Viral gastroenteritis – noroviruses and beyond.

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Viruses in May 2013

Acute Gastroenteritis

• Major cause of morbidity and mortality worldwide:
  > 700 million cases of acute diarrhoea yearly
  > 1.8 - 2.5 million deaths annually
   - all age groups (young, adolescents, middle aged, elderly)

In Australia:
• Estimated that 17.2 million cases of diarrhoea
  (Hall et al 2005)
• In children:
• >200,000 GP visits for mild-moderate disease
  (Hellard et al. 2003)
• 20,000 hospitalisations
  (Carlin et al, 2001)
Viruses associated with gastroenteritis

Major viral agents implicated in human disease:

- Rotaviruses
- Caliciviruses
  - Noroviruses
  - Sapoviruses
- Astroviruses
- Adenoviruses 40, 41

Norovirus

- Family Caliciviridae
- Non-enveloped icosahedral particles (27-34nm)
- Single capsid protein (58-60kDa)
- ss positive RNA genome, 7.4-7.7kb, (VPg, poly A)

- 4 genera (2 infect humans)
- No cell culture system for human viruses.
**Family Caliciviridae**

- Classification: four genera
  - **Norovirus** – found in human, cows and pigs
    - Most common cause of human illness
    - 5 genogroup: 3 infect humans, 1 bovine, 1 murine
    - 31 clusters (8 GI, 19 GII, 2 GIII, 1 GIV and 1 GV)
    - ORF2 differ by 60% by genogroups and 20-30% within genogroups
  - **Sapovirus**
    - found in humans and pigs
    - “Saporo-like” agents
  - **Vesivirus:**
    - Animal viruses – feline
  - **Lagovirus:**
    - Mainly in rabbits/hares.
    - Rarely has been isolated in humans

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**Role of norovirus in acute gastroenteritis**

- Norovirus is a major human pathogen across the globe:
  - Estimated to cause:
    - 95% of non-bacterial gastroenteritis in outbreaks in industrialized countries
    - 50% of all gastroenteritis outbreaks worldwide
    - all age groups susceptible
      - young, adolescents, adults, elderly
  - Estimates of disease burden of norovirus
    - USA: 21 million illness
      - >71,000 hospitalisations
      - 800 deaths annually (Lopman 2011; Scallan, 2011)
    - UK: 600,000 - million people/year
Role of norovirus in childhood disease

• In children <5yrs in developing countries, estimated to cause:
  over 1 million mild-moderate cases
  >200,000 deaths (Patel et al 2008)

• Norovirus is responsible for ~12% of severe gastroenteritis cases in children in developed setting
  – Hospitalisation rates vary between countries:
    Korea 36% 2005-2006
    Italy 47% 2004
    France 14%
    Chile 8% (53/684)
    South Africa 3.3% (43/1296)

So what is the role of norovirus in Australian children?

Norovirus prevalence in Victorian children

Infectious cause children admitted to RCH with acute gastroenteritis, n=1,250 (1998-2002)
- Rotavirus – 68%
- Norovirus – 9%

• Norovirus second most important cause of severe gastroenteritis in children (prior to rotavirus vaccine)

Kirkwood et al 2005
NoV genotype variation in children in Victoria

- Multiple types circulate each year
- GII.4 dominant type each year
- GII.3 has emerged as an important type in past 3 years

Kirkwood et al., 2005; Mahar et al, 2011

Importance of GII.3/GIIb in children worldwide

GII.3/GIIb is a prevalent type causing NV disease in children worldwide since at least 2001
- India (GII.3/GIIb)
- Tunisia (GII.3/GIIb)
- The Netherlands (GIIb)
- Japan (GII.3/GIIb)
- Thailand (GII.3)
- Italy (GIIb)
- Sweden (GIIb)
- Germany (GIIb)

This type is an important cause of disease in children, similar to impact of GII.4 overall.

Has the introduction of Rotavirus vaccine program had an impact on Norovirus disease?

**Rotavirus vaccine program – Australian perspective**

- Rotavirus vaccines available since 2006
  - Rotarix (GSK Bio); RotaTeq (Merck)
  - Introduced into National Immunisation Program: 1\textsuperscript{st} July 2007
    - provided free to all Australian birth cohort (eligible)
    - Northern Territory: Oct 2006
- Each state/territory decision on vaccine to use
  - RotaTeq (black)
    - Vic/ SA/ Wa/ QLD (60%)
  - Rotarix (yellow)
    - NSW/ NT/ TAS (40%)
Rotavirus vaccines in Australia

- So what has happened “post-vaccine” introduction?
- Vaccine coverage (Dec 2011)
  - 87%: one dose
  - 84% full course: Rotarix & RotaTeq - 2 or 3 dose

Number of hospitalisations coded as RV gastro cases: July 2001 to June 2012 (ACIR)

- 71% decline in rotavirus-coded hospitalisations in infants
- Equates to reduction of 7700 hospitalisations annually (from 261 to 75 per 100 000).
- > 38% decline in non-rotavirus coded AGE hospitalisations

> RVGE and ACGE admissions - SA & QLD.

Direct and indirect impact on rotavirus positive and all-cause gastroenteritis hospitalisations following the introduction of rotavirus vaccination (SA).
(Clarke et al Vaccine 2011)

Reduction in rotavirus hospitalisations in QLD post vaccine introduction.
(Buttery PIDJ 2011)

What impact has RV vaccine had on other infectious agents?
Burden of norovirus in Rotavirus vaccine era

- USA – evaluated causative agents associated acute gastroenteritis in children (1,295 - 2009 & 2010)
  - Norovirus – 21%
  - Rotavirus – 12%

Estimate that in children norovirus infection will results in:
- 1 in 278 will be hospitalised
- 1 in 14 will visit ER
- 1 in 6 will receive outpatient care

- Suggest that norovirus is now the leading cause of acute gastroenteritis in children under 5 in USA.
  (Payne NEJM 2013)

Norovirus transmission & outbreaks
How is norovirus transmitted?

Most common route for NV transmission is via faecal – oral route

Consumption of contaminated food:
- includes salads, ice, water, fresh fruit, bakery goods, cold meats
- poor food-handling, contaminated during preparation and service

Oysters:
NV can bind to the carbohydrates in the gut of shellfish
Sick crew members contaminated the oyster field

Secondary spread:
Aerosol / personal contact / fomites: toys, carpet, handles, surfaces etc.

Norovirus outbreaks settings

Norovirus can occur in any situation where groups gather, includes;
child-minding centres, school outings, camps, restaurants, hospitals, hostels, nursing homes, prisons and cruise ships.

• Outbreaks in 6 European countries (> 50 outbreaks).
- >60% of outbreaks in health-care facilities (eg hospitals, residential homes, schools, nursing homes) predominated.
  348 reported to CDC
  - 39% restaurants,
  - 30% nursing homes
  - 10% schools
**Norovirus outbreaks**

In UK, norovirus infection is associated with significant disease:
- 300-400 outbreaks/year,
- ~50% of hospital outbreaks/year
- 600,000 – 1 million cases each year

In 2012/13 season: 1309 gastro outbreaks
- 1172 (90%) reported ward/bay closures or restricted admissions,
- 882 (67%) were confirmed norovirus

**Winters of discontent**

Norovirus cases peak in winter. The disease struck early this year in the UK, but the overall number of cases may turn out to be no higher than normal

**Why are Noroviruses so infectious?**

Characteristics that facilitate their spread during epidemics
- Low infectious dose (15 viral particles)
- Large viral shedding in stool ($10^5$ – $10^{11}$)
- Prolonged asymptomatic shedding
- Strain diversity
  - multiple antigenic and genetic types
- Incomplete immunity
  - No long term immunity
  - Only genotype cluster specific
- Environmental stability
  - survive chlorine (10ppm)
  - Heating to 60C
**Virus shedding**

Recent studies have shown NV can be shed much longer than previously understood.

**Study 1.**
RT-PCR analysis on longitudinal faecal specimens collected 3-6 months after disease resolution.
- RNA detected 5-15 days after disease onset in 50% of children (4/8).
In a further 2 children, viral shedding was detected for 25 and 38 days, respectively. (Kirkwood et al JCV 2008)

**Study 2**
In elderly patients, the period of viral excretion was on average 28.7 days (median, 28.5 days), with a range of 13.5 to 44.5 days. (Tu et al. JCM 2008)

Thus viral RNA (& virus) was continually detected in post-recovery stage of illness, and transmission risk greater than previously thought.

**Norovirus epidemics**
Global epidemics of Norovirus

- Many global epidemics of NoV in past decade
- Rapid spread of strain:
  - Locally - within a community
  - Within country
  - International impact
- Global spread of NV strain responsible for increase in outbreaks.

Eg. Hunter 2004 variant
- 1st detected in Australia
- >600 outbreaks (OB) in 2004
- NZ – 213 OB June 04
- Hong Kong – 164 OB July 04
- Netherlands – 101 OB Oct 04
- UK - 101 OB Oct 04
- 223 OB Sept 05

Global epidemics of Norovirus

- Only G1.4 strains associated with global outbreaks
  - 1995/96 (US95/96 cluster) - USA
  - 2003/4 (Hunter) - Australia
  - 2006 (2006a) – Europe
  - 2006/7 (2006b) - Europe
  - 2009 (New Orleans) - USA
  - 2012/13 (Sydney-2012) - Sydney
- Increase in outbreak no. associated with each strain (2-5 fold).

NoV outbreaks in NSW. Gastroenteritis outbreaks reported to NSW Health compared to the NoV positives detected by POWH lab

Eden et al
J Clin Virol 2010
Why do GII.4 norovirus strains emergence?

The emergence of global epidemic GII.4 noroviruses is driven by two factors;

i) the generation of point mutations in antigenic regions of the viral capsid (genetic drift),

ii) through recombination between two noroviruses during a co-infection. Exchange of polymerase and capsid genes.

- analogous manner to influenza.

Genetic drift of GII-4 variants: Sept 2003 to Sept 2007

- for several months/years, one cluster of strains was predominant but then new strains emerge rapidly from another cluster.
Antigenic variation of GII.4 capsid protein over time.

Comparison of aa changes and structural location in GII.4 capsid proteins over time

- Each epidemic strain contains genetic differences to previous strains: changes in antibody blockade epitopes (A, D & E) - panel C & A.
- Predicted structure suggests GII.4 epidemic strains emergence with an altered antigenicity – panel D.

- Thus epitopes are evolving over time and correlate with the emergence of new GII.4 outbreak strains.
- GII.4 NoV persistence in the human population is driven by viral evolution that results in antigenic drift and escape from herd immunity.

Control Measures

- Control of norovirus outbreaks remains a challenge due to unique virus characteristics
- Emphasis on preventing/ stopping transmission:
  - early recognition of symptoms
  - Rapid implementation of good practices and environmental cleaning
  - Hand washing!!

- Prevention strategies: Vaccines
  - Norovirus Virus-like particles (GI.1) under clinical evaluation (Ligocyte- USA).
  - Phase II studies showed good homotypic protection
    - Reduced frequency of gastro events & norovirus infections
Conclusions

• Norovirus associated diarrhoea is a major cause of morbidity and mortality worldwide.
  – affect all age groups in all countries
  – Norovirus increased significance in post RV vaccine era
• Epidemics occur regularly
  – multiple transmission routes and vehicles
  – range of viral characteristics assist in emergence
• Global epidemics only occur with GII.4 strains,
• GII.3 important in children
  – emerge due to genetic and antigenic modifications
  – limited immune protection and genetic diversity

Thankyou!