Monitoring patients in the community with suspected 
*Escherichia coli* O157 infection during a large outbreak in Scotland in 1996

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SUMMARY

During outbreaks of *Escherichia coli* O157 a minority of patients with suspected infection develop haemolytic uraemic syndrome (HUS). The ability to identify this subgroup at an early stage is beneficial as mortality from HUS is high and may be influenced by intervention.

During the 1996 Central Scotland *E. coli* O157 outbreak, of 886 patients from the community with suspected infection monitored at an outbreak clinic, nine developed HUS. We assessed factors associated with the development of HUS in this group. Children and the elderly were at increased risk of HUS. However, high white cell count was as least as good a predictor of HUS as age. High white cell counts predicted development of HUS with a sensitivity of 89%, specificity of 87%, positive predictive value of 7% and a negative predictive value of over 99%. We have used the results from this study along with other currently available evidence to propose a monitoring protocol for patients from the community with suspected *E. coli* O157 infection.

INTRODUCTION

Since *Escherichia coli* O157 (*E. coli* O157) was first recognized as a cause of gastroenteritis in 1982 [1] it has become increasingly identified as a significant threat to the public health. Of patients with symptomatic infection approximately half have non-bloody diarrhoea whereas the remainder develop haemorrhagic colitis [2]. An estimated 2–7% of patients with symptomatic infection develop the life-threatening renal complication, haemolytic uraemic syndrome (HUS), or neurological complications, previously referred to as thrombotic thrombocytopenic purpura (TTP) [3]. HUS and TTP are different clinical manifestations of the same pathological microvascular process, due to systemic absorption of the Shiga toxin produced by *E. coli* O157 [4, 5], and are now uniformly referred to as HUS in the context of this infection.

Scotland has one of the highest incidences of reported *E. coli* O157 infection in the world [6]. Whilst most reported cases are sporadic [7] outbreaks continue to occur. In 1996 the largest outbreak to date in the United Kingdom occurred in central Scotland [8]. The outbreak involved 512 cases (337 confirmed or probable cases), of whom 34 developed HUS and 22 died (17 deaths were considered to be directly attributable to *E. coli* infection at the Fatal Accident Enquiry that followed the outbreak).

Early in the course of the outbreak the source of infection was traced to a butcher’s shop in Wishaw, a town in Central Scotland with a population of approximately 50000. The majority of cases lived in Wishaw and the surrounding area and understandably there was a great deal of public anxiety about the
outbreak within the town. To ease pressure placed on local primary- and secondary-care services a special community outbreak clinic was established in the local health centre. The clinic aimed to support the public health investigation, facilitate the provision of consistent public health advice to minimize secondary spread of the infection, and co-ordinate the care of cases.

The outbreak clinic was principally used to monitor patients from the local community with clinically suspected *E. coli* O157 infection. A patient with onset of diarrhoeal illness since the start of the outbreak was defined as having suspected infection and these patients could be referred to the clinic by their GPs. In addition the clinic was also used by patients required to submit samples for work exclusion purposes, and to follow up after discharge a number of known cases who were admitted to hospital early in the course of the outbreak.

A protocol to guide the management of patients with suspected *E. coli* O157 infection was drawn up at the start of the outbreak and was used consistently at the clinic. The protocol specifically aimed to confirm that patients fulfilled the case definition, ensure early diagnosis of HUS, and facilitate prompt and appropriate referral of patients requiring secondary care.

Stool microbiology and paired serology were performed to establish whether patients fulfilled the case definition (Table 1). Stool culture on Sorbital McConkey agar was performed locally, but other tests such as stool Immunomagnetic Separation, and serology were carried out at the Scottish *E. coli* O157 reference laboratory in Aberdeen. Due to delays in receiving final results from the reference laboratory, at the time patients were attending the clinic, whether they fulfilled the case definition was often still unknown.

To monitor for HUS, all patients with suspected infection had their haemoglobin, white cell count (WCC), platelets, blood film, lactate dehydrogenase level (LDH), and serum urea and creatinine checked every 2 days for 14 days. Standard criteria were developed to guide referral to secondary care. Referral was recommended for patients with severe clinical manifestations of infection (such as dehydration requiring parenteral fluid management) and patients whose laboratory findings indicated the imminent development of HUS (such as a rising LDH level of falling platelets) [8].

Previous studies have identified risk factors for HUS in patients with known *E. coli* O157 infection. Young children and the elderly have consistently been found to be more likely to develop HUS than young adults [2, 3, 9]. Studies involving children have suggested that a raised WCC early in the course of illness is also associated with an increased risk of HUS [10–12]. A high WCC has also been consistently shown to be an adverse prognostic indicator in hospitalized children with HUS secondary to *E. coli* O157 infection [13–15]. WCC in adults with *E. coli* O157 has never been assessed.

Gender, the presence of haemorrhagic colitis or fever, or the use of antimotility agents have been inconsistently associated with higher risk of HUS [2, 3, 11]. Retrospective analysis of all hospitalized cases from the Central Scotland outbreak suggested that patients taking antacids were at increased risk of HUS [16]. There is a lack of agreement regarding the role of antibiotics in HUS [17, 18] and it now seems that antibiotics of specific classes will have harmful and beneficial effects.

### Table 1. Case definition status of the 245 cases monitored at the community clinic

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Stool specimen positive*</th>
<th>Stool specimen negative†</th>
<th>Serology positive‡</th>
<th>Serology negative†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic or no history</td>
<td>Confirmed (19)</td>
<td>Possible (23)</td>
<td>Not a case</td>
<td></td>
</tr>
<tr>
<td>Non-bloody diarrhoea only</td>
<td>Confirmed (51)</td>
<td>Possible (15)</td>
<td>Not a case</td>
<td></td>
</tr>
<tr>
<td>Bloody diarrhoea and/or HUS</td>
<td>Confirmed (72)</td>
<td>Probable (28)</td>
<td>Possible (37)</td>
<td></td>
</tr>
</tbody>
</table>

* For the outbreak strain (*E. coli* O157:H7, phage type 2, verocytotoxin type 2 producing, DNA profile by pulse-field gel electrophoresis characteristic of the outbreak strain) either by primary culture or immunomagnetic separation.
† Or not done.
‡ Or post-mortem evidence of infection with the outbreak strain.
All the data relating to the patients monitored at the Wishaw clinic during the central Scotland outbreak have been validated and linked by the Information and Statistics Division of the NHS in Scotland [19]. The data include patients’ demographic features, limited clinical information such as the presence or absence of bloody diarrhoea, and all microbiological, biochemical, and haematological results. The data provide a unique opportunity to examine the features associated with the subsequent development of HUS in patients from a wide age range with suspected \textit{E. coli} O157 infection.

We examined the ability of age and patients’ WCC to predict the development of HUS in suspected infection. We have not examined other clinical features in detail. A separate analysis of all cases hospitalized during the central Scotland outbreak has shown no other significant association between these clinical features and subsequent development of HUS [16].

SUBJECTS AND METHODS

Patients with suspected \textit{E. coli} O157 infection (but not with established HUS) who were referred from primary care to the Wishaw clinic for monitoring were included in the study.

The case definitions employed during the outbreak and the number of cases meeting each definition are shown in Table 1. For this study a case was defined as any patient meeting the confirmed, probable, or possible case definitions.

During the outbreak and for the purposes of this study HUS was defined as follows:

(i) red cell fragmentation on blood film, and lactate dehydrogenase > 1.5 times the upper limit of normal;

(ii) thromocytopenia (platelets < 150 \times 10^9/1);

(iii) acute renal impairment (urea and creatinine above the normal range and rising) and/or new neurological signs.

The day on which all three criteria were met was deemed the day of onset of HUS.

The socio-economic status of patients was assessed by converting postcodes of residence into deprivation categories using the Carstairs and Morris index [20]. Deprivation categories are ranked 1–7, with 7 representing the most deprivation.

We first assessed the association in patients with suspected infection between age, gender, and presence of bloody diarrhoea, and subsequent development of HUS. We next mapped the clinical course of the patients who developed HUS in detail to identify which laboratory parameters became abnormal first. We then specifically assessed how well the WCC predicted the development of HUS in patients with suspected \textit{E. coli} O157 infection.

The sensitivity, specificity, and predictive values for a patient having one or more abnormally high WCC prior to the onset of HUS were calculated. An abnormally high result was defined as one above the age appropriate reference range specified by the local laboratory (reference ranges available on request). The exact method for calculating a confidence interval for a single sample proportion was used to calculate 95% confidence intervals for all results [21]. The analysis was repeated using neutrophil count rather than total WCC. Finally we assessed how well age and WCC considered together identified patients at highest risk of developing HUS.

RESULTS

In total 1198 people presented to the Wishaw clinic. Of these 229 did not meet the clinic’s criteria for

![Fig. 1. Community clinic patients eligible for inclusion in the study.](https://doi.org/10.1017/S0950268801006136)

![Fig. 2. The age and gender distribution of patients monitored at the community clinic.](https://www.cambridge.org/core/terms)
Table 2. The proportion of patients (cases) monitored at the community clinic that developed HUS; by presence of bloody diarrhoea

<table>
<thead>
<tr>
<th>Bloody diarrhoea</th>
<th>Number of patients (cases) monitored at the clinic</th>
<th>Number that developed HUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>133 (133)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Absent</td>
<td>753 (112)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Total</td>
<td>886 (245)</td>
<td>9 (9)</td>
</tr>
</tbody>
</table>

Fisher’s exact test for all patients, $P < 0.001$.
Fisher’s exact test for cases, $P = 0.514$.

assessment. A further 36 people had no blood samples taken. This group includes people required to submit microbiological samples only for possible work exclusion purposes. Therefore, 933 people underwent blood test monitoring according to the clinic protocol. Of the 933 patients 39 were referred from hospital for post discharge follow up. For seven patients it was unknown whether they were referred from primary or secondary care. The remainder were known to be referred from primary care. One person referred from primary care had established HUS at the time of referral so no information could be obtained on the features predating the development of HUS. Overall 886 patients were eligible for inclusion (Fig. 1).

This group is representative of patients presenting to primary care with suspected *E. coli* O157 infection during a community based outbreak. Of the 886 patients monitored, 245 were cases, of which 170 (69%) had confirmed or probable infection (Table 1). Twenty-seven of the cases were admitted to hospital, 9 developed HUS, and 2 died.

The age and sex distribution is shown in Figure 2. Of the patients monitored 89% were resident in areas assigned deprivation category 5 or 6. This reflects the fact that Wishaw and its surroundings is a relatively deprived area of Scotland.

Men (3/346) and women (6/540) monitored at the clinic were equally likely to develop HUS (Fisher’s exact test $P = 1.0$). Children < 15 years and adults > 64 years (7/298) however were significantly more likely than adults aged 15–64 years (2/588) to develop HUS (Fisher’s exact test $P = 0.008$).

The presence of bloody diarrhoea was significantly associated with development of HUS in all clinic attendees. However, bloody diarrhoea was not found to be significantly associated in the subset of persons fulfilling the case definition (Table 2). Three of the nine cases that developed complications progressed straight from non-bloody diarrhoea to HUS without having haemorrhagic colitis.

In terms of assessing the ability of laboratory parameters to predict HUS, we initially examined in detail the clinical course of the nine patients that developed complications (Table 3). The median interval between onset of symptoms and onset of HUS was 9 days (range 5–15). In general an elevated WCC preceded the development of HUS and also preceded changes in urea, creatinine, LDH, haemoglobin, and platelet levels, and the appearance of fragmented red cells (Table 4).

Eight of the nine patients with HUS had a high WCC at some point during their illness. In all eight the WCC became abnormal before the onset of HUS, a median of 1.5 days after the onset of symptoms, and 5 days (range 1–8) before the onset of HUS. In 7 of the 8 patients (the exception was a patient who did not develop a raised WCC until 14 days after the onset of symptoms) the WCC was abnormal on the first blood sample, obtained when the patients presented. These findings are compatible with results from the hospitalized cases, in whom the WCC on day two of illness was significantly higher in cases who developed HUS, preceding changes in other laboratory markers by several days [16].

The presence of one or more high WCC results predicted the subsequent development of HUS in all clinic attendees, with a sensitivity of 89%, specificity of 87%, positive predictive value of 7%, and negative predictive value of over 99% (Table 5). A high WCC similarly predicted the subsequent development of HUS in the cases, monitored at the clinic (Table 5).

As it is specifically neutrophils that are implicated in the pathophysiology of complicated *E. coli* O157 infection [22, 23], we also assessed how well the neutrophil count predicted the development of HUS. We found that the neutrophil count was not significantly better than the total WCC in predicting HUS.

Finally, as age group and WCC are the features most strongly associated with the subsequent development of HUS, we assessed the predictive value of
Table 3. Demographic and clinical details of the nine cases that developed HUS*

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age</th>
<th>Sex</th>
<th>Blood in stool</th>
<th>Case definition</th>
<th>Clinic</th>
<th>HUS</th>
<th>WCC</th>
<th>Hb</th>
<th>Fragmented red cells</th>
<th>LDH</th>
<th>Platelets</th>
<th>Urea</th>
<th>Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>F</td>
<td>Yes</td>
<td>Confirmed</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>M</td>
<td>Yes</td>
<td>Confirmed</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>N</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>F</td>
<td>Yes</td>
<td>Confirmed</td>
<td>3</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>3</td>
<td>N</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>M</td>
<td>No</td>
<td>Confirmed</td>
<td>2</td>
<td>7</td>
<td>2</td>
<td>N</td>
<td>7</td>
<td>4</td>
<td>7</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>F</td>
<td>Yes</td>
<td>Confirmed</td>
<td>1</td>
<td>9</td>
<td>1</td>
<td>N</td>
<td>7</td>
<td>1</td>
<td>9</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
<td>F</td>
<td>No</td>
<td>Confirmed</td>
<td>4</td>
<td>11</td>
<td>4</td>
<td>11</td>
<td>8</td>
<td>8</td>
<td>11</td>
<td>8</td>
<td>N</td>
</tr>
<tr>
<td>7</td>
<td>78</td>
<td>F</td>
<td>Yes</td>
<td>Probable</td>
<td>5</td>
<td>11</td>
<td>5</td>
<td>8</td>
<td>8</td>
<td>5</td>
<td>10</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>61</td>
<td>F</td>
<td>Yes</td>
<td>Confirmed</td>
<td>6</td>
<td>12</td>
<td>N</td>
<td>12</td>
<td>12</td>
<td>10</td>
<td>6</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>M</td>
<td>No</td>
<td>Confirmed</td>
<td>2</td>
<td>15</td>
<td>14</td>
<td>6</td>
<td>15</td>
<td>10</td>
<td>15</td>
<td>15</td>
<td>2</td>
</tr>
</tbody>
</table>

* Clinic, day of first attendance at clinic; HUS, day of onset HUS: All blood results, day of first recorded abnormal result (high or low as appropriate); Note all results are based on the day of onset of symptoms being day 0. N, indicates that no abnormal result for that blood parameter was recorded for that patient at any point during their illness (either before or after the onset of HUS).

Table 4. Median interval between onset of symptoms and first abnormal result in cases with HUS

<table>
<thead>
<tr>
<th>Blood parameter</th>
<th>Number of patients with an abnormal result recorded at some point during the course of their illness</th>
<th>Median interval between onset of symptoms and first recorded abnormal result (days)</th>
<th>Range (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WCC</td>
<td>8/9</td>
<td>1.5</td>
<td>0–14</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>8/9</td>
<td>7</td>
<td>1–12*</td>
</tr>
<tr>
<td>Fragmented red cells</td>
<td>9/9</td>
<td>7</td>
<td>3–15</td>
</tr>
<tr>
<td>LDH</td>
<td>9/9</td>
<td>4</td>
<td>1–10</td>
</tr>
<tr>
<td>Platelets</td>
<td>9/9</td>
<td>7</td>
<td>5–15</td>
</tr>
<tr>
<td>Urea</td>
<td>9/9</td>
<td>7</td>
<td>1–15</td>
</tr>
<tr>
<td>Creatinine</td>
<td>6/9</td>
<td>2</td>
<td>1–10</td>
</tr>
</tbody>
</table>

Day 0 is day of onset of symptoms.

* Note that 1 of the 8 patients who developed anaemia only did so after the onset of their HUS.

Table 5. The validity of a high white count result in predicting subsequent development of HUS in all patients (cases) monitored at the community clinic

<table>
<thead>
<tr>
<th>High white count</th>
<th>HUS</th>
<th>No HUS</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>8 (8)</td>
<td>113 (49)</td>
<td>121 (57)</td>
</tr>
<tr>
<td>Absent</td>
<td>1 (1)</td>
<td>764 (187)</td>
<td>765 (188)</td>
</tr>
<tr>
<td>Total</td>
<td>9 (9)</td>
<td>877 (236)</td>
<td>886 (245)</td>
</tr>
</tbody>
</table>

Summary of results for all patients
- Sensitivity: 88.9% (51.8–99.7%)
- Specificity: 87.1% (84.9–89.3%)
- Positive predictive value: 66.6% (2.9–126.6%)
- Negative predictive value: 99.9% (99.3–100.0%)

Summary of results for cases
- Sensitivity: 88.9% (51.8–99.7%)
- Specificity: 79.2% (74.1–84.4%)
- Positive predictive value: 140.0% (63–258.8%)
- Negative predictive value: 99.5% (97.1–100.0%)

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age group and WCC combined. The positive predictive value of age ( < 15 or > 64) alone was 7/298 (2.3%, 95% CI 0.9–4.8%); that of WCC alone was 8/121 (6.6%, 2.9–12.6%); and that of age and WCC combined was 7/50 (14%, 5.8–26.7%).

DISCUSSION

This study is unique in assessing features associated with the development of HUS in a large number of patients, from a wide age range, with suspected E. coli O157 infection monitored in a community setting during a large-scale outbreak.

We found that children and the elderly with suspected infection are at higher risk of developing HUS than young adults. This agrees with previous work involving patients with known E. coli O157 infection [2, 3, 9]. We found that bloody diarrhoea is not a good predictor of HUS and this too is in agreement with previously published work [24].

Significantly, this study also demonstrates the importance of a raised WCC as a predictor of HUS, in patients of all ages with suspected as well as confirmed E. coli O157 infection. Raised WCC is possibly a better predictor of HUS than age. Patients with normal WCC are at very low risk of HUS.

Additionally, development of a high WCC precedes changes in other laboratory parameters in HUS. This finding is in keeping with the fact that neutrophils carry Shiga toxin and therefore are likely to be pivotal to the pathogenesis of HUS [23]. Our findings thus confirm the value of laboratory monitoring in patients with suspected E. coli O157.

The clinic was invaluable in alleviating pressure on local services, and ensuring that patients received consistent information and were monitored and referred on to secondary care in a consistent way. In addition, it facilitated comprehensive data collection. We would recommend the establishment of a similar clinic during any large community-based outbreak.

The protocol used at the clinic required very comprehensive monitoring of all patients with suspected infection, including patients that we could now identify as being at very low risk of developing HUS. We would therefore, in future, recommend the following streamlined monitoring protocol for patients in the community with suspected E. coli O157 infection, targeting those at extremes of age who present with high WCC:

(i) All patients should have a stool culture performed.
(ii) All patients aged < 15 or > 64 years, and adults aged 15–64 years with low gastric acid levels, or who clinically appear systemically unwell, should have their full blood count and film, LDH, and serum urea and creatinine checked at presentation. This will identify patients with a raised WCC (indicating increased risk of HUS) and those with established HUS.
(iii) Patients with a raised WCC or other significant abnormality such as evidence of haemolysis should be clinically reviewed and have all blood tests repeated every 2 days until 14 days after the onset of symptoms, unless all abnormalities clearly resolve during that time.
(iv) Patients should be referred to secondary care if laboratory parameters indicative of HUS are clearly deteriorating.

Neither this nor any other monitoring protocol will identify all patients who develop HUS. Hence it is essential that in addition all patients with suspected E. coli O157 infection are fully informed of potential complications and are cautioned to represent for monitoring if their clinical condition deteriorates within the 14 days following the onset of their symptoms, since the early clinical features of HUS are non-specific.

Whilst we believe that these recommendations are based on current best evidence we recognize that the situation may develop in the future. For example, during an extremely large E. coli O157 outbreak in Japan in 1996, retrospective analysis found an elevated C reactive protein (CRP) to be predictive of the development of HUS in children [25]. CRP may therefore prove to be a useful additional monitoring tool for the management of future outbreaks, and its potential role should be evaluated further. Unfortunately, however, laboratory methods for the measurement of CRP are not currently standardized throughout the United Kingdom.

Another analysis of the same Japanese outbreak found patients who developed HUS had high circulating levels of thrombomodulin and endothelin compounds released by activated or damaged endothelial cells [26].

Early diagnosis allows patients to receive early supportive therapy such as dialysis, and potentially beneficial therapy such as plasma exchange [27]. Other specific therapies are currently under development, such as an oral verotoxin-binding agent now under-
going phase III clinical trials [28]. These specific therapies offer the hope of preventing, or improving the prognosis of, HUS.

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