A medical illustration of Clostridium difficile presented in the Centers for Disease Control and Prevention (CDC) publication entitled, Antibiotic Resistance Threats in the United States, 2019 (AR Threats Report). Medical Illustration by Jennifer Oosthuizen/CDC.

Handling the challenges of Norovirus and *C. difficile* infection

By Professor Laurence J. Walsh AO

There are several situations where dental staff could encounter patients who are infected with norovirus or with *Clostridium difficile* infections. They may be ambulant dental patients attending for regular dental care who live in the community or in residential aged care facilities. Alternatively, the dental practice may be providing an outreach program or domiciliary care where staff attend nursing homes or private homes to provide dental care. A further situation occurs when there are outbreaks of infectious diarrhoea in the community. Such outbreaks could be caused by:

- Viruses: noroviruses, rotavirus and adenoviruses;
- Protozoa: *Giardia, Cryptosporidium* and *Cyclospora*; and
- Bacteria: *Clostridum difficile, Shigella, Salmonella, Campylobacter* and toxigenic *Escherichia coli.*

Of these, the most common and important viral cause is noroviruses, while the most common and severe bacterial cause is *C. difficile*. The latter can develop after prolonged use of broad spectrum antibiotics, particularly clindamycin.

Noroviruses

There are over 100 different members of the norovirus family. All noroviruses (NoV) are non-enveloped, single-stranded RNA viruses. They are classified into genogroups and then into genotypes. The ***GII.4 2012 Sydney*** strain has been prominent in infections over the past decade, with numerous well-publicised norovirus outbreaks on cruise ships and in residential aged care facilities in Australia over that time.

NoV infections can have serious health consequences, causing morbidity and mortality, particularly in elderly patients, as well as in young children and people with compromised immune responses.

Annual fluctuations in the number and severity of cases are due to the emergence of novel strains of the virus. NoV are "shape-shifters", because they can, like other single-stranded RNA viruses, readily mutate to change their surface features, allowing them to avoid the human immune system.[1] It also makes the development of vaccines more complex.[2,3]

NoV are the leading cause of epidemics of acute gastroenteritis across the world, including infections that are food-borne. They infect both adults and children.[5-7] NoV infections are highly contagious, with a low infection dose needed to transmit the infection (as few as 10-100 virions). NoV have a large human reservoir, with the typical source patient for an outbreak being an individual who is chronically infected, immunocompromised, elderly, malnourished, or several of these.[8] Infected individuals may shed billions of virions in their vomitus and stool (with around one billion viral particles per gram of faeces). From an infected person, the viruses are spread rapidly by person-to-person transmission, through the faecal-oral route (e.g. through poor toilet hygiene practices) and indirectly from contact with contaminated objects (fomites) or by the consumption of contaminated food or water. Thus, from a single infected person, NoV infection can spread rapidly to other people in the community, as well as to healthcare providers. Waterborne outbreaks of NoV infection have occurred from swimming in a freshwater lake, or in a swimming pool with inadequate chlorination, or from drinking contaminated tap water or ice-containing beverages.[9]

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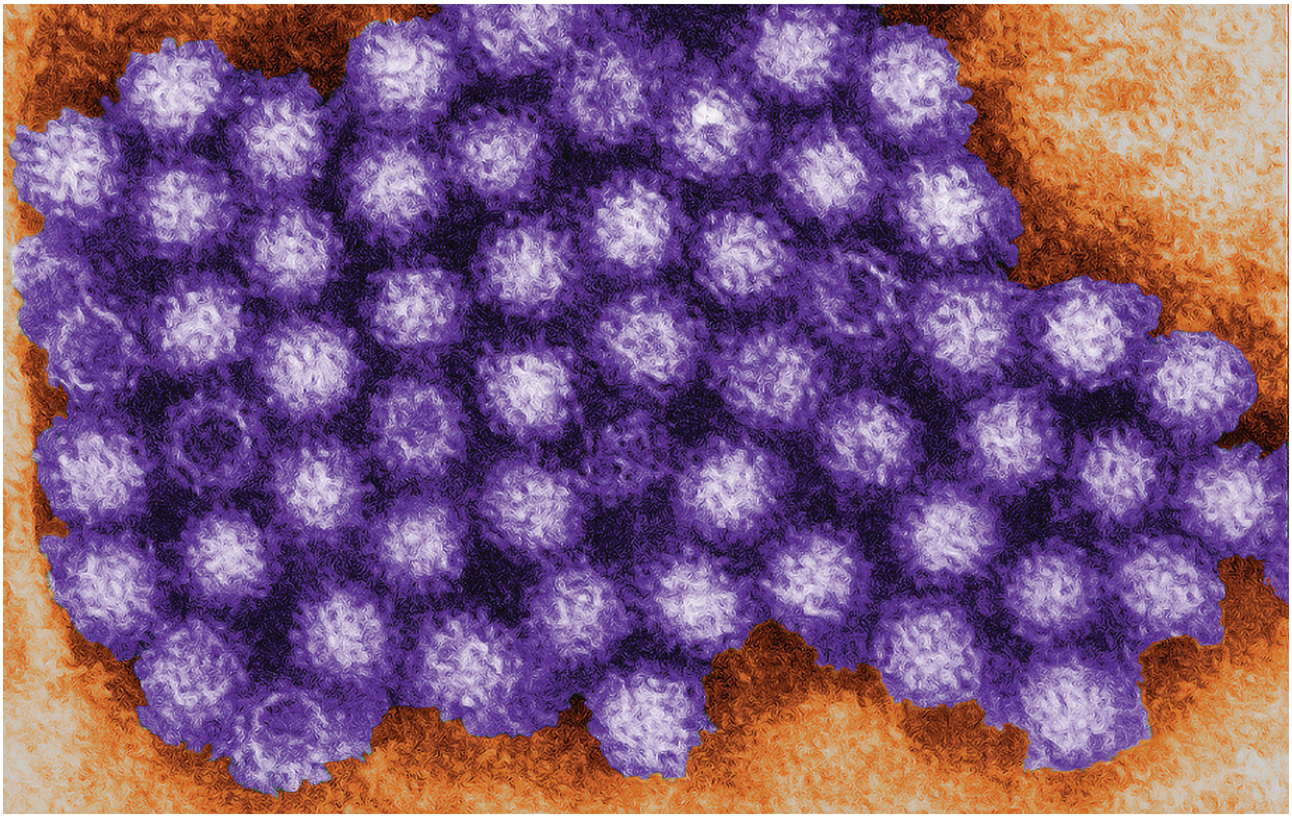
NoV infections follow a seasonal pattern, with most cases occurring during cooler winter months. The incubation period is 12 to 48 hours, followed by a self-limited illness that lasts 12 to 60 hours. Once ingested, noroviruses rapidly infect cells within the small intestine. Rupture of these intestinal cells drives the major symptoms of viral gastroenteritis, with acute onset nausea, abdominal cramps, vomiting and watery diarrhoea.

Because there are no specific antiviral medicines to treat NoV infections, management of infected patients is based primarily on replacement of their lost fluid and electrolytes. The goal of this supportive treatment is to reverse dehydration and electrolyte abnormalities. Anti-emetics and anti-motility agents may also play a role.



Digitally-colourised, transmission electron microscopic (TEM) image revealing some of the ultrastructural morphology displayed by a cluster of norovirus virions. Image courtesy of CDC/Charles D. Humphrey.

Norovirus infections in elderly patients

Older adults are at increased risk of severe NoV illness, compared to younger adults. The reasons behind this include age-related changes in immune (B and T lymphocyte) cell function and the presence of co-morbidities (such as immunosuppression, renal disease, cardiovascular disease and/or functional disability) that can reduce an individual's ability to mount a successful immune response to infection. This then results in more severe or extended symptoms or exacerbation of underlying conditions.[10]

There is a steep increase in NoV-associated mortality rates with age, rising to around 20% for those ≥65 years of age and 30% for those ≥70 years of age. In nursing homes, >90 % of NoV outbreaks involve transmission from person-to-person. This contact can occur through caregiving, close contact between residents and staff or frequent movement of infected individuals from room to room and between facilities. The rate of NoV infection in a nursing home is influenced by the level and adequacy of nursing support, as well as by the underlying health status of residents. Inadequate nursing care increases NoV-associated mortality.[10]

A 2015 systematic review of NoV infections in residents of nursing homes, which collated data from 29 studies, concluded that older adults are at greatly increased risk of severe NoV infections, with significant associated negative health outcomes. With elderly patients, hospitalisation rates were higher and infections were more severe and resulted in longer stays than for younger patients. NoV-associated mortality rates were approximately double for people once they were 65 years and older. Estimated annual NoV rates and number of cases among older adults in high income countries (including Australia) were up to 120 per 10,000, with up to 13,000 NoV-associated deaths per annum. NoV was responsible for approximately 10-20 % of hospitalisations for gastroenteritis and for 10-15 % of deaths from gastroenteritis. Up to 45% of nursing homes experienced a NoV outbreak each year.[10]

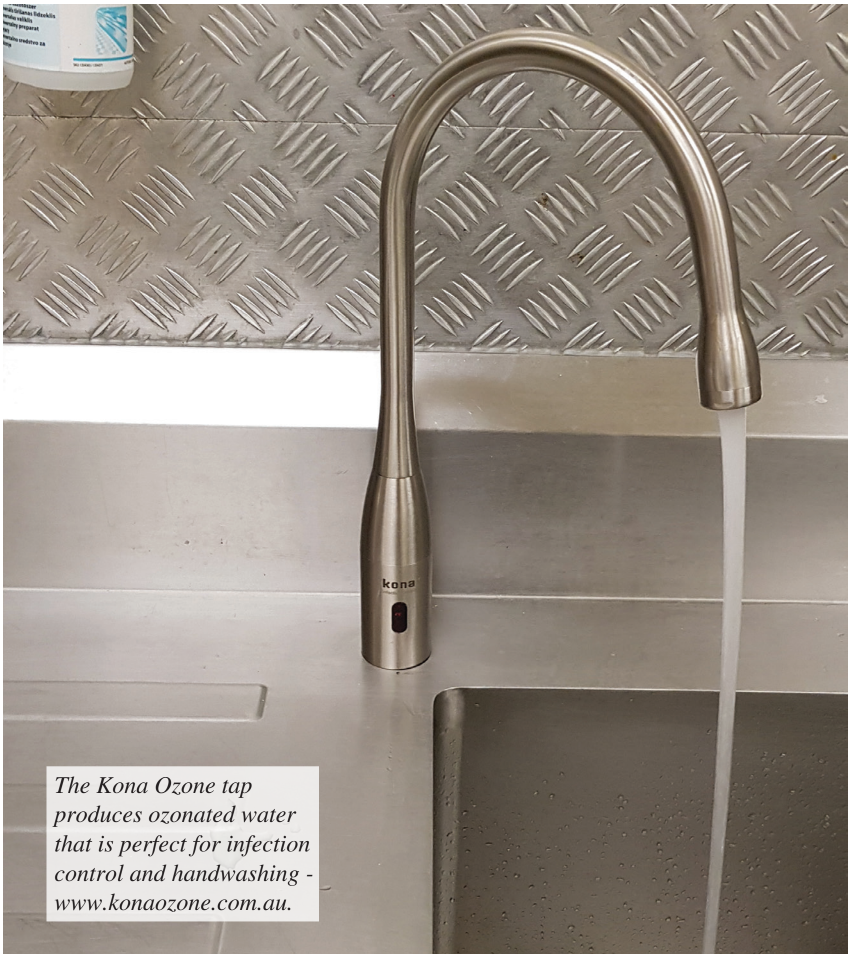
A norovirus outbreak will typically show two or more of the following features:

- Vomiting in more than half of the affected individuals;
- Typical incubation of 24-48 hours;
- Typical duration of 12-60 hours; and
- The absence of any bacterial pathogens in stool culture samples.

NoV infections have serious health consequences, causing morbidity and mortality, particularly in elderly patients, young children and people with compromised immune responses.[11-12]

Infection control challenges with NoV

Early recognition and prompt implementation of infection prevention and control measures are essential for limiting the severity of a norovirus outbreak. Those infection prevention and control measures must address both patients and their healthcare providers. NoV are quite able to survive in the general environment and are NOT readily inactivated by alcohol-based hand hygiene products.



The Kona Ozone tap produces ozonated water that is perfect for infection control and handwashing - www.konaozone.com.au.

In a nursing home setting, affected residents should be placed on contact precautions for at least 48 hours following symptom resolution (e.g. wearing gowns and gloves and a mask, performing hand hygiene with soap and water). The facility should minimise resident movements, suspend group activities and consider restricting access to an affected ward. Staff assignments should avoid having asymptomatic and potentially-exposed staff interact with asymptomatic and unexposed residents.[12]

Targeted infection control measures for NoV outbreaks also include: additional staff training on infection control practices; a comprehensive communication strategy for informing staff, patients and visitors of up-to-date outbreak information including education on symptoms, transmission and prevention strategies during suspected or confirmed norovirus outbreaks; and closure of wards or the entire nursing home. Closing off a ward for at least 72 hours after the last case of norovirus to allow thorough cleaning to be performed is designed to prevent new susceptible patients coming into contact with NoV. Ward closure is an expensive and difficult decision to make. Other control measures include screening of all visitors for gastrointestinal symptoms by nursing staff to stop any who screen positive from visiting patients for at least 3 days. Visitor restrictions have also been used, e.g. restricting visiting privileges to immediate family only and prohibiting or discouraging children from visiting during NoV outbreaks.[13]

Prevention of NoV infection relies on frequent hand hygiene, limiting contact with people who are infected with the virus and disinfection of contaminated environmental surfaces. There are no commercial NoV vaccines, although some vaccine candidates are going through clinical trials. A major challenge is that there are many NoV strains. It is unclear if a vaccine will provide durable protection against the large range of genetically and antigenically diverse NoV strains.

Hand Hygiene and NoV

One of the primary control strategies to interrupt NoV transmission during outbreaks is appropriate hand hygiene. The correct approach is to use liquid soap and running water for handwashing, for a minimum of 20 seconds, after patient contact with confirmed or suspected cases.

Conventional alcohol hand gels used in health care settings do not have sufficient virus-inhibitory effects. This could be due in part to their low water content. Studies of experimental human norovirus hand contamination have shown that a liquid soap wash and water rinse is superior to ethanol-based sanitizers.[14] As will be discussed further below, the water used for that handwashing procedure could be ozonated, to provide a potent disinfecting action.

Environmental disinfection and NoV

Environmental persistence of NoV has been reported in settings ranging from health care environments to food products and food preparation sites. In health care settings, studies have focused on the cleaning of high-touch surfaces, such as patient bathrooms, tables, chairs, computers and commodes, in addition to floors.[15-17]

Noroviruses are very resistant to chlorine-based products such as sodium hypochlorite and to water chlorination, even at free residual chlorine levels of 4 mg/litre (ppm) and contact times as long as 30 minutes. The fact that noroviruses are much more difficult to inactivate than other enteric viruses explains why outbreaks of waterborne disease caused by NoV have occurred so frequently.[18]

Water ozonation to enhance infection control

Ozone treatment is an effective approach for disinfection because ozone is an extremely reactive oxidant and a powerful and rapidly acting disinfectant. By oxidation, ozone causes a conformation (shape) change of viral capsid proteins. This either destroys the viral capsid or prevents the binding of the virus to receptors on host cells. It also attacks viral nuclei acids.[19]

Ozonation has been used to disinfect drinking water in Europe since 1906, because of its ability to destroy or inactivate bacteria, viruses, amoeba and parasites in clean water.[20,21] For similar reasons, it is also used widely to disinfect foods, inactivating bacteria and viruses as well as residues of pesticides.[22-27]

Ozone is effective at treating enteric viruses, such as rotaviruses and hepatitis A virus.[28-31] Ozone treatment is highly effective at inactivating NoV present in water.[32] It is likewise as effective when noroviruses are present on foods that are otherwise difficult to treat and are readily able to transmit NoV infections, such as berries.[33]

Raw sewage contains over 300 different viruses in addition to NoV, such as hepatitis A virus, hepatitis E virus, rotavirus, adenovirus, astrovirus, parvovirus, coronavirus, poliovirus and other enteroviruses. Ozonation is known to inactivate NoV as well as these other enteric viruses of concern and for this reason, it is used widely in wastewater disinfection as part of sewage treatment.[34-37] Ozone treatment of sewage eliminates all these viruses, preventing their release from the sewage treatment plant into natural watersheds, where many of these viruses can persist for long periods of time and from there, cause infections of new hosts who come into contact with contaminated water.[38]

More than 99% of NoV can be inactivated by ozone at 1 mg/litre (1 ppm) within 2 minutes. This process works well in both cold tap water (5°C) and water at room temperature (20°C). Temperatures in that range do not have a significant effect on the effectiveness of ozone for inactivating NoV.[39] As well as being highly effective, there is no residue after disinfection with ozone.

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The practical application of the above information is that specially designed taps which ozonate water are ideal for handwashing procedures in nursing homes. They can also be used in dental clinics and other health care facilities.

Clostridium difficile infection (CDI)

Older adults are at increased risk for infections caused by *C. difficile.* Fatal infections with this bacteria are common in adults aged ≥ 65 years. In fact, CDI is the leading cause of deaths from gastroenteritis, being then followed by noroviruses, followed then by bacteria such as *Shigella, Salmonella, Campylobacter* and *E. coli.* Additionally, ingestion of food contaminated with enterotoxins produced by *Staphylococcus aureus, Clostridum perfringens* and *Bacillus cereus* may also lead to outbreaks of nausea and vomiting in a nursing home.[12]

Once ingested by a vulnerable host, spores of by *C. difficile* germinate in the intestine to become toxin-producing vegetative bacteria. Infected patients experience a watery diarrhoea, sometimes accompanied by abdominal cramping and discomfort. While some patients may mount a fever, symptoms of nausea and vomiting are not typical features of CDI. This makes it possible to distinguish CDI from NoV, since NoV causes nausea and vomiting, but CDI does not.

The diagnosis of CDI is based on the patient having 3 or more unformed stools within 24 hours and a stool test positive for toxigenic *C. difficile* or demonstration of pseudomembranous colitis.

Because of their severe diarrhoea, patients with CDI need fluid support, electrolyte replacement and, for severe cases, parental therapy. Severe CDI can even cause an ileus, leading to a clinical presentation of abdominal pain and distention without diarrhoea, with the individual appearing toxic.

Age-specific risk factors for CDI include changes to the gut microbiome with advanced age and reduced functioning of the immune system. Older adults may be unable to mount a robust antibody response and thus be unable to neutralize the effects of *C. difficile* toxins.[12]

Both aging and residence in a nursing home result in a less diverse (and thus less resilient) gut microbiome. Subsequent exposure to antibiotics causes further disruption to the gut microbiome. This renders people who are then exposed to *C. difficile* spores vulnerable to infection for up to 90 days following completion of their treatment with the initial antibiotic.[12]

This point raises the importance of measures to establish and sustain a resilient and diverse gut microbiome, including the use of probiotics. Faecal microbiota transplants (FMT) are an effective and safe intervention for recurrent CDI, including amongst elderly patients.

Following an initial episode of CDI, up to one third of adults can develop recurrent disease, most often within 1–2 weeks of completing treatment with a second type of antibiotic, such as metronidazole or vancomycin. The choice is influenced by whether or not the patient is taking warfarin, with vancomycin the first-line agent for people taking warfarin.[12] Recurrent CDI is not due to resistance to these antibiotics but rather to re-exposure to *C. difficile* spores. These may be the same strain that caused the initial infection (i.e. causing a relapse), or from a new strain of *C. difficile* (thus causing a reinfection), with both happening in approximately equal frequency.

Many elderly patients are taking medications to suppress gastric acid production (such as proton pump inhibitors). These increase the likelihood of recurrent disease and so should be stopped unless there is a strong indication for their continued use.

Prevention of CDI is based on reducing exposure to antibiotics (especially to clindamycin, fluoroquinolones, cephalosporins, monobactams and carbapenems) and to the spores of *C. difficile*. To achieve the second part, it is necessary to reduce the contamination of the hands of healthcare providers and of the general environment with *C. difficile* spores. While symptomatic, people with CDI should remain on contact precautions, with healthcare providers removing their gown and gloves prior to exiting the room, followed by thorough hand washing with soap and water.

A key point is that alcohol-based hand rubs are NOT sufficient to kill or remove the spores that cause CDI.[12] Thus, effective handwashing is critical for preventing the spread and recurrence of CDI. Given the potent effects of ozone on vegetative bacteria and spores,[20-27] ozonation of tap water provides a logical approach to improving hygiene in nursing homes, dental clinics and other health care facilities by inactivating *C. difficile* and NoV on the hands of residents and staff and preventing outbreaks of infection.

About the author

Professor Laurence J. Walsh is based at The University of Queensland School of Dentistry. He serves as the technology editor and infection control of Australasian Dental Practice magazine and is the editor of the ADA Infection Control Guidelines. Prof. Walsh is a noted commentator on and user of new technologies.

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