug concentrations equal at least the *in vitro* minimal inhibitory concentration (MIC) for the infecting pathogen(s). Because of major methodologic problems, published data concerning the penetration of most antibiotics into the lung should probably be viewed with caution, and only general trends concerning concentrations achievable at the infected site in lung tissue can be derived from those studies (382, 383, 392).

For penicillins and cephalosporins, the bronchial secretion-to-serum drug concentration ratios range between 0.05 and 0.25. Fluoroquinolones have better penetration characteristics, and bronchial secretion concentrations are between 0.8 and 2 times those in serum. Aminoglycosides and tetracyclines have ratios of 0.2 to 0.6. Host-related as well as drug-related factors may, however, influence the penetration of antimicrobial drugs across the blood–bronchus and alveolar–capillary barriers. Thus, for those drugs, such as the β-lactams and glycopeptides, which do not cross membranes readily, penetration might increase in the presence of inflammation because of enhanced membrane permeability (393).

Several published reports have demonstrated a relationship among serum concentrations of β-lactams or other antibiotics, the MIC of the infecting organism, and the rate of bacterial eradication from respiratory secretions in patients with lung infection, thereby emphasizing that clinical and bacteriologic outcomes can be improved by optimizing the therapeutic regimen according to pharmacokinetic properties of the agent(s) selected for treatment (394–400). Most investigators distinguish between antimicrobial agents that kill by a concentration-dependent mechanism (e.g., aminoglycosides and fluoroquinolones) and those that kill by a time-dependent mechanism (e.g., β-lactams and vancomycin). Multivariate analyses based on 74 acutely ill patients, most with VAP, who were treated with intravenous ciprofloxacin (200 mg twice daily to 400 mg three times daily), demonstrated that the most important independent factor for probability of cure was a pharmacodynamic variable, that is, the 24-hour area under the concentration–time curve divided by the MIC (AUIC) (394). For AUIC < 125, the probabilities of clinical and microbiologic cures were 42 and 26%, respectively, but with AUIC > 125, the probabilities were 80 and 82%, respectively.

Pharmacokinetic–pharmacodynamic models have also been used to optimize aminoglycoside therapy for VAP caused by GNB (395). Seventy-eight patients with VAP were analyzed, and the investigators reported an 89% success rate for temperature normalization by Day 7 of therapy for C_{max}/MIC > 4.7 and an 86% success rate for leukocyte count normalization by Day 7 of therapy for C_{max}/MIC > 4.5. Logistic regression analysis predicted a 90% probability of temperature and leukocyte count normalizations by Day 7, if a C_{max}/MIC > 10 was achieved within the first 48 hours of aminoglycoside administration. Aggressive aminoglycoside doses immediately followed by pharmacokinetic monitoring for each patient would ensure that C_{max}/MIC target ratios are achieved early during therapy.

These findings confirm the need to adjust the target dose of antimicrobial agents used to treat severe pulmonary infection to an individual patient's pharmacokinetics and the susceptibilities of the putative bacterial pathogens. Development of *a priori* dosing algorithms based on the MIC, patient creatinine clearance and weight, and the clinician-specified AUIC target might therefore be a valid way to improve treatment of these patients, leading to a more precise approach than current guidelines for optimal use of antimicrobial agents (396–400).

Monotherapy versus Combination Therapy

Several studies have examined the use of a single antibiotic, for example, a third-generation cephalosporin, imipenem–cilastatin, or a fluoroquinolone, to treat VAP (401–412). In general, monotherapy has proven to be a useful alternative to combination therapy, with the same success rate and no more superinfections or colonizations by multiresistant pathogens. It should, however, be pointed out that most of those studies included patients with VAP diagnosed on clinical grounds alone, and that treatment efficacy was assessed using information provided by sputum or tracheal aspirate cultures and not by more specific techniques. Most industry-sponsored studies excluded the sickest patients and were designed to demonstrate therapeutic equivalence rather than superiority. Indeed, a more rigorous comparison of these two regimens, performed on the basis of follow-up PSB sample or BAL fluid cultures, is required before monotherapy can be strongly recommended to treat VAP (98).

Furthermore, for patients with severe infection due to *P. aeruginosa* or other multiresistant bacteria, such as *Klebsiella* spp. or *Acinetobacter* spp., combining an antipseudomonal β-lactam with an aminoglycoside or ciprofloxacin is likely to obtain a much better outcome than monotherapy, as previously shown (413–416). In a prospective clinical study of 200 patients with *P. aeruginosa* bacteremia, mortality rates for patients with pneumonia receiving monotherapy or combination therapy as the initial empiric treatment were 88% (7 of 8 patients) or 35% (7 of 20 patients), respectively ($p = 0.03$) (413). Similarly, for the subgroup of 55 patients who experienced hypotension within 72 hours of or on the day of the positive blood culture in a prospective observational study of 230 *Klebsiella* bacteremias, the mortality rate was significantly lower for those patients who received combination therapy (24%) than those given monotherapy (50%) (415). It should be noted, however, that the β-lactam agents used in those studies were older agents, with less potent activity than the advanced cephalosporins or the carbapenems available today.

A controlled, multicenter, randomized European trial including 129 patients with cancer, granulocytopenia, and gram-negative bacteremia supported an adjunctive role for an aminoglycoside (416). In that study, patients were randomized to one of three treatment arms (azlocillin plus amikacin, ceftazidime plus amikacin for 3 days, or ceftazidime plus amikacin for 9 days). Clinical response rates were highest with ceftazidime plus long-course (9 days) amikacin treatment. The benefit of the aminoglycoside was more pronounced when *P. aeruginosa* was implicated. Among patients with pseudomonal bacteremias, only 5 (38%) of 13 patients responded to ceftazidime–short-course amikacin treatment, whereas 8 (89%) of 9 patients responded to ceftazidime–long-course amikacin treatment. These data, although derived from a study not without methodologic flaws, suggest that combination therapy is the preferred therapeutic regimen for severe infections for which at least one of these difficult-to-treat bacteria is likely to be the causative organism.

To reassess the need for β-lactam–aminoglycoside combinations to treat severe infections, a prospective, randomized, controlled study compared imipemem alone with imipenem plus netilmicin as the empiric regimen for nosocomial pneumonia and other severe infections in nonneutropenic patients (411). Among the 280 patients enrolled in the study, 48% had pneumonia and required MV. The success rate was not significantly improved by adding an aminoglycoside to imipenem, and the failure rates and numbers of superinfections were similar for both groups. While the addition of netilmicin increased nephrotoxicity, neither colonization with imipenem-resistant *P. aeruginosa* strains nor clinical treatment failures due to the emergence of resistant *P. aeruginosa* were prevented. Another randomized study of 140 ICU patients with suspected pneumonia or bacteremia found imipenem to be as effective as cefotaxime plus amikacin (409). Meropenem was also demonstrated to be as effective as ceftazidime when given alone or in combination with amikacin (417, 418).

Because those studies included nonhomogeneous populations of patients with different types of infections and given the potential inaccuracy of using only clinical criteria to diagnose lung infection, further trials are needed to clarify these uncertainties. In the meantime, it is probably safer to use a β-lactam antibiotic in combination with an aminoglycoside or a quinolone for patients with severe VAP, at least for the first days of therapy, while culture results of pulmonary secretions are pending. It may be that monodrug therapies for nosocomial pneumonia would best be reserved for infections in which *P. aeruginosa* or other multiresistant microorganisms, such as *Klebsiella*, *Enterobacter*, *Citrobacter*, *Serratia*, or *Acinetobacter* spp., have been excluded as the etiologic agents (33, 75, 157, 413, 415).

Duration of Antimicrobial Therapy

Despite the thoroughness of some guidelines, the treatment durations proposed by the American Thoracic Society remain

rather imprecise (33). Those experts recommend that the duration be adapted to the severity of the disease, the time to clinical response, and the microorganism(s) responsible. A "long" treatment, that is, a minimum of 14 to 21 days, is prescribed for the following situations: multilobar involvement, malnutrition, cavitation, gram-negative necrotizing pneumonia, and/or isolation of *P. aeruginosa* or *Acinetobacter* spp. This duration is essentially justified by the high theoretical risk of relapse. A "short" treatment, lasting 7 to 10 days, is recommended for *S. aureus* or *H. influenzae* pneumonia.

In many trials comparing the efficacies of diverse antimicrobial agents, although the scheduled duration of treatment was 14 days, the observed time of administration was often about 10 days (388, 389, 391, 411, 419). However, it must be noted that this duration is an average that includes those patients who died early. In addition, in numerous studies, the diagnostic methods did not include quantitative techniques with, as a corollary, uncertainty as to the reality of the pneumonia.

From a conceptual point of view, there are three potential disadvantages for using "long-duration" antimicrobial therapy: effects on bacterial "ecology," antibiotic toxicity, and increased cost. As mentioned above, a relationship exists between antibiotic use and the selection of resistant bacteria (336, 338, 340, 365). It is widely accepted that antibiotic therapy plays a major role in this selection at an individual level, either by selecting strains naturally resistant to the administered antibiotic (e.g., *P. aeruginosa*, yeasts) or by selecting resistant bacteria by chromosomal mutation within an initially sensitive population. The causal relationship between antibiotic administration (and also its duration) and the frequency of resistance is more difficult to demonstrate at a collective level. However, strong arguments exist that support the concept that the total amount of antibiotics prescribed in a given hospital influences the level of resistance within that institution (336, 365, 420). In a study in which 102 consecutive patients with VAP were prospectively evaluated before and after the application of a clinical guideline restricting the total duration of antimicrobial therapy to 7 days in selected patients (those who were not bacteremic and not neutropenic, and who experienced defervescence in response to therapy), no statistically significant differences in hospital mortality and hospital lengths of stay were found between the two study groups; however, patients in the before-evaluation group, for whom the mean duration of treatment was 14.8 days, were more likely to develop a second episode of VAP compared with those in the after-evaluation group (358).

Antibiotics represent $\sim$ 20 to 50% of a hospital's drug expenditures (excluding antiretroviral agents) (379, 421). Bacteria isolated from nosocomial pneumonias occurring late in patients already receiving antibiotics are often multiresistant and necessitate the use of molecules with broad spectra of activity that are often expensive (107). It can reasonably be thought that, should a "short" duration of antibiotic therapy prove acceptable, the consequences in financial terms would be beneficial.

However, a regimen of insufficient duration can be the source of therapeutic failure or relapse, defined as the reappearance of signs of pneumonia and isolation of the same pathogen(s), which may or may not have acquired resistance. The risk is probably small for bacteria considered susceptible but might be high for certain strains, especially *P. aeruginosa* and MRSA, which are particularly difficult to eradicate from the respiratory tract (422). This situation is even further aggravated in certain immunocompromised patients. Thus, at present, a short-term regimen is rarely prescribed, despite the potential major advantages it could have in terms of bacterial ecology, the prevention of the emergence of multiresistant bacteria, and, obviously, lower costs. Lowering the amount of antibiotics administered to patients in the ICU is indeed a primary objective of every strategy aimed at preventing the emergence and dissemination of such bacteria (340, 423).

Antibiotic Rotation

Many studies have shown that alterations of antibiotic prescription patterns, such as restricting the use of a particular antibiotic or changing the empiric antibiotic of choice for a particular diagnosis, are associated with declines in antibiotic resistance (344, 359, 424–426). Theoretically, this decline is due to diminished selection pressure favoring resistance. Continuous modifications of selection pressure by rotating antibiotic therapy, therefore, might reduce the emergence of resistance and the associated morbidity. To date, however, the impact of predetermined, scheduled changes of empiric antibiotic therapy, rather than changes in response to the proliferation of any given pathogen, has not been fully tested in patients with VAP. In one study during which ciprofloxacin was used in place of ceftazidime for the empiric treatment of suspected GNB infections, VAP occurred significantly less frequently during the after period compared with the before period (7 versus 12%; $p = 0.03$) but no outcome differences were noted between the two groups of patients (427).

During a before–after study conducted over a 4-year period with 3,455 ICU patients to evaluate a new strategy of antibiotic use combining rotation of antibiotics and restricted use of ceftazidime and ciprofloxacin, the investigators observed a decrease from 231 (22%) to 161 (16%) VAP episodes in patients who received MV for more than 48 hours ($p < 0.01$), particularly for VAP occurring within the first 7 days of MV. In addition, they demonstrated significantly increased susceptibilities of *P. aeruginosa*, *Burkholderia cepacia*, and *S. aureus* (428).

A similar decline in the rates of infection caused by multiple classes of resistant bacteria was demonstrated by Raymond and coworkers when they tested antibiotic rotation in 1,456 consecutive admissions to the ICU (429). Furthermore, outcome analysis revealed a significant reduction of the mortality associated with infection (2.9 deaths per 100 admissions versus 9.6 deaths per 100 admissions; $p < 0.0001$) during rotation, which was confirmed by logistic regression analysis, with antibiotic rotation being an independent predictor of survival (OR, 6.3; 95% CI, 2.8 to 14.2). Further study in this area, including multicenter trials, evaluation of rotation intervals, evaluation of single versus multiple drug rotations, and long-term effects of antibiotic rotation is, however, necessary to understand these effects more completely. Whether antibiotic rotation can maintain lower levels of antimicrobial resistance and mortality over time remains to be seen.

To conclude, effective antimicrobial therapy and adequate supportive measures remain the mainstay of treatment for VAP. Persistently high mortality rates for pneumonia in the ICU argue, however, for the continued reassessment of our current therapeutic modalities and design of better protocols. More active and less toxic antibacterial agents are still needed, especially for some problematic pathogens, such as multiresistant nonfermenting GNB or MRSA. However, it should be emphasized that, in the event that one or several specific etiologic agents are identified by a reliable diagnostic technique, the choice of antimicrobial drugs is much easier, because the optimal treatment can be selected in light of the susceptibility pattern of the causative pathogens without resorting to broad-spectrum drugs or risking inappropriate treatment. Every possible effort should therefore be made to obtain, before new antibiotics are administered, reliable pulmonary specimens for

direct microscope examination and cultures from each patient clinically suspected of having developed VAP.

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Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY AND THE INFECTIOUS DISEASES SOCIETY OF AMERICA WAS APPROVED BY THE ATS BOARD OF DIRECTORS, DECEMBER 2004 AND THE IDSA GUIDELINE COMMITTEE, OCTOBER 2004

CONTENTS

EXECUTIVE SUMMARY

Since the initial 1996 American Thoracic Society (ATS) guideline on nosocomial pneumonia, a number of new developments have appeared, mandating a new evidence-based guideline for hospital-acquired pneumonia (HAP), including healthcare-associated pneumonia (HCAP) and ventilator-associated pneumonia (VAP). This document, prepared by a joint committee of the ATS and Infectious Diseases Society of America (IDSA), focuses on the epidemiology and pathogenesis of bacterial pneumonia in adults, and emphasizes modifiable risk factors for infection. In addition, the microbiology of HAP is reviewed, with an emphasis on multidrug-resistant (MDR) bacterial pathogens, such as *Pseudomonas aeruginosa*, *Acinetobacter* species, and methicillin-resistant *Staphylococcus aureus*. Controversies about diagnosis are discussed, emphasizing initial examination of lower respiratory tract samples for bacteria, and the rationale for both clinical and bacteriologic approaches, using either "semiquantitative" or "quantitative" microbiologic methods that help direct selection of appropriate antibiotic therapy. We also provide recommendations for additional diagnostic and therapeutic evaluations in patients with nonresolving pneumonia. This is an evidence-based document that emphasizes the issues of VAP, because there are far fewer data available about HAP in nonintubated patients and about HCAP. By extrapolation, patients who are not intubated and mechanically ventilated should be managed like patients with VAP, using the same approach to identify risk factors for infection with specific pathogens.

The major goals of this evidence-based guideline for the management of HAP, VAP, and HCAP emphasize early, appropriate antibiotics in adequate doses, while avoiding excessive antibiotics by de-escalation of initial antibiotic therapy, based on microbiologic cultures and the clinical response of the patient, and shortening the duration of therapy to the minimum effective period. The guideline recognizes the variability of bacteriology from one hospital to another and from one time period to another and recommends taking local microbiologic data into account when adapting treatment recommendations to any specific clinical setting. The initial, empiric antibiotic therapy algorithm includes two groups of patients: one with no need for broad-spectrum therapy, because these patients have early-onset HAP, VAP, or HCAP and no risk factors for MDR pathogens, and a second group that requires broad-spectrum therapy, because of late-onset pneumonia or other risk factors for infection with MDR pathogens.

Some of the key recommendations and principles in this new, evidence-based guideline are as follows:

- HCAP is included in the spectrum of HAP and VAP, and patients with HCAP need therapy for MDR pathogens.
- A lower respiratory tract culture needs to be collected from all patients before antibiotic therapy, but collection of cultures should not delay the initiation of therapy in critically ill patients.
- Either "semiquantitative" or "quantitative" culture data can be used for the management of patients with HAP.
- Lower respiratory tract cultures can be obtained broncho-

Am J Respir Crit Care Med Vol 171. pp 388–416, 2005
DOI: 10.1164/rccm.200405-644ST
Internet address: www.atsjournals.org

scopically or nonbronchoscopically, and can be cultured quantitatively or semiquantitatively.
- Quantitative cultures increase specificity of the diagnosis of HAP without deleterious consequences, and the specific quantitative technique should be chosen on the basis of local expertise and experience.
- Negative lower respiratory tract cultures can be used to stop antibiotic therapy in a patient who has had cultures obtained in the absence of an antibiotic change in the past 72 hours.
- Early, appropriate, broad-spectrum, antibiotic therapy should be prescribed with adequate doses to optimize antimicrobial efficacy.
- An empiric therapy regimen should include agents that are from a different antibiotic class than the patient has recently received.
- Combination therapy for a specific pathogen should be used judiciously in the therapy of HAP, and consideration should be given to short-duration (5 days) aminoglycoside therapy, when used in combination with a β-lactam to treat *P. aeruginosa* pneumonia.
- Linezolid is an alternative to vancomycin, and unconfirmed, preliminary data suggest it may have an advantage for proven VAP due to methicillin-resistant *S. aureus*.
- Colistin should be considered as therapy for patients with VAP due to a carbapenem-resistant *Acinetobacter* species.
- Aerosolized antibiotics may have value as adjunctive therapy in patients with VAP due to some MDR pathogens.
- De-escalation of antibiotics should be considered once data are available on the results of lower respiratory tract cultures and the patient's clinical response.
- A shorter duration of antibiotic therapy (7 to 8 days) is recommended for patients with uncomplicated HAP, VAP, or HCAP who have received initially appropriate therapy and have had a good clinical response, with no evidence of infection with nonfermenting gram-negative bacilli.

INTRODUCTION

As with all guidelines, these new recommendations, although evidence graded, need validation for their impact on the outcome of patients with HAP, VAP, and HCAP. In addition, this guideline points out areas of incomplete knowledge, which can be used to set an agenda for future research.

Hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and healthcare-associated pneumonia (HCAP) remain important causes of morbidity and mortality despite advances in antimicrobial therapy, better supportive care modalities, and the use of a wide-range of preventive measures (1–5). HAP is defined as pneumonia that occurs 48 hours or more after admission, which was not incubating at the time of admission (1, 3). HAP may be managed in a hospital ward or in the intensive care unit (ICU) when the illness is more severe. VAP refers to pneumonia that arises more than 48–72 hours after endotracheal intubation (2, 3). Although not included in this definition, some patients may require intubation after developing severe HAP and should be managed similar to patients with VAP. HCAP includes any patient who was hospitalized in an acute care hospital for two or more days within 90 days of the infection; resided in a nursing home or long-term care facility; received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection; or attended a hospital or hemodialysis clinic (3, 4, 6). Although this document focuses more on HAP and VAP, most of the principles overlap with HCAP. Because most of the current data have been collected from patients with VAP, and microbiologic data from nonintubated patients may be less accurate, most of our information is derived from those with VAP, but by extrapolation can be applied to all patients with HAP, emphasizing risk factors for infection with specific pathogens.

This guideline is an update of the 1996 consensus statement on HAP published by the American Thoracic Society (5). The principles and recommendations are largely based on data presented by committee members at a conference jointly sponsored by the American Thoracic Society (ATS) and the Infectious Disease Society of America (IDSA). The committee was composed of pulmonary, critical care, and infectious disease specialists with clinical and research interests in HAP, VAP, and HCAP. All major aspects of the epidemiology, pathogenesis, bacteriology, diagnosis, and antimicrobial treatment were reviewed by this group. Therapy recommendations are focused on antibiotic choice and patient stratification; adjunctive, nonantibiotic therapy of pneumonia is not discussed, but information on this topic is available elsewhere (7). Recommendations to reduce the risk of pneumonia are limited in this document to key, modifiable risk factors related to the pathogenesis of pneumonia to avoid redundancy with the more comprehensive Guidelines for Preventing Health-care–associated Pneumonia, prepared by the Centers for Disease Control and Prevention (CDC) and the Hospital Infection Control Practices Advisory Committee (HICPAC) (3).

The goal of our document is to provide a framework for the initial evaluation and management of the immunocompetent, adult patient with bacterial causes of HAP, VAP, or HCAP, and excludes patients who are known to be immunosuppressed by human immunodeficiency virus (HIV) infection, hematologic malignancy, chemotherapy-induced neutropenia, organ transplantation, and so on. At the outset, the ATS/IDSA Guideline Committee members recognized that currently, many patients with HAP, VAP, or HCAP are infected with multidrug-resistant (MDR) bacterial pathogens that threaten the adequacy of initial, empiric antibiotic therapy. At the same time, the committee members recognized that many studies have shown that excessive antibiotic use is a major factor contributing to increased frequency of antibiotic-resistant pathogens. Four major principles underlie the management of HAP, VAP, and HCAP:

- Avoid untreated or inadequately treated HAP, VAP, or HCAP, because the failure to initiate prompt appropriate and adequate therapy has been a consistent factor associated with increased mortality.
- Recognize the variability of bacteriology from one hospital to another, specific sites within the hospital, and from one time period to another, and use this information to alter the selection of an appropriate antibiotic treatment regimen for any specific clinical setting.
- Avoid the overuse of antibiotics by focusing on accurate diagnosis, tailoring therapy to the results of lower respiratory tract cultures, and shortening duration of therapy to the minimal effective period.
- Apply prevention strategies aimed at modifiable risk factors.

The ATS/IDSA guideline was established for use in the initial management of patients in whom HAP, VAP, or HCAP is suspected. Therapeutic algorithms are presented that are based on the expected antimicrobial susceptibility of the common bacterial pathogens, and with therapeutic regimens that can commonly lead to initial adequate antibiotic management.

This guideline is not meant to replace clinical judgment, but rather to give an organizational framework to patient management. Individual clinical situations can be highly complex and the judgment of a knowledgeable physician with all available information about a specific patient is essential for optimal clini-

TABLE 1. EVIDENCE-BASED GRADING SYSTEM USED TO RANK RECOMMENDATIONS

Evidence Level	Definition
Level I (high)	Evidence comes from well conducted, randomized controlled trials
Level II (moderate)	Evidence comes from well designed, controlled trials without randomization (including cohort, patient series, and case-control studies). Level II studies also include any large case series in which systematic analysis of disease patterns and/or microbial etiology was conducted, as well as reports of new therapies that were not collected in a randomized fashion
Level III (low)	Evidence comes from case studies and expert opinion. In some instances therapy recommendations come from antibiotic susceptibility data without clinical observations

Adapted from American Thoracic Society guidelines for the management of adults with community-acquired pneumonia (8).

cal management. As more laboratory and clinical data become available, therapy often needs to be streamlined or altered. Finally, our committee realizes that these guidelines will change over time, and that our current recommendations will need to be updated as new information becomes available.

METHODOLOGY USED TO PREPARE THE GUIDELINE

The ATS/IDSA Guideline Committee originally met as a group, with each individual being assigned a topic for review and presentation to the entire group. Each topic in the guideline was reviewed by more than one committee member, and after presentation of information, the committee discussed the data and formulated recommendations. Two committee members prepared each section of the document, and a draft document incorporating all sections was written and distributed to the committee for review and suggestions. The guideline was then revised and circulated to the committee for final comment. This final statement represents the results of this process and the opinions of the majority of committee members.

The grading system for our evidence-based recommendations was previously used for the updated ATS Community-acquired Pneumonia (CAP) statement, and the definitions of high-level (**Level I**), moderate-level (**Level II**), and low-level (**Level III**) evidence are summarized in Table 1 (8). All available and relevant, peer-reviewed studies published until July 2004 were considered. Much of the literature is observational, and only a few therapy trials have been conducted in a prospective, randomized fashion.

Nearly all of the evidence-based data on risk factors for bacterial HAP have been collected from observational studies, which cannot distinguish causation from noncausal association. Most of the studies have focused on patients with VAP, but the committee extrapolated the relationship between risk factors and bacteriology to all patients with HAP, including those with HCAP. Ultimate proof of causality, and ideally the best strategies for prevention of HAP, VAP, and HCAP, should be based on prospective, randomized trials. However, recommendations are further compromised when such trials provide conflicting results, often as a result of differences in definitions, study design, and the specific population studied. In addition, evidence-based recommendations are dynamic and may change as new therapies become available and as new interventions alter the natural history of the disease.

EPIDEMIOLOGY

Incidence

HAP is usually caused by bacteria, is currently the second most common nosocomial infection in the United States, and is associated with high mortality and morbidity (3). The presence of HAP increases hospital stay by an average of 7 to 9 days per patient and has been reported to produce an excess cost of more than $40,000 per patient (9–11). Although HAP is not a reportable illness, available data suggest that it occurs at a rate of between 5 and 10 cases per 1,000 hospital admissions, with the incidence increasing by as much as 6- to 20-fold in mechanically ventilated patients (9, 12, 13). It is often difficult to define the exact incidence of VAP, because there may be an overlap with other lower respiratory tract infections, such as infectious tracheobronchitis in mechanically ventilated patients. The exact incidence varies widely depending on the case definition of pneumonia and the population being evaluated (14). For example, the incidence of VAP may be up to two times higher in patients diagnosed by qualitative or semiquantitative sputum cultures compared with quantitative cultures of lower respiratory tract secretions (9, 15).

HAP accounts for up to 25% of all ICU infections and for more than 50% of the antibiotics prescribed (16). VAP occurs in 9–27% of all intubated patients (9, 11). In ICU patients, nearly 90% of episodes of HAP occur during mechanical ventilation. In mechanically ventilated patients, the incidence increases with duration of ventilation. The risk of VAP is highest early in the course of hospital stay, and is estimated to be 3%/day during the first 5 days of ventilation, 2%/day during Days 5 to 10 of ventilation, and 1%/day after this (17). Because most mechanical ventilation is short term, approximately half of all episodes of VAP occur within the first 4 days of mechanical ventilation. The intubation process itself contributes to the risk of infection, and when patients with acute respiratory failure are managed with noninvasive ventilation, nosocomial pneumonia is less common (18–20).

Time of onset of pneumonia is an important epidemiologic variable and risk factor for specific pathogens and outcomes in patients with HAP and VAP. Early-onset HAP and VAP, defined as occurring within the first 4 days of hospitalization, usually carry a better prognosis, and are more likely to be caused by antibiotic-sensitive bacteria. Late-onset HAP and VAP (5 days or more) are more likely to be caused by multidrug-resistant (MDR) pathogens, and are associated with increased patient mortality and morbidity. However, patients with early-onset HAP who have received prior antibiotics or who have had prior hospitalization within the past 90 days are at greater risk for colonization and infection with MDR pathogens and should be treated similar to patients with late-onset HAP or VAP (Table 2) (21).

The crude mortality rate for HAP may be as high as 30 to 70%, but many of these critically ill patients with HAP die of their underlying disease rather than pneumonia. The mortality related to the HAP or "attributable mortality" has been estimated to be between 33 and 50% in several case-matching studies of VAP. Increased mortality rates were associated with bacteremia, especially with *Pseudomonas aeruginosa* or *Acinetobacter* species, medical rather than surgical illness, and treatment with ineffective antibiotic therapy (22, 23). Other studies using similar methodology failed to identify any attributable mortality due to VAP,

TABLE 2. RISK FACTORS FOR MULTIDRUG-RESISTANT PATHOGENS CAUSING HOSPITAL-ACQUIRED PNEUMONIA, HEALTHCARE-ASSOCIATED PNEUMONIA, AND VENTILATOR-ASSOCIATED PNEUMONIA

- Antimicrobial therapy in preceding 90 d
- Current hospitalization of 5 d or more
- High frequency of antibiotic resistance in the community or in the specific hospital unit
- Presence of risk factors for HCAP:
  - Hospitalization for 2 d or more in the preceding 90 d
  - Residence in a nursing home or extended care facility
  - Home infusion therapy (including antibiotics)
  - Chronic dialysis within 30 d
  - Home wound care
  - Family member with multidrug-resistant pathogen
- Immunosuppressive disease and/or therapy

suggesting a variable outcome impact, according to the severity of underlying medical conditions (24–26).

Etiology

HAP, VAP, and HCAP may be caused by a wide spectrum of bacterial pathogens, may be polymicrobial, and are rarely due to viral or fungal pathogens in immunocompetent hosts (9, 12, 27–32). Common pathogens include aerobic gram-negative bacilli, such as *P. aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter* species. Infections due to gram-positive cocci, such as *Staphylococcus aureus*, particularly methicillin-resistant *S. aureus* (MRSA), have been rapidly emerging in the United States (16, 33). Pneumonia due to *S. aureus* is more common in patients with diabetes mellitus, head trauma, and those hospitalized in ICUs (34).

Significant growth of oropharyngeal commensals (viridans group streptococci, coagulase-negative staphylococci, *Neisseria* species, and *Corynebacterium* species) from distal bronchial specimens is difficult to interpret, but these organisms can produce infection in immunocompromised hosts and some immunocompetent patients (35). Rates of polymicrobial infection vary widely, but appear to be increasing, and are especially high in patients with adult respiratory distress syndrome (ARDS) (9, 12, 36–38).

The frequency of specific MDR pathogens causing HAP may vary by hospital, patient population, exposure to antibiotics, type of ICU patient, and changes over time, emphasizing the need for timely, local surveillance data (3, 8, 10, 21, 39–41). HAP involving anaerobic organisms may follow aspiration in nonintubated patients, but is rare in patients with VAP (28, 42).

Elderly patients represent a diverse population of patients with pneumonia, particularly HCAP. Elderly residents of long-term care facilities have been found to have a spectrum of pathogens that more closely resemble late-onset HAP and VAP (30, 31). In a study of 104 patients age 75 years and older with severe pneumonia, El-Solh found *S. aureus* (29%), enteric gram-negative rods (15%), *Streptococcus pneumoniae* (9%), and *Pseudomonas* species (4%) as the most frequent causes of nursing home-acquired pneumonia (30). In another study of 52 long-term care residents aged 70 years and above who failed to respond to 72 hours of antibiotics, MRSA (33%), gram-negative enterics (24%), and *Pseudomonas* species (14%) were the most frequent pathogens isolated by invasive diagnostics (bronchoscopy) (31). In the latter study, 72% had at least two comorbidities whereas 23% had three or more.

Few data are available about the bacteriology and risk factors for specific pathogens in patients with HAP and HCAP, and who are not mechanically ventilated. Data from comprehensive hospital-wide surveillance of nosocomial infections at the University of North Carolina have described the pathogens causing both VAP and nosocomial pneumonia in nonintubated patients during the years 2000–2003 (D. Weber and W. Rutala, unpublished data). Pathogens were isolated from 92% of mechanically ventilated patients with infection, and from 77% of nonventilated patients with infection. In general, the bacteriology of nonventilated patients was similar to that of ventilated patients, including infection with MDR pathogens such as methicillin-resistant *S. aureus* (MRSA), *P. aeruginosa*, *Acinetobacter* species, and *K. pneumoniae*. In fact, some organisms (MRSA and *K. pneumoniae*) were more common in nonventilated than ventilated patients, whereas certain resistant gram-negative bacilli were more common in patients with VAP (*P. aeruginosa, Stenotrophomonas maltophilia*, and *Acinetobacter* species). However, the latter group of more resistant gram-negative bacilli occurred with sufficient frequency in nonventilated patients that they should be considered when designing an empiric therapy regimen. Studies in nonventilated patients have not determined whether this population has risk factors for MDR pathogens that differ from the risk factors present in ventilated patients.

Emergence of selected multidrug-resistant bacteria. Rates of HAP due to MDR pathogens have increased dramatically in hospitalized patients, especially in intensive care and transplant patients (16). Risk factors for colonization and infection with MDR pathogens are summarized in Table 2 (21, 43). Data on mechanisms of antibiotic resistance for specific bacterial pathogens have provided new insight into the adaptability of these pathogens.

PSEUDOMONAS AERUGINOSA. P. aeruginosa, the most common MDR gram-negative bacterial pathogen causing HAP/VAP, has intrinsic resistance to many antimicrobial agents (44–46). This resistance is mediated by multiple efflux pumps, which may be expressed all the time or may be upregulated by mutation (47). Resistance to piperacillin, ceftazidime, cefepime, other oxyimino-β-lactams, imipenem and meropenem, aminoglycosides, or fluoroquinolones is increasing in the United States (16). Decreased expression of an outer membrane porin channel (OprD) can cause resistance to both imipenem and meropenem or, depending on the alteration in OprD, specific resistance to imipenem, but not other β-lactams (48). At present, some MDR isolates of *P. aeruginosa* are susceptible only to polymyxin B.

Although currently uncommon in the United States, there is concern about the acquisition of plasmid-mediated metallo-β-lactamases active against carbapenems and antipseudomonal penicillins and cephalosporins (49). The first such enzyme, IMP-1, appeared in Japan in 1991 and spread among *P. aeruginosa* and *Serratia marcescens*, and then to other gram-negative pathogens. Resistant strains of *P. aeruginosa* with IMP-type enzymes and other carbapenemases have been reported from additional countries in the Far East, Europe, Canada, Brazil, and recently in the United States (50).

KLEBSIELLA, ENTEROBACTER, AND *SERRATIA* SPECIES. *Klebsiella* species are intrinsically resistant to ampicillin and other aminopenicillins and can acquire resistance to cephalosporins and aztreonam by the production of extended-spectrum β-lactamases (ESBLs) (51). Plasmids encoding ESBLs often carry resistance to aminoglycosides and other drugs, but ESBL-producing strains remain susceptible to carbapenems. Five to 10% of oxyimino-β-lactam-resistant *K. pneumoniae* do not produce an ESBL, but rather a plasmid-mediated AmpC-type enzyme (52). Such strains usually are carbapenem susceptible, but may become resistant by loss of an outer membrane porin (53). *Enterobacter* species have a chromosomal AmpC β-lactamase that is inducible and also easily expressed at a high level by mutation with consequent resistance to oxyimino-β-lactams and α-methoxy-β-lactams,

such as cefoxitin and cefotetan, but continued susceptibility to carbapenems. *Citrobacter* and *Serratia* species have the same inducible AmpC β-lactamase and the same potential for resistance development. Although the AmpC enzyme of *E. coli* is not inducible, it can occasionally be hyperexpressed. Plasmid-mediated resistance, such as ESBL production, is a more common mechanism for β-lactam resistance in nosocomial isolates, and is increasingly recognized not only in isolates of *K. pneumoniae* and *E. coli*, but also *Enterobacter* species (54).

Acinetobacter species, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia*. Although generally less virulent than *P. aeruginosa*, *Acinetobacter* species have nonetheless become problem pathogens because of increasing resistance to commonly used antimicrobial agents (55). More than 85% of isolates are susceptible to carbapenems, but resistance is increasing due either to IMP-type metalloenzymes or carbapenemases of the OXA type (49). An alternative for therapy is sulbactam, usually employed as an enzyme inhibitor, but with direct antibacterial activity against *Acinetobacter* species (56). *S. maltophilia*, which shares with *B. cepacia* a tendency to colonize the respiratory tract rather than cause invasive disease, is uniformly resistant to carbapenems, because of a ubiquitous metallo-β-lactamase. *S. maltophilia* and *B. cepacia* are most likely to be susceptible to trimethoprim–sulfamethoxazole, ticarcillin–clavulanate, or a fluoroquinolone (55). *B. cepacia* is also usually susceptible to ceftazidime and carbapenems.

Methicillin-resistant *Staphylococcus aureus*. In the United States, more than 50% of the ICU infections caused by *S. aureus* are with methicillin-resistant organisms (16, 33). MRSA produces a penicillin-binding protein with reduced affinity for β-lactam antibiotics that is encoded by the *mecA* gene, which is carried by one of a family of four mobile genetic elements (57, 58). Strains with *mecA* are resistant to all commercially available β-lactams and many other antistaphylococcal drugs, with considerable country-to-country variability (59, 60). Although vancomycin-intermediate *S. aureus*, with a minimal inhibitory concentration (MIC) of 8–16 μg/ml, and high-level vancomycin-resistant *S. aureus*, with an MIC of 32–1,024 μg/ml or more, have been isolated from clinical specimens, none to date have caused respiratory tract infection and all have been sensitive to linezolid (61, 62). Unfortunately, linezolid resistance has emerged in *S. aureus*, but is currently rare (63).

Streptococcus pneumoniae and *Haemophilus influenzae*. *S. pneumoniae* and *H. influenzae* cause early-onset HAP in patients without other risk factors, are uncommon in late-onset infection, and frequently are community acquired. At present, many strains of *S. pneumoniae* are penicillin resistant due to altered penicillin-binding proteins. Some such strains are resistant as well to cephalosporins, macrolides, tetracyclines, and clindamycin (64). Despite low and moderate levels of resistance to penicillins and cephalosporins *in vitro*, clinical outcomes in patients with pneumococcal pneumonia and bacteremia treated with these agents have been satisfactory (65). All of the multidrug-resistant strains in the United States are currently sensitive to vancomycin or linezolid, and most remain sensitive to broad-spectrum quinolones. Resistance of *H. influenzae* to antibiotics other than penicillin and ampicillin is sufficiently rare so as not to present a problem in therapy.

Legionella pneumophila. The evidence for *Legionella pneumophila* as a cause of HAP is variable, but is increased in immunocompromised patients, such as organ transplant recipients or patients with HIV disease, as well as those with diabetes mellitus, underlying lung disease, or end-stage renal disease (29, 66–69). HAP due to *Legionella* species is more common in hospitals where the organism is present in the hospital water supply or where there is ongoing construction (3, 29, 66–69). Because detection is based on the widespread use of *Legionella* urinary antigen, rather than culture for *Legionella*, disease due to serogroups other than serogroup 1 may be underdiagnosed. Detailed strategies for prevention of *Legionella* infections and eradication procedures for *Legionella* species in cooling towers and the hospital water supply are outlined in the CDC/HICPAC Guidelines for Preventing Health-care–associated Pneumonia (3).

Fungal pathogens. Nosocomial pneumonia due to fungi, such as *Candida* species and *Aspergillus fumigatus*, may occur in organ transplant or immunocompromised, neutropenic patients, but is uncommon in immunocompetent patients (70–75). Nosocomial *Aspergillus* species infections suggest possible airborne transmission by spores, and may be associated with an environmental source such as contaminated air ducts or hospital construction. By comparison, isolation of *Candida albicans* and other *Candida* species from endotracheal aspirates is common, but usually represents colonization of the airways, rather than pneumonia in immunocompetent patients, and rarely requires treatment with antifungal therapy (70).

Viral pathogens. The incidence of HAP and VAP due to viruses is also low in immunocompetent hosts. Outbreaks of HAP, VAP, and HCAP due to viruses, such as influenza, parainfluenza, adenovirus, measles, and respiratory syncytial virus have been reported and are usually seasonal. Influenza, pararinfluenza, adenovirus, and respiratory syncytial virus account for 70% of the nosocomial viral cases of HAP, VAP, and HCAP (3, 76–78). Respiratory syncytial virus outbreaks of bronchiolitis and pneumonia are more common in children's wards and rare in immunocompetent adults (76). Diagnosis of these viral infections is often made by rapid antigen testing and viral culture or serologic assays.

Influenza A is probably the most common viral cause of HAP and HCAP in adult patients. Pneumonia in patients with influenza A or B may be due to the virus, to secondary bacterial infection, or both. Influenza is transmitted directly from person to person when infected persons sneeze, cough, or talk or indirectly by person–fomite–person transmission (3, 79–81). The use of influenza vaccine along with prophylaxis and early antiviral therapy among at-risk healthcare workers and high-risk patients with amantadine, rimantadine, or one of the neuraminidase inhibitors (oseltamivir and zanamivir) dramatically reduces the spread of influenza within hospital and healthcare facilities (3, 81–90). Amantadine and rimantadine are effective only for treatment and prophylaxis against influenza A strains, whereas neuraminidase inhibitors are effective against both influenza A and B.

Major Epidemiologic Points

1. Many patients with HAP, VAP, and HCAP are at increased risk for colonization and infection with MDR pathogens (**Level II**) (2–4, 6, 9, 11–13, 21, 22).
2. It is often difficult to define the exact incidence of HAP and VAP, because there may be an overlap with other lower respiratory tract infections, such as tracheobronchitis, especially in mechanically ventilated patients (**Level III**) (9, 12–14).
3. The exact incidence of HAP is usually between 5 and 15 cases per 1,000 hospital admissions depending on the case definition and study population; the exact incidence of VAP is 6- to 20-fold greater than in nonventilated patients (**Level II**) (9, 12–14).
4. HAP and VAP are a frequent cause of nosocomial infection that is associated with a higher crude mortality than other hospital-acquired infections (**Level II**) (3, 9, 16).
5. Patients with late-onset HAP and VAP are more likely to be infected with MDR pathogens and have higher

crude mortality than patients with early-onset disease; patients with early-onset HAP who have recently received antibiotics or had an admission to a healthcare facility are at risk for colonization and infection with MDR pathogens (**Level II**) (3, 9, 21, 22).

6. An increase in crude and attributable mortality for HAP and VAP is associated with the presence of MDR pathogens (**Level II**) (3, 5, 9–13, 21–23).
7. Bacteria cause most cases of HAP, VAP, and HCAP and many infections are polymicrobial; rates are especially high in patients with ARDS (**Level I**) (2, 4, 6, 9, 12, 36–38).
8. HAP, VAP, and HCAP are commonly caused by aerobic gram-negative bacilli, such as *P. aeruginosa, K. pneumoniae*, and *Acinetobacter* species, or by gram-positive cocci, such as *S. aureus*, much of which is MRSA; anaerobes are an uncommon cause of VAP (**Level II**) (9, 12, 28, 36–40, 42, 91).
9. Rates of *L. pneumophila* vary considerably between hospitals and disease occurs more commonly with serogroup 1 when the water supply is colonized or there is ongoing construction (**Level II**) (29, 66–69).
10. Nosocomial virus and fungal infections are uncommon causes of HAP and VAP in immunocompetent patients. Outbreaks of influenza have occurred sporadically and risk of infection can be substantially reduced with widespread effective infection control, vaccination, and use of antiinfluenza agents (**Level I**) (3, 70–75, 79–90).
11. The prevalence of MDR pathogens varies by patient population, hospital, and type of ICU, which underscores the need for local surveillance data (**Level II**) (3, 9, 41).
12. MDR pathogens are more commonly isolated from patients with severe, chronic underlying disease, those with risk factors for HCAP, and patients with late-onset HAP or VAP (**Level II**) (9, 21, 22, 30, 31, 39, 40, 91).

PATHOGENESIS

For HAP to occur, the delicate balance between host defenses and microbial propensity for colonization and invasion must shift in favor of the ability of the pathogens to persist and invade the lower respiratory tract. Sources of infection for HAP include healthcare devices or the environment (air, water, equipment, and fomites) and can occur with transfer of microorganisms between staff and patients (3, 9, 12, 13, 27, 66, 92, 93). A number of host- and treatment-related colonization factors, such as the severity of the patient's underlying disease, prior surgery, exposure to antibiotics, other medications, and exposure to invasive respiratory devices and equipment, are important in the pathogenesis of HAP and VAP (40, 93, 94)

HAP requires the entry of microbial pathogens into the lower respiratory tract, followed by colonization, which can then overwhelm the host's mechanical (ciliated epithelium and mucus), humoral (antibody and complement), and cellular (polymorphonuclear leukocytes, macrophages, and lymphocytes and their respective cytokines) defenses to establish infection (9, 94).

Aspiration of oropharyngeal pathogens or leakage of bacteria around the endotracheal tube cuff is the primary route of bacterial entry into the trachea (95–98). The stomach and sinuses have been suggested as potential reservoirs for certain bacteria colonizing the oropharynx and trachea, but their importance remains controversial (99–104). Some investigators postulate that colonization of the endotracheal tube with bacteria encased in biofilm may result in embolization into the alveoli during suctioning or bronchoscopy (105, 106). Inhalation of pathogens from contaminated aerosols, and direct inoculation, are less common (107, 108). Hematogenous spread from infected intravascular catheters or bacterial translocation from the gastrointestinal tract lumen are quite rare.

Major Points for Pathogenesis

1. Sources of pathogens for HAP include healthcare devices, the environment (air, water, equipment, and fomites), and commonly the transfer of microorganisms between the patient and staff or other patients (**Level II**) (3, 9, 12, 13, 27, 66, 92, 93).
2. A number of host- and treatment-related colonization factors, such as the severity of the patient's underlying disease, prior surgery, exposure to antibiotics, other medications, and exposure to invasive respiratory devices and equipment, are important in the pathogenesis of HAP and VAP (**Level II**) (40, 93, 94).
3. Aspiration of oropharyngeal pathogens, or leakage of secretions containing bacteria around the endotracheal tube cuff, are the primary routes of bacterial entry into the lower respiratory tract (**Level II**) (95–98).
4. Inhalation or direct inoculation of pathogens into the lower airway, hematogenous spread from infected intravenous catheters, and bacterial translocation from the gastrointestinal tract lumen are uncommon pathogenic mechanisms (**Level II**) (107, 108).
5. Infected biofilm in the endotracheal tube, with subsequent embolization to distal airways, may be important in the pathogenesis of VAP (**Level III**) (105, 106).
6. The stomach and sinuses may be potential reservoirs of nosocomial pathogens that contribute to bacterial colonization of the oropharynx, but their contribution is controversial, may vary by the population at risk, and may be decreasing with the changing natural history and management of HAP (**Level II**) (94, 99–104, 109).

MODIFIABLE RISK FACTORS

Risk factors for the development of HAP can be differentiated into modifiable and nonmodifiable conditions. Risk factors may also be patient related (male sex, preexisting pulmonary disease, or multiple organ system failure) or treatment related (intubation or enteral feeding). Modifiable risk factors for HAP are obvious targets for improved management and prophylaxis in several studies and in the comprehensive Guidelines for Preventing Health-care–associated Pneumonia, published by the Centers for Disease Control (3, 93, 110). Effective strategies include strict infection control, alcohol-based hand disinfection, use of microbiologic surveillance with timely availability of data on local MDR pathogens, monitoring and early removal of invasive devices, and programs to reduce or alter antibiotic-prescribing practices (3, 92, 93, 100, 110–113).

Intubation and Mechanical Ventilation

Intubation and mechanical ventilation increase the risk of HAP 6- to 21-fold and therefore should be avoided whenever possible (3, 94, 110, 114). Noninvasive positive-pressure ventilation, using a face mask, is an attractive alternative for patients with acute exacerbations of chronic obstructive pulmonary disease or acute hypoxemic respiratory failure, and for some immunosuppressed patients with pulmonary infiltrates and respiratory failure (18, 20, 115–119). Data suggest that use of noninvasive ventilation to avoid reintubation after initial extubation may not be a good strategy (115).

Specific strategies have been recommended to reduce the duration of mechanical ventilation, such as improved methods

of sedation and the use of protocols to facilitate and accelerate weaning (120–124). These interventions are dependent on adequate ICU staffing. Reintubation should be avoided, if possible, as it increases the risk of VAP (114).

Attention to the specific type of endotracheal tube, its maintenance, and the site of insertion may also be valuable. The use of oral endotracheal and orogastric tubes, rather than nasotracheal and nasogastric tubes, can reduce the frequency of nosocomial sinusitis and possibly HAP, although causality between sinusitis and HAP has not been firmly established (109, 125). Efforts to reduce the likelihood of aspiration of oropharyngeal bacteria around the endotracheal tube cuff and into the lower respiratory tract include limiting the use of sedative and paralytic agents that depress cough and other host-protective mechanisms, and maintaining endotracheal cuff pressure at greater than 20 cm H_2O (98, 126). Continuous aspiration of subglottic secretions, through the use of a specially designed endotracheal tube, has significantly reduced the incidence of early-onset VAP in several studies (97, 127–130).

VAP may also be related to colonization of the ventilator circuit (131). A large number of prospective, randomized trials have shown that the frequency of ventilator circuit change does not affect the incidence of HAP, but condensate collecting in the ventilator circuit can become contaminated from patient secretions (98, 132–135). Therefore, vigilance is needed to prevent inadvertently flushing the condensate into the lower airway or to in-line medication nebulizers when the patient turns or the bedrail is raised (98, 131–134, 136). Passive humidifiers or heat–moisture exchangers decrease ventilator circuit colonization but have not significantly reduced the incidence of VAP (128, 135–139).

Aspiration, Body Position, and Enteral Feeding

Supine patient positioning may also facilitate aspiration, which may be decreased by a semirecumbent positioning (140–142). Using radioactive labeled enteral feeding, cumulative numbers of endotracheal counts were higher when patients were placed in the completely supine position (0°) as compared with a semirecumbent position (45°) (140, 141). One randomized trial demonstrated a threefold reduction in the incidence of ICU-acquired HAP in patients treated in the semirecumbent position compared with patients treated completely supine (143). Infection in patients in the supine position was strongly associated with the simultaneous administration of enteral nutrition. Thus, intubated patients should be managed in a semirecumbent position, particularly during feeding.

Enteral nutrition has been considered a risk factor for the development of HAP, mainly because of an increased risk of aspiration of gastric contents (3, 144). However, its alternative, parenteral nutrition, is associated with higher risks for intravascular device-associated infections, complications of line insertions, higher costs, and loss of intestinal villous architecture, which may facilitate enteral microbial translocation. Although some have advised feeding critically ill patients enterally as early as possible, a strategy of early (i.e., Day 1 of intubation and ventilation) enteral feeding was, when compared with late administration (i.e., Day 5 of intubation), associated with a higher risk for ICU-acquired VAP (145, 146). Seven studies have evaluated the risks for ICU-acquired HAP in patients randomized to either gastric or postpyloric feeding (147). Although significant differences were not demonstrated in any individual study, postpyloric feeding was associated with a significant reduction in ICU-acquired HAP in metaanalysis (relative risk, 0.76; 95% confidence interval, 0.59 to 0.99) (147).

Modulation of Colonization: Oral Antiseptics and Antibiotics

The progression from colonization to tracheobronchitis to pneumonia is a dynamic equilibrium and the possibility to discern the different entities depends on the specificity of diagnostic tools. Oropharyngeal colonization, either present on admission or acquired during ICU stay, has been identified as an independent risk factor for the development of ICU-acquired HAP caused by enteric gram-negative bacteria and *P. aeruginosa* (101). In a randomized trial, DeRiso and coworkers demonstrated that the use of the oral antiseptic chlorhexidine significantly reduced rates of nosocomial infection in patients undergoing coronary artery bypass surgery (148).

Modulation of oropharyngeal colonization, by combinations of oral antibiotics, with or without systemic therapy, or by selective decontamination of the digestive tract (SDD), is also effective in significantly reducing the frequency of HAP, although methodologic study quality appeared to be inversely related to the magnitude of the preventive effects (93, 149–155).

In two prospective randomized trials SDD was associated with higher ICU survival among patients receiving SDD (156, 157). In the first study patients with a midrange APACHE II score on admission had a lower ICU mortality, although ICU mortality rates of all patients included did not differ significantly (156). In the largest study performed so far, SDD administered to 466 patients in one unit was associated with a relative risk for ICU mortality of 0.65 and with a relative risk of hospital mortality of 0.78, when compared with 472 patients admitted in a control ward (157). In addition, infections due to antibiotic-resistant microorganisms occurred more frequently in the control ward. Importantly, levels of antibiotic-resistant pathogens were low in both wards, with complete absence of MRSA. Moreover, a small preexisting difference in outcome between two wards and the absence of a cross-over design warrant confirmation of these beneficial effects of SDD.

The preventive effects of selective decontamination of the digestive tract for HAP have also been considerably lower in ICUs with high endemic levels of antibiotic resistance. In such a setting, selective decontamination of the digestive tract may increase the selective pressure for antibiotic-resistant microorganisms (158–164). Although selective decontamination of the digestive tract reduces HAP, routine prophylactic use of antibiotics should be discouraged, especially in hospital settings where there are high levels of antibiotic resistance.

The role of systemic antibiotics in the development of HAP is less clear. In one study, prior administration of antibiotics had an adjusted odds ratio of 3.1 (95% confidence interval, 1.4–6.9) for development of late-onset ICU-acquired HAP (165). Moreover, antibiotics clearly predispose patients to subsequent colonization and infection with antibiotic-resistant pathogens (21). In contrast, prior antibiotic exposure conferred protection (risk ratio, 0.37; 95% confidence interval, 0.27–0.51) for ICU-acquired HAP in another study (17). In addition, antibiotic use at the time of emergent intubation may prevent pneumonia within the first 48 hours of intubation (166). Preventive effects of intravenous antibiotics were evaluated in only one randomized trial: administration of cefuroxime for 24 hours, at the time of intubation; and it reduced the incidence of early-onset, ICU-acquired HAP in patients with closed head injury (167). However, circumstantial evidence of the efficacy of systemic antibiotics also follows from the results of metaanalyses of selective decontamination of the digestive tract, which have suggested that the intravenous component of the regimens was largely responsible for improved survival (149). In summary, prior administration of antibiotics for short duration may be beneficial in some patient groups, but when

given for prolonged periods may well place others at risk for subsequent infection with antibiotic-resistant microorganisms.

Stress Bleeding Prophylaxis, Transfusion, and Glucose Control

Both histamine Type 2 (H_2) antagonists and antacids have been identified as independent risk factors for ICU-acquired HAP. Sucralfate has been used for stress bleeding prophylaxis, as it does not decrease intragastric acidity or significantly increase gastric volume. Numerous randomized trials, using different doses and various study populations, have provided controversial results on the benefits of specific stress bleeding prophylaxis agents in relation to the increased risk of VAP (38, 99, 103, 104, 155, 168). One large randomized trial comparing antacids, H_2 blockers, and sucralfate reported no differences in rates of early-onset VAP, but rates of late-onset VAP were lower among patients treated with sucralfate (103). In one multicenter study of VAP in patients with ARDS, sucralfate and duration of exposure to sucralfate were associated with an increased risk of VAP (38). A large, double-blind, randomized trial comparing ranitidine with sucralfate demonstrated a trend to toward lower rates of VAP with sucralfate, but clinically significant gastrointestinal bleeding was 4% higher in the sucralfate group (104). Thus, if stress ulcer prophylaxis is indicated, the risks and benefits of each regimen should be weighed before prescribing either H_2 blockers or sucralfate.

A landmark prospective randomized trial comparing liberal and conservative "triggers" to transfusion in ICU patients not exhibiting active bleeding and without underlying cardiac disease demonstrated that awaiting a hemoglobin level of 7.0 g/dl as opposed to a level of 9.0 g/dl before initiating transfusion resulted in less transfusion and no adverse effects on outcome (169). In fact, in those patients less severely ill, as judged by low APACHE II scores, mortality was improved in the "restricted transfusion" group, a result thought to result from immunosuppressive effects of non–leukocyte-depleted red blood cell units with consequent increased risk for infection. Multiple studies have identified exposure to allogeneic blood products as a risk factor for postoperative infection and postoperative pneumonia, and the length of time of blood storage as another factor modulating risk (170–174). In one prospective randomized control trial the use of leukocyte-depleted red blood cell transfusions resulted in a reduced incidence of postoperative infections, and specifically a reduced incidence of pneumonia in patients undergoing colorectal surgery (172). Routine red blood cell transfusion should be conducted with a restricted transfusion trigger policy. Whether leukocyte-depleted red blood cell transfusions will further reduce the incidence of pneumonia in broad populations of patients at risk remains to be determined.

Hyperglycemia, relative insulin deficiency, or both may directly or indirectly increase the risk of complications and poor outcomes in critically ill patients. van den Berghe and coworkers randomized surgical intensive care unit patients to receive either intensive insulin therapy to maintain blood glucose levels between 80 and 110 mg/dl or to receive conventional treatment (175). The group receiving intensive insulin therapy had reduced mortality (4.6 versus 8%, $p < 0.04$) and the difference was greater in patients who remained in the intensive care unit more than 5 days (10.6 versus 20.2%, $p = 0.005$). When compared with the control group, those treated with intensive insulin therapy had a 46% reduction of bloodstream infections, decreased frequency of acute renal failure requiring dialysis by 41%, fewer antibiotic treatment days, and significantly shorter length of mechanical ventilation and ICU stay. Although the same degree of benefit may not be seen among patients with VAP as in other populations, aggressive treatment of hyperglycemia has both theoretical and clinical support.

Major Points and Recommendations for Modifiable Risk Factors

General prophylaxis.

1. Effective infection control measures: staff education, compliance with alcohol-based hand disinfection, and isolation to reduce cross-infection with MDR pathogens should be used routinely (**Level I**) (3, 93, 100, 110, 111).
2. Surveillance of ICU infections, to identify and quantify endemic and new MDR pathogens, and preparation of timely data for infection control and to guide appropriate, antimicrobial therapy in patients with suspected HAP or other nosocomial infections, are recommended (**Level II**) (3, 92, 93, 100, 110–113).

Intubation and mechanical ventilation.

1. Intubation and reintubation should be avoided, if possible, as it increases the risk of VAP (**Level I**) (3, 12, 93, 94, 114).
2. Noninvasive ventilation should be used whenever possible in selected patients with respiratory failure (**Level I**) (18, 20, 115–119).
3. Orotracheal intubation and orogastric tubes are preferred over nasotracheal intubation and nasogastric tubes to prevent nosocomial sinusitis and to reduce the risk of VAP, although direct causality has not been proved (**Level II**) (3, 93, 94, 109, 125).
4. Continuous aspiration of subglottic secretions can reduce the risk of early-onset VAP, and should be used, if available (**Level I**) (97, 128, 130).
5. The endotracheal tube cuff pressure should be maintained at greater than 20 cm H_2O to prevent leakage of bacterial pathogens around the cuff into the lower respiratory tract (**Level II**) (98, 126).
6. Contaminated condensate should be carefully emptied from ventilator circuits and condensate should be prevented from entering either the endotracheal tube or in-line medication nebulizers (**Level II**) (98, 131, 132).
7. Passive humidifiers or heat–moisture exchangers decrease ventilator circuit colonization, but have not consistently reduced the incidence of VAP, and thus they cannot be regarded as a pneumonia prevention tool (**Level I**) (135–139).
8. Reduced duration of intubation and mechanical ventilation may prevent VAP and can be achieved by protocols to improve the use of sedation and to accelerate weaning (**Level II**) (93, 120–122, 124).
9. Maintaining adequate staffing levels in the ICU can reduce length of stay, improve infection control practices, and reduce duration of mechanical ventilation (**Level II**) (121–124).

Aspiration, body position, and enteral feeding.

1. Patients should be kept in the semirecumbent position (30–45°) rather than supine to prevent aspiration, especially when receiving enteral feeding (**Level I**) (140–144).
2. Enteral nutrition is preferred over parenteral nutrition to reduce the risk of complications related to central intravenous catheters and to prevent reflux villous atrophy of the intestinal mucosa that may increase the risk of bacterial translocation (**Level I**) (3, 93, 145, 146).

Modulation of colonization: oral antiseptics and antibiotics.

1. Routine prophylaxis of HAP with oral antibiotics (selective decontamination of the digestive tract or SDD), with or without systemic antibiotics, reduces the incidence of ICU-acquired VAP, has helped contain outbreaks of

MDR bacteria (**Level I**), but is not recommended for routine use, especially in patients who may be colonized with MDR pathogens (**Level II**) (149–154, 156–159, 161–164, 176).

2. Prior administration of systemic antibiotics has reduced the risk of nosocomial pneumonia in some patient groups, but if a history of prior administration is present at the time of onset of infection, there should be increased suspicion of infection with MDR pathogens (**Level II**) (157–159, 161–164).
3. Prophylactic administration of systemic antibiotics for 24 hours at the time of emergent intubation has been demonstrated to prevent ICU-acquired HAP in patients with closed head injury in one study, but its routine use is not recommended until more data become available (**Level I**) (167).
4. Modulation of oropharyngeal colonization by the use of oral chlorhexidine has prevented ICU-acquired HAP in selected patient populations such as those undergoing coronary bypass grafting, but its routine use is not recommended until more data become available (**Level I**) (148).
5. Use daily interruption or lightening of sedation to avoid constant heavy sedation and try to avoid paralytic agents, both of which can depress cough and thereby increase the risk of HAP (**Level II**) (120).

Stress bleeding prophylaxis, transfusion, and hyperglycemia.

1. Comparative data from randomized trials suggest a trend toward reduced VAP with sucralfate, but there is a slightly higher rate of clinically significant gastric bleeding, compared with H_2 antagonists. If needed, stress bleeding prophylaxis with either H_2 antagonists or sucralfate is acceptable (**Level I**) (99–104, 155, 177–179).
2. Transfusion of red blood cell and other allogeneic blood products should follow a restricted transfusion trigger policy; leukocyte-depleted red blood cell transfusions can help to reduce HAP in selected patient populations (**Level I**) (169–174).
3. Intensive insulin therapy is recommended to maintain serum glucose levels between 80 and 110 mg/dl in ICU patients to reduce nosocomial blood stream infections, duration of mechanical ventilation, ICU stay, morbidity, and mortality (**Level I**) (175).

DIAGNOSTIC TESTING

Diagnostic testing is ordered for two purposes: to define whether a patient has pneumonia as the explanation for a constellation of new signs and symptoms and to determine the etiologic pathogen when pneumonia is present. Unfortunately, currently available tools cannot always reliably provide this information.

The diagnosis of HAP is suspected if the patient has a radiographic infiltrate that is new or progressive, along with clinical findings suggesting infection, which include the new onset of fever, purulent sputum, leukocytosis, and decline in oxygenation. When fever, leukocytosis, purulent sputum, and a positive culture of a sputum or tracheal aspirate are present without a new lung infiltrate, the diagnosis of nosocomial tracheobronchitis should be considered (180). When this definition has been applied to mechanically ventilated patients, nosocomial tracheobronchitis has been associated with a longer length of ICU stay and mechanical ventilation, without increased mortality (180). Antibiotic therapy may be beneficial in this group of patients (180, 181). In one prospective randomized trial of intubated patients with community-acquired bronchial infection, the use of antibiotic therapy led to a reduced incidence of subsequent pneumonia and mortality (181).

The diagnosis of HAP is difficult, and most studies of nonintubated patients have involved clinical diagnosis, with sputum culture, but bronchoscopy has been used less often, making the reliability of the bacteriologic information uncertain and the specificity of the diagnosis undefined (182). The accuracy of the clinical diagnosis of VAP has been investigated on the basis of autopsy findings or quantitative cultures of either protected specimen brush (PSB) or bronchoalveolar lavage (BAL) samples as the standard for comparison (183–186). Some studies have investigated the accuracy of a single clinical finding, whereas others included multiple criteria in their definition of pneumonia. These studies indicate that the diagnostic criteria of a radiographic infiltrate and at least one clinical feature (fever, leukocytosis, or purulent tracheal secretions) have high sensitivity but low specificity (especially for VAP). Combinations of signs and symptoms may increase the specificity. A study in which the diagnostic standard was histology plus positive microbiologic cultures of immediate postmortem lung samples, the presence of chest infiltrates, plus two of three clinical criteria resulted in 69% sensitivity and 75% specificity (187). When the three clinical variables were used the sensitivity declined, whereas the use of only one variable led to a decline in specificity.

For patients diagnosed with ARDS, suspicion of pneumonia should be high and the presence of only one of the three clinical criteria described should lead to more diagnostic testing (188). A high index of suspicion should also be present in patients who have unexplained hemodynamic instability or deterioration of blood gases during mechanical ventilation. In the absence of any of these findings, no further investigations are required. The incidence of colonization in hospitalized patients in general and even more in patients requiring endotracheal intubation is high (107). Antibiotic treatment of simple colonization is strongly discouraged. Routine monitoring of tracheal aspirate cultures to anticipate the etiology of a subsequent pneumonia has also been found to be misleading in a significant percentage of cases (189).

Although these criteria should raise suspicion of HAP, confirmation of the presence of pneumonia is much more difficult, and clinical parameters cannot be used to define the microbiologic etiology of pneumonia. The etiologic diagnosis generally requires a lower respiratory tract culture, but rarely may be made from blood or pleural fluid cultures. Respiratory tract cultures can include endotracheal aspirates, BAL or PSB specimens. Overall, the sensitivity of blood cultures is less than 25%, and when positive, the organisms may originate from an extrapulmonary source in a large percentage, even if VAP is also present (190). Although an etiologic diagnosis is made from a respiratory tract culture, colonization of the trachea precedes development of pneumonia in almost all cases of VAP, and thus a positive culture cannot always distinguish a pathogen from a colonizing organism. However, a sterile culture from the lower respiratory tract of an intubated patient, in the absence of a recent change in antibiotic therapy, is strong evidence that pneumonia is not present, and an extrapulmonary site of infection should be considered (191, 192). In addition, the absence of MDR microorganisms from any lower respiratory specimen in intubated patients, in the absence of a change in antibiotics within the last 72 hours, is strong evidence that they are not the causative pathogen. The time course of clearance of these difficult-to-treat microorganisms is usually slow, so even in the face of a recent change in antibiotic therapy sterile cultures may indicate that these organisms are not present (193). For these reasons, a lower respiratory tract sample for culture should be collected from all intubated patients when the diagnosis of pneumonia is being considered. The diagnostic yield and negative

predictive value of expectorated sputum in nonintubated patients have not been determined.

Major Points and Recommendations for Diagnosis

1. All patients should have a comprehensive medical history obtained and undergo physical examination to define the severity of HAP, to exclude other potential sources of infection, and to reveal the presence of specific conditions that can influence the likely etiologic pathogens (**Level II**) (9, 16, 194).
2. All patients should have a chest radiograph, preferably posteroanterior and lateral if not intubated, as portable chest radiographs have limited accuracy. The radiograph can help to define the severity of pneumonia (multilobar or not) and the presence of complications, such as effusions or cavitation (**Level II**) (5, 195).
3. Purulent tracheobronchitis may mimic many of the clinical signs of HAP and VAP, and may require antibiotic therapy, but prospective, randomized trials are needed (**Level III**) (180). Tracheal colonization is common in intubated patients, but in the absence of clinical findings is not a sign of infection, and does not require therapy or diagnostic evaluation (**Level II**) (40, 107).
4. Arterial oxygenation saturation should be measured in all patients to determine the need for supplemental oxygen. Arterial blood gas should be determined if concern exists regarding either metabolic or respiratory acidosis, and this test generally is needed to manage patients who require mechanical ventilation. These results, along with other laboratory studies (complete blood count, serum electrolytes, renal and liver function), can point to the presence of multiple organ dysfunction and thus help define the severity of illness (**Level II**) (38, 188).
5. All patients with suspected VAP should have blood cultures collected, recognizing that a positive result can indicate the presence of either pneumonia or extrapulmonary infection (**Level II**) (190).
6. A diagnostic thoracentesis to rule out a complicating empyema or parapneumonic effusion should be performed if the patient has a large pleural effusion or if the patient with a pleural effusion appears toxic (**Level III**) (5).
7. Samples of lower respiratory tract secretions should be obtained from all patients with suspected HAP, and should be collected before antibiotic changes. Samples can include an endotracheal aspirate, bronchoalveolar lavage sample, or protected specimen brush sample (**Level II**) (183, 184, 192, 196, 197).
8. In the absence of any clinical suspicion of HAP or nosocomial tracheobronchitis, no respiratory tract cultures should be obtained (**Level III**).
9. A sterile culture of respiratory secretions in the absence of a new antibiotic in the past 72 hours virtually rules out the presence of bacterial pneumonia, but viral or *Legionella* infection is still possible (**Level II**) (192). If these patients have clinical signs of infection, an extrapulmonary site of infection should be investigated (**Level II**) (190, 198).
10. For patients with ARDS, for whom it is difficult to demonstrate deterioration of radiographic images, at least one of the three clinical criteria or other signs of pneumonia, such as hemodynamic instability or deterioration of blood gases, should lead to more diagnostic testing (**Level II**) (38).

DIAGNOSTIC STRATEGIES AND APPROACHES

Because clinical suspicion of HAP/VAP is overly sensitive, further diagnostic strategies are required for optimal management. The goals of diagnostic approaches in patients with suspected HAP are to identify which patients have pulmonary infection; to ensure collection of appropriate cultures; to promote the use of early, effective antibiotic therapy, while allowing for streamlining or de-escalation when possible; and to identify patients who have extrapulmonary infection (Figure 1). The committee considered two different approaches to management, a clinical strategy and a bacteriologic strategy, and have incorporated features from both in the final recommendations.

Clinical Strategy

When the clinical approach is used, the presence of pneumonia is defined by new lung infiltrate plus clinical evidence that the infiltrate is of an infectious origin. The presence of a new or progressive radiographic infiltrate plus at least two of three clinical features (fever greater than 38°C, leukocytosis or leukopenia, and purulent secretions) represents the most accurate combination of criteria for starting empiric antibiotic therapy (187). Although sensitivity for the presence of pneumonia is increased if only one criterion is used, this occurs at the expense of specificity, leading to significantly more antibiotic treatment. Requiring all three clinical criteria is too insensitive and will result in many patients with true pneumonia not receiving therapy.

The etiologic cause of pneumonia is defined by semiquantitative cultures of endotracheal aspirates or sputum with initial microscopic examination. Tracheal aspirate cultures consistently grow more microorganisms than do invasive quantitative cultures, and most microbiology laboratories report the results in a semiquantitative fashion, describing growth as light, moderate, or heavy. In general, it is rare that a tracheal aspirate culture does not contain the pathogen(s) found in invasive quantitative cultures (191, 199, 200). Gram staining of polymorphonuclear leukocytes and macrophages and careful examination of the morphology of any bacteria found to be present, may improve diagnostic accuracy when correlated with culture results (201, 202). Conversely, a negative tracheal aspirate (absence of bacteria or inflammatory cells) in a patient without a recent (within 72 hours) change in antibiotics has a strong negative predictive value (94%) for VAP (203). A reliably performed Gram stain of tracheal aspirates has been demonstrated to result in a low incidence of inappropriate therapy when used to guide initial empiric antibiotic therapy (9, 198).

The clinical strategy emphasizes prompt empiric therapy for all patients suspected of having HAP. The driving force behind this strategy is the consistent finding that delay in the initiation of appropriate antibiotic therapy for patients with HAP is associated with increased mortality (37, 112, 204). The selection of initial antibiotic therapy is based on risk factors for specific pathogens, modified by knowledge of local patterns of antibiotic resistance and organism prevalence. Therapy is modified on the basis of the clinical response on Days 2 and 3, and the findings of semiquantitative cultures of lower respiratory tract secretions. This approach requires no specialized microbiologic methods, and all patients suspected of having pneumonia are treated. This avoids the problem of not treating some infected individuals. Use of an ICU-specific, broad-spectrum empiric therapy regiment can reduce the incidence of inappropriate initial therapy to less than 10% (198, 205).

The major limitation to the clinical approach is that it consistently leads to more antibiotic therapy than when therapy decisions are based on the findings (microscopy and quantitative cultures) of invasive (bronchoscopic) lower respiratory tract samples (198). The clinical approach is overly sensitive, and patients can be treated for pneumonia when another noninfectious process is responsible for the clinical findings. These processes may include congestive heart failure, atelectasis, pulmonary thrombo-

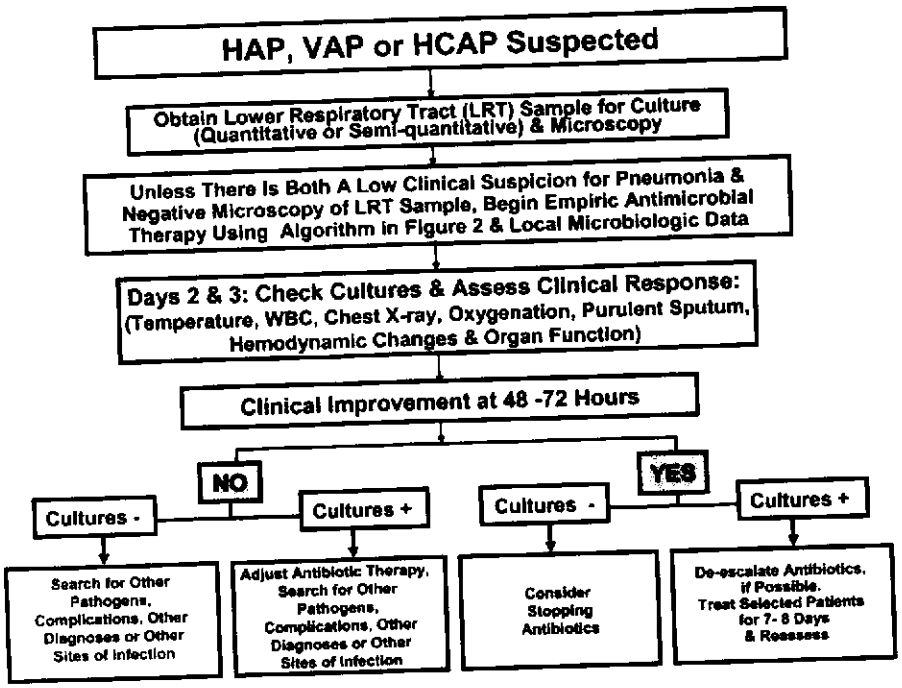

Figure 1. Summary of the management strategies for a patient with suspected hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), or healthcare-associated pneumonia (HCAP). The decision about antibiotic discontinuation may differ depending on the type of sample collected (PSB, BAL, or endotracheal aspirate), and whether the results are reported in quantitative or semiquantitative terms (*see* text for details).

embolism, pulmonary drug reactions, pulmonary hemorrhage, or ARDS. Even if the patient has pneumonia, reliance on semiquantitative cultures, which may not reliably separate true pathogens from colonizers, can lead to either more or broader spectrum antibiotic therapy than with a quantitative approach (198). These cultures have their greatest value if they are negative and the patient has not received new antibiotics within the past 72 hours. One other concern is that reliance on nonquantitative cultures could lead to a failure to recognize extrapulmonary infection at an early time point.

In an effort to improve the specificity of clinical diagnosis, Pugin and coworkers developed the clinical pulmonary infection score (CPIS), which combines clinical, radiographic, physiological (Pa_{O_2}/FI_{O_2}), and microbiologic data into a single numerical result (206). When the CPIS exceeded 6, good correlation with the presence of pneumonia, as defined by quantitative cultures of bronchoscopic and nonbronchoscopic BAL specimens, was found. However, in a subsequent study that used histology plus immediate postmortem quantitative lung cultures as the reference standard, the CPIS had a sensitivity of 77% and a specificity of 42% (187). One prospective study evaluated 79 episodes of suspected VAP, using the CPIS, and compared the findings with diagnoses established by BAL culture. Overall, the sensitivity and specificity of the score were low, although it improved if a Gram stain of a deep respiratory tract culture was added to the evaluation (201).

The original description of the CPIS required microbiologic data, and thus could not be used to screen for HAP. Singh and colleagues used a modified CPIS that did not rely on culture data to guide clinical management (207). Another approach was to calculate the score by using the results of a Gram stain of a BAL specimen or blind protected telescoping catheter sample, and score the findings as either positive or negative. Using this approach, the CPIS for patients with confirmed VAP was significantly higher than the value for nonconfirmed VAP (201).

If a clinical strategy is used, reevaluation of the decision to use antibiotics based on serial clinical evaluations, by Day 3 or sooner, is necessary, because patients who are improving will have signs of a good clinical response by this time point (193, 208). Singh and coworkers have shown that some patients with a low clinical suspicion of VAP (CPIS of 6 or less) can have antibiotics safely discontinued after 3 days, if the subsequent course suggests that the probability of pneumonia is still low (207). The modified CPIS used by Singh and coworkers appears to be an objective measure to define patients who can receive a short duration of therapy.

Major points and recommendations for the clinical strategy.

1. A reliable tracheal aspirate Gram stain can be used to direct initial empiric antimicrobial therapy and may increase the diagnostic value of the CPIS (**Level II**) (191, 199, 201, 209).
2. A negative tracheal aspirate (absence of bacteria or inflammatory cells) in a patient without a recent (within 72 hours) change in antibiotics has a strong negative predictive value (94%) for VAP and should lead to a search for alternative sources of fever (**Level II**) (203).
3. The presence of a new or progressive radiographic infiltrate plus at least two of three clinical features (fever greater than 38°C, leukocytosis or leukopenia, and purulent secretions) represent the most accurate clinical criteria for starting empiric antibiotic therapy (**Level II**) (187).
4. If a clinical strategy is used, reevaluation of the decision to use antibiotics based on the results of semiquantitative lower respiratory tract cultures and serial clinical evaluations, by Day 3 or sooner, is necessary (**Level II**) (193, 205, 207, 208).
5. A modified CPIS of 6 or less for 3 days, proposed by Singh and coworkers, is an objective criterion to select patients at low risk for early discontinuation of empiric treatment of HAP, but still requires validation in patients with more severe forms of VAP (**Level I**) (201, 207).

Bacteriologic Strategy

The bacteriologic strategy uses quantitative cultures of lower respiratory secretions (endotracheal aspirates, BAL or PSB speci-

mens collected with or without a bronchoscope) to define both the presence of pneumonia and the etiologic pathogen. Growth above a threshold concentration is required to diagnose VAP/HAP and to determine the causative microorganism(s). Growth below the threshold is assumed to be due to colonization or contamination. The bacteriologic strategy has been used to guide decisions about whether to start antibiotic therapy, which pathogens are responsible for infection, which antimicrobial agents to use, and whether to continue therapy.

Because the bacteriologic approach emphasizes avoidance of the problem of overtreatment with antibiotics by trying to separate colonizing from infecting pathogens, use of this method has consistently led to finding fewer microorganisms growing above the diagnostic threshold than are present in nonqualitative cultures of tracheal aspirates. When therapy decisions have been based on these data, fewer patients have been treated with antibiotics, and a potentially narrower spectrum of therapy was used, compared with the clinical approach (198, 210). Quantitative cultures have been demonstrated to have good diagnostic utility for the presence of pneumonia, especially in patients with a low or equivocal clinical suspicion of infection (211, 212).

The major concern with the bacteriologic approach is that a false negative culture can lead to a failure to treat either a specific patient or a specific pathogen, and that the results are not always consistent and reproducible (213–215). A major factor causing false negative quantitative cultures is a recent starting of or change in antibiotic therapy, especially in the preceding 24 hours, but up to 72 hours (192, 212). Therefore, ideally all quantitative cultures should be obtained before any antibiotic manipulation. This may not be possible in all situations, and in this setting a change in the diagnostic threshold may be helpful (212). For BAL, use of a threshold 10-fold lower than usual may avoid some false negative results in patients given antibiotics before testing. However, some patients with pneumonia will have culture growth below threshold, even without recent antibiotic changes, especially in early forms of infection (215–217).

Methodologic issues involved in the inconsistent results of published studies have been summarized in a meta-analysis (184). These include the evaluation of patients who did not meet recognized clinical criteria for the presence of pneumonia; prolonged time between the performance of a diagnostic test and the collection of confirmatory histopathologic information; inclusion of patients who had received antibiotic therapy before diagnostic testing, often without correcting for the duration of antibiotic therapy; and inclusion of patients studied by BAL performed with insufficient lavage volume (less than 140 ml). A major problem with all studies of HAP diagnosis is the absence of a "gold standard" with which diagnostic results can be compared. Even the best criteria for the presence of pneumonia, immediate postmortem histologic evaluation with microbiologic confirmation of infection, can be inaccurate. In addition, only a subgroup of patients with severe VAP is included in these types of studies.

In a prospective study of 148 patients receiving mechanical ventilation and in whom infectious pneumonia was suspected, Gibot and coworkers used a rapid immunoblot technique on BAL fluid, and found that levels of soluble triggering receptor expressed on myeloid cells (sTREM-1) were the strongest independent predictor of pneumonia (odds ratio, 41.5) (218). When commercially available, this marker, coupled with the classic clinical criteria and results of microbiologic cultures, may be a valuable tool with which to increase the specificity and maintain the sensitivity of HAP diagnosis (197).

Histologic data have demonstrated several characteristics of VAP pertinent to diagnostic testing, such as the finding that the process is often multifocal, frequently involving both lungs, generally in the posterior and lower segments (191, 215, 216). Postmortem studies have also demonstrated that VAP is often in multiple different phases of evolution at different sites at the same time (216). Prior antibiotic therapy can influence the number of bacteria found in lung tissue, and patients who have died in spite of prolonged therapy are likely to have organisms resistant to the agents used, whereas patients started on therapy within 24 (and up to 72) hours may have negative cultures, especially if the therapy is adequate (192). The multifocal nature of VAP suggests that BAL and endotracheal aspirates can provide more representative samples than the protected specimen brush (PSB), which samples only a single bronchial segment. Because of the diffuse bilateral nature of VAP and predominance in dependent lung segments, "blind" BAL and PSB may be as accurate as bronchoscopic sampling in some patients (219).

Another issue with the bacteriologic strategy is that culture results are not available immediately. Ancillary tests such as Giemsa stain for intracellular microorganisms, Gram stain, or differential cell counts can be used to increase the likelihood of a subsequent positive culture and can be used to guide the need for antibiotic therapy before culture results. In some studies, this approach has led to less use of antibiotics with no adverse outcomes, and a tendency to improved mortality (198, 201). Not all investigators agree about the safety of withholding therapy until quantitative results are available, and are positive, or to withdrawing therapy if cultures are negative, after empirically starting antimicrobials for suspected infection (198, 220–222). Clinically, these decisions have been guided by the degree of certainty of the diagnosis of pneumonia at the time of testing (pretest probability), and on the severity of illness of the patient (198). Thus, most investigators agree that patients with signs of infection, who are clinically unstable, should receive therapy, regardless of the initial bronchoscopic findings (198, 212).

The diagnostic threshold to discriminate infection from colonization varies with the technique used, and possibly by the clinical probability of infection (212). The threshold may be lowered if the patient has recently had a change in antibiotic therapy or if the probability of infection is high. Endotracheal aspirates can be cultured quantitatively, and with a threshold of 10^6 cfu/ml or more the sensitivity of this method for the presence of pneumonia has varied from 38 to 82%, with a mean of 76 ± 9%, and with a specificity ranging from 72 to 85%, with a mean of 75 ± 28% (209).

Bronchoscopic BAL studies have typically used a diagnostic threshold of 10^4 or 10^5 cfu/ml. Samples contaminated by upper airway secretions, as reflected by a high percentage of squamous epithelial cells, should be used with caution. A few studies have shown the technique to be reproducible, but not all bacteria are recovered above the diagnostic threshold when the procedure has been repeated in the same patient at the same site (223). An evidence-based review of 23 prospective studies of BAL in suspected VAP showed a sensitivity of 42–93%, with a mean of 73 ± 18% (186), and a specificity of 45–100%, with a mean of 82 ± 19%. In 12 studies, the detection of intracellular organisms in 2–5% of recovered cells was used to diagnose pneumonia, with a mean sensitivity of 69 ± 20% and a specificity of 75 ± 28% (186). The advantage of looking for intracellular organisms is the ability to obtain information of high predictive value in a rapid time frame, without waiting for the results of cultures to define the presence of pneumonia, although not the specific identity of the etiologic pathogen.

Quantitative cultures of PSB samples have used a diagnostic threshold of 10^3 cfu/ml or more. The quality of the PSB sample is difficult to measure, and the reproducibility is not exact, with as many as 25% of results on different sides of the diagnostic threshold, when comparing two samples collected from the same site in the same patient (183). The sensitivity and specificity range

from 33 to 100% (mean, 66 ± 19%) and from 50 to 100% (mean, 90 ± 15%). PSB appears to be more specific than sensitive for the presence of pneumonia, and a positive result greatly increases the likelihood of pneumonia being present (186).

The bacteriologic strategy does require specialized laboratory and clinical skills. In many clinical settings, bronchoscopy is not immediately available, especially in the evenings, and the collection of blind, nonbronchoscopic samples is an appealing alternative. Blind sampling can be done by BAL or PSB, or a blind bronchial suction sample can be taken. When BAL samples are obtained nonbronchoscopically, the threshold varies by technique and may be different from that of bronchoscopic BAL. The sensitivities of blind bronchial suction, blind mini-BAL, and blind PSB are 74–97, 63–100, and 58–86%, respectively (224). The specificity of these methods has varied from 74 to 100% for blind bronchial suction, from 66 to 96% for mini-BAL, and from 71 to 100% for blind PSB. In general, these techniques provide data similar to those of samples collected bronchoscopically, although with a trend toward more cultures above the diagnostic threshold. Side effects should be no greater and possibly less than with bronchoscopically collected samples.

Recommendation for the bacteriologic strategy. Quantitative cultures can be performed on endotracheal aspirates or samples collected either bronchoscopically or nonbronchoscopically, and each technique has its own diagnostic threshold and methodologic limitations. The choice of method depends on local expertise, experience, availability, and cost (**Level II**) (197, 198, 214, 224).

Recommended Diagnostic Strategy

To date, several decision analyses, one retrospective study, and four prospective studies have evaluated the impact of diagnostic strategies on the use of antibiotics and the outcomes of patients with suspected VAP (198, 211, 212, 220–222, 225). In three randomized single-center studies, no differences in mortality were found when invasive techniques (PSB and/or BAL) were compared with either quantitative or semiquantitative endotracheal aspirate culture techniques (220–222). However, these studies included few patients (51, 76, and 88, respectively) and antibiotics were continued in all patients, even those with negative cultures, thereby negating one of the potential advantages of the bacteriologic strategy. In fact, several prospective studies have concluded that antibiotics can be safely stopped in patients with negative quantitative cultures, with no adverse impact on mortality (15, 198, 226).

One large, prospective randomized trial did show an advantage to the quantitative bronchoscopic approach, when compared with a clinical approach in a multicenter study of 413 patients suspected of having HAP (198). Compared with patients managed clinically, those receiving invasive management had a lower mortality rate on Day 14 (16 and 25%; $p = 0.02$), but not on Day 28, and lower mean sepsis-related organ failure assessment scores on Days 3 and 7 ($p = 0.04$). At 28 days, the quantitative culture group had significantly more antibiotic-free days (11 ± 9 versus 7 ± 7 days; $p < 0.001$), but only a multivariate analysis showed a significant difference in mortality (hazard ratio, 1.54; 95% confidence interval, 1.10 to 2.16; $p = 0.01$). One strength of the study was that a high percentage of patients in both arms received adequate initial antibiotics, although more patients in the invasive group received adequate therapy than in the clinical group, and the impact of this difference on the observed mortality differences was uncertain. Another important consequence of quantitative culture results was that the presence of clinical signs of infection in patients with negative cultures was often an indication that an extrapulmonary site of infection was present. This study clearly showed that the quantitative approach could be applied safely, leading to less antibiotic use, and potentially reducing mortality. In the trial, about 10% of the patients managed with a quantitative strategy received antibiotic therapy regardless of bronchoscopic findings because of the presence of clinical instability and signs of sepsis.

Considering the available methods for diagnostic testing and the goals of using appropriate therapy in a timely manner, without overusing antibiotics, the committee has combined features of the clinical and bacteriologic approach into an algorithm shown in Figure 1. The decision to discontinue antibiotics, using this algorithm, may differ depending on the type of respiratory tract sample that is collected and whether the culture results are reported in quantitative or semiquantitative terms. Advocates of the bacteriologic approach support the discontinuation of antibiotics in clinically stable patients whose quantitative culture results of deep lung samples (BAL or PSB) fall below a diagnostic threshold. The utility of quantitative endotracheal aspirates for this decision is not as well defined. Advocates of the clinical strategy generally make a decision about antibiotic discontinuation based on the clinical course of the patient, supplemented by data from either quantitative or semiquantitative cultures from a lower respiratory tract sample, which could include an endotracheal aspirate, as well as a BAL or PSB sample.

Major Points and Recommendations for Comparing Diagnostic Strategies

1. A patients with suspected VAP should have a lower respiratory tract sample sent for culture, and extrapulmonary infection should be excluded, as part of the evaluation before administration of antibiotic therapy (**Level II**) (198).
2. If there is a high pretest probability of pneumonia, or in the 10% of patients with evidence of sepsis, prompt therapy is required, regardless of whether bacteria are found on microscopic examination of lower respiratory tract samples (**Level II**) (197, 198).
3. Diagnostic techniques that identify etiologic pathogens on the basis of qualitative cultures will lead to therapy for more organisms than diagnostic techniques based on quantitative cultures (**Level I**) (198, 220–222).
4. Semiquantitative cultures of tracheal aspirates cannot be used as reliably as quantitative cultures to define the presence of pneumonia and the need for antibiotic therapy (**Level I**) (198, 220–222).
5. If bronchoscopic sampling is not immediately available, nonbronchoscopic sampling can reliably obtain lower respiratory tract secretions for quantitative cultures, which can be used to guide antibiotic therapy decisions (**Level II**) (224).
6. The use of a bronchoscopic bacteriologic strategy has been shown to reduce 14-day mortality, compared with a clinical strategy, in one study of suspected VAP (**Level I**) (198).
7. Delays in the initiation of appropriate antibiotic therapy can increase the mortality of VAP and thus therapy should not be postponed for the purpose of performing diagnostic studies in patients who are clinically unstable (**Level II**) (37, 111, 198).

ANTIBIOTIC TREATMENT OF HOSPITAL-ACQUIRED PNEUMONIA

General Approach

Once the clinical decision has been made to initiate therapy, the overall approach to therapy for suspected HAP is shown in

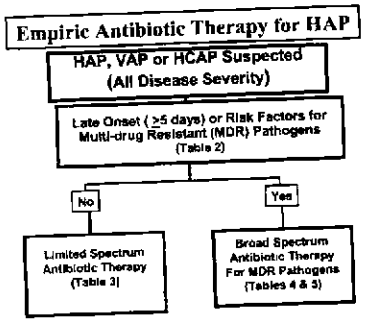

Figure 2. Algorithm for initiating empiric antibiotic therapy for hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and healthcare-associated pneumonia (HCAP).

Figure 2. Antibiotic selection for each patient should be based on the risk factors for MDR pathogens summarized in Table 2. The algorithms shown in Figures 1 and 2 provide the pathways for selection of appropriate antibiotics for the initial management of HAP, VAP, and HCAP on the basis of time of onset of disease and risk for MDR pathogens, as outlined in Tables 3 and 4. The adequate dosing of antibiotics for empiric therapy for MDR pathogens is summarized in Table 5. Broad-spectrum empiric antibiotic therapy should be accompanied by a commitment to deescalate antibiotics, on the basis of serial clinical and microbiologic data, to limit the emergence of resistance in the hospital.

The antimicrobial spectrum of activity, effective doses of antibiotics, pharmacokinetic profiles, adverse effects of individual antimicrobials, and the role of monotherapy were carefully reviewed by the consensus committee. Whenever possible, antibiotic recommendations were based on well-designed, controlled clinical trials, but when such data were not available, then the spectrum of activity, pharmacokinetic data, and reported clinical experience were taken into account. These initial empiric therapy recommendations require modification based on knowledge of the predominant pathogens in any specific clinical setting and the local patterns of antibiotic susceptibility. In addition, once the results of respiratory tract and blood cultures become available, therapy can often be focused or narrowed (i.e., de-escalation) on the basis of the identity of specific pathogens and their susceptibility to specific antibiotics (Figure 1). The algorithm shown in Figure 2 will lead to many patients receiving an initial broad-spectrum therapy, because risk factors for MDR pathogens are common, and thus it is important to use serial clinical evaluations and microbiologic data to deescalate therapy whenever possible.

Initial Empiric Antibiotic Therapy

The key decision in initial empiric therapy is whether the patient has risk factors for MDR organisms. Previously, the time of onset of HAP was used to classify patients as either "early onset" or "late onset," depending on whether the infection began within the first 4 days of hospitalization or later (5). However, many patients are admitted after a recent hospitalization or from a healthcare-associated facility (nursing home, dialysis center, etc.). These patients should be classified as at risk for MDR pathogens, regardless of when in the time course of the current hospitalization the pneumonia begins. Healthcare-associated infections are bacteriologically similar to hospital-acquired infections (4, 6, 43, 227). HCAP is defined by a positive respiratory tract culture, obtained within 48 hours of hospital admission, in a patient who has the criteria listed in Table 2 (43). Most patients with HCAP are at risk for infection with MDR organisms, but in studies of HAP and VAP, hospitalization for at least 5 days is required to increase the risk of infection with these organisms (21, 103).

One of the consequences of increasing antimicrobial resistance is an increased probability of inappropriate initial empiric antimicrobial treatment of infections (228). Inappropriate antimicrobial treatment represents the use of antibiotics with poor or no *in vitro* activity against the identified microorganisms causing infection at the tissue site of infection (e.g., empiric treatment with nafcillin for pneumonia subsequently documented to be MRSA). Because delays in the administration of appropriate therapy have been associated with excess hospital mortality from HAP (37, 111, 112, 229, 230), the prompt administration of empiric therapy for patients likely to have VAP is essential. Alvarez-Lerma showed that, among 490 episodes of pneumonia acquired in the ICU setting, 214 episodes (43.7%) required modification of the initial antibiotic regimen due to either isolation of a resistant microorganism (62.1%) or lack of clinical response to therapy (36.0%) (204). Attributable mortality from HAP was significantly lower among patients receiving initial appropriate antibiotic treatment compared with patients requiring a treatment change (16.2 versus 24.7%; $p = 0.034$).

Iregui and coworkers also documented an adverse outcome with initially delayed appropriate antimicrobial therapy in 107 patients with VAP and examined factors leading to such delays (112). Thirty-three (30.8%) patients received appropriate antibiotic treatment that was delayed 24 hours or more after patients initially met diagnostic criteria for VAP, often because of a delay in physician recognition of the presence of VAP and writing the orders for antimicrobial treatment ($n = 25$; 75.8%). Patients receiving delayed antimicrobial treatment had greater hospital

TABLE 3. INITIAL EMPIRIC ANTIBIOTIC THERAPY FOR HOSPITAL-ACQUIRED PNEUMONIA OR VENTILATOR-ASSOCIATED PNEUMONIA IN PATIENTS WITH NO KNOWN RISK FACTORS FOR MULTIDRUG-RESISTANT PATHOGENS, EARLY ONSET, AND ANY DISEASE SEVERITY

Potential Pathogen	Recommended Antibiotic*
Streptococcus pneumoniae†	Ceftriaxone
Haemophilus influenzae	*or*
Methicillin-sensitive *Staphylococcus aureus*	Levofloxacin, moxifloxacin, or ciprofloxacin
Antibiotic-sensitive enteric gram-negative bacilli	*or*
Escherichia coli	Ampicillin/sulbactam
Klebsiella pneumoniae	*or*
Enterobacter species	Ertapenem
Proteus species	
Serratia marcescens	

* *See* Table 5 for proper initial doses of antibiotics.

† The frequency of penicillin-resistant *S. pneumoniae* and multidrug-resistant *S. pneumoniae* is increasing; levofloxacin or moxifloxacin are preferred to ciprofloxacin and the role of other new quinolones, such as gatifloxacin, has not been established.

TABLE 4. INITIAL EMPIRIC THERAPY FOR HOSPITAL-ACQUIRED PNEUMONIA, VENTILATOR-ASSOCIATED PNEUMONIA, AND HEALTHCARE-ASSOCIATED PNEUMONIA IN PATIENTS WITH LATE-ONSET DISEASE OR RISK FACTORS FOR MULTIDRUG-RESISTANT PATHOGENS AND ALL DISEASE SEVERITY

Potential Pathogens	Combination Antibiotic Therapy*
Pathogens listed in Table 3 and MDR pathogens *Pseudomonas aeruginosa* *Klebsiella pneumoniae* (ESBL$^+$)† *Acinetobacter* species†	Antipseudomonal cephalosporin (cefepime, ceftazidime) *or* Antipseudomonal carbepenem (imipenem or meropenem) *or* β-Lactam/β-lactamase inhibitor (piperacillin–tazobactam) *plus* Antipseudomonal fluoroquinolone† (ciprofloxacin or levofloxacin) *or* Aminoglycoside (amikacin, gentamicin, or tobramycin) *plus*
Methicillin-resistant *Staphylococcus aureus* (MRSA) *Legionella pneumophila*†	Linezolid or vancomycin‡

* *See* Table 5 for adequate initial dosing of antibiotics. Initial antibiotic therapy should be adjusted or streamlined on the basis of microbiologic data and clinical response to therapy.

† If an ESBL$^+$ strain, such as *K. pneumoniae*, or an *Acinetobacter* species is suspected, a carbepenem is a reliable choice. If *L. pneumophila* is suspected, the combination antibiotic regimen should include a macolide (e.g., azithromycin) or a fluoroquinolone (e.g., ciprofloxacin or levofloxacin) should be used rather than an aminoglycoside.

‡ If MRSA risk factors are present or there is a high incidence locally.

TABLE 5. INITIAL INTRAVENOUS, ADULT DOSES OF ANTIBIOTICS FOR EMPIRIC THERAPY OF HOSPITAL-ACQUIRED PNEUMONIA, INCLUDING VENTILATOR-ASSOCIATED PNEUMONIA, AND HEALTHCARE-ASSOCIATED PNEUMONIA IN PATIENTS WITH LATE-ONSET DISEASE OR RISK FACTORS FOR MULTIDRUG-RESISTANT PATHOGENS

Antibiotic	Dosage*
Antipseudomonal cephalosporin	
Cefepime	1–2 g every 8–12 h
Ceftazidime	2 g every 8 h
Carbepenems	
Imipenem	500 mg every 6 h or 1 g every 8 h
Meropenem	1 g every 8 h
β-Lactam/β-lactamase inhibitor	
Piperacillin–tazobactam	4.5 g every 6 h
Aminoglycosides	
Gentamicin	7 mg/kg per d†
Tobramycin	7 mg/kg per d†
Amikacin	20 mg/kg per d†
Antipseudomonal quinolones	
Levofloxacin	750 mg every d
Ciprofloxacin	400 mg every 8 h
Vancomycin	15 mg/kg every 12 h‡
Linezolid	600 mg every 12 h

* Dosages are based on normal renal and hepatic function.

† Trough levels for gentamicin and tobramycin should be less than 1 μg/ml, and for amikacin they should be less than 4–5 μg/ml.

‡ Trough levels for vancomycin should be 15–20 μg/ml.

mortality compared with patients without the delay (69.7 versus 28.4%; $p < 0.001$). Delays in the administration of appropriate antibiotic treatment have also been associated with greater mortality for patients with severe sepsis, and with greater hospital costs and lengths of stay for patients with VAP (231, 232). A consistent factor leading to delays in appropriate therapy in these studies is the presence of resistant organisms, once again emphasizing the need to anticipate these pathogens in the selection of initial therapy in at-risk patients (205, 228).

Changing antimicrobial therapy once culture results are available may not reduce the excess risk of hospital mortality associated with inappropriate initial antibiotic therapy treatment (37, 204, 233). Therefore, selection of initial appropriate therapy (i.e., getting the antibiotic treatment right the first time) is an important aspect of care for hospitalized patients with serious infections. The regimens and adequate doses listed in Table 5 are therefore directed at the pathogens commonly associated with inappropriate initial empiric antimicrobial therapy. The most common pathogens include *P. aeruginosa*, *Acinetobacter* species, *K. pneumoniae*, *Enterobacter* species, and MRSA (37, 111, 204, 228–230, 233). Patients at risk for infection with these organisms should initially receive a combination of agents that can provide a broad spectrum of coverage to minimize the potential for inappropriate antibiotic treatment. In the therapy of suspected pseudomonal infection, therapy should involve a selected β-lactam plus either an antipseudomonal quinolone or an aminoglycoside. The choice of agents should be based on local patterns of antimicrobial susceptibility, and anticipated side effects, and should also take into account which therapies patients have recently received (within the past 2 weeks), striving not to repeat the same antimicrobial class, if possible.

For the initial antimicrobial therapy regimen to account for local bacteriologic patterns, each hospital and each ICU should ideally have their own antibiogram, which is updated as often as possible. Variability in the microorganisms associated with hospital-acquired infections among hospitals, as well as within the wards of large hospitals, has been demonstrated to occur (41, 234). In addition, changing temporal patterns of nosocomial pathogens and antimicrobial susceptibility have been described (235). Having current, and frequently updated, knowledge of such data can increase the likelihood that appropriate initial antibiotic treatment will be prescribed (205, 235).

When patients at risk for infection with MDR pathogens are identified, empiric therapy should be with agents that are known to be effective against these organisms. Trouillet and coworkers found that 57% of 135 consecutive episodes were caused by "potentially resistant" organisms (21). According to logistic regression analysis, three variables predicted potentially drug-resistant bacterial etiology for VAP: duration of mechanical ventilation, 7 days or more (odds ratio, 6.0); prior antibiotic use (odds ratio, 13.5); and prior use of broad-spectrum drugs (third-generation cephalosporin, fluoroquinolone, and/or a carbapenem) (odds ratio, 4.1). Of 15 different antimicrobial regimens, the combination of a carbapenem, amikacin, and vancomycin provided the broadest *in vitro* coverage against the spectrum of bacteria found in their ICU. Ibrahim and coworkers found that initial coverage for *P. aeruginosa* and methicillin-resistant *S. aureus* (MRSA), the two most common pathogens causing VAP in their ICU, required combination antimicrobial treatment with vancomycin, a carbapenem, and a fluoroquinolone to provide *in vitro* coverage for more than 90% of all the bacterial isolates (205). These studies suggest that each ICU should collect similar data to establish its own "best empiric therapy regimen," tailored to the antibiotic susceptibility patterns of the local flora.

If patients develop HAP during or shortly after antibiotic treatment for a different infection, the empiric therapy should probably involve an agent from a different antibiotic class. Recent exposure to a class of antibiotics can predict subsequent resistance to a variety of agents, usually to the same class but occasionally to other classes of agents as well (236).

Protocols for initial empiric therapy have emerged as a potentially effective means of avoiding unnecessary antibiotic administration while increasing the likelihood of initially appropriate therapy. The potential benefits of antibiotic therapy guidelines, through the use of a computerized system guiding antibiotic choice based on knowledge of local microbiology and general pharmacologic principles, have been demonstrated (113). This system reduced inappropriate empiric antibiotic administration compared with individual physician prescribing practices (237). Use of the automated guideline also significantly reduced orders for drugs to which patients were allergic, reduced overall adverse antibiotic-related events, reduced the total number of antiinfective doses prescribed, as well as reduced the medical costs associated with antimicrobial agents (113).

Nonautomated or partially automated protocols, often driven by hospital-based quality improvement teams, have also demonstrated efficacy. Bailey and coworkers randomized patients in two teaching hospitals to have their physicians contacted by pharmacists with consensus recommendations to discontinue intravenous antibiotics versus no intervention (238). The intervention significantly reduced antibiotic doses administered and mean antibiotic costs but was associated with increased labor costs. Similarly, Leibovici and coworkers developed a problem-oriented database decision support system that significantly reduced the unnecessary use of antibiotics and decreased inappropriate antibiotic administration, particularly to patients infected with multidrug-resistant gram-negative isolates, enterococci, and *S. aureus* (239).

Ibrahim and coworkers compared the management of 50 patients with VAP in a time period without an antibiotic protocol with 52 patients with VAP who were managed by an ICU-specific protocol (205). The protocol-directed therapy required initial intravenous combination antimicrobial treatment with vancomycin, imipenem, and ciprofloxacin. The guideline also required that after 48 hours antibiotic treatment be modified on the basis of the available culture results. De-escalation was achieved in 61.5% of patients. An additional feature of the protocol was an attempt to limit therapy to a 7-day course of appropriate antibiotic(s) for patients with VAP. Administration of antimicrobials beyond Day 7 was recommended only for patients with persistent signs and symptoms consistent with active infection (e.g., fever greater than 38.3°C, circulating leukocyte count greater than 10,000 mm^{-3}, lack of improvement on the chest radiograph, continued purulent sputum). Use of the guideline was associated with a statistically significant increase in the administration of appropriate antimicrobial treatment and a decrease in the development of secondary episodes of antibiotic-resistant VAP. A significant reduction in the total duration of antimicrobial treatment to 8.1 ± 5.1 days from 14.8 ± 8.1 days ($p < 0.001$) was achieved.

Major points and recommendations for initial antibiotic therapy.

1. Use the algorithm in Figure 2 to select an initial empiric therapy based on the absence or presence of risk factors for MDR pathogens (Tables 2–4) (**Level III**). These risk factors include prolonged duration of hospitalization (5 days or more), admission from a healthcare-related facility, and recent prolonged antibiotic therapy (**Level II**) (21, 43).
2. Choice of specific agents should be dictated by local microbiology, cost, availability, and formulary restrictions (**Level II**) (41, 205, 234).
3. Patients with healthcare-related pneumonia should be treated for potentially drug-resistant organisms, regardless of when during the hospital stay the pneumonia begins (**Level II**) (43).
4. Inappropriate therapy (failure of the etiologic pathogen to be sensitive to the administered antibiotic) is a major risk factor for excess mortality and length of stay for patients with HAP, and antibiotic-resistant organisms are the pathogens most commonly associated with inappropriate therapy (**Level II**) (228).
5. In selecting empiric therapy for patients who have recently received an antibiotic, an effort should be made to use an agent from a different antibiotic class, because recent therapy increases the probability of inappropriate therapy and can predispose to resistance to that same class of antibiotics (**Level III**) (236).
6. Initial antibiotic therapy should be given promptly because delays in administration may add to excess mortality resulting from VAP (**Level II**) (37, 112, 231, 232).
7. Initial empiric therapy is more likely to be appropriate if a protocol for antibiotic selection is developed on the basis of the recommendations in Tables 2–4, but adapted to local patterns of antibiotic resistance, with each ICU collecting this information and updating it on a regular basis (**Level II**) (205).

Appropriate Antibiotic Selection and Adequate Dosing

Optimal outcome in patients with HAP can best be achieved with the combination of appropriate initial therapy (the etiologic organism is sensitive to the therapeutic agent) and an adequate therapy regimen. To achieve adequate therapy, it is necessary not only to use the correct antibiotic, but also the optimal dose and the correct route of administration (oral, intravenous, or aerosol) to ensure that the antibiotic penetrates to the site of infection, and to use combination therapy if necessary. In the management of VAP, it is important to use doses of antibiotics that have been shown in clinical trials to have efficacy. Thus, for the empiric therapy of severe VAP, the correct doses of commonly used agents for patients with normal renal function are shown in Table 5 (240–247).

Pharmacodynamic properties of specific antibiotics should also be considered in selecting an adequate dosing regimen. Some antibiotics penetrate well and achieve high local concentrations in the lung whereas others do not. For example, most β-lactam antibiotics achieve less than 50% of their serum concentration in the lung, whereas fluoroquinolones and linezolid equal or exceed their serum concentration in bronchial secretions (5, 248). The relevance of these findings to outcomes in therapy remains to be defined.

The mechanism of action of certain agents can also affect dosing regimens, efficacy, and toxicity. Some antimicrobials are bactericidal whereas others are bacteriostatic. Even among the bactericidal agents, several mechanisms of killing can be present. Agents such as the aminoglycosides and quinolones are bactericidal in a concentration-dependent fashion, killing more rapidly at high concentrations. Other agents, such as vancomycin and the β-lactams, are also bactericidal, but in a more time-dependent fashion, with the degree of killing dependent on the time that the serum concentration is above the organism's minimal inhibitory concentration (MIC). Another difference is that some antibiotics have a "postantibiotic effect" (PAE), which means that these agents are able to suppress bacterial growth even after the antibiotic level falls below the MIC of the organism (5, 249, 250). With gram-negative bacilli, a prolonged PAE occurs with the use of aminoglycosides and quinolones. No PAE, or a short PAE against gram-negative bacilli, is seen with β-lactam antibiotics. One exception is the carbepenem antibiotics (imipenem or meropenem), which have shown a post-antibiotic effect against gram-negative bacilli such as *P. aeruginosa* (5, 251).

These pharmacodynamic effects lead to drug-specific dosing regimens. The β-lactams, with minimal concentration-dependent killing and a limited postantibiotic effect, are most effective if levels stay above the MIC of the infecting organism for as long as possible

(247). This requires frequent dosing, or even continuous infusion. On the other hand, quinolones and aminoglycosides can be dosed less often because of the prolonged postantibiotic effect. In addition, because of their concentration-dependent killing mechanism, efficacy may be improved by using a regimen that maximizes initial serum concentrations. Combining an entire day of therapy into a single daily (every 24 hours) dose can take advantage of both the concentration-dependent killing mechanism and the postantibiotic effect. This type of dosing regimen has been applied to the aminoglycosides to maximize efficacy and minimize toxicity, but clinical trials have produced conflicting results about the success of achieving these goals (252).

All patients with HAP and VAP should initially receive therapy intravenously, but conversion to oral/enteral therapy may be possible in certain responding patients. The quinolones and linezolid have oral formulations with bioavailability equivalent to the intravenous form, and this may facilitate conversion to oral therapy in patients with a good clinical response (below) and intact gastrointestinal tract function. Studies with quinolones have shown that early step-down to oral therapy is safe and effective (253, 254).

Local Instillation and Aerosolized Antibiotics

Local instillation or aerosolization is a way to enhance antibiotic penetration to the lower respiratory tract. In the past, the agents most commonly administered and studied in this fashion have been the aminoglycosides and polymyxin B (255, 256). Only a single prospective randomized trial has examined the impact of the adjunctive use of locally instilled tobramycin with intravenous therapy in the treatment of VAP (256). Although the addition of endotracheal tobramycin did not improve clinical outcome compared with placebo, microbiologic eradication was significantly greater in the patients receiving aerosolized antibiotics. The small number of patients in this study suggests that more data are needed on this type of therapy before determining its value.

Aerosolized antibiotics may also be useful to treat microorganisms that, on the basis of high MIC values, are "resistant" to systemic therapy. Anecdotal reports have appeared of patients with VAP due to MDR *P. aeruginosa* that is unresponsive to systemic antibiotics, but who have improved with the addition of aerosolized aminoglycosides or polymyxin B (255). Concern about aerosolized antibiotics leading to an increased risk of pneumonia due to resistant microorganisms was raised when these agents were used as prophylaxis, not as therapy (257). One side effect of aerosolized antibiotics has been bronchospasm, which can be induced by the antibiotic or the associated diluents present in certain preparations. The committee believed that further investigation into the use of aerosolized antibiotics is warranted.

Combination versus Monotherapy

Combination therapy is common practice in the therapy of suspected and proven gram-negative HAP. The commonly cited reason to use combination therapy is to achieve synergy in the therapy of *P. aeruginosa*. However, synergy has been clearly documented to be valuable only *in vitro* and in patients with neutropenia or bacteremic infection, which is uncommon in VAP (5, 258). The *in vitro* finding of synergy has been inconsistently demonstrated, and has been difficult to show as being clinically relevant (258, 259).

Combination regimens have also been recommended as a method to prevent the emergence of resistance during therapy, a common phenomenon when *P. aeruginosa* is treated with a variety of single agents and when *Enterobacter* is treated with third-generation cephalosporins (240, 260). Prevention of this type of antibiotic resistance by combination therapy has not been well documented (261). A metaanalysis has evaluated all prospective randomized trials of β-lactam monotherapy compared with β-lactam–aminoglycoside combination regimens in patients with sepsis, of whom at least 1,200 of the reported 7,586 patients had either HAP or VAP (262). In this evaluation, clinical failure was more common with combination therapy and there was no advantage in the therapy of *P. aeruginosa* infections, compared with monotherapy. In addition, combination therapy did not prevent the emergence of resistance during therapy, but did lead to a significantly higher rate of nephrotoxicity.

However, in spite of these data, another reason to use combination therapy, especially for the patients treated according to the regimens in Table 4, is to provide a broad-spectrum empiric regimen that is likely to include at least one drug that is active against the often MDR etiologic agent(s). Combination therapy should include agents from different antibiotic classes to avoid antagonism of therapeutic mechanisms. For gram-negatives, regimens usually involve combinations of two drugs from the β-lactam, quinolone, or aminoglycoside classes. Although quinolones can penetrate into the lung better than aminoglycosides and have less potential for nephrotoxicity, a trend toward improved survival has been seen with aminoglycoside-containing, but not with quinolone-containing, combinations (259). In some studies, combination therapy has been continued for less than the full course of therapy, with discontinuation of the aminoglycoside after 5 days if the patient is improving (235).

Monotherapy should be used when possible because combination therapy is often expensive and exposes patients to unnecessary antibiotics, thereby increasing the risk of MDR pathogens and adverse outcomes. Patients who develop nosocomial pneumonia with no risk factors for drug-resistant organisms are likely to respond to monotherapy with the antibiotics listed in Table 3. Monotherapy is also the standard when gram-positive HAP, including MRSA, is documented. Monotherapy with ciprofloxacin has been successful in patients with mild HAP (defined as a CPIS of 6 or less) but is less effective in severe HAP (207, 240). Agents that have been shown to be effective as monotherapy in patients with moderately severe HAP not due to MDR pathogens include ciprofloxacin, levofloxacin, imipenem, meropenem, cefepime, and piperacillin–tazobactam (240, 242–247). For monotherapy, these agents must be dosed optimally, as discussed above. To use monotherapy in patients with severe VAP, the committee believed that patients should initially receive combination therapy as described in Table 4, but therapy could be focused to a single agent if lower respiratory tract cultures did not demonstrate a resistant pathogen (205).

Duration of Therapy

Efforts to reduce the duration of therapy for VAP are justified by studies of the natural history of the response to therapy. Dennesen and colleagues demonstrated that when VAP was caused by *H. influenzae* and *S. pneumoniae*, the organisms could be rapidly eradicated from tracheal aspirates, whereas Enterobacteriaceae, *S. aureus*, and *P. aeruginosa* persisted despite *in vitro* susceptibility to the antibiotics administered (193). Significant improvements were observed for all clinical parameters, generally within the first 6 days of the start of antibiotics. The consequence of prolonged therapy to 14 days or more was newly acquired colonization, especially with *P. aeruginosa* and Enterobacteriaceae, generally during the second week of therapy. Luna and coworkers, using serial CPIS measurements, found that patients who survived VAP after receiving adequate therapy tended to have a clinical improvement by Days 3–5, especially reflected by improved Pa_{O_2}/FI_{O_2} ratio, whereas nonresponding patients did not have such a response during the same time period (208). These data support the premise that most patients with VAP, who receive appropriate antimicrobial therapy, have a good clinical response within the first 6 days. Prolonged therapy

simply leads to colonization with antibiotic resistant bacteria, which may precede a recurrent episode of VAP.

Reducing the duration of therapy in patients with VAP has led to good outcomes with less antibiotic use with a variety of different strategies. Singh and coworkers used a modification of the CPIS system to identify low-risk patients (CPIS of 6 or less) with suspected VAP who could be treated with 3 days of antibiotics as opposed to the conventional practice of 10 to 21 days of antibiotic therapy (207). Patients receiving the shorter course of antibiotic therapy had better clinical outcomes than patients receiving longer therapy, with fewer subsequent superinfections attributed to antibiotic-resistant pathogens, although many of these patients may not have had pneumonia. A multicenter, randomized, controlled trial demonstrated that patients who received appropriate, initial empiric therapy of VAP for 8 days had outcomes similar to those of patients who received therapy for 14 days (210). A trend to greater rates of relapse for short-duration therapy was seen if the etiologic agent was *P. aeruginosa* or an *Acinetobacter* species.

Major Points and Recommendations for Optimal Antibiotic Therapy

1. Empiric therapy of patients with severe HAP or VAP requires the use of antibiotics at optimal doses, to ensure maximum efficacy (**Level I**) (240, 242–247). Initial therapy should be administered to all patients intravenously, with a switch to oral/enteral therapy in selected patients with a good clinical response and a functioning intestinal tract. Highly bioavailable agents, such as the quinolones and linezolid, may be easily switched to oral therapy in such patients (**Level II**) (248, 253, 254).
2. Aerosolized antibiotics have not been proven to have value in the therapy of VAP (**Level I**) (256). However, they may be considered as adjunctive therapy in patients with MDR gram-negatives who are not responding to systemic therapy (**Level III**) (255).
3. Combination therapy should be used if patients are likely to be infected with MDR pathogens (**Level II**) (21, 205). No data have documented the superiority of this approach compared with monotherapy, except to enhance the likelihood of initially appropriate empiric therapy (**Level I**) (262).
4. If patients receive combination therapy with an aminoglycoside-containing regimen, the aminoglycoside can be stopped after 5–7 days in responding patients (**Level III**) (235).
5. Monotherapy with selected agents can be used for patients with severe HAP and VAP in the absence of resistant pathogens (**Level I**) (240, 242–247). Patients in this risk group should initially receive combination therapy until the results of lower respiratory tract cultures are known and confirm that a single agent can be used (**Level II**).
6. If patients receive an initially appropriate antibiotic regimen, efforts should be made to shorten the duration of therapy from the traditional 14 to 21 days to periods as short as 7 days, provided that the etiologic pathogen is not *P. aeruginosa*, and that the patient has a good clinical response with resolution of clinical features of infection (**Level I**) (210).

Specific Antibiotic Regimens

Although initial therapy is empiric, it may be possible on the basis of the recommendations in Tables 3 and 4, modified by knowledge of local microbiologic data, to choose a specific agent when an etiologic pathogen is identified. Recommended empiric therapy and optimal doses appear in Table 5. The choice of specific agents will be dictated by the results of sensitivity testing, the availability of these agents, and issues of cost and formulary restriction. Four MDR pathogens merit special discussion.

Pseudomonas aeruginosa. *P. aeruginosa* has the capacity to readily develop resistance to all known classes of antibiotics, and resistance can develop in 30–50% of patients currently receiving monotherapy, but no data show that this problem can be avoided by the use of combination therapy (240, 261). Cross-infection is also a serious problem and the antibiotics given to adjacent patients may affect the risk for infection with an antibiotic-resistant strain. As mentioned, the benefits of combination therapy are unclear, with the only data supporting this practice coming from a study of *P. aeruginosa* bacteremia (few of which were due to pneumonia) which showed that patients receiving combination therapy were less likely to die (258). A prospective study of an aminoglycoside added to a carbapenem did not show improved outcome or a difference in the rate of developing resistance during therapy, when compared with monotherapy with a carbapenem (261). In another prospective trial, combination therapy with a β-lactam and twice-daily aminoglycosides demonstrated an unacceptable 39% success rate for patients with VAP due to *P. aeruginosa* (263). A metaanalysis evaluating the addition of an aminoglycoside to β-lactam monotherapy showed no benefit for treatment of *P. aeruginosa* in patients with sepsis (262).

All the studies of combination therapy have used an aminoglycoside with a β-lactam, but none have used single daily dosing of the aminoglycoside, nor have they used the maximal effective dose. Whereas a quinolone could be an alternative to an aminoglycoside, with the theoretic advantage of improved respiratory tract penetration, no prospective study has compared a fluoroquinolone-based combination therapy with β-lactam monotherapy. If a quinolone is used in combination therapy for *P. aeruginosa*, ciprofloxacin or levofloxacin may be used on the basis of *in vitro* activity, but should be used only if local susceptibility data show activity of these agents. This remains a problem, because a significant fall in *P. aeruginosa* sensitivity to quinolones resulted with widespread use of these agents in hospital (264, 265). In these reports, levofloxacin had been used at a dosage of 500 mg/day and the impact of using higher dosages (750 mg daily) on resistance patterns is unknown (243). As mentioned, some anecdotal experience has suggested a value of aerosolized antibiotics as an adjunct to systemic therapy in patients with highly resistant *P. aeruginosa* pneumonia (255).

Acinetobacter *species*. The antibiotic armamentarium for treatment of *Acinetobacter* is limited because of native resistance to many classes of antibiotics. The most consistently effective antibiotics are the carbapenems, the sulbactam component of ampicillin–sulbactam, and the polymyxins. Although no randomized trial has been performed, a case series publication has demonstrated equivalent rates of clinical cure in a trauma surgery population with ampicillin–sulbactam compared with imipenem, including patients with imipenem-resistant isolates (56). The emergence of carbapenem-resistant clones suggests that optimal doses of carbapenems should be used. The significant nephrotoxicity of the polymyxins limits widespread intravenous use, but there are reports of efficacy with acceptable toxicity, and these agents can also be used as aerosolized therapy (255, 266). Susceptibility to aminoglycosides is variable and penetration may limit the delivery of adequate tissue levels of antibiotics, suggesting a possible role for aerosol delivery of these agents for selected patients with *Acinetobacter* pneumonia. One report has documented the efficacy and safety of colistin in patients with *Acinetobacter* VAP that was not susceptible to carbapenems (266). Colistin therapy led to a clinical cure in 57% of patients, and none had prolonged neuromuscular blockade as a side effect of therapy.

***Extended spectrum β-lactamase–producing* Enterobacteriaceae.** The hallmark of ESBL-producing Enterobacteriaceae is a variable response to cephalosporins and thus third-generation agents should be avoided as monotherapy when these pathogens are suspected or isolated (267). In particular, a third-generation cephalosporin should not be used for *Enterobacter* species because of the documented high frequency of resistance developing on therapy (260). Use of the fourth-generation cephalosporin cefepime for this infection is controversial and the safety of using cefepime in patients previously exposed to third-generation cephalosporins is not well documented (267, 268). A reliable choice is a carbapenem, which is generally active against these organisms (269). Because these microorganisms are also likely to demonstrate resistance to aminoglycosides and fluoroquinolones, the benefit of combination therapy is uncertain. Piperacillin–tazobactam has been used for the treatment of VAP, but the its efficacy against ESBL$^+$ organisms is uncertain and should be used with caution and at adequate doses (Table 5) (270). In a prospective analysis of in-hospital mortality associated with VAP, Fowler and coworkers found that use of an antipseudomonal penicillin with a β-lactamase inhibitor for VAP was associated with a lower risk of death (hazard ratio, 0.41; 95% confidence interval, 0.21–0.80; p = 0.009) than when other antibiotics were used (259).

***Methicillin-resistant* Staphylococcus aureus.** Although vancomycin has been the accepted standard of therapy for this pathogen, both industry-sponsored clinical trials and studies from individual centers have consistently reported clinical failure rates of 40% or greater with a standard dose (1 g every 12 hours) of vancomycin for MRSA pneumonia (271–273). Combination therapy with other agents, such as rifampin (274), aminoglycosides, and others, has been tried but no prospective clinical data have documented the value of this approach. Retrospective pharmacokinetic modeling has suggested that the vancomycin failures may be related to inadequate dosing (272). Many physicians have therefore tried to achieve a trough concentration 15 mg/L or more, but no prospective clinical data have shown the value of this practice. The use of continuous vancomycin infusions has not been shown to be clearly advantageous compared with twice-daily dosing (275).

Two new agents for serious gram-positive infections have been studied in patients with MRSA pneumonia. A prospective randomized trial of quinupristin–dalfopristin for gram-positive nosocomial pneumonia found worse clinical success rates than with vancomycin for MRSA HAP (271). In contrast, two large multicenter trials of linezolid demonstrated equivalence to vancomycin in patients with HAP (241, 276). When the two studies were combined and analyzed by multivariate techniques, linezolid was found to have a significant association with both clinical cure and lower mortality, especially for patients with VAP due to MRSA (241). This advantage may be due to the higher penetration of linezolid into the epithelial lining fluid than with vancomycin (248, 277). However, optimal dosing of vancomycin may not have been achieved in all patients, and prospective confirmation of these results is needed.

Although the superiority of linezolid over vancomycin for VAP due to MRSA still needs further validation, linezolid may be preferred in several clinical settings. In patients at risk for, or already with, renal insufficiency, physicians have a strong tendency to underdose vancomycin, Dosing vancomycin in patients with fluctuating renal function is difficult and requires frequent monitoring of levels. The presence of renal insufficiency was a significant predictor of vancomycin failure in a multivariate analysis of patients with VAP (241). A related concern is an increased risk of nephrotoxicity in patients with MRSA pneumonia who are receiving vancomycin along with other nephrotoxic medications, particularly aminoglycosides (275, 278, 279).

Antibiotic Heterogeneity and Antibiotic Cycling

Antibiotic cycling or rotation has been advocated as a potential strategy for reducing the emergence of antimicrobial resistance (280). In theory, a class of antibiotics or a specific antibiotic is withdrawn from use for a defined time period and reintroduced at a later point in time in an attempt to limit bacterial resistance to the cycled antimicrobial agents.

When outbreaks of infection with a specific strain of resistant bacteria have occurred, restricted access to specific antibiotics has successfully managed the problem, with generally no impact on the overall frequency of resistance (281). However, if disproportionate use of another antibiotic results, resistance rates may be affected. Rahal and coworkers restricted use of third-generation cephalosporins to combat an outbreak of ESBL$^+$ *Klebsiella* infections (281). Restriction of cephalosporins was accompanied by a 44% reduction in infection and colonization with the ESBL$^+$ *Klebsiella*. However, the use of imipenem increased by 140% during the intervention year and was associated with a 69% increase in the incidence of imipenem-resistant *P. aeruginosa* throughout the medical center. The clinical benefit of shifting resistance from one pathogen to another was uncertain.

Gerding and colleagues evaluated cycling of aminoglycosides over 10 years at the Minneapolis Veterans Affairs Medical Center, cycling amikacin and gentamicin (282). Using cycle times of 12 to 51 months, these investigators found significantly reduced resistance to gentamicin when amikacin was used. Return of resistance with the rapid reintroduction of gentamicin occurred whereas subsequent, more gradual reintroduction of gentamicin occurred without increased levels of resistance. This experience suggests that cycling of antibiotics within the same drug class, in some circumstances, could be an effective strategy for curbing antimicrobial resistance.

Kollef and coworkers examined the influence of a scheduled change in the preferred antibiotic for empiric therapy of infection on the incidence of nosocomial infections in a cardiac surgical ICU (283). A 6-month-before period, during which the traditional practice was to use ceftazidime for the empiric treatment of gram-negative bacterial infections, was followed by a 6-month-after period, during which ciprofloxacin was substituted. Unexpectedly, the overall incidence of VAP was significantly reduced in the after period, primarily as the result of a significant reduction in the incidence of VAP attributed to antibiotic-resistant gram-negative bacteria. Similarly, a lower incidence of antibiotic-resistant gram-negative bacteremia was also observed in the after period. This experience was followed by a series of scheduled antibiotic changes for the treatment of suspected gram-negative bacterial infections among patients admitted to the medical and surgical ICUs (284). The consequence of this policy was an overall improvement in the prescription of appropriate antimicrobial therapy as MDR infections decreased.

Gruson and colleagues observed a reduction in the incidence of VAP after introducing an antimicrobial program that consisted of supervised rotation and restricted use of ceftazidime and ciprofloxacin (235). The antibiotic selection was based on monthly reviews of the pathogens isolated from the intensive care unit and their antibiotic susceptibility patterns. They observed a decrease in the incidence of VAP, primarily because of a reduction in the number of episodes attributed to antibiotic-resistant gram-negative bacteria including *P. aeruginosa*, *B. cepacia*, *S. maltophilia*, and *Acinetobacter baumannii*. Their initial results could be sustained over a 5-year time period (285).

Major points and recommendations for selected MDR pathogens.

1. If *P. aeruginosa* pneumonia is documented, combination therapy is recommended. The principal justification is the high frequency of development of resistance on monotherapy (240). Although combination therapy will not necessarily prevent the development of resistance, combination therapy is more likely to avoid inappropriate and ineffective treatment of patients (**Level II**) (205).
2. If *Acinetobacter* species are documented to be present, the most active agents are the carbapenems, sulbactam, colistin, and polymyxin. There are no data documenting an improved outcome if these organisms are treated with a combination regimen (**Level II**) (56, 266).
3. If ESBL$^+$ Enterobacteriaceae are isolated, then monotherapy with a third-generation cephalosporin should be avoided. The most active agents are the carbapenems (**Level II**) (267).
4. Adjunctive therapy with an inhaled aminoglycoside or polymyxin for MDR gram-negative pneumonia should be considered, especially in patients who are not improving with systemic therapy (**Level III**) (255). More studies of this type of therapy are needed.
5. Linezolid is an alternative to vancomycin for the treatment of MRSA VAP and may be preferred on the basis of a subset analysis of two prospective randomized trials (**Level II**) (241, 276, 286). This agent may also be preferred if patients have renal insufficiency or are receiving other nephrotoxic agents, but more data are needed (**Level III**).
6. Antibiotic restriction can limit epidemics of infection with specific resistant pathogens. Heterogeneity of antibiotic prescriptions, including formal antibiotic cycling, may be able to reduce the overall frequency of antibiotic resistance. However, the long-term impact of this practice is unknown (**Level II**) (284, 285).

RESPONSE TO THERAPY

Modification of Empiric Antibiotic Regimens

Empiric antibiotics may need modification once the results of blood or respiratory tract cultures become available (Figure 1). Modification may be necessary if a resistant or unsuspected pathogen is found in a nonresponding patient. Alternatively, therapy can be deescalated or narrowed if an anticipated organism (such as *P. aeruginosa* or an *Acinetobacter* species) was not recovered or if the organism isolated is sensitive to a less broad-spectrum antibiotic than was used in the initial regimen.

Critical to the routine use of any of the proposed empiric antibiotic regimens is the ability to recognize when a patient is not responding appropriately. Unfortunately, little information about the natural course of HAP resolution is available. In addition, because of the unreliability in diagnosing the infection, the natural history of presumed HAP may differ, depending on what disease process is actually present in a given patient. Clinical response may also be related to patient factors (such as age and comorbidity), bacterial factors (such as antimicrobial resistance patterns and virulence), and other events that may occur during the course of HAP.

Defining the Normal Pattern of Resolution

Resolution of HAP can be defined either clinically or microbiologically. Clinical end points such as improvement, resolution, delayed resolution, relapse, failure, and death can be defined (287). Using this approach, clinical improvement usually becomes apparent after the first 48–72 hours of therapy and, therefore, the selected antimicrobial regimen should not be changed during this time unless progressive deterioration is noted or initial microbiologic studies so dictate (208, 287).

Appropriate respiratory tract cultures can be used to define microbiologic resolution. Using serial cultures, end points can be defined, such as bacterial eradication, superinfections (infection with a new organism), recurrent infection (elimination, then return, of original organism), or microbiologic persistence. Serial quantitative microbiologic studies of lower respiratory tract secretions can also define resolution end points (193). In one such study, repeat PSB samples collected 72 hours after starting therapy were used to define the bacteriologic response to therapy. The results of these microbiologic evaluations were compared with the clinical outcome (288). When the follow-up PSB sample showed no growth or less than 10^3 cfu/ml, a clinical therapeutic failure occurred only 7% of the time, whereas a finding of greater than 10^3 cfu/ml (microbiologic failure to eradicate) was associated with clinical failure in 55.8% of the patients. At present, use of early recognition of a microbiologic nonresponse to modify therapy has not been prospectively studied.

Chest radiographs are of limited value for defining clinical improvement in severe pneumonia, and initial radiographic deterioration is common, especially among patients who are bacteremic or who are infected with highly virulent organisms. In addition, radiographic improvement often lags behind clinical parameters, especially in the elderly and in individuals with coexisting disease (e.g., chronic obstructive pulmonary disease) (208). However, the finding of a rapidly deteriorating radiographic pattern, with a follow-up chest radiograph showing progression to multilobar involvement, a greater than 50% increase in the size of the infiltrate within 48 hours, development of cavitary disease, or significant pleural effusion, should raise concern (5).

Clinical parameters including the white blood cell count and measures of oxygenation and core temperature have been used in several studies to define the normal pattern of resolution of HAP. Dennesen and coworkers demonstrated that, among patients treated with initial appropriate antibiotic therapy, clinical improvement in these parameters occurred progressively during the first week of antibiotic treatment (193). Little further improvement in fever, white blood cell count, or the Pa_{O_2}/FI_{O_2} ratio occurred beyond 7 days of antibiotic treatment. Similarly, Luna and coworkers used changes in the CPIS as a measure of resolution or deterioration among patients with VAP, rather than its traditional application as a tool with which to diagnose pneumonia (208). Improvement in the CPIS occurring during the first 3 days of empiric treatment was associated with hospital survival whereas a lack of improvement in the CPIS predicted mortality. Inappropriate antibiotic treatment of VAP was also associated with a lack of clinical improvement in the CPIS, particularly in serial measurements of arterial oxygenation.

Reasons for Deterioration or Nonresolution

There are several possible causes for rapid deterioration or failure to improve. These include the possibility that the process being treated is not pneumonia or that certain host, bacterial, and therapeutic (antibiotic) factors have not been considered (Figure 3).

Many noninfectious processes may be mistakenly labeled as HAP, including atelectasis, congestive heart failure, pulmonary embolus with infarction, lung contusion (in trauma patients), and chemical pneumonitis from aspiration. Patients with ARDS can have fibroproliferative diffuse alveolar damage, whereas any mechanically ventilated patient can have pulmonary hemorrhage (195, 289). In one series, 26 of 69 ventilated patients with new lung infiltrates had pulmonary hemorrhage at autopsy, sometimes in association with pneumonia (195).

Host factors associated with a failure to improve during em-

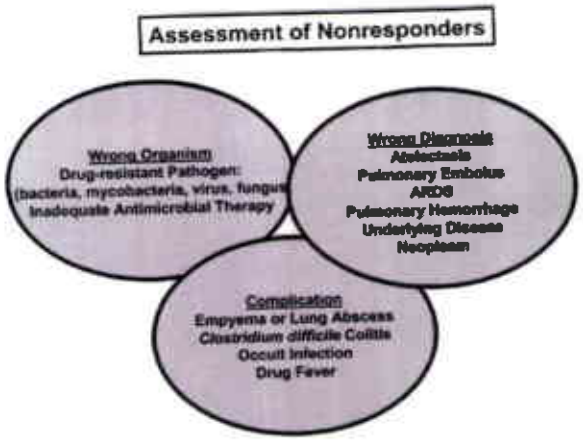

Figure 3. Possible causes for lack of clinical response to initial antibiotic therapy include the wrong organism, the wrong diagnosis, or other complications. ARDS = adult respiratory distress syndrome.

piric therapy include the presence of any condition that is known to increase mortality. These include prolonged mechanical ventilation, respiratory failure, an underlying fatal condition, age greater than 60 years, bilateral radiographic infiltrates, prior antibiotic therapy, prior pneumonia (i.e., the current episode represents superinfection), and/or chronic lung disease (12, 13, 287, 290).

Bacterial variables can also be associated with an adverse outcome of initial therapy. The infecting pathogen can be resistant at the outset to the chosen antibiotic or can acquire resistance during therapy, particularly *P. aeruginosa* treated with a single agent (240). Some organisms are inherently difficult to eradicate, even with effective therapy (288). In one study of *P. aeruginosa* pneumonia in an ICU, 20 of 34 patients survived an initial episode of infection. However, among the survivors, recurrent infection developed, as defined by clinical, radiographic, and bacteriologic criteria, in 50% (291). Certain types of infection are associated with a poor outcome, especially those with gram-negative bacilli, polymicrobial flora, or bacteria that have acquired antibiotic resistance (10, 290). In patients who are mechanically ventilated, superinfection with *P. aeruginosa* or *Acinetobacter* species has a particularly high mortality, approaching 90% in some series (292). Finally, pneumonia can be due to other pathogens (i.e., *Mycobacterium tuberculosis*, fungi, or respiratory viruses) or an unusual bacterial pathogen not included in the initial empiric regimen. In addition, some patients can have clinically unrecognized immunosuppression (e.g., acquired immunodeficiency syndrome), and unrecognized *Pneumocystis carinii* pneumonia may be a cause of nonresponse to therapy.

Certain complications during therapy can also lead to an apparent failure in response to therapy. Some patients with HAP can have other sources of fever simultaneously, particularly sinusitis, vascular catheter-related infection, pseudomembranous enterocolitis, or urinary tract infections (109, 293). Complications of the original pneumonia can also lead to failure, including development of lung abscess or empyema. Other considerations for persistent fever or pulmonary infiltrates include drug fever, sepsis with multiple system organ failure, or pulmonary embolus with secondary infarction.

Evaluation of the Nonresponding Patient

For patients who are deteriorating rapidly or not responding to initial therapy (Figures 1 and 3), it may be necessary to broaden antimicrobial coverage while awaiting the results of cultures and other diagnostic studies. An aggressive evaluation is required for this type of individual, starting with a careful differential diagnosis and a repeat sampling of lower respiratory tract secretions for culture and antimicrobial sensitivity patterns. This can be done by collecting an endotracheal aspirate if the patient is intubated, or by a bronchoscopic procedure with quantitative cultures for both intubated and nonintubated patients. Even though patients in this clinical setting are receiving antibiotics, the recovery by invasive methods of organisms at high concentrations is possible and may indicate that infection with a resistant organism is present (192). If cultures show a resistant or unusual pathogen, therapy can be modified appropriately. If cultures do not show a resistant or unsuspected pathogen, then consideration of a noninfectious process or of one of the complicating problems discussed previously is appropriate. This necessitates the changing of vascular access catheters and the culturing of blood, catheter line tips that have been removed, and urine, as well as other easily accessible sites.

Specialized radiologic procedures may be helpful in identifying anatomic reasons for failure. Lateral decubitus chest radiographs, ultrasound, or computerized tomographic scanning may reveal pleural fluid, which should be evaluated to exclude empyema. In addition, computerized tomographic scanning can separate pleural fluid from parenchymal disease and can demonstrate parenchymal abscesses, adenopathy, and pulmonary masses. Computerized tomographic scanning of extrathoracic sites may also help to identify other areas of infection, and particular attention should be focused on the abdomen in patients who have ARDS (294). One commonly infected site in patients with nasotracheal or nasogastric tubes in place is the sinuses, and computerized tomographic scanning can identify opacification or the presence of an air–fluid level in the sinuses. When these findings are present, sinus aspiration and culture may be necessary and may define the presence of infection, which can often coexist with HAP (109). Evaluation for pulmonary embolus may be needed for selected patients because pulmonary infarction can be confused with pneumonia.

If this microbiologic and radiographic evaluation is negative, a decision should be made concerning whether to observe the patient while either continuing or empirically changing antibiotics or to perform an open lung biopsy to obtain the diagnosis of an unusual pathogen or of a noninfectious illness that mimics pneumonia. There is debate about the value of open lung biopsy in nonimmunosuppressed patients with suspected HAP, VAP, or HCAP. The available evidence does not suggest a clear outcome benefit, and therefore the decision must be individualized. Bronchoscopy that demonstrates no unusual or resistant organisms, along with an aggressive but unrevealing search for extrapulmonary infectious foci, should be performed before performing an open lung biopsy. Even if bronchoscopic cultures and other diagnostic testing are not helpful, the decision to perform an open biopsy should be guided by the patient's clinical status. If there has been slow but progressive improvement, close observation alone may be the most appropriate course.

If the patient remains hemodynamically stable but does not show evidence of clinical improvement, and bronchoscopic and radiologic evaluations are unrevealing, an alteration in antibiotics or initiation of antiinflammatory therapy (corticosteroids) may be appropriate before proceeding with an open biopsy. However, if the patient deteriorates early (within the first 48–72 hours of therapy) or has initially improved but then deteriorates, additional antibiotics directed at resistant or "unusual" bacteria can be added while doing aggressive radiographic and microbiologic evaluations.

Major Points and Recommendations for Assessing Response to Therapy

1. A serial assessment of clinical parameters should be used to define the response to initial empiric therapy (**Level II**) (193, 208). Modifications of empiric therapy should be made on the basis of this information, in conjunction with microbiologic data (**Level III**).
2. Clinical improvement usually takes 48–72 hours, and thus therapy should not be changed during this time unless there is rapid clinical decline (**Level III**). Nonresponse to therapy is usually evident by Day 3, using an assessment of clinical parameters (**Level II**) (193, 208).
3. The responding patient should have de-escalation of antibiotics, narrowing therapy to the most focused regimen possible on the basis of culture data (**Level II**) (205).
4. The nonresponding patient should be evaluated for noninfectious mimics of pneumonia, unsuspected or drug-resistant organisms, extrapulmonary sites of infection, and complications of pneumonia and its therapy. Diagnostic testing should be directed to whichever of these causes is likely (**Level III**) (293).

SUGGESTED PERFORMANCE INDICATORS

1. Circulate HAP guidelines to appropriate medical staff (administrators for quality and safety, physicians, and nurses) for review.
2. Provide epidemiologic data on the prevalence and types of MDR pathogens in intensive care unit patients and current antibiograms, to select appropriate initial antibiotic therapy.
3. Select specific parts of the guideline for implementation by the medical and surgical services, including the intensive care units, and monitor compliance with the guidelines in relation to patient outcomes from HAP.
4. Identify modifiable risk factors for HAP, and develop programs to reduce the risk of pneumonia through changing these risk factors.

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Conflict of Interest Statement: M.J.B. received $5,000 for consultancy from Intrabiotics Pharmaceuticals, Inc. in 2003–2004, and his department received an unrestricted research grant of $30,000 from this company in 2003; J.C. received $14,000 in 2003–2004 for serving on an Advisory Board for Intrabiotics and has participated as a speaker in scientific meetings or courses organized and financed by various pharmaceutical companies (Pfizer, Wyeth, Brahms); W.A.C. received in 2001–2004 advisory committees/consultation fees of $5,500 from Bristol-Myers Squibb, $4,500 from Cubist Pharmaceuticals, $3,500 from GlaxoSmithKline, $3,000 from Bayer, $2,500 from Wyeth, and $2,000 from Pfizer/Pharmacia, and received research grants of $137,200 from GlaxoSmithKline, $108,000 from Sanofi-Aventis, $39,000 from Wyeth and $35,000 from Bayer; D.E.C. has received less than $3,000 per year for participating in the speaker's bureaus for Cubist, Merck, Elan, and Pfizer; J.-Y.F. has participated as a speaker in scientific meetings organized and financed by Pfizer and served on Advisory Boards for Intrabiotics and Wyeth; J.H. has served on Advisory Boards for Bayer, Lilly, Elan, and Pharmacia and has received less than $10,000 in speaker fees over the last three years for activities supported by Bayer, Pharmacia, and Ortho-Biotech; G.A.J. has received consultation or lecture fees from Bayer and Ortho-McNeil and grant support from Merck; M.H.K. has received honoraria for lectures from Pfizer, Elan, Bayer, Pharmacia, and Merck and has received an industry-sponsored research grant from Elan and has also served on the Advisory Boards of Pfizer, Elan, and Bayer; C.M.L. has received unrestricted and restricted research support and has participated as a speaker in scientific meetings or courses organized and/or financed by various pharmaceutical companies (Merck, Bayer, Pfizer, Bristol-Myers Squibb, Astra Zeneca, Aventis) and received $10,000 in 2003 and 2004 from AstraZeneca for participating in a multicenter clinical trial; L.A.M. received less than $10,000 over the last three years from Bayer, Pfizer, Osclent, Wyeth for advisory boards and speaker's bureaus and over $10,000 from Pfizer for speaker's bureau over the last three years and over $10,000 for research from Bayer, Pfizer, Ortho-McNeil, Aventis over the last three years; M.S.N. has served as a consultant or advisor over the past three years to Merck, Elan, Chiron, Pfizer, Bayer, AstraZeneca, and Wyeth-Ayerst and has also served as a lecturer over the past three years for Merck, Elan, Chiron, Pfizer, Bayer, AstraZeneca, Ortho-McNeil, and Wyeth-Ayerst and has also received research funding from Aerogen Pharmaceuticals and Bard Medical and has been a consultant for Aerogen in 2003 and 2004; A.T. received €900 for a conference given in a mini-symposium sponsored by GlaxoSmithKline, and in addition has participated on International Advisory Boards of Abbott (€2500), Aventis (€2000) and Bayer (€900) in the years 2003 and 2004; R.G.W. has received an Investigator-initiated research grant from Eli Lilly and Co. for $90,000 in 2003 and is a paid consultant to Pfizer Inc. (previously Pharmacia) and is on their speaker's bureau and has received approximately $6,000/year for the last three years and is a consultant to Mpex Pharmaceuticals, Peninsula Pharmaceuticals, Bayer, and Chiron Inc. and has spoken at scientific meetings and courses organized by Ortho-McNeil, WyethAyerst, and AstraZeneca.

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