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Inter-society consensus on the management of acute bloody diarrhea and shiga toxin-producing *Escherichia Coli* infection in the molecular microbiology era

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Title page

Title Inter-Society Consensus on the Management of Acute Bloody Diarrhea and Shiga Toxin-Producing Escherichia Coli Infection in the Molecular Microbiology Era.

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Abstract

Hemolytic uremic syndrome associated with Shiga toxin-producing *Escherichia coli* (STEC-HUS) infection is a major individual and public health challenge, and the leading cause of acute kidney injury in children. In Western countries, HUS complicates about 15% of STEC infections, which are responsible for acute bloody diarrhea (ABD) in at least 6–7% of cases in children (rising to over 15% during late summer). The widespread use of molecular microbiology techniques enables the diagnosis of STEC infection before HUS onset in an increasing number of patients, creating a potential window of preventive and therapeutic opportunities. Given the rapid progression of the disease, all children with ABD should be tested for Shiga toxin (Stx) encoding genes as early as possible. Stx-positive patients should then be closely monitored for HUS development by urine dipstick, to detect hemoglobinuria.

This proactive diagnostic approach creates the opportunity to anticipate the application of measures that have already been proven to mitigate the severity of HUS, among which stands the early and generous fluid administration, but most importantly opens a window to explore preventive and therapeutic interventions. In detail, even though antibiotics are not historically recommended in STEC infections, recent data suggest a promising potential preventive role for bacteriostatic agents (e.g., azithromycin) during the initial stages of the infection.

The aim of the present contribution is to share this approach to ABD and STEC infection as endorsed by the Italian scientific societies actively engaged in this area (AMCLI, SIGENP, SIMEUP, SIN, SIP, SIPPS, SITIP) through an intersocietal consensus. The goal is to promote the early diagnosis of STEC infection nationwide, thereby improving our understanding of the mechanisms of disease spreading, and hopefully reduce the rate of progression to HUS, its case fatality rate and possibly improve both short- and long-term outcomes.

Keywords:

Acute bloody diarrhea; Shiga toxin-producing *Escherichia coli*; hemolytic uremic syndrome.

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Introduction

The recent advances and increasing availability of molecular microbiology techniques for the diagnosis of infectious diseases offer promising therapeutic opportunities, while also introducing new challenges.

This document provides a concise overview of the most significant and recent developments concerning an endemic issue in our country: the infection caused by Shiga toxin-producing *Escherichia coli* (STEC). This condition is often characterized by a prodromal phase of acute bloody diarrhea (ABD) and may progress to a severe disease named hemolytic uremic syndrome (HUS).

This paper aims to highlight the available opportunities to prevent the onset of HUS and, when it occurs, to mitigate the severity of its clinical course. The present document is the result of a collaboration among several scientific societies, institutions, or organizations herein mentioned, which are or could be involved in managing STEC infections.

To facilitate consultation, the paper is organized around key statements, each accompanied by relevant insights, explanations, and supporting evidence.

Consensus methodology

As a first step, all Italian scientific societies considered relevant to the diagnosis, management, and surveillance of STEC infection and HUS were identified and formally invited to participate to the consensus process.

Voting participants included formally designated representatives of the participating scientific societies (AMCLI, SIGENP, SIMEUP, SIN, SIP, SIPPS, SITIP), as well as representatives of regional STEC surveillance networks and public health institutions, including the Italian National Health Institute (ISS), the Zooprophylactic Institutes within the involved regional surveillance networks, and national research institutes, such as CNR and DeFENS.

Participants were selected based on their recognized expertise and active role in clinical management, laboratory diagnosis, epidemiological surveillance, or public health control of STEC infection.

The consensus statements were initially drafted by the coordinating group following a critical review of the available literature, national epidemiological data, and existing recommendations.

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Statements were subsequently discussed and refined through iterative expert consultation before being submitted to a formal voting process. For each statement, the total number of voters and the percentage of agreement are reported in brackets. No a priori agreement threshold was predefined. This consensus document includes recommendations supported by different levels of evidence. Some statements are based on consolidated evidence derived from large observational studies, network-based analyses, and systematic reviews (e.g., early hydration strategies and urine dipstick monitoring for hemoglobinuria), while others rely on emerging evidence, including observational data, experimental studies, and proof-of-concept clinical experiences (e.g., the use of bacteriostatic antibiotics in STEC infection). Given the rarity of the disease and the ethical and logistical constraints of conducting randomized clinical trials in this setting, expert consensus remains an essential tool to guide clinical practice in areas where high-level evidence is still evolving.

Part 1 – Diagnosis

1. **In Western countries, ABD is generally caused by bacterial agents, including STEC (28; 97%).**

Acute diarrhea is an extremely common condition, particularly in the pediatric population: among preschool-aged children, the estimated frequency ranges from 500 to 2,000 events per 1,000 children per year [1]. In contrast, ABD — which is defined as the presence of "diarrhea with visible blood, even in minimal amounts or as reported by the patient or caregivers" — has a significantly lower estimated incidence, with approximately 3.3 cases per 1,000 children per year [2].

ABD can be caused by a variety of pathogens. In order of frequency, the most frequently identified bacterial causes of ABD in Northern Italy are *Campylobacter spp.*, *Salmonella spp.*, non-Shiga toxin-producing *Escherichia coli*, and STEC. Less commonly, *Clostridioides difficile*, *Yersinia spp.*, *Aeromonas spp.*, and *Shigella spp*. are also detected. In Italy, STEC ranks 4th among the most common etiological agents of ABD (**Table 1**), with a relative frequency of 5.1%, depending on the considered geographical area [3].

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Pathogen	**ABD, %**
Campylobacter	28.6
Salmonella spp.	15.4
Not-STEC EPEC	9.6
STEC	5.1
Stx1	17.8
Stx2	50.7
Stx1+2	31.5
Clostridium difficile	4.5
Aeromonas spp.	1.4
Yersinia spp.	2.9
NEGATIVE	34.3
Total	**100.0**

Table 1 Etiology of ABD in children and distribution of Stx types among STEC-positive cases. Legend: ABD, acute bloody diarrhea; STEC, Shiga toxin-producing *Escherichia coli*; EPEC, enteropathogenic *Escherichia coli*; Stx, Shiga toxin.

2. **ABD should be considered a medical emergency due to the risk of HUS (26; 97%).**

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The analysis of available epidemiological data suggests that, out of 100,000 cases of diarrhea, fewer than 500 are associated with the presence of blood, while the vast majority is represented by cases of simple secretory diarrhea (unpublished data from the ItalKid-HUS Network). Among the former group, approximately 20–25 cases of STEC infection are expected, and 3–4 of them are likely to progress to HUS. Therefore, by testing 18–20 patients with ABD, at least one case of STEC infection is expected to be identified. In contrast, more than 1,000 tests would be required to detect a single STEC-positive case among patients presenting with acute non-hemorrhagic diarrhea (**Figure 1**). The need to focus diagnostic efforts on ABD is further supported by the fact that the conversion rate from STEC infections without ABD to HUS is very low (<1%), and the resulting HUS cases are generally less severe and consequently follow a mild clinical course.

3. **Gastroenteric infection caused by STEC may progress to HUS depending on the bacterial virulence profile (28; 98%).**

STEC infection may progress to HUS in a variable percentage of cases (10–20%) [2].

The conversion rate from STEC infection to HUS is fairly influenced by the virulence profile of the bacteria. Shiga toxin 1 (Stx1) alone is rarely associated with HUS (<1%). The risk of developing HUS is higher when both Stx1 and Stx2 are present (12%), but the highest risk (23%) is observed in Stx2-positive patients [4].

Other factors predisposing to HUS or associated with increased disease severity include: age <5 years, dehydration, fever, leukocytosis (white blood cell count >20,000/mm^3), higher proportions of blood in the diarrhea, and use of anti-diarrheal medications or antibiotics (for the latter, see **Points 14–15**).

4. **The estimated annual incidence of STEC-HUS in pediatric age is approximately 6–7 cases per million age-related population, but the disease can also occur in adults (27; 100%).**

In Italy, the National HUS Registry reports between 50 and 70 cases annually in pediatric age, corresponding to an average annual incidence of 7 cases per million population [5,6]. The disease typically affects children under 6 years of age — accounting for approximately two thirds of cases — but it can also occur, albeit less frequently, in older age groups. When an adolescent presents with ABD, the likelihood of STEC infection and the associated risk of HUS is not negligible, even though ABD is significantly less frequent in adolescents compared to younger children (**Table 2**). In adults, the disease is likely underdiagnosed, and reliable incidence estimates are currently unavailable.

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Age group, years	ABD, n (%)	STEC infection, n (%)	HUS, n (%)
0–5	3217 (61.6)	203 (61.5)	92 (69.2)
5–10	1126 (21.5)	73 (22.1)	31 (23.3)
10–15	604 (11.6)	41 (12.4)	8 (6.0)
15–20	279 (5.3)	13 (4.0)	2 (1.5)
Total	**5226 (100.0)**	**300 (100.0)**	**133 (100.0)**

Table 2 Relative frequency of ABD, STEC infection, and HUS by age group. Data from the ItalKid-HUS Network (2010–2024). Legend: ABD, acute bloody diarrhea; STEC, Shiga toxin-producing *Escherichia coli*; HUS, hemolytic uremic syndrome.

5. **STEC infection and STEC-HUS may also affect adults (26; 100%).**

Although less frequently, STEC infections can also affect adults. In most cases, patients recover within a few days without sequelae; however, the infection can lead to HUS, with an unknown incidence in this cohort. Adults with STEC infection rarely present with ABD, and symptoms are often limited to mild dyspepsia. Older age is considered a negative prognostic factor (possibly due to the coexistence of comorbidities), along with the presence of pre-existing chronic kidney disease and dehydration [7,8]. Early identification of patients at risk of HUS is crucial, especially during outbreaks, when the number of clinically fragile individuals may rapidly increase. In families of children affected by HUS, it is common to find adults colonized by STEC, suggesting the possibility that the child may have been infected by an adult family member (or vice versa) [9].

Although the primary focus of this consensus document is pediatric STEC infection and HUS, selected data on adult patients are included to provide epidemiological and public health context. These adult data are presented for informational purposes only and do not constitute direct guidance for clinical management.

6. **At our latitudes, STEC infections and thus HUS have a peak incidence during the months of July–September (28; 100%).**

The disease shows a well-known seasonality, with an increase in cases during spring, summer, and autumn (**Figure 2**). In detail, the months of July, August, and September are the most affected.

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During this period, the likelihood that ABD is caused by STEC more than triples. In addition to its endemic form, the disease can also occur in outbreaks originating from a single contaminating source (typically a food product).

7. **The source of STEC infection remains unknown in 70% of cases (28; 100%).**

STEC infection is a zoonotic disease, with ruminants serving as the primary natural reservoir of the bacterium. The main source of infection is represented by animal-derived foods that have not undergone heat treatment, such as cooking or pasteurization. Traditionally, undercooked meats and unpasteurized dairy products have been considered the primary vehicles of infection. Therefore, it is advisable to avoid serving these foods to children due to their increased susceptibility to STEC infection and its complication, HUS. Other well-documented transmission routes include direct contact with ruminants, ingestion of or bathing in contaminated freshwater, consumption of plant-based foods potentially contaminated by animal feces (manure), and even human-to-human transmission, which is more common in household settings or preschools [9,10].

Moreover, in recent years, several STEC infection cases have also been reported in individuals returning from popular tourist destinations in Egypt [11].

Despite the aforementioned transmission pathways, the source of STEC infection remains unknown in 70% of cases. For this reason, it is essential to report every case to public health surveillance systems. Indeed, only through the comprehensive analysis of all reported cases can we gain a better understanding of the underlying mechanisms of STEC infection, which represents the prerequisite for developing and implementing effective primary prevention strategies.

8. **All ABD cases should undergo specific testing for the detection of Stx-encoding genes (28; 95%).**

STEC infections can now be identified through molecular biology techniques, which should be promptly applied to all cases of ABD. Both multiparametric molecular assays and syndromic molecular panels are currently available for this purpose. Multiparametric assays provide rapid results, but the turnaround times are closely dependent on the internal organization of the laboratory performing the test. Syndromic panels can be performed quickly and allow for results to be obtained within a few hours of sample receipt by the laboratory. Considering the potential for rapid clinical deterioration, case notification to the laboratory is considered good practice to ensure timely diagnostic processing.

It is important to underline that there is no indication to test for Stx-encoding genes in cases of non-bloody secretory diarrhea, unless specific risk factors are present:

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1. Occurrence within the context of STEC outbreaks;

2. Recent return from high-risk areas (e.g., South America, Egypt and Maghreb);

3. Close contact with confirmed STEC cases, such as household members.

For clinical diagnostic purposes, traditional microbiological methods are inadequate, as they are unable to detect all STEC strains. Likewise, immunochromatographic and immunoenzymatic assays have shown insufficient diagnostic sensitivity and may therefore prompt misleading results.

Due to the high sensitivity of molecular biology techniques, multiple positive results are not uncommon. Some molecular diagnostic systems also identify other *Escherichia coli* strains responsible for gastrointestinal pathology, such as EAEC, EPEC, ETEC, and EIEC. However, these strains do not require specific clinical measures if they are not Stx-producing. In cases where Stx-encoding genes are detected, the patient should be considered at risk of developing HUS. The risk of HUS varies depending on the Stx type involved [4].However, many currently available molecular assays do not discriminate between Stx1 and Stx2. This distinction is clinically relevant because Stx2-producing strains carry a higher risk of progression to HUS. Therefore, a positive result from a non-differentiating syndromic panel should prompt confirmatory testing at a reference laboratory. In general, toxin typing results at reference laboratories are available within 24–48 hours, depending on laboratory workload and transport logistics. Meanwhile, patient management should be approached with maximum caution, assuming the presence of Stx2. Definitive risk stratification requires additional testing to identify the specific toxin(s) involved (Stx1, Stx2, or both).

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Molecular testing is currently available at numerous microbiology laboratories, as shown in **Figure 3** and detailed in **Table 3**. The list may not be exhaustive and therefore may not include all centers already equipped to perform diagnostic testing for Stx-encoding genes, especially given the recent and rapid spread of these tests. We would be grateful for any communication regarding laboratories not included, so the list can be updated. Please send any addition to: ardissino@centroseu.org

9. **It is important that all cases of STEC infection are reported to the National Surveillance System for Infectious Diseases (PREMAL), and that Stx-positive samples (or isolated STEC strains) are forwarded to the regional and/or national reference laboratories for full characterization (28; 100%).**

Reporting positive STEC cases to the Public Health Units of the Department of Prevention (SISP) is mandatory since 2022 and allows timely identification of potential outbreaks. Prompt ABD/STEC notification is essential to detect multiple cases linked to the same pathogen and/or source,

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especially when patients are managed by different healthcare facilities across a wide geographic area. Following the report of suspected STEC cases, SISP, together with the Food and Nutrition Safety Services (SIAN), carries out an investigation to identify the source of infection. It is important to remark that, to date, in approximately 70% of HUS cases, the source remains unknown. Failure to report or delays in reporting significantly hinder the ability to identify the source of STEC infection, as the contaminated food might no longer be available by the time an inquiry is initiated.

The European and National Reference Laboratory for *Escherichia coli* is located at the Istituto Superiore di Sanità in Rome, where serotyping, virulence profiling, and genome sequencing are performed to trace common sources of infection. Equally important is early establishing contact with the regional pediatric nephrology hub in cases of Stx positivity, both to share relevant clinical information and to ensure timely referral in case of confirmed HUS.

Part II – Management

10. **The clinical course of the disease, from initial infection to HUS (when it occurs), is relatively standard and rapid: incubation, non-bloody diarrhea, bloody diarrhea, HUS (24; 99%).**

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The disease has a short incubation period, with the first symptoms appearing 3–5 days after ingestion of the bacterium. The infection is not always symptomatic, but when it is, the typical presentation is with abdominal pain and diarrhea; vomiting and fever are less frequent. In the first 24–48 hours, diarrhea is secretory (non-bloody), thus indistinguishable from the many cases of acute gastroenteritis that affect children. After 24–48 hours from the onset of symptoms, blood appears in the stool in approximately 80–90% of cases [12]. The presence of blood, often associated with mucus, can greatly vary, from slight blood streaks to large amounts. The extent of the blood component has prognostic value regarding the development of HUS, which will occur in 10–20% of cases after a minimum period of 2 days, with a median of 5, up to several days depending on the persistence of gastrointestinal symptoms. In other words, when diarrhea ends completely, the progression to HUS is unlikely. However, there are cases in which diarrhea persists for a long time, alternating phases of apparent remission and recurrence. In such circumstances, the risk of HUS remains as long as the enteritis has not completely resolved. In the presence of ABD, it is important in the Emergency Room settings to perform the urine dipstick for hemoglobinuria (uHb), which alone can exclude or confirm the suspicion of ongoing HUS (see also **Statement 11**).

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11. **The clinical management of a patient with STEC infection changes depending on the type of Stx produced by the STEC (21; 94%).**

The risk of developing HUS in case of STEC infection producing only Stx1 is negligible, whereas the coexistence of Stx2 and Stx1 increases the risk of conversion to HUS to about 12%, and to 23% if Stx2 is present alone [2,4]. Therefore, to assess the risk profile, it is essential to perform the suggested diagnostic workup, but initial measures should be carried out as if Stx2 was present, until a more definitive diagnosis is made.

12. **The management of a patient with STEC infection associated with Stx2 includes:**

    a. **Immediate diagnostic tests to confirm or exclude the presence of ongoing HUS;**

    b. **Fluid administration to correct dehydration or to maintain adequate intravascular volume (21; 99%).**

In cases of confirmed STEC infection with undefined Stx type or Stx2, if microhematuria is present, it is useful to perform blood and urinary tests to exclude the presence of ongoing HUS (complete blood count, lactate dehydrogenase levels, haptoglobin, kidney function, and urinalysis or urine dipstick for uHb). If HUS (platelet consumption, hemolysis, and renal damage) is not confirmed, the patients should be monitored for the risk of HUS during the following days, using urine dipstick to detect uHb, preferably every 12 hours if the patient is hospitalized or every 24 hours if at home [13]. When the patient is correctly hydrated and the clinical condition allows to keep adequate hydration, urine dipstick monitoring may be continued at home, performed by the physician or by other healthcare workers or by the parents if properly instructed. If the urine dipstick turns positive (uHb ≥2+), the blood tests will confirm (or exclude) the presence of the diagnostic triad for HUS (platelet consumption, hemolysis, and kidney damage), thereby ruling in or out the diagnosis (**Figure 4**).

13. **HUS is characterized by the following diagnostic triad: platelet consumption, mechanical (Coombs negative) hemolysis, kidney and multiorgan damage (24; 99%).**

HUS occurs with the classic triad: 1. **Platelet consumption** (platelets <150,000/mm³ or rapid halving of platelets count); 2. **Hemolysis** (microangiopathic hemolytic anemia with increased lactate dehydrogenase levels and haptoglobin consumption); 3. **Kidney damage** (increased serum creatinine, microhematuria with proteinuria), as well as **multiorgan ischemic damage** (liver, heart, pancreas, central nervous system, and, less commonly, other organs).

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Once established, HUS follows a clinical course with variable severity. The onset of anuria, hyponatremia, a white blood cell count >20,000/mm³, and elevated hemoglobin at presentation are all risk factors for more severe disease [14–16]. About 50% of patients require dialysis for a median of 5–6 days. Around 20% exhibit neurological symptoms (mainly seizures, but rarely also coma). Central nervous system involvement is the leading cause of death in HUS, occurring more frequently in the early stages of the disease in about 1–5% of cases.

After a variable period (5–10 days), thrombotic microangiopathy (TMA) typically resolves spontaneously, initially with normalization of platelets count, followed by kidney functional recovery and finally with stabilization and recovery of hemoglobin levels. Complete normalization of renal function (when it occurs) may take a prolonged period (sometimes years). Approximately 50% of cases fully recover, although the loss of some glomeruli may have long-term health consequences, potentially decades later. The remaining patients may experience varying degrees of renal damage (mainly proteinuria and hypertension, but also chronic renal failure of variable severity). Rarely (<5% of cases), patients may have end-stage kidney failure or permanent neurological damage [12].

14. **At onset, HUS may not be associated with anemia despite the presence of hemolysis due to the frequent coexistence of hemoconcentration (19; 100%).**

Approximately 25% of cases of STEC-HUS, at onset, do not have anemia, despite significant hemolysis indicated by very high lactate dehydrogenase levels (LDH) and haptoglobin consumption. This is due to the coexistence of hemoconcentration, which results from poor nutrition, vomiting, diarrhea, and fluid (and albumin) leakage through damaged endothelium [16]. This hemoconcentration state must be corrected rapidly because its presence is responsible for a worse disease course, both in the acute phase and in terms of long-term damage [17].

15. **The urine dipstick negativity for uHb is sufficient to exclude ongoing HUS, while a positive urine dipstick (uHb ≥2+) requires blood tests to rule in or out the diagnosis of HUS (18; 94%).**

In cases of STEC infection, it is helpful to start intravenous infusion (maintenance + replacement of loss) using isotonic or balanced solutions (Ringer's lactate), with sodium concentration >130 mEq/L. The use of isotonic solutions prevents hyponatremia in case of upcoming oligo-anuria. Intravenous infusion is crucial to optimize the child's hydration status, as it is known that, if HUS occurs in a dehydrated patient, the clinical course will be more severe [17,18].

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Patients with already ongoing HUS, may still benefit from generous infusion (10 mL/kg/hour, with a maximum of 300 mL/hour) of isotonic fluids until the child's usual weight is restored [17]. Transfusion of concentrated red blood cells (for Hb values <6 g/dL) is generally required in all children with HUS. Platelet transfusion, on the other hand, is reserved for patients with severe hemorrhagic manifestations (which are very rare) or those who require surgical procedures.

Patients may need dialysis until full recovery of renal function [18].

It should be highlighted that recent studies have documented as complement inhibitors have no indication for this condition despite analogies with atypical HUS and despite wide off-label use of these medications [19].

16. **In STEC infections, the use of antibiotics that induce bacterial lysis may precipitate the development of HUS (25; 98%).**

The use of antibiotics in patients with STEC infection is historically contraindicated because it induces bacteriophages carrying Stx genes and promotes their transcription. Subsequent bacterial lysis results in a massive release of Stx, increasing the risk of progression to HUS [20,21]. Despite this general assumption, in Japan, patients with STEC infection have been extensively treated with fosfomycin since the 1996 outbreak that affected 12,680 individuals [22]. Japanese colleagues report favorable results with this clinical approach [23,24].

17. **The early administration of antibiotics that do not induce bacterial wall lysis may reduce the risk of progression to HUS in STEC infections (23; 86%).**

Recent literature highlights that the increased risk of progression from STEC infection to HUS is associated with bactericidal antibiotics, including quinolones, beta-lactams, and sulfonamides, which increase Stx production and release by activating the bacterial SOS response [25,26]. This association has been consistently reported in observational studies and meta-analyses and supports the general recommendation to avoid bactericidal antibiotics in suspected or confirmed STEC infection.

In contrast, bacteriostatic antibiotics, such as azithromycin, do not induce bacterial wall lysis and may modulate Stx production. In greater detail, azithromycin has shown the ability to reduce Stx production *in vitro* and to exert a protective effect against neurological and gastrointestinal complications of STEC infection in animal models [27–30]. Observational clinical experiences also suggest a potential benefit of azithromycin use in patients with documented STEC infection [31–33]. A recent retrospective analysis reported that, out of 102 patients treated with azithromycin (10

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mg/kg/day, maximum dose of 500 mg for up to 5 days), only 5 developed HUS, compared to an expected number of 13 cases (4.9% vs. 13.2%) [34].

To date, no randomized controlled trial has evaluated the efficacy of azithromycin in preventing STEC-HUS, and further studies are ongoing to confirm the safety and efficacy of this new approach to STEC infection. Accordingly, the use of azithromycin in STEC infections remains off-label and should be considered by the treating physician on a case-by-case basis, after discussion and informed consent of patients and caregivers.

18. **Rarely, STEC infection may act as a trigger for atypical HUS due to complement dysregulation, complicating the differential diagnosis between typical and atypical HUS (17; 97%).**

Approximately 6–8% of the healthy population carries genetic variants affecting complement regulatory genes (CFH, CFI, CFB, CD46, and C3) that may potentially impair complement function. This latent genetic condition is typically unmasked by acute events or chronic illnesses (such as infections, vaccinations, childbirth, surgical procedures, trauma, autoimmune diseases, or cancers). The clinical manifestation of such complement dysregulation is atypical HUS (aHUS).

This implies that 6–8% of individuals who develop STEC infection may have an underlying genetic complement dysregulation and therefore may develop atypical HUS. In such scenarios, the coexistence of HUS clinical signs and STEC infection may lead to a straightforward diagnosis of STEC-HUS (typical), when in fact the condition may be atypical. Failure to make the correct differential diagnosis between typical and atypical HUS may result in suboptimal treatment. Atypical HUS due to complement dysregulation would benefit from specific therapy with a C5 inhibitor.

Useful clinical and laboratory clues to raise suspicion for aHUS in the presence of STEC infection are: persistently low C3 levels even after the acute phase of presumed STEC-HUS; severe hypertension at disease onset; no TMA remission after one week from onset; and lack of kidney function recovery.

Limitations

This consensus document has several limitations. First, it is primarily based on Italian epidemiological data, which may not fully reflect the situation in other countries. Second, diagnostic and laboratory resources vary regionally, potentially affecting the applicability of certain recommendations. Finally, the evidence base is rapidly evolving, particularly regarding

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antimicrobial strategies such as the use of azithromycin. Recommendations should therefore be interpreted with caution, and updates may be necessary as new data become available.

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Figures and tables

Figure 1 Estimated frequency of secretory diarrhea and ABD in children, with relative frequency of STEC infections and progression to HUS. Data from the ItalKid-HUS Network.

Legend: ABD, acute bloody diarrhea; Stx, Shiga toxin; HUS, hemolytic uremic syndrome.

Figure 2 Seasonality of ABD, STEC infection, and HUS. ABD occurs throughout the year, with a slightly higher incidence in summer–autumn. Stx-positive cases are more frequent in summer (about 20% of ABD in August–September). HUS distribution follows Stx positivity.

Legend: ABD, acute bloody diarrhea; Stx, Shiga toxin; STEC, Shiga toxin-producing *Escherichia coli*; HUS, hemolytic uremic syndrome.

Figure 3 Map of Italian laboratories currently offering molecular testing for Stx-encoding genes.

Figure 4 Management of ABD cases focused on the risk of STEC infection and HUS. All patients presenting with ABD should undergo clinical evaluation and PCR testing for Stx detection. Stx typing is essential to distinguish between Stx1 and Stx2, as Stx2 confers higher risk of progression to HUS. In patients positive for Stx2 or unknown Stx type, blood and urine tests are performed to exclude ongoing HUS. Fluid administration should be initiated to correct dehydration or maintain adequate intravascular volume. Urine dipstick monitoring for uHb is conducted every 12 hours in hospitalized patients or every 24 hours in outpatients. Off-label treatment with azithromycin may be considered based on clinical discretion, following discussion and informed consent of patients and caregivers. In case of uHb ≥2+ at urine dipstick, further blood tests investigating the presence of thrombocytopenia and hemolysis are needed to confirm HUS diagnosis and guide subsequent management.

Legend: ABD, acute bloody diarrhea; ER, Emergency Room; Stx, Shiga toxin; PCR, polymerase chain reaction; uHb, hemoglobinuria; PLT, platelets; STEC-HUS, Shiga toxin-producing *Escherichia coli*-associated hemolytic uremic syndrome; *Complete cell blood count, serum creatinine, urea, lactate dehydrogenase, albumin, liver enzymes, C reactive protein; §Isotonic solutions with target weight +5-10%% of usual weight; °azithromycin 10 mg/kg/day (max 500 mg/day) until diarrhea resolution (maximum of 5 days).

Table 3 Healthcare centers providing molecular testing for Stx-encoding genes in Italy and Republic of San Marino.

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Region	City	Hospital
ABRUZZO	PESCARA	Ospedale Spirito Santo
BASILICATA	POTENZA	AO Regionale San Carlo
	MATERA	PO Madonna delle Grazie
CALABRIA	COSENZA	AO di Cosenza PO Annunziata
	CATANZARO	Campus di Germaneto AOU Dulbecco
	REGGIO CALABRIA	Grande Ospedale Metropolitano
CAMPANIA	AVELLINO	AORN S. Giuseppe Moscati
	CASERTA	Ospedale SS. Anna e Sebastiano
	NAPOLI	AOU Federico II
		AOU Vanvitelli
		PO Cotugno AORN dei Colli
EMILIA ROMAGNA	PIACENZA	AUSL di Piacenza
	PARMA	AOU di Parma
	MODENA	AOU di Modena – Policlinico di Modena
	REGGIO EMILIA	IRCCS Arcispedale S. Maria Nuova
	BOLOGNA	IRCCS AOU Policlinico S. Orsola
	FERRARA	AOU S. Anna
	CESENA	Centro Servizi Pievesestina

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FRIULI VENEZIA-GIULIA	UDINE	AS Universitaria Friuli Centrale
	PORDENONE	PO Santa Maria degli Angeli
	TRIESTE	AS Universitaria Giuliano Isontina ASUGI
		IRCCS Burlo Garofalo
	MONFALCONE	AS Universitaria Giuliano Isontina ASUGI
LAZIO	ROMA	Ospedale Casilino
		IRCCS Fondazione Policlinico Universitario A. Gemelli
		Ospedale S. Filippo Neri
		Istituto Nazionale di Malattie Infettive L. Spallanzani
		Ospedale S. Pietro Fatebenefratelli
		AO S. Camillo Forlanini
		Ospedale Pediatrico Bambino Gesù
	LATINA	Ospedale S. Maria Goretti
	FROSINONE	Ospedale F. Spazziani
LIGURIA	GENOVA	Ospedale Infantile G. Gaslini
	PIETRA LIGURE	Ospedale Santa Corona
LOMBARDIA	MILANO	IRCCS Ca' Granda Ospedale Maggiore Policlinico
		ASST Grande Ospedale Metropolitano Niguarda

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		ASST Fatebenefratelli Sacco
	CREMA	Ospedale di Crema
	CREMONA	Ospedale di Cremona
	PAVIA	Fondazione IRCCS Ospedale S. Matteo
	VARESE	Ospedale F. del Ponte
	BERGAMO	Ospedale Papa Giovanni XXIII
MARCHE	ANCONA	AOU delle Marche
MOLISE	CAMPOBASSO	Ospedale Cardarelli
PIEMONTE	NOVARA	AOU Maggiore della Carità
	BIELLA	Ospedale degli Infermi
	TORINO	AOU Città della Salute e della Scienza di Torino
		Ospedale Amedeo di Savoia
	ALESSANDRIA	Presidio Civile SS. Antonio e Biagio
PUGLIA	FOGGIA	AOU Policlinico Riuniti
	SAN GIOVANNI ROTONDO	Ospedale Casa Sollievo della Sofferenza
	BARI	Policlinico di Bari
	TARANTO	Ospedale Santissima Annunziata
	LECCE	Ospedale F. Ferrari di Scorrano
	TRICASE	Ospedale Cardinale Panico
SARDEGNA	SASSARI	AOU Sassari

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	NUORO	Ospedale S. Francesco
	CAGLIARI	AOU di Cagliari
SICILIA	PALERMO	AOU Policlinico P. Giaccone
		Civico – Di Cristina – Benfratelli
		AO Ospedali Riuniti Villa Sofia – Cervello
	ENNA	PO Umberto I
	CALTANISETTA	PO S. Elia
	MESSINA	AOU Policlinico G. Martino
	CATANIA	AOU Policlinico G. Rodolico – S. Marco
		AO Cannizzaro, Ospedale per Emergenza, AO Garibaldi
	SIRACUSA	PO Umberto I
TOSCANA	FIRENZE	Ospedale Careggi
	LIVORNO	Ospedale Riuniti
	LUCCA	Ospedale S. Luca
	PISTOIA	Ospedale S. Jacopo
	AREZZO	Ospedale S. Donato
TRENTINO ALTO ADIGE	TRENTO	Ospedale S. Chiara
	BOLZANO	Ospedale Provinciale di Bolzano
UMBRIA	PERUGIA	AO S. Maria della Misericordia
	TERNI	AO S. Maria di Terni

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VALLE D'AOSTA	AOSTA	AO Beauregard
VENETO	VERONA	Ospedale Sacro Cuore - Don Calabria di Negrar
		AOU Integrata di Verona
	VICENZA	Ospedale S. Bortolo
	PADOVA	AOU Padova
	MESTRE	PO di Mestre
	TREVISO	Ospedale di Treviso
REP. DI SAN MARINO	SAN MARINO	Ospedale di Stato

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List of abbreviations

STEC, Shiga toxin-producing *Escherichia coli*; ABD, acute bloody diarrhea; HUS, hemolytic uremic syndrome; Stx, Shiga toxin; PREMAL, National Surveillance System for Infectious Diseases (Italy); SISP, Public Health Units, Department of Prevention; SIAN, Food and Nutrition Safety Services; LDH, lactate dehydrogenase; uHb, hemoglobinuria; aHUS, atypical HUS; TMA, thrombotic microangiopathy.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

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Authors' contributions

All authors contributed to the conception and development of the consensus document.

GA coordinated the project and oversaw manuscript preparation.

Authors marked with * actively participated in the first phase of the work, contributing to the acquisition of key data and perspectives.

All authors are members of the board and representatives of scientific societies, institutions, organizations and/or regional surveillance systems effectively or potentially involved in the topic. Their positions were defined through a structured voting process, which ensured a shared consensus on the key statements presented.

All authors reviewed and approved the final version of the manuscript.

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