

The Role of Prolonged Viral Gastrointestinal Infections in the Development of Immunodeficiency-Related Enteropathy

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Abstract Patients with primary immunodeficiencies are prone to develop enteropathy of unknown pathogenesis. We hypothesize that ineffective clearance of gastrointestinal pathogens, particularly viruses, in combination with defective immune regulation may cause inflammatory enteropathy in certain immunodeficient hosts. We reviewed publications related to prolonged enteric viral infection, immunodeficiency, and the subsequent development of inflammatory enteropathy. Prolonged infection with especially enteroviral infections was reported more often in immunocompromised hosts than in healthy individuals. Protracted enteric viral shedding was not always associated with the presence or duration of gastrointestinal symptoms. The development of immunodeficiency-associated enteropathy after prolonged viral infections was described in sporadic cases. Clinical consequences of viral gut infections in immunocompromised hosts comprise isolation issues and supportive care. Prospective studies in cohorts of immunodeficient patients are required to study the impact of prolonged enteric viral replication with respect to the pathogenesis of non-infectious enteropathy.

Keywords Immunodeficiency · Gastrointestinal viruses · Enteropathy · Prolonged shedding

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Abbreviations

CVID	Common variable immunodeficiency
HIV	Human immunodeficiency virus
IBD	Inflammatory bowel disease
NK cell	Natural killer cell
PID	Primary immunodeficiency
RT-PCR	Reverse transcription polymerase chain reaction
SCID	Severe combined immunodeficiency
VDPV	Vaccine-derived poliovirus
XLA	X-linked agammaglobulinemia

Introduction

Enteropathy involves pathologic changes in the intestine, commonly associated with inflammation, and is typically symptomatic [1]. The most common non-infectious enteropathies are inflammatory bowel diseases (IBD), of which the two major forms are ulcerative colitis and Crohn's disease. Other entities include autoimmune enteropathy, gluten-sensitive enteropathy or celiac disease, idiopathic (protein-losing) enteropathies, and syndrome-associated enteropathy, as observed in common variable immunodeficiency (CVID).

IBD is generally believed to result from a disturbed balance between mucosal immunity and the luminal microflora. Many components of the mucosal immune system have been implicated to contribute to IBD pathogenesis. Alterations in the first barriers, i.e., intestinal epithelium and innate immune system, consist of disease-associated genetic polymorphisms involved in, e.g., autophagy [2–6]. Second, defects in acquired immunity may contribute to the disease. Described perturbations in adaptive immunity include aberrant CD4⁺ T helper cell

responses [7] and susceptibility variants in the IL-23 receptor gene [8, 9]. Autoantibodies and increased numbers of B cells were found in IBD [10, 11]. These exaggerated adaptive immune responses may result in perpetual inflammation and intestinal damage.

Regarding microbial triggers, research is mostly aimed towards bacteria, but viruses may be involved as well [12]. Cadwell et al. show in mice with the Crohn's disease susceptibility gene *Atg16L1* that a specific persistent murine norovirus infection induces Paneth cell abnormalities. When subsequent intestinal injury was induced, these mice developed a severe inflammation resembling Crohn's disease. Intestinal injury remained self-limiting in wild-type mice and *Atg16L1* mice without a persistent norovirus infection. The authors conclude that a virus-plus-susceptibility interaction, combined with environmental factors and commensal bacteria, can determine the phenotype of hosts carrying risk alleles for inflammatory disease [13].

These findings suggest that common viruses may also initiate enteropathy in immunologically susceptible humans. Patients with primary immunodeficiencies (PID) are particularly prone to develop enteropathy [14–16]. IBD affects around 0.3% of the individuals in northern developed countries [17–20], while the estimated prevalence of enteropathy in PID patients is higher, e.g., 10% in CVID patients [15]. This immunodeficiency associated enteropathy causes significant morbidity and mortality and may necessitate immunosuppressive treatment [21]. PID patients frequently suffer from parasitic and bacterial gastrointestinal infections [22, 23], but regularly, gastrointestinal symptoms occur without the detection of a pathogen when using conventional screening methods. Recently, the detection of viruses has been facilitated by the development of molecular techniques [reverse transcription polymerase chain reaction (RT-PCR)], showing superior sensitivity when compared to viral cultures [24]. Patients with a defective cellular immunity, such as individuals with severe combined immunodeficiency (SCID), are evidently prone to viral infections, but the rate of infection is also enhanced in patients with antibody deficiencies. In some patients, these viruses may persist for several years [25, 26].

Taken together, we considered the possibility that inflammatory enteropathy in immunodeficiency can be triggered by common gastrointestinal virus infections. The continuous replication of a virus may cause intestinal changes, augmented by a persistent but aberrant immune response, leaving the gut in a perpetuating inflammatory state [26]. We reviewed the literature to define the prevalence of chronic common gastrointestinal virus shedding in both immunodeficient and immunocompetent individuals. In addition, we explored the potential association between these viruses and the development of enteropathy.

Methods

We systematically searched the MEDLINE database up to April 2011 for relevant peer-reviewed papers. Search details are depicted in Fig. 1. Search terms were designed to find articles concerning prolonged viral shedding, the relation between common enteric viruses and enteropathy, and the relation between common enteric viruses and immunodeficiency. Titles and subsequently abstracts were screened by two authors independently (AvdV and DHvK) based on predefined inclusion and exclusion criteria. Available full text papers were assessed for relevance and validity, and related articles and reference lists of relevant papers were screened.

Results

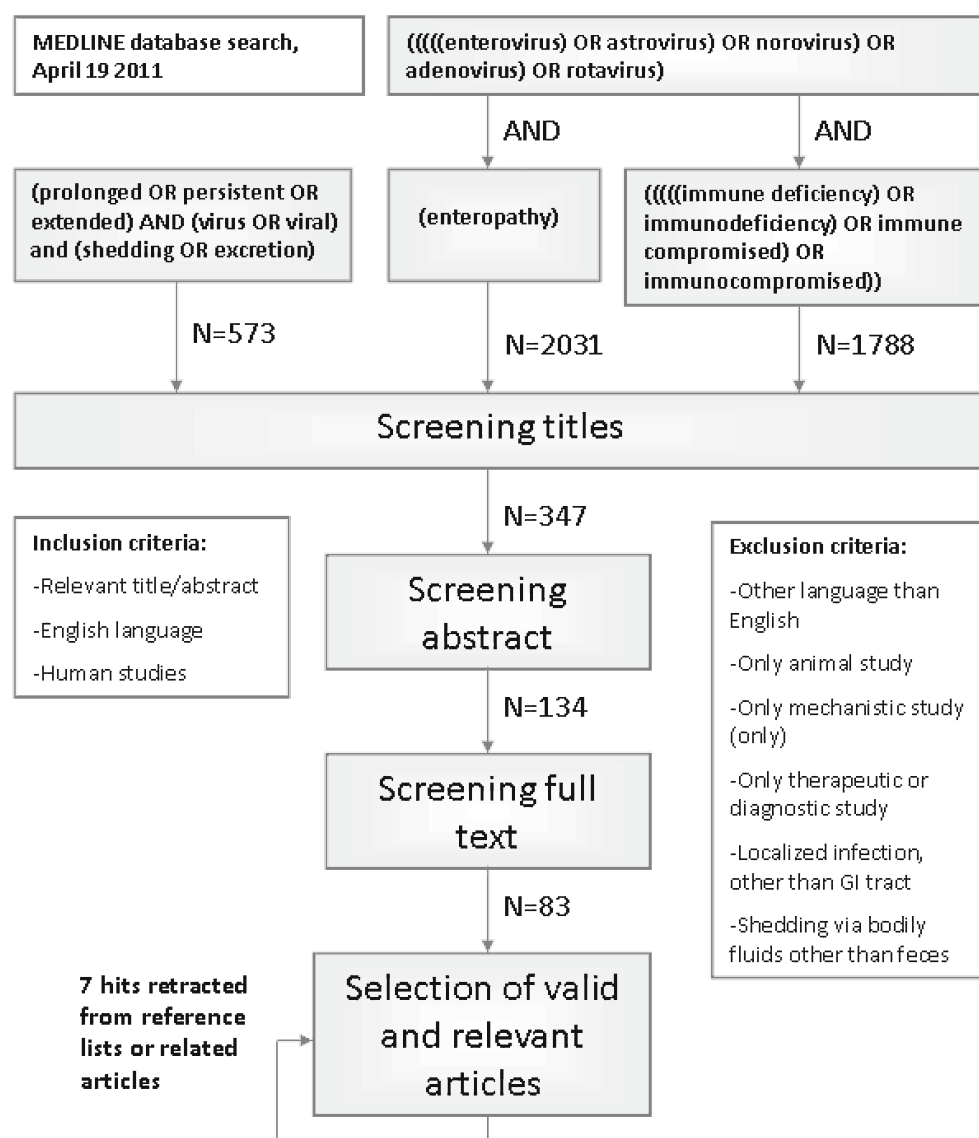
Ninety papers were reviewed of which 53 are summarized in Table 1. The occurrence of prolonged viral shedding is summarized per enteric virus for healthy and immunocompromised hosts; if data were available, the association with enteropathy is described.

Norovirus

Norovirus infection is with 5–36% the major culprit of gastroenteritis epidemics among adults and children [27, 28]. After challenging healthy individuals, fecal shedding of norovirus persisted for up to 2 weeks, especially in volunteers that developed symptoms [29]. Over 90% of individuals cleared norovirus within 3 weeks, although occasionally, fecal shedding persisted for up to 5 weeks [30]. Other studies in immunocompetent individuals showed a range of 13–56 days [31]. Viral shedding was not associated with clinical symptoms. In physiologically more susceptible children and elderly, fecal shedding ranged from 9 to 47 days, irrespective of clinical symptoms [32–34].

In immunodeficient individuals, viral shedding may be prolonged [35–38]. The median norovirus excretion was 16.5 and 28 days in immunosuppressed adults and children, respectively, compared to 4 days in previously healthy hospitalized patients [39]. In other immunocompromised patients, norovirus excretion lasted for a median of 13 weeks [30]. Pediatric oncology patients shedded norovirus for up to 140 [40] or 433 [41] days during an outbreak. The duration of shedding and presence of clinical symptoms were not always associated.

We identified one paper on the association of norovirus with enteropathy, describing exacerbations of inflammatory bowel disease associated with norovirus infections in children [42].

Fig. 1 Flow chart of literature selection procedure

Rotavirus

Rotavirus infection may cause severe gastroenteritis amongst children worldwide, resulting in 500,000 deaths a year [43, 44]. Symptoms associated with rotavirus disease usually last for 2–7 days [45–48]. The occurrence of symptoms was in some [49, 50] but not all [47, 51] studies related to rotavirus shedding.

Several studies have shown normal shedding periods of approximately 10 days in healthy children, while adults have not been described [45, 47, 52]. Extended fecal shedding occurred sporadically [47], but could persist in neonates for up to 75 days, albeit with low copy numbers of virus [51].

In immunocompromised hosts, prolonged fecal shedding has been documented more often, and gastrointestinal symptoms may persist for weeks [46, 50, 53]. Rotavirus shedding was present for at least 34 days in an 87-year-old

woman with impaired natural killer (NK) cell activity [54]. RotaTeq vaccine-derived rotavirus strains were shed for 1–12 months by SCID patients [55–57]. In human immunodeficiency virus (HIV) positive, oncology or SCID patients, excretion persisted for more than 2 [45, 46] to over 6 weeks [45, 50, 53, 58].

Rotaviruses were linked to enteropathic diseases in a prospective study, which showed that recurrent rotavirus infections increased the risk of developing celiac disease in genetically predisposed children [59]. In active celiac disease, but not in patients on a gluten-free diet, a subset of anti-transglutaminase IgA antibodies recognized rotavirus major neutralizing protein VP-7, suggesting possible involvement of rotavirus infection in the pathogenesis of the disease [60]. Additionally, two patients developed celiac disease following rotavirus infection, as demonstrated by an increase in anti-rotavirus antibodies that decreased during follow-up [61]. No differences were found in serum

Table 1 Literature on enteric virus shedding

References	Study population	Number	Diagnostic method	Duration symptoms, median [range]	Duration viral shedding, median [range]	Association symptoms and shedding
Norovirus						
Okhuysen et al. [29]	Healthy individuals	72	ELISA	N/A	Peak 72 h, up to 2 weeks	Partly ^a
Gallimore et al. [36]	Child with T-cell def, following BMT	1	RT-PCR	156 days	156 days	
Simon et al. [40]	Pediatric oncology patients	20	RT-PCR	7 days [1–140]	23 days [3–140]	
Murata et al. [33]	Children, 18 mo (3 months–7 years)	71	RT-PCR	<2 years: 7 days; 2–5 years: 3.5 days	16 days [5–47]	
Amar et al. [31]	Healthy adults (18–50 years)	16	RT-PCR	1 days [10–61 h]	28 days [13–56]	No ^b
Lee et al. [37]	10 month old, multiple organ transplant recipient	1	RT-PCR	Chronic diarrhea, duration not defined	114 d	
Ludwig et al. [41]	Pediatric oncology patients on immunosuppressants, 1.8 years [0.5–15.8]	9	RT-PCR	19 days [7–433]	46–64 days ^c [32–433]	No
Siebenga et al. [30]	Patients in tertiary care with norovirus infection; focus on 8 pt with shedding > 3 weeks, aged < 3 years (<i>n</i> = 5), 37, 67, and 69 years	8 ^d	RT-PCR	N/A	Immunocompetent: 14 days [7–35]	
Tu et al. [34]	Patients in an age-care facility, 85 years [58–93]	14	RT-PCR	3 days [1–4]	Immunosuppressed: 91 days [21–182]	No
Henke-Gendo et al. [39]	Hospitalized subjects, 64 years [14 days–89 years], 20 immunocompromised	75	RT-PCR	N/A	28.5 days [13.5–44.5]	No
Aoki et al. [32]	Patients in an age-care facility (60–98 years)	13	RT-PCR	3 days [1–6]	In healthy, 4 days [1–61]; in immunosuppressed, 16.5 days [1–53]; immunosuppressed children, 28 days [1–53]	No
Wingfield et al. [35]	36 years HIV + with poor therapy compliance	1	PCR	Chronic diarrhea > 6 months	13 days [9–32]	No
Schwartz et al. [38]	Immunosuppressed patients (chemotherapy or HSCT, 17–71 years) and staff members (20–56 years)	26 patients 11 staff members	RT-PCR	Patients 7 days [2–36]; staff 3 days [1–13]	481 days	
Rotavirus						
Saulsbury et al. [50]	Children with PID ^e 4 mo–18 years; controls < 3 years hospitalized for GE; healthy controls 6 mo–16 years	23 patients, 46 ill controls, 39 healthy controls	ELISA	2 patients diarrhea > 6 weeks, 2 patients with acute self-limiting GE < 12 days	1 SCID and 1 XLA > 6 weeks, 2 immunodeficient 10–12 days, 8 ill controls with no excretion at follow-up (2–12 days)	Yes
Mata et al. [48]	Children in rural Guatemala	45	ELISA	N/A	1–5 weeks (80% < 1 week)	No
Wilde et al. [52]	Children < 2 years in intermediate care ^f	9	RT-PCR and ELISA	N/A	9.5 days [1–19] RT-PCR; 5.7 days [1–17] ELISA	No
Gilger et al. [53]	Children with SCID, DiGeorge or AIDS 4–8 months	4	ELISA or EM	All had chronic rotavirus diarrhea until death	5.25 weeks [2–8]	
Richardson et al. [47]	Children admitted for severe rotavirus diarrhea, 1–39 mo	37	RT-PCR and EIA	4.5 d (mean), range 1–14 d diarrhea	10 d [4–57] by RT-PCR; 7 d [4–29] by EIA ^g	No
Cunliffe et al. [45]	In- and outpatient children, HIV+ and HIV−, median age 8–9 months [1–55]	29/102 HIV+; 45/348 HIV− ^h	EIA	2–3 days [0–12] diarrhea (HIV+/- similar)	6/29 HIV+ shed virus; 2 weeks [1–3 weeks]; 2/45 HIV− shed virus; 1.5 weeks [1–3 weeks]	No
Mori et al. [54]	Female 87 years with impaired NK cell activity	1	Rota-Kit	3 days	Min 34 days ⁱ	Yes
Rodriguez-Baez et al. [49]	Hospitalized children 0–6 years	309	ELISA	N/A	Max 7 days	

Table 1 (continued)

References	Study population	Number	Diagnostic method	Duration symptoms, median [range]	Duration viral shedding, median [range]	Association symptoms and shedding
Rayani et al. [46]	Pediatric cancer patients; Rota+ or –	28 patients, 28 controls	ELISA	7 days [4–34]	17 days [4–73]	
Ramani et al. [51]	Neonates	103 (33 with symptoms)	RT-PCR	0–4 days	Entire follow-up period [35–75 days]	no
Enterovirus 1; poliovirus						
Alexander et al. [70]	Review human polio excretion 1935–1995	373 WT polio, 1900 VAPV	Variable cell cultures	110 asymptomatic infections, 263 paralytic or meningitic poliomyelitis patients	3–4 weeks in many persons; up to 5–6 weeks in a smaller no. of persons	
Kew et al. [74]	16 year old male with CVID	1	Cell culture	Paralytic poliomyelitis at age 16 years	189 days confirmed, (est: 6.9–9.3 years)	
Bellmunt et al. [73]	CVID male, 7 years	1	Cell culture and RT-PCR	Poliomyelitis anterior onset at age 7	5.5 years ^j	
Martin et al. [75]	20 year old woman with hypogammaglobulinemia	1	Cell culture	Patient was fed monotypic Sabin 3 vaccine, no symptoms	+/- 21 months (631 days)	
Fiore et al. [78]	Patients with XLA, 14.5 years [3–33]	38	Cell culture	N/A	No excretion	
Halsey et al. [77]	XLA, CVID or IgAdef patients, 6.8–26.7 years	306 IgG; 40 IgA deficient	Cell culture and PCR	N/A	No long-term excretion found	
MacLennan et al. [25]	24y male, CVID	1	Cell culture	None	9 years confirmed, (est: 22 years)	
Martin et al. [71]	Healthy boy 1y, vaccinated with OPV	1	Cell culture and RT-PCR	None	4 months confirmed, (est: 10 months)	
Hennessey et al. [67]	HIV+adults 26–35 years [18–65]	419	Cell culture	N/A	No excretion	
Yang et al. [76]	8 year boy, diagnosed with CVID	1	Cell culture	Bulbospinal poliomyelitis onset at age 8 years	10 months ^k	
Asturias et al. [80]	HIV-infected children (3.6 years [1.5–15]) and adults (25.2 years) and children with cancer and >1 year of chemotherapy (8.7 years [2–16]); all OPV	94; 101; 50	Cell culture	N/A	No excretion	
Pavlov et al. [68, 69]	Immunodeficient children (mostly HIV+), aged 4 months–8 years	164	Viral culture			
Enterovirus 2; non polioviruses						
Bailey et al. [84]	SCID girl, 7 years, associated with CHH syndrome	1	RT-PCR	The children were hospitalized for various reasons	Polio detected in 13 patients; period unknown, person to person transmission not excluded	
Johnson et al. [85]	3.5 month old infant with agammaglobulinemia	1	Cell culture	not shown	22 months	
Liste et al. [86]	HIV+children, 1–60 months	6	ELISA	Admitted for pneumonia, diarrhea, failure to thrive	>70 days	
Chung et al. [65]	Hospitalized children with enterovirus, 1mn - 5 years	12	RT-PCR	N/A	1.6–6 months	
Gouandjika-Vasilache et al. [81]	HIV+adults, mean age, 32.5 years;	28	Cell culture and IF	Different symptoms, associated with EV infection	3–11 weeks (mostly 4–8 weeks)	
Cheng et al. [64]	A term neonate (symptoms 48 h after birth)	1	Cell culture	N/A	No polio excretion detected; other enteroviruses in only 1 sample	
Astrovirus			RT-PCR	13 days	23 days (after illness onset)	
Noel et al. [95]	2 SCID patients	2	Cell culture		32 and 102 days	
Mitchell et al. [91]	Children attending day care centres [2–30 m]	36	RT-PCR	N/A	EIA: 1.5 days [1–9]	
			EIA vs RT-PCR	59% had diarrhea 7.5 days [1–23]	RT-PCR: 4 days [1–35]	

Table 1 (continued)

References	Study population	Number	Diagnostic method	Duration symptoms, median [range]	Duration viral shedding, median [range]	Association symptoms and shedding
Maldonado et al. [92]	Rural Mayan birth cohort	271 infants	ELISA (confirmed by RT-PCR)	26% with astrovirus had symptoms	61% had astrovirus; of those, 70% was (intermittently) positive for 5 weeks [0–17]	
Gallimore et al. [90, 94]	8 months SCID patient with BMT 10-month-old IPEX patient with HSCT	1	RT-PCR	Diarrhea, duration unknown	156 days Around 120 days	
Adenovirus						
Van et al. [101]	Healthy children in day-care, mean 13 months	94	EIA	46% asymptomatic	Mean 3.9 days [1–14]	Yes ^l
Munoz et al. [103]	Hospital records of patients with positive adenovirus cultures	440	Cell culture		In immunocompromised patients 26.6 days [24–33]	
Lee [37]	10 month old, multiple organ transplant recipient	1	RT-PCR	Chronic diarrhea, duration unknown	114 days	
Curlin et al. [104]	HIV positive men	20	RT-PCR		4 [1–9]	
Other viruses						
<i>Picobirna</i> Grohmann et al. [117]	HIV positives	1	PAGE	Chronic diarrhea, 7mn	7 months	
<i>Picobirna</i> Gallimore et al. [116]	Healthy adult	1	PAGE	1 day mild diarrhea	107 days	
<i>Caliciviruses</i> Rockx et al. [114]	Community based cohort	99	RT-PCR	5 days	26% up to 22 d ^m	no

ELISA Enzyme-linked immunosorbent assay; **N/A** not assessed; **RT-PCR** reverse transcriptase polymerase chain reaction; **HIV** human immunodeficiency virus; **HSCT** hematopoietic stem cell transplantation; **PID** primary immunodeficiency; **GE** gastroenteritis; **SCID** severe combined immunodeficiency; **AIDS** acquired immunodeficiency syndrome; **NK cell** natural killer cell; **CVID** common variable immunodeficiency; **XLA** X-linked agammaglobulinemia; **OPV** oral polio vaccine; **CHH** cartilage-hair hypoplasia; **BMT** bone marrow transplantation; **IPEX** immunodeficiency polyendocrinopathy, enteropathy, X-linked syndrome

^a Prolonged shedding in >90% of ill, 50% of asymptomatics

^b Only symptomatic participants included; no difference between participants who met predefined criteria or those who did not

^c Last positive 46 days; first negative 64 days

^d This study found 131 patients norovirus positive; of those 131, eight patients (8.4%) excreted NoV for ≥3 weeks and were included

^e One SCID, eight CVID, three XLA, four IgA deficiency, three ataxia telangiectasia, two transient hypogammaglobulinemia, and two X-linked hyper IgM syndrome

^f Of the 40 children, the nine that were studied >5 days were aged 1 wk to 8 months

^g 30% excreted >20 days

^h 1,186 children studied, 450 had rotavirus infection (102+348); of these 74 (29+45) completed follow-up

ⁱ First positive sample March 5; last positive April 10, first negative April 26

^j 5.5 years confirmed; phylogenetic data suggested an additional 4–6 years of unrecognised poliovirus shedding before onset of paralysis

^l Virus excreted longer in symptomatic children (4.2+0.4 days vs. 2.8+0.5 days, $p=0.04$)

^m No samples from later timepoints examined, shedding could have continued longer. Newborns more likely to shed virus >15 days

rotavirus antibody levels between IBD patients and controls [62]. Finally, the report of a patient with protein-losing enteropathy after a Fontan surgery procedure suggested rotavirus to trigger this complication [63].

Enterovirus

Gastroenteritis due to enteroviruses is common, but severe and disseminated disease is usually restricted to young infants [53, 64, 65]. Several studies have investigated the duration of enterovirus excretion, most notably poliovirus. Vaccination program strategies have eradicated polio in several continents [66]; although due to the use of live oral poliovirus vaccine, and the fact that sporadic immunocompromised patients fail to clear the infection and thus become chronic excretors, vaccine-derived poliovirus (VDPV) still circulates in the population [67–69]. VDPV may be excreted up to 4–8 weeks by a large proportion of susceptible healthy individuals [65, 70]; one healthy infant excreted VDPV for 10 months [71].

Extended VDPV excretion particularly occurs in antibody deficiency syndromes [72], ranging from 21 months to 22 years in CVID and related hypogammaglobulinemias [25, 73–76]. Nineteen individuals with poliovirus excretion for >6 months are known to the World Health Organization [77]. Nonetheless, others did not find prolonged VDPV shedding in a cohort of 38 X-linked agammaglobulinemia (XLA) patients [78], 16 PID patients [79], and 346 IgG- or IgA-deficient patients [77], suggesting that these chronic carriers are incidental cases. In HIV-positive individuals, who predominantly have T cell defects but may develop humoral deficits, prolonged VDPV shedding (>6 months) has not been reported [67–69, 80–82], except for one study in which person-to-person transmission however could not be excluded [68, 69].

Data on prolonged shedding of other enteroviruses is scarce and limited to immunocompromised hosts [83]. Coxsackievirus shedding persisted for 10 more days after symptoms had subsided in a healthy neonate [64], while enteroviral excretion in immunodeficient patients ranged from 70 days to 22 months [84–86]. A patient with secondary antibody deficiency developed meningoencephalitis due to echovirus 13 [87]. Chronic meningoencephalitis was seen in XLA; here, an echovirus type 11 persisted for 7 years [88].

An association between long-term VDPV excretion and enteropathy has not been reported. However, one XLA patient developed enteropathy resembling Crohn's disease with enterovirus in the inflamed intestinal tissue and adjacent mesenteric lymph nodes, but not in biopsies of the surrounding unaffected ileocolonic tissue. This case illustrates the possibility of a relation between enterovirus and enteropathy in hypogammaglobulinemia [89].

Astrovirus

Astrovirus causes acute viral enteritis [66, 90]; in healthy children, shedding usually lasted several days, but could persist for up to 35 days, often asymptotically [91]. Results from a birth cohort of rural Mayan infants were very different from Western study cohorts; 61% was astrovirus positive during the 18-week study period. Seventy percent of them were positive for a median of 5 weeks, although patients that were intermittently positive were not excluded. Only one-quarter suffered from clinical symptoms [92].

Astrovirus infections are frequent in immunocompromised patients [66, 90, 93]. During an outbreak in a pediatric PID unit, two patients excreted astrovirus for 156 days [90, 94]. Two SCID patients excreted astrovirus for 32 and 102 days [95]. Astrovirus infections did not occur more frequently in HIV-positive individuals [96, 97]. No relation between astrovirus infection and enteropathy has been reported, excepting a case report that associates astrovirus infection with the onset of celiac disease [98].

Adenovirus

Adenovirus gastroenteritis occurs mostly in young children [99] and in immunodeficient populations [93, 100]. In healthy children, Van et al. showed that fecal shedding of adenovirus occurred for a mean period of 3.9 days (range 1–14). Adenovirus excretion was associated with symptoms in half of the infected population and persisted longer in symptomatic children [101]. In one third of another previously healthy pediatric population, diarrhea remained for over 2 weeks [99]. One study found prolonged viral shedding in 11 healthy infants for up to 515 days [102].

In the immunocompromised, adenovirus shedding was found to continue longer than in previously healthy children (22 vs. 8 days, respectively) [103]. Adenovirus shedding was reported for 114 days in a 10-month-old multiple organ transplant recipient and accompanied by norovirus shedding and chronic diarrhea [37]. Curlin et al. detected adenovirus in 75% of the HIV-positive male patients that underwent an intensive screening protocol for 18 weeks. Multiple recurrent adenoviral infections were found, lasting for a median of 4 days [1–9]. [104]

Adenovirus was implicated in celiac disease pathogenesis as homology was found between the early region Eb1 protein of human adenovirus serotype 12 and A-gliadin, the component activating celiac disease [105]. Neutralizing antibodies to adenovirus 12 were found in 80% of untreated celiac patients, compared to 33% and 31% in treated adults and children, respectively, and 0–13% healthy controls [106]. Conversely, studies on the presence of adenovirus 12 DNA on duodenal biopsy samples of celiac disease patients

found no evidence for a role in the pathogenesis of celiac disease [107, 108]. Second, adenovirus may play a role in HIV enteropathy [109], defined as enteropathy in HIV-positive patients after exclusion of other pathogens [110–112]. Thomas et al. found evidence for adenovirus colitis in four of 13 HIV-positive patients with adenovirus present in the stool and suggested that a proportion of HIV-positive patients with an enteric adenovirus infection may develop overt mucosal inflammation and chronic diarrhea [113].

Prolonged Fecal Excretion of Other Viruses

Although beyond the scope of this review, prolonged fecal excretion has been reported for several other viruses. Caliciviruses other than norovirus may be excreted in the feces up to 22 days in 26% of the cases, especially in infants [114]. Sapovirus is usually cleared within 2 weeks; some individuals however excreted the virus in high titers for 2–4 weeks [115]. Picobirnavirus was excreted for 107 days in an immunocompetent person without symptoms [116] and for 7 months in an HIV-infected person with chronic diarrhea [117]. Lastly, when plasma viral loads are high, non-enteric viruses can also be excreted in the feces; hepatitis E virus for example was excreted in the stool for 52 days [118] and influenza virus for >2 months in the stool of an immunocompromised child [119].

Discussion

We searched the scientific literature on prolonged viral infections in the gastrointestinal tract and the possibility of a relation with the occurrence of immunodeficiency related enteropathy. We found that prolonged carriage of several viruses, in particular enteroviruses, was described more often in immunodeficient patients than in healthy persons. Several reports describe exacerbations of non-infectious enteropathy triggered by viral infections. These findings

lend support to further explore the potential relation between chronic carriage of gastrointestinal viruses and the occurrence of non-infectious enteropathy in patients with primary immunodeficiencies.

Several reasons preclude a formal meta-analysis of the data provided in the literature. First, the majority of studies were retrospective, had small sample sizes, included various types of immunodeficiencies, and used different definitions to describe for example prolonged shedding of viruses in stool. Second, sample selection bias is inevitable, since primary immunodeficiency patients are monitored vigorously for viral infections. In many studies, the duration of viral shedding was not associated with the presence or duration of gastrointestinal symptoms; asymptomatic prolonged shedding may thus be missed, especially in the healthy population. Third, prolonged viral shedding could not always be clearly distinguished from re-infections. As a result, it is to date not feasible to draw conclusions at the level of patient groups or in the general population.

Nonetheless, several interesting observations were made. Table 2 suggests that prolonged shedding occurs more frequently in immunocompromised individuals, although these figures were not weighted for proportions of affected individuals. The susceptibility for prolonged carriage seems dependent on the virus genus and on the type of immunodeficiency; in general, immunodeficient individuals appear particularly susceptible to noro- and enteroviruses, but not to rotavirus. Norovirus infections depend on genetic susceptibility factors in the host; blood group O individuals are more susceptible, while individuals, homozygous for attenuating mutations in the *FUT2* gene [encoding $\alpha(1,2)$ fucosyltransferase] and thus not expressing the H type-1 oligosaccharide ligand required for Norwalk virus binding, were not infected upon challenge [120]. It remains unclear whether this concerns short- or long-term immunity and additional factors are probably involved. The lengthy enteroviral shedding in hypogammaglobulinemic patients

Table 2 Overview of the duration of enteric virus shedding per population

Range of shedding duration (days) in humans					
Virus	Immunocompetent		Immunocompromised		
	Adult	Infants, elderly	B cell	Combined	T cell
Norovirus	1–61	5–47	N/A	1–433	156; 481
Rotavirus	N/A	1–75	10–72	10–73	7–56
Enterovirus 1; poliovirus	21–42	0–120	0–3,285	No long-term excretors	No long-term (>180 days)
Enterovirus 2; non polio	N/A	77	> 70	660	48–180
Astrovirus	N/A	1–35	N/A	32; 102; 120; 156	N/A
Adenovirus	N/A	1–14, up to 515	24–114	24–114	1–9

N/A not assessed

supports the notion that its intestinal clearance depends on humoral immunity. Several classes of immunoglobulins are involved in antiviral immunity [121]. B1 B cells produce “natural” polyreactive IgM antibodies [122], which protect the host by, e.g., recruiting antigen into germinal centers. Here, in conjunction with CD4⁺ T cells, naive B cells develop into long-lived plasma cells or memory B cells, both responsible for long-term secretion of neutralizing specific antibodies. Particularly dimeric secretory IgA antibodies are essential, as they are transported across the intestinal epithelium [121]. HIV-related CD4⁺ T cell lymphopenia in infancy precludes the generation of those long-lived virus-specific memory B cells; while with HIV infection later in life, these memory B cells have already been formed and can survive without the presence of T helper cells [123]. Interestingly, HIV-positive patients did not demonstrate prolonged shedding, except for one study investigating HIV-seropositive infants [86].

SCID patients, expressing a combined T and B cell immunodeficiency, showed prolonged fecal shedding and symptomatic phases of gastrointestinal viruses. These infections thus contribute to the patient’s inherent failure to thrive. In contrast, patients with humoral immunodeficiencies can become chronic excretors but are usually asymptomatic. We hypothesize that in humoral immunodeficiencies, disturbed specific antibody formation precludes final clearance of the virus, but T cell immunity prevents a severe symptomatic course.

Literature on a possible association between gastrointestinal virus infections and the development of enteropathy was limited. Several studies suggested a link between certain viruses and enteropathy (Table 3). As these observations were made in singular patients [63, 89, 98], or contradicted by findings of other research groups [62, 107, 108], the relation remains uncertain. Studies describing enteropathy in PID patient groups (mostly antibody deficiencies) did not address the presence of enteric viruses in feces or gastrointestinal tract biopsy specimens [124–129], although Daniels et al. [130] found cytomegalovirus in a few CVID patients, which coincided with the presence of intraepithelial neutrophils. Apart from the presence or absence of prolonged viral infections, other factors may

play a role in the development of enteropathy, including factors that control the regulation of the immune system.

The clinical consequences of these findings include the following aspects. Ideally, patients with combined immunodeficiency should be screened at regular intervals for viral carriage in the gastrointestinal tract using RT-PCR. At present, however, these methods do not seem to be cost effective. Screening for viral shedding should therefore mostly be performed in the context of hygienic requirements, as findings may implicate isolation measures to prevent spreading of viruses. Furthermore, the presence of viral infections may be of prognostic value in case stem cell transplantation is considered. Patients with humoral immunodeficiency can also be chronic carriers of gastrointestinal viruses and may thus pose a risk to infect other patients. It remains however unclear what the yield of systematic evaluation by RT-PCR of patients with humoral immunodeficiency would be. We propose including chronic replication of viruses in the differential diagnosis of patients with humoral immunodeficiencies and concurrent enteropathy. We have described a patient that had chronic viral replication and eventually developed enteropathy, necessitating the use of immunosuppressive treatment, and it would thus seem logical to consider eradication treatment in some cases, although treatment options are usually limited.

Taken together, prolonged gastrointestinal virus carriage may occur occasionally, mainly in humoral or combined immunodeficiency. Viral shedding is generally not associated with the presence of clinical symptoms, and limited data linking enteric viruses to the development of enteropathy are available. As a result, prospective long-term cohort studies in PID patients are required in order to establish the prevalence of prolonged viral shedding, as well as to further explore its potential relation with non-infectious enteropathy. Specific PID patients could be screened for genetic variants related to enteropathy or virus susceptibility. Finally, *in vitro* studies aiming to unravel the interaction between virus and host at the molecular level may be valuable [131]. These studies will contribute to understanding of enteropathy in PID patients and may eventually facilitate preventive therapy in specific patient categories.

Table 3 Associations of enteric viruses with enteropathy

Virus	Type of enteropathy	Reference
Norovirus	Inflammatory bowel disease exacerbations	[41]
Rotavirus	Celiac disease	[57–59]
	Protein-losing enteropathy after Fontan surgery	[61]
Enterovirus	Crohn-like enteropathy in X-linked agammaglobulinemia	[87]
Astrovirus	Celiac disease	[96]
Adenovirus	Celiac disease	[103, 104]
	HIV or AIDS enteropathy	[111]

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