

Hemolytic uremic syndrome

Hemolytic-uremic syndrome (HUS) is characterized by a triad of symptoms, which are:

1. Coombs negative hemolytic anemia
2. thrombocytopenia
3. acute renal failure

HUS is the most common cause of acute renal failure in childhood, with the highest incidence in infancy and toddler age. It can arise from **post-infectious causes**, where it is either caused by a gastrointestinal infection with **enterohemorrhagic E. coli** (EHEC) and we classify it as **D + HUS** (*diarrhea associated HUS*) ^[1] ^[2], or a pneumococcal infection.

Under the designation **D–HUS** ("diarrhea non-associated HUS") is a heterogeneous group of diseases that are not associated with diarrhea. It usually has a **severe course**. It often leads to kidney failure, which is addressed by a **transplant**. After transplantation, there is still a risk of **recurrence**. ^[3]

Classification

The term hemolytic uremic syndromes includes a set of diseases, which can be divided according to etiology into **post-infectious etiology**, which includes D + HUS, pneumococcal HUS, or other infections associated with HUS, and **D-HUS** (diarrhea non-associated HUS).

D-HUS can be caused by regulatory disorders in **alternative complement pathway**, **ADAMTS 13** protease deficiency, congenital metabolic disorders of **vitamin B₁₂**, or by a drug reaction to **quinine**.

However, there is also HUS for which we do not know the exact etiology. Risk factors then include HIV infection, malignancies, chemotherapy, radiotherapy, transplantation, pregnancy, HELLP syndrome, SLE and more. ^[1]

D + HUS

Diarrhea associated HUS is a disease characterized by a specific clinical and laboratory picture, caused by an E. coli toxin.

Incidence and epidemiology

It mainly affects infants and toddlers. It is characterized by an **endemic occurrence** with a high incidence, for example in Argentina, and a low incidence in Europe. The number of new patients per year corresponds to **2,1 cases per 100 000 inhabitants**.^[1]

Etiology

EHEC colonizes the digestive tract of animals, most often **cows**.

Verotoxigenic enterohemorrhagic E. coli produces a **shiga-like toxin** and occurs in multiple forms (so-called serotypes). Serotypes O157: H7, O26, O111, O103, and O145 have the ability to cause this disease ^[1].

EHEC transmission occurs both between humans and by transmission from an infected animal or by ingesting its contaminated products (unpasteurized cow's or goat's milk, insufficiently heat-treated beef ("hamburger-disease"), home-made juices from EHEC-contaminated vegetables, swimming in a pool with contaminated water, etc...

A **small infectious dose** is associated with a probability of developing HUS in **15% of cases**. The incubation period is **3-8 days**.

Pathogenesis

Upon entry of EHEC into the digestive system, shiga-like toxin (Stx) is released, which adheres to the intestinal mucosa. It enters the bloodstream **transcellularly**. It binds to endothelial receptors in the blood. Upon binding, a number of inflammatory changes, induction of apoptosis, and blockade of the synthesis of a number of proteins may occur within the cell.

Stx also binds to glomerular capillary receptors, which it damages and at the same time induces **local intravascular coagulation**.

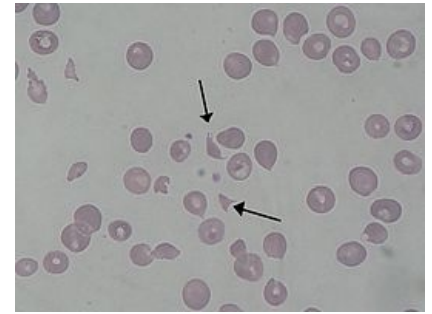
Diagnostics

Early symptoms include: bloody diarrhea (hemorrhagic enterocolitis), vomiting, and fever. Approximately **after a week**, pallor (anemia), petechiae (thrombocytopenia), oliguria, dehydration, edema (kidney failure), arterial hypertension, hematuria, and, if CNS is also affected, neurological symptoms (somnolence, impaired consciousness, convulsions, etc.) can be present.

Significant hemolytic anemia with erythrocyte deformity (schistocytes) and thrombocytopenia, which is often very severe, appear in the blood. The result of the Coombs test is negative. **Increased** levels of urea, creatinine, lactate dehydrogenase and bilirubin are present, while **decreased** levels of haptoglobin and **normal** levels of C3 complement are expected.

We observe proteinuria and hematuria in the urine.

One of the possible examinations is a kidney **ultrasound**. The pathological finding is an **enlarged** kidney and an **echotexture** in the cortex. Another method may be, for example, "serotyping" of E. coli or Stx detection in stool or blood.



Schistocytes

Therapy

Therapy is symptomatic. Transfusions, furosemide, antihypertensives, and others are administered. Renal function substitution by peritoneal dialysis or hemodialysis is also possible.

Antibiotics are not **recommended** due to the breakdown of bacteria, which would lead to further release of Stx.

Prognosis

The decisive factor is the duration of the oligo / anuria. Spontaneous remission should occur in **1-3 weeks**. If it does not occur, there is a risk of progression of glomerular filtration disorders and chronic renal failure.

D + HUS is lethal in approximately **5% of cases**. Risk factors include late diagnosis, severe hyperhydration, sepsis, and extrarenal symptoms (CNS).

In young children, it is the most common cause of **acute kidney failure** requiring **elimination therapy**. [3] [2] [1]

HUS associated with pneumococcal infection

This type of HUS arises as a complication of **primary pneumococcal infection**, most often in **children** under two years of age. It is associated with a difficult course with a mortality of around 30%. Pneumococcus produces the enzyme **neuraminidase**, which cleaves N-acetylmuramic acid from glycoproteins on the cell membrane of erythrocytes, platelets, and endothelial cells of glomeruli. This in turn leads to the detection of **Thomsen-Friedenreich antigen** (T antigen), which can then react with anti-T IgM antibodies present in the plasma.

A characteristic presentation is a positive **direct Coombs' test**.

Therapeutically, it is appropriate to use antibiotics or plasmapheresis. Conversely, the use of frozen plasma is contraindicated due to cold hemolysis (IgM has an ideal erythrocyte binding temperature of about 4 degrees). [1]

HUS induced by a complement regulation disorder

In this disorder, pathological activation of the complement system occurs. The mechanism is based on the formation of a **membranolytic complex with cytotoxic activity**. It arises either from a **genetic** mutation, or by **autoantibodies**, which lead to the activation of the alternative complement pathway. It can often end in **spontaneous remission**, [1] and is treated therapeutically by symptomatic adjustment of the internal environment or dialysis. Another treatment option is the use of plasmapheresis or fresh frozen plasma.

HUS with a genetic basis is usually associated with a poor prognosis. It often leads to the development of chronic renal failure with a transition to end-stage chronic renal failure. In extreme cases, it is necessary to replace kidney function. In some mutations a very high incidence of recurrence after kidney transplantation is described.

HUS arising from ADAMTS 13 protease deficiency

- *HUS / TTP (thrombotic thrombocytopenic purpura)*
- congenital and acquired form
- ADAMTS 13 is a metalloproteinase that cleaves multimers of von Willebrand factor, which binds platelets
- with ADAMTS 13 deficiency, thrombi form in many organs (brain, heart, kidneys)
- The clinical picture is similar to HUS, but is also accompanied by fever and more pronounced neurological and hematological symptoms.
- acute renal failure requiring dialysis is rather rare; frequent relapses, transition to chronicity;
- treatment: frozen plasma, alternatively plasmapheresis, sometimes immunosuppression, and if needed: splenectomy. [1]

HUS from other causes

- HUS is associated with some congenital defects of vitamin B12 metabolism - manifestation in neonatal or early infant age
- after quinine administration (drug-induced HUS)
- In case of malignancies, HUS incidence is very likely due to therapy
- in patients after organ transplants and bone marrow transplants treated with calcineurin inhibitors
- secondary forms after administration of antiaggregants (ticlodipine, clopidogrel)
- during pregnancy, most often during the 3rd trimester
- in HIV patients and in patients with systemic lupus erythematosus, antiphospholipid syndrome, and in individuals with chronic glomerulonephritis.^[1]

References

Related articles

- Acute renal failure
- Proteinuria in Children
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Citations

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