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Review

Norovirus: a challenging pathogen

Chong W. Ong MBBS(Hons), FRACP, FRCPA

Department of Infectious Diseases and Microbiology, Royal Hobart Hospital, 48 Liverpool Street Hobart, Tas. 7000, Australia. Email: chong.ong.work@gmail.com

Abstract. Noroviruses account for over 90% of all viral gastroenteritis cases and ~50% of all outbreaks worldwide. Each year in Australia, there are an estimated 1.8 million cases. Cases may be sporadic or part of outbreaks, occurring in either the community or healthcare setting. Outbreaks are associated with significant morbidity and some mortality. They incur substantial costs and can be difficult to control in healthcare institutions or other closed settings.

Multiple factors (related to virus biological properties, human immune responses or inadequate management modalities) make it a challenging pathogen to control. They include: multiple transmission routes, low infectious dose, environmental survival, spread and persistence, diagnostic difficulty, hand hygiene controversies, imperfect immunity and immune evasion, asymptomatic and prolonged shedding, lack of vaccine and lack of antiviral treatment. The purpose of this article is to promote a better understanding of these factors in order that health professionals may be better equipped to manage the problems posed by noroviruses.

Until large-scale effective vaccination and specific treatments become available, the safeguarding of food and water supplies and the rigorous and timely application of outbreak management and infection control measures will remain the key to norovirus disease prevention and control.

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Introduction

Noroviruses account for over 90% of all viral gastroenteritis cases and ~50% of all outbreaks worldwide.[1] Infections occur at all ages and cause up to 200 000 deaths annually in children under 5 years of age in developing countries.[2] Each year in Australia, there are an estimated 1.8 million cases, making it the commonest cause of gastroenteritis.[3] Cases may be sporadic or part of outbreaks which occur in closed settings, such as hospitals, hotels, cruise ships, day-care centres and residential aged-care institutions. Outbreaks have significant health and cost implications and are difficult to control. This article highlights the reasons why norovirus is so challenging to manage.

Background

The syndrome of sudden-onset, self-limiting vomiting and diarrhoea, peaking in the colder season, was first described in 1929 by Zahorsky, and named 'Hyperemesis hemis' or 'winter-vomiting disease'.[4] In 1972, the causative agent, Norwalk virus, was identified and characterised.[5,6] Subsequently, similar viruses were described.[7] Norwalk virus became the prototypic agent of the genus *Norovirus* (previously called 'Norwalk-like viruses'), one of five genera within the family *Caliciviridae*.[1]

Noroviruses are non-enveloped, contain an RNA genome and cannot be cultured effectively *in vitro*.[8] They can be classified into five genogroups (GI through GV), which are sub-divided into at least 34 genotypes. Human disease is primarily caused by GI and GII noroviruses, with most worldwide outbreaks since 2001 caused by GII.4 (i.e. genogroup II, genotype 4) strains.[9,10] Significant strain diversity exists, even within a single genogroup and genotype. For example, GII.4 has evolved linearly over time, giving rise to multiple strain clusters.[11] During the past decade, new GII.4 strains have emerged every 2 to 3 years, replacing previously predominant GII.4 strains. Emergence of these new norovirus strains has often, but not always, led to increased outbreak activity.[9] In March 2012, a new GII.4 norovirus strain was identified in Australia. Named GII.4 Sydney, this emergent strain has since caused acute gastroenteritis outbreaks in multiple countries,[12] apparently replacing the previously predominant strain, GII.4 New Orleans, in the USA and UK.[9,13] Compared with other genotypes, GII.4 outbreaks are associated with more hospitalisations and deaths.[14]

Clinical features

Norovirus gastroenteritis has an incubation period of 12 to 48 h. Illness begins with acute onset of nausea, vomiting, abdominal cramps and myalgias.[1,8,15] Fever occurs in less than 50% of cases. Non-bloody diarrhoea is the commonest symptom, occurring in over 90% of cases.[16] Resolution of symptoms generally occurs in 2 to 3 days, but symptoms can last for longer (e.g. 4 to 6 days or beyond) in hospitalised

Implications

- Norovirus outbreaks cause significant morbidity, some mortality, incur substantial costs and are difficult to control
- Multiple factors (related to virus biological properties, human immune responses or inadequate management modalities) make it a challenging pathogen
- Safeguarding food and water supplies and applying outbreak management and infection control measures remain the key to prevention and control

patients, the elderly and children.[16–18] Asymptomatic infection is also possible.[19] Symptomatic disease ranges from mild to severe. Complications include dehydration, necrotising enterocolitis (mainly in neonates)[20,21] and death (mainly in older persons).[22–24] Post-infectious irritable bowel syndrome may occur.[25]

In the immunocompromised, prolonged symptomatic illness and prolonged shedding after symptom resolution may both occur. In outbreaks among haematology and oncology patients, median virus shedding was 2 to 3 weeks longer than median symptom duration, with some patients symptomatic or shedding for months and even over 1 year,[26–28] thereby indicating the emergence of the entity called 'chronic norovirus gastroenteritis'.[29]

Impact and cost

Norovirus gastroenteritis outbreaks are very costly and consume health resources. A GII.4 outbreak from January to May 2004 at Johns Hopkins Hospital (Baltimore, Maryland, USA) involved 265 healthcare workers (HCW) and 90 patients.[30] It resulted in closure to new admissions (at various times) of an intensive care unit, coronary care unit (CCU) and psychiatry ward. The CCU had to be emptied for cleaning and 138 echocardiograms were delayed. Psychiatry group therapy was suspended. Complete visitor prohibition to the areas was necessary. Nursing staff were cohorted and not permitted to attend shared meals or catered conferences. The cost of the outbreak was estimated at US$657 644 for lost revenue due to closure of units to new admissions, cleaning, equipment replacement and payment of over 2500 h of sick leave and overtime.

In an economic model focussing solely on lost bed-days (i.e. not including any additional costs), it was estimated that an outbreak in a 15-bed ward starting with a single symptomatic case would result, by the fifth day after admission of the index case, in five infected (four symptomatic) patients and would cost US$38 914 ± US$14 439, if the norovirus-attributable length of stay of each case was 4 to 6 days and no control measures were instituted.[31]

In Edinburgh, NHS (National Health Service) Lothian, from September 2007 to June 2009, there were 192 unit outbreaks. Lost bed-days and staff absence due to gastroenteritis cost NHS Lothian £1.2 million for the two norovirus seasons.[32] A study in Avon, England, identified 227 unit outbreaks from April 2002 to March 2003, with 63% being norovirus-related. Bed-days lost plus staff absence was calculated to cost £635 000 per 1000 beds. By extrapolation, gastroenteritis outbreaks likely cost the entire English NHS £115 million that year.[33]

Box 1. Factors making norovirus a challenging pathogen to control

- Multiple transmission routes
- Low infectious dose
- Environmental survival, spread and persistence
- Diagnostic difficulty
- Hand hygiene controversies
- Imperfect immunity and immune evasion
- Asymptomatic and prolonged shedding
- Lack of vaccine
- Lack of antiviral treatment

Box 2. Transmission of norovirus[15]

- Waterborne
  - Drinking (potable) water
  - Recreational (lake or swimming pool) water
- Foodborne
  - Shellfish (oysters, clams), salads, cake frosting and meats
  - Undercooked, contaminated foods or improper hand hygiene by an infected food-handler
- Person-to-person
  - Vomitus and faeces

What makes norovirus a challenging pathogen?

Several factors make norovirus a challenging pathogen to control. Refer to Box 1.

Multiple routes of transmission

Humans are the only known reservoir for human norovirus. Transmission occurs by three general routes: foodborne, waterborne, and person-to-person.[15] Refer to Box 2.

Community outbreaks are often associated with contaminated food or water. In healthcare settings, outbreaks tend to be associated with person-to-person transmission, although contaminated food and water (e.g. hospital kitchen) may sometimes be implicated.[34] Person-to-person transmission occurs through: (1) direct contact with faeces or vomitus from infected cases, (2) contact with contaminated fomites or the environment or (3) aerosolisation and droplets (usually from the infected person vomiting). The final common pathway is ultimately ingestion of virus particles (virions) arriving in the mouth or upper aerodigestive tract.[15]

While contact resulting in faecal–oral transmission has generally been accepted, outbreaks from aerosols generated by vomiting have also been documented.[35] For example, in a