This 7-month-old boy came to the emergency room for evaluation of breathing problems. He had a 10-day history of cough, fever, and decreased oral intake. He had been seen at an outside hospital several days earlier and was diagnosed with a viral infection.

Several days after that first visit, he was called to return because of a positive blood culture. He was admitted to that hospital; a repeat blood culture was negative, and the initial blood culture was thought to be a contaminant. He was found to have an enterovirus growing from his nasal secretions; he was discharged despite the fact that he was having persistent fevers. He came to our emergency room 2 days later because of persisting fever.

He was the 6-pound 15-ounce product of a full-term pregnancy to a gravida 1 para 1 (G1P1) woman. There were no perinatal problems. He had received his 2- and 4-month immunizations and had yet to receive his 6-month immunizations. The family history was remarkable for the father who had a history of asthma and the mother who had a history of anemia and hypothyroidism.

In addition, the mother’s brother had a history of failure to thrive and recurrent pneumonia and died at 11 months of pneumonia and heart failure. Another brother of the mother was stillborn. This family history was obtained several days after admission. Past medical history was remarkable in that he was hospitalized once for pneumonia at 4 months.

On exam, he was alert but in moderate respiratory distress. His pulse was 145, respiratory rate 62, blood pressure 94/60, and temperature of 36.6°C rectally. Weight was in the 15th percentile, length below the 5th percentile. HEENT exam was unremarkable. Neck was supple without adenopathy. S1 and S2 were normal with physiologic splitting and no murmurs. Upper and lower extremity pulses were normal. He was tachypneic with subcostal retractions and decreased breath sounds on the left side of his chest. Abdomen was soft and nontender without masses. Liver edge was palpable at the umbilicus. Genitalia and neurologic exam were normal.

Serum chemistries were normal, save for albumin 2.3 g/dL. Hemoglobin was 7.3 g/dL, white blood cell count 18,000/mm³ with 50% lymphocytes and 42% neutrophils; platelet count 780,000/mm³. CRP was 17 mg/dL. Chest X-ray showed moderately enlarged heart with normal vascularity. EKG showed normal sinus rhythm with low voltage and nonspecific ST changes. Echocardiogram revealed a large pericardial effusion with tamponade physiology.

**Liver edge was palpable at the umbilicus.**

Robert Listernick, MD, moderator: First question, what defines a contaminant blood culture?

Ben Katz, MD, pediatric infectious disease physician: First, most true pathogens will grow within 24 to 48 hours. Second, the physician must look at the clinical context and decide whether the positive culture makes sense. For instance, coagulase negative *Staphylococcus*, which we generally regard as a contaminant, might be a true pathogen in a neonate or a child with an indwelling catheter. Finally, the actual organism needs to be considered.
Dr. Listernick: I didn’t state it, but the initial gram stain showed gram-negative coccobacilli, and the blood culture grew *Moraxella catarrhalis*.

Dr. Katz: That organism is not a common source of bacteremia but is not a common contaminant either. *M. catarrhalis* bacteremia has been reported, mainly in people with respiratory infections and/or immunodeficiency.

Dr. Listernick: What about the enterovirus that was recovered?

Dr. Katz: Children aren’t generally colonized with enterovirus. However, they may have shedding of the virus over a long period of time following an acute infection. You need to look at the clinical context: Do the child’s symptoms fit an enteroviral infection? They may have in this case.

Dr. Listernick: So the child was found by echocardiogram to have a large pericardial effusion with taponade physiology. Can you elaborate?

Jeffrey Gossett, MD, pediatric cardiologist: Essentially, the pericardial effusion limits the heart’s ability to fill and to pump blood. As pericardial fluid and intrapericardial pressure increases, the ventricles cannot fill completely, and cardiac output declines. The pericardial sac can accumulate a great deal of fluid, particularly if it happens gradually over a relatively long period of time, but rapid accumulation of fluid is very poorly tolerated.

Dr. Listernick: Before you knew about the presence of the pericardial effusion, could other conditions cause similar physiology?

Dr. Gossett: Constrictive pericarditis due to a thickened fibrotic pericardium can lead to the same low output cardiac state. This may occur after infections, such as tuberculosis or bacterial purulent pericarditis, radiation therapy, or cardiac surgery.

Dr. Listernick: What were you thinking when you identified the pericardial effusion?

Dr. Gossett: First, this kid is really sick and needs to be stabilized. Volume resuscitation can be extremely helpful to enhance filling of the heart and cardiac output. At the same time, evacuation of the pericardial fluid was essential in order to improve cardiac output. Before we examined the fluid, I felt that the most likely explanation was viral pericarditis.

In an older child, rheumatologic causes, such as lupus, would be highly likely. Purulent pericarditis or an oncologic process, such as leukemia, that present in this fashion are extremely uncommon but are remote possibilities. If this child had had heart surgery, postpericardiotomy syndrome would be a possibility.

Dr. Listernick: You removed 145 cc of cloudy, yellow pericardial fluid and left in a pericardial drain. There were 2,100/mm³ white blood cells and 900/mm³ red blood cells with 95% neutrophils. The gram stain revealed intracellular gram-negative
coccobacilli. Pericardial fluid protein was 4.5 g/dL. The culture grew *M. catarrhalis*.

**Dr. Katz:** He has purulent pericarditis. I would have expected many more white blood cells. However, the pericardial fluid is extremely proteinaceous, and there are 95% neutrophils. *M. catarrhalis* is part of the mouth flora, generally a cause of otitis media, sinusitis, and pneumonia occasionally. It’s not a terribly pathogenic organism. It’s an extremely unusual cause of purulent pericarditis. I would have expected *Staphylococcus aureus*, which is by far the most common cause of purulent pericarditis.

**Stanford T. Shulman, MD, pediatric infectious disease physician:** Prior to the introduction of the *Haemophilus influenzae* type b vaccine, that organism was a significant cause of purulent pericarditis. *H. influenzae* infections have almost completely disappeared thanks to the vaccine. The key in this case is that *M. catarrhalis* is a very low virulence organism and, as such, red flags should be raised. Perhaps alone this might not be enough to suggest the possibility of an immunodeficiency syndrome, but coupled with the family history that was obtained subsequently, it becomes more obvious.

**Dr. Listernick:** The family history clearly suggests the possibility of an X-linked syndrome. What do you think?

**Ramsay Fuleihan, MD, pediatric immunologist:** My personal bias is that when there’s a strong reason to suspect an underlying immunodeficiency syndrome, whether it’s an unusual family history or an unusual infection, I would prefer to perform an immunologic evaluation before he has a second infection.

**Key Learning Points**

1. Most true pathogens grow in blood cultures within 24 to 48 hours.
2. Causes of pericardial effusions include viral and purulent pericarditis, rheumatologic conditions, such as lupus, and malignancies, such as leukemia.
3. X-linked immunodeficiency syndromes involving the humoral immune system include X-linked agammaglobulinemia, a variety of genetic defects leading to hyper-IgM syndrome and defects in the NF-kappa B essential modulator (NEMO) pathway.
4. Defects in the NEMO pathway have been associated with a variety of clinical syndromes, including incontinentia pigmenti; osteopetrosis with ectodermal dysplasia; primary lymphedema; X-linked immunodeficiency with ectodermal dysplasia; and a form of hyper-IgM syndrome.

**Dr. Listernick:** Before we discuss the possibility of immunodeficiency, how was the purulent pericarditis treated?

**Dr. Gossett:** Antibiotics are obviously important, but we should approach this as we would any abscess; drainage is the key to success. Generally, the pericardial sac needs to be washed out in an open procedure so as to prevent fibrotic scarring and the development of subsequent constrictive pericarditis. The cardiothoracic surgeon performed the washout and a pericardial window was created.

**Dr. Listernick:** Can you explain a pericardial window?

**Dr. Gossett:** The surgeon rectects a piece of the pericardium to prevent reaccumulation of fluid by allowing the fluid to drain into the left pleural space.

**Dr. Listernick:** The outside blood culture, our blood culture, and the pericardial fluid all grew *M. catarrhalis*. So now we should discuss immunodeficiency syndromes.

**Dr. Fleishman:** Given the family history, the first condition one should consider is X-linked agammaglobulinemia, previously known as Bruton agammaglobulinemia. This occurs as a result of a mutation of the gene Bruton tyrosine kinase on the X-chromosome. This leads to a near complete absence of B cells and humoral immunity. These boys generally present in the first year of life with recurrent or severe sinopulmonary infections.

**Dr. Listernick:** In this patient, serum IgG was very low, IgA and IgE were normal, and IgM was quite elevated.

**Dr. Fuleihan:** That eliminates the possibility of X-linked agammaglobulinemia in which all the immunoglobulins are low to absent. The next possibility we should consider is hyper-IgM syndrome. This is caused by mutations in the gene coding for *CD40* ligand that is expressed on T-lymphocytes and normally allows B cells to switch from making IgM to making the other immunoglobulins (IgG, IgA, and IgE). This actually can be the result of a number of different mutations in the *CD40* pathway, the most common being X-linked.

Once again, these children present in infancy with recurrent sinopulmonary infections or chronic diarrhea and failure to thrive. They are often neu-
tropenic. Another form of X-linked hyper-IgM syndrome, which this child clearly does not have, is associated with hypohidrotic ectodermal dysplasia. By using a monoclonal antibody against CD40 ligand and measuring soluble CD40, we eliminated this category of diseases.

**Dr. Listerick:** So X-linked hyper-IgM syndrome has been eliminated. I have to ask about terminal complement deficiency syndromes. I’m aware that terminal complement deficiencies can lead to recurrent *Neisseria* infections. Because *M. catarrhalis* is a close cousin to *Neisseria* species, is this group of immunodeficiencies a consideration?

**Dr. Shulman:** There are a number of *Neisseria* species that are common mouth flora (*N. sicca, N. lactamica*, etc.) that do not cause infections in those individuals. Terminal complement deficiencies generally lead to recurrent meningococcal or gonococcal infections only.

**Dr. Listerick:** So what should we consider next?

**Dr. Fuleihan:** NF-kappa B essential modulator (NEMO) regulates NF-kappaB signaling. NF-kappa B is responsible for transcription of a variety of genes involved in the inflammatory cascade and the immune system. The signaling via CD40 goes through the NEMO complex. Defects in the NEMO pathway have been associated with a variety of clinical syndromes, ranging from incontinentia pigmenti; osteopetrosis with ectodermal dysplasia and primary lymphedema; to X-linked immunodeficiency with ectodermal dysplasia. Patients have also been described who have an X-linked hyper-IgM phenotype, who have recurrent bacterial infections, as well as unusual infections with organisms, such as atypical mycobacteria.

**Dr. Listerick:** So how do we proceed?

**Dr. Fuleihan:** While we’re waiting for a definitive molecular diagnosis, he needs to be treated with intravenous immunoglobulin. A question would be whether he’s a candidate for stem cell transplantation.

**Reggie Duerst, MD, pediatric oncologist:** Our experience has been that stem cell transplantation in patients who have defects in the NEMO pathway has been bleak. It probably relates to the ubiquity of NF-kappa B in a variety of body tissues. For example, although we can restore normal humoral immunity through stem cell transplantation, defects in the innate immune system remain.

**Dr. Listerick:** For the moment, he’ll receive intravenous immunoglobulin while awaiting the results of the genetic testing. Thank you, everyone.

**A note from the editors:** Several months after the conference, the patient was found to have a mutation in NEMO and is awaiting stem cell transplantation.