Occasional reviews

Acute respiratory distress syndrome and nosocomial pneumonia

Torsten T Bauer, Antoni Torres

The acute respiratory distress syndrome (ARDS) and nosocomial pneumonia share aetiological, physiopathological, and diagnostic properties that justify consideration of the relationship between these two diseases. The aetiology of ARDS can be separated into direct and indirect lung injury. In cases with indirect lung injury such as necrotising pancreatitis the cause of the lung injury may not be readily apparent, whereas in direct lung injury due to aspiration of gastric contents or pneumonia the role of infection is more clear. Sloane and co-workers, in a series of 153 patients, reported pneumonia as the underlying aetiology in 31% of all patients who developed ARDS.[1] Furthermore, most patients with ARDS require mechanical ventilation which increases the risk of nosocomial pneumonia.[2–4] This report reviews recent studies on the prevalence, incidence, and impact of nosocomial pneumonia on outcome in patients with ARDS.

Prevalence

Data on the prevalence of nosocomial pneumonia causing ARDS are not readily available. Although post mortem studies have shown that nosocomial pneumonia can be diagnosed by lower respiratory tract sampling in combination with quantitative bacterial cultures—for example, endotracheal aspirates or protected specimen brush—the lack of a true gold standard decreases the validity of the interpretation in vivo.[5] In addition, to obtain reliable data on the prevalence of nosocomial pneumonia the microbiological and clinical data must be obtained within 24 hours of the onset of ARDS.

From 1995 to 1998 a total of 50 cases of ARDS were investigated with all required measurements at the University Hospital of Barcelona and the prevalence of nosocomial pneumonia in patients with ARDS was estimated to be 8% (four of 50). This figure included the coexistence of three conditions: (1) evolutionary and clinical criteria of ARDS,[6 7] (2) clinical criteria of pneumonia,[8] and (3) microbiological criteria of pneumonia.[9] It is noteworthy that colonisation of the lower airways in patients with ARDS (bacterial growth above the threshold without clinical signs of infection) was as high 28% (14/50). This is most probably caused by the long duration of prior mechanical ventilation in these

patients, an issue that will be addressed in more depth later in this review. Nevertheless, it has to be kept in mind that a prevalence of at least 8% should be subtracted from the incidence figures in the following section since these infections might already have been present at the onset of ARDS.

Incidence

Appreciation of the definitions and diagnostic methods used is important in interpreting the incidence of pneumonia. Initial data on the frequency of secondary nosocomial pneumonia in 103 patients with ARDS were presented by Seidenfeld and co-workers.[10] This study did not focus exclusively on the frequency of pneumonia and included other nosocomial infections (tables 1 and 2). Nosocomial pneumonia occurred in 56 of the 103 patients (54%); in 51 the major site of infection was the lung or pleura and in five others infection involved the lung.

Two clinical trials have been conducted to determine the incidence of nosocomial pneumonia more precisely. Lower respiratory tract specimens were cultured quantitatively and interpreted together with clinical criteria of pneumonia.[8 11] In a surveillance study of 306 patients with ARDS by Sutherland and co-workers[12] consecutive data were available from 105 patients. Samples obtained by protected specimen brush (PSB) or bronchoalveolar lavage (BAL) showed bacterial growth above the defined thresholds in 16 of the 105 patients (15%) during the 21 day surveillance period. The incidence of nosocomial pneumonia according to clinical criteria was 33% (35/105) and only four patients had both microbiological and clinical criteria (4%). Delclaux and co-workers investigated the incidence of both nosocomial pneumonia and lower respiratory tract colonisation in patients with ARDS.[13] Lower respiratory tract specimens were taken in addition to scheduled surveillance samples every 48–72 hours when clinical criteria for pneumonia were met. A plugged telescopic catheter (PTC) without bronchoscopic guidance was used for sampling, but additional bronchoscopically guided sampling was initiated in case of significant bacterial growth in PTC samples. The incidence of 60% was based on the agreement of microbiological and clinical criteria (18/30 patients). Lower respiratory tract colonisation, defined as bacterial growth below

Hospital Clinic I Provincial, Servei de Pneumologia I Al.lèrgia Respiratoria, Villarroel 170, E-08036 Barcelona, Spain
T T Bauer
A Torres

Correspondence to:
Dr A Torres.

the threshold or absence of clinical criteria in case of growth above the threshold, was found in 14 of the 30 patients (47%). These authors were the first to give an accurate figure for the incidence density related to the duration of mechanical ventilation (4.2/100 days).

A study by Meduri and co-workers used another type of study design to estimate the incidence of nosocomial pneumonia in patients with ARDS. Only those who already fulfilled the clinical criteria of nosocomial pneumonia were investigated using bronchoscopic bilateral BAL.[14] The timing of sampling and hence the incidence depends largely on the accuracy of the clinical criteria. The incidence of nosocomial pneumonia according to microbiological and clinical criteria was 43% in patients with ARDS (table 2). However, the primary objective of this study was to evaluate the diagnostic yield of bilateral BAL sampling and the incidence might have been biased by inclusion criteria. Chastre and co-workers sampled the lower respiratory tract only in the presence of clinical criteria of pulmonary infection and

included all patients admitted to the intensive care unit.[15] PSB and BAL were used for sampling and nosocomial pneumonia was assumed when microbiological and clinical criteria agreed (table 1). Of the 243 patients under study, 56 developed ARDS (23%) and the incidence of nosocomial pneumonia in this group was 55% (31/56). The incidence of nosocomial pneumonia in ARDS patients was significantly higher than in patients without ARDS (53/187, 28%). This seems to support a clinical belief that ARDS predisposes to pneumonia, a concept derived from a necropsy study that found a high rate of pneumonia (73%) in the lungs of patients on mechanical ventilation for ARDS.[16]

It has been reasoned that impaired defence mechanisms such as neutrophil function make patients with ARDS prone to pulmonary infection.[17 18] However, patients with ARDS in the study by Chastre and co-workers were also on mechanical ventilation nine days longer than control patients[15] and it has been shown that the incidence of nosocomial pneumonia

Table 1   Incidence of nosocomial pneumonia and ARDS: methods used

Authors	Study				Diagnosis of pneumonia	
	No. of patients	Inclusion criteria	Design	Mean (SD) MV	Clinical criteria	Sampling method
Seidenfeld et al[10]	129	ARDS	Observational for infections	—	1. Positive sputum culture 2. New radiographic infiltrates 3. Clinical evidence of infection	—
Sutherland et al[12]	105	ARDS	Surveillance, specimens on days 3, 7, 14, and 21	25[a]	1. Fever (>38.3°C, rectal) 2. Leucocytosis (>10 000/mm³) 3. Purulent sputum with bacterial growth or positive Gram stain 4. Focal radiographic infiltrate[b]	PSB, BAL
Delclaux et al[13]	30	ARDS	Surveillance, specimens taken every 48–72 h	19 (12)	1. Fever (≥38.3°C) 2. Leucocytosis (>10 000/mm³) 3. Increased volume or purulent sputum 4. Focal radiographic infiltrate[b]	PTC, BAL
Meduri et al[14]	111	ARDS and clinical criteria of pneumonia	Diagnostic comparison	23 (14)[c]	Fever (≥38.3°C) and at least one of the following: 1. New and persistent infiltrates in 2. The chest radiograph 3. Leucocytosis (>10 000/mm³) 4. Purulent tracheal aspiration	Bilateral BAL
Chastre et al[15]	56	MV ≥48 hours, ARDS identified during ICU stay	Observational, specimens taken on clinical suspicion of pneumonia	26 (26)	1. Clinical deterioration 2. Fever, or 3. Modification of chest radiograph	PSB, BAL, ICO

BAL = bronchoalveolar lavage; EA = endotracheal aspirate; MV = duration of mechanical ventilation during the study period; ICO = intracellular organisms; PSB = protected specimen brush; PTC = single-sheathed plugged telescopic catheter.
[a]No standard deviation given.
[b]At least three criteria for possible pneumonia; all four criteria for probable pneumonia.
[c]For all episodes.

Table 2   Incidence of nosocomial pneumonia and ARDS: synopsis of results

	Incidence of pneumonia				Antibiotics		Mortality	
	Clinical criteria n (%)	Microbiological criteria n (%)	Density (/1000 days MV)	Clinical and microbiological criteria n (%)	Frequency	Management	Overall n (%)	Infection vs no infection n (%)
Seidenfeld et al[10]	56/103 (54)	–	–	–	–	None	37/129 (29)	49/56 (88); 43/73 (56)
Sutherland et al[12]	35/105 (33)	16/105 (15)	6[a]	4/105 (4)	179/203 (88)[b]	Not reported	46/105 (44)	6/16 (38); 40/89 (45)
Delclaux et al[13]	Not given	18/30 (60)	42[c]	30/30 (100)	30/30 (100)	No changes prior to sampling	25/30 (83)	14/18 (78); 11/12 (92)
Meduri et al[14]	Not applicable	40/94 (43)	19[a]	40/94[d]	107/344 (31)[e]	Classification of antibiotic treatment[34]	(64)[f]	Not given
Chastre et al[15]	Not given	31/56 (55)	21[a]		29/31 (94)	No changes prior to sampling	54/56 (61)	16/31 (52); 18/25 (72)

[a]Figure estimated from mean duration of mechanical ventilation.
[b]Antimicrobial therapy during lavage (n = 203).
[c]Figure given.
[d]For all episodes.
[e]Figures for BAL examined and with antibiotics >48 hours.
[f]Crude mortality not given.

increases with the duration of mechanical ventilation.[19] The probability of nosocomial pneumonia was similar in patients with and without ARDS when Chastre and co-workers corrected their data for the duration of mechanical ventilation.[15] It therefore seems, at least from clinical data, that the high incidence of nosocomial pneumonia in ARDS patients is related to the length of mechanical ventilation rather than a predisposition to infection. However, a case-control study matched for the duration of mechanical ventilation would be desirable to investigate this issue further.

Microbiology

The type of causative micro-organisms is affected by the duration of mechanical ventilation prior to the onset of nosocomial pneumonia. Micro-organisms recovered from the lung in patients developing pneumonia after less than five days of mechanical ventilation are generally those similar to commensal oropharyngeal colonisation.[20] Tracheal intubation and the bypass of defence mechanisms are factors which facilitate bacterial growth during that period.[2 21] The micro-organisms found are usually Gram positive cocci such as *Staphylococcus aureus* and *Streptococcus pneumoniae* or Gram negative rods such as *Haemophilus influenzae*. After five days of mechanical ventilation the pathogenesis of nosocomial pneumonia becomes more complex and probably involves microaspiration of gastric contents (which at this time is no longer sterile) or translocation of bacteria from the intestine to the lungs.[22 23] Accordingly, the spectrum of recovered micro-organisms is shifted towards Gram negative rods such as *Escherichia coli* and *Klebsiella* spp and, especially if patients have been pretreated with antibiotics, to potentially drug resistant micro-organisms such as methicillin resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Acinetobacter* spp.[24 25]

All studies have reported finding bacteria predominantly from these two groups, which is in accordance with the long duration of mechanical ventilation in ARDS patients. Seidenfeld and co-workers reported *Pseudomonas aeruginosa* (17%), *Escherichia coli* (14%), and *Klebsiella* spp (12%) as the most common micro-organisms[10] and, in the series of patients studied by Sutherland and co-workers, *Pseudomonas* and *Acinetobacter* species were the most commonly identified Gram negative organisms. Gram positive cocci were also recovered frequently but the bacterial load was generally low.[12] The percentage of Gram negative organisms increased sharply from 23% on day 3 to more than 50% on subsequent days. These results were corroborated by Delclaux and co-workers who found 12 of 24 episodes of nosocomial pneumonia to be caused by *Pseudomonas aeruginosa* or *Acinetobacter baumanii*. Chastre and co-workers[15] identified methicillin-resistant *Staphylococcus aureus* (23%), non-fermenting Gram negative bacilli (*Pseudomonas aeruginosa*, *Acinetobacter baumanii*, and *Stenotrophomonas maltophilia*) (21%), and Enterobacteriaceae (21%), and these findings were confirmed by the microbiological results of Meduri and co-workers.[14]

Diagnosis of nosocomial pneumonia in patients with ARDS

The findings of these studies suggest that the incidence of nosocomial pneumonia in patients with ARDS ranges from 15% to 60% depending on the diagnostic criteria and tools employed. While the diagnostic criteria for ARDS are fairly homogeneous,[6 7] a wide range of diagnostic criteria have been used for the diagnosis of nosocomial pneumonia. All sampling methods have been subject to controversy and have been extensively reviewed elsewhere.[26–37] The lack of a true gold standard has been a central issue and a brief analysis of post mortem data may help to select the most adequate sampling method.

Fàbregas and co-workers examined histological specimens from lungs of patients who had been on mechanical ventilation for at least 48 hours[5] and found all stages of pneumonia disseminated in a multifocal heterogeneous pattern. A sampling method that covers large areas might therefore be most likely to identify bacterial growth. Wermert and co-workers showed in an animal model of pneumonia that the diagnostic yield was highest with endotracheal aspirates.[38] The diagnostic yield is also increased by the use of a method that assesses the bacterial burden of both lungs such as bilateral BAL.[14]

In addition, the incidence of nosocomial pneumonia is dependent on the accuracy of the clinical definition. However, a diagnosis of pneumonia in ARDS patients may be difficult even with standardised clinical criteria.[29] Fever, leucocytosis, or leucopenia may be present even in the absence of pulmonary infection in patients with ARDS.[10] Purulent secretions are of limited diagnostic value for nosocomial pneumonia as some mechanically ventilated patients develop purulent bronchitis, particularly during long periods of ventilation.[39] Rouby *et al* found that bronchiolitis without pneumonia was a not infrequent finding in mechanically ventilated patients.[40] In contrast, nosocomial pneumonia may be missed due to peripheral pneumonic foci which hinder the passage of secretions to the central airways. Chest radiography may not always reveal new infiltrates in patients with a condition that is already defined by bilateral condensations,[6] and computed tomographic scanning has only a modest accuracy for the diagnosis of pneumonia in patients with ARDS.[41]

Contributing role of prior antibiotic treatment

The yield of all microbiological methods is influenced by the use of previous antibiotic treatment. Wimberley and co-workers found that antibiotic treatment suppressed bacterial growth in culture[42] and higher bacterial counts were consistently found in patients who did not receive antibiotics.[43] This has led to the consensus that quantitative cultures of BAL fluid should not be done in patients who have received antibiotics during the preceding 48

hours.[34] There are two reasons why this strategy cannot be followed in studies of the prevalence or incidence of nosocomial pneumonia in ARDS patients. Firstly, patients who develop ARDS are in a serious medical condition following a long stay in hospital or the ICU. The likelihood that these patients received an antibiotic for a condition other than pulmonary infections at the onset of ARDS is high and withdrawal for diagnostic purposes is unjustified in most cases. Secondly, if microbiological sampling is scheduled by clinical criteria the patient may have already received antibiotics. Therefore, one accepted strategy in the diagnosis of nosocomial pneumonia is to maintain the type and dose of antibiotic drugs unchanged for at least three days before sampling.

All reported studies give information on their policy to antibiotic treatment except the early study by Seidenfeld and co-workers (table 2). In our study on the prevalence of nosocomial pneumonia in ARDS nearly all patients received antibiotics (48/50, 94%) but the bacterial recovery was only different in patients who had been on the same antibiotic treatment for more than seven days. Stratification of antibiotic use should be adopted in surveillance studies with fixed sampling intervals. However, this was not done in the study by Sutherland *et al* which may explain, in part, the low reported incidence (15% for microbiological criteria and 4% for microbiological and clinical criteria).[12] In the two surveillance studies by Delclaux and Chastre almost all patients (100% and 94%, respectively) received antibiotics during the course of ARDS, but no antibiotic was introduced or modified three days before sampling.[13] The authors attributed the higher incidence of nosocomial pneumonia in their series of patients (60% and 55%, respectively) at least in part to their strict antibiotic policy. Meduri and co-workers concluded that prior antibiotic treatment received for an earlier infection unrelated to the suspected pneumonia did not affect the diagnostic yield of BAL bacterial cultures[14] which has been shown earlier.[36 44] The contributing role of antibiotics in this type of study therefore remains to be defined.

Outcome
A controversial issue is the excess mortality caused by pneumonia in patients with ARDS. Whereas nosocomial pneumonia in patients without ARDS is clearly associated with a higher mortality,[24 45] no study to date has reported an increased mortality due to pulmonary infection or colonisation in patients with ARDS. One reason for this lack of evidence is probably the a priori high mortality in patients with ARDS. While recent developments in aggressive treatment of ARDS may lead to a lower mortality, it was as high as 83% in some series.[13 46] Seidenfeld and co-workers reported better survival in patients with ARDS in the absence of infection, but a subanalysis for pneumonia was not available.[10] Sutherland *et al* reported the lowest overall mortality (44%) but found no differences between patients with ARDS alone (40/89, 45%) and those with

ARDS and pneumonia (6/16, 38%).[12] Delclaux *et al* could not confirm that infection contributed to the mortality in their selected group of severely ill patients with ARDS (table 2).[13] Although pneumonia in patients without ARDS was associated with a higher mortality than in patients without pneumonia (47% vs. 28%, p = 0.001), the occurrence of nosocomial pneumonia did not influence overall mortality in patients with ARDS (table 2).[15] Because of the high mortality and the large number of contributing factors, case-control studies are needed to clarify the impact of nosocomial pneumonia on the mortality of patients with ARDS.[47]

Conclusions
The prevalence of nosocomial pneumonia complicated by ARDS is around 8% if microbiological and clinical criteria are taken into account. The incidence of pulmonary infection complicating ARDS varies with the study design, but an estimate that every second patient with ARDS will suffer at least one episode of pneumonia during the course of mechanical ventilation reflects clinical experience and data in reported studies. However, whether the higher incidence of nosocomial pneumonia in patients with ARDS is the consequence of an increased susceptibility to pulmonary infection or simply the effect of prolonged mechanical ventilation is uncertain.

In clinical practice a microbiological surveillance system seems to be justified because the incidence of nosocomial pneumonia during the course of ARDS is high and inadequate antibiotic treatment of nosocomial pneumonia is associated with a poor outcome.[48] An endotracheal aspirate is a possible adequate sampling method for this purpose since it is easy to perform, covers a large sampling area, and has low complication rates. In addition, the daily observation of sputum volume and degree of purulence together with changes in chest radiographs and gas exchange is mandatory to identify the clinical signs of pneumonia correctly. A scoring system such as the clinical pulmonary infection score may help to overcome problems associated with subjective judgement and staff rotation.[35 40] Respiratory tract sampling should be initiated as soon as the clinical diagnosis of nosocomial pneumonia becomes evident. Antibiotic treatment should be started immediately, either empirically[9] or guided by micro-organisms recovered in survey samples. The spectrum of the antibiotic drug can be adjusted to the microbiological results as they become available. Future case-control studies must clarify the so far unresolved question of whether an episode of nosocomial pneumonia further increases mortality in patients with ARDS.

Dr Bauer is a research fellow from the Medizinische Klinik, Abteilung für Pneumologie, Allergologie und Schlafmedizin,

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