Medical Grand Rounds
Parkland Memorial Hospital

D I F F U S E A L V E O L A R
H E M O R R H A G E S Y N D R O M E S

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DIFFUSE ALVEOLAR HEMORRHAGE SYNDROMES

Bleeding into the lung with or without hemoptysis is common in a wide variety of pulmonary disorders. These disorders originate not only from infectious, neoplastic, or embolic causes (1), but also from diverse entities such as mitral stenosis (2), uremia (3), fat embolization (4), and disseminated intravascular coagulation (5).

Table 1

The Alveolar Hemorrhage Syndromes

Antibasement membrane antibody (ABMA) disease (Goodpasture's Disease)
Collagen vascular diseases and vasculitides
Idiopathic rapidly progressive glomerulonephritis (RPGN)
Chemical or drug-related
Idiopathic pulmonary hemosiderosis

The term alveolar hemorrhage syndrome, however, is limited to a group of disorders with diffuse bleeding from pulmonary capillaries into alveolar spaces thought to be due to immunologic mechanisms, Table 1 (6-9). The specific features of each syndrome will be considered independently. However, in an individual patient it may be difficult to even determine that alveolar hemorrhage is responsible for the clinical symptomatology. Thus, general aspects of immune alveolar hemorrhage which pertain to all of these entities will be considered first.

Table 2

Clinical Manifestations of Immune Alveolar Hemorrhage Syndromes

Primary
- Hemoptysis
- Radiographic infiltrates
- Anemia

Secondary
- Dyspnea
- Fever
- Chest Pain

The primary manifestations of these syndromes from which the diagnosis is usually suspected are hemoptysis, radiographic infiltrates and anemia, Table 2. Some patients also have dyspnea, fever, or substernal chest pain, but these latter

symptoms are nonspecific and may even obscure the correct diagnosis.

The amount of hemoptysis is quite variable among patients and at different times in the same patient ranging from minor blood streaking of sputum to massive expectoration of blood, and the amount of hemoptysis correlates poorly with the extent of radiographic pulmonary hemorrhage (6, 8). Hemoptysis is the most common initial symptom, and tends to recur in bouts with intervening bleeding-free intervals (10, 11). In some patients, however, there may be no recognized hemoptysis during the entire course of the disease.

Table 3

Chest X-Ray Manifestations During 29 Bleeding Episodes in Patients with Alveolar Hemorrhage

	n	Percent of Total	Percent of Infiltrates
Normal	7	25	
Bilateral, symmetrical nodules (1-4 mm) to confluent	20	69	91
Mid and lower lung zones sparing periphery	21	72	95
Clear to faint nodularity <48 hrs after bleed	22	76	100
Complete clearing in <2 wks	22	76	100

Bowley, et al.: Clin. Radiol. 30:419, 1979.

The chest radiographic manifestations of alveolar hemorrhage are nonspecific and are indistinguishable from pulmonary edema or a diffuse infection such as viral pneumonia (12). In one study of 29 bleeding episodes in 25 patients 25% of the episodes were associated with a normal chest x-ray, Table 3 (13). When present, infiltrates are almost always bilateral and relatively symmetrical. Infiltrates take the form of small, ill defined nodules, or the nodules may coalesce to become confluent and yield the picture of consolidation. They occur in the mid and lower lung zones sparing the periphery of the lung. When bleeding ceases the infiltrates clear to a faint nodularity within 48 hours, and complete clearing typically occurs within 2 weeks.

Table 4

Chest Radiographic Findings Suggesting Pneumonia or Pulmonary Edema in Patients with an Alveolar Hemorrhage Syndrome

Infiltrates unilateral
Infiltrates in an apex or costophrenic angle
Infiltrates obscuring the heart margin or diaphragm
Infiltrates limited by a fissure
Pleural effusion or Kerly B lines

Bowley, et al.: Clin. Radiol. 30:419, 1979.

The same study indicated chest radiographic findings suggesting pneumonia or pulmonary edema rather than or in addition to alveolar hemorrhage, Table 4 (13). Unilateral infiltrates are rarely due to alveolar hemorrhage. Similarly, infiltrates in an apex or costophrenic angle, infiltrates obscuring the heart margin or diaphragm and infiltrates limited by a fissure are not likely due to alveolar hemorrhage. A pleural effusion or Kerly B lines usually mean heart failure or volume overload.

Thus, the radiographic manifestations of alveolar hemorrhage are not sufficiently specific, even in the presence of hemoptysis, to be considered diagnostic of this syndrome. More sophisticated radiographic procedures such as chest CT or magnetic resonance imaging do not contribute to improved diagnostic capabilities (14-16).

Table 5

Anemia at Presentation in 74 Patients with the Diffuse Alveolar Hemorrhage Syndrome

Study	No. Pts	Hemoglobin (gm/dl) ≤10	Hematocrit (vol %) ≤35	% Pts Anemic
Walker, et al.[1]	16	15		94
Johnson, et al.[2]	17		16	94
Boyce, et al.[3]	45	23		51

[1]Irish Med. J. 75:328, 1982; [2]Medicine 64:219, 1985; [3]Am. J. Kid. Dis. 8:31, 1986.

Anemia is usually present at the time of presentation in patients with a diffuse alveolar hemorrhage syndrome, Table 5 (17-19). In two recent, representative series significant anemia was almost universally present with an average hemoglobin of 8.9 gm/dl or hematocrit of 25.2 vol %. A third recent study indicated only that about half of the patients had a hemoglobin

concentration less than 10 gm/dl, and thus many patients may have had some degree of anemia that was less severe. Taken together, at least 75% of patients are seriously anemic at the time of presentation, and it is likely that at least 90% of patients have some degree of anemia. The anemia is due to acute blood loss in the lungs; patients have been noted to have falls in hemoglobin concentration of 1.5 to 3 gm/dl in 24 hours (20). The fall in hemoglobin correlates poorly with the extent of lung infiltrates. Laboratory findings of iron deficiency occur only in patients who give a history suggestive of chronic disease.

Thus, one should consider an alveolar hemorrhage syndrome in the differential diagnosis of a patient who presents with hemoptysis, radiographic infiltrates and anemia. Unfortunately, however, these symptoms are not specific. This triad of findings is not present in each patient and even when present does not ensure that an alveolar hemorrhage syndrome exists.

Table 6

Additional Procedures to Diagnose
Diffuse Alveolar Hemorrhage

Correlation of changes in hemoglobin concentration and chest x-rays

Radiolabeled autologous erythrocytes

Hemosiderin laden macrophages in sputum

Fiberoptic bronchoscopy

Carbon monoxide uptake

A variety of additional procedures have been utilized in an attempt to diagnose diffuse alveolar hemorrhage more precisely, Table 6. Perhaps the easiest of these is to correlate changes in hemoglobin concentration and the chest x-rays; specifically, one would expect new infiltrates at a time of hemorrhage as indicated by a falling hemoglobin concentration. This procedure which is not always successful ensures a delay in diagnosis and therapy which may be catastrophic (21). One group has reported the use of radiolabeled autologous erythrocytes in the diagnosis of idiopathic pulmonary hemosiderosis (22). Serial scintigraphic scanning of the chest showed significant pulmonary sequestration of sodium chromate Cr 51 labelled erythrocytes. Although this is a perfectly reasonable procedure, it use has apparently been limited to this single case or to pediatric patients.

Red blood cells in alveoli are ingested by alveolar macrophages which process the hemoglobulin to form ferritiin and other degradative products. These are identified as hemosiderin when stained by acid ferrocyanide. In older studies the finding of hemosiderin laden macrophages in sputum was used to

substantiate a diagnosis of an alveolar hemorrhage syndrome. This procedure however is not even mentioned in recent series of adults. I presume that a search of sputum for hemosiderin laden macrophages has been abandoned for three reasons. First, the finding is not specific and may be found with any type of pulmonary bleeding. Second, the procedure has never been standardized to indicate the necessary fraction of macrophages which contain hemosiderin to be significant. Third, many patients with an alveolar hemorrhage syndrome do not have a productive cough. A somewhat more aggressive variant of this approach, the use of fiberoptic bronchoscopy, may be more useful.

Table 7

Recovery of Hemosiderin Laden Macrophages
in BAL of Patients with Occult Lung Hemorrhage

Study	Hemosiderin Content				Macs w/ Hemosiderin			
	Normal		Bleed		Normal		Bleed	
	n	Score	n	Score	n	%	n	%
Finley, et al.[1]	6	<41	3	>206				
Drew, et al.[2]	7	<25	9	>75				
Sherman, et al.[3]					5	<3	4	90

[1]Am. Rev. Respir. Dis. 112:23, 1975; [2]Am. Rev. Respir. Dis. 116:215, 1977; [3]Chest 86:409, 1984.

Three studies in anticoagulated or immunocompromised patients and a study in children with idiopathic pulmonary hemosiderosis have indicated that fiberoptic bronchoscopy with bronchoalveolar lavage is useful in diagnosing pulmonary hemorrhage, Table 7 (23-26). In two of the studies an estimate of the hemosiderin content of macrophages was scored in a standard manner in normal controls and in patients who were proven to have alveolar hemorrhage. This technique resulted in a good separation of the two groups. In the third study the percent of macrophages containing hemosiderin also clearly separated normal persons from patients with alveolar hemorrhage. False negative results may be obtained in the first 24 to 48 hours after the onset of bleeding, since that interval is necessary for the macrophages to ingest erythrocytes and degrade hemoglobin (25, 26). Only one study reported a significant number of patients with causes of lung disease other than hemorrhage (26). Thus, the sensitivity and specificity of the procedure can not be calculated. However, since a variety of other pulmonary diseases must be considered in patients with suspected alveolar hemorrhage and radiographic infiltrates, bronchoscopy is probably indicated and may establish an alternate diagnosis.

Table 8

Diffusion Capacity per Unit Lung Volume (DL/V_A) in Patients with Alveolar Hemorrhage

Study	n	Pred DL/V_A Base	DL/V_A Bleed	DL/V_A Base/Bleed	Hemop	Abn CXR
Evan, et al.[1]	8	72%	160%	223%		
Bowley, et al.[2]	17			231%		78%
Greening, et al.[3]	39			219%	54%	82%

[1]N. Engl. J. Med. 295:1391, 1976; [2]Clin. Radiol. 30:413, 1979; [3]Clin. Science 60:507, 1981.

A group of investigators at Hammersmith Hospital in London has demonstrated that the measurement of a patient's diffusion capacity is helpful in managing patients with alveolar hemorrhage, Table 8 (20, 27, 28). They reasoned that during the measurement of a single breath diffusion capacity carbon monoxide diffuses from alveolar gas into the pulmonary capillaries where the rate of uptake depends on the number of available hemoglobin combining sites. In the presence of lung hemorrhage the extravascular blood should take up an additional quantity of carbon monoxide and cause the diffusion capacity corrected for lung volume to be abnormally high. In a series of studies it was found that during times of hemorrhage the DL/V_A averaged 160% of its predicted value and over 200% of the baseline value for that patient. It is difficult to assess the sensitivity of the measurement, but the specificity was thought to be good, since reversible rises of DL/V_A of 50% or more were never observed in normal subjects or patients with other lung diseases, including pulmonary edema. It should be noted, however, that the baseline DL/V_A of these patients at times of no bleeding tends to be low. Since the baseline value is not likely to be known at the time of original presentation, the measurement might be normal or even low yielding a false negative result. Thus, the measurement is more useful in diagnosing episodes of lung hemorrhage in patients already known to have the syndrome than in making the original diagnosis. In one of their studies the investigators noted that only half of the patients had hemoptysis at the time the DL/V_A indicated lung bleeding, and in two of the studies it was found that abnormal chest x-rays occurred in only 80% of bleeding episodes.

Thus, a normal or high diffusion capacity suggests the diagnosis of alveolar hemorrhage in an appropriate patient, and an increase in diffusion capacity by 50% above baseline should suggests a bleeding episode in a patient in whom the diagnosis has been established.

Since the evidence so far presented emphasizes that the findings of hemoptysis, radiographic infiltrate and anemia are nonspecific, the physician may not know how aggressively to pursue this diagnosis. The most useful indicator then becomes the presence or absence of renal impairment, since all of the immune alveolar hemorrhage syndromes except for idiopathic pulmonary hemosiderosis are usually associated with renal disease.

Table 9

Laboratory Data Related to Renal Disease in Patients with Newly Diagnosed Alveolar Hemorrhage

Study	n	Serum Creatinine M ± SD (mg/dl)	Proteinuria	RBC
Benoit, et al.[1]	52		100%	94%
Briggs, et al.[2]	18	4.5 ± 7.1	44%	
Walker, et al.[3]	12	5.4 ± 5.4	100%	100%
Johnson, et al.[4]	17	4.9 ± 6.9	94%	

[1]Am. J. Med. 37:424, 1964; [2]Medicine 58:348, 1979; [3]Irish Med. J. 75:328, 1982; [4]Medicine 64:219, 1985.

Laboratory data related to renal disease in patients with newly diagnosed alveolar hemorrhage are presented in Table 9 (10, 17, 18, 29). Renal function is usually impaired at time of presentation as indicated by a high serum creatinine. However, the standard deviations are large indicating a wide range of impairment. Indeed, 17% of the patients had a normal serum creatinine, while the highest value at time of admission was 30 mg/dl. In 3 of 4 reported series virtually all patients had proteinuria. Walker found an average of 187 mg/dl of protein on the initial urinalysis, and Johnson found an average of 4.3 g/24 hrs. Almost all patients reported had red blood cells in the urine, and many had RBC and granular casts. White blood cells were uncommon. These data indicate that urinary findings of glomerular disease in association with pulmonary disease should alert the physician to the possibility of alveolar hemorrhage. An awareness of this association might lower the recentlyreported 2.6 month average time from onset of symptoms to diagnosis (29).

Table 10

Relative Frequency of the Causes of Pulmonary Hemorrhage with Glomerulonephritis

Disease	Series Ref 1	Ref 2	Ref 3	Total	
ABMA disease	10	2	8	20	28%
CV or vasculitis	10	2	21	33	45%
RPGN	5	2	12	19	26%
Chemical related	1			1	1%
Total	26	6	41	73	

[1]Medicine 63:343, 1984; [2]Am. J. Roentgenol. 130:1441, 1978; [3]Comp. Therapy 14:40, 1988.

The relative frequency of the causes of pulmonary hemorrhage with glomerulonephritis may be estimated from available series, Table 10 (8, 30, 31). Collagen vascular diseases or vasculitis account for about half of these patients, while antibasement membrane antibody disease and rapidly progressive glomerulonephritis each cause about one-quarter. Having investigated the features that these separate diseases may have in common, we shall now turn to the specific findings of each disease, beginning with antibasement membrane antibody disease.

ANTIBASEMENT MEMBRANE ANTIBODY (ABMA) DISEASE (Goodpasture's Disease)

Table 11

History of Goodpasture's Syndrome
Phase 1

1919 Goodpasture[1] describes alveolar hemorrhage (AH) with glomerulonephritis (GN) in a patient recovering from Influenza A.

1958 Stanton and Tange[2] report patients with AH and GN and suggest the name of Goodpasture's Syndrome.

1964 Benoit, et al.[3], summarize the 52 cases reported and suggest alveolar hemorrhage with nephritis is a specific nosologic entity.

[1]Am. J. Med. Sci. 158:863, 1919; [2]Aust. Ann. Med. 7:132, 1958; [3]Am. J. Med. 37:424, 1964.

A review of the history of antibasement membrane antibody disease is useful in explaining the confusion associated with the term Goodpasture's Syndrome, Table 11. In 1919 during an investigation of the cause of influenza Ernest Goodpasture reported the autopsy of one patient who died of respiratory failure while recovering from influenza (32). At autopsy "the lung gave the impression of having been injected with blood through the bronchi so that all the air spaces were filled", and the kidney showed proliferative glomerulonephritis. There were only scattered reports of similar cases until 1958 when Stanton and Tange reported nine patients with alveolar hemorrhage and glomerulonephritis and suggested the name Goodpasture's Syndrome for this entity (33). By 1964 Benoit and colleagues were able to collect reports of 52 patients (10). These authors suggested that the syndrome was sufficiently distinctive to be regarded as a specific nosologic entity. Thus, the term Goodpasture's Syndrome was established for any patient with alveolar hemorrhage and glomerulonephritis.

Table 12

History of Goodpasture's Syndrome
Phase 2

1964	Scheer and Grossman[1] demonstrate linear deposition of gamma globulin in kidneys.
1965	Sturgill and Westervelt[2] demonstrate linear deposition of IgG in lungs.
1967	Lerner, et al.[3], describe ABMA in serum and cause nephritis in monkeys with antibodies from serum or eluted from kidneys.
1969	Koffler, et al.[4], demonstrate that antibodies eluted from lungs or kidneys crossreact with the other organ.
1971	Martinez and Kohler[5] suggest that the term Goodpasture's Syndrome be limited to patients with demonstrable ABMA in serum, kidneys, or lungs.

[1]Ann. Int. Med. 60:1009, 1964; [2]JAMA 194:172, 1965;
[3]J. Exp. Med. 126:989, 1967; [4]Am. J. Pathol. 54:392, 1969;
[5]Ann. Int. Med. 75:67, 1971.

Also in 1964 Scheer and Grossman demonstrated gamma globulin in linear deposits on glomerular basement membranes of two patients with this syndrome, Table 12 (34). No antibody was found in the lung or blood. The following year Sturgill and Westervelt were able to demonstrate linear deposits of IgG in the lungs of a patient (35). In 1967 Lerner and colleagues described antibasement membrane antibodies in the serum and

kidneys of six humans with Goodpasture's Syndrome and produced glomerulonephritis in monkeys with these antibodies (36). In 1969 Koffler and colleagues demonstrated that anti-basement membrane antibodies eluted from the lungs of a patient with Goodpasture's Syndrome reacted with glomerular basement membranes of human and monkey kidney, while antibody eluted from the kidneys reacted with alveolar septal membranes (37). Thus, in five years the pathogenetic mechanism of the antibasement membrane antibody syndrome was determined, although the inciting mechanism for antibody production was not elucidated. By 1971 Martinez and Kohler suggested that the term Goodpasture's Syndrome be limited to patients with demonstrable antibasement membrane activity in serum, kidneys or lungs (38). Unfortunately, the term had already become synonymous with any patient with alveolar hemorrhage and glomerulonephritis, and many authors have continued to use this eponym without regard to the cause.

Table 13

History of Goodpasture's Syndrome
Phase 3

1989 Hudson, et al., suggest that the three essential elements of Goodpasture's Syndrome are:

1. Glomerulonephritis
2. Pulmonary hemorrhage
3. Anti-collagen-α3 (IV) antibody formation

Laboratory Investigation 61:256, 1989.

In the last decade major advances have been made in understanding the molecular architecture of basement membrane components, and the evidence generated indicates that the Goodpasture's antigen is a very specific component of collagen. This has allowed Wieslander's group to suggest that the three essential elements of Goodpasture's Syndrome are glomerulonephritis, pulmonary hemorrhage and anti-collagen-α3 (IV) antibody formation, Table 13 (39). Thus, it is reasonable to use the term Goodpasture's disease for those patients with antibodies against basement membranes and alveolar hemorrhage and not broadly used to include all patients with alveolar hemorrhage and glomerulonephritis.

Table 14

Clinical Features of ABMA (Goodpasture's) Disease at Presentation

	n	Men	Age, yrs M ± SD	Sympt at Onset Pul	Renal	Simul
Wilson, Dixon[1]	53	39	26.7 ± 12.4	12	29	12
Sissons, et al.[2]	10	7	40.4 ± 15.7	10	0	0
McPhaul, Mullins[3]	32	27	29.9 ± 11.7	-	-	-
Briggs, et al.[4]	18	16	21.0 ± 2.9	6	7	5
Walker, et al.[5]	12	9	33.0 ± 21.6	8	2	2
Johnson, et al.[6]	17	15	23.8 ± 4.9	15	2	0
Total	142	113	27.8 ± 12.9	51(46%)	40(36%)	19(17%)

[1]Kidney International 3:74, 1943; [2]Brit. Med. J. 4:11, 1974; [3]J. Clin. Invest 57:351, 1976; [4]Medicine 58:348, 1979; [5]Irish Med. J. 75:328, 1982; [6]Medicine 64:219, 1985.

The clinical features of Goodpasture's disease at the time of presentation for medical care have been recorded in several series, Table 14 (17, 18, 29, 40-42). These data are derived from 142 patients with a firm diagnosis of anti-glomerular basement membrane antibodies. The clinical findings may be biased toward patients with renal disease without pulmonary hemorrhage in that admissions to the two largest series, those by Wilson and Dixon and by McPhaul and Mullins, were from renal services specifically investigating glomerulonephritis. Nevertheless, one gets a reasonable picture of the patient population. Eighty percent of patients with this syndrome are men. It is predominately a disease of young adults with the average age at onset of about 28 years. Although the youngest of these 142 patients was 5 and the oldest was 82 years old, only 12 patients were less than 18 and only 10 over 50 years of age. These findings also support the contention that alveolar hemorrhage in a child is more likely to be idiopathic pulmonary hemosiderosis than Goodpasture's disease. Forty-six percent of patients presented due to pulmonary symptoms, predominately hemoptysis, dyspnea or both. Thirty-six percent of patients presented with symptoms of urinary disease such as nausea, vomiting, hematuria or edema. Seventeen percent of the patients presented with both pulmonary and renal symptoms. The interval between onset of symptoms and admission is often weeks to months and occasionally years (43).

The severity of symptoms at onset is quite variable. Some patients have had only minor hemoptysis, while others present in

respiratory failure with wide spread lung bleeding. Similarly, some patients have only mild proteinuria and hematuria with a normal creatinine, while others present in overt renal failure. During the course of the illness most patients have both alveolar hemorrhage and glomerulonephritis, but 10 to 30 percent have glomerulonephritis without a pulmonary syndrome (44). The patients without a pulmonary component are classified as Idiopathic Crescentic Glomerulonephritis, Type I, or Rapidly Progressive Glomerulonephritis, Type I (44). Alveolar hemorrhage without glomerulonephritis is rare (45). Animal investigations have demonstrated that heterologous ABMA when injected into monkeys or rabbits localizes in the kidneys but not the lungs. Additionally, sheep injected with human lung basement membrane develop ABMA-mediated glomerulonephritis without lung disease (36, 46, 47). However, rabbits prebreathed with 100% oxygen bind ABMA to alveolar basement membranes resulting in a fatal lung injury (46). Oxygen breathing acts to increase capillary permeability in the lungs. These observations suggest that increased capillary permeability may be necessary for ABMA to bind to pulmonary capillary basement membranes. Donaghy and Rees suggested that a similar mechanism in man results from cigarette smoking (48). They found that among their 47 patients with proven ABMA all 37 cigarette smokers had lung hemorrhage while only two of ten non-smokers had this symptom. Others, however, have failed to confirm this observation (49).

The course of untreated ABMA disease is unpredictable (50). Although spontaneous remissions have been reported to occur, alveolar hemorrhage may progress quite rapidly and prove fatal. Similarly, renal function may deteriorate in days from normal to destroyed kidneys. Thus, it is imperative to make the diagnosis rapidly.

Table 15

Sites to Identify Anti-Basement Membrane Antibody Serum

Technique	Percent of Assays Positive			
	Good-pasture's	RPGN I	Immune Complex RPGN	Other
Gel diffusion[1]		5	0	
Indirect immunofluorescence[1]		40	0	0
Hemagglutination[2]	100	31		"Many"
Radioimmunoassay[3]	97	83	1	0.5
ELISA (GP antigen)[4]	100		0	0

[1]J. Immunol. 103:1168, 1969; [2]Lancet 2:207, 1972;
[3]Contemp. Issues Nephrol. 3:35, 1979;
[4]J. Immunol. Meth. 118:73, 1989.

The potential sites to identify antibasement membrane antibody include serum, lungs, and kidneys. Various techniques have been used to identify serum antibodies, Table 15 (51-60). Gel diffusion and indirect immunofluorescence have proven to be too insensitive. Hemagglutination is considerably more sensitive but yields too many false positives. Radioimmunoassays have been used for many years with very satisfactory results. About 97% of patients with Goodpasture's disease have positive assays, and about 83% of patients with Rapidly Progressive Glomerulonephritis, Type I are positive. Conversely, only about 1% of patients with immune complex mediated RPGN and only a half percent of other types of glomerulonephritis yield positive results. More recently, enzyme-linked immunosorbent assays (ELISA) have been utilized owing to the relative simplicity of the method. All of these assays, including the ELISA, use purified bacterial collagenase solubilized glomerular basement membrane as the ligand in assays for human autoantibody. Since this is an impure antigen, one might expect variability in results. Very recently, primarily through the work of Wieslander and his associates, the Goodpasture antigen has been specifically localized to a noncollagenous domain of Type IV collagen and found to be a newly discovered chain ($\alpha 3$) of collagen IV (39, 61-72). This group has devised an ELISA using this purified antigen and found that the serum of 100% of patients with Goodpasture's disease had the appropriate antibody, while the serum of patients with other renal diseases did not (60). It was also demonstrated that some patients had low titers of antibodies against laminin, 7S domain, and entactin. It was speculated that these antibodies might reflect a secondary response in which they are produced against other antigens that are released from glomerular basement membrane during the course of nephritis.

Parkland sends serum for antibody determination to a reference laboratory which uses an ELISA. The test utilizes a partially purified glomerular basement membrane antigen, the preparation of which was described in 1983 (73). The sensitivity and crossreaction rate is probably similar to that described for radioimmunoassays in Table 15. To the best of my knowledge the ELISA with pure Goodpasture's antigen is not yet available commercially. Testing at the Parkland reference laboratory is performed each Tuesday and Thursday, and results may be reported by phone the same day if requested.

Table 16

Sites to Identify Anti-Basement Membrane Antibody
Bronchoscopically Obtained Lung Tissue

Study	Number Patients	Immuno Positive	Percent Positive
Abboud, et al.[1]	1	1	
Hogan, et al.[2]	2	2	
Beechler, et al.[3]	6	6	
Johnson, et al.[4]	10	3	
Total	19	12	63

[1]Ann. Intern. Med. 89:635, 1978;
[2]Am. Rev. Respir. Dis. 118:537, 1978;
[3]Am. Rev. Respir. Dis. 121:869, 1980;
[4]Medicine 64:219, 1985.

As previously indicated, linear deposits of IgG have been demonstrated in alveolar walls by immunofluorescence techniques and have been demonstrated to crossreact with glomerular basement membrane (35, 37). Several investigators have suggested that the diagnosis of Goodpasture's disease may be made from transbronchial biopsies obtained by fiberoptic bronchoscopy, Table 16 (18, 74-76). Although these data suggest that the technique is modestly sensitive, too few patients have been reported to assess the technique adequately. Even at autopsy not all patients have had linear deposits detected, and in those lungs which have deposits it has been noted that the deposition may be regional or focal which may cause sampling errors during bronchoscopy (54, 77, 78). Since percutaneous renal biopsy is always positive, it is not reasonable to perform fiberoptic bronchoscopy for this purpose alone. If the patient is to have bronchoscopy to help determine the etiology of hemoptysis and infiltrates, transbronchial biopsies might be obtained for this purpose. As in other diffuse diseases, at least six biopsies should be taken to decrease sampling error. Open lung biopsy is rarely indicated in patients with diffuse alveolar hemorrhage and certainly would not be done solely to detect immunoglobulins.

Table 17

Sites to Identify Anti-Basement Membrane Antibody
Percutaneous Kidney Biopsy

Light microscopy	Glomerular crescents
Electron microscopy	Gaps in glomerular basement membrane; collapsed, denuded capillaries with fibrin microthrombi. No electron-dense deposits.
Immunofluorescence	Linear deposits of IgG (rarely also IgA, IgM) along the glomerular basement membrane. Complement deposits in 2/3.

Contemp. Issues Nephrol. 3:35, 1979; Mech. Immunopathol. p. 181, 1979.

Percutaneous kidney biopsy has been the traditional method of making the diagnosis in antibasement membrane antibody disease, Table 17. Kidney biopsy is usually performed even when serum antibodies are known to be present, since the percentage of glomeruli effected gives an estimate of prognosis and may be helpful in therapy. Light microscopy reveals extensive proliferation of cells within Bowman's space, usually effecting 50% or more of the glomeruli (44, 54, 79). This lesion is referred to as a crescent and in the absence of other primary glomerular disease, infection or multisystem disease leads to the diagnosis of idiopathic crescentic glomerulonephritis. The clinical course is typically progressive deterioration of renal function over days, weeks, or a few months and is therefore frequently referred to as rapidly progressive glomerulonephritis. The lesion, however, is not specific for anti-basement membrane antibody disease. The process may progress to glomerular obsolescence in as short an interval as a few weeks, but the course is unpredictable and the crescents may resolve without residue.

Electron microscopy may show gaps in the glomerular basement membrane with collapsed, denuded capillaries with fibrin microthrombi. Electron-dense deposits are not usually seen. These findings are also not specific.

Immunofluorescent staining reveals a smooth linear deposit of IgG along glomerular capillaries which may sometimes contain modest amounts of IgA or IgM. The linear deposits are accompanied by C3 deposition in a similar pattern in about two-thirds of cases. It is these findings that are virtually diagnostic of ABMA disease. In some diabetic patients, and occasionally in other diseases, a fainter linear

immunofluorescence may be found on the basement membranes due to albumin; these deposits are usually easily distinguished from IgG. Immunofluorescence also reveals anti-tubular basement membrane IgG antibodies in about 70% of patients.

Table 18

Induction of the Anti-Basement Membrane Antibody Response

Familial occurrence	Male cousins, brothers, female twins (ABMA)
HLA-DR2	72.5% ABMA patients 25.3% controls
Suggested precipitants	
Influenza A	Solvent inhalation
Upper respiratory infection	Glue sniffing
Hydrocarbon fumes	

In his recent, scholarly Grand Rounds on Collagen Autoimmunity Dr. Hugo Jasin has described in some detail the newly recognized Goodpasture antigen in glomerular basement membrane, anti-collagen-α3 (IV), and I can add nothing to his discussion in that regard. However, a few comments are in order concerning events which have been proposed to induce the anti-basement membrane antibody response, Table 18. Familial occurrence has been reported in male cousins, brothers and female twins (80-82). In the first two families the patients had classic clinical findings of Goodpasture's disease, but antibasement membrane antibodies were not sought. In the female twins linear antibodies were present on renal biopsy. Stronger evidence for a genetic predisposition to form these autoantibodies is the finding in each of four studies that the incidence of the HLA antigen DR2 is much higher in patients with antibasement membrane antibodies than in normal persons (83-86). It is proposed that these susceptable persons develop autoantibodies when exposed to toxic environmental agents. Among the suggested precipitants is influenza A, the presumed inciting agent in the index patient described by Goodpasture. At least two patients with antiglomerular basement membrane antibodies have been described in association with influenza infection (40, 87). A viral-like syndrome, especially an upper respiratory infection, occurs in about 30% of patients before the onset of alveolar hemorrhage, but no studies have sought the specific etiology (54, 88). Beirne and his associates have frequently reported heavy exposure to various hydrocarbons in patients presenting with anti-glomerular basement membrane antibody disease, but they also find this association with other types of renal diseases (89, 90). Two cases of antiglomerular basement membrane nephritis have been reported after solvent exposure, and a case after glue sniffing (91, 92). Thus, there have been several infectious or chemical agents potentially associated with the onset of this disease which may have induced the autoantibody

response. However, neither these or other recognized insults have preceded the onset of disease in the majority of patients.

Table 19

Pulse Steroid Therapy for Life Threatening Alveolar Hemorrhage

Methylprednisolone 30 mg/kg/d IV over 30 mins.
Repeat daily or every other day for 3 doses
Continue as Prednisone 1-2 mg/kg/d PO

Medicine 63:343, 1984; Medicine 64:219, 1985.

When a patient presents with a syndrome recognized to be alveolar hemorrhage with renal disease, some finite interval will be necessary to obtain the results of all testing and arrive at the correct diagnosis. Many patients have life threatening alveolar hemorrhage during this interval. Fortunately, it has been reported that pulse steroid therapy is successful in controlling hemorrhage within 24-48 hours in about 90% of patients irrespective of the etiology of the syndrome, Table 19 (8, 18, 93, 94). Many different regimens have been used with success, and the one indicated is only representative. All regimens have in common the use of a large amount of methylprednisolone intravenously, usually about a gram at a time, over the course of three to six days followed by a substantial dose of prednisone by mouth.

Pulse steroid therapy was originally used for kidney transplant rejection. It is interesting, therefore, that this therapy is of no benefit in preventing renal deterioration in patients with Goodpasture's disease. Immunosuppression and plasma exchange are the modalities of therapy used for renal disease.

Table 20

Outcome of Patient with Goodpasture's Disease with Immunosuppression and Supportive Therapy

Year	No. Pts.	Death	Renal Failure	Normal Function
1964[1]	52	50 (96%)		2 (4%)
1973[2]	53	26 (50%)	21 (40%)	6 (11%)
1982-85[3,4]	21	5 (24%)	9 (43%)	7 (33%)

[1]Am. J. Med. 37:424, 1964; [2]Kidney Intl. 3:74, 1973;
[3]Am. J. Nephrol. 2:301, 1982; [4]Medicine 64:219, 1985.

Before evaluating therapy, however, it is instructive to review the outcome of patients with Goodpasture's disease over the past 30 years, Table 20 (10, 18, 40, 95). Patients treated in the 1950's and 1960's, some of whom may not have had Goodpasture's disease as it is currently defined, had a remarkably poor outcome with a mortality rate of 96%. Patients treated in the late 1960's and early 1970's generally received some type of immunosuppression in addition to supportive therapy. Nevertheless, half of these patients died, and most of the remainder developed renal failure. By the 1980's the mortality rate had dropped to 25%, and about a third of the patients recovered with normal renal function. This almost surely relates not only to better immunosuppressive and supportive care but also to the recognization of milder cases due to measurement of circulating anti-glomerular basement membrane antibody (45, 96). It is against this background that therapy must be evaluated.

Table 21

Plasma Exchange for Antibasement Membrane Disease

Arterial and venous access to cell sorter

Usually 4 liters of plasma removed

Replacement fluids:
- Plasma protein fraction (semipure albumin solution)
- Cryoprecipitate depleted plasma
- Type specific plasma

Daily to every third day exchange

Continue until ABMA activity minimal

Ann. Rev. Med. 31:167, 1980; Am. J. Nephrol 2:301, 1982; Medicine 64:219, 1985.

Shortly after the description of antibasement membrane antibodies Lockwood and his colleagues at Hammersmith Hospital reasoned that patients might be improved by a rapid removal of circulating antibodies by plasma exchange (97). Various methods have subsequently been described, Table 21 (18, 95, 98). Arterial and venous access are obtained and the conduits connected to some type of commercially available cell sorter. Four liters of plasma are usually removed per treatment. The replacement fluids vary from center to center. Lockwood uses a plasma protein fraction to produce hypogammaglobulinemia, hypocomplementemia and hypofibrinogenemia (98). Simpson and colleagues use cryoprecipitate depleted plasma to only moderately reduce levels of fibrinogen and produce decreased functional complement activity (95). On the other hand, type specific frozen plasma is used by Johnson and colleagues in order to deplete only the antibasement membrane antibodies (18). The plasma exchanges are performed every one to three days and are

continued until antibasement membrane antibody activity is minimal. Plasma exchange has been reported in single cases to small series of patients with Goodpasture's disease by many clinicians (17, 29, 99-114). It is clear that the circulating concentration of antibasement membrane antibody is more rapidly reduced with than without plasma exchange. Further, as reviewed by Couser, the data on 186 patients suggest a favorable effect on the pulmonary disease in about 90% and on renal disease in about 40% (115). However, these estimates are made by comparison of patients with plasma exchange to historical controls. Clearly, controlled trials are necessary to validate this impression.

Table 22

Plasma Exchange vs Immunosuppression or Supportive Care in Goodpasture's Disease

Crescents on Renal Biopsy	Immunosuppression + Plasma Exchange			Immunosuppression or Supportive		
	n	Better	Worse	n	Better	Worse
<50%	10	7	3	9	7	2
>50%	9	0	9	9	0	9

Am. J. Nephrol. 2:301, 1982; Medicine 64:219, 1985.

Only two studies have compared immunosuppression and plasma exchange to concurrent patients treated with immunosuppression or supportive care alone (18, 95). Only one of these studies utilized randomization of therapy. Virtually all studies have shown that patients with very high creatinines, on the order of 8 mg/dl, oligo or anuria, or greater than 50% of glomeruli containing crescents are unlikely to have return of renal function irrespective of therapy. Thus, it is reasonable to separate the results of these patients into those with fewer than and those with more than 50% of glomeruli with crescents. When compared in this manner, the patients who received immunosuppression and plasma exchange had virtually the same outcome as those patients who received only immunosuppression or supportive care.

Several observations should be made concerning plasma exchange. First, the number of patients presented in Table 22 is too few for valid comparison. Far larger, stratified, randomized studies are necessary to determined if plasma exchange improves patients with Goodpasture's disease. Indeed, noted authorities reviewing all of the data available have markedly differing enthusiasm for plasma exchange (115, 116). Second, there is a strong concensus that plasma exchange decreases the incidence of alveolar hemorrhage. Third, the reduction of circulating antibodies may allow more early kidney transplantation in patients with end stage renal disease. Whether these latter features are sufficiently important to outweigh the infectious

and other risks of patients undergoing plasma exchange is a matter of judgment (95, 117).

Table 23

A Reasonable Therapeutic Regimen for Patients with Goodpasture's Disease

Prednisone: 2 mg/kg daily X 1 week; 1 mg/kg daily X 3 weeks
Taper to alternate day for 3 months
Pulse doses for serious alveolar hemorrhage

Cyclophosphamide: 2 mg/kg daily X 3 mos; then 1 mg/kg daily
Decrease dose for WBC <4000, platelets <100,000

Plasma exchange if no anuria, creatinine <8 mg/dl and crescents 30-70%.

Medicine 64:219, 1985.

There is no agreed regimen for immunosuppression, but each contains prednisone and cyclophosphamide, Table 23. The dosage used by Johnson and his colleagues is representative of most authorities. Prednisone is begun orally at 2 mg/kg daily for a week followed by 1 mg/kg daily for three weeks and is then tapered to alternate day therapy for about three months. If at any time the patient has serious alveolar hemorrhage, pulse doses of methyprednisolone intravenously are used. Cyclophosphamide is begun orally at the same time as prednisone in a dose of 2 mg/kg daily for three months. The dose is then reduced to 1 mg/kg daily until there are no or only low concentrations of antiglomerular basement membrane antibodies in serum. The dose of cyclophosphamide is adjusted for white blood cell counts less then 4,000, platelet counts less than 100,000 or for renal failure.

All data suggest that plasma exchange is of no benefit for kidney preservation if the initial damage is severe. More recent data suggest that patients with well preserved renal function and fewer than 30% crescents on renal biopsy do well with immunosuppression alone. Thus, it seems reasonable to me to spare patients with very good and with very poor renal function the potential dangers of plasma exchange. For those patients with intermediate degrees of renal disease at the time of presentation, plasma exchange may be beneficial.

The long term prognosis for patients with Goodpasture's disease is difficult to predict. The current concept is that the disease is usually self-limited and the antibody response is transient so that therapy can usually be discontinued within a year. However, reports of patients who have had hemoptysis for up to 12 years before the diagnosis is made, and of patients who have been treated successfully with a disappearance of antibodies which then recur three years later, suggest that the disease is

not invariably a single transient episode (118, 119). Thus, even after successful therapy, periodic measurements of antiglomerular basement membrane antibody titers indefinitely seem prudent. If the kidneys have been destroyed in the first episode, transplantation should be delayed until circulating antibodies have disappeared (116, 120).

COLLAGEN VASCULAR DISEASES AND VASCULITIDES

Table 24

Collagen Vascular Diseases and Vasculitides
"Frequently" Associated with Alveolar Hemorrhage

Systemic lupus erythematosus
Wegener's granulomatosis
Nonspecific systemic necrotizing vasculitis

The most frequent causes of the alveolar hemorrhage syndrome may be the collagen vascular diseases and vasculitides. Three of these diseases, systemic lupus erythematosus, Wegener's granulomatosis and nonspecific systemic necrotizing vasculitis are the most frequent diseases in this regard, Table 24. Each will be considered separately.

Table 25

Collagen Vascular Diseases and Vasculitides Rarely
Associated with Alveolar Hemorrhage

Behcet's Syndrome
Churg-Strauss Syndrome
Endocarditis-related vasculitis
Mixed cryoglobulinemia
Henoch-Schonlein purpura
Mixed connective tissue disease
Polyarteritis nodosa
Progressive systemic sclerosis
Rheumatoid arthritis
Tumor-related vasculitis

Alveolar hemorrhage is less frequently associated with at least ten other diseases in this classification, Table 25 (8, 38, 120-128). Indeed, the association of these diseases with alveolar hemorrhage is sufficiently uncommon to merit a case report and therefore they will not be considered independently.

Table 26

Pulmonary Manifestations of Systemic Lupus Erythematosus

Pulmonary Manifestation	Approximate Frequency
Pleurisy with or without effusion	50%
Interstitial infiltrates	30%
Lupus pneumonitis	12%
Alveolar hemorrhage	2%

Clin. and Exper. Rheumatol. 3:269, 1985.

Pulmonary manifestations of systemic lupus erythematosus (SLE) have been reported to occur in up to 80% of patients, Table 26 (129). Pleurisy with or without effusion and interstitial infiltrates, which may be infiltration of alveolar septa by chronic inflammatory cells or may be pulmonary fibrosis, are the most common. Lupus pneumonitis which has an incidence of 12% is an acute, fulminant illness manifest by prostration, fever, tachypnea, hypoxemia and alveolar infiltrates. Alveolar hemorrhage is the least common manifestation of this entity with an occurrence of approximately 2% (130, 131).

Table 27

Clinical Findings in Patients with Alveolar Hemorrhage due to Systemic Lupus Erythematosus

The diagnosis of SLE usually antedates AH by months to years.

Presenting signs and symptoms may include cough, dyspnea, fever, rales, hypoxemia and alveolar infiltrates; hemoptysis usually varies from blood streaking to massive, but many patients have none.

Seventy-five percent have urinary findings of glomerulonephritis, but seriously compromised renal function is rare.

Seventy-five percent of patients have died in respiratory failure.

Pulmonary capillaritis is the basic lesion. Immune complexes are usually found in lungs and kidneys.

The clinical findings in patients with alveolar hemorrhage due to systemic lupus erythematosus are nonspecific, Table 27 (131-142). The diagnosis of SLE most commonly antedates alveolar hemorrhage by months or years. The longest interval reported has

been 23 years. Conversely, a small number of patients were reported to have hemoptysis for up to five years prior to the diagnosis of SLE. Patients present with a combination of signs and symptoms which may include cough, dyspnea, fever, rales, hypoxemia and alveolar infiltrates. Hemoptysis frequently occurs and may be minimal with only blood streaking or of a massive amount. A surprising number of patients, even those dying in acute respiratory failure from alveolar hemorrhage, do not have hemoptysis. Since these signs and symptoms are nonspecific, many patients have initially been thought to have an infectious pneumonia or lupus pneumonitis prior to the establishment of the correct diagnosis by open lung biopsy or more commonly by autopsy. Seventy-five percent have urinary findings of glomerulonephritis, but seriously compromised renal function is rare. Seventy-five percent of these patients have died in respiratory failure. It is apparent that these mortality statistics are skewed and that milder disease is simply not recognized.

Pulmonary capillaritis is the basic lesion and may be recognized by light microscopy (143, 144). The lesion is a small-vessel vasculitis characterized by acute inflammation and necrosis involving capillaries and sometimes arterioles and small muscular arteries. Alveolar septa are infiltrated with necrotic neutrophils, frequently with fibrinoid necrosis of alveolar walls, and fibrin microthrombi. These findings are those described as leukocytoclastic vasculitis elsewhere in the body. When investigated, immune complexes are usually found in both the lungs and kidneys. Immune complexes are also found in the lungs of patients with lupus pneumonitis. Thus, it has been suggested that alveolar hemorrhage is simply one end of the spectrum of lupus pneumonitis. If the diagnosis of alveolar hemorrhage is made, pulse methylprednisolone is indicated (8).

Table 28

Clinical Findings in Patients with Alveolar Hemorrhage due to Wegener's Granulomatosis

	Approximate Frequency
Arthritis/Arthralgia	87%
Alveolar hemorrhage at outset	60%
Hemoptysis	100%
Anemia	92%
Renal failure	66%
Skin involvement	75%
Upper airway	50%
Death	55%

Am. J. Med. Sci. 297:390, 1989.

The clinical findings in patients with alveolar hemorrhage due to Wegener's granulomatosis vary from those of SLE and from the usual presentation of patients with classic Wegener's, Table 28 (8, 145-155). Although patients who are ultimately proven to have Wegener's usually have had mild symptoms such as arthralgias or arthritis, most have not been diagnosed at the time they present with alveolar hemorrhage. Hemoptysis, which is the most common presenting symptoms, is usually massive and is associated with the typical radiographic infiltrates seen in other alveolar hemorrhage syndromes but not with the nodular lesions seen with classic Wegener's. Since anemia exists at presentation in a majority of patients, it is likely that the alveolar hemorrhage preceded the onset of symptoms. At least two-thirds of patients with Wegener's have concurrent renal failure and many have been initially misdiagnosed as Goodpasture's disease. Patients with alveolar hemorrhage also have a higher incidence of skin and a lower incidence of upper airway involvement. The reported mortality rate of 55% of these episodes is somewhat better than that reported in similar episodes of patients with lupus.

The histologic lesion in the lungs is capillaritis which is identical to that seen in patients with lupus (156). Immune complexes are usually not found in the lungs, although they have been rarely investigated. Renal biopsy however usually reveals necrotizing glomerulonephritis with deposition of immune complexes.

Table 29

Immunosuppressive Therapy for Fulminant
Wegener's Granulomatosis

Cyclophosphamide 4-5 mg/kg/d PO
Adjust dose guided by leukocyte count

Methylprednisolone 2 mg/kg/d IV for "few days"

Prednisone 1 mg/kg/d PO for 2-4 weeks

Prednisone taper over 1-2 mos. to 60 mg on alternate days

Ann. Intern. Med. 98:76, 1983.

There are no controlled studies of therapy for fulminant Wegener's granulomatosis. Table 29 indicates the therapy suggested by Fauci and colleagues for any form of fulminant disease (157). The dose of cyclophosphamide is higher than that recommended for standard Wegener's or for Goodpasture's. On the other hand, the dose of methylprednisolone recommended is considerably less than pulse steroid therapy, Table 19, and physicians with a larger experience with alveolar hemorrhage syndromes suggest the latter (8). Contrary to the experience with Goodpasture's, this therapy usually not only controls alveolar hemorrhage but also prevents renal deterioration.

Table 30

Organs Involved in 10 Patients with Alveolar Hemorrhage Due to Nonspecific Systemic Necrotizing Vasculitis

Organs Involved	Number
Skin	9
Lung	5
Kidney	4
Peripheral nerves	3
Muscles	3
Gastrointestinal/liver	3
Major artery	2

Am. J. Med. 82:79, 1986.

In the confusing terminology of the vasculitides, the term nonspecific systemic necrotizing vasculitis used by Leatherman (158) is synonymous with microscopic polyarteritis used by the Hammersmith group (152) and is probably a synonym for the polyangitis overlap syndrome used by Fauci and the NIH group (159). These patients are characterized by widespread organ involvement of vasculitis in various sized, including very small, vessels which leads to an unrecognizable clinical syndrome or an overlap between the findings of two recognizable vasculitic diseases such as Wegener's and polyarteritis nodosum. The clinical manifestations are quite broad depending on the organs involved by a vasculitis (8, 125, 152, 158-165). The frequency of organ involvement of ten patients followed at the NIH were reported by Leavitt and Fauci, Table 30 (159). The patients had an average age of 25 years and frequently had nonspecific symptoms such as fever and arthralgia, but additional symptoms depended on the organs involved. The skin is involved with the necrotizing vasculitis in almost all patients, and the lungs and kidney are the next most likely organs of involvement. A high fraction of patients have serious renal disease at the time of presentation, and alveolar hemorrhage occurs in about 30% (152). The manifestations of alveolar hemorrhage are no different from those described with other syndromes and frequently occur at the time of first diagnosis. The hemorrhage is due to a pulmonary capillaritis which is identical to that seen in SLE or Wegener's (143). Treatment should probably include pulse steroid therapy, Table 19, followed by the immunosuppressive therapy recommended by Fauci for fulminant Wegener's granulomatous, Table 29. I am able to find no patients followed for a protracted interval with nonspecific systemic necrotizing vasculitis, and hence the prognosis is not clear.

IDIOPATHIC RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (RPGN)

Table 31

Idiopathic Crescentic Glomerulonephritis with RPGN

Extensive involvement of glomeruli with crescents.

No infectious or multisystem disease.

Progressive deterioration of renal function over days, weeks or a few months.

Without therapy fewer than 10-20% of patients escape dialysis therapy within 6 months.

Primary Glomerular Disease, Chapter 26 in The Kidney, 1981.

Idiopathic crescentic glomerulonephritis with rapidly progressive glomerulonephritis has been defined by Glassock and his colleagues as indicating extensive involvement of glomeruli with crescents in the absence of infectious or multisystem disease, Table 31 (44). There is progressive deterioration of renal function over days, weeks or a few months. Without therapy fewer than 10-20% of patients escape dialysis within 6 months.

Table 32

Classification of Idiopathic Diffuse Crescentic Glomerulonephritis with RPGN

Type I Antiglomerular basement membrane antibody without alveolar hemorrhage.

Type II Immune complex disease without systemic disease.

Type III Unknown pathogenesis (NID disease). Renal vasculitis.

Primary Glomerular Disease, Chapter 26 in The Kidney, 1981; Am. J. Nephrol. 2:57, 1982.

The classification of rapidly progressive glomerulonephritis is as confused as the classification of the vasculitides. The classification given here is that of Glassock and associates with additions from the classification of Couser, Table 32 (44, 115). You will recall that 10 to 30% of patients with antiglomerular basement membrane antibody in a linear pattern on glomerular

capillaries do not have alveolar hemorrhage. In this schema patients without alveolar hemorrhage are designated as Type I RPGN. Although most patients with immune complex deposits in glomeruli have a post infectious glomerulonephritis or glomerulonephritis associated with collagen-vascular disease or some form of primary renal disease, a few patients may have a small number of immune complexes demonstrated in the absence of systemic disease. In this classification these patients are called Type II RPGN. There are additional patients who have neither antiglomerular basement membrane antibody nor immune complexes and therefore have a disease of unknown pathogenesis, sometimes referred to as NID, indicating no immune deposits. These patients are classified as Type III RPGN. These patients frequently have a focal necrotizing glomerular lesion and some authorities feel that patients with RPGN without immune deposits have the same lesion that is now referred to as renal vasculitis (115, 166, 167). This concept is strengthened by the demonstration of elevated levels of antineutrophil cytoplasmic antibodies in patients with idiopathic necrotizing and crescentic glomerulonephritis similar to the findings of patients with systemic vasculitides such as microscopic polyarteritis and Wegener's granulomatosis (168).

Couser argues that antiglomerular basement membrane antibody disease should not be categorized with other forms of idiopathic glomerulonephritis. Therefore, Couser would include as idiopathic RPGN those patients whose kidneys show a few, scattered immune complexes and those patients with no immune deposits. When categorized in this way all patients in this group follow a similar clinical course and one that is similar to that of renal vasculitis.

Table 33

Features of 16 Patients with RPGN Type III

Symptoms	Frequency	Laboratory	Frequency
Constitutional	50%	Anemia	88%
Pulmonary	50%	Elevated ESR	100%
Musculoskeletal	50%	Normal compl	100%
Gastrointestinal	25%	Anti-GBM	0%
Neurological	10%	C1q binding	0%

Kidney Intl. 15:184, 1979.

Patients with RPGN Type III frequently have constitutional symptoms such as fever, malaise and weight loss, and about half have pulmonary and musculoskeletal symptoms, Table 33 (169). About one-quarter have gastrointestinal symptoms and 10%

neurological symptoms. The patients are usually anemic, always have an elevated sedimentation rate, normal complement, and no antiglomerular basement membrane antibodies or demonstrable circulating immune complexes. The pulmonary symptoms typically include hemoptysis and radiographic infiltrates. In most reports the alveolar hemorrhage is mild, but massive, life threatening alveolar hemorrhage has been reported (8).

There are no controlled trials of therapy in RPGN Type III. Some authorities believe that plasma exchange should be utilized (170, 171), while others believe that pulse methyprednisolone therapy alone is equally satisfactory (172-175). Recent reviews favor pulse steroid therapy but note that all manifestations of renal disease seldom disappear (44, 115). These patients are thought to be reasonable candidates for transplantation if necessary, but the risk of recurrence in renal allografts is not known.

CHEMICAL OR DRUG-RELATED

Table 34

Alveolar Hemorrhage in Patients Treated with Penicillamine

At least 8 cases reported during treatment for Wilson's disease, rheumatoid arthritis or primary biliary cirrhosis.

Treated for 2-20 years with $\geq$750 mg/d.

Renal disease variable.

2/2 patients had circulating and 2/4 renal immune complexes.

Treat with immunosuppression, ? plasmapheresis.

Penicillamine has been reported to cause alveolar hemorrhage which is thought to be immunologically induced in at least 8 cases during treatment for Wilson's disease, rheumatoid arthritis or primary biliary cirrhosis, Table 34 (176-181). These patients have all been treated for a protracted interval of from 2 to 20 years with at least 750 mg and usually about 2 grams of penicillamine per day. The alveolar hemorrhage is typically severe with hemoptysis, but renal disease is quite variable. Patients have presented with renal failure, mild disease with only findings in the urinary sediment or virtually no evidence of kidney involvement. However, 2 of 2 patients tested have had circulating immune complexes, and 2 of 4 kidney biopsies have been similarly involved. Thus, it is thought that these patients

have had RPGN Type II when renal disease existed. Treatment has been with immunosuppression in all patients and plasmapheresis in 2.

Table 35

Pulmonary Disease Due to Trimellitic Anhydride

Trimellitic anhydride is a chemical used in the manufacture of plastics, epoxy resin coatings and paints.

Chemical irritation of airways, asthma, hypersensitivity pneumonitis and the pulmonary disease-anemia syndrome may result from heavy exposure.

Pulmonary disease-anemia syndrome is alveolar hemorrhage without extrapulmonary involvement associated with iron deficiency anemia and antibodies against trimellityl-substituted human proteins.

Trimellitic anhydride is a chemical used in the manufacture of plastics, epoxy resin coatings and paints, Table 35 (182-185). When inhaled in heavy concentration by workers in these industries it may cause a direct chemical irritation of airways, an asthma-rhinitis syndrome mediated by IgE antibody directed against trimellityl conjugated human respiratory tract proteins, hypersensitivity pneumonitis or the pulmonary disease-anemia syndrome. These latter two syndromes are accompanied by substantial levels of serum antibody directed against trimellityl-substituted human proteins. In the pulmonary disease-anemia syndrome patients have usually worked in the environment of the trimellitic anhydride for one or two months and then have the onset of symptoms including cough, anterior chest discomfort, minor hemoptysis and dyspnea over four to ten days. These symptoms progress to severe respiratory distress with striking hemoptysis, fever, chills and weakness. Iron deficiency anemia is present at the time of admission. Removal from exposure and supportive care are usually all the therapy necessary for resolution, and no permanent residua occur.

IDIOPATHIC PULMONARY HEMOSIDEROSIS

Table 36

Idiopathic Pulmonary Hemosiderosis
Definition

IPH is a syndrome of AH which occurs in the absence of identifiable pulmonary abnormalities or of systemic disorders such as ABMA disease, SLE, vasculitis or RPGN. IPH is, therefore, a diagnosis of exclusion. An immune origin is suggested by lymphocyte and plasma cell infiltrates in the lungs, or elevated serum IgA concentration or lymphadenopathy/splenomegaly in some patients.

Idiopathic pulmonary hemosiderosis is a syndrome of alveolar hemorrhage that occurs in the absence of identifiable pulmonary abnormalities or systemic disorders such as ABMA disease, SLE, vasculitis or RPGN, Table 36. IPH is, therefore, a diagnosis of exclusion. Since alveolar hemorrhage may precede other manifestations of systemic diseases, patients must be observed for protracted intervals to be sure that the diagnosis of IPH is secure (132-134, 186-190). An immune origin of the disease is suggested by lymphocyte and plasma cell infiltrates in the lungs (191, 192), elevated serum IgA concentrations (193-195), and the occurrence of lymphadenopathy or splenomegaly in about 20% (196).

Table 37

Idiopathic Pulmonary Hemosiderosis
Clinical Course

About 80% of patients have onset of symptoms in childhood and 20% from 16 to 30 years old.

All patients have chronic cough with iron deficiency anemia at time of diagnosis.

Children tend to have acute episodes which may be fatal. Adults usually have a milder disease without acute changes. Prolonged remissions are common in either age group.

The histologic and EM findings are not definitive. Recurrent episodes may lead to pulmonary fibrosis; pulmonary hypertension and cor pulmonale may ensue.

About 80% of patients have the onset of symptoms in childhood, usually from infancy until ten years old, Table 37. About 20% begin at 16 years or older, usually before age 30

(196). Virtually all patients have a chronic nonproductive cough, and iron deficiency anemia at the time of diagnosis (196-199). Children tend to have acute episodes of severe coughing, frequently with dyspnea and fever, which may be fatal. Adults usually have a milder disease without acute changes. Prolonged remissions are common in either age group. Histologic findings do not reveal the cause of bleeding, and there is disagreement over interpretation of EM changes (191, 192, 200-202). Recurrent episodes may lead to pulmonary fibrosis, with a restrictive lung defect and low diffusion capacity (199, 203). Pulmonary hypertension and cor pulmonale leading to death may also ensue. Steroid therapy with or without immunosuppressive agents is frequently employed. Many investigators feel steroids are indicated in acute bleeding episodes, and some are enthusiastic about long term immunosuppressive therapy (191, 204). However, in this chronic disease with spontaneous remissions it is not possible to determine the value of therapy from available data.

Table 38

Status of 68 Patients with Idiopathic Pulmonary Hemosiderosis at Time of Report

Status	Yrs. After 1st Sympt.	No. Pts	%
Death	3.3	20	29
Active disease	5.5	17	25
Inactive but pulm. sympts.	5.4	12	17
No activity, no symptoms	4.5	19	30

Am. J. Med. 32:499, 1962.

The best data on the prognosis of patients with IPH was compiled many years ago, Table 38 (196). Recent studies have confirmed these results thus making them representative of the current status of IPH (197). Among 68 patients 20 or 29% had died with an average duration of symptoms of 3.3 years. Active disease was present for about 5 1/2 years in another 25%, and an additional 17% were thought to have inactive disease but continued with symptoms such as exertional dyspnea and persistent anemia. About 30% of patients had no apparent activity or symptoms an average of 4 1/2 years after onset of symptoms. Since the disease may have quiescent intervals of up to ten years, it is not possible to know if 30% of the patients are actually well.

Table 39

Two Variants of Idiopathic Pulmonary Hemosiderosis

Sensitivity to cow's milk protein
- Onset days to weeks after birth (≤6 mos)
- Coughing, vomiting, diarrhea, rhinitis, recurrent fever, hemoptysis, hematemasis
- Precipitins to cow's milk, iron deficiency anemia, >11% eosinophiles
- Improvement with a milk-free diet

Celiac disease
- Typical IPH, 3/6 patients with villous atrophy of small bowel mucosa
- Improvement of GI symptoms with gluten-free diet

Am. J. Dis. Child 103:634, 1962; Q. J. Med. 197:95, 1981.

Two variants of idiopathic pulmonary hemosiderosis have been described, Table 39. One of these is a sensitivity to cow's milk protein (205, 206). The onset of symptoms is days to weeks after birth and usually less than six months. The infants have a combination of symptoms including coughing, vomiting, diarrhea, rhinitis, recurrent fever, hemoptysis and hematemasis. All reveal precipitins to cow's milk protein, iron deficiency anemia and greater than 11% eosinophiles. The symptoms improved with a milk-free diet, but the impact of diet on the pulmonary disease is not clear from published reports. When investigated most patients with IPH have not had these precipitins.

Celiac disease in association with idiopathic pulmonary hemosiderosis has been described in a limited number of adult patients (207). Among six adults with typical IPH three had intestinal symptoms with villous atrophy described in small bowel mucosa biopsy specimens. There was improvement of gastrointestinal symptoms with a gluten-free diet, but there was apparently no impact on the pulmonary disease. The relationship between each of these gastrointestinal syndromes and pulmonary disease is at present a matter of speculation.

SUMMARY

The alveolar hemorrhage syndromes are a group of conditions causing diffuse alveolar bleeding due to an immunologic abnormality. Since the cardinal symptom of hemoptysis may be minimal or absent, and since the differential diagnosis of hemoptysis and radiographic infiltrates is broad, the diagnosis is frequently delayed. Anemia, particularly when secondary to iron deficiency, and urinary findings suggest the correct diagnosis. Fiberoptic bronchoscopy and measurement of the

diffusion capacity are useful diagnostic tools in confirming alveolar hemorrhage.

When patients present with severe pulmonary hemorrhage treatment with very high dose intravenous methyprednisolone, pulse steroid therapy, is indicated even before a specific etiologic cause is determined. Subsequent therapy depends on the specific disease process but usually involves immunosuppression and in some cases plasma exchange.

Renal failure is common and the overall prognosis is guarded regardless of the etiology of the syndrome. Death may result from severe alveolar hemorrhage, complications of renal failure, complications of immunosuppression or from extrapulmonary progression of the primary disease process.

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