Sensitivity Factors and Human Pathology Related to Infections of Producing Escherichia Coli of Shiga-Toxin

Saïd Oulkheir¹, *, Khadija Ounine², Mohamed Aghrouch³, Smail Chadli¹

¹High Institute of Nursing Professions and Health Techniques, ISPITS, Agadir, Morocco
²Laboratory of Applied Microbiology Department of Biology, Faculty of Sciences, Ibn Tofail University, Kenitra, Morocco
³Laboratory of Medical Analysis, Hospital Hassan II, Agadir, Morocco

Email address:
oulkheirs@gmail.com (S. Oulkheir)
*Corresponding author

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Abstract: Escherichia coli O157: H7 is the main serotype E. coli responsible for disease in humans. STEC strains (Shiga-toxin-producing E. coli) are all strains with genes encoding Stx toxin cytotoxic for Vero cell cultures (kidney cell of African green monkey), hence the name "verotoxin" also called "Shiga toxin" because of its great similarity to a toxin produced by Shigella dysenteriae. Infections caused by EHEC (Enterohemorrhagic E. coli) are a major problem due to the extreme severity of the clinical manifestations they can generate. These translate into a banal or bloody diarrhea may develop in 5-8% of cases, mainly in young children, to a serious complication hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP) in adults. The identification of susceptibility factors of clinical interest because it may allow early specific treatment of patients at risk of complications.

Keywords: Enterohemorrhagic E. coli, Factors of Susceptibility, Hemolytic Uremic Syndrome, Shiga-toxin-Producing E. coli, Shigatoxin

1. Introduction

Shigatoxin-producing Escherichia coli (STEC) are pathogens responsible for human infections with various clinical manifestations. Since their first description, strains of E. coli O157: H7 and other enterohemorrhagic E. coli (EHEC) are known to be the main infectious agents responsible for haemorrhagic diarrhea. These E. coli produce one or more shiga-toxins (stx) or Vero cytotoxins.

In humans, after ingestion of a low infectious dose (less than 100 CFU) [1] and after an incubation of 3 to 4 days for up to 10 days [2], STEC infections can be painted Clinics ranging from benign diarrhea to hemorrhagic colitis. The latter are sometimes complicated after a few days of uremic haemolytic syndrome (HUS) in children and elderly subjects and more rarely in thrombotic and thrombocytopenic purpura (PTT) in adults [3].

SHU and PTT have common lesions of endothelial cells of microcirculation followed by cell swelling, platelet aggregation and thrombosis. The manifestations are determined by the most affected vascular bed: that of the kidneys for the SHU, that of the nervous system for the PTT. These two conditions are characterized by severe microangiopathy and a marked reduction in platelet count and hemoglobin.

The analysis of major E. coli O157: H7 epidemics identified certain susceptibility factors to STEC infections. Among those at risk in these epidemics, some are asymptomatic and show no clinical signs, others develop only moderate forms, others have severe or even fatal complications.

This bibliographic synthesis is aimed at presenting the various clinical manifestations associated with Shiga-producing Escherichia coli infections from a symptomatological, diagnostic, and therapeutic angle.
2. Sensitivity Factors for STEC Infections

Analysis of major epidemics with *Escherichia coli* O157: H7 identified certain susceptibility factors to STEC infections. Among those at risk in these epidemics, some are asymptomatic and show no clinical signs, others develop only moderate forms, others have severe or even fatal complications. The identification of sensitivity factors is of clinical interest because it could allow early specific management of patients at risk for kidney complications. Sensitivity factors identified include:

2.1. Age

Populations most at risk of developing infections and severe forms are children under 15 years of age (the distribution of HUS cases in children shows the highest incidence in children less than 15 years of age 3 years), and persons aged over 65 years. During the 1996 epidemic in Scotland, the risk of developing complications (HUS / PTT) was 4 times higher for these categories than between 15 and 65 years [4].

2.2. Immunity

Breeders’ families would be protected by repeated exposure to STEC [5]. Moreover, primary-infected adult mice are resistant to a new intestinal colonization by O157: in this experimental model, the absence of colonization is correlated with the presence of immunoglobulin A directed against O157 [6].

2.3. Changes in the Gastrointestinal Tract

*Changes in the gastrointestinal tract* (decreased gastric acidity, slowed transit, malnutrition)

It has been suggested that many children with O157: H7 infection in Japan have an unbalanced diet. An experimental model allowed to show a very marked increase in the sensitivity of mice subjected to a deficient diet, low in protein (75% of them die, while all control mice survive). This deficient diet significantly affects the development of the intestinal epithelium and immune cells, and plays a role on the intestinal flora [7].

2.4. The Number and the Distribution of the Receptors of the Toxins Stx

The young children would have more receptors Gb3 to the renal level, which would explain the frequency of the complications of type SHU [8].

3. The Various Human Pathologies Linked to STEC

3.1. Hemorrhagic Colitis

Haemorrhagic colitis is the main clinical manifestation of *Escherichia coli* O157: H7 infection [3, 9]. This manifestation is characterized by abdominal cramps, initially aqueous and then bloody diarrhea in a patient generally apyretic or subfebrile [3]. Blood diarrhea is found in 90% of the cases diagnosed [9].

The incubation period of 2 to 10 days is longer than that observed for other infectious diarrhea [10]. The evolution is generally spontaneous favorable in a few days. Nausea, vomiting, headache and chills have also been reported, but their frequency is lower.

Radiological examination sometimes shows images of distension of the ascending colon and caecum [11]. In some cases, images of mucosal edema can be seen in the ascending and transverse colon [12]. Bleeding inside the right colon sometimes extended to the transverse colon can be evidenced by scintigraphy. The main changes observed are edema, superficial ulceration, fibrin exudate and hemorrhage within the submucosa. Multifocal lesions are most frequently found in the caecum and ascending colon [13, 14]. Lesions similar to those described in ischemic colitis (coagulation necrosis and acute inflammation of the mucosa with preservation of crypts) or similar to those described in infectious colitis (infiltration of lamina propria and crypts by neutrophils) or Lesions identical to those found in Clostridium difficile pseudomembranous colitis have also been described [14].

The rate of hospitalization during hemorrhagic colitis varies from 3 to 82% [10, 15-17]. There is no specific treatment. Treatment is symptomatic [11]. STECs are not the only microorganisms potentially responsible for bloody diarrhea. Bacteria such as *Campylobacter* sp., *Shigella* sp., *Clostridium difficile*, certain viruses and parasites (amoebae) may also be implicated in the etiology of bloody diarrhea.

3.2. Hemolytic Uremic Syndrome (HUS)

The typical SHU affects mostly children under 3 years of age and occurs suddenly after bloody prodromal diarrhea in most cases. It was not until 1983 that [18] establish the relationship between intestinal infection at STEC and the occurrence of HUS. The onset of HUS occurs on average one week after the onset of digestive symptoms. Two to seven percent of patients with intestinal infection with *E. coli* O157: H7 will develop HUS. This incidence is higher in children and the elderly: 10% in children under 10 years and 10 to 20% in elderly subjects [3]. Typical HUS, or post-diarrheal HUS, accounts for approximately 90% of HUS cases in children and is the leading cause of renal failure in infants. It occurs mostly in summer. Its beginning is brutal. Renal prognosis is favorable in about 2/3 of cases [19]. It corresponds to lesions of glomerular thrombotic microangiopathy or cortical necrosis. It is characterized by a triad of symptoms associating haemolytic anemia with schizocytosis, thrombocytopenia and acute renal failure [20].

3.3. Clinical Aspects

In most cases, the typical post-diarrhea SHU pattern is characteristic and does not pose a diagnostic problem [21].
After a prodromal phase characterized by acute gastroenteritis, often febrile, with abdominal pain, vomiting, often bloody diarrhea, for 1 to 15 days, the onset of HUS is abrupt, characterized by the typical combination of A hemolytic anemia (hemoglobin less than 80g/L) with schizocytes (usually 2-10%), thrombocytopenia, usually around 40-50 000 / mm3, and insufficiency Renal disease with high levels of urea and creatinine. About half of the children are anuric. If diuresis is preserved, microscopic haematuria and proteinuria are constant in the first few days. The diagnosis of delayed anuria in infants with diarrhea, hyponatremia and hypervolemia with arterial hypertension are often present at admission when water intakes have been maintained to prevent dehydration due to diarrhea. Serum potassium, which may be low initially due to diarrhea, increases rapidly, as well as blood levels of phosphorus and uric acid. Blood levels of calcium and bicarbonates are often low. Polynucleosis is common. An involvement of other organs than the kidney is possible [19, 22]:
- Severe haemorrhagic colitis is observed in 10-20% of cases, with prolonged melena, abdominal pain, vomiting, subocclusive state or rectal prolapse. More rarely invagination, necrosis with perforation of the colon wall and secondary stenosis may occur. The small intestine can also be affected.
- Acute pancreatitis is seen in about 20% of cases, with serum levels. Amylase and lipase. Necrotizing pancreatitis and insulin-dependent diabetes mellitus, either transient or permanent, are more rare.
- An involvement of the central nervous system is observed in about 20% of cases and can condition the vital prognosis. The most frequent symptoms are focal or generalized convulsions, torpor or even coma. Hemiparesis, cortical blindness or at most brain stem damage and decerebration may occur. These complications are related either to edema or to vascular microthrombi with cerebral infarction. Cerebral scanners may be normal initially, or show hypodense areas. Magnetic resonance imaging is often more sensitive to detecting brain lesions. Central nervous system involvement is currently the leading cause of death in France. A survey, 4 of the 286 children with HUS between 1993 and 1996 died (1.4%), all with central nervous system involvement[23]. Many children recover without sequelae, some have neurological sequelae.
- Hepatic involvement, mostly benign, is observed in approximately 40% of cases; It is simply marked by hepatomegaly and an elevation of transaminases. Biliary obstruction due to hemolysis may occur. Biliary obstruction due to hemolysis may occur.
- Cardiac involvement (observed in less than 1% of cases) with myocarditis, cardiogenic shock, cardiomyopathy, or pulmonary involvement (observed in less than 1% of cases).

3.4. Anatomical Pathology

The most common renal lesion is Glomerular Thrombotic Microangiopathy (MAT) [19] characterized by thickening of the walls of the glomerular capillaries, with a double contour appearance due to enlargement of the endothelial space associated with a fibrillar appearance of the mesangial matrix. Changes in pre-glomerular arterioles, characterized by enlarged endothelial space, are associated with glomerular lesions.

The second type of renal lesion is cortical necrosis, more or less extensive. In the most severe forms, lesions of the vascular endothelium are not limited to the kidneys, and affect other organs such as the central nervous system and the pancreas.

3.5. Symptomatic Treatment

Hydro-electrolyte intake is calculated so as to avoid dehydration if the child still has diarrhea and vomiting, and overhydration if it is anuric. The nutritional and hydro-electrolyte intakes are provided orally, optionally enterally at a constant rate with a gastric tube. Caloric and protein intakes must correspond to 100% of the recommended amounts. If vomiting, diarrhea and colitis persist, parenteral nutrition is required. If the child is anuric, dialysis is indicated, in order to provide adequate nutrition without inducing a volumic overload. Most oliguric or anuric children should be dialysed by a peritoneal dialysis technique. Hemodialysis or haemodiafiltration is indicated if intestinal distention or recent abdominal surgery contraindicates peritoneal dialysis. Filtered globular pellets must be transfused if the hemoglobin is less than 60-70 g / L. Platelet transfusions are indicated only if the platelet count is below 10,000 - 20,000/mm3 with bleeding or if surgery is required. There is no specific treatment for colitis, apart from suppressing dietary intakes and initiating parenteral nutrition as long as necessary. Surgery may be indicated in case of perforation, severe ischemia or secondary intestinal stenosis. In case of diabetes, an insulin treatment is indicated. Necrotizing pancreatitis will be treated by appropriate measures (gastric aspiration, somatostatin, anti-H2 agent, parenteral nutrition). Convulsions are treated with intra-rectal or intravenous diazepam, followed if necessary by intramuscular phenobarbital or intravenous phenytoin. In the case of a convulsive condition, a continuous infusion of phenobarbital and artificial ventilation are necessary. There is no specific treatment modifying the evolution of HUS. Heparin, thrombolytic agents and perfusions of fresh frozen plasma do not yield any significant benefit. Plasma exchange does not appear to be effective, although it is generally attempted in patients with central nervous system involvement.

3.6. Prognosis

The mortality rate in the acute phase is currently less than 5% [23, 24]. Vital prognosis is involved in cases with multivisceral involvement including the central nervous system. Five to 10% of children progress to end-stage renal disease, rarely from the start, more often after recovering some renal function with chronic renal failure for a few years. After 5-10 years of follow-up, 40-65% of children
have no obvious kidney sequelae (no proteinuria, no hypertension, normal blood creatinine). However, after 15 or more years of follow-up, 20-40% of patients have proteinuria and/or arterial hypertension, up to 20% of patients with chronic or terminal renal insufficiency. These problems may appear after several years of apparent healing [24-26]. There is never a typical HUS recurrence after renal transplantation.

In the acute phase, the elements of poor renal prognosis are the presence of severe colic involvement with rectal prolapese, severe central nervous system involvement and neutrophilic polynucleosis greater than 20000/mm3. It is as if the severity of microvascularization at the intestinal and central nervous system levels reflects the severity of microvascuature at the renal level [24]. Moreover, recent studies indicate that the transport of Stx between the intestine and the target organs, that is to say the endothelia of the renal microvascuature, is assured by neutrophilic polynuclear cells [27], which, a priori, is related to the unfavorable prognostic significance of the initial polynucleosis.

The long-term renal prognosis of the child's typical SHU is all the more reserved in that the duration of initial anuria was greater [19, 24-26]. It was shown that antivirals of more than 8 days were associated with a significant risk of renal insufficiency in the medium and long term. Renal biopsies done at the time showed that these cases corresponded most often to lesions of cortical necrosis or lesions of glomerular thrombotic microangiopathy affecting more than 50% of the glomeruli. It is also known that the persistence of excessive proteinuria or micro-albuminuria at a distance from the acute phase is an element of poor prognosis. Currently, renal biopsies for prognostic purposes are no longer practiced, the phase is an element of poor prognosis. Currently, renal proteinuria or micro-albuminuria at a distance from the acute polynucleosis greater than 20000/mm3. It is as if the severity of microvascularization at the intestinal and central nervous system levels reflects the severity of microvascuature at the renal level [24]. Moreover, recent studies indicate that the transport of Stx between the intestine and the target organs, that is to say the endothelia of the renal microvascuature, is assured by neutrophilic polynuclear cells [27], which, a priori, is related to the unfavorable prognostic significance of the initial polynucleosis.

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In practice, it is advisable to maintain surveillance (blood pressure, proteinuria, microalbuminuria, serum creatinine once a year) in the very long term when an aneurysm of one week or more has occurred, since it is Patients may have significant histological lesions. On the other hand, this type of monitoring is unnecessary in patients who have never had anuria or when it only lasted a few days, followed by a rapid recovery of normal glomerular filtration without arterial hypertension or proteinuria, Nor micro-albuminuria for the next 3 to 5 years.

### 3.7. Thrombotic and Thrombocytopenic Purpura (PTT)

Thrombotic and thrombocytopenic purpura (PTT) is a clinical entity described for the first time by Moschcowitz (1925) [28]. As for HUS, the etiology of PTT can be of various origins (toxic, autoimmune ...), and the relationship between E. coli O157: H7 infection and the appearance of this syndrome is recent [29]. The PTT mainly affects adults. It is a syndrome characterized by microangiopathic haemolytic anemia, thrombocytopenia, fever, neurological disorders with acute renal failure. Prodomal diarrhea is generally absent [30].

### 3.8. Clinical Manifestations

Hemolysis is a characteristic manifestation of this disease. Anemia is associated with schizocytes, circulating erythroblastiosis, hyperreticuloctysis and variable thrombocytopenia. Discrete jaundice can be observed, and there may be petechiae, but generally to a lesser degree than in idiopathic thrombocytopenic purpura (PTI). Coagulation tests are usually normal or minimally disturbed. Antinuclear antibodies are positive in 20% of cases. Uterine, gastrointestinal or other haemorrhages occur in some patients, but severe bleeding is rare. Many patients are febrile and many have nonspecific symptoms such as nausea, abdominal pain or arthralgia. The spleen and liver are usually not palpable.

The duration of the PTT is usually from a few days to a few weeks, but it can sometimes last for months. When the disease progresses, it can affect the central nervous system and the kidneys, and in most cases it is the main cause of death. Neurological signs are observed in 90% of fatal cases. These are initially changes in behavior with confusion, delirium and unconsciousness. Signs of focal involvement include epileptic seizures, hemiparesis, aphasia and visual field abnormalities. These neurological symptoms can fluctuate and end in coma. The attack of myocardial vessels may be the cause of sudden death in some patients.

### 3.9. Pathogenesis

The manifestations can be explained by platelet thrombi and localized fibrin deposits. The arterioles are filled with hyaline material, presumably composed of platelets and fibrin. This same material can be found at the subendothelial level of otherwise unharmed vessels. Immunofluorescence studies have shown the existence of immunoglobulins and complement in the arterioles. These are often the site of microaneurysms. Numerous controversies exist about the specificity of these abnormalities, some authors finding them in hemolytic uremic syndrome (especially in the kidney) and in disseminated intravascular coagulation. Most adult PTT cases are associated with von Willebrand factor (vWF) protease deficiency due to the presence of vWF anti-protease antibodies. This deficiency explains the presence in the plasma of multimers of very high molecular weight of the vWF at the origin of a thrombocytopenia due to hyperplate aggregation.

### 3.10. Diagnostic

The association of hemolytic anemia with schizocytes, thrombocytopenia, fever, neurological disorders and impairment of renal function is practically pathognomonic of PTT.

### 3.11. Treatment and Prognosis

Until recently, the disease was almost always fatal. A very large number of therapeutic modalities have been proposed with varying results. The treatment of acute PTT has changed.
radically in recent years. Corticosteroids and heparin or emergency splenectomy were discontinued and enthusiasm for antiplatelet therapy decreased. Treatment has increasingly focused on the use of exsanguinotransfusions or repeated plasmapheresis associated with the perfusion of fresh frozen plasma. With this therapeutic approach, overall mortality has declined significantly, with more than half of the cases progressing. Most patients who pass the acute phase cure completely without renal or neurological sequelae. Some patients have a chronic, recurrent form and require maintenance treatment by plasmapheresis and plasma infusions. Rare diseases are controlled only by corticosteroids.

3.12. New Clinical Aspects

Recently, authors have described the development of SHU in the course of urinary infections due to STEC strains [31, 32], the appearance of isolated PTT [33]. SHU without prodromal diarrhea associated with infection criteria to STEC (this was the case in 9 out of 122 patients, or 7% in a French survey) [23] and whose evolution was that of a typical HUS without relapse.

4. Treatment of STEC Infections

Despite the sensitivity to many classes of antibiotics of the majority of strains of Escherichia coli O157: H7, the use of antibiotics is still controversial: with regard to the duration of the disease, no significant difference is found in the different studies between patients receiving antibiotics and those not treated. In addition, the use of antibiotics leads to aggravation of the infection by destruction of the bacteria, resulting in higher concentrations of free toxins and thus more available for systemic absorption [9, 12, 34, 35].

An important recent finding is that, in subjects with Escherichia coli O157: H7 diarrhea, antibiotics (beta-lactamins, trimethoprim sulfamethoxazole or quinolones) do not prevent the onset of HUS but, on the contrary, by promoting the release of Stx toxins from bacteria [36]. This means that antibiotics are contraindicated in people with Escherichia coli O157: H7 diarrhea and in those around them, especially when they have diarrhea, or in the event of an epidemic of Escherichia coli O157: H7 diarrhea. It is also very likely that the administration of transit-retardants in patients with Escherichia coli O157: H7 diarrhea increases the risk of HUS occurring [34, 37].

This should not jeopardize the administration of antibiotics in children with bloody diarrhea with fever. This prescription is justified by the fact that these problems may be due to intestinal infection with Shigella or Salmonella, with possibly positive blood cultures. Unfortunately, current techniques do not allow for the rapid determination of this differential diagnosis, but it is likely that molecular diagnostic techniques will allow identification within a few hours in a few years. Ideally, techniques should be available to rapidly involve responsibility for Escherichia coli O157: H7, which would contraindicate the administration of antibiotics. New therapeutic strategies are being developed, in particular Synsorb Pk®, an orally administered resin composed of silica carrying Stx-binding saccharide receptors.

Trials in Canada and Japan show that administration in the first 2 days after onset of diarrhea decreases the risk of HUS but does not prevent severe forms of central nervous system involvement [38]. There is currently no vaccine available although many vaccine approaches have been made in animals [39, 40]. Two vaccination strategies seem conceivable:
- antitoxin vaccination to prevent systemic complications of toxins, although some anti-Stx1 and anti-Stx2 vaccines have been shown to be ineffective in animals [39, 40, 41];
- vaccination to prevent colonization by EHEC using vaccines directed against adhesion factors such as intimin, or LPS from O157 [40, 42].

5. Conclusion

Considered as pathogens emerge EHECs are responsible for foodborne illnesses that can cause serious illness. The risk of these infections is all the more important especially in children under 3 years old and the elderly. The prevention of these pathologies requires simple rules of food hygiene, which must be known to all. Collaboration between specialized laboratories is essential to improve epidemiological surveillance and develop new approaches for the treatment of these infections.

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