suggestive of a vector mite bite, and a positive serodiagnostic for *O. tsutsugamushi* without other rickettsial serologies. The reversal of an evolution apparently headed to a fatal outcome under a treatment active on *O. tsutsugamushi* provides a strong additional presumption. Antibody titers may seem low, but since serodiagnostics were performed tardily, these titers may have already been decreasing. Another explanation would be an impaired immune response that could explain the disease severity and the persistent efficacy of antibiotic therapy at a late stage.

Pneumonia is a well-documented complication of rickettsial diseases, but ARDS is rare (6 cases) [3,–7]. Our observation seems to confirm that western practitioners should suspect scrub typhus in travelers returning from Southeast Asia with respiratory symptoms (if travel conditions make vector bites possible), because of the potentially severe course.

The use of tetracyclines in populations at risk of scrub typhus has dramatically reduced the associated mortality rate and probably explains the decrease in severe complications [2,8]. Other active antibiotics include chloramphenicol [2] and ciprofloxacin [9]. Data on the clinical efficacy of fluoroquinolones are scarce. Ofloxacin was prescribed to our patient to broaden the spectrum of antibiotic therapy. When the diagnosis of scrub typhus was suspected, retrospective analysis of the clinical course strongly suggested a link between improvement and ofloxacin administration. The decision not to add a tetracycline to the therapeutic regimen was thus taken, and the patient’s condition continued to improve. Therefore, ofloxacin activity seems likely, all the more so because a spontaneously favorable outcome, impossible to rule out, is made unlikely but the severity of the MOF. The description of doxycycline and chloramphenicol-resistant strains of *O. tsutsugamushi* in northern Thailand [10] would make the efficacy of fluoroquinolones in scrub typhus an interesting therapeutic alternative. Such efficacy is suggested by the case that we describe here, although it is clear that evidence beyond a single case is needed.

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References


Acute Community-Acquired Diarrhea Requiring Hospital Admission in Swiss Children

In order to ascertain the prevalence of agents that cause childhood diarrheal illness, stool specimens of 312 consecutive children with community-acquired diarrhea requiring admission were evaluated. Pathogens were detected in 166 (53%) of the 312 children (≥2 pathogens in 28 children): Rotavirus (*n* = 75), *Salmonella* spp. (*n* = 37), *Campylobacter* spp. (*n* = 24), *Shigella* spp. (*n* = 5), *Giardia* spp. (*n* = 4), *Yersinia* spp. (*n* = 2), *Aeromonas* spp. (*n* = 15), *Cryptosporidium* (*n* = 15), enteropathogenic *Escherichia coli* (*n* = 13), enterotoxigenic *E. coli* (*n* = 7), and enterohemorrhagic *E. coli* (*n* = 5). In conclusion, acute childhood diarrheal illness pathogens, such as *Aeromonas*, *Cryptosporidium*, and diarrheagenic *E. coli*, account for a large proportion of patients with a microbiologically positive stool specimen.

Acute childhood diarrheal illness represents a major cause of morbidity even in temperate, industrialized areas. Infectious agents long been known to cause acute diarrheal illness in such climates areas include *Salmonella* spp., *Shigella* spp., *Campylobacter* spp., *Yersinia* spp., *Rotavirus* and *Giardia lamblia* [1]. Recent advances in our understanding of enteric pathogens and improved diagnostic techniques have identified new agents of diarrhea, such as *Cryptosporidium parvum*, diarrheagenic *Escherichia coli*, or *Aeromonas* spp. [1].

Because the relative frequency of the different etiologic agents

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linked with acute infectious diarrhea greatly varies according to the geographic and socioeconomic settings [1], we undertook a study of the etiology and clinical features of community-acquired diarrheal illness in children admitted to the Department of Pediatrics, University of Bern, Switzerland.

The Department of Pediatrics, University of Bern, Switzerland, is a 60-bed pediatric teaching hospital that serves as tertiary referral center. The catchment area has a population of approximately 400,000 people of various social and ethnic backgrounds.

All patients aged between 5 weeks and 15 years who required hospital admission because of an acute, community-acquired diarrheal illness were eligible. Acute diarrhea was defined as an hospital admission because of an acute, community-acquired diarrheal illness. Approximately 400,000 people of various social and ethnic backgrounds were admitted to the Department of Pediatrics, University of Bern, Switzerland.

Table 1. Age, symptoms, and signs in 166 children with diarrhea, according to pathogens identified in stool specimens.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>n</th>
<th>Age, y</th>
<th>Body temperature, ºC</th>
<th>History of stay in hot climate</th>
<th>History of diarrheal contact</th>
<th>Bloody stool</th>
<th>Volume depletion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotavirus</td>
<td>75</td>
<td>1.4 (0.9–2.0)</td>
<td>39.2 (37.9–39.2)</td>
<td>93</td>
<td>4</td>
<td>27</td>
<td>5</td>
</tr>
<tr>
<td>Salmonella spp.</td>
<td>37</td>
<td>2.8 (1.4–4.3)</td>
<td>39.9 (39.1–40.3)</td>
<td>89</td>
<td>16</td>
<td>49</td>
<td>51</td>
</tr>
<tr>
<td>Campylobacter spp.</td>
<td>24</td>
<td>2.7 (0.6–7.9)</td>
<td>39.1 (37.8–39.3)</td>
<td>79</td>
<td>29</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>Shigella spp.</td>
<td>5</td>
<td>4.4 (3.1–6.3)</td>
<td>39.0 (39.0–39.3)</td>
<td>80</td>
<td>60</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>Aeromonas spp.</td>
<td>15</td>
<td>1.2 (0.6–2.0)</td>
<td>38.0 (37.0–39.0)</td>
<td>60</td>
<td>27</td>
<td>33</td>
<td>20</td>
</tr>
<tr>
<td>Cryptosporidium spp.</td>
<td>15</td>
<td>1.7 (1.2–2.2)</td>
<td>39.1 (38.3–39.3)</td>
<td>80</td>
<td>20</td>
<td>40</td>
<td>7</td>
</tr>
<tr>
<td>Enteropathogenic E. coli</td>
<td>13</td>
<td>1.4 (0.5–3.0)</td>
<td>37.6 (37.3–38.4)</td>
<td>69</td>
<td>23</td>
<td>23</td>
<td>8</td>
</tr>
<tr>
<td>Enterotoxigenic E. coli</td>
<td>7</td>
<td>0.6 (0.4–1.4)</td>
<td>37.9 (37.6–38.5)</td>
<td>86</td>
<td>57</td>
<td>57</td>
<td>9</td>
</tr>
<tr>
<td>Enterohemorrhagic E. coli</td>
<td>5</td>
<td>0.7 (0.4–1.5)</td>
<td>38.2 (37.7–38.9)</td>
<td>80</td>
<td>20</td>
<td>40</td>
<td>100</td>
</tr>
</tbody>
</table>

NOTE. Data are either median (interquartile range) or relative frequency. Data are percentages, unless otherwise indicated. Only pathogens isolated in ≥5 children are considered. Two or more pathogens were found in 28 of the 166 patients (this fact accounts for apparent mathematical discrepancies). E. coli, Escherichia coli.  

* P < 0.01 vs. Aeromonas spp. or diarrheagenic E. coli.  
** P < 0.01 vs. Rotavirus, Aeromonas spp., Cryptosporidium spp., and diarrheagenic E. coli.  
† P < 0.05 vs. Rotavirus, Campylobacter spp., Aeromonas spp., Cryptosporidium spp., and enteropathogenic or enterotoxigenic E. coli.  
‡ P < 0.05 vs. Rotavirus, Salmonella, Campylobacter, Aeromonas, Cryptosporidium, and enteropathogenic or enterohemorrhagic E. coli.  
§ P < 0.05 vs. Rotavirus, Salmonella spp., Campylobacter, Shigella spp., Aeromonas spp., and Cryptosporidium spp.  
¶ None of the isolates belonged to the serogroup O157.

The history before admission and the initial physical examination were used to ascertain a recent (<10 days) stay in a hot climate, poorly industrialized country, a recent diarrheal contact (at home or at a nursery), the quality of stools (watery or grossly bloody, by examination), the rectal body temperature (on admission), and the degree of extracellular volume depletion (assumed to be moderate in patients with 2 and severe in those with ≥3 of the following signs: altered skin elasticity, sunken eyes, dry mucous membranes, absent tears, or delayed capillary refill). A complete WBC count in peripheral blood was performed in all patients. Leukocytosis was defined as a WBC count higher than the age dependent upper reference value [3]; children aged ≤24 months, 17.5 × 10³ cells/L; children aged 25 months to 5 years, 15.5 × 10³ cells/L; and children aged ≥6 years, 13.5 × 10³ cells/L. The leukocytes were differentiated by microscopy, and a segmented neutrophil granulocyte was defined by at least 1 indentation of the nucleus to less than one-third of the maximal nuclear diameter. A shift to the left was defined as nonsegmented polymorphonuclear cells >10% of the total WBC count [3].

In the 312 patients, a stool specimen was collected within 24 h of admission and processed for Rotavirus, Salmonella spp., Campylobacter spp., Yersinia spp., Giardia lamblia, and C. parvum at the Institute for Clinical Microbiology, University of Bern, Switzerland. Standard laboratory techniques were used for Salmonella spp., Campylobacter spp., Shigella spp., and Yersinia spp. [4]. G. lamblia and C. parvum were detected in a fresh stool specimen fixed by use of the sodium acetate-acetic acid formalin medium. The specimen was concentrated, and a wet mount was examined for the presence of cysts and trophozoites of G. lamblia or oocysts of C. parvum, identified by staining the specimen by use of auramine-carbol-fuchsin and visualized by fluorescent microscopy [5].

Aeromonas spp., enteropathogenic E. coli, enterotoxigenic E. coli, and enterohemorrhagic E. coli were isolated at the Reference Laboratory for Foodborne Diseases, University of Bern. Briefly, stool samples were streaked onto cefsulodin-irgasan-novobiocin agar for isolation of Aeromonas spp. and MacConkey agar for isolation of E. coli [6]. Suspect colonies on cefsulodin-irgasan-novobiocin agar were subcultured onto Simmons citrate medium and blood agar, and oxidase- and citrate-negative colonies were identified by use of standard procedures [7]. For identification of diarrheagenic E. coli, 6 representative colonies were picked from the MacConkey agar, identified by conventional procedures, and used in a colony-blot hybridization assay. Probes and conditions used for the detection of
Enteropathogenic E. coli (probes for the virulence plasmid associated EAF and chromosomal eaeA genes), and enterohemorrhagic E. coli (probes for Shigatoxin and the virulence gene eaeA) have been described elsewhere [8–10]. Enteroinvasive E. coli were detected by use of a digoxigenin-labeled ipaH probe [11] produced by PCR using the primer pair 5'-TGAGA-3' and 5'-CGGTCAGCCACCCTC-TGAGA-3' (reverse), and genomic deoxyribonucleic acid of Shigella flexneri NZ 194-95 as a template.

Isolates of enterohemorrhagic E. coli were agglutinated in antisera against O157 and H7 antigens of E. coli in commercially available sera including passage of the strains in semisolid motility medium to enhance expression of flagellar antigens. The presence of O157 antigens was also assessed by agglutination in a latex reagent, rapid sorbitol fermentation was assessed on Sorbitol-MacConkey plates (Oxoid, Basingstoke, UK), and production of glucuronidase was measured with a fluorogenic substrate (Bactident; Merck, Germany).

The results are given as relative frequency or as median and interquartile range. The chi2 test (with the Yates correction) and the 2-tailed Kruskal-Wallis test (with the Bonferroni adjustment) were used for analysis [12]. Differences that had a probability >.05 by the appropriate null hypothesis were considered insignificant.

Pathogens were detected in stool samples from 166 of the 312 patients with acute diarrheal illness included in the study (≥2 pathogens were found concomitantly in 28 children): Rotavirus, Salmonella spp., Shigella spp., Aeromonas spp., Cryptosporidium spp., diarrheagenic E. coli, and Campylobacter spp. were isolated each in at least 5 children (table 1). G. lamblia (n = 4; 1.3%) and Yersinia spp. (n = 2; 0.6%) were detected in a small minority of patients. No enteroinvasive E. coli were detected.

The salient characteristics of patient history and clinical presentation are summarized in tables 1 and 2. Children infected with Salmonella spp., Campylobacter spp., or Shigella spp., were significantly older than were children infected with Rotavirus, Cryptosporidium spp., Aeromonas spp., or diarrheagenic E. coli. A history of travel abroad was given by roughly two-thirds of patients infected with Shigella and enterotoxigenic E. coli, whereas on average 85% of the other pathogens were domestically acquired. Although the body temperature was significantly higher in patients with acute diarrheal illness caused by Rotavirus, Salmonella spp., Campylobacter spp., or C. parvum, there was a considerable overlap with findings in patients infected with other pathogens, and clinical symptoms did not permit a clear distinction of diarrheal syndromes. This was also true for the results of the total WBC count. Peripheral blood leukocytosis was noted in the majority of the patients with acute diarrheal illness caused by diarrheagenic E.

**Table 2.** Peripheral blood total WBC count in 166 children with diarrhea, according to pathogens identified in stool specimens.

<table>
<thead>
<tr>
<th>Pathogen identified</th>
<th>n</th>
<th>Total WBC count, ×10⁹ cells/L</th>
<th>Leukocytosis, % of patients</th>
<th>Nonsegmented PMN increased, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotavirus</td>
<td>75</td>
<td>13.2 (9.6-17.3)</td>
<td>24</td>
<td>40</td>
</tr>
<tr>
<td>Salmonella spp.</td>
<td>37</td>
<td>11.0 (8.4-15.9)</td>
<td>24</td>
<td>70a</td>
</tr>
<tr>
<td>Campylobacter spp.</td>
<td>24</td>
<td>11.5 (8.0-15.4)</td>
<td>25</td>
<td>54a</td>
</tr>
<tr>
<td>Shigella spp.</td>
<td>5</td>
<td>14.1 (12.3-18.1)</td>
<td>40</td>
<td>80a</td>
</tr>
<tr>
<td>Aeromonas spp.</td>
<td>15</td>
<td>9.6 (7.0-13.1)</td>
<td>13</td>
<td>27</td>
</tr>
<tr>
<td>Cryptosporidium spp.</td>
<td>15</td>
<td>14.9 (10.2-19.6)</td>
<td>47</td>
<td>33</td>
</tr>
<tr>
<td>Enteropathogenic E. coli</td>
<td>13</td>
<td>17.6 (13.8-19.2)</td>
<td>62b</td>
<td>15</td>
</tr>
<tr>
<td>Enterotoxigenic E. coli</td>
<td>7</td>
<td>18.3 (15.9-20.0)</td>
<td>57b</td>
<td>14</td>
</tr>
<tr>
<td>Enterohemorrhagic E. coli</td>
<td>5</td>
<td>18.9 (17.0-22.5)</td>
<td>80b</td>
<td>80a</td>
</tr>
</tbody>
</table>

**NOTE.** Data are either median (interquartile range) or relative frequency. Only pathogens isolated in ≥5 children are considered. Two or more pathogens were found in 28 of the 166 patients (this fact accounts for apparent mathematical discrepancies). Leukocytosis was defined according to the literature [3] and "shift to the left" nonsegmented PMN >10% of the total WBC count [3]. E. coli, Escherichia coli; PMN, polymorphonuclear cells.

* P < .01 vs. Rotavirus, Aeromonas species, Cryptosporidium species, enteropathogenic E. coli, and enterotoxigenic E. coli.

b P < .01 vs. Rotavirus, Salmonella species, Campylobacter species, Shigella species, Aeromonas species, and Cryptosporidium species.
A shift to the left was noted in the majority of the children with diarrhea caused by *Salmonella* spp., *Campylobacter* spp., *Shigella* spp., or enterohemorrhagic *E. coli*. However, grossly bloody diarrhea was present in all patients infected with enterohemorrhagic *E. coli* (80% of those with shigellosis and 51% of those with salmonellosis). The extracellular volume depletion was slightly more pronounced (moderate or severe) in patients with acute diarrheal illness caused by diarrheagenic *E. coli*. An 8-month-old girl with bloody diarrhea caused by enterohemorrhagic *E. coli* developed hemolytic uremic syndrome. Children with acute diarrheal illness were admitted throughout the year (figure 1). However, admissions tended to be more frequent during the warmer months. No etiology-specific seasonality was noted.

The results of the present study demonstrate that in this region pathogens, such as *C. parvum*, enteropathogenic *E. coli*, enterotoxigenic *E. coli*, enterohemorrhagic *E. coli*, or *Aeromonas* spp., play an important role in the etiology of inpatients with acute diarrheal illness, as indicated by the fact that these pathogens were isolated in stool specimens from 18% of the pediatric patients with acute community acquired diarrheal illness that required admission.

The well-established pathogens Rotavirus, *Salmonella* spp., *Campylobacter* spp., *Shigella* spp., and *Yersinia* spp. [1] still represent a major cause of acute diarrheal illness in Swiss children. Compared with a survey performed at this institution from 1981 through 1984 [4], the relative frequency of acute diarrheal illness caused by Rotavirus tended to decrease (from 42% to 24%). In contrast, there was an increase in diarrhea caused by *Salmonella* spp. (from 9% to 12%) and *Campylobacter* spp. (from 3% to 8%).

The most frequent so-called emerging pathogen in this study was *C. parvum*. This protozoan was long known to cause diarrheal diseases in the immunocompromised but is now a recognized agent of acute diarrhea in all groups of patients [12]. *Cryptosporidium* also causes an important number of sporadic cases of diarrhea worldwide, with widely differing prevalence rates among regions [12]. The identification of *Cryptosporidium* is important for prognostic, epidemiological, and therapeutic reasons, since the symptoms tend to persist or recur for prolonged periods [13]. The organism is easily transmitted from person to person, and no uniformly efficacious therapy is available [12].

In this study, *Aeromonas* spp. was detected in 4.8% of the stool specimens. This frequency is similar to that reported from other industrialized countries (2.2%–10%). Although the epidemiological association between diarrheal disease and the presence of *Aeromonas* spp. in stools has been firmly established in many studies worldwide, there is still some controversy about its role as a pathogen [7]. A common clinical picture caused by isolates of *Aeromonas* spp. emerges from the literature: acute-onset watery diarrhea in infants and toddlers with slightly elevated body temperature. Vomiting is less common than in diarrhea caused by other pathogens, and the total WBC count rarely shows a leukocytosis or a shift to the left [14].

The most significant advances in our understanding of enteric pathogens have been made in the study of strains of *E. coli* that cause diarrhea [15]. Enteropathogenic, enterotoxigenic, and enterohemorrhagic [15] *E. coli* accounted together for 8.0% of the positive stool specimens in the present study. Thus, as a group, these pathogens were as prevalent as *Campylobacter* spp., being the third most frequent pathogens isolated. Among the diarrheagenic *E. coli*, enteropathogenic *E. coli* was the most common type detected. Although often considered a pathogen in developing countries, 77% of the cases observed were domestically acquired, which concurs with recent observations in the United States [16]. The second most prevalent category of diarrheagenic *E. coli* were enterotoxigenic *E. coli*. They are the main agent of travelers’ diarrhea, and, consistent with this, all but one of the patients shedding this organism had recently traveled to areas where this pathogen is prevalent [15].

The most important new pathogen in terms of the severity of associated illness, as well as its public health impact, is enterohemorrhagic *E. coli* [15]. All 5 case patients showed the typical picture of hemorrhagic colitis, including severe abdominal pain and grossly bloody diarrhea. Some individuals develop hemolytic uremic syndrome after the initial diarrheal phase of illness [17], as was observed in 1 of the patients with enterohemorrhagic *E. coli* infection. None of the isolates belonged to the *E. coli* serogroup O157, consistent with the rarity of this strain in most European countries [9, 15]. The enterohemorrhagic *E. coli* prevalence in the present study is similar to data obtained several years ago [10].

Despite attempts to identify many pathogens, no pathogen was isolated in ~50% of cases. Several viral pathogens like Astrovirus or other enteric viruses [18, 19] as well as parasites, were not looked for.

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References

Rapid Progressive Subacute Sclerosing Panencephalitis in a 2-Year-Old Child with Congenital Athyreosis

We present the unique case of a 2-year-old girl with congenital athyreosis who acquired primary measles virus infection at the age of 18 months, coincidentally with an Epstein-Barr virus infection. First neurologic symptoms of subacute sclerosing panencephalitis appeared 5 months later, and the girl died within 6 months after a rapid progressive illness. Factors possibly predisposing to this extraordinary disease course—primary measles virus infection at an early age and lack of evidence for immunodeficiency—are discussed.

Subacute sclerosing panencephalitis (SSPE) is a rare subacute infection of the CNS caused by measles virus (MV) [1]. The invariably fatal disease occurs several years after primary MV infection [2] and is characterized by uncontrolled replication of mutated and defective MV in neuronal and glial cells [3]. MV infection that occurs before 2 years of age is associated with a risk for SSPE that is 16 times as high as the risk associated with infection after 5 years of age [4]. SSPE that occurs before 2 years of age is extremely rare; we only found 2 cases in the literature [5, 6]. Although the characteristic course of the disease is slowly progressive, rare fulminating cases also have been reported [6, 7]. Most of these children had primary MV infection at an early age or coincidentally with a second viral infection. We report on the case of a 2-year-old girl with congenital athyreosis who suffered primary MV infection coincidentally with an Epstein-Barr virus (EBV) infection at 18 months of age and who developed fulminating SSPE 5 months later.

Figure 1. MRI from the brain of a 25-month-old patient with subacute sclerosing panencephalitis, showing increased signal intensity of the complete right hemisphere and the left frontal lobe.