Norovirus Understanding diversity in relation to detection, healthcare impact, control and prevention

Prof. Marion Koopmans, Erasmus University of Rotterdam, The Netherlands
Broadcast live from the 2014 Healthcare Infection Society conference, Lyon, France

Norovirus background
- Most common etiology of acute gastro-enteritis
- Transmission person-to-person, environmental, foodborne, waterborne, zoonotic?
- Mostly mild illness, self limiting
- More severe disease in persons with co-morbidities
  - Cardiovascular patients (OR 17.1, 2.2-403)
  - Renal transplant recipients (OR 13, 1.7-281)
  - Age >65 (OR 11.6, 1.9-204)
  - Immunosuppression (OR 5.7, 1.8-20.1)
- Sporadic cases and outbreaks
- Short-lived immunity

Norovirus diagnostics
- No cell culture model (?)
- RT-PCR based for individual patients
  - Conserved genome targets
  - Note genetic diversity: validation of PCR assays is difficult (GII4 and GII3 most commonly detected in patients)
- ELISA for outbreak diagnostics (insufficient sensitivity for case-based diagnostics)
- Genotyping
  - May be used in outbreak investigations
  - Capsid and polymerase gene based

Family, genus, genogroups, genotypes, variants

Dominant Variant (GII.4)
- GGI
  - Seasonal
  - ~20%
- GGI
  - More varied
  - ~80%
- Food

Clarke et al., 2010; Verhoef et al., 2011; Kroneman et al., 2013

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Typing tool and nomenclature; www.noronet.nl

Norovirus-GeneTyping Tool Version 1.0

Report:
- Genotype and subtype assignment
- Downloadable results = reference sequences in multiple file formats
- Phylogenetic tree against reference strains
- Alignment
- PAUP log file

Details of method
- Tables of the reference sequences for each taxonomic level

Batch job option (e.g. retyping of up to 10,000 sequences to adapt to standardized nomenclature)

Downloadable results + reference sequences in multiple file formats

Report:
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Based on outcome of nomenclature discussion

http://www.rivm.nl/en/Topics/N/NoroNet

Noronet entries, 16 November 2013-16 November 2014
N = 1700

Features from the noronet module

GII4 noroviruses persist through evolution

Effects of mutations:
- Escape mutants (drift)
- New host range
- No protective immunity
- Differences in host cell binding
- New host range

Siebenga et al., 2008; Allen et al., 2008; Parre et al., 2012; Tan et al., 2003
Lindemans et al., 2008; Bok et al., 2009; Siebenga et al., 2010

Increased severity risk groups (age, comorbidity, immunocompromised)
- Increase in hospitalisations
- Mortality
- Chronic infections

Van Asten et al., 2011; Lopman et al., 2004; Mattner et al., 2006; Randy et al., 2010; Siebenga et al., 2008

Genetic susceptibility: wide range of options

Takahashi et al. Transplantation Reviews, 2010;
Shanker et al. J Viral, 2011

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Genotypes differ in host binding

May become relevant when looking into antivirals

1. Rapid identification
2. Immediate implementation of infection control measures
3. Debate on alcohol based desinfectants *(no model)*
4. Experimental evidence for decontamination with H₂O₂
5. Preclinical evidence for post exposure prophylaxis

Outbreaks reflect high prevalence of NoV in community

Ahmed et al., Lancet, 2014

Notifications for infectious gastro-enteritis from hospitals, Germany

1. Most by children. (Beersma et al., 2009)
2. Increase Dx omitted patients (X ray, coloscopy, biopsies) (Beersma et al., 2012)
3. Mainly GII3 and GII4 (Sukhrie et al., 2011)
4. 1:1 ratio of infected HCW to (recognized) patients (Sukhrie et al., 2012)
5. Virus evolution in chronic shedders (Siebenga et al., 2008)
6. Transmission from chronic shedders (Sukhrie et al., 2008)
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Chronic norovirus (>90 days) patients in the Erasmus Mc, Netherlands, 2006 - 2013

All patients have severe underlying illness: 21 of 26 (81%) patients have undergone a solid organ or stem cell transplantation.

Use of strain typing for hospital epidemiology

Strain typing on partial genome sequence against background
- Assignment of clusters
- Ruling out clusters
- Resolution depends on genotype

Transmission chain analysis (who infected whom?)

Review of studies showing evidence for complications and/or sequellae
Petrignani et al., in preparation

Hospital epidemiology using NGS

Fig. 1. Time course of virus shedding in (a) symptomatic and (b) asymptomatic subjects. Median and 95% interval of the predicted virus concentration (log_{10} number of viruses/mL) are shown. Also shown are observed virus concentrations, as measured C, values translated by means of the standard curve (Supplementary Fig. A5). Multiple observations from the same subject are connected.
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HCW without symptoms marginally contribute to spread of infection
HCW with symptoms do

Sukhrie et al., 2012

Human norovirus culture in B cells, with bacterial extract containing HBGA

If confirmed:
Immunological studies
Infectivity studies
Inactivation studies

Jones et al., science, 2014

Take home messages
NoV infection is widely underdiagnosed
NoV diagnostics should be routine, as part of hospital infection prevention policy
Check product information for validation against uncommon genotypes
Be aware of chronic norovirus in immunocompromised patients
Strain typing / sequencing may inform hospital epidemiology or source tracking

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Global noronet and FBVE network

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