PedsCases Podcast Scripts

This is a text version of a podcast from Pedscases.com on "**Hemolytic Uremic Syndrome.**" These podcasts are designed to give medical students an overview of key topics in pediatrics. The audio versions are accessible on iTunes or at www.pedcases.com/podcasts.

Hemolytic Uremic Syndrome

Developed by Dr. Magdalena Riedl Khursigara and Dr. Chia Wei Teoh for pedscases.com
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Introduction:

Hello, my name is Magdalena Riedl and I am a second year resident at The Hospital for Sick Children and the University of Toronto. In this episode, I will present an approach to hemolytic uremic syndrome. During my PhD, I worked on projects related to the pathogenesis of hemolytic uremic syndrome (HUS). This podcast was made in conjunction with PedsCases and supervised by Dr. Chia Wei Teoh, staff nephrologist at The Hospital for Sick Children.

Objectives:

The **objectives** of this podcast include:
- To review the etiology and pathophysiology of HUS
- To discuss the clinical presentation of HUS
- To review the diagnosis of HUS
- To discuss the management of HUS

Clinical Case:

A 3-year-old boy is brought to the emergency department by his parents with the chief complaint of new onset bruising. He is also very fatigued, which parents think is due to the diarrhea that he has had over the last 4 days. According to his parents, the diarrhea is improving and they haven't seen any blood in the stool today, but there was blood in the stool when his diarrhea first started.

Upon further questioning, his parents tell you that he is a previously healthy boy and that nobody else in the family has developed diarrhea. They report that they were eating home-made hamburgers 2 days before the diarrhea started. Furthermore, mom tells you that he hasn't had any urine output today and that his last urine was very dark. Mom thought this was due to the diarrhea and decreased fluid intake.

At triage his vitals were as follows: Temperature 36.5, heart rate 140/min and blood pressure taken from his right upper arm was 115/85.

On exam you notice several bruises on his chins and arms, and small petechiae including where the nurse measured his blood pressure. His cardiac/respiratory and abdominal exam are normal. His mucus membranes are dry and his capillary refill time is 4 seconds.

Etyology and pathophysiology:

Hemolytic uremic syndrome is characterized – as the name implies – by non-immune hemolytic anemia, thrombocytopenia and renal failure.

In childhood (especially in children < 10 years of age) the majority of HUS cases are caused by an infection with enterohemorrhagic E.coli that produces Shiga toxin and is often referred to as EHEC/STEC HUS. Cattle are the main hosts - Shiga toxin is contained in their feces and therefore infections occur via the feco-oral route. Infection occurs after eating raw/undercooked beef, petting of animals or consumption of contaminated foods/fluids. Sometimes major contaminations can lead to outbreaks during which adults can also be affected. Ingestion of the toxin leads to diarrhea that can often be bloody. In about 15% of patients, the shiga toxin gets into the blood stream and bind to its receptor Gb3, primarily on kidney endothelial cells. There it inhibits protein synthesis causing endothelial cell injury and damage. Why HUS occurs mainly in children – except during outbreaks – remains unclear.

The underlying pathophysiology is endothelial cell injury and damage of small vessels, especially in the kidney. But other organs such as the CNS, liver, pancreas, lung and heart can be involved. This endothelial damage causes platelet activation and formation of thrombi. Thrombocytopenia occurs due to consumption of platelets within these clots. Hemolytic anemia occurs due to mechanical breakdown of the RBCs when they try to pass through those thrombi. Therefore hemolytic anemia is Coombs negative, as it doesn't involve autoantibodies. Uremia or renal failure occurs as clots occlude the small vessels within the kidney and lead to decreased kidney function.

About 10% of patients – children and adults – present with a recurrent form of HUS, called atypical HUS. In the majority of these patients, a genetic defect in complement proteins is found. These mutations result in over-activation of the complement system, which causes endothelial cell damage and subsequently HUS in the absence of Shigatoxin. These children present with recurrent episodes of HUS, that can occur spontaneously, but often triggered by infections such as URTI or non-bloody diarrhea.

Very rarely, HUS in childhood can also be caused by other infections such as Streptococcus pneumoniae or influenza. These children present with pneumonia or sepsis, in addition to signs and symptoms of HUS. This is believed to be caused by neuraminidase shedding parts of the glycocalyx and therefore exposing the Thomsen-Friedenreich antigen on blood and endothelial cells. Preformed host IgM will bind and initiate the cascade leading to HUS.

Clinical symptoms:

In our case the symptoms suggesting this patient has STEC HUS was the history of bloody diarrhea followed by signs and symptoms of anemia, thrombocytopenia and renal failure. Clinical symptoms for thrombocytopenia include bleeding, such as repeated nose bleeds or bleeding gums when brushing your teeth, as well as increased amount and size of bruises or petechiae. Clinical symptoms for anemia include fatigue and pallor. Clinical signs for kidney failure can include decreased urine output, very concentrated urine, microscopic hematuria and proteinuria. In rare instances, there can be macroscopic hematuria. Edema can occur as a result of kidney failure, but is often not marked as affected children are commonly dehydrated from the diarrhea and have a history of reduced oral intake. Our patient had several of these symptoms.

Diagnosis:

HUS is a clinical diagnosis including the history of diarrhea and if available, exposure to life-stock or raw/undercooked meat and lab work that shows the triad of hemolytic anemia, thrombocytopenia and impairment of renal function.
Hemolytic anemia is characterized by low hemoglobin, elevated LDH - released from damaged red blood cells, low or undetectable haptoglobin as it will bind to all the released NO from damaged RBCs and schistocytes on peripheral blood smear. As the hemolytic anemia is non-immune mediated – with the exception of pneumococcal HUS - Coombs test is negative. Often patients have an increased WBC count due to high neutrophil counts. Impaired renal function can be detected by increase in creatinine and urea or decrease of urine output. Kidney injury can lead to electrolyte disturbances such as hyperkalemia, hyperphosphatemia, hypocalcemia and hyponatremia, as well as acid-base imbalances, elevated BP and proteinuria/hematuria. You should also confirm the presence of Shigatoxin by sending stool samples for detection of EHEC and Shigatoxin.

Complications of HUS:

Patients with STEC HUS can also develop extra-renal symptoms. CNS symptoms include seizures, decreased level of consciousness, encephalopathy, hallucinations and headache. GI manifestations encompass pancreatitis, transaminitis and abdominal pain. Cardiac dysfunction or multi-organ failure are rare, but can be fatal. Predictors for poor outcome include CNS involvement, hyponatremia, leukocytosis and haemoconcentration at initial presentation.

Case:

Blood work shows a hemoglobin of 78 g/L (normal range: 110-140 g/L), platelet count of $25x10^9$/L (normal range: 150-400 $x10^9$/L) and WBC count of $9x10^9$/L (normal range: 5-12 $x10^9$/L). A blood smear showed numerous schistocytes and Coombs test was negative. Serum LDH was 5200 units/L (normal range: 500-920 units/L) and haptoglobin was <0.08 g/L (normal range: 0.32-1.98 g/L). His sodium is 132 mmol/L (normal range: 135-145 mmol/L), his potassium is 4.5 mmol/L (normal range 3.7-5 mmol/L), phosphate/calcium are within normal limits. His creatinine is 200umol/L (normal range: <36 mmol/L) and his urea is 17mmol/L (normal range: 3-7 mmol/L). His urine is very concentrated and shows 3g/L protein (normal: neg) and 2+ RBCs (normal: neg).

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You make the diagnosis of hemolytic uremic syndrome and with the history and patient's age you consider it is most likely to be caused by an infection with Shiga toxin producing E.coli O157: H7.

What can we do for the patient? Is there any treatment?
Unfortunately there is no specific treatment for STEC HUS except for supportive measures. If hemodynamically unstable or if significantly anemic the patient should receive a RBC transfusion. Platelet transfusions should not be given routinely, unless the patient is actively bleeding or if a surgical intervention (ie peritoneal dialysis catheter insertion) is required. Supportive measures for renal impairment include fluid and dietary restriction (potassium and/or phosphate), treatment of hypertension and if needed treatment of potentially life-threatening electrolyte disorders (ie hyperkalaemia). Monitoring of fluid inputs and outputs is critical to avoid fluid overload. Despite maximal supportive medical treatment, short-term dialysis may be needed in up to 2/3 of patients. The overall prognosis is good for patients with STEC HUS - usually with recovery of their renal function and no recurrence of the disease. However, patients are at risk of developing proteinuria, hypertension and chronic kidney disease over the long-term, thus necessitating follow up monitoring of blood pressure, urine for protein and kidney function.

Patients with atypical HUS previously progressed to end-stage kidney disease requiring long-term dialysis and kidney transplantation. Unfortunately, in these patients, recurrence of HUS occurred in many patients post-transplant as well, leading to graft loss. However, the advent of a monoclonal antibody (eculizumab) that blocks the complement system has transformed the outcomes in patients with atypical HUS. Successful treatment with this monoclonal antibody has led to significant recovery from acute episodes of HUS and prevented disease recurrence in patients. In patients who have progressed to end-stage kidney disease, treatment with this monoclonal antibody has allowed them to receive kidney transplants without the risk of losing the graft due to disease recurrence.

How is our patient doing after he was diagnosed with STEC HUS?
Our patient was admitted to the nephrology ward. Despite adequate fluid management his urine output declined further and peritoneal dialysis was initiated. His serum creatinine peaked at 300 umol/L. A few days later he started to improve, first with improvement of his platelet counts and LDH followed by improvement in urine output. Peritoneal dialysis was discontinued after 1 week. We were able to discharge him home after a few more days with improving hematologic parameters and renal function. His serum creatinine on discharge was 50 umol/L. He was seen 2 months later in our outpatient clinic. At that point his hemoglobin, platelet count and creatinine had normalized, no protein on dipstick was found and his blood pressure was within limits. We arranged for annual follow-up to monitor for potential development of proteinuria and hypertension as he may be at risk of developing CKD in the long-term.

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Review

This brings us to the end of this Podcast. **Let's review** what we have learned.

1. HUS is an uncommon disease, and typically presents with the triad of: hemolytic anemia, thrombocytopenia and renal failure.
2. In children it is mainly caused by Shigatoxin which is referred to as STEC HUS.
3. There is no specific treatment for STEC HUS, except for supportive medical measures including meticulous fluid management, acute medical management of electrolyte/acid-base abnormalities and dialysis as indicated.
4. Overall prognosis of STEC HUS is good, however affected children may have increased risk of developing proteinuria, hypertension and CKD, thus requiring long-term follow up.
5. In rare instances, patients have atypical HUS, a recurrent form, which is associated with genetic defects in the complement system, leading to overactivation of the complement system. The prognosis of this disease has improved in the last decade with eculizumab, a monoclonal antibody that blocks the complement system.

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