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ARDS*

A Clinicopathological Confrontation

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Background: **The heterogeneity of populations meeting criteria for ARDS may explain in part why no specific treatment has yet been shown to decrease mortality. To define the pathologic alterations associated with the syndrome, particularly the typical pattern of diffuse alveolar damage (DAD), and to evaluate whether etiologies or precipitating factors were missed, we evaluated patients who died with a clinical diagnosis of ARDS and who had a postmortem examination.**

Methods: **We conducted a 3-year (2002 to 2004) review of all patients with ARDS (using the American-European Consensus Conference criteria) who died in our ICU and had a postmortem examination. Discrepancies between antemortem and postmortem diagnoses were classified as major and minor using the Goldman classification.**

Results: **Of 9,184 hospital admissions, 376 patients had a clinical diagnosis of ARDS. Of these, 169 died; 69 had a postmortem examination, and 64 of these had complete data for analysis. The main cause of death was multiple organ failure (27 of 64 patients). Postmortem examination revealed DAD in 32 patients (50%), pneumonia without DAD in 16 patients (25%), and invasive pulmonary aspergillosis in 8 patients (12.5%). Major unexpected findings were found in 15 patients (23%): 7 Goldman class I (including 4 cases of invasive pulmonary aspergillosis and 1 of disseminated tuberculosis) and 8 Goldman class II.**

Conclusions: **In this study, ARDS remains a heterogeneous syndrome because only half of patients with ARDS had typical DAD. Open lung biopsy, if performed, might have led to appropriate therapy and potentially better outcome in five of the patients.** ***(CHEST 2009; 135:944–949)***

Key words: ARDS; Aspergillus; biopsy, lung; lung pathology

Abbreviations: AECC = American-European Consensus Conference; DAD = diffuse alveolar damage; F_{IO_2} = fraction of inspired oxygen

ARDS remains a major problem in critically ill patients. Despite substantial progress in the understanding of ARDS physiopathology, mortality rates remain high at 40 to 46%.[1–3] Although some supportive therapies have been demonstrated to be associated with improved outcomes, for example, low tidal volume ventilation,[4] no specific treatment directed against the pathophysiological mechanisms of ARDS has been identified that can substantially reduce mortality rates.[5,6] In 1992, the American European Consensus Conference (AECC) on ARDS was convened to provide "clarity and uniformity" in the definitions of acute lung injury and ARDS.[7] Acute lung injury was defined as "a syndrome of inflammation and increased permeability that is associated with a constellation of clinical, radiologic, and physiologic abnormalities that cannot be explained by, but may coexist with, left atrial or pulmonary capillary hypertension."[7] Although the AECC criteria have been widely used in daily practice and in clinical research, they have often been

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criticized and questioned.[8–11] The clinical criteria for ARDS reflect nonspecific functional abnormalities of the respiratory system rather than a precise structural anomaly. The typical anatomical feature of ARDS is diffuse alveolar damage (DAD),[7,12] but the correlation between clinical criteria of ARDS and DAD is not well established.[13] Moreover, ARDS may occur in association with a number of diseases, and it is not certain that the same management should be applied to all patients. Hence the heterogeneity of the patient groups included in therapeutic studies remains problematic.[14,15] Other definitions of ARDS and additional criteria have been proposed,[8,16] and some authors have stressed the importance of histologic examination of pulmonary tissue to define etiology, assess severity, and orient therapeutic management of ARDS[17–19]; however, the precise role of lung biopsy in this approach has not been clearly defined.

The purpose of our study was to review the clinical-pathologic correlates in patients who died with ARDS and underwent an autopsy, in order to define the pathologic alterations associated with the syndrome with particular reference to the typical pattern of DAD and to evaluate whether undiagnosed causal or aggravating factors were missed. We also speculated on whether or not a lung biopsy could have guided clinical management.

Materials and Methods

The study was approved by the ethics committee of Erasme Hospital, which waived the need for informed consent in view of the observational nature of the study. We reviewed the clinical charts and postmortem pathologic results of all adult patients (> 18 years of age) who died with ARDS over a 3-year period (January 2002 to December 2004) in the 35 medico-surgical-bed ICU of Erasme University Hospital, in whom a postmortem examination had been conducted. ARDS was defined clinically according to the AECC criteria,[7] including the presence of acute bilateral pulmonary infiltrates, a Pao_2/fraction of inspired oxygen (Fio_2) ratio < 200 mm Hg, and a pulmonary artery balloon-occluded pressure < 18 mm Hg or the absence of signs of left cardiac failure. In addition to epidemiologic data, we collected information on risk factors for ARDS, duration of ICU hospitalization, and the time lapses between diagnosis of ARDS and death, and between death and postmortem examination. Causes of ARDS were divided into "pulmonary" (*eg*, lung infection, aspiration, pulmonary contusion) and "extrapulmonary" (*eg*, nonpulmonary sepsis, pancreatitis). We defined severe hypoxemia as a Pao_2/Fio_2 ratio < 100 mm Hg and/or administration of inhaled nitric oxide for life-threatening hypoxemia.

We classified the causes of death into multiorgan failure, refractory shock (unable to maintain mean arterial pressure at > 70 mm Hg despite high doses of vasopressors), refractory hypoxemia (unable to maintain Pao_2 > 60 mm Hg), brain death, and others. We also noted whether patients had a decision made to withhold or withdraw life-sustaining therapy.

As a general principle in our department, and in accordance with Belgian law, postmortem examinations were carried out if there was no formal objection from the next of kin (presumed consent). All postmortem examinations were carried out in the Pathology Department according to standard procedures. Lung weights in patients with and without DAD were compared overall and in male and female patients separately. After tissue sampling from all pulmonary lobes, fixation in formol and inclusion in paraffin blocks, the hematoxylin-eosin slides were examined independently by two pathologists, with the second pathologist blinded to the initial pathologist's findings. We separated histologic lung lesions into infectious and noninfectious. Taking DAD lesions as the reference for histologic diagnosis of ARDS,[12,20] we calculated the rate of agreement between the clinical diagnosis of ARDS and the histologic diagnosis.

The degree of agreement between clinical and postmortem diagnoses was classified according to the criteria of Goldman and colleagues.[21] A Goldman I discrepancy is a missed major diagnosis that if known in life would have altered therapy and possibly survival. A Goldman II discrepancy is a missed major diagnosis that would not have altered therapy or survival. A class III discrepancy refers to a missed minor diagnosis associated with the terminal disease but not directly responsible for death, and a class IV discrepancy refers to other missed minor diagnoses. Class V corresponds to full agreement between clinical diagnosis and postmortem findings.

Results

From a total of 9,184 admissions to the ICU during the 3-year period, 376 patients (4.1%) met the ARDS criteria. Of these, 169 patients (45%) died, and a postmortem examination was performed in 69 of them (41%). Complete data could be retrieved for 64 patients, who thus represent the database for this study (Fig 1).

Table 1 lists the characteristics of the 64 patients. The mean (± SD) Pao_2/Fio_2 ratio measured at the time of ARDS diagnosis was 128 ± 36 mm Hg. ARDS was due to pulmonary causes (primary ARDS) in 53% of cases, mainly infection (41%).

The primary cause of death was multiorgan failure (42%), followed by refractory shock (31%); refractory hypoxia was responsible for 14% of the deaths (Table 1). The median time interval between ARDS diagnosis and death was 6 days (range, 0 to 48 days). The median time interval between death and autopsy was 1 day (range, 0 to 3 days).

Table 2 shows the results of microscopic examination of the lungs at autopsy. Of the 64 patients, only 32 (50%) had typical DAD lesions (Fig 2); these were associated with pulmonary infection in 9 patients. Lesions of (broncho) pneumonia without DAD were found in 16 cases (25%). Invasive pulmonary aspergillosis was found in eight patients (12.5%), associated with DAD in four cases. DAD lesions were observed in 18 of the patients (53%) in whom primary ARDS was clinically diagnosed, and in 14 of those patients (47%) in whom secondary ARDS was diagnosed ($p = 0.61$). The lungs were somewhat heavier in patients with than in

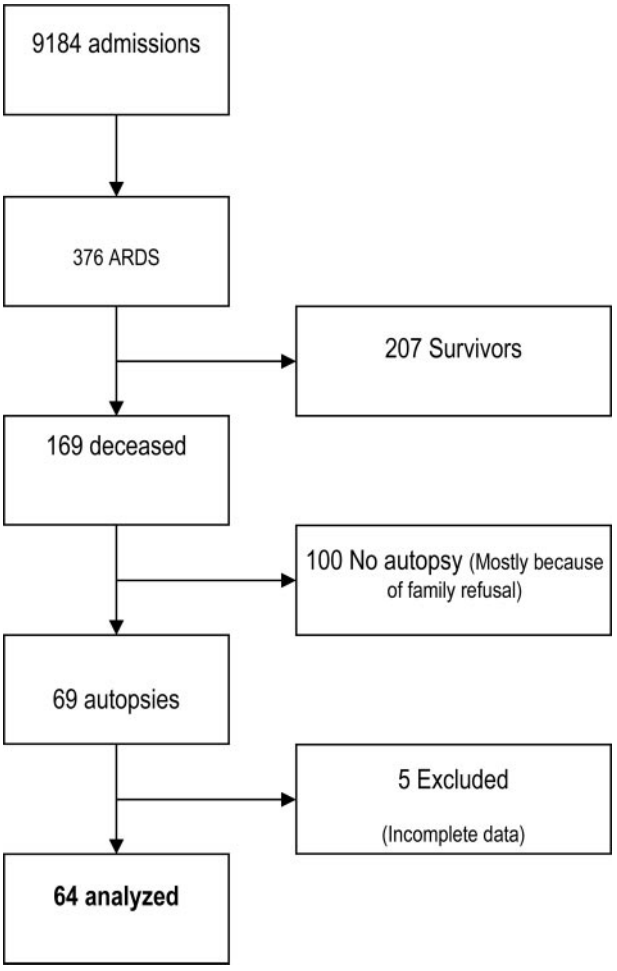

FIGURE 1. Flow diagram of patient inclusion.

Table 1—*Demographic Data and Characteristics of the Study Population (n = 64)

Variables	Values
Age, yr	62 ± 18
Male gender	38 (59)
ICU length of stay, d	11 (2–135)
PaO_2/FIO_2 measured at ARDS diagnosis, mm Hg	128 ± 36
PaO_2/FIO_2 before death, mm Hg	126 ± 54
Severe hypoxemia	20 (31)
Reason for ICU admission	
Medical	43 (67)
Pulmonary	19 (30)
Digestive	10 (16)
Infectious (other than pulmonary)	8 (13)
Cardiovascular	3 (5)
Neurologic	3 (5)
Surgical	21 (33)
Cardiovascular	9 (14)
Digestive	6 (9)
Thoracic	3 (5)
Trauma	2 (3)
Neurologic	1 (2)
ARDS etiology (supposed)	
Pulmonary (primary)	34 (53)
Infectious	26 (41)
Inhalation	2 (3)
Contusion	1 (2)
Other	6 (9)
Extrapulmonary (secondary)	30 (47)
Sepsis	23 (36)
Pancreatitis	4 (7)
Multiple transfusions (TRALI)	2 (3)
Other	1 (2)
Interval between ARDS diagnosis and death, d	6 (0–48)
Primary cause of death (clinically determined)	
Multiple organ failure	27 (42)
Refractory shock	20 (31)
Refractory hypoxemia	9 (14)
Brain death	5 (8)
Other	2 (3)
Therapeutic withholding/withdrawing	32 (50)

*Values are given as mean ±/SD, No. (%), or median (range). TRALI = transfusion-related acute lung injury. Severe hypoxemia was defined as a PaO_2/FIO_2 ratio < 100 mm Hg and/or administration of inhaled nitric oxide. Refractory hypoxemia was defined as an impossibility to maintain PaO_2 > 60 mm Hg.

those without DAD, but the differences did not reach statistical significance (Table 2).

Autopsy revealed unexpected major diagnoses in 15 patients (23%), including 7 Goldman class I and 8 class II discrepancies (Table 3); the class I discrepancies included 4 cases of invasive aspergillosis. Of these four patients with undiagnosed invasive aspergillosis, one had AIDS, and one had received prolonged corticosteroid therapy. Microbiological analysis of tracheal secretions was positive premortem for Aspergillus spp in only one of the four patients. Among the four cases of invasive aspergillosis that were diagnosed premortem, three patients had been receiving long-term treatment with systemic corticosteroids (two for hematologic malignancy and one for COPD).

DISCUSSION

ARDS is a syndrome associated with a number of different diagnoses. The question is whether it is useful to try and identify a precise histologic lesion for which we currently have no specific treatment, or is this merely an academic exercise?

Our study shows that only 50% of patients with ARDS diagnosed clinically using current criteria actually had DAD lesions. Only a few other studies have evaluated rates of DAD in patients with ARDS, and they have reported similar findings.[13,17,18] In a review of postmortem examinations in ICU patients, Esteban and coworkers[13] observed that only 66% of the 127 patients meeting the clinical criteria of ARDS actually had the typical DAD lesions. In another study of postmortem data, the same investi-

Table 2—*Lung Pathology at Postmortem

Variables	Values
DAD	
Total	32 (50)
Exudative phase	16 (25)
Organized phase	16 (25)
Isolated	20 (31)
Associated with	12 (19)
Pneumonia/bronchopneumonia	4
Pulmonary invasive aspergillosis	4
Pneumocystis carinii (*jiroveci*) pneumonia	1
Pulmonary infarct	1
Congestion	1
Lymphangioleiomyomatosis + microthrombi	1
Other pathologic diagnoses (not associated with DAD)	
Pneumonia/bronchopneumonia	16 (25)
Congestion	7 (11)
Pulmonary invasive aspergillosis	4 (6)
Chronic nonspecific inflammatory changes	3
Pulmonary embolism	2
Alveolar hemorrhage	2
Usual interstitial pneumonia	2
P carinii (*jiroveci*) pneumonia	1
Pulmonary infarct	1
Acute pulmonary graft rejection	1
Inhalation pneumonia	1
Bronchiolitis obliterans organizing pneumonia	1
Lung weight,† g	NB normal total lung weight ~ 800 gm
With DAD (left/right)	879 ± 325/995 ± 344
Male	956 ± 306/1040 ± 340
Female	779 ± 327/937 ± 352
Without DAD (left/right)	791 ± 284/874 ± 306
Male	881 ± 313/954 ± 350
Female	641 ± 136/742 ± 148

*Values are given as No. (%) or mean ± SD. One patient can present more than one pathologic diagnosis.

†p = Not significant for with DAD vs without DAD; Mann-Whitney test.

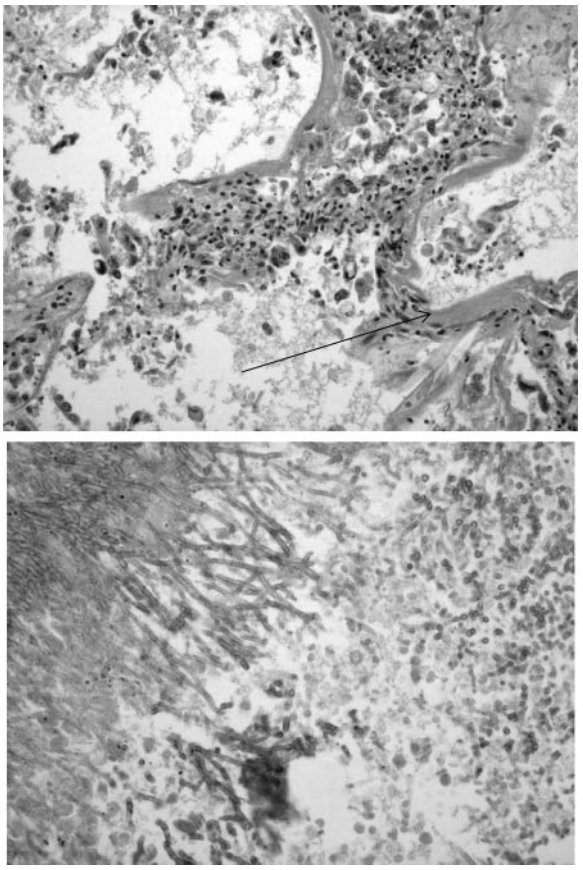

FIGURE 2. Typical microscopic findings. *Top*: patient with DAD showing hyaline membranes (arrow) [hematoxylin-eosin, original ×200]. *Bottom*: patient with invasive aspergillosis showing aspergillus filae (periodic acid-Schiff stain, original ×400).

gators compared the accuracy of three clinical definitions of ARDS and showed that the sensitivity of the AECC criteria for DAD was 83% and the specificity only 51%.[22] Studies on lung biopsy have reported similar findings. In a retrospective review of pulmonary biopsy results in 57 patients with ARDS, Patel and coworkers[17] reported that a diagnosis other than DAD was found in 60% of the cases. Another retrospective review[18] of 41 pulmonary biopsies, performed early (less than a week after endotracheal intubation), reported the presence of specific diagnoses other than DAD in 44% of the cases, leading to treatment changes in 73% of the cases.

The treatment of ARDS remains essentially supportive and causal. However, some diagnoses can escape the clinician. In our series, the main missed pulmonary diagnosis was invasive pulmonary aspergillosis. One may argue that if a lung biopsy had been performed in such patients, treatment with antifungal agents might have been initiated and outcomes improved, although it is possible that even with appropriate treatment the clinical course would

Table 3—*Major Missed Diagnoses, Discovered Postmortem*

Class	Missed Diagnosis	Cases, No.
I	Pulmonary invasive aspergillosis	4
	Pulmonary embolism	1
	Bacterial endocarditis	1
	Disseminated tuberculosis	1
II	Pulmonary embolism	2
	Acute pancreatitis	1
	Upper digestive hemorrhage	1
	Renal infarct (thrombus)	1
	Acute peritonitis	1
	Nephrolithiasis + dilation	1
	Renal neoplasm	1

not have been altered in these severely compromised patients. Pulmonary invasive aspergillosis is increasingly recognized as affecting not only immunocompromised patients, but also ICU patients without classical risk factors, and it is associated with a dramatic mortality rate of almost 90%.[23] Diagnosis of invasive aspergillosis is difficult because the presence of Aspergillus spp in the airways may represent simple colonization rather than infection.[24] The incidence of invasive aspergillosis seems to be underestimated in ICU patients, and the available diagnostic tests are neither sensitive nor specific.[25] This being the case, pulmonary biopsy could play a decisive role in the diagnosis of this infection. A previous postmortem review carried out in our hospital[26,27] revealed 19 major diagnostic errors in 222 ICU patients who underwent autopsy, including invasive aspergillosis in 6 patients, 5 of whom were immunocompromised (treated with long-term steroids for COPD).

We also missed one case of disseminated tuberculosis that may have benefited from appropriate antimicrobial therapy. Thus, of the seven major clinically missed diagnoses in our series, five would likely have been identified with an open lung biopsy, which could have altered their management and potentially their outcome (although this remains speculative). Autopsy revealed that 20 of our patients (31%) had DAD not associated with an infectious process; some of these patients, if identified by lung biopsy, may have benefited from corticotherapy, although the use of corticosteroids in ARDS remains controversial.[28] In a prospective study, Papazian and coworkers[19] showed that pulmonary biopsies performed in selected patients could result in a change in therapy in 78 of 100 cases. The selected patients were those who showed no improvement after 5 days of treatment, despite negative microbiological results, suggesting that they may benefit from corticotherapy. These authors reported only minor complications of the procedure, as have other studies on pulmonary biopsies in patients with ARDS.[17,18] In our series, many of our patients would have met the 5-day criteria to perform open lung biopsy proposed by Papazian et al.[19]

In our study, the primary cause of death in these patients with ARDS was multiorgan failure (42% of cases); refractory hypoxemia was the cause of death in only 14% of cases. This finding is in agreement with previous studies.[29–32] ARDS must be perceived as a systemic disease because most patients die of multiorgan failure rather than refractory hypoxia; and its management must focus mainly on the identification and treatment of causal factors and on the systemic management of the patient in order to prevent other organ failures.[33,34]

Some authors[14,15] have suggested that the dearth of positive results from studies of treatments for ARDS could be at least partly due to the heterogeneity of the ARDS populations studied, which makes it impossible to target new therapies on the patient groups most likely to benefit. The most significant improvement in ARDS-related mortality figures has been achieved by limiting tidal volumes so as to minimize ventilator-induced lung injury.[4] Our study results support the suggestion that the concept of ARDS as a syndrome is not a very useful entity, and perhaps it is time for other approaches to be introduced that can better characterize these patients.

The present study has several limitations. First, it is limited by its retrospective design. Patients were included according to a clinical diagnosis of ARDS documented in their charts by the attending physician, and some cases, therefore, may have been missed. However, this would likely only have involved patients with milder cases of ARDS, who would have been less likely to die and hence should not have affected our study population. Second, the results may be influenced by the fact that only patients who died were included; thus only the most severe ARDS cases were included, so the results may not reflect the general ARDS population. Nevertheless, because the decision to perform an open lung biopsy is only considered in severely ill patients, our results are relevant to the discussion of the role of lung biopsy in ARDS management.

Conclusion

In our study of 64 autopsies of ARDS patients, only half the patients in whom ARDS had been clinically diagnosed had the typical pathologic DAD lesions. Invasive aspergillosis was present in eight patients. There were seven major missed diagnoses, including four cases of pulmonary invasive aspergillosis and one case of invasive tuberculosis in which open lung biopsy may have helped orient therapy.

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