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Introduction

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

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

General methodological limitations

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

Incidence

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

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

Microbiology

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

Attributable mortality and morbidity

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

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

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

Current state of knowledge and unresolved controversies

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

in the ICU, ICU-acquired pneumonia, and VAP are not available.

- Whether VAP really leads to an increased mortality can only be established by a prospective interventional study to prevent VAP.

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

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

Pathology of ICU-acquired pneumonia

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

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

Lessons from animal model

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

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

Pulmonary response to acute bacterial challenge

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

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

The systemic response to lung infection

Cytokine-mediated lung host defense

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

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

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

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

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

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

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

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

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

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

Current state of knowledge and unresolved controversies

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

There are still important controversies remaining:

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

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

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

Instrumentation

Presence of endotracheal tube (ETT)

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

Reintubation

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

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

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

Oro-/naso-gastric feeding tubes

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

Body position

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

Pharmacologic agents

Use of sedation/paralysis

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

Systemic antibiotic use

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

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

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

Gastric pH-raising drugs

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

Ventilator management

Circuit, humidifier, and suctioning management

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

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

Other factors

General preventive measures: hand washing and oral antiseptics

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

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

Physiotherapy

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

Subglottic secretion drainage

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

Current state of knowledge and unresolved controversies

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

posture, and long-term antibiotic use increase the risk of ICU-AP.

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

Question 4: diagnosis of ICU-acquired pneumonia

Sensitivity and specificity of clinical assessment

Clinical signs such as fevers (core temperature >38.3°C), leukocytosis (>10,000/mm³) or leukopenia (<5,000/mm³), purulent secretions, and the presence of a new and persistent radiographic infiltrate taken separately have limited value for the diagnosis of VAP [34, 43]. While chest radiographic findings are traditionally considered the cornerstone for diagnosing pneumonia, many patients have abnormal chest radiographs from causes other than pneumonia [139]. Moreover, there is poor interobserver agreement on the presence or absence of specific radiologic findings [140]. While CT scans detect infiltrates not seen on chest radiographs in one-third of the cases [23], the clinical importance of these small infiltrates is unknown.

In an attempt to simulate "clinical judgment," Pugin and colleagues combined information on body temperature, white blood cell count, volume and appearance of tracheal secretions, oxygenation, chest X-ray, and tracheal aspirate culture into a clinical pulmonary infection score (CPIS) (Table 1) [141]. A high CPIS value was predictive of a large number of bacteria in BAL fluid and diagnosed ventilator-associated pneumonia with a sensitivity and specificity of 72–85% and 85–91%, respectively [25, 142]. When this scoring system was incorporated in a clinical management algorithm, overall antibiotic use was substantially reduced [120]. The use of the CPIS is attractive because it is quantitative, and can define the pre-test probability of pneumonia. However, it, too, has several drawbacks. Its use is validated in only a small number of studies and relatively small numbers of patients [25, 141, 143], and its validity in ARDS patients is questionable. In the CPIS, several factors are subjective, so that the same patient might be judged to require or not need antibiotics by different observers. The appli-

cation of the CPIS does not follow the pattern of clinical logical reasoning. For example, all of the elements of the CPIS are given equal weighting. In practice, most clinicians would probably attribute greater importance to some features such as a new lobar infiltrate, while others, such as leukocytosis, would be considered non-specific. Finally, formal calculation of the CPIS is not widely used and could become complex if weighting factors are used.

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

Table 1 Clinical pulmonary infection score calculation. (*ARDS* acute respiratory distress syndrome, *CHF* congestive heart failure, *PaO₂/FiO₂* ratio of arterial oxygen pressure to fraction of inspired oxygen)

Temperature (°C)

>or equal to 36.5 and < or equal to 38.4 = 0 point
>or equal to 38.5 and < or equal to 38.9 = 1 point
>or equal to 39 and < or equal to 36 = 2 points

Blood leukocytes, mm³

>or equal to 4,000 and < or equal to 11,000 = 0 point
<4, 000 or >11,000 = 1 point + band forms > equal to 50%
= add 1 point

Tracheal secretions

Absence of tracheal secretions = 0 point
Presence of nonpurulent tracheal secretions = 1 point
Presence of purulent tracheal secretions = 2 points

Oxygenation: PaO_2/FiO_2, mmHg

>240 or ARDS (ARDS defined as PaO_2/FiO_2, or equal to 200, pulmonary arterial wedge pressure
<or equal to 18 mmHg and acute bilateral infiltrates) = 0 point
<or equal to 240 and no ARDS = 2 points

Pulmonary radiography

No infiltrate = 0 point
Diffuse (or patchy) infiltrate = 1 point
Localized infiltrate = 2 points

Progression of pulmonary infiltrate

No radiographic progression = 0 point
Radiographic progression (after CHF and ARDS excluded)
= 2 points

Culture of tracheal aspirate

Pathogenic bacteria cultured in rare or light quantity or no growth
= 0 point
Pathogenic bacteria cultured in moderate or heavy quantity
= 1 point
Same pathogenic bacteria seen on Gram stain, add 1 point

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

Interpretation of microbiologic data

Technical considerations

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

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

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

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

Effect of prior antibiotic therapy

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

Current state of knowledge and unresolved controversies

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

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

Question 5: optimal therapeutic approaches to ICU-acquired pneumonia

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

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

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

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

24-h laboratory support has limited the general acceptance of this method.

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

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

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

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

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

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

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

ing early signs of pneumonia which rapidly clear, or who have negative cultures despite persistent clinical signs of pneumonia.

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

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

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

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

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

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

Current state of knowledge and unresolved controversies

The decision to start antibiotics:

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

The decision to discontinue antibiotics 48–72 h later.

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

Other unresolved controversies:

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

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