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CONTENTS

CHAPTER 1

Norovirus as a Foodborne Disease Hazard

Kirsten Mattison[1]

Contents

Abstract

Norovirus (NoV) is the most common cause of infectious gastroenteritis in the world. Gastroenteritis caused by bacterial and parasitic pathogens is commonly linked to food sources, but the link between NoV and contaminated foods has been more difficult to establish. Even when epidemiological information indicates that an outbreak originated with food, the presence of NoV in the suspect product may not be confirmed. If food is found to contain a common strain of NoV that circulates widely in the community, it is not possible to use strain typing to link the contamination to patient cases. Although food is certainly implicated in NoV spread, there are additional person-to-person and fomite transmission routes that have been shown to be important. NoV has an extremely low infectious dose, is stable in the environment, and resists disinfection. Cell culture methods are not available, so viability cannot be determined. Finally, many NoV outbreaks

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originate with when an infected food handler contaminates ready-to-eat food, which can be interpreted as foodborne or person-to-person transmission. This review will discuss both the physical characteristics of NoVs and the available epidemiological information with particular reference to the role of foods in NoV transmission.

I. INTRODUCTION TO NOROVIRUS

Norovirus is a genus of the *Caliciviridae* family, named for the cup-shaped depressions visible in the capsid by electron microscopy (Fauquet *et al.*, 2005). Other genera within *Caliciviridae* are *Lagovirus* that infects rabbits and hares, *Vesivirus*, infecting multiple animal species including cats and sea lions, and *Sapovirus* that infects humans.

The human caliciviruses, norovirus (NoV) and sapovirus, have also been described as small round structured viruses, for their 27–30 nm capsids. The NoV capsid consists of 180 copies of the VP1 major capsid protein packed as an icosahedron (Prasad *et al.*, 1999) and the VP2 minor capsid protein, which may contribute to stability (Bertolotti-Ciarlet *et al.*, 2002). The S domain of VP1 forms the inner shell of the capsid, while the P domain protrudes from the capsid surface and contributes to binding the histoblood group antigen receptor (Cao *et al.*, 2007) and antigenicity (Donaldson *et al.*, 2008; Lindesmith *et al.*, 2010).

The NoV genome is approximately 7.5 kb in length and contains three open reading frames (Jiang *et al.*, 1993). ORF1 codes for a polyprotein that is cleaved by the viral protease into at least six nonstructural proteins including the viral Vpg, protease, and RNA-dependent RNA polymerase (Sosnovtsev *et al.*, 2006). ORF2 codes for the major capsid protein VP1, and ORF3 codes for the minor capsid protein VP2 (Green, 2007). The P domain of VP1, in particular the P2 subdomain, is the most variable region of the NoV genome, while the 5′ untranslated region (UTR) and the junction between ORF1 and ORF2 are the most highly conserved regions of the genome (Kageyama *et al.*, 2003). The P2 subdomain is associated with NoV antigenic variation (Lindesmith *et al.*, 2008; Siebenga *et al.*, 2007b), while the highly conserved regions are the sites of initiation for transcription of the viral genomic and subgenomic RNAs (Asanaka *et al.*, 2005; Bull *et al.*, 2005; Lambden *et al.*, 1995).

Sequence analysis of the major capsid protein, VP1, groups NoV into five genogroups that contain at least 29 genetic clusters (Zheng *et al.*, 2006). Most of the strains associated with human infection belong to genogroup I (GI) or GII, while GIII viruses infect cattle, GIV viruses infect humans and canines, and GV viruses infect mice.

NoV infection causes acute vomiting, diarrhea, and abdominal cramps (Koopmans, 2008). Fever is reported in approximately 40% of NoV cases (Kaplan *et al.*, 1982; Wyatt *et al.*, 1974). Cases typically become symptomatic 24–48 h after infection, and the illness typically resolves after 48–72 h (Teunis *et al.*, 2008; Wyatt *et al.*, 1974). Both symptomatic illness and asymptomatic shedding have been shown to last longer in children, as well as hospitalized or immunocompromised patients (Kirkwood and Streitberg, 2008; Lopman *et al.*, 2004; Rockx *et al.*, 2002; Simon *et al.*, 2006). Attempts have been made to correlate levels of NoV shedding with a particular genogroup or with disease severity, but to date, no clear picture has emerged (Ajami *et al.*, 2010; Barreira *et al.*, 2010; Chan *et al.*, 2006; Lee *et al.*, 2007). Deaths have been associated with NoV infection due to severe dehydration in sensitive populations (Chadwick *et al.*, 2000; Dedman *et al.*, 1998; Stuart *et al.*, 2010).

NoVs infect all age groups and are the most common cause of infectious gastroenteritis in both community and healthcare settings (de Wit *et al.*, 2001b; Estes *et al.*, 2006; Green *et al.*, 2002; Lopman *et al.*, 2003, 2004). See Table 1.1 for a summary of some published NoV outbreak reports. Although outbreaks occur throughout the year (Alain and Denis, 2007), there seems to be increased NoV activity in the colder months in temperate climates (Dey *et al.*, 2010; Greer *et al.*, 2009; Lopman *et al.*, 2009; Rohayem, 2009). A precise description of NoV prevalence worldwide is not possible, due to differences in surveillance systems and in detection methods, but reports suggest that anywhere from 5% to 30% of tested cases of gastroenteritis are caused by NoV (Amar *et al.*, 2007; Bon *et al.*, 1999; de Wit *et al.*, 2001a; Monica *et al.*, 2007; Oh *et al.*, 2003; O'Ryan *et al.*, 2000; Pang *et al.*, 1999; Parashar *et al.*, 2004). Repeated infection with the same NoV strain is possible, as natural infection does not appear to confer long-lasting immunity (Johnson *et al.*, 1990; Parrino *et al.*, 1977).

II. NOROVIRUS GENETIC TYPES AND OUTBREAK ASSOCIATION

Of all the NoV genetic clusters, the GII.4 cluster represents the majority of NoV detected by public health testing laboratories (Adamson *et al.*, 2007; Ho *et al.*, 2006; Ike *et al.*, 2006; Kearney *et al.*, 2007; Maunula and Von Bonsdorff, 2005; Park *et al.*, 2010; Reuter *et al.*, 2008; Siebenga *et al.*, 2007a; Tu *et al.*, 2007). This cluster is identified around the world (Siebenga *et al.*, 2009) and has been circulating for at least 35 years (Bok *et al.*, 2009). The GII.4 strains have been shown to have a higher mutation rate than other clusters (Bull *et al.*, 2010), possibly associated with specific amino acid changes in the viral polymerase (Bruggink and Marshall, 2008, 2009). Six major strain variants of GII.4 NoV were identified between 1990 and 2006 (Lindesmith *et al.*, 2008;

TABLE 1.1 Examples of norovirus outbreak reports published since 2005

Outbreak type	Outbreak source	Data available	NoV genotype	Reference
Person to person	Contact among patients, relatives, and staff in a nursing home/hospital	Epidemiology and NoV from cases	NR[a]	Grima *et al.* (2009), Grmek Kosnik *et al.* (2007), Leuenberger *et al.* (2007), Simon *et al.* (2006), Sommer *et al.* (2009)
	Contact among patients, relatives, and staff in multiple nursing homes	Epidemiology and NoV from cases	GII	Calderon-Margalit *et al.* (2005)
	Contact among students at a university residence	Epidemiology and NoV from cases	NR	Honish *et al.* (2008)
	Contact among guests at a hotel	Epidemiology and NoV from cases	NR	Michel *et al.* (2007)
	Contact between passengers on a ship	Epidemiology and NoV from cases	NR, GII.1, GII.4, GII.5	Chimonas *et al.* (2008), Sasakì *et al.* (2006)
	Contact between passengers on a flight	Epidemiology and NoV from cases	NR	Holmes and Simmons (2009), Kirking *et al.* (2010)
	Contact among evacuees in a shelter	Epidemiology and NoV from cases	NR, GII.17	Nomura *et al.* (2008), Yee *et al.* (2007)
	Contact between infants/children at a nursery	Epidemiology and NoV from cases	GI.4, GII.3, GII.6	Uchino *et al.* (2006), Tsugawa *et al.* (2006)
	Exposure to vomit	Epidemiology and NoV from cases	NR, GII.4	Holmes and Simmons (2009), Kuo *et al.* (2009b), Schmid *et al.* (2005b)
Fomites	Environmental surfaces in a long-term care facility	NoV sequenced from swabs and cases	GII.4	Wu *et al.* (2005)

	Surfaces in shared houseboats	NoV detected from swabs and cases	NR	Jones *et al.* (2007)
	Computer surfaces in a school	NoV sequenced from swabs and cases	GII	CDC (2008)
	Juice dispensing taps at a hotel	NoV sequenced from cases with no other contact	GII.4	Visser *et al.* (2010)
Food handlers	Rolls prepared by symptomatic baker	NoV sequenced from worker and cases	GII	de Wit *et al.* (2007)
	Sandwiches and salads prepared by symptomatic handler	NoV sequenced from worker and cases	GI.3	Sala *et al.* (2005)
	Pastry prepared by symptomatic handler	NoV sequenced from worker and cases	GII.4	Oogane *et al.* (2008)
	Wedding cakes decorated by symptomatic handler	NoV sequenced from worker and cases	NR	Friedman *et al.* (2005)
	Salads prepared by symptomatic handler	NoV sequenced from worker and cases	GII.7	Schmid *et al.* (2007)
	Burgers assembled by handler who later became symptomatic	NoV sequenced from worker and cases	GI.3	Zomer *et al.* (2010)
	Salads prepared by handler who later became symptomatic	NoV sequenced from worker and cases	GII.6	Vivancos *et al.* (2009)
	Food served at a seminar, handler had been previously symptomatic	NoV sequenced from recovering worker and cases	GI.3	Nordgren *et al.* (2010)
	Sandwiches prepared by asymptomatic handler	NoV amplified from child of worker and cases	GII	Kuo *et al.* (2009a)

(*continued*)

TABLE 1.1 (*continued*)

Outbreak type	Outbreak source	Data available	NoV genotype	Reference
	Sandwiches prepared by asymptomatic handler	NoV detected from worker and cases	NR	Godoy *et al.* (2005)
Food and water	Hotel/resort/camp water source	NoV sequenced from water and clinical specimens	Multiple, GIIb	Hewitt *et al.* (2007), Kim *et al.* (2005), Migliorati *et al.* (2008), ter Waarbeek *et al.* (2010)
	Municipal water supply	NoV detected or sequenced in water and clinical specimens	NR, multiple, GI.5	Gallay *et al.* (2006), Scarcella *et al.* (2009), Werber *et al.* (2009)
	Flood water	Epidemiology	NR	Schmid *et al.* (2005a)
	Recreational water	NoV detected in water and clinical specimens	NR	Podewils *et al.* (2007), Sartorius *et al.* (2007)
	Shellfish	NoV sequenced in food and clinical specimens	Multiple	David *et al.* (2007), Gallimore *et al.* (2005a), Huppatz *et al.* (2008), Iizuka *et al.* (2010), Le Guyader *et al.* (2006b, 2010), Ng *et al.* (2005), Sala *et al.* (2009), Symes *et al.* (2007), Webby *et al.* (2007), Westrell *et al.* (2010)
	Frozen raspberries	Epidemiology, NoV sequenced in food and clinical specimens	NR, GI.4	Hjertqvist *et al.* (2006), Korsager *et al.* (2005), Maunula *et al.* (2009)
	Lettuce	Epidemiology, NoV sequenced in food and clinical specimens	Multiple	Ethelberg *et al.* (2010), Gallimore *et al.* (2005b), Wadl *et al.* (2010)

[a] NR = not reported.

Siebenga *et al.*, 2007b; Zheng *et al.*, 2010). In each year, a novel strain was seen to circulate, the number of NoV outbreaks increased to atypical levels in many countries simultaneously (Johansen *et al.*, 2008; Lopman *et al.*, 2004; Siebenga *et al.*, 2010). The testing of archived patient sera supports a hypothesis where herd immunity is acquired at the community level to an existing GII.4 strain, reducing the number and size of outbreaks in years without novel variants (Cannon *et al.*, 2009). The detection of a new variant strain in the summer has been proposed as a predictor for winter epidemic seasons of NoV infection (Verhoef *et al.*, 2008).

GII.4 NoVs are the most common genotype in outbreak statistics. However, most data is obtained from institutions, and it is primarily in closed or semiclosed settings that GII.4 NoVs have the largest impact (Blanton *et al.*, 2006; Bruggink *et al.*, 2010; Kittigul *et al.*, 2010; Lopman *et al.*, 2003; Pang *et al.*, 2010). Studies that examine NoV genetic diversity in sewage and in environmental samples typically identify a much larger proportion of GI and other GII viruses. For example, 11 different NoV types were detected in only 49 Dutch sewage samples (van den Berg *et al.*, 2005). Testing in France and Italy also determined that sewage samples contained a mixture of GI and GII viruses in raw and treated sewage (da Silva *et al.*, 2007; La Rosa *et al.*, 2010). Environmental water samples have also been shown to contain both GI and GII NoVs (Kamel *et al.*, 2010; La Rosa *et al.*, 2007).

When outbreak surveillance focuses on food and waterborne transmission routes, the GII.4 NoV no longer predominate as a source of illness (Bon *et al.*, 2005; Koek *et al.*, 2006; Lysen *et al.*, 2009; Pang *et al.*, 2010). GI NoVs are the most common strains identified in cases of waterborne transmission (Lysen *et al.*, 2009), while a mixture of GI and GII genotypes has been associated with shellfish-related outbreaks (Bon *et al.*, 2005; Kageyama *et al.*, 2004). This distinction has been presented as a mechanism to predict the origin of an outbreak based on the genetic typing of the infecting NoV strain, with a non-GII.4 etiology indicative of potential food or waterborne transmission (Verhoef *et al.*, 2009; Verhoef *et al.*, 2010). The GII.4 NoVs circulate widely in the community and exhibit very little sequence variation within an epidemic season (Dingle, 2004), making it difficult to establish an unambiguous epidemiological link between a positive food product and the patient. Food testing could therefore be focused on non-GII.4 outbreaks where the link between clinical and environmental samples is more likely to be clearly established.

III. NOROVIRUS OUTBREAKS SPREAD PERSON TO PERSON

NoV can spread directly from person to person due to their low infectious dose. Human volunteer studies have estimated that a single infectious NoV particle could cause illness in a susceptible individual (Teunis *et al.*, 2008).

There is a wide range of reported NoV attack rates during outbreaks (Harris *et al.*, 2010), but this is probably complicated by differing genetic susceptibilities among those exposed. Different blood groups or Lewis antigen profiles may confer susceptibility to different NoV genetic types (Cheetham *et al.*, 2007; Hutson *et al.*, 2005; Lindesmith *et al.*, 2003). Although most studies agree that secretor positive individuals (with a functional FUT2 allele) are susceptible to NoV infection, there are reports of NoV illness in secretor negative persons (Carlsson *et al.*, 2009; Marionneau *et al.*, 2005).

Many large surveillance studies have shown that the majority of NoV outbreaks are caused by GII.4 NoV spread directly from person to person in hospitals and long-term care facilities (Doyle *et al.*, 2009; Godoy *et al.*, 2009; Kelly *et al.*, 2008). It has been suggested that the predominance of GII.4 infections can be explained by higher attack rates and more symptomatic disease during GII.4 outbreaks than during infections with other genetic types (Friesema *et al.*, 2009b).

There is a large reservoir of NoV in the community, as evidenced by surveys of community acquired and sporadic cases of gastroenteritis (Buesa *et al.*, 2002; Haustein *et al.*, 2009; Karsten *et al.*, 2009; Lindell *et al.*, 2005). Syndromic surveillance of vomiting reports also indicates that the presence of NoV infections is constantly fluctuating in different areas (Cooper *et al.*, 2008). This widespread reservoir means that NoVs are continually introduced into hospital settings where they can spread rapidly despite efforts to interrupt transmission (Cunliffe *et al.*, 2010; Koopmans, 2009; Sommer *et al.*, 2009). Preventing the introduction of this widespread pathogen is nearly impossible (Koopmans, 2009; Yee *et al.*, 2007).

NoV outbreaks that are spread directly from person to person do not usually implicate a single-point source introduction, and the course of the outbreak can be complicated (Grmek Kosnik *et al.*, 2007). Multiple links between outbreaks in different sectors or in different institutions may be suggested, but only some of these will be supported by epidemiological evidence (Calderon-Margalit *et al.*, 2005; Lopman, 2006; Schmid *et al.*, 2005b). Multiple strains circulating in a single outbreak and the transfer of infected persons between facilities can complicate epidemiology and prolong the outbreak (Uchino *et al.*, 2006; Yamagami and Hara, 2007). There is the additional complication that hospital patients and long-term care facility residents have other, pre-existing health concerns that can contribute to an increased severity or prolonged course of NoV disease (Siebenga *et al.*, 2008; Simon *et al.*, 2006; Tsang *et al.*, 2008; Westhoff *et al.*, 2009).

Other closed or semiclosed settings where large person-to-person NoV outbreaks have been documented are associated with travel, on cruise ships and on airplanes. Cruise ships represent an interesting situation