Many immunologic disorders have been associated with diffuse pulmonary capillary hemorrhage, as listed in the following tabulation:

A. Antibasement membrane antibody (ABMA) disease
B. Vasculitides and collagen vascular diseases
   1. Nonspecific systemic necrotizing vasculitis
   2. Systemic lupus erythematosus (SLE)
   3. Wegener's granulomatosis
   4. Henoch-Schönlein syndrome
   5. Polyarteritis nodosa
   6. Behçet's disease
   7. Essential mixed cryoglobulinemia
   8. Endocarditis-related vasculitis
   9. Tumor-related vasculitis
   10. Rheumatoid arthritis
   11. Progressive systemic sclerosis
   12. Mixed connective tissue disease
C. Idiopathic rapidly progressive glomerulonephritis (RPGN)
   1. Immune complex-mediated
   2. Without immune deposit
D. Chemical or drug-related
   1. D-Penicillamine
   2. Trimelillic anhydride
E. Idiopathic pulmonary hemosiderosis

Immune alveolar hemorrhage (IAH) is usually due to ABMA or one of the vasculitides but also occurs in the setting of idiopathic RPGN or following exposure to certain drugs or chemicals. A similar pattern of diffuse alveolar hemorrhage is observed in idiopathic pulmonary hemosiderosis. This disorder is suspected of having immune etiology and will therefore be included in this review of IAH.

Immune alveolar hemorrhage in adults usually occurs with glomerulonephritis. Our experience and that of Holdsworth et al suggest that 40 to 60 percent of the patients with IAH and glomerulonephritis will have an identifiable vasculitis at presentation. An additional 15 to 30 percent of the patients have IAH and idiopathic RPGN, ie, acute crescentic glomerulonephritis without definite vasculitis or ABMA. Some of the latter patients have a glomerular lesion that is highly suggestive of renal vasculitis, and some will eventually develop extrarenal manifestations of vasculitis. Therefore, the vasculitides are probably responsible for 50 to 80 percent of the cases of IAH and glomerulonephritis in adults. In our experience, vasculitis-related IAH is most often due to a predominantly small-vessel vasculitis that uniformly causes necrotizing glomerulonephritis and variably affects other organs. We have used the term, nonspecific systemic necrotizing vasculitis, to define this disorder, but others would categorize these cases as microscopic polyarteritis or polyangiitis overlap syndrome. Wegener's granulomatosis and SLE account for most of the remaining cases of vasculitis-related IAH.

Antibasement membrane antibody disease is responsible for the 20 to 40 percent of the cases of IAH and glomerulonephritis that are not related to the vasculitides or idiopathic RPGN. The term, Goodpasture's syndrome, is often used in specific reference to IAH and glomerulonephritis caused by ABMA; however, this eponym was coined before the discovery of ABMA to define the clinical syndrome of IAH and glomerulonephritis. The original clinical definition is preferred by some authors. Due to lack of agreement on its most appropriate usage, this eponym will not be used in this review.

Idiopathic pulmonary hemosiderosis is defined as IAH that occurs without glomerulonephritis or other extrapulmonary disease and that cannot be ascribed to one of the immune disorders or chemicals listed in the previous tabulation. Idiopathic pulmonary hemosiderosis primarily affects children and is an uncommon cause of adult IAH.

**Diagnosis of IAH**

The clinical and roentgenographic manifestations of IAH are similar regardless of its etiology. These consist of hemoptysis, infiltrates on the chest roentgenogram,
anemia, dyspnea, and occasionally fever or chest pain.3-5 The three most consistent features, upon which clinical recognition of IAH is usually dependent, are hemoptysis, pulmonary infiltrates, and anemia. The quantity of hemoptysis is variable and is not a reliable index of the degree of IAH, because alveolar bleeding does not readily gain access to central airways.6-8 Massive hemoptysis is unusual, even when IAH is extensive. The chest roentgenogram typically shows an alveolar or mixed alveolar-interstitial pattern.9-11 A distribution like pulmonary edema is most common, but focal and sometimes migratory shadows are also observed. The anemia of IAH is due primarily to acute intrapulmonary blood loss. Iron deficiency may be contributory if bleeding has been long-term.12 In our experience the triad of hemoptysis, infiltrates, and anemia has been present in nearly all cases of acute IAH,2 however, active IAH does occur without hemoptysis4,10 or with a normal chest roentgenogram.13

The differential diagnosis of IAH includes the many other causes of hemoptysis and pulmonary infiltrates. Two considerations are very helpful in arriving at a prompt diagnosis of IAH: (1) the clinical setting in which hemoptysis and infiltrates occur; and (2) determining whether the alveolar filling process represents frank hemorrhage. The clinical setting is very important, because IAH is typically associated with glomerulonephritis. Extrapulmonary features (eg, purpura, synovitis, and mononeuritis multiplex) may also be present if the underlying disorder is vasculitis or SLE. Isolated IAH is uncommon, but does occur in idiopathic pulmonary hemosiderosis and occasionally may be the presenting manifestation of ABMA disease14 or one of the vasculitides.15-17

Even when the clinical setting is appropriate, IAH still must be differentiated from other alveolar filling processes. In addition to examination of sputum and measurement of the wedge pressure, tests that indicate whether or not alveoli are filled with blood are useful in differentiating IAH from pneumonia and pulmonary edema. Comparison of sequential hemoglobins with chest roentgenograms is very helpful. Active IAH often causes the hemoglobin level to fall 2 to 4 g/dl or more over 24 to 48 hours.3,37,38 In the appropriate clinical setting, the association of frank hemoptysis and bilateral infiltrates with an otherwise unexplained fall in hemoglobin level is highly suggestive of IAH. Conversely, a stable hemoglobin level in the face of progressive alveolar shadowing serves to exclude IAH.

Alveolar hemorrhage can be detected by measuring the uptake of carbon monoxide by the lung, because the large pool of extravascular erythrocytes will bind inhaled carbon monoxide.37,38 As initially described, diagnosis of alveolar hemorrhage was based upon the slow rate of disappearance of radiolabelled carbon monoxide.37 Subsequently, the standard single-breath techniques of measuring carbon monoxide uptake have been used to monitor IAH in ABMA disease.38,39 Rees4 has found an increase in the kCO of 30 percent or more over baseline to be a reliable indicator of recent (<48 hours) IAH. Most patients who present with IAH do not have a baseline value for comparison; however, a markedly elevated result would be suggestive of alveolar hemorrhage. Another limitation of this technique is that many patients are too ill to be tested properly.

Bronchoalveolar lavage (BAL) has also been used to diagnose diffuse alveolar hemorrhage40 and can be performed in virtually all cases, regardless of the severity of the disease. The lavage effluent in diffuse alveolar hemorrhage is usually bloody and contains abundant hemosiderin in macrophages. It may require up to 48 hours after an acute hemorrhage for macrophages to show much hemosiderin.41 Recent observations in a large number of immunocompromised patients who underwent both BAL and open lung biopsy have shown that the hemosiderin content of macrophages very reliably predicted the degree of hemorrhage in sections of tissue (Jeffrey Jones, M.D., oral communication, December, 1986). Lavage may be particularly useful when infection is being considered in the differential diagnosis.41

Diffuse alveolar hemorrhage is not limited to immune and idiopathic disorders; for example, extensive pulmonary hemorrhage can result from mitral stenosis42 (or rarely other causes of high pulmonary venous pressure), diffuse necrotizing infection (eg, Aspergillus, Pseudomonas, and, rarely, Legionella43), severe coagulopathy,44 acute leukemia,45 fat embolism,46 and lymphangiography.47 The nonimmune causes of alveolar hemorrhage are usually easily defined by the clinical setting or by relatively straightforward diagnostic techniques such as examination of sputum, studies of coagulation, echocardiography, or measurement of the wedge pressure. Pulmonary emboli also cause alveolar hemorrhage,50 but unlike IAH the infiltrates are usually pleural-based and seldom diffuse, and the degree of hemorrhage is not enough to cause anemia. Anticoagulation may prove disastrous to patients with IAH.51 Pulmonary angiography is therefore mandatory if pulmonary emboli and IAH cannot be otherwise differentiated with absolute confidence.

Differentiation of IAH and hemorrhagic pulmonary edema due to advanced renal failure with volume overload may be difficult. Early measurement of wedge pressure may be helpful, but an elevated value does not exclude IAH. Although pulmonary hemorrhage has been reported to result solely from azotemic hypervolemia,52-54 clinical observation and a large postmortem study55 indicate that this is very uncommon. Therefore, evidence of major hemorrhage (large hemoptysis; abrupt fall in hemoglobin level; elevated

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carbon monoxide diffusing capacity; grossly bloody BAL with abundant hemosiderin in macrophages) suggests concomitant IAH and the need for empiric therapy while dialysis and efforts to clarify the underlying disorder are undertaken. If the evidence for major hemorrhage is less convincing, the response to dialysis alone should be revealing, since pulmonary edema should clear rapidly.

**Defining the Cause of IAH**

Although many diseases may cause IAH, six disorders account for the great majority of cases: (1) ABMA disease; (2) nonspecific systemic necrotizing vasculitis; (3) Wegener's granulomatosis; (4) SLE; (5) idiopathic RPGN; and (6) idiopathic pulmonary hemosiderosis. These disorders are differentiated primarily by their extrapulmonary clinicopathologic features. Renal biopsy, serologic studies, and clinical assessment of involvement of extrapulmonary organs are especially useful for defining the etiology of IAH. Biopsy of the lung is seldom indicated.

Antibasement membrane antibody causes IAH, glomerulonephritis, or both. Organs other than the lungs and kidneys are unaffected. Sixty to 80 percent of the patients have pulmonary involvement, and the vast majority of these individuals also have glomerulonephritis. Renal function may be normal at the time of presentation, but microscopic hematuria is present in nearly 90 percent of the cases. A documented case of ABMA-mediated IAH without glomerular deposits of ABMA has yet to be reported.

Diagnosis of ABMA disease is established by renal biopsy and serum assay of ABMA. Renal biopsy often reveals a diffuse crescentic glomerulonephritis, but focal glomerulonephritis or even histologically normal glomeruli may be observed. The hallmark of ABMA-mediated glomerulonephritis is the presence of linear deposits of IgG in glomeruli by immunofluorescence. Nonspecific linear staining for IgG can be seen in diabetes and rarely in other disorders, but in these instances, there is also linear staining for albumin, and ABMA is not found in serum. Serum ABMA is detected by radioimmunoassay, enzyme-linked immunosorbent assay (ELISA), and indirect immunofluorescence. Radioimmunoassay is a sensitive (97 percent) and specific (98 percent) method for diagnosing ABMA-mediated IAH. The ELISA is also a very reliable technique for diagnosing ABMA disease. Radioimmunoassay and ELISA are performed by few laboratories; therefore, results may not be available for several days. Indirect immunofluorescence is available at many institutions and can be performed within a few hours. A strongly positive result with negative controls is diagnostic of ABMA disease, but this technique is less sensitive than radioimmunoassay or ELISA at detecting circulating ABMA (Alfred Fish, M.D., oral communication, December, 1986).

Another method of diagnosing ABMA-mediated IAH is lung biopsy. Although the histopathologic features are nonspecific, linear deposits of ABMA can be demonstrated along alveolar septa by immunofluorescent techniques. Transbronchial biopsy of the lung was originally reported to be a sensitive method for demonstrating ABMA in the lung; however, a recent study found false-negative results in seven of ten patients with ABMA-related IAH who underwent transbronchial biopsy. From a practical standpoint, lung biopsy is rarely needed to diagnose ABMA disease because of the ease and reliability of establishing a diagnosis by renal biopsy and serum assay of ABMA.

The IAH of systemic necrotizing vasculitis is nearly always associated with glomerulonephritis. The skin, joints, nervous system, or gastrointestinal tract may also be involved. These extrarenal features serve to distinguish vasculitis-related IAH and glomerulonephritis from ABMA disease. In addition, the findings from renal biopsy in systemic necrotizing vasculitis and ABMA disease are different. Renal vasculitis typically causes a focal and segmental necrotizing glomerulonephritis with absent or minimal immune deposits. Frank extraglomerular arteritis is seldom observed in specimens from percutaneous biopsy.

The pulmonary pathology of vasculitis-related IAH is somewhat analogous to the vasculitic lesions in the kidney in that the predominant changes are seen in capillaries rather than larger vessels. Mark and Ramirez recently reviewed the histopathologic features in 13 cases of vasculitis-related IAH and found pulmonary capillaritis in all cases. Arteriolitis or venulitis was seen in only five of the 13 cases, and involvement of larger vessels was not observed. Recognition of pulmonary capillaritis may be difficult, especially for pathologists who are not experts in the pathology of non-neoplastic pulmonary disease. In addition, similar changes can be seen in other conditions (eg, idiopathic pulmonary hemosiderosis and diffuse alveolar damage). The value of open lung biopsy in diagnosing vasculitis-related IAH is therefore uncertain and would seem to add little to the information provided by clinical examination and renal biopsy.

Wegener's granulomatosis shares many clinical and pathologic features with nonspecific systemic vasculitis, including a similar renal histopathology. Characteristic lesions of the upper and lower respiratory tract serve to distinguish this disorder from other vasculitides. Patients who present with IAH as the initial manifestation of Wegener's granulomatosis may not have distinctive features such as sinus disease or cavitary pulmonary nodules. In addition, open biopsy of IAH may reveal only pulmonary capillaritis. Therefore, it may be difficult or impossible to differ-
entiate Wegener's granulomatosis from nonspecific systemic vasculitis when the pulmonary disease is IAH without focal nodules or cavities. When IAH does coexist with cavitary lesions or nodules in the lung, a diagnosis of Wegener's granulomatosis is very likely, and lung biopsy of the focal lesion should provide a specific diagnosis.8,63

Immune alveolar hemorrhage in SLE is generally accompanied by active extrapulmonary disease (fever, arthritis, glomerulonephritis, hypocomplementemia, etc).3,8,41 A diagnosis of SLE has usually been established prior to the development of IAH; therefore, the nature of the underlying immune disorder is seldom in question; however, certain features of active SLE may make it difficult to differentiate IAH from nonimmune pulmonary disorders.44 These include immune thrombocytopenia that may cause pulmonary hemorrhage with nonimmune pulmonary insults, immune hemolysis that may cause abrupt changes in hemoglobin, and the prior use of immunosuppressive therapy that increases the risk of infections characterized by blood vessel invasion and resultant pulmonary hemorrhage (eg, invasive Aspergillus; Pseudomonas pneumonia).

Idiopathic RPGN with IAH is diagnosed when the renal biopsy shows crescentic glomerulonephritis without arteritis or linear immunofluorescence and there are no extrarenal features of a multisystem immune disorder. Glomerular immunofluorescence may reveal either a granular pattern (immune complexes)49 or, more often, minimal or no immune deposits.3,65 An underlying vasculitis is almost certainly responsible for this syndrome if the renal lesion is a segmental necrotizing glomerulonephritis and immune deposits are sparse or absent.39,57 Occult vasculitis is less certain if other pathologic features are observed.

Idiopathic pulmonary hemosiderosis is the only major cause of IAH that does not involve the kidneys or other extrapulmonary organs. This diagnosis is likely when isolated IAH is associated with a negative serum assay for ABMA. Open lung biopsy may strengthen a clinical diagnosis of idiopathic pulmonary hemosiderosis by excluding frank pulmonary vasculitis or the presence of immune deposits.37,95 Histopathologic features include intra-alveolar hemorrhage, hemosiderin-laden macrophages, and interstitial fibrosis.57 The relative prominence of each of these features will depend upon the chronicity of the disorder and the interval since the most recent acute exacerbation. Secondary causes of pulmonary hemosiderosis, especially mitral stenosis, must be excluded by clinical examination and echocardiography. Patients diagnosed as having idiopathic pulmonary hemosiderosis must be followed carefully for the possible evolution of a multisystem disorder such as SLE59 or vasculitis.96

**Therapy**

The major causes of IAH are, for the most part, serious diseases that will likely cause organ failure or death if left untreated. This is especially true of the diseases that cause glomerulonephritis. Therapy for these diseases must be evaluated with respect to its effect on both pulmonary and renal manifestations of disease.

The early experience with corticosteroids and other immunosuppressive agents in ABMA disease was disappointing, primarily because of their inability to prevent end-stage renal disease.67 Plasmapheresis was introduced by Lockwood and associates in 1975 in an attempt to more rapidly remove ABMA from the circulation. Peters et al68 have reviewed the results of combined immunosuppression and plasmapheresis in the management of 41 patients with ABMA disease. In 29 (88 percent) of 33 cases, IAH responded to treatment. Sixteen (39 percent) of 41 patients had stable or improved renal function at the end of therapy. Renal outcome was almost entirely dependent upon the degree of renal impairment at the time when treatment was initiated. The presence of oligo-anuria or a serum level of creatinine of 7 mg/dl or more predicted a poor outcome in 23 of 24 cases. Nonoliguric patients almost uniformly did well. Johnson et al96 recently reported the results of a randomized trial of immunosuppression alone (prednisone and cyclophosphamide) vs immunosuppression with plasma exchange in the treatment of patients with ABMA disease. Although renal outcome was somewhat better for those patients who received plasma exchange, the initial degree of renal impairment and the number of crescents in the specimen from renal biopsy were more important determinants of outcome than the type of therapy received. Nine patients in the study by Johnson et al96 received pulse methylprednisolone for acute exacerbations of IAH, and all responded well.96 Others have reported success with pulse methylprednisolone in managing ABMA-mediated IAH.5,97 On balance, the available data would support the use of combined plasmapheresis and immunosuppression for patients with ABMA disease who do not have advanced renal insufficiency at presentation. Pulse methylprednisolone alone may be acceptable as initial treatment for those patients who have active IAH and little hope of recovering renal function. Patients with ABMA-mediated renal failure can successfully undergo kidney transplantation at a later date.91

Our experience with pulse methylprednisolone for acute severe IAH related to vasculitides and idiopathic RPGN has been favorable.9 Ten of 11 patients responded to therapy within 24 to 48 hours, as evidenced initially by a lessening of hemoptysis and stabilization of hemoglobin level and later by improvement in gas exchange and the chest roentgenogram. Corticosteroids alone are not optimal therapy for Wegener's
granulomatosis. Systemic necrotizing vasculitis that jeopardizes the kidneys and other vital organs may also respond better to cyclophosphamide when used in addition to corticosteroids. Because of this consideration, together with the fact that Wegener's granulomatosis presenting as IAH may not be easily defined by open lung biopsy, we have generally recommended that patients with vasculitis-related IAH and glomerulonephritis receive corticosteroids and cyclophosphamide without undergoing lung biopsy. This recommendation also applies to IAH and idiopathic RPGN when the renal biopsy shows a focal and segmental necrotizing glomerulonephritis. Unlike ABMA disease, renal failure caused by idiopathic or vasculitis-related crescentic glomerulonephritis may reverse with intensive therapy.

Idiopathic pulmonary hemosiderosis has a tendency to undergo spontaneous remissions that may last variable periods of time. The efficacy of therapy for this disorder is therefore difficult to evaluate. Sorger and Sommers reviewed the literature in 1962 and concluded that corticosteroids were probably beneficial for acute exacerbations, but did not clearly affect the long-term prognosis. Case reports describing a response to azathioprine or plasmapheresis following corticosteroid failure have been published.

Treatment of patients with active IAH should begin before the underlying disorder has been determined, because of the need to control pulmonary bleeding as rapidly as possible. Almost 40 percent of our patients with IAH required mechanical ventilation with positive end-expiratory pressure, yet many of these individuals had experienced hemoptysis and dyspnea for several days. Empiric pulse methylprednisolone should be given to all patients with active IAH. It is safe and easy to administer and usually controls IAH related to vasculitis and ABMA. Cyclophosphamide may also be given if there is unequivocal evidence of glomerulonephritis, because it will be used as part of the regimen of treatment for both vasculitis and ABMA disease. This agent probably does not have immediate benefit, and it is therefore less critical that therapy with it be started within the first 24 hours. Empiric plasmapheresis until ABMA disease is excluded has also been recommended. Our approach has usually been to begin treatment with pulse methylprednisolone, and sometimes cyclophosphamide, but withhold plasmapheresis until a diagnosis of ABMA disease is established. This approach is based upon the premise that a kidney biopsy will be obtained promptly and that the immunofluorescent pattern will be established six to eight hours after the biopsy is obtained. Also, a serum ABMA titer is determined by ELISA within 24 hours of admission. If a renal biopsy cannot be obtained quickly and serum ABMA by radioimmunoassay or ELISA is not readily available, then it would be prudent to treat those patients who have unequivocal clinical evidence of IAH and glomerulonephritis with combined immunosuppression and plasmapheresis until a firm diagnosis can be established.

An important aspect of managing IAH is to eliminate factors that may exacerbate capillary bleeding. High pulmonary venous pressure should be avoided, and the pulmonary capillary wedge pressure should be measured if there is any doubt as to volume status. Infection should be treated promptly, because it has been shown that exacerbation of IAH may be triggered by infection, usually at extrapulmonary sites, through unclear mechanisms. Coagulation disorders, including uremic platelet dysfunction, should be corrected. Lastly, cigarette smoking has been reported to be an important cofactor in ABMA-mediated IAH and should be avoided.

References
Immune Alveolar Hemorrhage (James W. Leathem)


