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Review

# Hemolytic uremic syndrome: differential diagnosis with the onset of inflammatory bowel diseases

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**Summary.** *Background:* Shiga-toxin Escherichia coli productor (STEC) provokes frequently an important intestinal damage that may be considered in differential diagnosis with the onset of Inflammatory Bowel Disease (IBD). The aim of this work is to review in the current literature about Hemolytic Uremic Syndrome (HUS) and IBD symptoms at the onset, comparing the clinical presentation and symptoms, as the timing of diagnosis and of the correct treatment of both these conditions is a fundamental prognostic factor. A focus is made about the association between typical or atypical HUS and IBD and a possible renal involvement in patient with IBD (IgA-nephropathy). *Methods:* A systematic review of scientific articles was performed consulting the databases PubMed, Medline, Google Scholar, and consulting most recent textbooks of Pediatric Nephrology. *Results:* In STEC-associated HUS, that accounts for 90% of cases of HUS in children, the microangiopathic manifestations are usually preceded by gastrointestinal symptoms. Initial presentation may be considered in differential diagnosis with IBD onset. The transverse and ascending colon are the segments most commonly affected, but any area from the esophagus to the perianal area can be involved. The more serious manifestations include severe hemorrhagic colitis, bowel necrosis and perforation, rectal prolapse, peritonitis and intussusception. Severe gastrointestinal involvement may result in life-threatening complications as toxic megacolon and transmural necrosis of the colon with perforation, as in Ulcerative Colitis (UC). Transmural necrosis of the colon may lead to subsequent colonic stricture, as in Crohn Disease (CD). Perianal lesions and strictures are described. In some studies, intestinal biopsies were performed to exclude IBD. Elevation of pancreatic enzymes is common. Liver damage and cholecystitis are other described complications. There is no specific form of therapy for STEC HUS, but appropriate fluid and electrolyte management (better hyperhydration when possible), avoiding antidiarrheal drugs, and possibly avoiding antibiotic therapy, are recommended as the best practice. In atypical HUS (aHUS) gastrointestinal manifestation are rare, but recently a study evidenced that gastrointestinal complications are common in aHUS in presence of factor-H autoantibodies. Some report of patients with IBD and contemporary atypical-HUS were found, both for CD and UC. The authors conclude that deregulation of the alternative complement pathway may manifest in other organs besides the kidney. Finally, searching for STEC-infection, or broadly for Escherichia coli (E. coli) infection, and IBD onset, some reviews suggest a possible role of adherent invasive E. coli (AIEC) on the pathogenesis of IBD. *Conclusions:* The current literature shows that gastrointestinal complications of HUS are quite exclusive of STEC-associated HUS, whereas aHUS have usually mild or absent intestinal involvement. Severe presentation as toxic megacolon, perforation, ulcerative colitis, peritonitis is similar to IBD at the onset. Moreover, some types of E. coli (AIEC) have been considered a risk factor for IBD. Recent literature on aHUS shows that intestinal complications are more common than described before, particularly for patients with anti-H factor antibodies. Moreover, we found some report of patient with both aHUS and IBD, who benefit from anti-C5 antibodies injection (Eculizumab). (www.actabiomedica.it)

**Key words:** Hemolytic Uremic Syndrome (HUS), Inflammatory Bowel Disease (IBD), Shiga-Toxin E. Coli (STEC)

## Background

Shiga-toxin E.coli productor (STEC) provokes frequently an important intestinal damage that may be considered in differential diagnosis with the onset of Inflammatory Bowel Disease (IBD). The aim of this work is to review in the current literature the reported similarities and differences between Hemolytic Uremic Syndrome (HUS) and IBD symptoms at the begin, as the timing of diagnosis and of the correct treatments of both these conditions is a fundamental prognostic factor. An association between typical or atypical HUS (aHUS) and IBD is searched in literature and case reports, as it has already been established a possible renal involvement in patient with IBD (IgA-nephropaty).

## Methods

A review of scientific articles was performed consulting the databases PubMed, Medline, Google Scholar, and consulting most recent textbooks of Pediatric Nephrology.

## Results

The HUS is a clinical diagnosis at first, defined by simultaneous occurrence of microangiopathy (MAT) with hemolytic anemia, thrombocytopenia and acute kidney injury. In the past HUS has been divided in diarrhea-positive HUS also called "typical", and diarrhea negative HUS, or "atypical" HUS (aHUS) (1-3). Shiga-toxin productor E. coli (STEC)-associated HUS is considered at first. In 70% of cases in North America and Western Europe the most frequent serotype is O157:H7, but other serotypes are reported (O111:H8, O103:H2, O121, O145, O26, and O113 (4, 5). In STEC-associated HUS, that accounts 90% of cases of HUS in children, the microangiopathic manifestations are usually preceded by gastrointestinal symptoms lasting about 2 weeks, with symptoms including abdominal pain, vomiting, diarrhea, bloody stools. However about 25% of cases of STEC-associated HUS do not present with diarrhea (1-5). The Shiga-toxin like (Stx) produced by E. coli is responsible to direct damage and to complement alternative-pathway activation. E. coli strains that produced Stx-2 were most commonly associated with HUS. Stx are picked up by polarized gastrointestinal cells via transcellular pathways and translocate into the circulation. Once the endothelial cell internalizes the toxin, it can inhibit protein synthesis, induce the apoptosis to start, and induce endothelial changes in a thrombogenic phenotype (1, 5-9). In a primate model of HUS, it resulted that the rate of gastrointestinal absorption plays an important role (4). After the bacteria colonize the colon, they cause a severe colitis. Thereafter, based on the presence of specific pathogen-associated molecular patterns which interfere with the host response, SEU may appear presenting with renal failure and neurological symptoms (6, 7). In vitro studies have demonstrated that several cytokines are involved, TNF-alfa seems to play an important role in the cellular damage. However STEC associated HUS is finally characterized by the activation of the alternative pathway of the complement, which results in microangiopathic vasculitis (1, 6, 7).

Initial presentation of STEC associated HUS may be considered in differential diagnosis with IBD onset.

IBD include Crohn's Disease (CD) and Ulcerative Colitis (UD), that are both chronic inflammatory diseases characterized intestinal inflammation with variable extent and a possible systemic involvement. The onset of CD is variable from abdominal symptoms (abdominal pain, bloody stool, vomit), perianal manifestations (fistulas, tags, strictures), and extra-intestinal symptoms (cutaneous lesions, growth failure, anemia, uveitis, etc.). Any area in the gastrointestinal tract can be involved (10, 11). UC is usually segmental, but it can present even with severe pancolitis. Usually, it presents with bloody diarrhea and abdominal pain. Possible life-threatening complications include perforation or toxic megacolon, and surgery may be required. While the inflammation and injury in UC is limited to the mucosa, CD is a transmural process (10, 11).

Once a person is exposed to STEC, diarrhea typically occurs after 3-7 days and contains blood in about 85% of children. When the diarrhea starts resolving, about only 15 % of infected patients develop HUS (1, Figure 1). The kidney and gastrointestinal tract are the

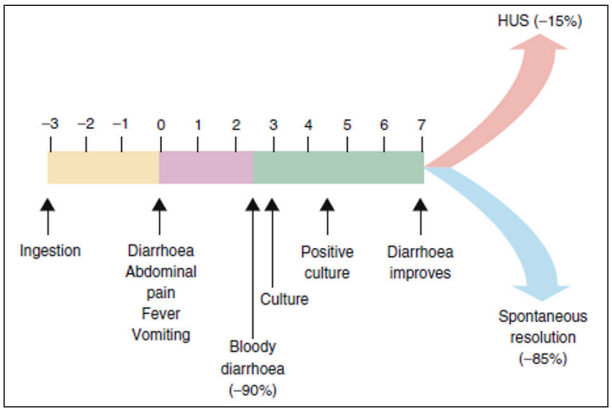


**Figure 1.**

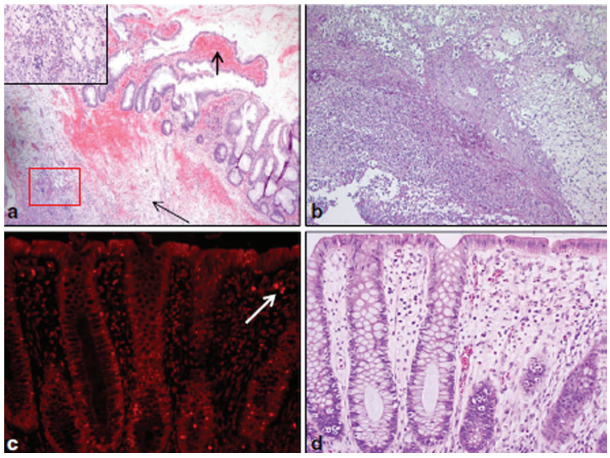


**Figure 2.**

organs most commonly affected, but an involvement of central nervous system, pancreatic, and myocardial involvement may also be present (1, 2, 8). Gastrointestinal symptoms with STEC-associated infection lead to a worse renal prognosis in comparison to patient with scarce intestinal symptoms (12). The transverse and ascending colon are the segments most commonly affected, but any area from the esophagus to the perianal area can be involved. The more serious manifestations include severe hemorrhagic colitis, which may be misdiagnosed as UC, bowel necrosis and perforation, rectal prolapse, peritonitis and intussusception. Severe gastrointestinal involvement can result in life-threatening complication as toxic megacolon and transmural necrosis of the colon with perforation. Transmural necrosis of the colon may lead to subsequent colonic stricture, as in CD. Perianal lesions and anal strictures are described (13-18). It is reported that for some patient intestinal sigmoidectomy was needed for severe complications (perforation, ulceration); in other patients, biopsies were performed in order to exclude IBD. In all cases specific histological findings (TUNEL-cells) suggest that apoptosis is the main mechanism of cell injury (15, Figure 2). Gastrointestinal complications can be lethal, and early surgery may sometimes be necessary. However, no correlation has been demonstrated between the severity of the gastrointestinal manifestations and clinical or biological signs (16).

The incidence of colonic perforation and stricture secondary to HUS is estimated to 1% and 3%, respectively (16, 17). Two peaks in the diagnosis of colonic stricture are described: the first from one to two months, and the second peak over 1 year after the acute event. Histological findings in stricture areas are characterized by granuloma formation and edema in the submucosal layer, and/or fibrosis in all the layers of the stricture. Both the vascular injury (MAT) and chronic inflammation secondary to an acute phase are hypothesized as possible pathogenetic mechanisms (17). Elevation of pancreatic enzymes, liver damage and cholecystitis are other described complications (1, 2, 19). Severe gastrointestinal complications are associated with a poor renal outcome (20).

There is no specific therapy for STEC HUS and the standard of care remains supportive. General management of acute kidney injury includes appropriate fluid and electrolyte management (hyperhydration when possible), often antihypertensive therapy, and initiation of renal replacement therapy when appropriate, to treat anemia and to avoid antidiarrheal drugs (1-3, 21, 22). Some studies have demonstrated that children who received antibiotic therapy were more likely to develop HUS. In vitro studies have shown that some antibiotics promote production and release of Stx from bacteria. Other studies and metanalyses have not demonstrated such an association, but antibiotic administration remains controversial and finally it is considered not safe in the clinical practice (1-3, 22).

Most of the literature affirm that aHUS rarely is in differential diagnosis with IBD at the onset, as the gastrointestinal manifestations are often absent or mild (1-3, 23). Underlying causes of aHUS are now better understood as genetic causes or secondary ones

(autoimmunity, drugs). It may manifest at all ages but is more frequent in adults (1-3). aHUS often presents with nonspecific symptoms, before the onset of the renal involvement, which is typically nephrotic or nephritic syndrome. A preceding illness, particularly a respiratory or gastrointestinal infection, is often reported as a trigger. Gastrointestinal symptoms and diseases have been described in the form of vomiting, hepatitis, pancreatitis, and rarely intestinal bleeding (1-3, 23). A recent study has evidenced that gastrointestinal complications and symptoms, as well as pancreatitis, are more common in aHUS with anti-factor-H autoantibodies (24). In other papers is also reported that some patients develop ischemic colitis and may be misdiagnosed as acute appendicitis or acute ulcerative colitis (1, 23). Regarding the direct associations between IBD and HUS, Peraldi et al. hypothesized the relationship between thrombogenic status in IBD and HUS development, reporting two cases of HUS in patient with CD, one of which was non-STEC associated (25). Another recent case report has described the development of diarrhea and non-STEC associated HUS with a concomitant diagnosis of CD in an adult patient (26). An association with aHUS and UC is also described. In a report, a young adult patient with UC recovered after Eculizumab treatment after developing aHUS with anti-factor H antibodies (27). In a second report, a 16 years old patient with UC developed aHUS (without anti-H factor antibodies) and received anti-C5 injection with benefit for both his renal and gastrointestinal disease (28). The authors conclude that deregulation of the alternative complement pathway may manifest in other organs besides the kidney and maybe hyperactivity of the alternative complement cascade plays a role in the pathogenesis of IBD (27). However, this affirmation is based only in in-vitro experimentations and probably requires further investigations. Recently, some authors conclude that while a direct causal relationship cannot always be established, improvement in IBD symptoms has been demonstrated after treatment with complement blockade (27-29). Finally, searching for STEC-infection, or broadly for E. coli infection, and IBD onset, some reviews suggest a possible role of adherent invasive E. coli (AIEC) on the pathogenesis of IBD (30).

## Conclusions

The current literature shows that gastrointestinal complications of HUS are quite exclusive of STEC-associated HUS, whereas aHUS have usually mild or absent intestinal involvement. Gastrointestinal complications are mostly related to the Stx action for its apoptotic effect. When the gastrointestinal involvement is important, the clinical presentation is similar to IBD at the onset, therefore differential diagnosis may take a few days, several laboratory and imaging exams. Colonic strictures are possible described complications, as in CD. For these similarities, some patients underwent endoscopy with intestinal biopsies. Early differential diagnosis is important to start a correct and prompt treatment. Laboratory exams showing renal involvement, thrombocytopenia and hemolytic anemia are the first elements that can help differentiating the two conditions, although they often need to be repeated. HUS and IBD have other points in common. Whereas no case of IBD after STEC-associated HUS are reported, some type of E. coli (AIEC) are considered as risk factor for IBD onset. Histological findings on intestinal stricture after STEC-associated HUS are similar to CD. Recent literature on aHUS shows that intestinal complications are more common than described before, particularly for patients with anti-H factor antibodies. Moreover, a few reports of patients with both aHUS and UC were found, who benefited from anti-C5 antibodies injection (Eculizumab). Other reports of patient with CD who developed non-STEC associated HUS, support the hypothesis of a possible common pathogenesis.

## References

1. Avner ED, Harmon WE, Niaudet P et al. Pediatric Nephrology 7th edition. Springer Heidelberg New York 2016.
2. Geary DF, Schaefer F. Comprehensive Pediatric Nephrology. MOSBY Elsevier Philadelphia 2008.
3. Noris M, Remuzzi G. Hemolytic uremic syndrome. J Am Soc Nephrol 2005; 16: 1035-50.
4. Tarr PI, Gordon CA, Chandler WL. Shiga-toxin producing Escherichia coli and hemolytic uremic syndrome. Lancet 2005; 365: 1073-86.
5. Tozzi AE, Caprioli A, et al. Shiga toxin-producing Escherichia coli infections associated with hemolytic uremic syndrome, Italy, 1988-2000. Emerg Infect Dis 2003; 9(1): 106-8.

6. Kaper JB, O'Brien AD. Overview and Historical Perspectives. Microbiol Spectr 2014; 2.
7. Karpam D, Stahl AL. Enterohemorrhagic Escherichia coli Pathogenesis and the Host Response. Microbiol Spectr 2014; 2.
8. Matussek A, Jernberg C et al. Genetic makeup of Shiga toxin-producing Escherichia coli in relation to clinical symptoms and duration of shedding: a microarray analysis of isolates from Swedish children. Eur J Clin Microbiol Infect Dis 2017; 36: 1433-1441.
9. Zoja C, Buelli S, Morigi M. Shiga toxin-associated hemolytic uremic syndrome: pathophysiology of endothelial dysfunction. Pediatr Nephrol 2010; 25: 2231-40.
10. Rosen MJ, Dhawan A, Saaed SA. Inflammatory Bowel Disease in Children and Adolescents. JAMA Pediatr 2015 Nov; 169(11): 1053-60
11. Herzog D, Fournier N, et al. Prevalence of intestinal complications in inflammatory bowel disease: a comparison between paediatric-onset and adult-onset patients. Eur Jour Gastroenterol Hepatol 2017; 29(8): 926-931.
12. Gianviti A, Tozzi AE, et al. Risk factors for poor renal prognosis in children with hemolytic uremic syndrome. Pediatr Nephrol 2003; 18: 1229-35.
13. Bannas P, Fraedrich K, et al. Shiga toxin producing E.coli O104:H4 outbreak 2011 in Germany: radiological features of enterohemorhagic colitis. Rofo 2013; 185: 434-9.
14. Rahman RC, Cobenas CJ, et al. Hemorrhagic colitis in postdiarrheal hemolytic uremic syndrome; retrospective analysis of 54 children. Pediatr Nephrol 2012; 27: 229-33.
15. Bekassy ZD, Toledo CC, et al. Intestinal damage in enterohemorrhagic E. coli infection. Pediatr Nephrol 2011; 26: 2059-71.
16. de Buys Roessingh AS, de Lagausie P, et al. Gastrointestinal complications of post-diarrheal hemolytic uremic syndrome. Eur J Pediatr Surg 2007; 17: 328-34.
17. Masumoto K, Nishimoto Y, Taguchi T. Colonic stricture secondary to hemolytic uremic syndrome caused by Escherichia coli O-157. Pediatr Nephrol 2005; 20: 1496-9.
18. Rieder F, Zimmerman EM, et al. Crohn's disease complicated by strictures: a systematic review. Gut 2013; 62(7): 1072-1084.
19. Grodinsky S, Telmesani A, et al. Gastrointestinal manifestations of hemolytic uremic syndrome: recognition of pancreatitis. J Pediatr Gastroenterol Nutr 1990; 11: 518-24.
20. Bernard A, Tounian P, et al. Digestive manifestations in hemolytic uremic syndrome in children. Arch Pediatr 1996; 3: 533-40.
21. Ake JA, Jelacic S et al. Relative nephroprotection during Escherichia coli O157:H7 infections: association with intravenous volume expansion. Pediatrics 2005; 115: 673-80.
22. Wong CS, Jelacic S, et al. The risk of hemolytic uremic syndrome after antibiotic treatment of Escherichia coli O157:H7 infections. N Engl J Med 2000; 342: 1930-6.
23. Noris M, et al. Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. Clin J Am Soc Nephrol 2010; 5(10): 1844–59.
24. Formeck C, Swiatecka-Urban A. Extra-renal manifestations of atypical hemolytic uremic syndrome. Pediatr Nephrol 2018 Aug 14. [Epub ahead of print]
25. Peraldi MN, Akposso K, et al. Haemolytic-uraemic syndrome in patients with Crohn's disease. Nephrol Dial Transplant 1997; 12: 2744-5.
26. Hoffmeister A, Wittenburg H, et al. A 32-year-old patient with diarrhoe and acute kidney failure. Internist (Berl) 2006; 47: 1063-1067.
27. Green H, Harari E, et al. Atypical HUS due to factor H antibodies in an adult patient successfully treated with Eculizumab. Ren Fail 2014; 36(7): 1119-21.
28. Webb TN, Griffiths H, et al. Atypical Hemolytic Uremic Syndrome and Chronic Ulcerative Colitis Treated with Eculizumab. Int J Med Pharm Case Reports 2015; 4(5): 105-112.
29. Johswich K, Martin M, Bleich A, et al. Role of the C5a receptor (C5aR) in acute and chronic dextran sulfate-induced models of inflammatory bowel disease. Inflamm Bowel Dis 2009; 15(12): 1812-1823.
30. Martinez-Medina M, Garcia-Jil LJ. Escherichia coli in chronic inflammatory bowel diseases: An update on adherent invasive Escherichia coli pathogenicity. World J Gastrointest Pathophysiol 2014; 5(3): 213-227.

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