

Acute Interstitial Pneumonia (AIP): Relationship to Hamman-Rich Syndrome, Diffuse Alveolar Damage (DAD), and Acute Respiratory Distress Syndrome (ARDS)

Sanjay Mukhopadhyay, M.D.¹ Joseph G. Parambil, M.D.²

¹Department of Pathology, State University of New York Upstate Medical University, Syracuse, New York

²Respiratory Institute, Cleveland Clinic, Cleveland, Ohio

Address for correspondence and reprint requests Sanjay Mukhopadhyay, M.D., Department of Pathology, State University of New York Upstate Medical University, 750 E. Adams St., Syracuse, NY 13210 (e-mail: mukhopas@upstate.edu).

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Abstract

Acute interstitial pneumonia (AIP) is a term used for an idiopathic form of acute lung injury characterized clinically by acute respiratory failure with bilateral lung infiltrates and histologically by diffuse alveolar damage (DAD), a combination of findings previously known as the Hamman-Rich syndrome. This review aims to clarify the diagnostic criteria of AIP, its relationship with DAD and acute respiratory distress syndrome (ARDS), key etiologies that need to be excluded before making the diagnosis, and the salient clinical features. Cases that meet clinical and pathologic criteria for AIP overlap substantially with those that fulfill clinical criteria for ARDS. The main differences between AIP and ARDS are that AIP requires a histologic diagnosis of DAD and exclusion of known etiologies. AIP should also be distinguished from “acute exacerbation of IPF,” a condition in which acute lung injury (usually DAD) supervenes on underlying usual interstitial pneumonia (UIP)/idiopathic pulmonary fibrosis (IPF).

Keywords

- ▶ acute interstitial pneumonia
- ▶ acute lung injury
- ▶ acute respiratory distress syndrome
- ▶ diffuse alveolar damage

A subset of patients who present with acute respiratory symptoms go on to develop acute hypoxic respiratory failure with bilateral lung infiltrates. These patients fulfill clinical criteria for the acute respiratory distress syndrome (ARDS), including (1) acute onset, (2) $\text{PaO}_2\text{:FI}\text{O}_2$ ratio ≤ 200 mm Hg, (3) bilateral pulmonary infiltrates on chest radiographs, and (4) the absence of congestive heart failure, defined as pulmonary artery wedge pressure ≤ 18 mm Hg (when measured) or no clinical evidence of left atrial hypertension.¹ Defined in this way, the criteria for ARDS are purely clinical and do not require histological input. Although this definition has the virtue of ease of clinical application, it makes ARDS a “mixed bag” in terms of etiology and underlying pathology, rather than a well-defined clinicopathological entity.^{2–5} From an etiologic standpoint, ARDS occurs in a wide variety of well-known settings, including infection/sepsis, shock, trauma, aspiration and oxygen toxicity, among many others⁶; a few cases occur without an apparent cause or underlying context.

With regard to underlying pathology, the most common histological finding in ARDS is diffuse alveolar damage (DAD).^{2,5,7} However, other entities such as infectious pneumonias, culture-negative acute bronchopneumonia, capillaritis with alveolar hemorrhage, eosinophilic pneumonia, and organizing pneumonia are found to be the underlying pathology in a surprisingly high proportion of cases of ARDS.^{2,5} The challenge for the clinician managing patients with ARDS is to identify cases that have a treatable or potentially reversible cause, and distinguish them from those in whom the etiology is unknown and the response to therapy is likely to be poor. The existence of cases with the latter combination of dismal circumstances has been known since 1935, when Louis Hamman and Arnold Rich described four patients with acute respiratory failure of unknown etiology. All four patients died of respiratory failure and were found at autopsy to have a distinctive underlying pathology characterized by diffuse interstitial fibroblast proliferation—a finding that in

modern times is recognized as the organizing stage of DAD.^{8,9} This *acute* idiopathic condition was subsequently given the eponym *Hamman-Rich syndrome*. Over the years, however, the term *Hamman-Rich syndrome* began to be incorrectly used as an all-inclusive expression for all forms of lung fibrosis, including *chronic* forms of pulmonary interstitial fibrosis.^{10,11} The term *acute interstitial pneumonia (AIP)* was introduced in 1986 by Katzenstein et al for cases identical to the Hamman-Rich syndrome to highlight the fact that the Hamman-Rich syndrome is an *acute* form of idiopathic interstitial lung disease, clinically and histologically distinct from *chronic* forms of idiopathic interstitial lung disease, the prototype of which is usual interstitial pneumonia (UIP)/idiopathic pulmonary fibrosis (IPF).^{12–14}

This review clarifies the diagnostic criteria and terminology of AIP, discusses the etiologies that need to be excluded before a diagnosis of AIP can be made, highlights entities that should be considered in the differential diagnosis, and outlines the salient clinical and pathological features.

Definition (Diagnostic Criteria)

The key elements for a diagnosis of AIP are as follows^{12,14–16}:

1. Acute onset of respiratory symptoms resulting in severe hypoxia and, in most cases, acute respiratory failure
2. Bilateral lung infiltrates on radiographs
3. The absence of an identifiable etiology or predisposing condition despite adequate clinical investigation (see later discussion)
4. Histological documentation of DAD

The term *AIP* has the virtue of communicating the acute presentation and the prominent involvement of the pulmonary interstitium, which was the original intent of the term. In this way, the term *AIP* was an improvement over the eponym *Hamman-Rich syndrome*, which conveyed no useful information to the reader. However, although one source of confusion was eliminated (it is now clear that the Hamman-Rich syndrome is an acute interstitial process), the term *AIP* does not mention the underlying pathology (DAD), or the requirement that known causes of DAD be excluded before making the diagnosis. The current terminology is confusing in that DAD due to known causes is simply referred to as DAD (stating the cause), whereas DAD of unknown cause is termed AIP, implying that the lack of an identifiable etiology defines a discrete entity. The reader will note obvious parallels to UIP, which is termed UIP (stating the cause) when it occurs in the context of a known etiology such as systemic sclerosis, whereas the term *IPF* is applied when UIP is of unknown etiology.

Some published articles have used the term *AIP* for any patient with acute respiratory failure and bilateral infiltrates on radiographs that are assumed to be “interstitial.” Such cases of “AIP” do not meet the diagnostic criteria for AIP, in that either an underlying cause is present^{17–19} or there is no histological documentation of DAD.^{18,19} The following discussion refers only to cases that meet the diagnostic criteria of

AIP already enumerated here. ▶ **Table 1** provides a summary of the published series of AIP.^{9,12,20–29}

Clinical Features

AIP can affect patients of any age and sex. Patients have ranged from 13 to 79 years of age.^{12,29} There is no gender predilection. The condition has been reported in pregnancy.¹² Many (but not all) patients with AIP were previously healthy. The disease is often preceded by a viral-like or flulike prodromal illness or upper respiratory tract infection characterized by fatigue and myalgias, followed by acute onset of dyspnea and cough, accompanied in some patients by fever.^{9,23,29} Fever may precede respiratory symptoms.²⁹ The acuteness of the onset of symptoms is a defining feature of AIP; the duration of symptoms in the original series ranged from 2 to 11 days.¹² However, subsequent series have included patients with symptom durations up to 2 months.^{23,27,29} Physical findings are variable but include tachypnea, cyanosis, crackles, and wheezes.²³ Because digital clubbing is not a feature of AIP but is seen in patients with acute exacerbation of IPF (presumably caused by the underlying chronic fibrotic process), it has been suggested as a useful clinical finding in separating these two entities.²⁸ Most patients with AIP are hypoxic on room air, and nearly all require mechanical ventilation.²³ Laboratory findings are nonspecific and unhelpful. Many patients show a nonspecific leukocytosis with neutrophilia.

Radiology

The main radiological finding in DAD is the presence of bilateral lung infiltrates, which vary from patchy to diffuse and are often described as alveolar. The high-resolution computed tomographic (CT) findings of AIP have been well described.^{20–22,30} They include bilateral ground-glass opacities and/or bilateral airspace consolidation (opacification) (▶ **Fig. 1**). These findings can be seen in other diseases and are therefore nonspecific. Although traction bronchiectasis and honeycombing have been observed in some patients with putative AIP,³⁰ it is likely that these features indicate the presence of an underlying chronic interstitial fibrosing process such as UIP/IPF rather than pure DAD/AIP (see “Acute Exacerbation of IPF”).²⁰

Pathology of AIP—Diffuse Alveolar Damage

Because the histological finding of DAD is one of the key diagnostic criteria of AIP, a lung biopsy is required at some point during the clinical course; in patients who die without an antemortem biopsy, histological examination of the lungs at autopsy can confirm the diagnosis. Most patients undergo surgical lung biopsies (open or video-assisted thoracoscopy), although DAD is diagnosable on transbronchial biopsies. Histologically, the characteristic feature of DAD in its early (acute) stages is the formation of *hyaline membranes*, which are eosinophilic linear structures composed of necrotic alveolar epithelial cells and serum proteins extruded from

Table 1 Published Series of AIP

First Author (Year)	Number of Patients	Causes of DAD That Were Excluded in the Study	Outcome
Katzenstein (1986) ¹²	8	Not specified	6 of 8 died; 2 survived to discharge (one died at 6 months)
Olson (1990) ⁹	29	Collagen vascular disease (rheumatoid arthritis, SLE, scleroderma), severe hypotensive episode, infection, COPD, radiation, nitrofurantoin, cyclophosphamide, bleomycin, Wegener granulomatosis, asbestos exposure, hairy cell leukemia	17 of 29 died; 12 survived, some for up to 2 years; no histological features could discriminate survivors from nonsurvivors
Primack (1993) ²⁰	9	Infections, including viral Cases with underlying UIP/IPF and SLE were not excluded	8 of 9 died within 3 months of presentation
Ichikado (1997) ²¹	14	Not specified	All patients died within 2 weeks to 6 months
Johkoh (1999) ²²	36	Not specified	Not available
Vourlekis (2000) ²³	13	Infections, cancer chemotherapy, collagen vascular diseases, AIDS, organ transplant, SIRS, toxic exposures	12 of 13 required mechanical ventilation; 4 died in hospital; 8 survived (hospital survival: 67%)
Quefatieh (2003) ²⁴	8	Dermatomyositis, infectious pneumonia/sepsis, cocaine, carmustine	7 of 8 survived to hospital discharge
Rice (2003) ²⁵	6	Dermatomyositis, rheumatoid arthritis, Still disease, SLE	All patients died (this was an autopsy series)
Bonaccorsi (2003) ²⁶	4	Infection, collagen vascular disease	3 of 4 died between 7 and 38 days
Suh (2006) ²⁷	10	Infections, drugs, collagen vascular diseases, acute exacerbation of IPF	8 of 10 survived to hospital discharge; survivors were followed from 12 to 78 months; most were asymptomatic on follow-up
Parambil (2007) ²⁸	12	Infections, noninfectious complications of transplantation, acute exacerbation of IPF, connective tissue diseases (rheumatoid arthritis, polymyositis/dermatomyositis, diffuse systemic sclerosis, mixed connective tissue disease), drugs, radiation	6 of 12 died (50% hospital mortality)
Avnon (2009) ²⁹	9	Cardiac disease, infections, autoimmune disease, malignancy	All patients died within 5–26 days of admission to intensive care unit (100% mortality)

AIDS, acquired immunodeficiency syndrome; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; SIRS, systemic inflammatory response syndrome; SLE, systemic lupus erythematosus; UIP, usual interstitial pneumonia.

damaged, leaky capillaries. As the disease progresses (organizes), hyaline membranes are resorbed, and fibroblasts begin to migrate into the alveolar septa (interstitium). In later stages (organizing DAD, also known as fibroproliferative DAD), the histology is dominated by *interstitial thickening by fibroblasts* (—Fig. 2). Hyaline membranes may be focal or absent at this stage, presumably because they are resorbed into the interstitium.¹² Histologically, therefore, DAD evolves from a stage where interstitial involvement is subtle (early stage, with hyaline membranes) to a stage where interstitial involvement is prominent and obvious (late/organizing stage). Perhaps because interstitial involvement is more obvious in the organizing stage of DAD, early series of AIP emphasized the histological features of this stage of the disease.^{8,9,12} However, because acute and organizing DAD frequently coexist in

the same biopsy,¹¹ because small biopsies may sample only areas showing the acute stage when both stages are present, and because there is no clear-cut dividing line between acute and organizing DAD (the process is a continuum), we see no good reason to restrict the definition of AIP to cases that show only organizing DAD. Stated another way, there is no reason to exclude from the definition of AIP those cases that show only acute DAD.

In addition to hyaline membranes and proliferating interstitial fibroblasts, several other histological findings are variably present in DAD, many of which often distract practicing pathologists from the correct diagnosis. These include alveolar collapse/atelectasis, hyperplasia of type 2 pneumocytes (which may be marked), edema within the alveolar septa, thrombi within small pulmonary arteries, squamous



Figure 1 Bilateral diffuse pulmonary infiltrates in acute interstitial pneumonia (AIP). This radiological picture is not specific for AIP.

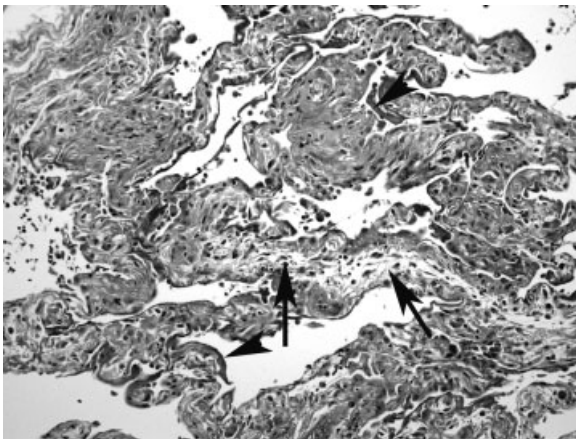


Figure 2 Histological findings in acute interstitial pneumonia (AIP). The histological basis of acute interstitial pneumonia is diffuse alveolar damage (DAD), which is characterized by hyaline membranes in the acute stage and interstitial fibroblast proliferation in the late (organizing) stage. This histological image illustrates the characteristic diffuse interstitial thickening (caused by proliferating fibroblasts) seen in the organizing stage of DAD. Hyaline membrane remnants (arrowheads) are focally present, as are interstitial fibroblasts (long arrows) (hematoxylin and eosin stain, 100 \times).

metaplasia (often exuberant), and mild interstitial chronic inflammation. Inflammatory cells, especially neutrophils, are scant in most cases, differentiating AIP from entities such as acute bronchopneumonia and acute necrotizing capillaritis. Organisms are, by definition, absent. Cases in which organisms are apparent on biopsy should not be termed AIP; instead, they should be referred to simply as DAD, and the cause should be stated.

The role of lung biopsy is not just limited to identifying DAD but also extends to identification of an underlying etiology. In a study of 58 cases of DAD diagnosed on surgical lung biopsies, the biopsy provided the etiology in six (10%), mainly by identifying underlying UIP (hence diagnosing acute exacerbation of IPF) or an infection such as cytomegalovirus (CMV).²⁸ In immunocompromised patients who at first glance appear to have DAD of unknown cause on histological

examination, performing a Grocott's methenamine silver (GMS) stain for fungal organisms can be helpful given that *Pneumocystis* pneumonia can occasionally manifest histologically as DAD instead of the usual intraalveolar frothy material.^{31,32}

Etiology of DAD—What to Exclude before Diagnosing AIP

As already mentioned, DAD is the pathological basis of AIP. Because AIP is defined as an idiopathic entity, known causes of DAD need to be excluded before the term AIP is applied. In practice, the usual diagnostic sequence is that the finding of DAD on a lung biopsy prompts consideration of AIP, and it is at this point that exclusion of underlying occult etiologies becomes an issue. Some causes of DAD, such as sepsis, prior chemotherapy, or obvious massive trauma, are clinically obvious at the time of diagnosis. Additionally, in most cases, an initial effort to exclude infection has already been made by this time. However, other etiologies such as drug toxicities or connective tissue diseases may not have been considered prior to a pathological diagnosis of DAD. Although there are no standard recommendations for required testing, the study by Olson et al is a good reference for clinicians looking for a summary of the main etiologies to exclude,⁹ namely infections, connective tissue diseases, and drug toxicities (► **Table 2**).^{28,33–56} Comprehensive lists of causes have been compiled elsewhere, especially with respect to drug toxicities.^{51,52,54} Some authors have included organ transplant recipients in series of AIP,¹² but others would exclude such patients because these cases have now been determined to be specific noninfectious, transplant-related pulmonary complications and have been labeled idiopathic pneumonia syndrome, peri-engraftment respiratory distress syndrome, and diffuse alveolar hemorrhage syndrome.^{23,57}

Infection is the most important etiology to exclude in patients in whom a diagnosis of AIP is being considered clinically, or in whom DAD has been diagnosed on a lung biopsy. This should take the form of microbiological and serological testing, including cultures of sputum, blood, bronchial washings, and/or bronchoalveolar lavage (BAL) fluid. It is important to remember (for pulmonologists or surgeons performing lung biopsies) that a representative piece of biopsied lung tissue should be submitted for cultures. Histological examination can be the key diagnostic modality for detecting organisms that are impossible to culture (e.g., *Pneumocystis*), or detected late in cultures (such as many mycobacteria, *Blastomyces* and *Histoplasma*). These organisms are often easily and rapidly detected by histological examination of lung biopsy specimens. *Pneumocystis* pneumonia, in particular, should always be considered in the differential diagnosis of an AIP-like clinical presentation in immunocompromised patients because *Pneumocystis* can cause DAD histologically^{31,32} and manifest as ARDS clinically.² *Pneumocystis* organisms may be difficult or impossible to detect by modalities other than histological examination. CMV can also be identified as a cause of DAD by histological

Table 2 Known Causes of Diffuse Alveolar Damage

Causes of DAD	Examples
Infection	Viruses Influenza, seasonal and pandemic ³³⁻³⁵ Herpes simplex virus type 1 ^{28,36} Cytomegalovirus ^{28,37-39} Adenovirus ⁴⁰ Respiratory syncytial virus ^{28,41} Fungi Disseminated histoplasmosis ⁴² Cryptococcal pneumonia ²⁸ Nontuberculous mycobacterial infection ²⁸
Connective tissue diseases	Rheumatoid arthritis ^{25,28,43,44} Polymyositis/dermatomyositis ^{24,25,28,43,45,46} Systemic lupus erythematosus ²⁵ Systemic sclerosis (scleroderma) ^{28,43,47} Mixed connective tissue disease ^{28,43} Sjögren syndrome ⁴⁸ Anti-Jo-1 tRNA synthetase syndrome ⁴⁹
Drugs ⁵⁰⁻⁵⁴	Amiodarone Bleomycin Busulfan Carmustine (BCNU) Cocaine Cyclophosphamide Cytosine-arabinoside (Ara-C) Gemcitabine Nitrofurantoin
Aspiration ⁵⁵	
Noninfectious complications of organ transplantation ²⁸	
Oxygen toxicity ⁵⁶	

examination, either by identification of the pathognomonic inclusions on routine hematoxylin and eosin (H&E)-stained sections or by immunohistochemistry.^{28,37}

Connective tissue diseases (collagen vascular diseases) are another major group of diseases that may manifest pathologically as DAD.⁵⁸ The main connective tissue diseases that are associated with DAD are dermatomyositis/polymyositis (including the antisynthetase syndrome), systemic sclerosis (scleroderma), systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, and mixed connective tissue disease (► **Table 2**). DAD usually occurs in patients with established disease, and is discovered either at presentation along with other systemic features, or later in the course of the illness. However, it can occasionally be the presenting manifestation of the disease.^{43,46} Therefore, the histological finding of DAD on lung biopsy in a patient without an apparent underlying etiology should always prompt a work-up for connective tissue disease. The required serological tests to perform and the interpretation of the results in the context of these lung-dominant undifferentiated connective tissue diseases is still a moving target; the issues surrounding this problem have been well summarized by Fischer and colleagues.⁵⁸

DAD is the most commonly reported histological manifestation of drug toxicity.⁵² Many drugs can cause DAD, the most classic being chemotherapeutic agents such as bleomycin and

busulfan. Of the nonchemotherapeutic agents, amiodarone and nitrofurantoin are perhaps some of the best-known causes. Drug-related lung disease is always a complicated diagnosis that is difficult if not impossible to prove. In most cases, a presumptive diagnosis of drug toxicity is based on onset of disease after commencement of drug therapy, amelioration of symptoms with cessation of therapy, and exclusion of other causes, the most important being infection. Although lung biopsies help to exclude infection and pinpoint the underlying pathological manifestation (including DAD), it is important to stress that *no specific pathological findings are unique to drug-related lung disease, or pathognomonic of any specific drug*. Despite the difficulty in implicating a drug with certainty, the occurrence of DAD in the context of therapy with a drug known to be associated with DAD should exclude a diagnosis of AIP.

Pathogenesis

DAD (and thus AIP) is a manifestation of acute lung injury. Regardless of the type of injurious agent, the injury typically damages alveolar epithelium as well as alveolar septal capillary endothelium. Histologically, injury to these two elements (epithelium and endothelium) results in a mixture of debris derived from necrotic epithelial cells and serum proteins derived from the injured capillaries that forms hyaline membranes. The subsequent repair reaction, termed the organizing, proliferative, or fibroproliferative stage of DAD, is characterized by incorporation of hyaline membranes into the interstitium accompanied by marked proliferation of fibroblasts within the interstitium. The assertion that the fibroblasts are indeed proliferating rapidly is supported by multiple techniques, including incorporation of tritiated thymidine, and a high Ki-67 labeling index by immunohistochemistry.^{12,59} The presence of histologically diffuse fibroblast proliferation separates organizing DAD (AIP) from UIP, in which most of the fibrosis is chronologically “older” (manifested mainly by collagen deposition), with only tiny foci of fibroblast proliferation.¹³

Differential Diagnosis

The differential diagnosis of AIP includes infection, congestive heart failure, ARDS, acute exacerbation of IPF, and DAD due to known causes.

Infection

As already mentioned, the clinical and radiological features of fulminant infections can be identical to those of AIP. Therefore, every attempt should be made to identify an organism before a label of AIP is applied. Clinicians should request appropriate microbiological and serological tests, and pathologists should examine biopsy specimens for organisms. If the patient is immunocompromised, it is vital that this information be provided to the pathologist because this increases the intensity of the search for an organism and may trigger the use of special histochemical or immunohistochemical stains.

Congestive Heart Failure

Congestive heart failure (CHF) often enters the differential diagnosis of patients eventually shown to have AIP. Exclusion of CHF is a key criterion in the definition of ARDS, and the same applies to AIP. Radiologically, ARDS and AIP can be indistinguishable from cardiogenic pulmonary edema.⁴ In fact, ARDS and AIP are often referred to as noncardiogenic pulmonary edema, a somewhat misleading term given that the pathology in these cases is DAD rather than edema. Today, the diagnosis of CHF can be made reliably with the use of various noninvasive tools such as echocardiography and serum B-type natriuretic peptide (BNP) levels. In unclear cases the use of Swan-Ganz catheterization to obtain pulmonary capillary wedge pressure helps to establish the diagnosis.

ARDS

There are so many common features between ARDS and AIP—acute onset of symptoms, severe hypoxia, bilateral infiltrates on radiographs, respiratory failure requiring mechanical ventilation, poor prognosis, high fatality rate, and DAD on histology—that the reader may well wonder why ARDS and AIP are not the same entity!^{3,11,60} In fact, AIP has occasionally been labeled idiopathic ARDS. Comparison of the diagnostic criteria for ARDS and AIP reveals that the definitions are nearly identical, with two key differences. First, ARDS is defined solely by clinical criteria, whereas the criteria for AIP require both clinical and pathological input, thus mandating histological examination of the lung for diagnosis. This makes AIP a somewhat more narrowly defined entity, whereas ARDS, being diagnosed on clinical grounds, is more heterogeneous in terms of underlying pathology.^{2,61} For example, in some cases that meet the clinical definition of ARDS, histological examination reveals not DAD but other findings such as infectious pneumonia, capillaritis with alveolar hemorrhage, or organizing pneumonia. Second, the definition of AIP requires that the disorder be of unknown etiology, whereas the definition of ARDS holds true regardless of whether an underlying cause is identified.

With these definitions in mind, therefore, ARDS and AIP should be conceptualized not as two distinct entities or diseases, but as differing ways of defining subsets of patients with severe acute lung injury. Because the definitions overlap, both diagnoses can often be applied to the same patient. Thus some patients with ARDS fulfill the clinical and histological criteria for AIP, and virtually all patients with AIP meet the clinical diagnostic criteria for ARDS.^{9,11,14} The relationship between ARDS and AIP is illustrated schematically in **Fig. 3**. The presence of multiorgan failure in ARDS and its absence in AIP has been cited as a difference between the two entities.²⁴ Although multiorgan failure is more common in ARDS than in AIP,²⁴ there are no published data to show that multiorgan failure is an accurate discriminator between these conditions.

Acute Exacerbation of IPF

The preceding discussion may lead the reader to think that interstitial fibrosis can always be neatly categorized into acute and chronic forms. However, there is a group of patients

with chronic interstitial fibrosis (either established or occult) who develop superimposed acute lung injury (which may also involve fibrosis), thus developing a mixed acute-on-chronic fibrosing picture. The classic example is patients with known UIP/IPF who develop superimposed DAD, often of unknown cause.^{62–65} Although the resultant acute idiopathic illness is similar to AIP, the key difference is in the presence of underlying chronic fibrosis. Therefore, the appropriate term for this condition is not AIP but *acute exacerbation of IPF*.^{64,66} The existence of such acute-on-chronic cases explains why it has been so difficult in the past to neatly separate acute forms of pulmonary fibrosis (such as AIP) from chronic forms such as UIP/IPF. Some of these patients already have a known underlying occult chronic interstitial lung disease (e.g., IPF) when the acute injury supervenes, whereas in others the superimposed acute lung injury is the first manifestation of lung disease, and the underlying chronic interstitial fibrosis is discovered only when the superimposed acute lung injury brings the patient to clinical attention. Evidence of a mixture of chronic and acute processes is often difficult to demonstrate but can be sought in several ways. Clinically, a patient with known chronic pulmonary fibrosis may suddenly deteriorate and develop acute respiratory failure. Radiologically, there may be evidence of chronic interstitial fibrosis (honeycombing and traction bronchiectasis/brochiolectasis)⁶⁶ as well as acute interstitial fibrosis (ground-glass opacities or consolidation). Finally, histology, which is the gold standard in evaluating such cases, may show a combination of acute and chronic processes such as DAD and UIP in the same biopsy.^{9,65} It is likely that reports of traction bronchiectasis and honeycombing (features typically seen in UIP) in purported cases of AIP represent occult underlying UIP rather than pure AIP.²¹ In fact, traction bronchiectasis and honeycomb change have been claimed to be adverse prognostic features in AIP, an observation which (in hindsight) suggests that these patients had underlying UIP, which may be a better explanation for their worse prognosis than if they had AIP alone.

DAD Due to Known Causes

DAD caused by known etiologies is clinically and radiologically identical to AIP, the only difference being one of terminology. As discussed in the prior sections, known causes of DAD need to be excluded clinically before the term *AIP* is used.

Treatment

There is no proven effective therapy for AIP.²³ Virtually all patients require mechanical ventilation and supportive care. A lung-protective strategy in mechanical ventilation has been advocated based on its established benefits in ARDS. Many patients are treated with high-dose intravenous corticosteroids,⁶¹ the use of which is based on reports of lower mortality in ARDS with such therapy,⁶⁷ and claims that high-dose pulse corticosteroid therapy may lower mortality.²⁷ Others, however, have found no beneficial effect of corticosteroid therapy in AIP,^{23,29} a reflection of the unproven benefit of corticosteroid therapy in the broader mixed bag of

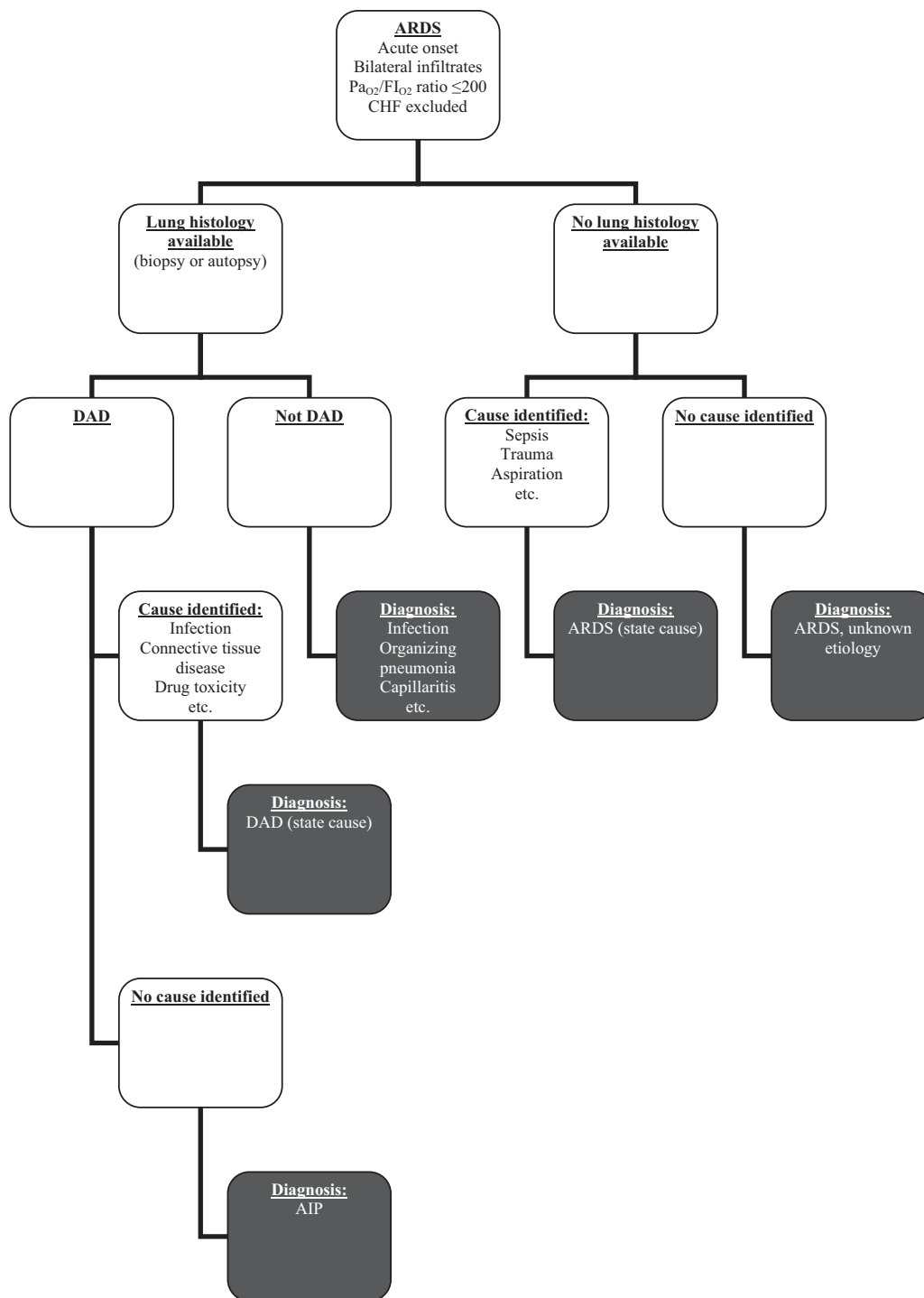


Figure 3 Flowchart showing relationship between acute respiratory distress syndrome and acute interstitial pneumonia.

ARDS in general.⁶⁸⁻⁷⁰ An evidence-based approach to the therapy of AIP is very difficult because of the rarity of the diagnosis and because all reports of the condition to date are small, descriptive case series.

Prognosis

The prognosis of AIP is poor (similar to that for ARDS), with most patients dying of acute respiratory failure or its com-

plications despite mechanical ventilation and high-dose corticosteroid therapy.^{12,23,29} Overall, approximately half of patients die within 2 months.⁶¹ However, variable numbers of survivors have been reported in most series.^{9,12,23,24,27,28} It is well documented that some patients with AIP survive the initial hospitalization but die of recurrent AIP, pneumonia, or CHF within a few months after discharge.^{9,23}

Outliers in terms of prognosis are the reports by Quefatieh et al and Suh et al, which have reported lower mortality

rates.^{24,27} In the series reported by Quefatieh et al, only one of eight patients died. The reasons for this strikingly low mortality are unclear, although the authors claimed that early and more frequent corticosteroid therapy in their patients may have been responsible. In Suh et al's series, eight of 10 patients survived to discharge. The authors claimed that their lower mortality may have been achieved by a combination of early lung biopsy, pulse high-dose corticosteroids, and a lung-protective strategy during mechanical ventilation. Most series of AIP have not been able to replicate these findings, the mortality in the majority of these ranging from 50 to 100%^{9,20,21,26,28,29} despite the use of intravenous high-dose corticosteroids^{9,26,28,29} and lung-protective ventilation strategies.²⁹

In one study of DAD, the hospital mortality rate from AIP (50%) was similar to that from DAD due to known causes (53%), suggesting that in patients who have DAD as their underlying pathology, identification of an underlying etiology does not necessarily improve the outcome.²⁸ In fact, to date, no consistent clinical or pathological features identify those patients with DAD who are likely to have a better outcome.^{9,61}

Long-term survival is possible after recovery from AIP, with documented survival for up to 2 to 4 years after diagnosis.^{9,23} Progression of AIP to chronic interstitial lung disease and honeycomb change has been reported, which seems to imply that AIP can evolve into UIP.²³ However, an alternative explanation for this observation is that the apparent episode of "AIP" was actually an acute exacerbation of underlying occult IPF, which may not have been detected at the time of the initial acute injury. Subsequently, the underlying chronic fibrosis may have become manifest over a period of time, at which time honeycombing became apparent.²³

Summary

1. The defining features of AIP are rapid onset of respiratory symptoms, development of acute respiratory failure with bilateral lung infiltrates on radiographs, absence of an identifiable cause or predisposing illness despite adequate microbiological and serological studies, and documentation of DAD on histology (antemortem by surgical lung biopsy or postmortem at autopsy). The condition overlaps with ARDS, although it is defined differently (i.e., requires histological diagnosis of DAD and exclusion of known causes).
2. Almost all patients with AIP require mechanical ventilation. Most are treated with high-dose intravenous corticosteroids. Response to therapy is variable and usually poor. The mortality is greater than 50% in most series. However, a subset of patients survives to discharge.
3. DAD is characterized histologically by hyaline membranes in the early (acute) stage and interstitial fibroblast proliferation in later (organizing) stages. DAD is a purely pathological diagnosis, but AIP is not. By definition, AIP cannot be diagnosed by pathologists without knowledge of the

clinical setting (acute respiratory failure, bilateral infiltrates, absence of etiology).

4. In the presence of radiological or pathological evidence of underlying UIP/IPF, the combination of acute respiratory failure and DAD should be termed acute exacerbation of IPF rather than AIP, even if the etiology is unknown, as is frequently the case. Patients with acute exacerbation of IPF—like those with AIP—have a poor prognosis, with the additional complication of underlying irreversible chronic pulmonary fibrosis.

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