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Investigation of Acute Idiopathic Pulmonary Hemorrhage Among Infants — Massachusetts, December 2002–June 2003

During 1993–1996, investigation of cases of acute idiopathic pulmonary hemorrhage (AIPH) among infants in Cleveland, Ohio (1), suggested an association between AIPH and being male, exposure to molds (notably *Stachybotrys chartarum*), exposure to environmental tobacco smoke, and lack of breastfeeding. However, reviews of that investigation by CDC and external consultants identified shortcomings in the methodology and determined that no association between AIPH and exposure to molds had been established (2). The reviewers recommended that CDC collaborate with state and local public health officials to investigate future cases of AIPH, particularly when clusters are identified. During December 2002–June 2003, four cases of AIPH among full-term infants were reported in the Boston, Massachusetts, area. In a 4-month period, three of the infants were patients at the same hospital, which typically has one case of AIPH among infants per year. CDC, in collaboration with the Massachusetts Department of Public Health (MDPH), investigated this cluster, the first reported since CDC's case definition* for AIPH in infants was published in 2001. This report summarizes the results of that investigation, which determined that two of the infants had von Willebrand disease (vWD), an inherited bleeding disorder, and one had borderline test results for vWD. The findings suggest that the infants with AIPH might have had underlying acquired or genetic susceptibility that predisposed them to pulmonary bleeding. Before a diagnosis of AIPH is

made, clinicians should use tests to rule out vWD and other bleeding disorders.

Reviewers of the earlier investigation of AIPH among infants recommended that investigators consider associations with multiple possible etiologies. These etiologies might include environmental factors such as exposure to mold, evidence of pests, tobacco smoke, and exposure to multiple allergens and biologically active compounds. Because of the overlap between AIPH in infants and sudden infant death syndrome (SIDS) (3), investigators also were advised to consider risk factors for SIDS.

In the Boston area investigation, CDC and MDPH reviewed December 2001–June 2003 admission records of pediatric and neonatal intensive care units (PICUs and NICUs) and hospital discharge records at each of the four area hospitals with PICUs and found no additional cases. For each of the four cases that were consistent with the CDC case definition, investigators used a standard data abstraction form to collect information about family demographics, prenatal and birth histories, diet and medication, preexisting medical conditions, and medical procedures and tests after admission for AIPH. Blood samples collected from the four infants were sent to CDC's hemostasis laboratory and tested for vWD and other bleeding disorders.

CDC and MDPH investigators visited the homes of the four infants. During each home visit, investigators conducted a 1–2-hour interview with family members to obtain additional information about family travel, medical history, and self-reported environmental exposures. An indoor-air-quality inspector from MDPH visually examined each home for signs of water damage and mold. Four weeks after the initial home visit, investigators conducted environmental sampling for fungi and mold spores in the homes of three of the four infants. For one infant, no environmental sampling was possible because the family had relocated; reported water and mold damage in the home already had been remediated. Environmental samples (e.g., air, dust, and surface) were taken from different areas in the homes, including the location where the infant was reported to have spent the most time. In each area, air sampling was performed under varying conditions (e.g., with room ceiling fans on or off and before and after foot traffic). Floor registers and electrical outlets were sampled to detect reservoirs of mold in heating, ventilation, and air conditioning ductwork and behind walls. Air samples were tested to identify total spores and culturable fungi.

The four infants were male and, at onset of illness, had a median age of 48 days (range: 28–77 days). All four infants had symptoms of upper respiratory illness <2 weeks before their pulmonary hemorrhage (Table). On admission to the hospital, each infant required intubation and mechanical

*A clinically confirmed case was defined as an illness in a previously healthy infant aged <1 year with a gestational age of ≥ 32 weeks, no history of neonatal medical problems that might cause pulmonary hemorrhage, and whose illness is consistent with the following criteria: 1) abrupt or sudden onset of overt bleeding or frank evidence of blood in the airway; 2) severe presentation leading to acute respiratory distress or respiratory failure, resulting in hospitalization in a pediatric intensive care unit with intubation and mechanical ventilation; and 3) diffuse, bilateral pulmonary infiltrates on chest radiograph or computerized tomography of the chest.

Source: CDC. Availability of case definition for acute idiopathic pulmonary hemorrhage among infants. *MMWR* 2001;50:494–5.

ventilation. All four infants had evidence of blood in the airway (i.e., identified by bronchoscopy in three and by bronchoalveolar lavage fluid containing hemosiderin-laden macrophages in the fourth). The four infants had a median stay in the PICU of 8 days (range: 7–9 days). All were discharged in good health.

Although a history of vWD was reported only by the family of infant A (Table), testing at CDC's hemostasis laboratory revealed that both infant A and infant B had laboratory evidence of vWD, and infant D had borderline von Willebrand factor antigen and ristocetin cofactor results consistent with a vWD diagnosis. All laboratory tests for bleeding disorders for infant C were within the normal range. Infant B also had a history of recurring bruising and possibly gastrointestinal bleeding. Although he received vitamin K at birth, infant B also had characteristics that might predispose to vitamin-K deficiency, including antibiotic use by the mother and infant (4). The family of infant D reported finding him face down on a couch at the time hemoptysis was first observed, suggesting the possibility of unintentional asphyxia.

The environmental investigation of the infants' homes determined that one primary residence had flooded and three had undergone recent renovations; infants A, B, and D were exposed to increased indoor concentrations of dust and particulate matter within a few days of their bleeding events. Although only one family reported visible mold, indications of active fungal growth were present in all the homes. Common molds, such as species of *Cladosporium* and *Penicillium* were the dominant culturable species identified in each of the homes tested. One *S. chartarum* spore was found in the basement of one home, and seven *S. chartarum* spores were found in another home.

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Editorial Note: Although the rate of AIPH among infants in the United States is unknown, the condition is thought to be rare (5); what national AIPH data exist are inconsistent and likely unreliable (3). CDC has reported clusters of AIPH among infants in Cleveland, Ohio, and Chicago, Illinois (3,6); however, the specific etiologic factors for AIPH remain unknown. Previous studies have not reported an association between pulmonary hemorrhage and vWD, although specific

testing for vWD might not have been conducted. The most common inherited bleeding disorder, vWD has multiple variants affecting an estimated 1%–3% of the U.S. population (7); persons with vWD tend to have mucocutaneous bleeding. For infants A, B, and D, a previously undiagnosed bleeding diathesis might have contributed to their hemorrhage; hematologic tests confirmed the diagnosis of vWD in two infants (infants A and B) and suggested vWD in the third (infant D). The hematologic test findings appear consistent with a reported family history of vWD for infant A and with unexplained facial bruising in infant B that occurred before his hemorrhage; infant B also had risk factors that might have been associated with transient vitamin-K deficiency. For infant D, acute unintentional asphyxia, a known risk factor for pulmonary hemorrhage, might have been a contributing factor.

All the infants in this cluster also were exposed to certain environmental factors that might have affected their lungs, including environmental tobacco smoke, particulate matter (e.g., construction dust), and mold. *Cladosporium* and *Penicillium*, the molds most commonly identified in each of the homes, typically are the most abundant fungal genera in indoor air (8). Total fungal spore counts in two of the homes were at concentrations that have been associated with increased risk for lower respiratory illness (9), and all four infants were treated presumptively for respiratory infections before their hemorrhage episodes. Only seven spores of *S. chartarum* were found in one home, and a single spore was found in another. Although the full significance of spore counts is not known, toxic and other non-IgE-mediated health effects that have been hypothesized to occur with exposure to *S. chartarum* appear unlikely to have contributed to these AIPH cases (10).

The findings in this report are subject to at least three limitations. First, the findings are from a case series; because no comparison group was used, definitive conclusions cannot be made about the hypotheses. Second, the findings are limited by the intervals between the illnesses and interviews of family members (range: 1 week–6 months); families with longer intervals might have been less likely to remember all of the circumstances related to the illness. Finally, the intervals between illnesses and environmental sampling (range: 3 weeks–7 months) might have resulted in samples that were not representative of the environment at the time of illness onset.

When cases of AIPH among infants occur, tests should be undertaken to rule out vWD and other bleeding disorders. If vWD is identified, appropriate therapy should be initiated to reduce the time course and severity of bleeding. Testing for vWD also might help to further explain any interaction between predisposing acquired or genetic vWD and environmental or infectious factors.

TABLE. Summary of epidemiologic, laboratory, and environmental findings from four reported cases of acute idiopathic pulmonary hemorrhage (AIPH) among infants — Massachusetts, December 2002–June 2003

Epidemiologic/ Environmental findings	Infant A	Infant B	Infant C		Infant D
Epidemiologic					
Date of illness onset	December 2002	February 2003	April 2003		June 2003
Age at illness onset	45 days	28 days	77 days		50 days
Race/Ethnicity	White, non-Hispanic	Asian	White, non-Hispanic		White, non-Hispanic
Sex	Male	Male	Male		Male
Maternal perinatal and/or infant antibiotic use	Yes/No	Yes/Yes	No/No		Yes/Yes
Upper respiratory infection symptoms <2 weeks of AIPH	Yes	Yes	Yes		Yes
Reported family history of bleeding disorders	von Willebrand disease	None	None		None
Infant history of susceptibility to bruising	No	Yes	No		No
Possible history of unintentional asphyxiation or trauma	No	No	No		Yes
Abnormal hospital hematology laboratory findings	Hemoglobin: reduced, 8.7g/dL Platelets: elevated, 574K	Partial thromboplastin time: elevated, 40–60 sec	Platelets: elevated, 567K Fibrinogen: elevated, 626 mg/dL		Platelets: elevated, 571K Prothrombin time: normal Partial thromboplastin time: normal
CDC hemostasis laboratory results*					
von Willebrand factor antigen	Reduced, 64%	Borderline, 66%	Normal, 151%		Borderline, 56%
Ristocetin cofactor	Borderline, 69%	Reduced, 41%	Normal, 144%		Borderline, 52%
Factor VIII	Normal, 94%	Reduced, 40%	Normal, 167%		Normal, 70%
ABO blood type	B	B	Not tested		O
			Parents' home		In-laws' home
Reported cigarette smoking in the home	Yes	No	No	No	No
Reported flooding in the home	Yes	No	No	Yes	No
Reported mold in the home	Yes	No	No	No	No
Home renovations during infant's life	Yes	Yes	No	No	Yes
Range of culturable fungal counts (cfu/m ³) for all samples collected	No sampling performed	304–394	197–500	18–768	215–1,430
Dominant genera		<i>Cladosporium</i> , <i>Penicillium</i>	<i>Cladosporium</i> , <i>Penicillium</i>	<i>Cladosporium</i> , <i>Penicillium</i> , <i>Chaetomium</i>	<i>Cladosporium</i> , <i>Penicillium</i>
Location with maximum value		Infant's room	Infant's room	Basement	Basement
Range of total spore counts (spores/m ³) for all samples collected	No sampling performed	1,633–2,369	1,099–19,500	33–2,869	1,836–33,460
Dominant genera		<i>Penicillium</i> / <i>Aspergillus</i> types, <i>Cladosporium</i> , Basidiospores	Smuts, <i>Penicillium</i> / <i>Aspergillus</i> types, <i>Cladosporium</i> , <i>Botrytis</i> , Basidiospores	<i>Cladosporium</i> , <i>Penicillium</i> / <i>Aspergillus</i> types, Basidiospores, <i>Chaetomium</i>	Basidiospores, <i>Cladosporium</i> , <i>Penicillium</i> / <i>Aspergillus</i> types
Location with maximum value		Infant's room	Infant's room	Basement	Basement
Amount of <i>Stachybotrys chartarum</i> found in home (spores/m ³)	No sampling performed	None	Basement: one spore, 33	None	Infant's bedroom: two spores, 67 Parent's bedroom: three spores, 100 (electrical outlet); one spore, 33 (ambient) Basement: one spore, 33 Hallway: positive identification from tape lift of ceiling stain

* Normal reference ranges — Blood type O: von Willebrand disease factor (vWF) antigen 48%–199%, ristocetin cofactor 38%–166%, factor VIII 49%–190%, blood type non-O: vWF antigen 66%–245%, ristocetin cofactor 60%–205%, factor VIII 66%–224%.

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Progress Towards Poliomyelitis Eradication — Egypt, 2003–2004

Since 1988, the estimated number of wild poliovirus (WPV) cases worldwide has decreased >99%, and three World Health Organization (WHO) regions (Americas, European, and Western Pacific) are now certified as polio-free. Substantial progress has been made in the Eastern Mediterranean Region, where 18 of the 22 countries are polio-free and polio remains endemic in only three countries (Afghanistan, Egypt, and Pakistan). This report summarizes progress towards polio eradication in Egypt from 2003 through mid-2004 and describes the measures needed to ensure successful interruption of poliovirus transmission.

Routine Vaccination

Since 1994, reported routine vaccination coverage of infants (aged <12 months) with >3 doses of oral poliovirus vaccine (OPV) has remained >90% in Egypt. During 2003, reported routine coverage of infants with >4 doses of OPV was >95%. Coverage with >4 doses of OPV was >95% in 234 (94%) of 250 districts and was 90%–95% in the remaining 16 districts.

Supplementary Immunization Activities (SIAs)

In 2003, Egypt conducted four rounds of National Immunization Days (NIDs)* and three rounds of Subnational Immunization Days (SNIDs)†. As of June 2004, Egypt has conducted two rounds of NIDs and one round of SNIDs. In addition, two mop-up rounds§ were conducted in June and July in response to a confirmed polio case in May. SNIDs implemented in 2003 and 2004 targeted mainly Greater Cairo¶ and governorates in Upper Egypt that were the focus of WPV circulation in 2003 and 2004. All SIAs in 2003 and 2004 were conducted by using an intensified house-to-house approach. Further improvements in SIA quality were introduced in 2004, including revised tally sheets, supervisory guidelines and checklists, and training materials. The increasingly high quality of these SIA rounds was documented by international observers and independent monitor surveys (Ministry of Health and Population [EMOHP], unpublished data, 2004). Administrative data indicate that the number of children vaccinated during NIDs increased by approximately 15%, from 9.8 million in the December 2002 round to 11.3 million in the April 2004 round.

WPV Surveillance

Surveillance for acute flaccid paralysis (AFP) cases in Egypt improved substantially in 2003 and 2004 (Table) in response to recommendations from the Egypt Technical Advisory Group (TAG) made in March 2002, which included strengthening central level supervision and data management and increased awareness of reporting. Nationwide, the nonpolio AFP rate per 100,000 children aged <15 years reached 2.5 in 2003 and increased to 3.3 in 2004 (annualized as of June 2004). In 2004, a total of 23 governorates achieved a nonpolio AFP rate of >2.0 cases per 100,000 children aged <15 years, compared with 21 governorates in 2003. The four governorates with rates below 2.0 in 2003 had low population density. Adequate stool specimens were collected within 14 days of paralysis onset from 93% and 94% of persons with AFP nationwide in 2003

* Mass campaigns conducted during a short period (days) in which 2 doses of OPV are administered in two rounds 4–6 weeks apart to all children in the target group (usually those aged <5 years) regardless of previous vaccination history.

† Campaigns similar to NIDs but confined to part of the country.

§ Intensive house-to-house vaccination with OPV in districts with populations at high risk, conducted in two rounds, 4–6 weeks apart.

¶ *Greater Cairo*: Cairo, Giza, and Kalioubia Governorates. *Upper Egypt*: governorates located on the River Nile south of Giza and Cairo, from Fayoum to Aswan. *Lower Egypt*: governorates located north of Cairo and Giza, including Suez Governorate and excluding Matrouh, and North and South Sinai Governorates.