Noroviruses - Looking at the Evidence for What We Know and What We Do
Dr Chong Wei Ong, Canberra Hospital and Health Services
Broadcast live from the 2017 conference of the Australasian College of Infection Control

Noroviruses
Looking at the Evidence for What We Know and What We Do

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DISCLOSURE
I have no conflicts of interest to declare.

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Background

- about 18% of all cases of acute gastroenteritis worldwide
- about 50% of all gastroenteritis outbreaks worldwide
- 677 million cases in 2010, over 200 000 deaths
- infects persons of all ages
- sporadic vs outbreaks
- “winter vomiting illness”


- Incubation period : 12–48 h
- Nausea, vomiting, abdominal cramps, myalgias, and non-bloody diarrhea, fever [<50%]
- Mild to severe
- Resolution in 2–3 days [up to 4–6 days in hospitalized patients, the elderly and children < age 11 years of age]


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New strain “GII.4-Sydney (Mar 2012)” goes worldwide
Jul 2012 – Jan 2013:
813 outbreaks reported
– 720 (89%) ward/bay closures or restrictions to admissions


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Outbreak management measures

• Strict hand hygiene
• PPE use (gown/gloves/mask/goggles)
• Enhanced Environmental cleaning and disinfection
• Isolation / exclusion [until 48 hrs after last diarrhoeal stool]
  • Hospital patients : contact / droplet precautions
  • Visitor : restrictions
  • Staff : cohorting / exclusion
• Facility / ward closures
• Food safety measures

CDNA. Guidelines for the public health management of gastroenteritis outbreaks due to norovirus or suspected viral agents in Australia 2010. Commonwealth of Australia.

Evidence challenges

PubMed search (1 Nov 2017)
“norovirus”
5194 papers

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Infection control measures for norovirus: a systematic review of outbreaks in semi-enclosed settings
J.P. Harris a,*, B.A. Lopman a, S.J. O’Brien b
Journal of Hospital Infection (2010) 74, 1–9

• assess the evidence for effectiveness of control measures
• 72 outbreaks reported in 47 papers
• differences experienced whether control measures were implemented or not

• ‘We found no evidence that implementing infection control measures affected the duration of outbreaks, or the attack rates either overall (all settings combined) or within particular settings.’

• CONCLUSION : ‘Sound infection control procedures are key to controlling norovirus outbreaks but unfortunately, the present body of the published literature does not provide an evidence-base for the value of specific measures.’
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GUIDELINE FOR THE PREVENTION AND CONTROL OF NOROVIRUS GASTROENTERITIS OUTBREAKS IN HEALTHCARE SETTINGS
Taranisia MacCannell, PhD, MSc1; Craig A. Umscheid, MD, MSCE2; Rajender K. Agarwal, MD, MPH2; Ingi Lee, MD, MSCE2; Gretchen Kuntz, MSW, MSLIS2; Kurt B. Stevenson, MD, MPH3 and the Healthcare Infection Control Practices Advisory Committee (HICPAC)4

1 Division of Healthcare Quality Promotion Centers for Disease Control and Prevention Atlanta, GA
2 Center for Evidence-based Practice University of Pennsylvania Health System Philadelphia, PA
3 Division of Infectious Diseases The Ohio State University, Columbus, OH

OCTOBER 2011

HICPAC Categorization Scheme for Recommendations

<table>
<thead>
<tr>
<th>Rank</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category IA</td>
<td>A strong recommendation supported by high to moderate quality evidence suggesting net clinical benefits or harms.</td>
</tr>
<tr>
<td>Category IB</td>
<td>A strong recommendation supported by low-quality evidence suggesting net clinical benefits or harms, or an accepted practice (e.g., aseptic technique) supported by low to very low-quality evidence.</td>
</tr>
<tr>
<td>Category IC</td>
<td>A strong recommendation required by state or federal regulation.</td>
</tr>
<tr>
<td>Category II</td>
<td>A weak recommendation supported by any quality evidence suggesting a tradeoff between clinical benefits and harms.</td>
</tr>
<tr>
<td>Recommendation for further research</td>
<td>An unresolved issue for which there is low to very low-quality evidence with uncertain tradeoffs between benefits and harms.</td>
</tr>
</tbody>
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<td>Category IA</td>
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</tr>
<tr>
<td>Category IB</td>
<td>27</td>
</tr>
<tr>
<td>Category IC</td>
<td>6</td>
</tr>
<tr>
<td>Category II</td>
<td>19</td>
</tr>
<tr>
<td>Recommendation for further research</td>
<td>8</td>
</tr>
</tbody>
</table>


Human noroviruses – ‘uncultivable’

- Biology / pathogenesis / transmission – infectivity of particles
- Immune responses
- Diagnostic tests – significance of RNA detection
- Disinfectants / Virucidal agents
- Treatment / Antiviral drugs
- Vaccine

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Research & application issues

- Observational or descriptive studies
  - not controlled
  - each outbreak is different
  - ethics of RCT
- Multiple interventions
- Heterogeneity of settings
- Incomplete adherence to control measures
- Basic science technical difficulties
- Applicability of basic science to clinical setting

Evidence challenges

- **Adequacy (Absence)**
- **Antagonism**
- **Applicability**
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Selected topics

- Hand hygiene
- Isolation / exclusion
- Personal protective equipment

Hand hygiene

Alcohol-based hand rub
or
soap and water?

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Method of evaluating reduction in infectivity

In general:
Virus culture with/without hand sanitizer

**BUT**

Human norovirus (HuNoV) “cannot” be cultured

- Human norovirus (HuNoV)
  - Quantitative RNA by RT-PCR with/without hand sanitizer
    - Presence of RNA does not necessarily mean infectivity
    - Sanitizers target capsid
  - Virus culture with/without hand sanitizer using surrogate (Feline Calicivirus FCV vs Murine Norovirus MNV)
    - Correlation between FCV and MNV variable
    - Correlation to RT-PCR poor

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Alcohol-based hand rub (ABHR) v. Soap / water

- Finger pad testing – genomic copies determined by RT-PCR

<table>
<thead>
<tr>
<th></th>
<th>MuNoV1</th>
<th>HuNoV G1.4</th>
<th>HuNoV GII.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soap and water</td>
<td>&gt;5 log(_{10})</td>
<td>&gt;6 log(_{10})</td>
<td>4 log(_{10})</td>
</tr>
<tr>
<td>30 sec</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propanol hand-rub</td>
<td>&gt;1.2 log(_{10})</td>
<td>&gt;2.6 log(_{10})</td>
<td>&gt;3.3 log(_{10})</td>
</tr>
<tr>
<td>30 sec</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- “Washing hands with soap and water is better than using alcohol-based hand disinfectants in removing noroviruses from hands.”


In vitro comparison

Tube suspension test:

**ALCOHOL**
- A 45% ethanol
- B 55% ethanol
- C 90% ethanol

**SOAP**
- D 1% triclosan soap
- E 4% chlorhexidine soap
- F Povidone iodine (0.8%) soap

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David D. Blaney, MD, MPH,a,b Elizabeth R. Daly, MPH,a,b Kathryn B. Kirkland, MD,a Jon Eric Tongen, PhD, MSPH,a,b,c
Fassy Tassler Kelso, PhD,a and Elizabeth A. Talbot, MD,b,c
Atlanta, Georgia; Concord and Hanover, New Hampshire; Augusta, Maine; and Burlington, Vermont

- Survey
  - 91 of 160 facilities (60%) responded
  - 61 facilities reported 73 outbreaks;
    29 confirmed as norovirus
  - Self-report: no objective data on hand hygiene practices

Facilities reporting that staff were equally or more likely to use ABHS than soap and water for routine hand hygiene had higher odds of a confirmed norovirus outbreak than facilities with staff less likely to use ABHS (adjusted odds ratio, 6.06; 95% confidence interval: 1.44-33.99).

This study suggests that preferential use of ABHS over soap and water for routine hand hygiene might be associated with increased risk of norovirus outbreaks in LTCFs.


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• Cross sectional study: association, not causation
• Multivariate analysis failed to take into account hand hygiene compliance
• Alternate hypothesis for association: better infection control = better detection
  – univariate analysis: having an IC practitioner associated with greater likelihood of confirmed HuNoV outbreak

“Researchers have the responsibility to draw valid conclusions from their studies.”

Jury still out???

• WHO
  – “WHO experts recommend the use of alcohol-based handrubs during outbreaks of noroviral gastroenteritis.”
• CDC
  – “… hand washing with soap and running water … reduce norovirus contamination … whereas hand sanitizers might serve as an effective adjunct … but should not be considered a substitute…”

• NHMRC
  – “Hand hygiene should be performed using soap and water when *Clostridium difficile* or non-enveloped viruses such as norovirus are known or suspected to be present and gloves have not been worn.”


Isolation and exclusion

Should infected patients be isolated?

When should infected patients be removed from isolation?

When should infected staff be allowed back to work?
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Norovirus infections in a tertiary care centre - individual cases do not necessarily lead to an outbreak
• Monitored exposed asymptomatic patients next to infectious patients for symptom development
• Of 102 patients exposed to 94 infectious patients only 11 patients developed typical norovirus symptoms - secondary attack rate only 10.8%
• CONCLUSIONS:
  1. Patient-to-patient transmission is potentially overestimated
  2. Future prevention strategies should consider personal risk factors of exposed patients


• Peak viral shedding
  – 3 days post-symptom onset


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• Asymptomatic shedding
  – After symptomatic infection
    • Median 28 days [range 13-56 days] (months or years in immunosuppressed)
  – Before symptomatic infection
    • 3 to 14 hr before symptom onset
  – During asymptomatic infection
    • Prevalence: 1.0% to 49.2%
    • ?? lower viral loads than symptomatic infection


Nosocomial Transmission of Norovirus Is Mainly Caused by Symptomatic Cases

• Netherlands; 5 nosocomial outbreaks; n = 28
• Enhanced sampling – 65 extra cases (with and without symptoms; patients and staff)
• Shedding kinetics – prediction of infection onset
• Modelling of transmission pathways and reproduction numbers


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Chronic Norovirus Infections

- Primary Immunodeficiency
  - Common Variable Immune deficiency
  - Severe Combined Immune deficiency
- Haematologic malignancies
- Stem Cell Transplantation
- Solid Organ Cancers
- Solid Organ transplant recipients
- HIV infection (advanced)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Shedding (days)</th>
<th>Genotype (variant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>PID/Hyper IgM, stem cell transplant</td>
<td>939</td>
<td>GII.4 (Apeldoorn 2007)</td>
</tr>
<tr>
<td>D</td>
<td>HIV/carcinoma CD4 = 8</td>
<td>205</td>
<td>GII.4 (New Orleans 2009)</td>
</tr>
<tr>
<td>E</td>
<td>PID/SCID</td>
<td>554</td>
<td>GII.4 (New Orleans 2009)</td>
</tr>
<tr>
<td>H</td>
<td>PID/CVID</td>
<td>641</td>
<td>GII.4 (New Orleans 2009)</td>
</tr>
<tr>
<td>I</td>
<td>Leukemia/ALL</td>
<td>417</td>
<td>GII.4 (New Orleans 2009)</td>
</tr>
<tr>
<td>M</td>
<td>PID/IRAK4 deficiency</td>
<td>385</td>
<td>GII.4 (not assigned)</td>
</tr>
<tr>
<td>O</td>
<td>PID/PLAID</td>
<td>304</td>
<td>GII.4 (not assigned)</td>
</tr>
<tr>
<td>P</td>
<td>PID/SCID</td>
<td>677</td>
<td>GII.2</td>
</tr>
</tbody>
</table>

NOROVIRUS SHEDDING DURATION

PID / SCT / Haem and solid organ cancer:
Median 485.5 (range 205 – 939) days

Solid Organ Transplant:
Median 218 (range 32 – 1164) days

Bok K et al. Open Forum Infect Dis. 2016 Sep 8:3(ofw169.
### Personal Protective Equipment

Should masks be worn by healthcare staff during patient care?

<table>
<thead>
<tr>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
<td>2007</td>
<td>2010</td>
<td>2011</td>
<td>2012</td>
</tr>
<tr>
<td>Infection control Precautions</td>
<td>Standard</td>
<td>Contact + Droplet (if faecally incontinent)</td>
<td>Standard [sporadic] Contact [outbreak]</td>
<td>“Contact”</td>
</tr>
<tr>
<td>Remarks</td>
<td>Contact - if incontinent; Mask use if cleaning heavily soiled area</td>
<td>Mask use if patient symptomatic</td>
<td>Mask use if anticipated facial splash especially from vomiting patient</td>
<td>Mask only if there is a risk of droplets or aerosols</td>
</tr>
</tbody>
</table>

Person-to-person transmission

• Contact with faeces or vomitus
  – Direct contact
  – Fomites / environmental contamination
  – Aerosolisation / droplets

Airborne Norovirus

• 48 air samples collected during norovirus outbreaks in 8 healthcare facilities – 47% positive for virus

<table>
<thead>
<tr>
<th>Location (air sample)</th>
<th>Positive / Total samples (%)</th>
<th>Range of Norovirus GII, Genomes/m3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients’ rooms</td>
<td>14 / 26 (54%)</td>
<td>$1.46 \times 10^1$–$2.35 \times 10^3$</td>
</tr>
<tr>
<td>Nurses’ stations</td>
<td>3 / 6 (50%)</td>
<td>$1.35 \times 10^1$–$1.22 \times 10^2$</td>
</tr>
<tr>
<td>Hallway/common areas</td>
<td>6 /16 (38%)</td>
<td>$1.54 \times 10^1$–$5.43 \times 10^2$</td>
</tr>
</tbody>
</table>

• HCW may inhale up to 60 copies of virus during a 5-minute stay in room – then ingest – may be sufficient to cause disease

• **Consider use of full airborne precautions**
CONCLUSION

• Much of what we do is based on low quality or ‘difficult’ evidence
• Guidelines are useful but don’t get dogmatic
• More research is needed – well-designed to answer questions; not simply ad hoc
  – Basic science (cultivable)
  – Interventions
• Until then, follow guidelines plus use new data
• Lots of common sense!

Discussion paper

Infection control: Evidence-based common sense

Stephanie J. Dancer a,b,*

• When compared against classical sciences, infection control is very much the ‘new kid-on-the-block’.
• …activities directed by infection prevention and control are more likely to reflect ‘common sense’ rather than robust evidence…
• Common sense, however defined, eventually turns into scientific evidence at some stage but this progression relies upon continued accumulation, evaluation and integration of evidence by professionals and policy makers.

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Thank you

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