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SECTION I

Viral gastroenteritis: Causes, pathophysiology, immunology, treatment, and epidemiology

Introduction

Acute gastroenteritis is one of the most common illnesses affecting man and may be caused by a large variety of different microbes. The condition affects mainly children and the elderly, but increasingly also adults of all ages, often following foreign travel or the ingestion of contaminated food and water. Infection with gastroenteritis agents can be asymptomatic, or be followed by mild or severe disease including vomiting or diarrhoea or both, and can be fatal as a consequence of severe dehydration. In developing countries infants and young children (<5 years of age) may have repeated episodes of diarrhoea and vomiting amounting to a total of over a billion episodes per annum of which approximately 150 million are moderate to severe, and an estimated 2.4-2.8 million deaths occur; this represents one-quarter of all deaths in children under 5 years (Bern et al., 1992; Murray and Lopez, 1997). In developed countries diarrhoea occurs less frequently, and the disease is fatal in only a very few cases; however, it leads to many hospitalizations and has considerable economic impact (Glass et al., 2001).

Causative agents

The spectrum of causative agents differs in developed and developing countries. In developing countries about one quarter of diarrhoeal episodes are due to infection with enterotoxigenic E. coli (ETEC). Enteropathogenic E. coli (EPEC), Shigella species and Campylobacter are the cause of 15%, and rotavirus is the cause of 10-15% of episodes. In addition parasitic agents, e.g. Entamoeba and Giardia, occur in 5% of episodes. In developed countries, bacterial causes of diarrhoea in children are <5%, whilst rotaviruses and other viruses cause 32% and 15% of cases, respectively. In more than one third of the cases no causative agent is found.

Besides rotaviruses as the main etiologic agent, there are many other viral causes of diarrhoea. The main diarrhoeogenic agents comprise four virus families: rotaviruses, enteric adenoviruses, human caliciviruses (Norwalk- and Sapporo-like viruses, now termed noro- and sapoviruses) and astroviruses, and cause diarrhoea at frequencies of 20-30%, 5%, 5-10%, and 5%, respectively. Recently data from Vesikari’s group have shown that the degree of undiagnosed diarrhoeal illness (‘diagnostic gap’; Flewett et al., 1987) depends critically on the severity of illness: in only 15% of moderately to
severely ill children was no microbiological causative agent found, whereas in children with mild diarrhoea this percentage amounted to about 40% (Pang et al., 2000; Vesikari, 2001). In this study, the relative distribution of pathogens was: rotaviruses 24%, caliciviruses 19%, adenoviruses 4%, astroviruses 4%, indicating an improvement of diagnostic procedures and a more important role for caliciviruses as a cause of diarrhoea than was previously recognised. Data reported from outbreak investigations among children in Japan showed that human caliciviruses were an even more frequent cause than rotaviruses (Nakata et al., 2000). In addition to the four main families of viruses, other viruses have been identified as causing human diarrhoea: toroviruses (Koopmans et al., 1993), picobirnaviruses (Grohmann et al., 1993) and enteroviruses (Yamashita et al., 1991, 1993). The involvement of coronavirus and parvoviruses that are well known causes of diarrhoea in animals, as causes of human disease is controversial. In the immunocompromised host (children with severe combined immunodeficiency (SCID), AIDS patients, tissue and organ transplant recipients etc.) viruses normally not causing disease in man are found as causes of chronic gastroenteritis (Grohmann et al., 1993). Among those are mainly viruses of the herpes group (cytomegalovirus, herpes simplex virus), picobirnaviruses and adenoviruses other than the enteric adenoviruses. UD Parashar and R Glass have given a general overview of this area (Section I, Chapter 1).

Pathophysiology

The mucosa of the small intestine consists of arrays of long villi interspersed by crypts near their base. Villi and crypts are covered by a continuous monolayer of epithelial cells, those on the villi being highly differentiated for the purposes of absorption (particularly at the tip of the villi) and those in the crypts being undifferentiated and acting as a reservoir for proliferation and differentiation into absorptive cells. Crypts secrete chloride and immunoglobulin A (see below) into the gut lumen. Normally, villous absorption exceeds secretion (= net absorption).

Some viruses infect the mature enterocyte in the middle or upper villous epithelium of the small intestine (rotaviruses, adenoviruses, astroviruses); other viruses infect the crypt cells, e.g. parvoviruses (panleukopenia virus) and toroviruses (Breda virus) in animal models (Moon, 1994). Mainly the proximal small intestine is infected. After viral replication, epithelial cells become necrotic and are sloughed off, leading to a loss of enzymes breaking down carbohydrates and proteins (lactase, peptidases) and to primary malabsorption. This also leads to villous atrophy, followed by reactive crypt cell hyperplasia with increased numbers of mitoses in enteroblasts, cellular infiltration of the submucosa and hypersecretion which adds to the severity of diarrhoea. Recovery from the loss of the villi is relatively quick (7-10 days).

In the initial stages of diarrhoea, a marked ischemia is observed in the villi, preceding the death of enterocytes and suggesting that the observed changes are the result of localized systemic responses triggered by the infection of enterocytes and that diarrhoea is not simply the direct result of impaired enterocyte function (Starkey
et al., 1986; Osborne et al., 1988; Stephen and Osborne, 1988). Recently, the first viral enterotoxin has been described in rotavirus infection (Tian et al., 1995; Ball et al., 1996; see Section II, Chapter 6). Furthermore, the autonomous nervous system seems to be affected in decreasing the mobility of the small intestine, thus contributing to the development of diarrhoea (Burrows and Merritt, 1984; Lundgren et al., 2000). Pathophysiologically the diarrhoea is due to several factors: decreased glucose mediated sodium adsorption accompanied by increased undigested lactose in the gut lumen, and crypt hypersecretion as a consequence of electrolyte movements under the condition of increased cellular division (Stephen, 1988; Greenberg et al., 1994). F Michelangeli and MR Ruiz have reviewed research on the pathophysiology of the gut in the context of viral diarrhoea (Section I, Chapter 2), and O Lundgren and L Svensson the role of the enteric nervous system which has recently been recognised as very important in this process (Section I, Chapter 3).

Immunology

The gastrointestinal immune system provides a significant proportion of the body’s overall immune responses. The gut is the organ in which most immunoglobulins are produced. Gut associated lymphocytic tissue (GALT) occurs in Peyer’s patches, scattered lymph node follicles, lymphoid cells in the epithelium, and submucosal lymphocytes. There are about $10^{10}$ immunoglobulin (Ig)-producing lymphocytes per metre of small bowel, compared to $2.5 \times 10^{10}$ Ig-producing cells in bone marrow, spleen and lymph nodes together (Brandtzaeg, 1988). Most of the immunocytes in the gut produce dimers or polymers of immunoglobulins of subclass A (IgA) containing a small interconnecting peptide (J-chain). Those IgA dimers or polymers can be transported to the basal membrane of epithelium to a “secretory component” (SC) protein which acts as a specific receptor. IgA is then transcytosed through the epithelial cell and secreted into the gut lumen. The daily production in the gut is 40mg/kg of IgA which is more than the total daily production of IgG (30 mg/kg). The function of these IgAs is in bacterial neutralization, viral neutralization or antibody-dependent cytotoxicity (ADCC). IgA may also be involved in intracellular “neutralization” (Burns et al., 1996; Desselberger, 1998). In rotavirus infections copro-IgAs were found to be the best correlate of protection (Coulson et al., 1992; Feng et al., 1994; Burns et al., 1996; Feng et al., 1997). By contrast, antibody directed against Norwalk-like viruses was not well correlated with subsequent protection (Parrino et al., 1977; Graham et al., 1994; Gray et al., 1994). P Brandtzaeg and F E Johansen have produced a comprehensive update of this area of research (Section I, Chapter 4).

Treatment

Treatment of infantile diarrhoea is mainly by oral or intravenous rehydration. Several formulae of oral rehydration solution (ORS) have been devised, are recommended
by WHO and are widely used, mainly in developing countries (Bhan et al., 1994). In severe cases intravenous fluid substitution with modified Ringer’s solution is recommended (Santosham et al., 1992). Oral immunoglobulins have been tried (Guarino et al., 1994) but are not part of a standard treatment regime. The use of antimotility drugs in children is generally not advised due to severe side effects (Desselberger, 1999). However, enkephalinase inhibitors (racecadotril) which decrease hypersecretion but do not affect motility, have recently been demonstrated to be a safe and effective treatment of childhood diarrhoea (Salazar-Lindo et al., 2000). The discussion of treatment options of viral diarrhoea has been dealt with by D Bass (Section I, Chapter 5).

### Epidemiology

Despite the low mortality rate of infections with gastroenteritis viruses in developed countries, the disease burden is considerable. Thus, it has been calculated that children in the United States will experience 1.5-2.5 episodes of diarrhoea per year but an estimated 2 million children will visit a doctor or clinic, and 160,000 children will be hospitalized (Tucker et al., 1998). A total of 400,000 adults in the United States is annually discharged from hospital with diarrhoea as their diagnosis, and 10-12% of all children hospitalized below the age of 5 years have diarrhoea (Glass et al., 2001).

Viral gastroenteritis occurs in two distinct epidemiological patterns, endemic childhood diarrhoea and epidemic disease (Table 1; Glass et al., 2001). The endemic childhood disease is mainly due to infection with rotaviruses, astroviruses and enteric adenoviruses. Transmission is mainly by person-to-person spread, but also possibly droplets, fomites or possibly zoonotic transmission. By the age of 5 years antibodies to these viruses are found in practically every child. By contrast, epidemic disease is found in all ages, mainly caused by Norwalk- and Sapporo-like viruses (human caliciviruses), rotaviruses of group B (in China), and sometimes astroviruses. They are mainly transmitted by food and water, but also by human-to-human contact (secondary cases). Human caliciviruses can infect repeatedly, even in the presence of virus-specific antibody, suggesting that the immunity is shortlived.

Whilst endemic childhood disease is likely to be controlled best by a vaccine programme, epidemic disease can be limited by outbreak control measures, improvements in food safety, and control of people handling or processing food. Risk factors to acquired diarrhoeal disease may be increased susceptibility (infants and the elderly), congenital and acquired immunodeficiencies (SCID, HIV-infected patients, transplant recipients), increased exposure by travel to developing countries, low socio-economic living conditions, ingestion of high risk foods or contaminated water, as well as concentration of susceptible people in hospital wards, extended care facilities for the elderly, day care centres, cruise ships and holiday camps.

An outline of epidemiological features of viral gastroenteritis is found in the chapter by UD Parashar and R Glass (Section I, Chapter 1).

Many of the research, management and surveillance aspects considered in this general section (I) will be returned to in the following, more specialised sections (II-VI).
The book updates, complements and actualises recent monographs on viral gastroenteritis (Kapikian, ed, 1994; Chiba et al., eds, 1997; Chadwick and Goode, eds, 2001; Cohen et al., eds, 2002).

Table 1
Epidemiological patterns of viruses causing acute gastroenteritis

| Viruses                  | Endemic disease in childhood | Epidemic disease |
|--------------------------|------------------------------|------------------|
| Group A rotaviruses      |                              | Human caliciviruses |
| Astroviruses             |                              | Group B rotaviruses |
| Enteric adenoviruses     |                              | Astroviruses      |
| Human caliciviruses      |                              |                  |
| Group C rotaviruses?     |                              |                  |
| Toroviruses?             |                              |                  |
| Coronavirus??            |                              |                  |
| Mode of transmission     | person-to-person             | Food             |
|                          | droplets and aerosols        | Water            |
|                          | fomites                      | person-to-person |
|                          |                              | droplets and aerosols |
| Reservoir                | Humans                       | Humans           |
|                          |                              | Animals?         |
| Immune states            | High prevalence of specific  | seroconversion in epidemic |
|                          | antibody by 5 years of age   |                  |
| Immunity                 | good                         | short term (human caliciviruses) |
| Virus variants           | limited per site, variable between sites | Many genomic variants |
| Public health control measures | Vaccine (Group A rotaviruses) | outbreak control, improved safety of food supply and handling, water surveillance |

* Slightly modified from Glass et al., 2001

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