Update on Rotavirus and Other Viral Causes of Acute Gastroenteritis

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Objectives:
- Updated information about norovirus and rotavirus
- Public health impact of rotavirus vaccination program
- Current epidemiological trends
- Importance of public health surveillance systems

Global Impact of Gastroenteritis
(Diarrheal Diseases)

www.who.int/vaccine_research/diseases/diarrhoeal/en/print.html

United States Impact of Gastroenteritis

- Estimates of foodborne illness in the U.S.
  http://www.cdc.gov/foodborneburden/index.html
  - Each year:
    - 48 million people (1 in 6) get sick
    - 128,000 hospitalized
    - 3000 die
  - Estimates can be compounded by community spread
  - Only the common cold reported more often than GE of all cases

Foodborne Gastroenteritis

www.cdc.gov/ncidod/dbmd/diseaseinfo/foodborneinfections_g.htm

Bacterial Agents
- Campylobacter spp.
- Salmonella spp.
- E. coli STEC, ETEC, Other
- Shigella spp.
- S. aureus
- C. perfringens
- C. botulinum
- L. monocytogenes
- V. cholerae
- V. parahaemolyticus
- V. vulnificus
- Vibrio spp.
- B. cereus
- Y. enterocolitica
- Strep spp., Gsp A
- Brucella spp.

Viral Agents
- Norovirus
- Hepatitis A
- Rotavirus
- Sapovirus
- Astrovirus
- Other ???

Protozoan Agents
- Giardia intestinalis
- Cryptosporidium parvum
- Cyclospora cayetanensis
- Toxoplasma gondii
- Trichinella spp.

Noroviruses 2011

http://www.cdc.gov/ncidod/dvbd/revb/gastro/norovirus.htm


A nasty bug and getting nastier
- New pandemic strain identified
- Immunity strain-specific and non-enduring
- Highly contagious; environmentally stable
- Food-borne and community-acquired
- Targets restaurants, schools, chronic care facilities, and cruise ships
- Critical need for personal hygiene!
**Norovirus**

**Virology**
- Family Caliciviridae—ssRNA, non-enveloped, 26-34nm viruses
- 4 genera:
  - Lagovirus
  - Vesivirus
  - Sapovirus
  - Norovirus
  - 5 genogroups
    - GI, GII, GIV—humans
    - GIII—pigs and cows
    - GV—mice
  - 6:25 genotypes (genetic clusters)
  - Ongoing emergence (drift) resulting in strains among genotypes
  - Genogroups currently predominate worldwide

**Reservoir**
- Humans are only known reservoir for human infection

**Modes of Transmission**
- High levels of virus found in stool and vomit
- Transmission via:
  - Food
  - Water
  - Direct person-to-person contact
  - 2° and 3° cases following point-source outbreak
  - Contact with contaminated object or surface
  - Airborne via aerosolization of vomitus

**Epidemiology(1)**

**Clinical Features**
- Incubation period—30-51hr
- Duration of illness—24-72 hours
- Clinical effects across the age spectrum
  - Acute onset of nausea and cramping
  - Vomiting (more prevalent among children) and moderate diarrhea (more prevalent among adults) are hallmarks
  - Low-grade fever in up to 50% of cases
  - Variable constitutional symptoms (e.g., chills, malaise, headache, myalgia)
- Dehydration is most common complication
- May require i.v. replacement fluids
- Most patients recover without incident; fatalities rare

**Epidemiology(II)**

**Pathogenesis and Immunity**
- Exact mechanism of diarrhea and vomiting unknown
- Observation: asymptomatic infection may occur in 30% of infections
  - Susceptibility to infection and illness severity genetically determined
  - Link to ABH histo-blood group antigens
  - Role for asymptomatics in transmission?
- Recent GII.4 strains cause more severe disease
  - More intense symptoms, more fever, longer illness duration (3-4d); greater transmissability
  - Immunity strain-specific, but short-lived (months?)
  - Re-infection common

**Antigenic Diversity**

**Epidemiology(III)**

**Characteristics That Facilitate Spread:**
- Low infectious dose (<10-100 viral particles)
- Prolonged (up to 4w or more) viral shedding even in asymptomatic (>90%)
  - Increased risk from infected food handlers
  - Viral shedding vs. infectivity
- Environmental stability and persistence
  - Survives:
    - up to 10 ppm chlorine
    - freezing
    - up to 60°C
    - use of many routine disinfectants
Norovirus Transmissibility

Outbreaks of Acute Gastroenteritis Settings in the U.S. - 2006

<table>
<thead>
<tr>
<th>Setting</th>
<th>Number of Outbreaks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cruise ships</td>
<td>37</td>
</tr>
<tr>
<td>Long-term care facilities</td>
<td>37</td>
</tr>
<tr>
<td>Restaurants</td>
<td>13</td>
</tr>
<tr>
<td>Hospitals</td>
<td>7</td>
</tr>
<tr>
<td>Colleges</td>
<td>3</td>
</tr>
<tr>
<td>Parties</td>
<td>3</td>
</tr>
<tr>
<td>Other: Schools, daycare, etc.</td>
<td>26</td>
</tr>
<tr>
<td>Total</td>
<td>126</td>
</tr>
</tbody>
</table>

Norovirus Epidemiology (III) - Seasonality

Norovirus Prevention and Control

Prospects for a vaccine
- The clinical and public health motivation is present
- Significant obstacles
  - Is morbidity/mortality severe enough?
  - Lack of in vitro propagation methods
  - Lack of long-term protective immunity
    - A local infection
    - Antigenic diversity:
      - multiple genotypes, strains
      - "influenza-like" drift
      - Pandemic-like global spread of new strains

Recommended Measures
- Practice good hand hygiene
- Aggressive disinfection of contaminated surfaces
- Do not return to work or school until 24-72h after symptoms resolve
  - Particularly important with food handlers
- Aggressive measures for outbreak control in healthcare and LTCFs
**ROTAVIRUS**

**Public Health Importance**

- Most important cause of severe, dehydrating GE in children <5y in all socio-economic groups in all regions of the world
- Responsible for ~ 6% of all mortality in children < 5y
  - Mortality predominately in developing world
    - > 500,000 deaths annually; >2,000,000 hospitalized
    - Malnutrition, less access to Rx, synergy with other pathogens
- However, the story is changing

**Mortality Rate per 100,000 Child Deaths due to Rotavirus Disease**

- > 500,000 deaths annually; >2,000,000 hospitalized
- Malnutrition, less access to Rx, synergy with other pathogens
- However, the story is changing

**Rotavirus**

**Virology**

- Family: Reoviridae
  - dsRNA, 11 segments, non-enveloped
- 7 serogroups A-G; only A, B, C infect humans
- Many serotypes within serogroup A
  - 4 responsible for 90% of pediatric cases worldwide. However...
    - Serotype prevalence varies geographically
    - Reassortment and antigenic drift occur

**Rotavirus**

**Clinical Features**

- Incubation period----24-72 h
- Duration of illness---- 3 to 8d
- Most severe illness in infants 6m – 2yrs
  - Fever, vomiting, diarrhea
  - Dehydration with severe electrolyte abnormalities
- Exacerbating factors: malnutrition, immunodeficiency & poor sanitation
- Decrease in illness severity with age

**Rotavirus**

**Pathogenesis and Immunity**

- Mechanisms of diarrhea and vomiting complex and incompletely understood
- As many as 50% infections subclinical
- Complex immune response
  - Innate, cellular, and humoral mechanisms
  - Re-infections common throughout life; succeeding illnesses milder
  - This is the case even if initial infections asymptomatic

**Rotavirus**

**Epidemiology**

- Human reservoir
- Transmission: person-to-person
  - fecal-oral: very rarely waterborne, foodborne
  - respiratory?
- Characteristics that facilitate spread
  - Virus shed in very large amounts; prolonged shedding
  - Small infectious dose
  - Environmental stability
- Seasonality (“back in the day”)
  - Marked Winter-Spring peak in temperate climates
**Rotavirus**

**Prevention and control**

- Vaccine represents the most promising public health control measure
  - Natural infection provides protection against disease
  - Treatments not readily available
  - Transmission unaffected by improvements in sanitation and hygiene
  - Cost effective

**Wisconsin State Laboratory of Hygiene**

**Rotavirus Vaccines**

- **Rotarix®**
  - Monovalent contains genotype G1P[8]
  - Relies on heterotypic immunity
  - Licensed by FDA in 2008
  - Widely used in Brazil

- **Rotaeq®**
  - Pentavalent vaccine containing G1, G2, G3, G4, P[8]
  - Licensed by FDA in 2006
  - ACIP recommendations in 2006

**Wisconsin State Laboratory of Hygiene**

**Early Returns in the Wisconsin are Promising As Well (I)**

**Early Returns in the Wisconsin are Promising As Well (II)**
No (170 countries or 88% of countries)
Yes (17 countries or 9% of countries)
Yes (Part of the country) (2 countries or 1% of countries)
Introduction in 2009 (6 countries or 3% of countries)
Yes (Risk groups) (1 country or 0.5% of countries)

In 2008, Peru and South Africa had introduced in parts of the country and Colombia for risk groups

Norovirus vs. Rotavirus
An interesting public health comparison

One on the rise
vs.
One on the decline

Norovirus: Laboratory methods

- Cell culture
- RT-PCR
  - High sensitivity, specificity, throughput, same day results.
  - Limitations: Infectious virus, inhibitors
- EIA
  - Sensitivity =55% compared with RT-PCR (Moe, 2004).
  - Specificity =83 to 96% (Gray, et al., 2007)

Norovirus: National Surveillance

- CaliciNet
  - 17 states certified March 2010
  - Wisconsin one of 5 SPHL selected
  - Specimens received from 3 Midwest states
  - Sequences deposited in national database
  - Objectives:
    - Improve surveillance
    - Real-time data exchange
    - Linking clusters of illness
    - Monitor for emerging strains

CaliciNet: Geographical representation

No (17 countries or 88% of countries)
Yes (Part of the country) (2 countries or 1% of countries)
Introduction in 2008 (6 countries or 3% of countries)
No (170 countries or 88% of countries)
**Norovirus diversity**

Norovirus Outbreaks (n =444) reported to CaliciNet
Oct 1, 2009 - May 31, 2010

- May 2009: 100
- April 2010: 200
- March 2010: 100
- February 2010: 50
- January 2010: 25
- December 2009: 15
- November 2009: 10
- October 2009: 5

Norovirus genotypes in WI Sept. 2009-May 2010

- GI.1: 30%
- GII.2: 20%
- GII.3: 10%
- GII.4: 10%
- GII.6: 10%
- GII.3B: 5%
- GII.4_Minerva: 5%
- GII.4_NewOrleans: 5%
- GI.4: 5%

Norovirus genotypes in WI Sept. 2010-Jan. 2011

- GI.1: 20%
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- GII.3: 10%
- GII.4: 10%
- GII.6: 10%
- GII.3B: 5%
- GII.4_Minerva: 5%
- GII.4_NewOrleans: 5%
- GI.4: 5%

**Norovirus WI Surveillance**

- Wisconsin strain surveillance

**Norovirus Epidemiology**

- PANDEMICS occur every 2-4 years!
  - Emergence of novel GII.4
  - Possess different epidemiological profile
  - Attack rate
  - Vomiting & diarrhea
  - Duration of illness
  - 2002 GII.4_Farmington Hills
  - 2006 GII.4_Minerva
  - WDPH investigated 106 AGE v. 23 in 2005!
  - 2010 GII.4_New Orleans
  - WDPH investigated 37 outbreaks in December 2010!

**Norovirus Summary**

- Genetically diverse
- Antigenic drift
- GII.4 pandemic potential
- National and community impact uncertain
- Vaccine faces many challenges
- Knowledge base continues to expand

**Rotavirus Laboratory methods**

- EIA: Sensitivity >90%
  - BioRad Pathfinder, Vidas, Rotaclone, etc…
- Limitations:
  - NPV high
  - PPV low
  - GpA specific
- RT-PCR
- Sequencing
**Rotavirus Molecular Epidemiology**

- US Rotavirus strain surveillance data: 2005-2008 (Hull et al., 2011)

<table>
<thead>
<tr>
<th>Year</th>
<th>Genotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005-06</td>
<td>G1 predominate</td>
</tr>
<tr>
<td>2006-07</td>
<td>G1 predominate</td>
</tr>
<tr>
<td>2007-08</td>
<td>G1 &amp; G3 predominate, G2, G9</td>
</tr>
</tbody>
</table>

**Rotavirus vaccine: Impact on strain diversity and age distribution**

- Key findings (Hull J et al., 2011)
  - Reports from Brazil & Australia described changes in genotype prevalence post-vaccine
  - US: G3 emerged as predominate rotavirus genotype in some sentinel sites (2007-2008)
  - G3 predominated in states primarily using RotaTeq® (natural fluctuation vs. vaccine driven)
  - Mean age of rotavirus patients increased from 13 to 17.8 months in 2007-2008.
  - Is diversity natural fluctuation or vaccine driven??

**Rotavirus surveillance—Wisconsin**

- Collaboration between CDC/WSLH/WI Clinical Laboratories
- Aim is to assist CDC with national strain surveillance
  - Monitor for emerging strains
  - Change in genotype prevalence
  - Ensure vaccines are effective

**Rotavirus specimen submission**

- Please send **ALL** rotavirus positive specimens to WSLH
  - **NO cost** for shipping if using Dunham
  - Specimens can be sent weekly (refrigerated)
  - Sent with Flu surveillance specimens
  - Raw stool or VTM acceptable

**Rotavirus Summary**

- Diverse genome
- Vaccine impact on morbidity & prevalence
- Vaccine impact on strain evolution (genotypes G&P included in vaccine)
  - Brazil and US noted a shift in prevalence of other genotypes following vaccination (Gentsch et al., 2009). Natural fluctuation or vaccine driven?
  - Importance of monitoring viral genotype prevalence.

**Future Concerns**

- Monitoring for emerging strains of norovirus and rotavirus.
- No national surveillance system for norovirus
  - Difficult to assess public health impact
- Emergence of sapovirus
  - Studies have concluded that sapovirus infections are increasing in Europe (Svraka et al., 2010).
- What is the significance of other viral etiologies?
  - Adenovirus 40/41, astrovirus, sapovirus, unknown
Diagnostic gap

• What role do viruses other than norovirus play in outbreaks and AGE morbidity in the US?
  ➢ Etiologies unknown in 12-41% of outbreaks (Lyman et al., 2009 & Finkbeiner et al., 2009).

WI NFBO investigation data:

<table>
<thead>
<tr>
<th>Year</th>
<th>NV</th>
<th>Unknown</th>
<th>%</th>
<th>Other</th>
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</thead>
<tbody>
<tr>
<td>2006</td>
<td>64</td>
<td>13</td>
<td>15.3</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>41</td>
<td>12</td>
<td>22.6</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>90</td>
<td>5</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>102</td>
<td>21</td>
<td>17.1</td>
<td>Sapovirus</td>
</tr>
<tr>
<td>2010</td>
<td>110</td>
<td>27</td>
<td>19.7</td>
<td></td>
</tr>
</tbody>
</table>

References

- Valazquez et al. (1996) Rotavirus infection in infants as protection against subsequent infections NEJM 335: 1022-1028.