Nationwide study of haemolytic uraemic syndrome: clinical, microbiological, and epidemiological features

Abstract

**Aims**—To establish the incidence and aetiology of haemolytic uraemic syndrome (HUS) in Australia and compare clinical and microbial characteristics of sporadic and outbreak cases.

**Methods**—National active surveillance through the Australian Paediatric Surveillance Unit with monthly case notification from paediatricians, July 1994 to June 1998. Children under 15 years presenting with microangiopathic haemolytic anaemia, thrombocytopenia, and acute renal impairment were identified.

**Results**—Ninety-eight cases were identified (incidence 0.64 per 105 years/annum). Eighty-four were associated with diarrhoea (64 sporadic, 20 constituting an outbreak) and 14 were atypical. Shiga toxin producing *Escherichia coli* (STEC) O111:H− was the most common isolate in sporadic HUS and caused the outbreak. However O111:H+ isolates from outbreak and sporadic cases differed in phage type and subtyping by DNA electrophoresis. STEC isolates from sporadic cases included O26:H−, O113:H21, O130:H11, OR:H9, O157:H−, ONT:H7, and ONT:H+. STEC O157:H7 was not isolated from any case. Only O111:H+ isolates produced both Shiga toxins 1 and 2 and possessed genes encoding *E. coli* attaching and effacing gene ( intimin) and enterohemolysin. Outbreak cases had worse gastrointestinal and renal disease at presentation and more extrarenal complications.

**Conclusions**—Linking national surveillance with a specialised laboratory service allowed estimation of HUS incidence and provided information on its aetiology. In contrast to North America, Japan, and the British Isles, STEC O157:H7 is rare in Australia; however, non-O157:H7 STEC cause severe disease including outbreaks. Disease severity in outbreak cases may relate to yet unidentified virulence factors of the O111:H− strain isolated.

Keywords: Shiga toxin; *E. coli*; haemolytic uraemic syndrome; surveillance

Haemolytic uraemic syndrome (HUS) is characterised by microangiopathic haemolytic anaemia, thrombocytopenia, and acute renal impairment. It is usually preceded by diarrhoea, often bloody. Karmali et al first identified the association between HUS and infection with Shiga toxin producing *Escherichia coli* (STEC) O157:H7 in children, which is now well established. STEC were previously known as verotoxin producing *E. coli*. In North America and Europe most HUS is caused by STEC of serotype O157:H7 and major outbreaks have occurred following ingestion of contaminated food or drink, swimming in contaminated water, contact with farm animals, through environmental contamination, or person to person spread. While the major cause of infection in humans is STEC O157:H7, other serotypes also may cause diarrhoea and HUS. Differences in the occurrence of STEC serotypes appear to be geographic; data suggest non-O157:H7 STEC strains predominate in Australia and contribute to disease in several other countries. Although typically associated with intestinal infection, HUS may also follow urinary tract infection with STEC or systemic infection with neuraminidase producing bacteria. HUS may be familial or associated with immunodeficiency, immunosuppression, and pregnancy.

The epidemiology of HUS in the southern hemisphere is poorly described. Although diarrhoea associated HUS occurs in Australia, STEC O157:H7 has rarely been implicated. This may reflect the fact that diagnostic laboratories do not routinely test for this STEC in patients with diarrhoea or may indicate that HUS in Australia is caused by different STEC than are commonly implicated in Europe and North America. The frequency of STEC associated disease in Australia is unknown. We undertook nationwide surveillance of HUS, as a marker of STEC related disease, through the Australian Paediatric Surveillance Unit (APSU). Study aims were to determine the incidence, demographic, and clinical characteristics of HUS and to examine the aetiological role of STEC. During surveillance the first major outbreak of HUS in Australia occurred, providing a unique opportunity to compare clinical, epidemiological, and microbiological characteristics of sporadic and outbreak HUS.

**Methods**

**CASE ASCERTAINMENT, CASE DEFINITION, AND CASE CLASSIFICATION**

Cases were ascertained prospectively through the APSU by active, national surveillance between July 1994 and June 1998 inclusive.
All paediatric specialists in Australia were sent a monthly, reply paid report card and asked to indicate whether they had seen any child under 15 years of age in the previous month with any of the conditions listed on the card, including HUS. HUS was defined as “microangiopathic haemolytic anaemia (haemoglobin <100 g/l with microscopic evidence of fragmented red blood cells), thrombocytopenia (platelet count <100 000 × 10⁹),” and acute renal impairment (oliguria or anuria with increased serum urea and creatinine)”. During the study period over 900 clinicians were mailed and over 93% report cards were returned to the APSU each month. The APSU notified study investigators of reported cases of HUS each month. Investigators obtained further information on individual cases (clinical presentation, outcome, demographics, and laboratory results) from clinicians notifying cases by standardised postal questionnaire (96% of questionnaires were returned). Data provided was de-identified to maintain patient anonymity. Diarrhoea associated cases of HUS were classified as “sporadic” or “outbreak” cases. The single outbreak consisted of cases occurring in South Australia in January and February 1995 and in whom a common causative organism was subsequently confirmed. Cases with no significant gastrointestinal disease or isolation of STEC in the stool and with a family history of HUS, with an atypical or relapsing course or with confirmed systemic infection with a neuraminidase producing organism, were classified as “atypical”. The ethics committee of the Children’s Hospital at Westmead, Sydney approved the study.

**Microbiology**

Clinicians reporting cases were asked to send paired serum samples and a stool sample or rectal swab and E coli isolates from faeces or implicated food, if available, to a centralised laboratory for isolation and characterisation of STEC isolates. Colonies from stool specimens, obtained as soon as possible after the diagnosis of HUS and cultured on MacConkey agar, were tested for agglutinating antibodies to O antigens 26, 111, and 157.36 Stx1 or Stx2 was identified, of whom five had an atypical or relapsing course, four were familial, three were associated with pneumococcal infection, one was associated with immunodeficiency, and one had an STEC associated urinary tract infection.26 The median age of cases at diagnosis was 31 months (interquartile range 16–70 months) and 70/98 (71%) children were under 5 years of age. Ninety one (92%) children were hospitalised for a median (interquartile range) of 14 (7–21) days.

The reported annual incidence of HUS (with 95% CI) was 0.64 (0.52 to 0.78) per 10⁵ children under 15 years. Incidence was significantly higher in children under 5 years (1.35 (1.06 to 1.72) per 10⁵) than in those aged 5–14 years (0.28 (0.18 to 0.39) per 10⁵; Fisher’s exact test, p < 0.0001). When outbreak cases were excluded from the analysis, the overall incidence was slightly, though not significantly lower.

Figure 1 shows the distribution of cases by type and month of presentation. During the entire study period there was a significantly higher incidence of cases during summer months (χ² test for trend, p < 0.001). This seasonal distribution persisted when outbreak and atypical cases were excluded. However, when the data were analysed by individual year of occurrence, a significant increase in sporadic cases in the summer only occurred in 1994–95, at the time of the outbreak. All sporadic cases

**Analysis of Data**

Incidence estimates and confidence intervals were calculated using Stat-Exact. Comparison of outbreak and sporadic groups was made using Student’s t test, Mann–Whitney U test, and χ² or Fisher’s exact tests. Incidence trends were analysed using the Cochran–Armitage trend.

**Results**

**Categorisation of Cases, Incidence, Seasonal, and Geographic Distribution**

In a 48 month period, 98 cases of HUS were identified, of which 84 (86%) were associated with gastrointestinal symptoms. Sixty four were sporadic cases and 20 comprised a single outbreak in South Australia occurring in January and February 1995.31 32 Fourteen “atypical” cases were identified, of whom five had an atypical or relapsing course, four were familial, three were associated with pneumococcal infection, one was associated with immunodeficiency, and one had an STEC associated urinary tract infection.26 The median age of cases at diagnosis was 31 months (interquartile range 16–70 months) and 70/98 (71%) children were under 5 years of age. Ninety one (92%) children were hospitalised for a median (interquartile range) of 14 (7–21) days.

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![Figure 1: Seasonal distribution of HUS cases by type: July 1994 to June 1998 (n = 98). Incidence of sporadic HUS decreased significantly over the study period (p < 0.001; Cochran–Armitage trend). Overall a seasonal (summer) peak in incidence was seen (p < 0.001).](www.archdischild.com)
COMPARISON OF OUTBREAK AND SPORADIC CASES WITH DIARRHOEA

Table 1 shows laboratory and clinical features of children with diarrhoea associated HUS. The outbreak group was significantly older than the sporadic group and the proportion of children under 5 years was lower. There was no gender bias. Duration of hospitalisation was significantly longer in the outbreak group.

The minimum haemoglobin and maximum neutrophil counts were not significantly different between groups (table 1). Maximum serum creatinine was significantly higher in the outbreak group and minimum serum sodium concentrations were significantly lower in the outbreak group.

Eighty per cent of outbreak and 80% of sporadic children had persistent hypertension and renal failure.

Although a diarrhoea prodrome was present in all 84 children, outbreak cases had a shorter prodrome and a much higher rate of macroscopic bloody diarrhoea (table 1). In outbreak cases the diarrhoea prodrome lasted between one and seven days and in sporadic cases, one to 30 days. Significantly more outbreak cases had severe haemorrhagic colitis. Left hemicolectomy was required in one outbreak case with ischaemic colon and partial colectomy in another. One sporadic case required appendicectomy and omentectomy. Vomiting was reported in around 80% of both groups.

Acute pancreatitis occurred in one outbreak case and hyperglycaemia was significantly more frequent in the outbreak group (table 1). Insulin was required in two outbreak cases and one sporadic case. The proportion of children with central nervous system complications (intracranial bleed or infarct, retinal haemorrhage, encephalopathy, seizure) was higher in the outbreak group. One sporadic case had anterior compartment syndrome caused by rhabdomyolysis and required fasciotomy of the right leg. An iliac vein thrombosis occurred in one child in the outbreak group.

Three of 84 patients died (table 1). A 4 year old girl with outbreak HUS and acute renal failure, multiple cerebral haemorrhagic infarcts, and extensive colonic necrosis died two days after diagnosis. A 10 year old boy with sporadic HUS and STEC O111 in the stool died eight days after diagnosis, from cardiac complications (myocarditis with pericardial effusion and tamponade). A 1 year old boy with sporadic HUS died within 12 months of diagnosis with persistent hypertension and renal failure.

OUTCOME

Twelve month follow up data were available on all 19 survivors of the outbreak and 43 of 62 survivors of sporadic HUS. Six of 19 outbreak cases and four of 43 sporadic cases had chronic renal failure (persistent elevation of creatinine and/or glomerular filtration rate of <80 ml/ min/1.73 m$^2$) at follow up ($p = 0.06$). Hypertension persisted at 12 months in four sporadic but no outbreak cases. No survivors of the outbreak developed end stage renal failure, defined as requiring chronic dialysis (whether or not awaiting transplantation) or having had renal transplantation. Of the three sporadic cases that developed end stage renal failure by 12 months after diagnosis, one had had a kidney transplant, one was awaiting transplantation, and one had died. One sporadic case had persistent insulin dependent diabetes mellitus. Five children with sporadic HUS had seizures at follow up. Three of these developed seizures following discharge from hospital, so their aetiological relation to HUS is unclear.

MICROBIOLOGY

Stool and/or serum samples were available from all outbreak cases. STEC serotype O111:H$-$ was isolated from 16/20 stools from
Table 2  Characteristics of STEC isolates in diarrhoea associated HUS

<table>
<thead>
<tr>
<th>No. of isolates</th>
<th>Serotype</th>
<th>Sorbitol fermentation</th>
<th>Stx1†</th>
<th>Stx2†</th>
<th>eae</th>
<th>Enterohaemolysin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outbreak HUS*</td>
<td>O111:H−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>16</td>
<td>O111:H−</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>O111:H−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>O113:H21</td>
<td>+</td>
<td>−</td>
<td>+</td>
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<td>−</td>
</tr>
<tr>
<td>1</td>
<td>O130:H11</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>1</td>
<td>O157:H−</td>
<td>−</td>
<td>+</td>
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<tr>
<td>1</td>
<td>O157:H−</td>
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<tr>
<td>1</td>
<td>O157:H−</td>
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<td>+</td>
<td>+</td>
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<tr>
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<td>O117:H−</td>
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</tr>
<tr>
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<td>OR:H9</td>
<td>−</td>
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<td>+</td>
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<td>−</td>
</tr>
</tbody>
</table>

Specimens were investigated on 20/20 epidemic cases and 50/64 endemic cases.

*Paton et al.†
‡Virulence associated features not determined on this isolate.
‡Obtained from a patient who was also infected with a Shiga toxin 2 producing strain of Entero-

bacter cloacae.⁹

Table 2 shows virulence associated characteristics of STEC isolates. All O111:H− strains from outbreak and sporadic cases produced Stx1 and Stx2 and carried the eae and enterohemolysin genes. However, PFGE analysis of the outbreak and sporadic O111:H− strains showed them to be different (fig 2). Furthermore, some O111:H− strains obtained from children with HUS in New South Wales around the time of the South Australian outbreak displayed a different phage type, colicin type and had different plasmid profiles compared to the epidemic strain.¹⁵ Of the non-O111:H− strains isolated and examined for the presence of virulence associated factors, all but three carried the enterohemolysin gene and produced enterohemolysin (table 2). Two of the strains that did not produce enterohemolysin were of indeterminate serotype and produced only Stx1 or Stx2. All non-O111 STEC produced either Stx1 or Stx2 but only one produced both. Five strains did not carry the eae gene. One sporadic case without STEC infection had a Salmonella species, one Salmonella plus Giardia lamblia, and two Campylobacter jejuni in the stool. The STEC O5:H− isolate from an atypical case with urinary tract

infection produced Stx1 and Stx2 and carried the gene for enterohemolysin but not that for eae.²⁵

Serum was available from 30 children with sporadic HUS, but as only one serum sample was available from most cases, we selected a high agglutinating antibody titre (>1/640) to indicate recent infection with E coli strains of serogroups O26, O111, or O157. Five patients showed increased antibody to O157, one of whom was also culture positive for STEC O157:H−. All 25 other sera investigated for antibodies to serogroup O157 showed a titre of <1/80. Three patients who were culture positive for STEC O111: H−, had an antibody titre to O111 of >1/640. The other five O111 culture positive patients identified in this study did not undergo serological examination. One patient with negative stool culture had a titre of >1/2560 to O111. No patient showed increased antibody titres to O26.

Discussion

The epidemiology of HUS in Australia has not been described previously. Four years of national surveillance through the APSU identified 80 cases under 15 years of age with HUS. Approximately 90% had diarrhoea associated HUS and 20 were affected during an outbreak of STEC O111:H− transmitted by contaminated mettwurst. Diarrhoea associated HUS was associated with at least eight different STEC serotypes. Although up to seven cases were associated with STEC O157, no strains of O157:H− were isolated, indicating major geographical differences in strain prevalence.
worldwide. Comparison of clinical features of sporadic and outbreak cases of HUS suggests the outbreak strain caused more severe disease at presentation, although specific microbial factors accounting for these differences were not identified.

The active nature of the surveillance, high return rate of monthly report cards and questionnaires, and inclusion on our mailing list of all known paediatric specialists in Australia, suggest that we identified the majority of HUS cases. No other national data set is available for comparison. The incidence of HUS in children under 5 years (1.35 (95% CI 1.06 to 1.72) per 10^5) was lower than that reported in Canada (3.11 per 10^5 children <5 years) and the British Isles (3.3 per 10^5 children). In Minnesota the incidence of HUS in children under 5 was 5.8 per 10^5 in 1988 and 2.1 per 10^5 in 1994–95. In the later study, one HUS case was reported for every 4.3–5.2 cases of STEC infection. This greatly overestimates the ratio of HUS to gastroenteritis as many cases of STEC induced gastroenteritis are unrecognised. This is borne out by a spate of recent outbreaks of STEC O157:H7 diarrhoea in Japan affecting 9845 children, of whom 149 developed HUS.

Previous studies suggest a summer peak of STEC infection and HUS. Overall our studies showed a seasonal (summer) peak in incidence. However, when analysed by individual year, a summer peak in sporadic HUS occurred only in the year of the outbreak. Interestingly, this increase was Australia wide and not restricted to the area of the outbreak. Further, the outbreak cases occurring at this time were microbiologically distinct from sporadic cases.

This suggests that climatic or environmental factors operating throughout the country may have contributed to a high background incidence of STEC infection during this period, caused by a variety of STEC, and also increased the risk of an outbreak.

Comparison of sporadic and outbreak groups indicates the outbreak strain was associated with more severe disease at presentation, but the reason for this is unclear. Epidemiological studies suggest the young and elderly have increased susceptibility to diarrhoea associated HUS but that older children have a worse outcome. In this study, outbreak patients were previously well but significantly older than those with sporadic HUS. This may reflect the fact that younger children are less likely to eat fermented sausage. While this study concurs with previous studies in finding that a short diarrhoea prodrome and bloody diarrhoea were indicative of more severe disease, there was no association between neutrophil count and severity. Inoculum size may also be important in determining disease severity, although the South Australian data showed low numbers of the causative agent in the food vehicle, suggesting that this was not the explanation in this outbreak.

Microbial factors are likely to be important determinants of disease severity. In HUS, Stx is encoded proteins, or subtype, and/or unrecognised host susceptibility factors. Expression of the eae gene is required for bacterial production of intimin, an outer membrane protein involved in the attachment of the STEC to epithelial cells. STEC frequently produce enterohemolysin but the roles of this and other plasmid encoded factors in disease are unknown. The O111:H- strains, which caused the outbreak and those found to be associated with sporadic HUS, exhibited all the pathogenicity traits described above. However, comparison of outbreak O111:H- isolates with several O111:H- isolates from sporadic cases revealed differences in phage type and DNA restriction fragment length polymorphism, indicating that different O111:H- strains were responsible for outbreak and sporadic HUS. Genetic differences in the outbreak strain may contribute to differences in virulence by virtue of the presence of currently unknown virulence determinants or of different quantities of known determinants. A recent Minnesota study reported that molecular subtyping of strains isolated from the local community allowed the authors to identify mini-outbreaks which would not have been recognised with standard microbial characterisation. Molecular subtyping is also useful for O111 STEC and may provide a mechanism to identify strains with different degrees of virulence.

In this study, several non-O157:H7 strains were identified in children with HUS, as previously recognised. Apart from O111, only one of these produced both Stx1 and Stx2. Three strains lacked the eae gene and two of these were negative for enterohemolysin. The aetiological role of such strains in HUS is open to question, given that Stx1 and Stx2 are encoded by somewhat promiscuous bacteriophages which are readily transmitted between different strains of E coli. Thus, the ability to produce Stx may be acquired by a relatively harmless E coli resident in the intestinal tract from a virulent STEC strain that was not detected when the stool sample was taken. In such cases serological investigation may shed light on the aetiological agent by permitting detection of antibodies to O antigens associated with the most frequent STEC O serogroups. This applied to four patients in this study who were culture negative, but displayed increased antibody titres to O157. Detection of antibodies to Stx1 and Stx2, as well as to intimin or functionally related, chromosomally encoded proteins, enterohemolysin, and flagella antigens may also provide useful retrospective information about the causative organism in culture negative patients. In this study, the relatively low isolation rate (40%) of STEC overall and of O157 strains in particular, from children with sporadic HUS may have been a result of an undue delay in obtaining samples for culture and transporting them to the laboratory. Isolation rates of O157 strains could conceivably have been improved by selective enrichment, for example, by using...
immunomagnetic enrichment of faecal samples. Such strategies, however, would probably have biased the data against non-O157 strains.

Medium-term progression of diarrhoea associated with HUS in this study was similar to that reported previously. Despite differences in disease severity at presentation, follow up at 12 months indicated no significant differences between outbreak and sporadic groups in rates of chronic renal failure and end stage renal failure. Mortality rates and prevalence of hypertension, central nervous, and gastrointestinal complications in groups were also similar.

In conclusion, nationwide HUS surveillance through APSU, which is ongoing, provided new information on the burden of HUS in Australia and enabled linkage of epidemiological, clinical, and microbiological data. We identified 12 non-O157:H7 strains of STEC associated with HUS including one O111:H−, which was responsible for an outbreak. The heterogeneity of isolates and the absence of O157:H7 differ from the current situation in most countries. The observation that O157 isolates were non-motile and failed to produce the full array of virulence associated determinants suggests a comparatively reduced virulence of Australian representatives of this serogroup and may explain their failure to become established in this country. This study was unique in allowing comparison of outbreak and sporadic diarrhoea associated HUS occurring during surveillance and indicates that outbreak cases had more severe disease at presentation. Examination of microbial pathogenicity factors of isolated strains supported the notion that the outbreak of HUS may have been associated with a more virulent strain of STEC than strains causing sporadic disease.

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