Viral Agents of Paediatric Gastroenteritis

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Viruses in May 2009
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)
Viral agents of gastroenteritis

- Many viruses identified which cause diarrhoea in humans.
- Commonly implicated viruses include:
  - Rotavirus (1973 - Bishop)
  - Norovirus
  - Astrovirus
  - Adenovirus (Ad40/41)

Other viruses – role is less clear:
- Aichi virus
- Bocavirus
- Torovirus
- Picobirnavirus
Causative agents of acute gastroenteritis

To better understand role of enteric viruses in paediatric diarrhoea.

We conducted of survey of aetiology of 1,283 children admitted to RCH with acute gastroenteritis 1998-2002.
Main causes of acute gastroenteritis in children admitted to hospital:

- Rotavirus
- Calicivirus
Rotavirus - Background

- Rotavirus is the single most important cause of severe diarrhoea in infants and young children worldwide.
- Democratic disease: infects all children regardless of socio-economic status.
  - Accounts for 35-50% of diarrhoea
- First infection most severe diarrhoea,
  - 111 million cases worldwide
  - 24 million outpatient visits worldwide
  - 500,000 deaths worldwide
- Primary rotavirus infection does not confer immunity against re-infection, but does protect against development of clinically severe disease.
Estimated Global Distribution of deaths due to Rotavirus Infection

(n=600,000)

1 dot = 1000 deaths
Background

In Australia: rotavirus induced diarrhoea results in:

- 120,000 doctors visits,
- 25,000 emergency department visits,
- 10,000 hospitalisations annually,
- 3-5 deaths (since 2001)

- Improvements in standards of sanitation and hygiene have not been able to control the incidence of rotavirus, so vaccination only realistic option.
Rotavirus age distribution

- Symptomatic infection in children (0-5yrs)
- Asymptomatic infection – adults (except elderly)
- Peak incidence of clinical illness among children is <24 months of age.
- Data of children admitted to hospital collected 2002 – 2006 (NRRC; n= 3278)
  - 20% by 0-6 months
  - 25% by 7-12 months
  - 31% by 13-24 months
  - 76% by 24 months

Australian children admitted to hospital with RV diarrhoea
Seasonal variation

Seasonal peaks in RV disease in temperate climates

Winter epidemics of admissions of children <5 years

VIC, NSW, QLD, SA, WA & TAS - seasonal peaks (July - Sept)

NT: year round, but variable epidemics

Distribution of RV in children hospitalised to RCH with diarrhoea: 1980-1992
Diagnosis

- Detection of virus/antigen in stools (peaks at day 3-4 of disease)

ELISA – DAKO/IDEIA
Latex Agglutination
Electron microscopy (labour intensive)
RT-PCR
**Rotavirus vaccines**

Two vaccines introduced into National Immunisation schedule – 1\textsuperscript{st} July 2007.
- oral, live attenuated vaccines.

- **GSK (Rotarix)**
  monovalent human strain - G1P[8]
- **Merck (RotaTeq)**
  animal-human reassortants (5 strains)
  bovine rotavirus with single human rotavirus gene substitutions.

Both are highly effective in protecting against severe-moderate rotavirus disease.
Rotavirus Structure

RNA Segment

1. VP1
2. VP2
3. VP3
4. VP4
5. NSP1
6. VP6
7. NSP2
8. NSP3
9. VP7
10. NSP4
11. NSP5

Protein

VP2

VP4 Neutralization antigen

VP6 Subgroup antigen

VP7 Neutralization antigen

Subcore
Rotavirus genotypes & Summary of Australia-wide G types: 1997-2006

Worldwide:
10 human G serotypes
11 human P genotypes

110 possible G-P combinations
(only 42 identified)

5 globally common types
- G1P8, G2P4, G3P8, G4P8, G9P8
- represent >85% of all strains
- occasionally other G/P types may represent be regionally common

N= 7,198 samples analysed.
Collected from collaborating centres Australia-wide
Australia-wide distribution of G types: 1997-2008

- Individual types can fluctuate each year, with multiple types present every year.
- Post vaccine era: too early to tell whether vaccine does impact on circulating strains.
  - Common types still persisted – G1 dominant
  - Identified some rare types – G8 & P[9]
Family *Caliciviridae*

- Nonenveloped icosahedral particles (27-34nm)
- Single capsid protein (58-60kDa)
- ss positive RNA genome, 7.4-7.7kb

- Diverse family:
  4 genera of which 2 infect humans

- No cell culture system for human viruses.
Role of norovirus in acute gastroenteritis

• Leading cause of non-bacterial gastroenteritis in outbreaks in industrialised countries – all ages.
• Molecular diagnostics have identified norovirus in 60-95% of outbreak cases in many countries.
  – USA – 81% of 226 OB in 2000-2004
  – Netherlands – 78% of 941 OB in 1994-2005
• Estimates of disease burden of norovirus in USA
  – 23 million illness
  – 50,000 hospitalisations (Mead et al 1999)
• Settings:
  – Many occur in institutions such as nursing homes, hospital wards, and schools, but restaurants and cruise ships are also common settings.
  – Transmission: often contaminated food or water
Role of norovirus in childhood disease

- Norovirus is emerging as a cause of acute sporadic gastroenteritis in children admitted to hospital.
- Approx 20 studies conducted over past 15 years, have shown that NV can range from 3% - 31% as cause of severe disease (ER visit or hospitalisation).
  - Chile: 8% (53/684) - 1997-99
  - varied from 2- 16%
  - Germany: 13% (28/217) - 2001
  - Spain: 7.7% (63/201) - 1996/97

What is happening in Australia?
Incidence of norovirus in Australian children

5 year study:
250 children had no pathogen identified.

RT-PCR identified NV in 113 samples.

Overall incidence rate of 9.2% (113/1,233) as sole pathogen.
Caliciviridae diagnosis

- **Diagnosis**
  - Culture – not developed
  - EM
    - laborious and relatively insensitive
      (requiring $10^6$ to $10^7$ particles/g or ml of faeces).
  - EIA
    - While specific, they do not detect all genetic clusters
  - RT-PCR
    - Multiple PCR assays described in literature to capsid and polymerase gene.
**Calicivirus Classification**

Family *Caliciviridae*

4 genera based on capsid sequence

- **Norovirus** - humans
  (most commonly implicated in disease)
- **Sapovirus** - humans
- **Lagovirus** - rabbits
- **Vesiviruses** - many animals

**Norovirus**

- Genogroup 1: 8 genetic clusters
- Genogroup II: 17 genetic clusters
- Genogroup 4: 1 cluster
Yearly distribution of calicivirus strains
Why are Noroviruses so Infectious? Characteristics that facilitate their spread during epidemics

- Low infectious dose
- Strain diversity
  - multiple antigenic and genetic types
- Prolonged asymptomatic shedding
- Incomplete immunity
  - No long term immunity
  - Only genotype cluster specific
**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.
Global epidemics of Norovirus

• Only NV G11.4 strains associated with global activity/spread
• Rapid spread of strain:
  Locally- within a community
  Within country
  Internationally
• Four global NV outbreaks identified.
  – 1995/96 (US95/96 cluster)
  – 2003/4 (Hunter)
  – 2006 (2006a)
  – 2006/7 (2006b)
• Responsible for increase in outbreak no. - often 2-5 fold higher.

Laboratory Reports of Norovirus-Positive Specimens in England and Wales, 1991 to 2006

Lopman et al., 2008 PLoS Med 187-189
World wide distribution of the “Hunter” G11.4 strain

In 2004 marked increase in OB identifies – corresponded with the emergence of the hunter NV strain
-NSW – 370 OB, by April 159 OB in QLD.

Spread globally:
June and Nov 2004
-New Zealand – 213 OB (June)
-Hong Kong – 164 OB (July)
-Netherlands – 101 OB (Oct)
-UK – 101 OB (Oct) & 223 (Sept 2005)

1. Australia
2. NZ
3. Hong Kong
4. Netherlands
5. Canada
Conclusions

• Viral diarrhoea in children is a major cause of morbidity and mortality worldwide.
• Multiple viral agents are recognised as causes of acute gastroenteritis in children.
• Vaccine programs are in place for rotavirus, and early indications are that they are very effective. None available for Norovirus in foreseeable future.

Ongoing studies are required to understand epidemiology-rare/novel rotavirus that may evade vaccination, and emergence of new viral agents.
Thankyou!