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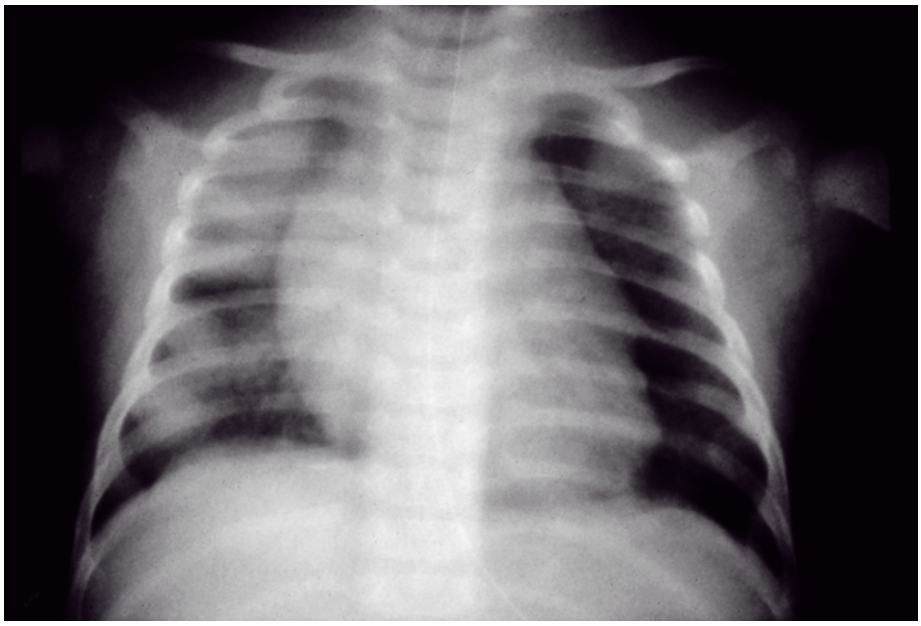
Acute Idiopathic Pulmonary Hemorrhage Among Infants

Recommendations from the Working Group for Investigation and Surveillance



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On the Cover: Chest radiograph of an infant upon initial examination; radiograph indicates idiopathic pulmonary hemorrhage with bilateral pulmonary infiltrates. Reprinted with permission of Dorr G. Dearborn, Ph.D., M.D., Case School of Medicine, Cleveland, Ohio.

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Acute Idiopathic Pulmonary Hemorrhage Among Infants

Recommendations from the Working Group for Investigation and Surveillance

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Summary

This report presents CDC's recommended case definitions and surveillance practices for Acute Idiopathic Pulmonary Hemorrhage (AIPH). In 1994 and 1997, CDC reported clusters of acute pulmonary hemorrhage (APH) among infants in Cleveland, Ohio. Subsequent reviews of these investigations identified shortcomings in the conduct of the studies and concluded that the investigations did not prove an association between APH among infants and exposure to molds. In response to recommendations from these reviews, with assistance of external consultants, CDC staff developed a plan to conduct surveillance for and investigation of AIPH. In developing this response, CDC recommends a definition for a clinically confirmed case of AIPH among infants on the basis of evidence of blood in the airway, age ≤1 year, absence of medical conditions related to pulmonary hemorrhage, and severe acute respiratory distress or respiratory failure. CDC recommends that pediatric intensive care units (PICUs) report cases that meet the CDC case definition to state health departments. CDC staff will study the number of reported cases of AIPH among infants and also review the Cleveland and Chicago case series to determine the degree to which the present case definition applies to them. If these reviews establish that AIPH among infants is a public health problem, on the basis of its magnitude or geographic or temporal distribution, targeted case surveillance will be initiated based on the distribution of cases. CDC staff will work with state and local health departments to investigate reported clusters of cases of AIPH among infants.

Background

This report presents CDC's recommendations for case definitions for Acute Idiopathic Pulmonary Hemorrhage (AIPH) among infants and CDC's plan for retrospective surveillance for AIPH among infants, including a study to evaluate the feasibility of using *International Classification of Diseases* (ICD) (*1*) codes for surveillance for AIPH.

In 1994 and 1997, CDC reported clusters of acute pulmonary hemorrhage (APH) among infants (*2,3*) in Cleveland, Ohio. During 1992–1994, a similar cluster occurred in the Chicago area (*4*). In Cleveland, risk factors for illness included male sex; lack of breast-feeding; residence in households with smokers; residence in homes where water damage had occurred during the previous 6 months; and residence in homes with increased quantities of fungi, including *Stachybotrys atra*.

Reviews by CDC staff and external consultants of these investigations identified shortcomings in the conduct of the studies (*5*). These panels concluded that the investigations did not prove an association between APH among infants and exposure to molds, specifically *S. chartarum* (*atra*). These reviewers recommended that CDC, pediatric pulmonologists, and state and local public health officials collaborate to

- develop a standard surveillance case definition;
- develop standard protocols for data collection and environmental assessment;
- implement surveillance for AIPH;
- investigate cases of AIPH among infants, particularly when clusters are identified, considering associations with multiple possible etiologies; and
- enhance sampling and laboratory analytic methods to improve assessment of environmental exposures to molds and fungi (*5*).

In response to the reviewers' recommendations, CDC staff developed a plan to conduct surveillance for AIPH, investigate clusters of cases, and conduct studies. In formulating this response, CDC convened three meetings to establish a case definition and classification scheme for public health surveillance for AIPH, recommend a standard home environmental investigation protocol, and outline a plan for surveillance and investigation of AIPH among infants. As a consequence of these meetings, CDC has determined that a series of surveillance activities should be initiated to direct future efforts. In addition to providing an overview of the results of the three meetings, this report describes surveillance activities and how results from those activities can guide efforts to investigate the burden and etiology of AIPH among infants.

The material in this report originated in the National Center for Environmental Health, Richard J. Jackson, M.D., Director; and the Division of Environmental Hazards and Health Effects, Michael A. McGeehin, Ph.D., Director.

AIPH among infants is a diagnosis of exclusion. Certain syndromes (Box 1) and other disease states can occur with pulmonary hemorrhage. Thus, differential diagnoses and neonatal medical problems that can cause pulmonary hemorrhage should be ruled out.

Meeting Panelists and Goals

Three meetings of panelists were convened to advise CDC staff regarding investigation of AIPH among infants. The Case Definition Panel included three pediatric pulmonologists, one pediatric intensive care specialist, one pediatric pathologist, two epidemiologists, and one environmental epidemiologist. The purpose of this panel was to recommend a case definition for use in public health surveillance for AIPH to facilitate case finding. Case finding will facilitate documentation of the burden of the condition and identification of possible etiologic agents or risk factors.

The Surveillance Implementation Panel included one pediatrician, one pediatric pulmonologist, one forensic pathologist, three epidemiologists (including one state epidemiologist), and four environmental epidemiologists (including one state epidemiologist and one toxicologist). Its purpose was to recommend a standard approach for public health surveillance for AIPH.

The Home/Indoor Environment and Laboratory Investigation Panel included two mycologists, one biochemist, two microbiologists, two industrial hygienists, two toxicologists, and one environmental epidemiologist. Its purpose was to recommend standard approaches and protocols for environmental data collection, laboratory analysis, and data interpretation during public health surveillance for AIPH.

For each of the three areas, group discussion led by a moderator was based on prepared questions. Participants produced written summaries, which form the basis of the recommendations provided in this report.

BOX 1. Pulmonary hemorrhage terminology

The term used for the cluster of cases reported in Cleveland* was pediatric idiopathic pulmonary hemorrhage and hemosiderosis. The term pulmonary hemorrhage has been used to describe situations with identifiable causes of bleeding.† Idiopathic pulmonary hemosiderosis (IPH)§ or primary hemosiderosis¶ has been used to denote presumably idiopathic bleeds or the accumulation of iron as hemosiderin.§ The terms pulmonary hemorrhage and primary hemosiderosis are often used interchangeably.** The new *International Classification of Diseases*, Tenth Revision (ICD-10) mortality coding system†† has no code for idiopathic pulmonary hemosiderosis. The CDC definition of a case of AIPH in an infant uses the term pulmonary hemosiderosis as a pathological finding to denote the possible occurrence of pulmonary hemorrhage, and not to describe a clinical syndrome.

The term pulmonary hemorrhage encompasses multiple clinical syndromes, including

- diffuse pulmonary hemorrhage;§§
- pulmonary hemorrhage of the newborn (ICD-9: 770.3; ICD-10: P26)¶¶ or hemoptysis;
- cough with hemorrhage;
- pulmonary hemorrhage not otherwise specified (ICD-9: 786.3; ICD-10 R04, R04.2); and
- idiopathic pulmonary hemosiderosis (ICD-9: 516.1, no ICD-10 code).

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¶ Hay JG, Turner-Warwick M. Pulmonary hemosiderosis, hemorrhagic syndromes and other rare infiltrative disorders. In: Murray JF, Nadel JA, eds. Textbook of respiratory medicine. Philadelphia, PA: W.B. Saunders, 1988:1501–5.

** Boat TF. Pulmonary hemorrhage and hemoptysis. In: Chernick V, Boat TF, Kendig E, eds. Kendig's disorders of the respiratory tract in children. 6th ed. Philadelphia, PA: W.B. Saunders, 1998:623–33.

†† World Health Organization. International statistical classification of diseases and related health problems. 10th rev. Geneva, Switzerland: World Health Organization, 1992.

§§ Hay JG, Turner-Warwick M. Pulmonary hemosiderosis, hemorrhagic syndromes and other rare infiltrative disorders. In: Murray JF, Nadel JA, eds. Textbook of respiratory medicine. Philadelphia, PA: W.B. Saunders, 1988:1501–5. CDC. Availability of case definition for acute idiopathic pulmonary hemorrhage in infants [Notice to readers]. MMWR 2001;50:494–5. Schwarz MI, Cherniack RM, King TE. Diffuse alveolar hemorrhage and other rare infiltrative disorders. In: Murray JF, Nadel JA, eds. Textbook of respiratory medicine 3rd ed. Philadelphia, PA: W.B. Saunders, 2000:1733–55.

¶¶ Schwarz MI, Cherniack RM, King TE Jr. Diffuse alveolar hemorrhage and other rare infiltrative disorders. In: Murray JF, Nadel JA, eds. Textbook of respiratory medicine 2nd ed. Philadelphia, PA: W.B. Saunders, 1994:1889–912. Cutz E. Idiopathic pulmonary hemosiderosis and related disorders in infancy and childhood. Perspect Pediatr Pathol 1987;11:47–81. Miller RR: Diffuse pulmonary hemorrhage. In: Thurlbeck WM, Churg AM, eds. Pathology of the lung. 2nd ed. New York, NY: Thieme Medical Publishers, 1995:365–73. Castile R, Kleinberg F. Pathogenesis and management of massive pulmonary hemorrhage in the neonate: case report of a normal survivor. Mayo Clin Proc 1976;51:155–8.

Case Definition

Case Classification and Severity Criteria

AIPH is the sudden onset of pulmonary hemorrhage in a previously healthy infant in whom differential diagnoses and neonatal medical problems that might cause pulmonary hemorrhage have been ruled out. Pulmonary hemorrhage can appear as hemoptysis or blood in the nose or airway with no evidence of upper respiratory or gastrointestinal bleeding. Patients have acute, severe respiratory distress or failure, requiring mechanical ventilation and chest radiograph (CXR), and usually demonstrate bilateral infiltrates.

AIPH among infants and sudden infant death syndrome (SIDS) potentially share similar risk factors (e.g., age group and maternal cigarette smoking). Also, in certain cases, SIDS is associated with pulmonary hemorrhage found at autopsy (*6,7*). Thus, factors that are known risk factors for SIDS should be identified when evaluating an infant possibly having AIPH. Potential information sources for case-identification and case-status classification during an investigation of pulmonary hemorrhage are provided (Table 1).

Clinically Confirmed Cases of AIPH Among Infants

Criteria for a confirmed case include pulmonary hemorrhage in a previously healthy infant aged ≤1 year with a gestational age of ≥32 weeks, with no history of neonatal medical problems that might cause pulmonary hemorrhage, and whose condition meets all of the following three criteria:

- Abrupt or sudden onset of overt bleeding or obvious evidence of blood in the airway, including
  - — epistaxis, hemoptysis, or frank blood in the airway below the larynx at visualization, not caused by any medical procedure (e.g., laryngoscopy or intubation); or
  - — identification of hemosiderin-laden macrophages (>20% of pulmonary macrophages containing hemosiderin on bronchoalveolar lavage or biopsy specimen). A source of bleeding from the nose and oropharynx should be ruled out at the time of admission.
- Severe-appearing illness leading to acute respiratory distress or respiratory failure, resulting in hospitalization in a pediatric intensive care unit (PICU) or neonatal intensive care unit (NICU) with intubation and mechanical ventilation.
- Diffuse unilateral or bilateral pulmonary infiltrates visible on CXR or computerized tomography (CT) of the chest. CXR or chest CT findings should be documented within 48 hours of examination of the infant.

A previously healthy infant should

- have been discharged from the hospital after birth with an uneventful course before the occurrence of bronchoalveolar hemorrhage;
- never have been previously intubated, nor required respiratory support with oxygen;

TABLE 1. Information sources for infant acute idiopathic pulmonary hemorrhage case identification and case-status classification

Potential data source	Potential information
Health-care admission notes from house officer, attending physician, nurses, or social worker	• Notations of physical abuse, sudden infant death syndrome, or history of smoking in the home
Chest radiograph or chest computerized tomography (CT)	• Presence of infiltrates on pre- versus postintubation chest radiograph or CT
Hematology laboratory	• Hemoglobin; hematocrit; red cell indices; white cell count and differential; or arterial blood gas • If unavailable, original recording of oxygen saturation by oximetry, before supplemental oxygen was administered, or the first oximetry and recorded oxygen flow • Coagulation profile
Fiber-optic bronchoscopy or blind lavage of the lower airway with a catheter*	• Percentage hemosiderin-laden macrophages — If >20%, hemorrhage >48 hours before examination is indicated — If <20%, bleeding might have been <48 hours before examination • Percentage of lipid-laden macrophages • Cultures include viral, bacterial, and fungal (silver stain) • Cell differential
Immunology tests	• Milk precipitins • Immunoglobulins (e.g., IgG and subclasses)
Stool	• Guaiac

* Infant should be stable enough to tolerate the procedure during the first 48 hours of mechanical support. Perform to guide diagnosis and therapy† for unstable patients with a life-threatening event based on clinical judgment (**Source:** Jean-Baptiste E. Clinical assessment and management of massive hemoptysis. Crit Care Med 2000;28:1642–7).

- not have evidence of physical abuse;
- not have any abnormality identified on admission or follow-up bronchoscopy that would explain the bleeding; and
- not have neonatal medical problems that can cause pulmonary hemorrhage.

CDC will adhere closely to this case definition, requiring that all the criteria be met for a confirmed case. The definition for a clinically confirmed case excludes pulmonary hemorrhage among older children and infants with restricted access to a PICU. Because no criteria exist for postmortem examinations, this definition excludes infants who die before hospital and PICU admission, whose illness might have met the case definition. However, the definitions for probable and suspect cases (see the following) will capture the majority of these cases and allow identification of illness among infants who die before examination by a physician.

Probable Cases of AIPH Among Infants

Criteria for a probable case include a previously healthy infant aged ≤1 year with a gestational age of ≥32 weeks,

- who has a sudden onset of bleeding from the airway, with or without respiratory distress, with or without intubation, and with or without pulmonary infiltrates on CXR or chest CT;
  or
- who died and had evidence of bleeding from the airway found on autopsy or postmortem; had been in respiratory distress; would or should have been intubated in the opinion of a clinician; and would have had infiltrates on CXR or chest CT.

Suspected Cases of AIPH Among Infants

Criteria for a suspected case include a previously healthy infant,

- who died and had evidence of bleeding from the airway found on autopsy or postmortem or who
- either did not have chest imaging studies or had imaging studies that indicated no pulmonary infiltrates.

Respiratory distress or intubation is not required for a suspected case.

Severity Classification Scheme for AIPH Among Infants

Because of the potential for variation in symptoms among infants for each of the criteria, different case combinations might be related to the timing or duration of symptoms, disease severity, pathologic processes, or etiologic agents associated with AIPH among infants. A discussion of the proposed case-classification categories for AIPH among infants is provided (Tables 2 and 3).

TABLE 2. Acute idiopathic pulmonary hemorrhage among infants case-classification scheme

Case status categories*	First criterion: Abrupt onset of bleeding from lower airway	Second criterion: Intubated; acute respiratory distress or respiratory failure	Third criterion: CXR/CT† chest; diffuse, bilateral pulmonary infiltrates
Clinically confirmed, 1	First criterion met	Second criterion met	Third criterion met
Clinically confirmed, 2	First criterion met	Second criterion met	Unilateral pulmonary infiltrates
Probable, 1	First criterion met	In PICU§ with severe respiratory distress, but not intubated	Third criterion met
Probable, 2	a. First criterion met	Not in severe respiratory distress	Third criterion met
	b. First criterion met	In PICU with severe respiratory distress, but not intubated	Unilateral pulmonary infiltrates
Probable, 3	a. Infant died; diagnosis of bleeding based on autopsy or postmortem findings	Would have been intubated in the opinion of the clinician	Third criterion met
	b. Infant died; diagnosis of bleeding based on autopsy or postmortem findings	Would have been intubated in the opinion of the clinician	Unilateral pulmonary infiltrates
	c. First criterion met	Second criterion met	No pulmonary infiltrates
Probable, 4	a. First criterion met	In PICU with severe respiratory distress, but not intubated	No pulmonary infiltrates
	b. First criterion met	Not in severe respiratory distress	Unilateral pulmonary infiltrates
Probable, 5	a. Infant died; diagnosis of bleeding based on autopsy or postmortem findings	Not in severe respiratory distress	Unilateral pulmonary infiltrates
	b. First criterion met	Not in severe respiratory distress	No pulmonary infiltrates
Suspected	a. Infant died; diagnosis of bleeding based on autopsy or postmortem findings	Would have been intubated in the opinion of the clinician	No pulmonary infiltrates; no CXR/CT
	b. Infant died; diagnosis of bleeding based on autopsy or postmortem findings	Not in severe respiratory distress	No pulmonary infiltrates; no CXR/CT

* Rankings of 1–5 represent categories with decreasing levels of certainty; 1 = highly probable, and 5 = least probable. The letter designations, a, b, and c represent approximately equivalent levels within each criterion.
† CXR = chest radiograph; CT = computerized tomography.
§ PICU = pediatric intensive care unit.

TABLE 3. Acute idiopathic pulmonary hemorrhage (AIPH) among infants case-classification category information

Case-classification category*	Discussion
Clinically confirmed, 2	• Bleeding might begin in a localized region of one lung with dispersion of blood to other areas of the lung through the airways • Initial chest radiograph (CXR) might indicate unilateral infiltrates, but following dispersion indicates diffuse infiltrates • Infants with unilateral infiltrates are considered confirmed for AIPH, but their characteristics might be different from infants with diffuse infiltrates
Probable, 1	• Not considered confirmed because identification depends on lavage or biopsy finding of hemosiderin-laden macrophages and not on active bleeding or recovering blood from below the larynx
Probable, 2a or 2b	• Work of breathing might vary for infants with a similar pathology (e.g., resulting from different body temperature, serum glucose levels, and duration of respiratory distress) • Infants who do not need intubation would not have acute bleeding directly identified from below the glottis
Probable, 3a, 3b, 5a, or suspected	• Upon initial examination, infants' circumstances might vary; information should be collected to identify these circumstances as best as possible during data abstraction so that the categories can be expanded if needed during data analysis • The circumstances might be that 1) the attending physician intended to intubate an infant who died; 2) the clinician who reviewed the death of an infant with postmortem findings consistent with pulmonary hemorrhage secondary to clinical respiratory failure thought the infant should have been intubated; 3) the infant died before arrival at the hospital and therefore was not intubated nor received thoracic imaging studies • Age-specific normochromic, normocytic, or microangiopathic anemia might indicate different pathophysiologic processes and in conjunction with appropriate clinical signs and symptoms might be supportive of a diagnosis of AIPH

* Rankings of 1–5 represent categories with decreasing levels of certainty; 1 = highly probable, and 5 = least probable. The letter designations a, b, and c represent approximately equivalent levels within each category (see also Table 2).

A summary of clinical features of AIPH among infants (Table 4) (Box 2) and neonatal medical problems and differential diagnoses that should be ruled out before classifying a case as AIPH among infants (Box 3) are included. Other differential diagnoses associated with pulmonary hemorrhage are listed (Table 5).

Feasibility Study To Determine the Concordance of ICD Codes for Pulmonary Hemorrhage with the CDC Case Definition

Prospective nationwide surveillance for cases of AIPH among infants is difficult to justify on the basis of the available epidemiologic data. In addition to the limitations reported for the Cleveland study (*5*), no risk factors were conclusively linked to disease in the Chicago investigation (*4*), and only one other cluster (in Detroit) was reported during 1992–1996 (*7*).

CDC will retrospectively review cases of pulmonary hemorrhage to determine the public health impact of AIPH among infants and to generate hypotheses regarding the importance of risk factors possibly associated with AIPH among infants. If that review indicates that AIPH among infants is a separate clinical entity and that these cases have occurred in clusters, or that an increase in incidence or mortality is associated with these cases, CDC will initiate prospective surveillance and case ascertainment to identify cases for epidemiologic studies designed to confirm or disprove associations between pulmonary hemorrhage host factors, environmental factors, and biologic agents, including such molds as *S. chartarum* (*5*).

Retrospective Review by Using Existing Data Sources

The ability to use existing data sources should substantially facilitate both determining the public health impact of AIPH among infants. However, the reliable data regarding mortality from pulmonary hemorrhage is only available at the national level. CDC conducted a preliminary evaluation of ICD codes for surveillance of pulmonary hemorrhage among infants to determine whether existing data sources can be used to estimate the magnitude of the problem of AIPH among infants. CDC examined data from the National Hospital Discharge Survey (NHDS) and National Mortality Data. Possible cases of AIPH among infants were identified by using ICD-9 codes 770.3, 784.7, 784.8, 786.3, and 516.1 (Table 6).

Infants identified by ICD-9 codes 770.3 and 786.3 differ from the cases reported in Cleveland. In the national datasets, the majority of cases of pulmonary hemorrhage had diagnoses such as prematurity or immaturity and death occurring within the first 7 days of life. The Cleveland cases occurred among stable, healthy, mature infants who had been discharged from the hospital to their homes after birth and subsequently experienced pulmonary hemorrhage (*8–10*). Thus, the estimates of deaths and hospital admissions for cases of pulmonary hemorrhage using ICD codes 770.3 and 786.3 does not distinctly identify infants with AIPH as defined by CDC. In addition, these national datasets do not determine if infants had identifiable etiologies or complications before their discharge from the hospital or their death. Because the estimated number of hospitalized cases with a primary diagnosis of pulmonary hemorrhage was less than the number of deaths, these national datasets might not be reliable for surveillance for infantile pulmonary hemorrhage. These analyses might be better performed by using state-based data.

A retrospective review for AIPH among infants will be performed in metropolitan cities in those states with the highest death rates and with ≥100 deaths associated with pulmonary hemorrhage among infants, on the basis of relevant ICD-9 and ICD-10 codes used from 1979 to the most recent available data. By focusing on PICUs and NICUs with substantial numbers of deaths, cases from innercity catchment areas, where the incidence of AIPH among infants is suspected to be higher, will be captured. Potential cases will be identified by using standardized methods of case ascertainment and data collection from hospital discharge and mortality data sources, based on ICD codes. Potential cases will be compared with the recommended case definition by reviewing medical records related to all cases of pulmonary hemorrhage observed since 1979 among children aged ≤2 years.

This retrospective review of AIPH among infants will

- determine whether AIPH among infants is a distinct clinical entity within existing ICD-9/ICD-10 diagnostic codes for pulmonary hemorrhage;
- describe the epidemiology of pulmonary hemorrhage;
- identify trends in the frequency of cases and the geographic distribution and clustering of cases;
- estimate the public health impact of AIPH among infants;
- identify groups at high risk for AIPH among infants; and
- determine the need for prospective surveillance as a source of cases for a case-control study.

The data will be reviewed to determine how these cases, including the apparent case clusters of AIPH among infants in Cleveland and Chicago, have been coded on hospital discharge abstracts, and how deaths attributed to the syndrome have been characterized on death certificates. Both Ohio and Illinois meet the criteria of ≥100 deaths from pulmonary hemorrhage. In Cleveland and Chicago, this review also will

TABLE 4. Clinical features of acute idiopathic pulmonary hemorrhage (AIPH) among infants

Sign or symptom	Finding
Previous acute or chronic disease	No evidence of cow milk protein allergy or associated respiratory, heart, kidney, or pancreatic disease*
Prodrome	Abrupt cessation of crying or unusual crying or irritability hours to days before the initial recognition of blood in the airway†
Fever	Not observed§
Initial examination	Decreased muscle tone and dusky pallor minutes to hours before progressing to sudden onset of hypoxemic respiratory distress or failure¶
Epistaxis	Hours to days before onset of respiratory failure**
Hemoptysis with or without epistaxis	Accompanies or immediately precedes respiratory failure††
Pulmonary hemorrhage	Acute and appears to be idiopathic§§
Respiratory distress	Characterized by tachypnea, grunting, and chest retractions¶¶
Signs of pulmonary hemorrhage	Diffusely diminished breath sounds without the presence of rales or rhonchi***
Respiratory support	Often requires intubation and mechanical ventilation; intubation when required is for 2–7 days†††
First chest radiograph (CXR)	Often demonstrates bilateral pulmonary infiltrates within the first 24 hours§§§
Follow-up CXR	Typically, alveolar infiltrates begin to clear within the first 24–48 hours¶¶¶
Visualization of pulmonary hemorrhage	Atraumatic intubation; bronchoscopy including inspection of upper airway****
Source of pulmonary hemorrhage	Typically, no source from the lung or gastrointestinal tract; presumed to be from diffuse alveolar capillary injury††††
Hemosiderin-laden macrophages	Typically, found in bronchoalveolar lavage fluid; might not be present in an infant experiencing an acute, initial pulmonary bleed§§§§
	Indicates evidence of bleeding into the lungs; finding >20% of total pulmonary macrophages containing hemosiderin can be consistent with pulmonary hemorrhage that occurred >48 hours before examination¶¶¶¶
Anemia (age-specific)	First 48 hours, fragmented or damaged red blood cells, hemoglobinuria; microangiopathic anemia might be indicative of a hemolytic process; normochromic normocytic might be consistent with acute, abrupt blood loss*****
Immune complexes	Serum negative for antiglomerular basement membrane antibody, anticytoplasmic neutrophilic antibody, complement titers, serum immune complexes, and antinuclear antibody†††††
Vasculitis or vascular malformation	None; spontaneous recovery with or without supportive care indicates these pathophysiologic processes are not the cause of bleeding
Platelet count, prothrombin time, and partial prothrombin time	Typically normal§§§§§

* **Sources**: 1) Levy J, Wilmott RW. Pulmonary hemosiderosis. Pediatr Pulmonol 1986;2:384–91. 2) Miller RR: Pulmonary disease in the immunocompromised host. In: Thurlbeck WM, Churg AM, eds. Pathology of the lung. 2nd ed. New York, NY: Thieme Medical Publishers, 1995;349–64. 3) Dearborn D, Yike I, Sorenson WG, Miller MJ, Etzel RA. Overview of investigations into pulmonary hemorrhage among infants in Cleveland, Ohio. Environ Health Perspect 1999;107(Suppl 3):495–9. 4) Etzel R, Montana E, Sorenson W, Kullman G, et al. Acute pulmonary hemorrhage among infants associated with exposure to *Stachybotrys atra* and other fungi. Arch Pediatr Adolesc Med 1998;152:757–62.

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¶ **Sources**: 1) Levy J, Wilmott RW. Pulmonary hemosiderosis. Pediatr Pulmonol 1986;2:384–91. 2) Dearborn D, Yike I, Sorenson WG, Miller MJ, Etzel RA. Overview of investigations into pulmonary hemorrhage among infants in Cleveland, Ohio. Environ Health Perspect 1999;107(Suppl 3):495–9. 3) CDC. Acute pulmonary hemorrhage/hemosiderosis among infants—Cleveland, January 1993–November 1994. MMWR 1994;43:881–3. 4) Dearborn, D. Clinical profile of thirty infants with idiopathic pulmonary hemorrhage in Cleveland (Unpublished manuscript). 5) Dearborn, D. Pulmonary hemorrhage among infants and children. Curr Opin Pediatry 1997;9:219–24.

TABLE 4. (*Continued*) Clinical features of acute idiopathic pulmonary hemorrhage (AIPH) among infants

** **Sources**: 1) Dearborn D, Yike I, Sorenson WG, Miller MJ, Etzel RA. Overview of investigations into pulmonary hemorrhage among infants in Cleveland, Ohio. Environ Health Perspect 1999;107(Suppl 3):495–9. 2) CDC. Acute pulmonary hemorrhage/hemosiderosis among infants—Cleveland, January 1993–November 1994. MMWR 1994;43:881–3. 3) Dearborn, D. Clinical profile of thirty infants with idiopathic pulmonary hemorrhage in Cleveland (Unpublished manuscript). 4) Dearborn, D. Pulmonary hemorrhage among infants and children. Curr Opin Pediatry 1997;9:219–24.

†† **Sources**: 1) Levy J, Wilmott RW. Pulmonary hemosiderosis. Pediatr Pulmonol 1986;2:384–91. 2) Etzel R, Montana E, Sorenson W, Kullman G, et al. Acute pulmonary hemorrhage among infants associated with exposure to *Stachybotrys atra* and other fungi. Arch Pediatr Adolesc Med 1998;152:757–62. 3) CDC. Acute pulmonary hemorrhage/hemosiderosis among infants—Cleveland, January 1993–November 1994. MMWR 1994;43:881–3. 4) Dearborn, D. Pulmonary hemorrhage among infants and children. Curr Opin Pediatry 1997;9:219–24. 5) CDC. Acute pulmonary hemorrhage among infants Chicago, April 1992–November 1994. MMWR 1995;44:67–74. 6) Flappan S, Protnoy J, Jones P, Barnes C. Infant pulmonary hemorrhage in a suburban home with water damage and mold (*Stachybotrys atra*). Environ Health Perspect 1999;107:927–30. 7) Novotny W, Dixit A. Pulmonary hemorrhage in an infant following 2 weeks of fungal exposure. Arch Pediatr Adolesc Med 2000;154:271–5.

§§ Primary diagnostic criteria.

¶¶ **Sources**: 1) Levy J, Wilmott RW. Pulmonary hemosiderosis. Pediatr Pulmonol 1986;2:384–91. 2) CDC. Acute pulmonary hemorrhage/hemosiderosis among infants—Cleveland, January 1993–November 1994. MMWR 1994;43:881–3.

*** **Source**: Etzel R, Montana E, Sorenson W, Kullman G, et al. Acute pulmonary hemorrhage among infants associated with exposure to *Stachybotrys atra* and other fungi. Arch Pediatr Adolesc Med 1998;152:757–62.

††† **Sources**: 1) Etzel R, Montana E, Sorenson W, Kullman G, et al. Acute pulmonary hemorrhage among infants associated with exposure to *Stachybotrys atra* and other fungi. Arch Pediatr Adolesc Med 1998;152:757–62. 2) CDC. Acute pulmonary hemorrhage/hemosiderosis among infants—Cleveland, January 1993–November 1994. MMWR 1994;43:881–3. 3) Pappas M, Sarnaik AP, Meert K, Hasan RA, Lieh-Lai MW. Idiopathic pulmonary hemorrhage in infancy. Chest 1996;110:553–5. 4) Flappan S, Protnoy J, Jones P, Barnes C. Infant pulmonary hemorrhage in a suburban home with water damage and mold (*Stachybotrys atra*). Environ Health Perspect 1999;107:927–30. 5) Novotny W, Dixit A. Pulmonary hemorrhage in an infant following 2 weeks of fungal exposure. Arch Pediatr Adolesc Med 2000;154:271–5.

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BOX 2. Clinical descriptions of pulmonary hemorrhage

In early texts, pulmonary hemorrhage was not commonly described in children, although it was noted to occur.* Blood found in the airways or alveoli of humans can result from different anatomic sites. Specific sites can include alveoli, large or small conducting airways, or the nasopharynx and gastrointestinal tract with pulmonary aspiration. Regardless of the origin of blood entering the lung, substantial amounts of blood lead to impaired gas exchange, altered pulmonary mechanics, and respiratory distress. Different pathophysiologic processes are associated with pulmonary hemorrhage. These can be divided into

- conditions where bleeding occurs at sites of normal tissue with mechanical disruption causing a loss of vascular integrity (e.g., intentional suffocation and mitral valve disease);
- vascular inflammation, whereby the inflammatory process causes a loss of vascular integrity (e.g., vasculitis secondary to such conditions as collagen vascular diseases);
- vascular malformations, whereby a combination of altered vascular integrity and physical influences (e.g., Laplace's law†) lead to disruption of the blood vessel; and
- coagulopathies, which usually also require additional physical disruption of the blood vessel through greater than normal transpulmonary vascular pressures.

The manifestations of pulmonary hemorrhage can be classified into different syndromes. Diffuse pulmonary hemorrhage is usually diagnosed by bronchoscopy, either by virtue of grossly bloody lavage fluid or by the presence of hemosiderin-laden macrophages in bronchoalveolar lavage. In biopsy and autopsy tissue, the diagnosis is made on the basis of the presence of recent blood and hemosiderin in the alveolar spaces or the interstitium.§ In the immunocompromised host, intra-alveolar bleeding can result from thrombocytopenia often associated with other factors. Diffuse pulmonary hemorrhage (DPH) can either be secondary to other disease states, associated with other organ dysfunction, or be isolated. Isolated causes of DPH include lung immaturity, cow milk hypersensitivity, pulmonary capillary hemangiomatosis, and idiopathic causes.¶

Pulmonary hemorrhage of the newborn (ICD-9: 770.3; ICD-10: P26) is manifested by focal hemorrhage into airspaces or the interstitium in the lungs of infants with hyaline membrane disease, bronchopulmonary dysplasia, and other neonatal pulmonary disorders.** These infants are most often male, preterm, small for gestational age, and have a history of perinatal stress.†† The etiology and pathogenesis of the disorder has not been elucidated.

Hemoptysis, cough with hemorrhage, pulmonary hemorrhage not otherwise specified (ICD-9: 786.3; ICD-10 R04, R04.2) is an acute manifestation of bleeding from the airway. This ICD category captures all the nonneonatal (and certain neonatal) diagnoses of pulmonary hemorrhage. Children with pulmonary hemorrhage might not appear to have hemoptysis if they swallow their sputum.

Consensus is lacking on the meaning of the term idiopathic pulmonary hemosiderosis (ICD-9: 516.1, no ICD-10 code). One pathology text states that the term denotes a separate clinical entity of which diffuse pulmonary hemorrhage is the major manifestation.§§ A later edition of the same text¶¶ notes that the presence of hemosiderin in lung macrophages indicates degradation products of hemoglobin. Hemosiderin is thus a pathologic state indicative of bleeding of any type into the lungs*** secondary to the processing of hemoglobin in the red blood cells in the airway by alveolar macrophages.††† Adults with active alveolar hemorrhage have high hemosiderin scores in bronchoalveolar lavage fluid,§§§ but hemosiderin-containing macrophages have limited differential diagnostic value.¶¶¶ In one clinical text, the term means diffuse recurrent intrapulmonary hemorrhage that is not secondary to bleeding from trauma, bleeding from the airways, tumors, or left ventricular failure.**** Another author†††† describes variants of primary and secondary pulmonary hemosiderosis.

On review of National Hospital Discharge Survey data for 1979–1996 and national mortality data for 1979–1998 for ICD-9 code 516.1 for infants, no instances were found in either dataset where ICD-9 code 516.1 was the primary listed diagnosis. However, in 207 cases, this code was the other listed diagnosis. This indicates that idiopathic pulmonary hemorrhage is usually an accompanying diagnosis to other diagnoses that result in hospitalization or death among infants.

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† Laplace's law describes the relation between the transmural pressure difference ($\ddot{A}P$), wall tension (T), and diameter (D) related to the surface tension in a concave surface (e.g., inside a blood vessel); $\ddot{A}P = 4T/D$.

§ **Sources**: 1) CDC. Availability of case definition for acute idiopathic pulmonary hemorrhage among infants [Notice to readers]. MMWR 2001;50:494–5. 2) Schwarz MI, Cherniack RM, King TE. Diffuse alveolar hemorrhage and other rare infiltrative disorders. In: Murray JF, Nadel JA, eds. Textbook of respiratory medicine. 3rd ed. Philadelphia, PA: W.B. Saunders 2000:1733–55.

¶ **Source**: Boat TF. Pulmonary hemorrhage and hemoptysis. In: Chernick V, Boat TF, Kendig E, eds. Kendig's disorders of the respiratory tract in children. 6th ed. Philadelphia, PA: W.B. Saunders, 1998:623–33.

BOX 2. (*Continued*) Clinical descriptions of pulmonary hemorrhage

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§§ **Source**: Miller RR. Diffuse pulmonary hemorrhage. In: Thurlbeck WM, Churg AM, eds. Pathology of the lung. 2nd ed. New York, NY: Thieme Medical Publishers, 1995: 365–73.

¶¶ **Source**: Miller RR: Pulmonary disease in the immunocompromised host. In: Thurlbeck WM, Churg AM, eds. Pathology of the lung. 2nd ed. New York, NY: Thieme Medical Publishers, 1995:349–64.

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¶¶¶ **Source**: Richter GW. Iron-loaded cell—the pathology of iron storage. Am J Pathol 1978;91:361–406.

**** **Source**: Hay JH, Turner-Warwick M. Pulmonary hemosiderosis, hemorrhagic conditions and other rare infiltrative disorders. In: Murray JF, Nadel JA, eds. Textbook of respiratory medicine. Philadelphia, PA: W.B. Saunders, 1988:1501–5.

†††† **Source**: Levy J, Wilmott RW. Pulmonary hemosiderosis. Pediatr Pulmonol 1986;2:384–91. 4) Coffin C, Schechtman K, Cole F, Dehner L. Neonatal and infantile pulmonary hemorrhage: an autopsy study with clinical correlation. Pediatr Pulmonol 1993;13:583–9.

BOX 3. Neonatal medical problems associated with pulmonary hemorrhage

- Asphyxia
- Bronchopulmonary dysplasia
- Chronic lung disease
- Congenital mitral stenosis
- Cor triatriatum, pulmonary
- Hemolytic diseases affecting the newborn
- Hyaline membrane disease
- Instrumentation of the nasopharynx or airway
- Intubation
- Left-to-right cardiac shunts
- Left-sided obstructive cardiac lesions disease
- Mechanical ventilation
- Nasogastric feeding tubes
- Persistent pulmonary hypertension of the newborn
- Respiratory distress syndrome
- Surfactant administration
- Venoocclusive disorders

determine the positive predictive value (PPV) between the clusters of pulmonary hemorrhage cases previously reported and the CDC definition of AIPH among infants. Because the relation between IPH, pulmonary hemorrhage, and AIPH among infants is not clearly understood in terms of rate, etiology, and risk factors, this analysis will define basic demographics of cases among infants and whether the proposed case definition for AIPH among infants is clearly distinguishable from other conditions. The magnitude and dimensions of AIPH among infants will be determined by describing the distribution of cases on the basis of ICD codes and the CDC case definition. This will involve enumerating cases, determining hospital discharge and mortality rates, and describing the distributions for available demographic variables (e.g., temporal and urban versus rural differences), if any.

Investigation of Suspected Clusters of AIPH Among Infants

If an apparent cluster of cases of pulmonary hemorrhage occurs, CDC recommends that state health departments initiate an investigation. CDC staff will work with each state, upon request, to evaluate case reports to assist the epidemiologic and environmental investigation, if any. State health departments can use existing protocols for outbreak or cluster investigations and collect information to determine if cases meet the CDC case definition for AIPH among infants. Because these cases probably will be identified in PICUs, CDC recommends that if PICU staff identify any suspected cases, they report them to their state epidemiologist.

For each case of AIPH in an infant, CDC recommends that PICU and NICU staff collect clinical information to certify case status, demographic information, and reports regarding the status of the patient's home. PICU and NICU staff also should carefully document illnesses that are similar clinically to AIPH, even if another specific etiology is confirmed, because they might offer additional information or indicate the need to re-assess the case definition.

TABLE 5. Differential diagnoses associated with pulmonary hemorrhage

System or indication	Examples of disorders
Pulmonary	• Congenital or acquired lung disorders • Premature lung disease • Primary ciliary dyskinesia • Bronchiectasis • Cystic fibrosis • Chronic aspiration or gastroesophageal reflux with airway soiling • Diffuse alveolar injury (e.g., caused by caustic inhalation, toxins, radiation, pharmacologic drugs, or insecticides)
Cardiac	• Pulmonary hypertension • Congenital heart disease with increased right-sided blood flow • Myocarditis • Pulmonary vascular congestion • Mitral stenosis • Congestive heart failure • Veno-occlusive disorders
Hematologic	• Thrombocytopenia • Congenital or acquired coagulopathies; bleeding disorders (e.g., hemophilia or Von Willebrand disease); transient vitamin K deficiency, which can be caused by using anticonvulsant drugs during pregnancy, failure to give vitamin K at birth, antibiotic use by the infant, exclusive breast feeding by the mother, and use of anticonvulsant drugs or herbal teas while breast feeding • Diffuse intravascular coagulopathy
Vascular	• Hemangiomas; vasculitis (rare among infants) (e.g., Henoch Schonlein purpura)
Gastrointestinal	• Celiac disease
Renal	• Nephritis — With immune complexes (e.g., Goodpasture syndrome) — Without immune complexes
Sudden Infant Death Syndrome (SIDS)*	
Evidence of physical abuse†	
Evidence of unintentional injury§	
Infections	• Lung and systemic infections
Collagen vascular and immunologic diseases¶	• Wegener's granulomatosis • Tuberous sclerosis • Lymphangiomyomatosis or lymphangioleiomyomatosis • Pulmonary-renal syndrome • Systemic lupus erythematosis

* Factors not covered in the inclusion and exclusion criteria for acute idiopathic pulmonary hemorrhage that are known risk factors for SIDS should be identified — race, low birthweight, prematurity, co-sleeping, or type of bedding.
† Unexplained or repeated injuries (e.g., welts, bruises, or burns); injuries in the shape of an object (e.g., belt buckle or electric cord); injuries not likely to happen given the age or ability of the child (e.g., broken bones in a child too young to walk or climb).
§ From parental or guardian history or injuries that are possible given the age or ability of the child.
¶ Rare among infants.

If performed, environmental assessment of the home to gather pertinent risk-assessment data should use standard protocols designed by trained environmental health professionals. At a minimum, the assessment should involve visual inspection, including checks for dampness, water damage, obvious mold, evidence of pests, and environmental tobacco smoke. Depending on the assessed need for further evaluation and the resources available, additional investigation might include determining moisture content, settled dust sampling, air sampling for different allergens, and biologically active compounds, and other investigations as needed.

Conclusion

CDC recommends a definition for a clinically confirmed case of AIPH among infants on the basis of 1) evidence of blood in the airway; 2.) age ≤1 year; 3) absence of medical conditions related to pulmonary hemorrhage; and 4) severe acute respiratory distress or respiratory failure, requiring admission to a PICU with intubation and mechanical ventilation. CDC recommends that PICUs report cases that meet the CDC case definition to state health departments and to CDC.

CDC will retrospectively analyze state-level mortality and hospitalization data based on ICD codes and will retrospec-

TABLE 6. Number of infants with primary and other listed diagnosis of pulmonary hemorrhage — National Hospital Discharge Survey (NHDS) and National Mortality Data (NMD) datasets*

Type of diagnosis	Acute idiopathic pulmonary hemorrhage ICD-9 code 770.3	786.3	Total
NHDS data, 1979–1996			
Primary listed diagnosis	1,041	342	**1,383**
Any listed diagnosis	11,801	3,485	**15,286**
NMD data, 1979–1997			
Primary listed diagnosis	2,685	46	**2,731**

* Using codes from the *International Classifications of Diseases*, 9th revision (**Source:** World Health Organization. International classification of diseases. 9th rev. Clinical modification [ICD-9-CM]. Geneva, Switzerland: World Health Organization, 1978.)

tively review discharges for pulmonary hemorrhage in selected PICUs. These studies will

- distinguish between the clinical findings associated with different symptoms of AIPH among infants;
- determine whether ICD codes capture cases that meet the CDC-recommended case definition for AIPH among infants;
- determine whether AIPH among infants is a distinct recognizable clinical entity;
- determine the proportion of cases ascertained retrospectively through ICD-9 codes that meet the clinical case definition by estimating PPV of ICD-coded data; and
- define the magnitude of AIPH among infants and the need for conducting etiologic studies.

CDC will review the Cleveland and Chicago case series to determine the degree to which the present case definition applies to them. In addition, CDC will evaluate the present case definition on the basis of data from initial surveillance findings and modify it as appropriate.

If these reviews establish that AIPH among infants is a public health problem on the basis of increasing numbers or clusters of cases geographically or temporally, targeted prospective case surveillance will be initiated. If prospective surveillance is initiated, CDC will maintain a database of current cases of AIPH among infants, reported by PICUs that meet the case definition. The database will serve as a source of cases for case-control studies to determine etiology. CDC will work with state and local health departments to investigate clusters of AIPH among infants cases.

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trust•wor•thy: *adj*

('trəst-"wər-thē) 1 : worthy of belief

2 : capable of being depended upon;

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