

The management of acute bloody diarrhoea potentially caused by vero cytotoxin-producing *Escherichia coli* in children

A guide for primary care, secondary care and public health practitioners



A clinical guideline for health care practitioners in England concerning the management of acute bloody diarrhoea in children, with particular reference to VTEC infection, and the need for urgent referral of such cases.

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Preamble

Caveat

This guidance has been written for a target audience of healthcare practitioners in England.

Clinical practitioners in Scotland should refer to the guidance issued by the Scottish Health Protection Network¹, with which this guideline is consistent.

Status of guideline

This guide was developed by the guideline development group listed in Appendix 3. It has been endorsed by the Royal College of Paediatrics and Child Health (RCPCH), The Royal College of General Practitioners (RCGP) and the Health Protection Agency (HPA) following peer review.

Currency of guideline

The guideline will remain extant for three years from the date of publication, unless withdrawn, or revised at an earlier stage by the RCPCH or HPA.

Terminology

This guideline contains references to vero cytotoxin-producing *Escherichia coli* (VTEC), the most important strain of which in the UK is *E. coli* O157. References may also be found in the literature to Verocytotoxin-producing *Escherichia coli*, Verotoxigenic *Escherichia coli*, and Shiga-toxin-producing or Shiga-like toxin-producing *Escherichia coli* O157 (STEC); all of these terms are synonymous.

Workload & resource implications

The group of authors considered the implications of the recommendations made in this guideline and concluded that, aside from the timing of referral of children with acute bloody diarrhoea, no significant impact on potential resource and workload is to be expected.

Recommendations on implementation of the guideline

Primary care teams are asked to review their practice protocols to reflect the recommendation that they seek urgent advice from a paediatrician whenever a child is reported to have had a single acute episode of bloody diarrhoea

Secondary care services are asked to ensure that emergency medicine departments are made aware of the need to seek specialist paediatric review of children whenever a child is reported to have had a single acute episode of bloody diarrhoea and that paediatric medicine departments are made aware of these guidelines and their recommendations on clinical investigation and management of such cases.

Declaration of interests

None of these authors or members of the guideline development group have declared any competing interests that may affect the independence of the views expressed in these guidelines.

Publication date

The publication date of this guide is July 2011.

Audience

This guideline is aimed at primary care teams, emergency medicine departments, departments of paediatric medicine and paediatric nephrology and public health and health protection practitioners.

Aims & objectives

1. To provide primary care clinicians with an understanding of the need to seek urgent specialist advice whenever a child is reported to have had a single acute episode of bloody diarrhoea
2. To provide secondary care clinicians with guidance on the assessment and management of such referrals
3. To ensure that all clinical staff are aware of the need for urgent public health action where VTEC infection is suspected.

Executive summary

Acute bloody diarrhoea in children is rare and is commonly associated with intestinal infections, especially vero cytotoxin-producing *Escherichia coli* (VTEC) and *Campylobacter* species.

Urgent advice should be sought from a paediatric specialist whenever a child up to the age of 16 years of age presents at primary care, or an emergency department, having suffered a single acute episode of bloody diarrhoea. This is to ensure that a prompt diagnosis is made, including consideration of infection by VTEC, and other serious treatable disorders. Prompt management, including good infection control procedures, will help to ensure that the risk of further spread of disease is minimised if VTEC is present.

Clinicians should have a high index of suspicion that VTEC infection is present where the patient has been in recent close contact with:

- ruminant animals (principally cattle, goats, sheep), their faeces, and faecally contaminated environments (such as at open farm visits)
- where there has been contact with another known or suspected case of VTEC
- where an outbreak of VTEC infection is known, or suspected, to be present locally

Where VTEC infection is considered in the differential diagnosis, clinicians should be mindful of the potential contraindications concerning the use of anti-motility drugs and certain analgesics. Active fluid resuscitation should be used and specialist guidance sought before initiating antibiotic treatment.

In England the Health Protection (Notification) Regulations 2010 require clinicians to report cases of haemolytic uraemic syndrome (HUS) or infectious bloody diarrhoea to the proper officer of the local authority; these regulations also require all diagnostic laboratories to notify the HPA of any finding of vero cytotoxin-producing *Escherichia coli* (VTEC) (including *E.coli* O157) in a human sample. Similar requirements exist for Scotland, Wales and Northern Ireland.

The NICE guidance 'Diarrhoea and vomiting: diagnosis, assessment and management in children younger than 5 years', is an especially important document that provides evidence based guidance on the management of diarrhoea and vomiting in young children, including diagnosis, fluid management, and nutritional management².

Epidemiology

Diarrhoeal illnesses

Diarrhoeal illnesses in childhood are relatively commonplace, the most frequent causes being infectious gastro-intestinal diseases. A fuller list of differential diagnoses of bloody diarrhoea in children is given at **Appendix 1**.

Of the infectious agents isolated from children in England with enteric infections in 2009, rotavirus was found most commonly (56%), followed by *Campylobacter* (28%), *Salmonella* (11%), norovirus (3%), *Shigella* (1%), and VTEC *Escherichia coli* (1%).

Bloody diarrhoea in children, when due to acute enteric infection, is usually caused by either *Campylobacter species* (mainly *C. jejuni*), where bloody diarrhoea may be present in up to 29% of cases³, and VTEC infections where bloody diarrhoea may be present in up to 90% of cases.⁴

Therefore, although VTEC is a rare cause of enteric illness, the probability of a case of bloody diarrhoea having VTEC infection is much higher than in non-bloody diarrhoea and must be considered as an important indicator that VTEC infection may be present.

VTEC

The annual number of cases of VTEC infections reported in children in England was in the range 780 - 970 cases per year in the period 2005 - 2009. Seasonal variation in the identification of VTEC O157 infections in England and Wales has been reported since 1989, with a significant peak in the number of case occurring during the late spring, summer and autumn being observed*.

The incubation period for diarrhoeal illness caused by infection with VTEC is usually three to four days, but has been occasionally recorded as up to 14 days.

* Derived from data published by the HPA on laboratory isolations in children aged up to 16 years of age.
<http://www.hpa.org.uk>

HUS

Approximately 15% of cases of VTEC infection will develop Haemolytic Uraemic Syndrome (HUS)⁵. The development of HUS may occur up to two weeks after the initial onset of symptoms⁶, and may develop after apparent recovery from the initial acute illness.

In most cases of HUS, renal function recovers although long-term renal and/or extra-renal sequelae such as hypertension and renal insufficiency can develop.⁷

In the UK and Ireland, the two British Paediatric Surveillance Unit prospective surveys (1985-1988⁸ and 1997-2001⁹) of HUS in children under 16 years reported a strong association in the incidence of HUS and age, with children under five years of age being most commonly affected. The mortality rate of HUS in the first of these surveys was reported to be 5.6%. This decreased to 1.8% in the second survey.

Definition of acute bloody diarrhoea

It is recommended, for the purposes of assessing acute illness in children that the definition of acute bloody diarrhoea is: **A sudden onset of diarrhoea (passing of liquid or watery stools) where frank blood is present.**

Where the symptoms are acute and frank blood is present a history of multiple episodes of passing blood stained liquid stool is not required and referral should be made on the evidence of a single episode.

Primary care management of acute bloody diarrhoea in children

Primary care practitioners are recommended to always seek urgent specialist advice whenever a child is reported to have had a single acute episode of bloody diarrhoea. Referral is an emergency where significant dehydration, acute abdominal pain, or signs and symptoms indicating a differential diagnosis that includes the possible need for surgical intervention, are present.

Primary care practitioners should have a high index of suspicion of VTEC infection in a child who has recently (within 21 days) visited an open farm, where there has been contact with another known or suspected case of VTEC, or who is living in an area where a suspected or confirmed outbreak of VTEC infection exists.

Do not treat with antibiotics, non-steroidal anti inflammatory drugs, narcotic analgesics or anti-motility drugs before referral.

Infectious bloody diarrhoea must be reported promptly, preferably by telephone, to the local Health Protection Unit HPU.

Secondary care management of acute bloody diarrhoea

Diagnosis of VTEC

VTEC infection should always be suspected where acute bloody diarrhoea is present, and will often be accompanied by abdominal pain, fever, pallor, petechiae and oliguria, which are markers of more severe disease.

Whenever a request is received from a primary care practitioner, or from an emergency department clinician, for specialist advice concerning a child with acute bloody diarrhoea, the child should be assessed urgently in a secondary care setting by a paediatric specialist.

Definitive diagnosis of VTEC infection is dependent upon microbiological isolation and characterisation of the causative organism or the demonstration of antibodies to O157 lipopolysaccharide (O157 LPS antibodies). UK NHS and public health laboratories routinely test faecal specimens from all cases of acute diarrhoeal illnesses for the presence of VTEC using a national standard method.¹⁰ However, it is helpful to ensure that the laboratory request clearly contains the information that the patient is suffering from bloody diarrhoea and that VTEC is in the differential diagnosis. All isolates of potential VTEC are sent to the national reference laboratory for confirmation.

Initial microbiological identification of a suspected VTEC will take 24-48 hours and reference laboratory confirmation a further 48-72 hours. Therefore, the appropriate clinical and public health management of potential VTEC disease should not be delayed whilst awaiting confirmatory microbiological results.

Where the initial laboratory investigations have not isolated a potential VTEC, and yet there is strong clinical suspicion of VTEC infection, the managing clinician must discuss this with the consultant microbiologist to ensure that further investigations are performed by the appropriate reference laboratory to detect atypical or unusual VTEC strains. This would usually involve PCR detection of verocytotoxin genes and other virulence markers. Serum for specific antibodies may also be sent at least 10 days after onset. The microbiologist should liaise with the reference laboratory in order to optimise the range of investigations performed in each case.

Diagnosis of HUS

HUS comprises microangiopathic haemolytic anaemia, thrombocytopenia and acute renal failure. Early clinical signs may not be specific and it is recommended that the assessment of all cases of bloody diarrhoea should include the following investigations in order to identify the possible onset of HUS:

Blood	Faeces	Urine	Clinical
Full blood count and film	Culture	Microscopy	Temperature
Urea & electrolytes	(please ensure that the request form is marked with bloody diarrhoea as a clinical detail if present)	Near patient (dipstick) testing for Haematuria and Proteinuria	Pulse
Liver function tests			Respiratory rate
Lactate dehydrogenase			Blood pressure
C-Reactive protein			Weight
Clotting screen			Assessment of hydration

The following observations may be helpful in the interpretation of these investigations†:

Investigation	Indication of VTEC/HUS	Comment
Full blood count including blood film for fragmented RBCs	Raised White Blood Cells (WBC) also beware: Features of microangiopathic haemolysis such as: <ul style="list-style-type: none"> • Falling haemoglobin • Fragmented RBCs on blood film examination • Low/falling platelet count 	Raised WBC and falling platelets are early indicators of development of HUS ^{6 11} If VTEC is confirmed, a high WBC is a marker of severity and is associated with increased likelihood of HUS (89% sensitivity, 99.5% specificity ¹¹)
Urea and electrolytes	Rising urea and creatinine	A rise in urea and creatinine may be secondary to dehydration but if associated with haemolysis and thrombocytopenia indicates onset of HUS
Biochemistry	High Lactate Dehydrogenase (LDH)	High LDH is an early indicator of development of HUS
Urinalysis	Haematuria/proteinuria on urinalysis	Haematuria/proteinuria appear early in the evolution of HUS
Clotting screen	Abnormal result	Reduced, rather than prolonged values, may be seen during active HUS disease

These investigations should be repeated if, and when any clinical deterioration occurs, noting that HUS usually arises within 14 days after the onset of diarrhoea due to VTEC infection^{12 13}. The mean period reported in the UK is 6-8 days although this interval may be more prolonged⁹. Where VTEC infection is established vigilance for the onset of HUS should, therefore, be maintained for at least two weeks following the date that diarrhoea first occurred.

Infectious bloody diarrhoea, HUS, or the isolation of a VTEC must be reported promptly by telephone to the local Health Protection Unit.

† Adapted, with permission, from the guideline ‘management of acute bloody diarrhoea and known/potential VTEC cases’ from Lanarkshire by Adrian Sie, Andrew Todd & Josephine Pravinkumar

Treatment of VTEC

There is evidence that the best outcome of treatment of VTEC infection may be achieved by:

- Early fluid resuscitation.
- Withholding of opiate analgesia.
- Withholding of anti-motility agents.
- Withholding of non steroidal anti-inflammatory drugs (NSAIDs).
- Caution in the use of antibiotics.

Intravenous volume expansion has been associated with nephroprotection in VTEC infections.^{14‡} An association with the risk of developing HUS or neurological complications of VTEC infection have been reported with the use of anti-motility agents and opioid analgesics.^{5 6 15} NSAIDs may have adverse effects on renal blood flow.¹⁶

The NICE clinical guideline 'Diarrhoea and vomiting: diagnosis, assessment and management in children younger than 5 years' found some evidence that antibiotic treatment might have been a risk factor for HUS, although this finding was not consistent between studies. They concluded '... [that] there was insufficient evidence to recommend antibiotic treatment for VTEC infection...'². This view is supported by other clinical reports, trials and meta-analyses at all ages,^{17 18} whilst other reports have suggested that antibiotics are contraindicated.^{19 20} The use of antibiotics should, therefore, be governed by good paediatric practice as indicated by needs other than the suspicion of enteric VTEC infection.

NICE guidance also states that 'Children with VTEC infection are at risk of developing HUS. These children should be monitored for the development of microangiopathic haemolytic anaemia, thrombocytopenia and renal insufficiency. This should be done in consultation with an appropriate specialist'.² Access to renal replacement therapy thus needs to be considered and reviewed regularly as renal failure is a foreseeable complication in up to 15% of cases of symptomatic VTEC infection.

‡ In this study 2 patients suffered complications potentially linked to fluid resuscitation and it is recommended that careful peri- and post infusion monitoring is performed.

Advice to parents and carers

When to seek help

Parents and carers should be advised to seek immediate medical advice whenever a child passes liquid or watery stools where frank blood is present.

Whilst awaiting medical assessment parents and carers should be advised to ensure that the child continues to drink suitable fluids. The NICE guidance on the management of D&V in children under five years on the primary prevention of dehydration in children with gastroenteritis but without clinical dehydration recommends²:

- To continue breastfeeding and other milk feeds.
- Encourage fluid intake.
- Discourage the drinking of fruit juices and carbonated drinks, especially in those at increased risk of dehydration.
- Offer oral rehydration salt (ORS) solution as supplemental fluid to those at increased risk of dehydration.

Caring for household contacts of cases of VTEC infection

Secondary infection can occur in household type settings. Any cases of diarrhoea arising in close contacts of a diagnosed, or suspected case, of VTEC infection must be investigated promptly.

Advice should be given that good personal hygiene must be maintained by all children and adults in any household where one or more cases of VTEC infection are diagnosed or suspected.

There are no observational or randomised trial data that provide evidence on the effectiveness of antibiotic prophylaxis for household contacts, or members of a group who have had common exposure to a suspected source of VTEC infection. The use of prophylactic antibiotics is therefore not recommended.

Exclusion from schools and other social settings

Any child aged five years or younger who has been diagnosed with a VTEC infection should not go to a school, pre-school group, nursery or other child care or minding group until well, and tests arranged in association with the local health protection team have shown them to no longer be infectious (two negative faecal specimens taken not less than 24 hours apart, the first to be taken not earlier than 24 hours after symptoms have ceased).

Older children should not go to school and other social settings until they are well and 48 hours have elapsed after passing their first normal stool. In children older than five years who are not able to maintain good personal hygiene, the local Health Protection Service should be consulted on the need to undertake microbiological testing to ensure that they are free from infection before returning to school.

Detailed guidance on exclusion from schools and workplaces in England, and criteria for returning, are given in the HPA VTEC Operational Manual.²¹

Public health management of VTEC

Public health practitioners in England should be guided in their management of cases and incidents of VTEC infection by reference to the HPA's VTEC Manual.²¹ The principal elements of protection of public health are:

- Prevention of occurrence of outbreaks of disease by ensuring that good hygiene and health and safety practices are observed in settings where VTEC may be present.
- Prompt notification of cases of haemolytic uraemic syndrome (HUS) or infectious bloody diarrhoea and laboratory isolates of vero cytotoxin-producing *Escherichia coli* (VTEC).
- Identification and isolation of the source of infection.
- Prevention of person to person spread, especially in the family setting, and between children with poor hygiene.
- Ensuring that during outbreaks, there is good awareness by parents and carers about the need to seek early clinical advice.

Health Protection Units should ensure that clinical colleagues are informed of the possibility that an outbreak of VTEC is occurring in their locality in order to ensure:

- Early referral of possible cases for specialist review and care.
- Prompt reporting of further cases of infectious bloody diarrhoea, HUS, or the isolation of a VTEC.

Appendix 1: Causes of bloody diarrhoea (real or apparent in infants and children)

Infants aged ≤1 year		Children aged >1 year	
Common causes	Less common / rare causes	Common causes	Less common / rare causes
Intestinal infection Infant colitis: <ul style="list-style-type: none"> • Non-specific colitis • Breast milk colitis • Cow's milk colitis 	Intestinal ischaemia <ul style="list-style-type: none"> • Intussusception • Malrotation and volvulus Necrotising enterocolitis Hirschsprung's disease Inflammatory bowel disease: <ul style="list-style-type: none"> • Crohn's colitis • Ulcerative colitis Systemic vasculitis Factitious illness	Intestinal infection Inflammatory bowel disease <ul style="list-style-type: none"> • Crohn's colitis • Ulcerative colitis Juvenile polyp	Intestinal ischaemia <ul style="list-style-type: none"> • Intussusception • Malrotation and volvulus Mucosal prolapse syndrome Henoch-Schönlein purpura or other forms of systemic Vasculitis Factitious illness

Reproduced, with permission, from Management of bloody diarrhoea in children in primary care by M Stephen Murphy³

Appendix 2: Methodology

Systematic methods were used to search for evidence. All current extant UK guidelines were identified and reviewed, and a systematic search of the peer reviewed literature to elaborate the current known epidemiology of bloody diarrhoea, the consequent incidence of HUS, clinical outcomes and effectiveness of interventions.

The NICE guidance on diarrhoea and vomiting in children under five was also referenced and the guideline checked for consistency against this document.

Searches were run on the Medline database (January 1966 to January 2011) and the Embase database (January 1980 to April 2011). English language articles were preferred, but articles in other languages were considered where extant translations were available.

All papers identified at the abstract stage for possible inclusion were obtained. Full copies of the studies that met the inclusion criteria were critically appraised to determine whether they were of sufficient quality to inform the evidence review.

A discussion paper was developed by the chair of the development group based around the review of literature. This was developed into a clinical guideline during the course of two teleconference meetings and a subsequent round of email revisions undertaken by the whole development group.

The guideline development group included experts in:

- Public health.
- Hospital based microbiology.
- Public health laboratory microbiology.
- Paediatrics.
- Paediatric nephrology.
- Gastro-intestinal diseases epidemiology.
- Infectious diseases.

The document was examined against the AGREE-II criteria (available at www.agreetrust.org).

The guideline writing committee was selected to ensure an appropriate representation of external experts and included representation from:

- The RCPCH, including the following special interest sub-groups:
 - British Paediatric Allergy, Immunology and Infectious Diseases Group
 - Paediatric Microbiology Committee
- The RCGP.
- The HPA.
- British Association for Paediatric Nephrology.

Details of the search criteria used, and commentary on the AGREE-II compliance used are available in an extended methodology document.

Appendix 3: Guideline development group

The following group have, at various stages of the development of this guideline, kindly contributed their time and expertise to its development and review:

Dr Maureen Baker, General Practitioner, Royal College of General Practitioners, London.

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Dr David Shortland, Consultant Paediatrician, Poole NHS Trust, Dorset and Vice President (Health Services) RCPCH.

*Dr Adrian Sie**, Consultant Paediatrician, Wishaw General Hospital, Lanarkshire, Scotland.

Dr John Simpson, Deputy Director, Emergency Response, HPA, Porton Down, Salisbury.

Dr Gail Thomson, Consultant in Infectious Diseases, HPA, Porton Down, Salisbury.

Members of the group also represented the following RCPCH special interest groups:

*RCPCH special interest group British Paediatric Allergy, Immunology and Infection Group (BPAIIG)

**British Association for Paediatric Nephrology Clinical Standards & Guidelines Committee

***RCPCH paediatric Microbiology Committee

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