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## **Management of Diarrhea in Barth Syndrome**

Although individuals with Barth syndrome are known to have an increased risk for bacterial infections, viral infections that cause diarrhea also present special management problems for Barth syndrome, in large part due to the physiological consequences of the reduced muscle mass characteristic of Barth syndrome. Failure to recognize and provide for the special medical needs of a person with reduced muscle mass can be life-threatening during a diarrheal illness, when reduced muscle mass limits the body's ability to compensate for the large fluid and electrolyte changes that can occur. Having reduced muscle mass also limits nutritional reserve, which is important for any protracted illness. In addition, the low blood cholesterol levels that are characteristic of Barth syndrome also may play a role in both the prolongation of a viral or bacterial gastroenteritis and the cause of non-infectious diarrhea. Outlined below are several basic principles that should guide the management of a moderate to severe diarrheal illness in a child or adult with Barth syndrome.

### **Electrolytes – Potassium and Sodium**

Of several principal electrolytes in the body, sodium, potassium, chloride and bicarbonate, potassium deserves the most attention in Barth syndrome because of the increased risk for cardiac arrhythmia that an abnormally low or high serum potassium level creates. As the largest reservoir in the body for potassium, muscle serves as the principal regulator of the blood potassium level, efficiently replacing potassium that is lost through vomiting or diarrhea.

Consequently, a person with substantially reduced muscle mass experiences more rapid potassium depletion during diarrhea and requires more frequent than usual testing of the serum potassium level to determine replacement needs, if any. However, even when the serum potassium level is dangerously low, patients with reduced muscle mass can rapidly develop hyperkalemia (high blood potassium level) when given intravenous fluids containing “standard” amounts of potassium, because

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there is insufficient muscle tissue to “buffer” the amount of potassium given intravenously. As a result, replacing an apparent potassium deficit with intravenous fluids requires frequent monitoring of serum electrolytes, often three times a day, to avoid hypo- or hyperkalemia. To some degree, there can be a similar problem in maintaining a normal serum phosphate level, but hypophosphatemia usually becomes clinically important during the first few days of hospitalization only when a Barth patient is given large amounts of intravenous glucose without any dietary or intravenous source of phosphate.

While careful regulation of the serum potassium level is especially important to prevent arrhythmias in Barth syndrome, control of sodium during diarrheal illnesses also deserves attention. This is because the body’s supply of sodium is an important determinant of blood pressure and because many Barth individuals, especially adolescents and young adults, have trouble with low blood pressure caused by peripheral vascular instability. In other words, whereas most people when mildly dehydrated maintain their blood pressure by constricting blood vessels and thereby shrinking the blood volume in less critical parts of the body, mild dehydration in many Barth individuals often causes debilitating hypotension and fatigue. Therefore, because vomiting and diarrhea lead to losses of sodium as well as potassium, replacement fluids should contain more sodium than most fruit juices or sodas have. Examples include chicken broth and similar clear soups, Gatorade, and specially designed rehydration solutions available over-the-counter in pharmacies.

### **Nutrition and Fasting**

The reduced muscle mass of persons with Barth syndrome can substantially limit their ability to handle fasting stress. This is because, during fasting or long periods of reduced protein nutrition, muscle becomes the principal source of amino acids needed to maintain normal rates of protein synthesis and other amino acid requiring metabolic systems in the most important tissues, such as the brain, heart and immune system. Most children and adults with normal muscle mass can tolerate many days of minimal or no protein intake without significantly impairing the protein synthesis needed to fight infections or handle the myriad metabolic consequences of an illness. However, in those with Barth syndrome, plasma amino acids often decrease to levels that seriously impair protein synthesis after only one or two days of fasting or the extended period of inadequate protein intake associated with many viruses and other infections.

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As a result, parenteral (intravenous) amino acid nutrition should always be started after 24 hours of hospitalization for more serious illnesses if the illness is likely to prevent a return to normal nutrition within the first 24 hours of hospitalization. This can be done as a full parenteral nutrition (preferred), or as intravenous supplemental amino acids at the rate of 1 gram/kilogram/day. For less severe illnesses treated at home, at least one-half gram of protein per kilogram body weight should be consumed, if possible. Increased attention to amino acid nutrition is particularly important in Barth syndrome children and adults, who are at an increased risk of infection and must have the protein synthetic resources to maintain the natural physical barriers to infection, such as the intestinal mucosa, during a gastroenteritis. Indeed, almost all serious bacterial infections in Barth individuals are not caught from other persons but instead are the Barth individual's own bacteria that normally reside benignly in the respiratory tract lining, gastrointestinal tract, or skin but become able to invade because of weakening of these important barriers to bacteria. This is why the greatest protection against bacterial infection in Barth syndrome comes not from hand washing or avoidance of crowds but from good nutrition.

### **Hypocholesterolemia**

Hypocholesterolemia (low blood cholesterol level) is common in Barth syndrome, but its cause remains uncertain. Because some children with Barth syndrome seem to have diarrhea unusually frequently, hypocholesterolemia could be caused by increased intestinal losses of cholesterol-derived bile acids, which are known to cause watery diarrhea when they are not absorbed by the small intestine and instead pass into the large bowel. However, recent research has shown that cells from Barth syndrome children have an abnormally low rate of cholesterol synthesis, which may be the primary cause of or exacerbate other causes of hypocholesterolemia in Barth syndrome. Because the liver uses cholesterol to make bile acids needed for the absorption of dietary fat, a decreased rate of cholesterol synthesis could lead to inadequate bile acid production and increased diarrhea due to fat malabsorption. Although Barth children usually do not have classic signs of fat malabsorption, such as large greasy stools, an occasional Barth patient has been found to have increased amounts of fat in the stool, which could reflect decreased bile acid synthesis or secretion by the liver. Anecdotally, some Barth patients with poor growth and/or diarrhea have seemed to improve when egg yolk is added to the diet, but whether or

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not cholesterol supplementation by egg yolk or purified cholesterol has a role in the routine treatment of Barth syndrome has not been determined.

Because a constant loss of cholesterol-derived bile acids in diarrhea can cause hypocholesterolemia, bile acid malabsorption should also be considered in Barth patients with chronic diarrhea and hypocholesterolemia. If the cause of a “secretory” (watery) diarrhea is bile acid malabsorption, then relatively small doses of cholestyramine, which binds the irritating bile acids, can be effective in controlling the diarrhea. Transient bile acid malabsorption is a relatively common cause in anyone of watery diarrhea associated with viral illnesses, and abrupt cessation of watery diarrhea upon treatment with cholestyramine is presumptive evidence that the diarrhea is caused by bile acid malabsorption. Although cholestyramine occasionally causes problems such as constipation or formation of intestinal bezoars and, with chronic use, will lower cholesterol levels, such side effects rarely develop when cholestyramine is used for short periods of time.

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