Advances in Microbiology, 2014, 4, 377-389
Published Online May 2014 in SciRes. http://www.scirp.org/journal/aim
http://dx.doi.org/10.4236/aim.2014.47045

Scientific Research

Serotypes of Non-O157 Shigatoxigenic *Escherichia coli* (STEC)

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Received 31 March 2014; revised 30 April 2014; accepted 7 May 2014

Abstract

Non-O157 STEC has been shown to have a diverse ecological distribution among food-animals. It has been associated with both outbreaks and individual cases of severe illness. This group of the organisms is now considered as a major contributor to human disease. The clinical description of the diseases caused by these organisms is reviewed. The host specificity of these pathogens is described and discussed. These organisms appear widespread among food animals like cattle and sheep, and can therefore affect a range of foods directly from the meat and excretions of these animals being used in farming practices. This article reviews the origins, diversity and pathogenesis of non-O157 STEC.

Keywords

***Escherichia coli*, Shiga Toxin, Non-O157, Serotype**

1. Introduction

Until the 1940's, *E. coli* were not recognized as possible enteric pathogens, as they comprise about 1% of the total faecal flora of humans and most warm blooded animals [1]. When Escherich first isolated these organisms from faeces and reported them as *Bacterium coli commune*, he did not realize their pathogenic potential [2]-[4]. They were seen as a part of the commensal faecal flora of humans and animals. Their main interest was as indicators of faecal contamination of waters and foods, and their differentiation from the accepted closely related pathogenic strains of *Salmonella* and *Shigella* [5]. Nevertheless, there were occasional reports considering strains of *E. coli* as possible pathogens. These included reports from Germany [6] [7] in the 1920's and in 1933

[8] and one from 1935 [9] from USA. However, it was the study by Bray [10] in1945 from Aberdeen, UK that really forced many to accept that certain strains of *E. coli* are able to cause disease in infants and the term Enteropathogenic *E. coli* (EPEC) became a suitable description for these pathogens.

The problem that these EPEC posed was that the strains apparently causing disease were indistinguishable from the commensal ones using the tests then available. Only when some unusual phenotypic character was noted, e.g. mutability [9], an unusual smell [10] was the initial diagnosis possible. It was the pioneering studies by Kauffmann [11]-[14] that established a serotyping scheme based on the somatic "O" antigens and the flagellar "H" antigens. His initial scheme included strains isolated from a variety of sources such as faeces of healthy individual cases of peritonitis, appendicitis and urinary tract infections. Very rapidly, once some of the EPEC strains were added to the serotypes, the numbers grew from the initial 25 "O" antigens to reach O145 in the 1960's and are now at O186 [5] and the H antigens are at H56 [16]. Thus, including Rough (OR) and non-motile strains (H-), there are potentially over 10,000 (186 × 56 = 10,416) *E. coli* OH serotypes, thus making "OH" serotyping a very useful discriminating tool, though there are some instances, to be discussed later, where more than one clone has been shown to have the same serotype.

2. Shiga Toxigenic *E. coli*

Thus, the situation in the 1970's was that most *E. coli* were considered commensals, EPEC [17] and the recently discovered Enterotoxigenic *E. coli* (ETEC) [18] [19] were being accepted as pathogens. Meanwhile, the toxins, now named Shiga toxins, which were first described over a century ago by scientists working in Germany [20] [21] were found to be produced by strains of *Shigella dysenterie* Type 1 (then named *Shigella shiga*). For many years it seemed that these toxins played no major role in the course of infections due to these strains of *Shigella* [22]. Volunteers, who had been fed an invasive low-toxin-producing, chlorate-resistant mutant of *Sh. Dysenteriae* I, suffered less severe symptoms than those who had been fed the wild type strain [23], and nevertheless it remained as an "orphan toxin". It was the pioneering observations of von Gasser in Switzerland [24], who realized a connection between the Shiga toxin and the development of Haemolytic Uraemic Syndrome (HUS) during the course of infections with *Sh. dysenterie* Type 1.

It took over two more decades when studies from Canada [25] revealed that some strains of *E. coli* can produce toxins that destroy certain cell types including Vero cells. Further studies [26]-[28] revealed that these toxins soon described as Verotoxins were similar to the Shiga toxin and that there were actually two toxins which became known as Verotoxin 1 and 2, or Shiga toxin 1 or 2. *E. coli* that produce one or both these toxins became known as Verocytotogenic *E. coli* (VTEC) or Shigatoxingenic *E. coli* (STEC). These two terms are interchangeable.

Following the description of the STEC a number of reports appeared in the literature describing the isolation of STEC with human disease [29] [30] and from a healthy individual [31]. Reinvestigation of an outbreak some years earlier suggested that it may well have been due to an STEC O111 [32]. Other reports during the 1980's accumulated and these have been summarised and reviewed in 1989 [33].

The investigation [34] of two outbreaks of unusual gastrointestinal illness characterized by severe abdominal cramps, grossly bloody diarrhoea where thorough faecal examination failed to yield any of the expected pathogen was the first report that created interest in STEC. In all 43 patients were studied of which 25 had become ill in Oregon (USA) between December 1981 and February 1982 and 18 in Michigan (USA), who had become ill between May and June 1982. In both of the outbreaks, full case—control studies were performed with either one or two age-matched and neighbourhood-matched controls. A questionnaire had been developed following interviews with the cases. They especially looked at exposure to specific food taking particular note of the restaurants, which may have been implicated. Details of the foods eaten and the hygiene standards and the food-handling procedures were examined.

From faecal specimens of each patient five colonies of *E. coli* were selected and serotyped. A particular serotype O157:H7 was identified and established as the aetiological agent for these outbreaks based on the observations that it was only isolated from ill persons and not from the healthy controls. Thus this serotype, which the authors considered "rare", having been isolated only once before in 1975 from a similar case, has since become the main pathogenic STEC serotype associated with STEC infects. This happened because strains of this clone were not able to ferment the carbohydrate, sorbitol, and thus could easily be selected on primary isolation plates [35]. Other media soon followed, which were even more selective [36]-[38] and thus all the other STEC serotypes were largely ignored. They were not sought so obviously they were not found.

3. Ecology of *E. coli*

In order to understand the ecology of the STEC, which primarily are *E. coli*, with all the characteristics of this species, which has adapted itself to be an inhabitant of the human alimentary tract as well as the alimentary tract of many animals, including ones which are part of the human food chain including cattle, sheep, pigs and chickens.

To obtain a greater understanding of the situation in the intestinal tract of a healthy human and so establish a baseline [39], the complete faeces from nine healthy adults were studied. Ten sites were microbiologically assessed and at least 10 *E. coli*-like colonies were collected from each site. From some sites many more colonies were selected. A great diversity of types was present, however, in all stools except one a single predominant type was present at all ten sites. Despite well over 100 colonies being selected from each stool, when some samples were tested using selective media serotypes were isolated which were not among unselected group.

An extensive study [40] on the acquisition by neonates of their *E. coli*, showed that *E. coli* are present in the vagina of women and that the acquisition of these *E. coli* by babies is related to the length of time that the birth takes, and it was also noted that there is a relationship between the *E. coli* found in the faeces of the mothers, the mucus swallowed by the babies at birth and subsequently in the faeces of the babies.

Caesarian section babies were generally not likely to become colonized by their mothers' faecal *E. coli*, but they were colonized as rapidly as vaginally delivered babies. These studies showed that it was the babies, who had become colonized earlier, became the foci for the spread the *E. coli* to other babies. A mild outbreak of diarrhoea in the neonatal ward, [41] in which the earlier studies on the spread of commensal *E. coli* had been carried out, due to the serotype of O125.K70.H21, showed that this serotype spread far more widely despite full control measures being taken, while commensal *E. coli* spread to a similar extent as in the earlier studies.

In addition, during the earlier studies it was noted that strains underwent variation, this included loss or gain of motility and thus the H antigen, O agglutinability by becoming rough, losing or gaining antibiotic resistances and carbohydrate fermentation patterns [42] [43]. New commensal strains are continuously acquired and resident strains are lost in this pattern of human behavior, especially if the individual does not always eat at home [44] [45]. A host specificity on the carriage of commensal *E. coli* has also been observed with serotypes of cattle isolates differing from typical human serotypes [46] [47]. These factors all need to be taken into consideration, when studying the spread and infectivity of STEC.

4. Isolation and Characterization of Non-O157 STEC

As discussed above there is no specific medium, which will definitively select for non-O157 STEC as the various means available for selection of O157 STEC. However, strains of sorbitol-fermenting O157 STEC have been found and these pose similar problems to those posed by the non-O157 STEC [48] [49]. These problems are largely being overcome and it should not become a technical problem to isolate and characterize non-O157 STEC as well as Sorbitol-fermenting O157 STEC. A recent study [50] clearly showed that this is achievable.

5. Diversity of STEC Serotypes

From the first published report of STEC serotypes in 1980 [51], a list has been kept of all published non-O157:H7/H-reports in which the full O:H serotype(s) has been identified. This list now has over 6600 entries at the beginning of 2014. Of this list of published STEC serotypes 1152 different serotypes are listed. The sources of these STEC serotypes are listed as well as the country of origin and the date of publication. An extract of this table is given in **Table 1**. In this diversity there were many STEC serotypes that appear only once, examples are O22:H1, isolated from a human case of diarrhoea in Belgium reported in 1997 [52]; O70:H35, isolated from a human with HUS in Germany in 2002 [53]; O107:H3 isolated from beef in Belgium in 2010 [54]; an infected human case in Germany yielding STEC O125:H10 in 2004 [55]; O139:H7, isolated from beef in U.S.A. in 2011 [56]; and O161:H2, isolated from healthy cattle in Japan in 2004 [57]. One has to assume that these STEC serotypes as well as the many others, which have only been isolated and reported once may well have the potential to spread more. It must be remembered that the STEC serotype O157:H7 was considered "rare" when first isolated in 1982 [34].

STEC serotype O104:H4 was isolated once from a case of HUS in Korea in 2006 [58] and again in 2008 from a case of HUS in Germany [59] [60]. This was part of a study on rarer STEC serotypes and they conclude that

Table 1. Extract from sources of over 6600 published STEC Serotypes, from 1980 to 2014.

O:H Serotype	Source	Condition	Country	Date Reported	reference
O1:H-	Human	H	Germany	1992	[104]
O1:H-	Human	HUS	Germany	1992	[104]
O1:H-	Human	HUS	Czech Republic	1994	[105]
O8:H16	Cattle	H	Argentina	2010	[106]
O111:H8	Cattle	HC	Canada	1994	[107]
O111:H8	Human	D	Asia	1996	[108]
O128:H2	Human	H	Australia	2012	[109]
O174:H2	Human	BD	Switzerland	2011	[110]

D = diarrhoea; BD = bloody diarrhoea; H = healthy; HUS = hemolytic uremic syndrome; HC = hemorrhagic colitis.

"at least some of these strains might represent emerging clones in the human population" but only mention in this context serotypes O111:H10, O113:H21 and O121:H19. They point out that these isolates "can be used in future studies as a reference to compare EHEC isolated in other countries from HUS patients. This would allow timely discovery of the emergence of new non-O157 clones associated with HUS and the virulence traits that they contain".

While they did not place serotype O104:H4 in the top list, no-one could have predicted the major outbreak that started in Germany and spread across Europe and to the rest of the world due to O104:H4 [61] [62]. In this paper, which was published on line on 23rd June 2011, the authors already report over 810 cases of HUS of which 39 were fatal and 2684 non-HUS cases since the outbreak started in May. All the isolates belonged to one clone and combined the virulence profiles of typical STEC and enteroaggregative *E. coli*. When the outbreak had run its course it was found that it had affected nearly 4000 patients in 16 countries and in addition smaller outbreak with the same organism occurred in June 2011 in South West France. It was found after extensive epidemiological investigations that "the incriminated food vehicles of the German and French STECO104:H4 outbreaks were sprouts grown from fenugreek seeds. Studies at the level of the European Union have shown that a fenugreek seed batch produced in Egypt as far back as the winter of 2008/2009 was the only connection between the outbreaks of illness in Germany and France [63]". Parts of this fenugreek seed batch had been used for sprout production on farms in Lower Saxony, as well as the hostel in France. "The European Commission subsequently ordered the recall and safe disposal of certain fenugreek seed batches from Egypt and imposed an import ban on fenugreek seeds and other plant-based foods from Egypt for a limited time period" [62]. This example shows that there must be constant vigil for STEC and shows that any single isolate of an STEC could acquire additional virulence factors and certainly other outbreaks like the O104:H4 outbreaks are likely to occur.

6. Host Specificity of STEC Serotypes

At the other extreme there are very frequently cited STEC serotypes, for which an ecological assessment can be made. In **Table 2** are summarized the sources of some of the more commonly isolated STEC serotypes. This shows that of the pathogenic non-O157 serotypes most frequently reported from human infections, those belonging to O serogroups O26; O111; O113; and O174, cattle are the main source while those belonging to O128 serogroup are mainly found in sheep. A study from Norway [64] strongly suggested that the STEC isolates from sheep and cattle are distinctly different both with respect to serotype as well as *stx* profile although they were isolated from the same farm. In addition it was shown that these strains are more related to isolates within the same serotype with the same *stx* profile than to isolates with different serotypes from the same farm. In this study strains with the serotype O128:H2 were most commonly isolated from sheep, while strains of O113:H4 and O113:H21 were isolated from cattle just as has been found when the world literature was reviewed and as summarized in **Table 2**.

Whilst strains of serotype O111:H- are probably the most common isolate of serious non-O157 STEC infections and has been isolated from cattle, this isolation rate is smaller than expected. This may be due to the fact

Table 2. Sources of some important STEC serotypes.

Serotype	Human Diseased	Human Healthy	Human?	Cattle Diseased	Cattle Healthy	Cattle?	Beef	Sheep Healthy	Sheep Meat	Other	Total
O5:H-	23	0	1	6	16	0	2	14	4	10	76
O26:H-	53	2	7	2	7	1	0	1	0	6	79
O26:H11	126	0	10	6	38	2	6	7	0	13	208
O111H-	89	2	5	6	19	1	2	0	0	0	124
O111:H2	6	0	0	0	1	0	0	0	0	0	7
O111:H8	25	0	2	4	6	0	1	0	0	0	38
O113:H-	4	3	1	1	11	1	3	0	0	2	26
O113:H4	11	5	1	0	14	1	10	2	0	10	54
O113:H21	29	0	6	10	41	1	18	0	0	23	128
O128:H-	10	0	1	0	1	1	1	9	0	5	28
O128:H2	32	8	1	0	2	0	5	15	0	17	80
O174:H8	5	6	0	1	3	0	2	9	1	12	39
O174:H21	21	3	3	0	30	1	13	1	1	12	85

that it occurs in small numbers only [65], or it may be present in a non-toxigenic form and when selective methods testing for the presence of *stx*-positive *E. coli* are used these strains are missed. When such non-selective methods were used it was noted that non-*stx* strains of *E. coli* O111 were commonly isolated [66]. Apart from lacking the toxigenic ability these strains were identical to their toxigenic counterparts as isolated from cattle and from human disease.

7. Toxin Subtype Differences among STEC Serotypes

Studies during the 1990's clearly showed that there were a number of subtypes of the two main Shiga toxins with at least ten gene variants of stx_2 being described [67]-[75]. There are similar reports of subtypes of stx_1 but the genes for stx_1 are highly conserved [76] [77]. Of these toxin subtypes stx_{1c} has been shown to be the most common Shiga toxin 1 subtype, which can be isolated from ovine sources [78]. The study by Koch *et al.* [76] showed an association with ovine sources.

In the examples cited above it was noted that certain O:H serotypes, were more likely to be associated with either a bovine source or an ovine source (**Table 2**). However, while it can generally be assumed that a given O:H serotype will belong to one particular clone, this need not necessarily be the case. It was shown that strains of STEC serotype O5:H- fall into two groups of phenotypically different clones. The reports of the isolations of this serotype from healthy sheep and healthy cattle are 14 and 16 respectively and this may superficially suggest a lack of host specificity. However, it was shown that the ovine-derived STEC O5:H- were phenotypically quite distinct from the bovine derived ones. It is also noteworthy, that the toxin sub-types of these two clones differ (**Table 3**) and with this difference the clinical outcome of human infections differs [79].

These observations, if confirmed with other STEC serotypes, suggest that there is a "double host specificity". The STEC strains are host specific with respect to their animal reservoir and the toxin-carrying phages are specific to their specific bacterial host. In addition in the case of animals carrying toxin-less strains that are otherwise like their toxigenic counterparts, it would be important in an outbreak situation to test for the presence of the toxin-carrying bacteriophages.

This phenomenon was observed even with non-toxigenic strains of O157:H7, being present in multiple animal and environmental sources [80]. Similarly observations at the same time showed that while STEC O26 strains could be isolated from faecal specimens of patients early in the illness but later non-toxigenic strains of O26 were isolated from the same patients [81]. These studies suggest that the STEC O26 and non-toxigenic O26

Table 3. Phenotypic differences between the two clones of STEC O5:H-.

Characteristic	Bovine source	Ovine Source
Toxins	*stx*$_{1c}$/*stx*$_1$ & *stx*$_{2c}$	*stx*$_1$
Haemolysin	*ehxA*	*ehxA*
Intimin	-	*eaeb*
Urease	-	+
Animal source	Healthy sheep	Calves with diarrhoea
Human Pathology	HUS	Diarrhoea & (? HUS)

strains "exist as a dynamic system whose members undergo ephemeral interconversions via loss and gain of *Stx*-encoding phages to yield different pathotypes." This can have implications not only in the diagnosis of STEC related disease but also other clinical, epidemiological and evolutionary studies. Some of these implications were considered further [82]. It was considered that the importance of these findings should not be underestimated. Currently the diagnoses of human infections due to STEC only looks for *stx*-producing strains and this may well give misleading results and provide totally misleading answers of the epidemiological situation. The potential virulence of these non-toxigenic strains must be considered in any disease or outbreak situation. If the studies on the animal hosts such as cattle and sheep show that they regularly harbor these non-toxigenic "potential" STEC and which acquire their *stx*-converting bacteriophages only under certain as yet undefined conditions, a completely new light onto the epidemiology of STEC infections is shone.

8. Epidemiology of STEC Serotypes

Studies on the epidemiology of non-O157 STEC infections are limited by the fact that generally in outbreaks in which STEC are suspected, most investigations stop, when an O157 is found and identified. It should be noted that in studies on the carriage of STEC by food-animal strains of STEC O157 are not uncommonly isolated, but these, when found, appear to be present in only small numbers compared to the presence of other STEC (**Table 4**) [83]-[87]. Thus when an outbreak occurs as a result of food contaminated with STEC originally derived from animal sources, STEC O157 may well be present albeit in small numbers, while there may be a much larger group of non-STEC present, which have not been isolated as they were not sought or considered. Such an outbreak may well be erroneously labeled as due to STEC O157. This situation was discussed as long ago as 1996 [88], when an outbreak was described in which the main causative organism was STEC O111:H- [89] although a number of other STEC serotypes were also found. On the basis of later serological investigations, it was found that the number of complications and the complication score increased as the number of infecting STEC, which were detected increased [90].

In the meantime, outbreaks and individual cases associated with non-O157 STEC have been reported from around the world of which the O104:H4 outbreak of 2011 [62] was probably the largest. However, to quote just one example [91] strains of STEC O26:H11/H- have been isolated from human cases in Switzerland and from cattle. Sheep carried a related clone of the same serotype. Further studies [92] led to the conclusion that: "A new highly virulent clone of EHEC O26 has emerged in Europe. Its reservoirs and sources warrant identification."

With the introduction of new media [93] such as the chromogenic agar medium designed for the detection and isolation of STEC belonging to the "O" serogroups O26, O45, O103, O121, and O145, these serogroups at least will be able to be selected for from primary isolation media. Furthermore PCR techniques developed many years ago and developed further [94] will at least indicate whether an STEC is present and then using standard microbiological techniques and careful colony selection should enable non-O157 STEC to be isolated.

Another recent outbreak [95] ascribed to strains of STEC O145 in 2010 in the United States of America, centred on the state of Ohio but spread to other states again showed the importance of maintaining an awareness of the importance of non-O157 STEC. In their discussion, the authors point out: "Providers should test all patients with bloody diarrhea for non-O157 and O157 STEC infections, and laboratories should follow recommendations to perform concurrent Shiga toxin testing and culture to improve detection of non-O157 STEC infections."

Table 4. Isolations of STEC O157, where all STEC are sought.

Country	Animal	No. STEC	No. different serotypes	No. O157:H7/O157:H-	Reference
Brazil	Cattle	68	42	0	83
Australia	Sheep	249	49	1	86
Australia	Cattle	203	32*	4	87
USA	Cattle	43	25	3	84
France	Cattle	62	33	3	85

Note: *strains of STEC O157:H8, phenotypically significantly different from the O157:H7/H-.

9. Human Disease Associated with STEC

According to the CDC Shiga toxin-producing *Escherichia coli* (STEC) are estimated to cause more than 265,000 cases of illness per annum in the United States. Annually more than 3600 hospitalizations and 30 deaths are recorded [96]. Illness is characterised by severe abdominal pain and cramping and watery diarrhoea which may become grossly bloody and lasts five to ten days. Fever is usually mild or absent. Asymptomatic infection can occur. A small proportion of infected patients present with hemolytic uremic syndrome (HUS), a severe complication characterized by renal failure, hemolytic anemia, and thrombocytopenia and is defined using the following criteria: 1) evidence on peripheral blood film of red blood cell destruction with a packed cell volume of <30%; 2) a platelet count of $<150 \times 10^9$/L; and 3) serum creatinine above the upper limit of normal for age, in patients in whom other reasons for coagulopathy (e.g. septicaemia) do not exist [97].

HUS carries a measurable morbidity and mortality. HUS most often affects children aged less than five years and the elderly. Renal failure may require renal replacement therapy (dialysis). Other organ systems may suffer damage through small vessel thrombosis involving a process of thrombotic thrombocytopenia. The brain is a major target organ. Some 40% of patients developing HUS require renal replacement therapy for a period of time and about 20% will have permanent renal dysfunction. Neurological injury is often severe and remains the most frequent cause of acute mortality in patients with STEC-associated HUS. It has been shown that inflammatory mediators contribute to the pathogenesis of HUS and complications. Abnormal activation of the alternative complement pathway appears to contribute to pathogenesis of HUS disease [98].

Why some patients have severe disease and poorer outcomes than others is explained by both host factors (extremes of age, distribution and number of *stx* receptors, etc.) and certain virulence factors of the STEC strain(s) responsible. Clues to the underlying (bacterial) mechanisms involved in causation of severe disease are emerging; we have shown that multiple STEC serotype infection is associated with more severe disease and significant complications [90]. Isolates producing *Stx2a* and, to a lesser extent, *Stx2d* have been shown to be commonly associated with HUS [99]. Strains genetically predisposed to production of large amounts of *stx*2 have been shown to cause more severe disease, for example, the demonstration of genetic polymorphisms upstream of *stx2* in regions involved in *stx2* expression. *In vitro* studies using Clade 8 strains of STEC O157:H7 (shown to be associated with severe disease) show *S*tx2 up regulation in these strains (but not other clades) exposed to bovine epithelial cells [100]. The findings of this research suggest that differences in disease severity observed between O157:H7 clades could be explained by differential *Stx*2 production. Clade 8 strains have also been observed to overexpress genes of the locus of enterocyte effacement [100] [101]. Thus the virulence of clade 8 strains likely reflects the upregulation of several discrete virulence systems. These mechanisms could also apply to non-O157:H7 strains. Further research is required to understand the genetic basis and biological significance of differential *stx*2 expression.

Many questions remain in regard to the pathogenesis of STEC infection; the very low infectious dose is one: how do only a very few organisms overcome colonization resistance to infect the colon and cause disease? Both host and pathogen virulence factors are probably important. For instance, protein calorie restriction significantly lowers the infectious dose in a mouse model [102] and the role of urease [103] in overcoming colonization resistance. These examples provide impetus for future research. Another area of research should be the host specificity discussed above. In the list of published STEC serotypes, there are many, which have been reported only once and others, which are reported frequently. This is another area in which fruitful investigations can be made.

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