Acute Respiratory Distress Syndrome and Pneumonia: A Comprehensive Review of Clinical Data

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Acute respiratory distress syndrome (ARDS) and pneumonia are closely correlated in the critically ill patient. Whereas ARDS is often complicated by nosocomial pneumonia, pulmonary infection is also the most frequent single cause of ARDS. The prevalence of pneumonia during the course of ARDS seems to be particularly high, but whether persons with ARDS are more susceptible to pneumonia or simply have more risk factors remains unknown because of methodological limitations. Recent research suggests that host factors have a major bearing on the development of ARDS. To date, sepsis seems to be the principal link between pneumonia and ARDS. However, prospective observational data on this supposed sequence are not available. The individual role of specific pathogens for the development of ARDS is difficult to assess, because prospective studies are missing. Respiratory viruses have received particular attention, but this review suggests that infections with coronavirus and avian influenza virus (H5N1) are associated with a high incidence of ARDS.

Acute respiratory distress syndrome (ARDS) is currently diagnosed using 4 criteria, and its etiology can be differentiated into direct and indirect lung injury [1, 2]. Community-acquired pneumonia (CAP) is firmly diagnosed by clinical and radiographic criteria, but the diagnosis of ventilator-associated pneumonia (VAP) imposes considerable difficulties, even when adequate lower respiratory tract samples are collected (table 1). This is especially true when ARDS and pneumonia have to be differentiated in clinical practice [3]. The pathophysiology of pulmonary infiltrates in pneumonia is well defined, but the mechanisms behind the development of ARDS are still not fully understood. The hallmark of ARDS is the increased permeability of the edema, which is interpreted as being an accumulation of protein-rich edema fluid in the alveoli and is mediated by inflammation of various mechanisms [4].

The diagnoses of ARDS and pneumonia both require radiographic infiltrates; severe pneumonia is frequently of acute onset and shows bilateral infiltrates on chest radiography and severe acute respiratory failure not due to cardiac failure. Thus, it is virtually impossible to differentiate acute severe bilateral pneumonia from ARDS on clinical grounds alone. Accordingly, in a recent study of the association of ARDS with pneumonia by a comparison of clinical diagnoses based on the American-European Consensus Conference Criteria [1] and histopathologic evidence for diffuse alveolar damage [5, 3], pneumonia was the most frequent mimic of ARDS. In the 43 patients who met ARDS criteria but who did not have diffuse alveolar damage, pneumonia was the most prevalent finding (32 [74%] of 43 patients) [3]. Pneumonia is also the most frequent lung condition leading to ARDS. In a series of 153 patients, Sloane et al. [6] reported pneumonia as the underlying etiology in 31% of all patients who developed ARDS, and virtually all patients with ARDS require mechanical ventilation, a major risk factor for the development of VAP [7–9].

Therefore, this review is focused on the following topics: (1) pneumonia as a cause of direct lung injury in the immunocompetent host, (2) nosocomial pneumonia as a complication of ARDS, and (3) the impact of various infectious etiologies on the induction of ARDS. This review will exclude therapeutic issues dealing with either pneumonia or ARDS, because the published information associated with these issues has been updated recently [10, 11]. We reviewed international reports identified by searches of PubMed with relevant keywords. We also searched

Table 1. Definition of acute respiratory distress syndrome (ARDS) and acute lung injury (ALI), according to the American-European Consensus Conference and the Johanson criteria.

Acute onset
Bilateral infiltrates on chest radiograph
Noncardiogenic pulmonary edema, defined as a pulmonary arterial
  wedge pressure of ≤18 mm Hg or no clinical evidence of left
  arterial hypertension
PaO_2/FIO_2 of <200 (for ARDS) or <300 (for ALI)
New and persistent infiltrates and 2 of the following:
  Leukocytosis or leukopenia
  Fever (body temperature, >38.3°C)
  Purulent sputum

NOTE. Adapted from [1, 71].

cited references in retrieved articles, reviewed articles we have collected over many years, and used knowledge of new data presented at international scientific meetings. We gave priority to clinically relevant articles, rather than reports of randomized controlled trials, and case reports, case series reports, and retrospective studies were used for this systematic review.

ARDS COMPLICATING THE COURSE OF PNEUMONIA

The sequence from bacterial pneumonia to ARDS can be followed more accurately in persons with CAP [11]. Estenssoro et al. [12] observed 3050 patients admitted to intensive care units during a 15-month study period; 1193 patients (39%) were mechanically ventilated, and 235 met the criteria for ARDS (7.7% of the total number of patients, and 19.7% of the ventilated patients). The predominant etiology of ARDS was sepsis (44%), and pneumonia was the most frequent single entity (65 cases). The authors did not differentiate between CAP and nosocomial pneumonia, and they have not followed-up with patients with pneumonia who have not developed ARDS to identify risk factors. The figures given by this group were comparable with those of previous studies that used similar ARDS criteria [13–16], with pneumonia remaining the most frequent single cause of sepsis. However, to draw meaningful conclusions, we need larger, prospective cohort studies that observe patients with CAP for progression to ARDS.

To further identify the reasons why severe CAP progresses to ARDS, it is important to first discover why severe CAP progresses to sepsis. In a prospective cohort study [17], 280 patients with CAP were included, and 31 subjects (11%) were identified who met the criteria for septic shock. In a multivariate analysis incorporating age; sex; the presence of chronic pulmonary, cardiac, renal, hepatic, or neurologic disease; alcohol consumption; prior antibiotic exposure; delayed antibiotic therapy; and TNF-α genotype, the only factors that remained significant predictors of septic shock were LTα+250

genotype and increasing age. The study design was repeated with a focus on the possible role of the intracellular adhesion molecule type 1 but failed to yield a significant association between CAP and sepsis [18]. Ten (4%) of the 289 patients in the cohort had ARDS, but it was not noted whether sepsis or septic shock preceded ARDS. These data, however, did not directly address the issue of whether sepsis is the required link between ARDS and pneumonia. Thus, risk factors for both development of severe sepsis and ARDS in the course of CAP remain undefined.

PNEUMONIA COMPLICATING ARDS

The issue of assessing the impact of pneumonia during the natural course of ARDS is obscured by the uncertainties in diagnosing nosocomial pneumonia. All approaches to construct firm diagnostic criteria for VAP have their inherent limitations. In particular, even the most reliable measure of diagnosing VAP using quantitative cultures of bronchoscopically retrieved respiratory samples (by protected specimen brush and/or bronchoalveolar lavage) does not preclude false-negative and false-positive results in the range of 10%–30% [19, 20]. Accordingly, the incidence of pneumonia during the course of ARDS reported in various studies varies largely. The issue has been reviewed in detail by Iregui and Kollef [21].

Delclaux et al. [22] performed a prospective study of lower respiratory tract colonization and infection in 30 patients with severe ARDS by repeated quantitative culture of plugged telescoping catheter specimens every 48–72 h after the development of ARDS. Using clinical and microbiological criteria, these investigators found an incidence of VAP of 60% (4.2 episodes per 100 ventilator-days). Previous lower respiratory tract colonization with similar microorganisms preceded the development of VAP in almost all cases. In line with these data, Markowicz et al. [23] found an incidence of VAP of 37% among patients with ARDS. The incidence of early-onset pneumonia (<5 days) was 35%, and the incidence of late-onset VAP was reported to be as high as 65%.

Meduri et al. [24] found that 43% of patients with ARDS in their study had VAP using bilateral bronchoalveolar lavage. Similarly, Chastre et al. [25] obtained samples from the lower airways using bronchoalveolar lavage and protected specimen brush on critically ill patients with clinical evidence of VAP. The occurrence of VAP was significantly higher among patients with ARDS (55%) than among patients without ARDS (28%). These data suggest that ARDS may be a risk factor that predisposes ill persons to VAP, as suggested by other investigators [26]. However, the prolonged duration of mechanical ventilation for patients with ARDS may be more important in predisposing them to VAP than ARDS itself [25, 27].

We investigated a cohort of patients fulfilling ARDS criteria with diagnostic tools for nosocomial pneumonia within the

first 24 h of the diagnosis. Overall, 12 (22%) of 55 patients were clinically suspected of having nosocomial pneumonia on the first day after receiving a diagnosis for ARDS. Infection could be microbiologically confirmed in 7 (58%) of them. Thus, the microbiologically confirmed pneumonia rate within 24 h of each patient's first diagnosis of ARDS was 13%. All 7 patients with microbiologically confirmed nosocomial pneumonia had been admitted to the hospital at least 6 days before receiving a diagnosis (range, 6–43 days) and had been mechanically ventilated for >48 h [28].

Helpful information regarding the differentiation between the etiologies of bilateral pulmonary infiltrates (ARDS vs. pneumonia) may come from the interpretation of triggering receptor expressed on myeloid cells [29, 30]. The investigators used soluble triggering receptor expressed on myeloid cells in samples of bronchoalveolar lavage fluid as a marker of pneumonia in patients receiving mechanical ventilation [29]. In mechanically ventilated patients with VAP, the detection of soluble triggering receptor expressed on myeloid cells type 1 was a much more accurate diagnostic tool than any clinical finding. It was the strongest independent factor, predicting pneumonia (OR, 41.5) according to a logistic regression analysis with a sensitivity of 98% and a specificity of 90%. The control group included a large number of patients with ARDS (31 [48%] of 64 patients), and the differential power of soluble triggering receptor expressed on myeloid cells should be tested under this specific hypothesis. However, because soluble triggering receptor expressed on myeloid cells has been shown to be elevated in newly admitted, critically ill patients with suspected sepsis, this will exclude a large patient group with extrapulmonary pathogenesis of ARDS caused by sepsis [31].

THE INVOLVEMENT OF SPECIFIC PATHOGENS ON THE DEVELOPMENT OF ARDS

The study of the role of specific pathogens in inducing ARDS is complex, because known risk factors for ARDS (e.g., sepsis, shock, trauma, and/or gastric aspiration) would all have to be balanced. Relevant data mainly derive from small case series and case reports. These investigations may be biased toward reporting more-severe cases, leaving milder cases unrecognized. For this reason, table 2 may represent a spectrum of more-severe illnesses caused by known bacterial, viral, and parasite infections with preceding pneumonia or pulmonary involvement.

BACTERIA

The literature is obviously biased toward case reports and seems to be restricted to a group of bacteria previously referred to as "atypical" [32–36]. This is most likely because, in cases with known risk etiologies for severe pneumonias, such as *Streptococcus pneumoniae* and/or *Pseudomonas aeruginosa* infections [37], the sequence pneumonia => sepsis => ARDS is quite

obvious and is not considered to be noteworthy. Markowicz et al. [23] compared 134 patients with ARDS with 744 patients without ARDS and found that nonfermenting, gram-negative bacteria caused significantly more cases of pneumonia among patients with ARDS. Mortality rates were comparable between the 2 groups, but the incidence of pneumonia increased with time on mechanical ventilation. In cases of pneumonia due to *P. aeruginosa,* specific cytotoxic mediators may explain the high rate of lung injury during infection [38].

The definite diagnoses of infections with *Mycoplasma, Chlamydia,* and *Legionella* species requires more effort, and infection may be undiscovered for some time, enhancing the severity and the probability of sepsis and/or ARDS. All except 1 patient [39] received an initial empiric antimicrobial treatment that cannot be considered fully ineffective against the pathogen. Routine investigation failed to identify a pathogen, and the etiology was suspected or proven later, during the course of the disease. Therefore, the available data should not be interpreted as evidence for a specific role of these pathogens in inducing lung injury.

Tuberculosis is not a common primary cause of respiratory failure requiring mechanical ventilation; therefore, it is also not instantly associated with ARDS [40]. Agarwal et al. [41] reviewed all patients (187) with ARDS and found severe pneumonia (in 65 [35%]) and sepsis (in 62 [33%]) to be the most relevant underlying illnesses. They provide information for 9 patients (5%) with ARDS and tuberculosis. All patients were mechanically ventilated, and Ziehl-Neelsen staining did not reveal acid-fast bacilli in any of the patients. Fiberoptic bronchoscopy and transbronchial lung biopsy were performed for 7 (78%) of 9 patients, and histopathological examination was used for all patients. The mortality rate (2 [22%] of 9 patients) was remarkably low, compared with those in previous reports of patients with pulmonary tuberculosis requiring mechanical ventilation (27 [66%] of 41 patients) [42] or patients with miliary tuberculosis and ARDS (2 [33%] of 6 patients) [43]. Sharma et al. [44] found a prolonged duration of illness, miliary tuberculosis, absolute lymphocytopenia, and an elevated liver enzyme level to be independent predictors for the development of ARDS. However, they reviewed a cohort of 2733 patients and reported 29 patients with ARDS (1%), confirming the low prevalence of severe lung injury in patients with tuberculosis.

VIRUSES

The proportion of viral etiologies in CAP has been recently investigated among 338 hospitalized patients [45]. The prevalence of viral pneumonia was 9% (31 of 338 persons), and the prevalence of mixed viral and/or bacterial pneumonia was 18% (61 of 338 persons). Influenza A was by far the most common viral etiology, and the annual prevalence showed a seasonal pattern. It seemed that persons with mixed infections were at increased risk to progress to sepsis or septic shock;

Table 2. Reports of pneumonia and acute respiratory distress syndrome (ARDS), by type of pathogen.

Reference, by pathogen type	Type of study	Disease	Etiology	Initial antibiotic therapy	Intervention	Sepsis	Proportion (%) of patients who survived	Notes
Bacteria								
[32]	Case report	CAP	*Chlamydia pneumoniae*	Cefuroxim (3 doses of 750 mg) + erythromycin (4 doses of 500 mg)	Change in antibiotic therapy (erythromycin-azithromycin)	No	1/1 (100)	…
[33]	Case report	sCAP	*C. pneumoniae*	Cefriaxone, erythromycin, penicillin	Prone position, venovenous oxygenation	Yes	1/1 (100)	Sepsis and multiorgan failure
[34]	Case report	Pneumonia and encephalitis	*C. pneumoniae*	Cefotaxim (8 g per day) + erythromycin (4 g per day)	Not reported	No	1/1 (100)	Doxycycline administered after improvement
[36]	Case report	Initial enteric infection, pneumonia	*Mycoplasma pneumoniae*	Ciprofloxacin (2 doses of 400 mg)	Added cefriaxone (2 doses of 1 g) and trovafloxacin (1 dose of 300 mg); second change in antibiotic therapy (imipenem, 4 doses of 500 mg; and clarithromycin, 4 doses of 500 mg); steroid pulses	Yes	1/1 (100)	…
[35]	Case report	Q fever	*Coxiella burnetii*	Cefriaxone (1 dose of 2 g) + erythromycin (2 doses of 500 mg)	Change in antibiotic therapy (doxycycline, 1 dose of 200 mg); prone position	Not mentioned	1/1 (100)	…
[39]	Case report	Pneumonia	*Legionella pneumophilia*	Panipenem–betamipron	Change in antibiotic therapy (erythromycin and ciprofloxacin)	Not mentioned	1/1 (100)	Article in Japanese
[72]	Retrospective	Leptospirosis	*Leptospira interrogans*	Not reported	Not reported	Not mentioned	0/3 (0)	13 (50%) of 26 patients had pulmonary infiltrates, 3 (12%) of 26 developed ARDS
Tuberculosis								
[41]	Retrospective	Pulmonary tuberculosis	*Mycobacterium tuberculosis*	Isoiniazid, rifampicin, pyrazinamide, ethambutol	Not reported	Not mentioned	7/9 (78)	Mean age 45 ± 13 years, no corticosteroids

Table 2. *(Continued.)*

Reference, by pathogen type	Type of study	Disease	Etiology	Initial antibiotic therapy	Intervention	Sepsis	Proportion (%) of patients who survived	Notes
[43]	Retrospective	Miliary tuberculosis	*M. tuberculosis*	Standard treatment	Amphotericin B for 1 patient with kala-azar	Not mentioned	4/6 (66)	3/6 (50%) with "predisposing condition" (rheumatoid arthritis, kala-azar, pregnancy), diagnosis by liver biopsy 4/6 cases (66%)
Virus								
[73]	Retrospective	Pneumonia	Varicella-zoster virus	Acyclovir	None	Not mentioned	3/3 (100)	Immunocompetent adults, 3 of 10 with ARDS
[64]	Retrospective	14 (15%) of 92 patients had pneumonia	Varicella-zoster virus	Acyclovir	5 (36%) of 14 patients receiving antibiotics	No	2/3 (66)	3 of 14 patients developed ARDS 3, 5, and 8 days after infection; all but 1 patient had previous contact with a varicella-infected patient
[59]	Case report	Pneumonia	Varicella-zoster virus	Acyclovir	Corticosteroids	Yes	1/1 (100)	Immunocompetent, disseminated intravascular coagulation
[60]	Case report	Pneumonia	Varicella-zoster virus	Acyclovir	None	Not mentioned	1/1 (100)	Immunocompetent, non–HIV-infected
[61]	Case report	Pneumonia	Varicella-zoster virus	Acyclovir	Corticosteroids	Not mentioned	1/1 (100)	Fast response after corticosteroids
[62]	Case report	Pneumonia	Varicella-zoster virus	Acyclovir	Intravenous immunoglobulins (5 days)	...	1/1 (100)	Immunocompetent adult
[46]	Observational	Influenza (50% of patients), pneumonia (50%)	Influenza A	52 (95%) of 55 patients received amantadine	36 (65%) of 55 patients receiving antibiotics	No	54/55 (98)	18 of 55 patients had pneumonia; ARDS not mentioned; outbreak in Chile
[74]	Case report	Pneumonia	Avian influenza A virus (H7N7)	Cefuroxim (3 doses of 750 mg) + erythromycin (4 doses of 1000 mg)	Aciclovir	Yes	...	Pneumonia => sepsis and multiorgan failure => ARDS
[48]	Case series of 3 outbreaks	Influenza, pneumonia	Avian influenza A virus (H5N1)	Oseltamivir	...	...	...	...
[75]	Observational	Influenza, pneumonia	Avian influenza A virus (H5N1)	Oseltamivir, ribavirin	Corticosteroids	...	2/10 (20)	7 of 8 patients receiving corticosteroids died
	Case series	Influenza, pneumonia	Avian influenza A virus (H5N1)	Broad spectrum antibiotics (10 of 10 patients), oseltamivir (5 of 10), ribavirin (2 of 10)	Corticosteroids (8 of 10 patients)	...	...	...

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Ref	Study type	Disease	Pathogen	Treatment	Further interventions	Sepsis	Mortality, n/N (%)	Notes
[51]	Retrospective	SARS	Coronavirus	Ribavirin, corticosteroids, immunoglobulins	...	Not mentioned	12/33 (36)	Risk factors for ARDS were age >65 years, diabetes mellitus, and elevated LDH
[52]	Prospective	SARS	Coronavirus	Amoxicillin-clavulanate (3 doses of 1–2 g), azitromycin (1 dose of 500 mg), ribavirin (8 mg/kg)	Hydrocortisone (200 mg/day); sepsis and nosocomial pneumonia required additional antibiotics for 10 patients	10 Patients	11/13 (85)	20% Of patients developed ARDS during week 3 of the study
[53]	Prospective	SARS	Coronavirus	Cefotaxim (4 doses of 1 g) plus either levofloxacin (1 dose of 500 mg) or clarithromycin (2 doses of 500 mg); oseltamivir	When fever persisted >48 h, ribavirin and methylprednisolone were given	"Sepsis induced organ failure was considered to have contributed to death in 5 cases"	No data for patients with ARDS	21 (15%) of 138 patients progressed to ARDS
Parasite								
[76]	Case report	Malaria	Plasmodium falciparum	Quinine	Prone position	Yes	1/1 (100)	Child
[68]	Retrospective	Malaria	P. falciparum	Quinine, clindamycin	inhaled nitric oxide, kinetic therapy; extracorporeal venovenous oxygenation	Not mentioned	1/4 (25)	7 of 104 patients were admitted to the intensive care unit, 4 developed ARDS
[69]	Retrospective	Malaria	P. falciparum	Quinine	Antibiotic therapy for concomitant bacterial infection	Yes, all patients required vasoactive drugs	8/12 (67)	12 (30%) of 40 patients in the intensive care unit developed acute lung injury; 8 (20%) of 40 developed ARDS
[70]	Retrospective	Severe malaria and nonsevere malaria	P. falciparum	Quinine, tetracycline (16 of 93 patients)	Antibiotic therapy for concomitant bacterial infection, symptomatic therapy	Yes, 24 of 93 patients with severe malaria	...	Severe malaria only: 14 (15%) of 93 patients developed acute lung injury; 12 (13%) of 93 developed ARDS

NOTE. Most reports excluded information regarding sepsis and the targeted therapy for it. Therefore, the absence of any mentioning of further interventions in this table does not necessarily imply that specific measures to improve survival of critically ill patients have not been performed. Survival had to be summarized from the reports and was sometimes not mentioned, explicitly for ARDS patients. Therefore, these figures vary widely and do not represent exact mortality figures. CAP, community-acquired pneumonia; SARS, severe acute respiratory syndrome; sCAP, severe community-acquired pneumonia.

however, data on ARDS were not provided in this study. Also, in their observational study, Rabagliati et al. [46] did not provide this information for their cohort of 55 hospitalized patients with influenza, but stated that 18 (33%) of 55 patients had pneumonia and that only 1 patient died. Surprisingly, no additional information from observational trials regarding the issue of Influenza A and ARDS in the immunocompetent host is available. However, it may be assumed that the progression of Influenza A infection from severe CAP to sepsis and/or septic shock to ARDS is a rare event, in contrast to the currently evaluated human cases of avian influenza virus infection.

In the clinical description of 10 cases of H5N1 infection in Vietnam, ARDS is not explicitly mentioned, but severe respiratory failure was present in 9 of 10 cases, bilateral pulmonary infiltrates "occurred," and mortality was 80%, indicating that the criteria for ARDS may have been fulfilled in a high percentage of patients [47]. At least descriptive information regarding the prevalence of ARDS among human infections with H5N1 can be derived from the Thai pediatric case series. The pulmonary infiltration in the observed children "occasionally progressed, with subsequent deterioration to a final common pattern of acute respiratory distress syndrome" [48, p. 793], and almost all patients with ARDS died. Because of the paramount interest, virtually no confirmed cases remained unpublished; therefore, it must be assumed that the progression to ARDS is common among human avian influenza virus infections. The clinical picture of H5N1 infection has been recently reviewed, and it was reported that the average levels of plasma IFN-α among patients with avian influenza A who died were ~3 times as high as those among healthy controls [49]. It was speculated that such responses may be responsible in part for the sepsis syndrome, ARDS, and multiorgan failure observed in many patients with H5N1 infection.

Studies of infection due to coronavirus and severe acute respiratory syndrome (SARS) have improved our understanding of viral infections and severe respiratory disease. Whereas SARS is a qualitative term that does not define the severity of lung injury, ARDS is a quantitative term [50]. Hence, coronavirus infection can provoke SARS that is severe enough to be called ARDS, but SARS is not always characterized by coronavirus infection. Consequently, Chen et al. [51] identified ARDS in only 33 (49%) of 67 patients with SARS. They described age >65 years (OR, 10.6), diabetes mellitus (OR, 13.7), and lactate dehydrogenase (OR, 8.4) as being independent predictors of ARDS. The overall mortality was 31% (21 of 67 patients), and 21 (64%) of 33 patients developed ARDS. Peiris et al. [52] found lower figures; 15 (20%) of 75 patients progressed to ARDS during the 3-week follow-up period. They also identified age and chronic hepatitis B virus infection treated with lamuvidine as being significant risk factors, but did not mention LDH. The mortality reported in this study was surprisingly low (5 [5%] of 75 patients); after subtracting the 2 patients who died from myocardial infarction, only 2 (15%) of 13 patients died from sepsis and ARDS [52]. Reports from several other series have suggested that a substantial number of patients develop respiratory failure and ARDS, with 17%–30% of patients requiring admission to an intensive care unit [53, 54] and a 21-day mortality of 3.6% [55].

Varicella infection (chickenpox) is a common contagious infection caused by varicella-zoster virus that has a benign outcome in children. Pneumonia is the most frequent complication of varicella infections in healthy adults [56, 57] and the leading cause of death among vaccine-preventable diseases [58]. The case reports describe young males with bilateral infiltrates with a rapid progression to ARDS [59–62]. The anti-infective treatment invariably contains acyclovir, and in some cases, the treatment contains corticosteroid and/or immunoglobulins. One review found that 6 of 15 patients had life-threatening varicella pneumonia treated with corticosteroids [63]. These patients had significantly shorter hospital and intensive care unit stays (10 and 8 days, respectively), and no patient died. A newer case series of 14 patients with severe varicella pneumonia established the diagnosis of ARDS in 3 of 14 patients, and 1 patient died. All but 1 patient in this series had previous contact with a varicella-infected patient and no varicella infection during childhood [64]. Varicella infections go along with the characteristic rash; therefore, the diagnosis and treatment are almost always established immediately, and bilateral infiltrates seem to be common.

PARASITES

Parasitic infection with pulmonary involvement in immunocompetent patients may be regarded as a rare disease, depending on the geographical location [65]. It has to be considered regularly in acute eosinophilic pneumonia, and a list of pathogens can be derived from the literature [66, 67]. Malaria due to infection with *Plasmodium falciparum* is, however, noted remarkably often in the literature as being associated with ARDS. Losert et al. [68] reviewed 104 patients admitted to the hospital with malaria, of whom 66% had *P. falciparum* infections, and 7 of these were admitted to the intensive care unit. Four patients underwent intubation and mechanical ventilation and developed ARDS, and 3 patients died. In another study [69], only intensive care unit patients were considered, and 8 (20%) of 40 developed ARDS, with a mortality of 50%. Complications of malaria, such as coma, sepsis, or shock, were more prevalent among the group of patients with acute lung injury in this study and in the retrospective report by Bruneel et al. [70]. Therefore, we would like to support the hypothesis that ARDS is associated with the multiorgan failure that complicates the course of severe infection with *P. falciparum*, but the mechanisms seem to be independent from the causative agent [69, 70].

CONCLUSIONS

To date, sepsis seems to be the principal link between pneumonia and ARDS. However, prospective observational data on this supposed sequence are not available. The prevalence of pneumonia during the course of ARDS seems to be particularly high, but whether patients with ARDS are more susceptible to pneumonia or simply have more risk factors remains unknown because of limitations in the methodology of the diagnosis of VAP and ARDS. Recent research suggests that host factors have a major bearing on the development of ARDS. Accordingly, the individual role of specific pathogens in the development of ARDS is difficult to assess. Most recently, new respiratory viruses have received particular attention, and this review suggests that infections with coronavirus and avian influenza virus are associated with an exceptionally high incidence of lung injury and ARDS.

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