# *C. difficile* Infection

November 2010

# Microbiology

- Anaerobic Gram negative spore forming bacillus
- Difficult to culture –"difficile"
- *Hall et al* 1935
  - first described / nonpathogenic
- *George et al* BMJ 1978 / *Larson et al* Lancet 1978
  - association of *C difficile* with pseudomembranous colitis
- Pathogenic strains produce two protein exotoxins
  - Toxin A & Toxin B
    - Genes found on Pathogenecity Locus (PaLoc)
  - Binary Toxin - ?? Role in CDAD

# Epidemiology

- Ubiquitous
  - soil, hospital environments, daycares/nursing homes
- Asymptomatic carriage
  - 15 - 63%  neonates
  - 3 - 33%  infants/toddlers < 2 years
  - up to 8.3%  children > 2 years
  - < 3%  adults
    - 7-26% if in acute care facility
      - 20-50% if C difficile endemic
    - 5-7% elderly in long term care facility
- Association with other enteric pathogens
  - Salmonella/Campylobacter/Shigella/ Giardia/Rotavirus

# Epidemiology

Asymptomatic colonization

- *Shim et al* Lancet 1998
  - protective effect of colonization
- *Kyne et al* NEJM 2000
  - High antibody response to *C difficile* Toxin A(and B)

    → protective
- Toxigenic strains in neonates
  - Immature colonic flora permits colonization
  - Enterocytes lack Toxin A receptors

# Epidemiology

- USA- 3 million cases /year
  - Case mortality- 1-2.5%

Acquisition

  - primarily in hospital setting
    - Hands of HCWs
    - Bedrails/floors/windowsills/toilets
      - inadequately cleaned commodes/bedpans

Rate of acquisition

  - 13% for hospital stays < 2 weeks
  - 50% with hospital stays > 4 weeks
  - Sharing room:
    - *C difficile* + patient – acquisition - 3.2 days
    - *C difficile* – patient – acquisition - 18.9 days

# Epidemiology

- Hospital acquired – up to 87%
  - leading cause of hospital acquired diarrhea ( 20-45%)
  - 1/3 develop CDAD median of 2-3 days after acquisition
- Community acquired – 20%
- 15% - acquired in hospital but symptoms develop at home
- *Kelly et al* – 1998
  - 43% symptom onset at home

Antibiotic Associated diarrhea- not *C difficile* associated

- 5-10%
  - decrease anaerobic flora
  - decrease carbohydrate metabolism
  - osmotic diarrhea

# Epidemiology - CMAJ 2004

## Canada - 1997 survey

- Incidence
  - 38-95 cases/100,000 patient days
  - 3.4-8.4 cases/1000 admissions
- Case fatality – 1.5% directly attributable/15.2% crude
- Cost of readmission- $128,000
- Community acquired – 7.7-12 cases/100,000 person-years
- Prevalence of + cultures:
  - hospital -7-11%
  - LTC - 5-7%
  - ambulatory - < 2%

# Epidemiology

## Canadian Nosocomial Infection Surveillance Program :2004-2005

- Incidence
  - 4.3 cases/1000 admissions
- Case fatality –14.9% crude
  - Attributable - 2.3% directly / 3.5% indirectly
- 23% hyper toxin producing strain (NAP1)
  - UK( 027)/USA(BI)
    - Mutation in *tcdC* gene ( PFGE)
- Quebec and Ontario → increase in cases
- Deaths attributable to CDAD- increased 4-fold

# Epidemiology

## Hypervirulent strain

*tcdC* gene in pathogenicity locus (PaLoc) region of chromosome

→ Negatively regulates production of Toxins A & B

Mutation → loss of negative regulation

→ hyperproduction of toxins and increased virulence

- Mutations at location (-18)(-1) within the gene

Up to 2,000 deaths in Quebec

# Epidemiology

## BC CDAD Project March 2008

- all isolates collected for 1 month - Kelowna

- 8 isolates

Mean age -73.8 yrs

87.5% males/12.5% females

NAP1 (hypervirulent strain) - 1 isolate ( 12.5%)

Any mutation in *tcdC* gene- 4 isolates ( 50%)

Wild type strain – 4 isolates ( 50%)

# Risk factors

- History of Antibiotic use
- Chemotherapy
- Proton Pump Inhibitors- ??
- Medications that alter intestinal motility
- Gastrointestinal tract procedures- (25 fold risk)
- Surgery
- Age > 60 ( 10 fold risk )
- Severe/multiple underlying illnesses
- Hospitalization > 72 hours
- Admission to ICU

# Risk Factors

## History of Antibiotic Use

- Days to months after use
  - 4-9 days
- Increased risk with multiple dose
- > 3 days therapy
- Single dose
  - Surgical prophylaxis/dental prophylaxis
    - AHA guidelines

# Risk Factors

## History of Antibiotic use

- Culprits
  - Clindamycin/cephalosporins(3rd gen) / amoxicillin
  - Quinolones
- Protective
  - Aminoglycosides/macrolides/TMP-SMX/tetracyclines

Note: all antibiotics have been associated including vancomycin/metronidazole

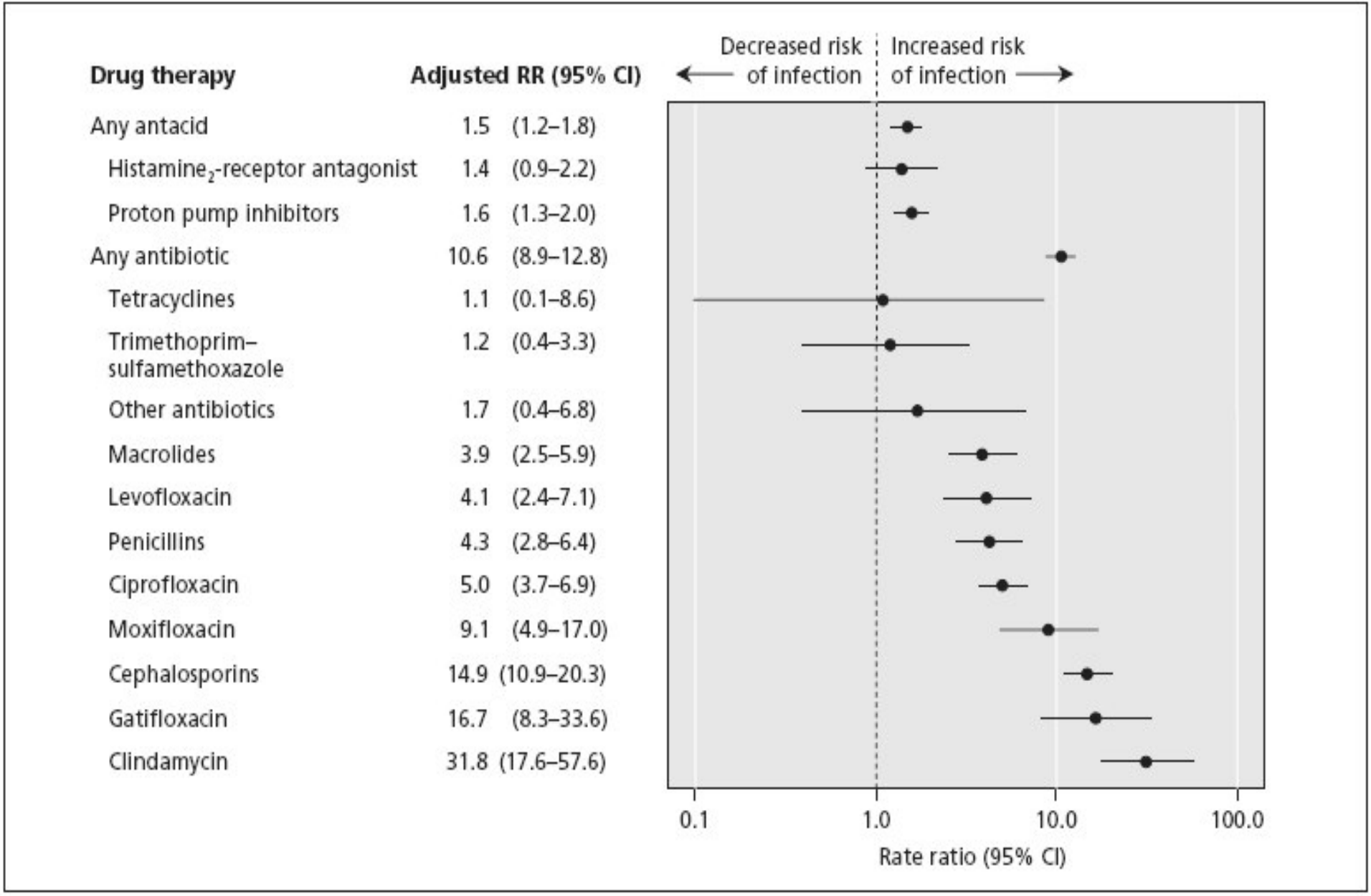


**Figure 3:** Adjusted rate ratios (RRs) of *Clostridium difficile* infection among patients exposed to antibiotics and gastric suppressive therapy in the 45 days before the index date compared with patients not exposed in that period. Adjustments were made for the variables in Table 1 and for the agents listed in the above figure. CI = 95% confidence interval.

# Pathophysiology

- Disruption of normal colonic flora
- Colonization of *C difficile*
  - ingestion of heat-resistant spores
    → convert to vegetative forms in colon

asymptomatic

or

symptomatic state

# Pathophysiology

## Toxigenic Strains → CDAD

- Toxin A - inactivates macrophages/mast cells
  → production of inflammatory mediators
  → fluid secretion/increased mucosal permeability
  – Toxic to neurons/aberrant calcium release
- Toxin B - cytotoxic in vitro/little enterotoxic activity
  – leukocyte chemotaxis/upregulation of cytokines

*Barbut et al* JCM 2002
Toxin A- / Toxin B + virulent *C difficile* described

# Pathophysiology

## Result

→ Actin disaggregation / cytoskeletal rearrangement

→ Profound colonic inflammatory response

- ↑ WBC
- Focal ulcerations
- Accumulation of purulent necrotic debris

  → typical pseudomembranes

# Clinical Manifestations

Asymptomatic → mild→ life threatening colitis

- Asymptomatic - 20% of culture +
- Diarrhea
  - 4-9 days after initiation antibiotic therapy ( 1 day-10 weeks)
  - 72 hours after admission - ↑ risk CDAD
  - watery
  - lower abdominal pain
  - bloody – uncommon (5-10%)
    - occult blood common

# Clinical Manifestations

- Systemic symptoms
  - Fever (30-50%) - usually low grade
  - Anorexia
  - Nausea
  - Malaise
- 1-3% - Fulminant colitis
  - Little or no diarrhea
  - Toxic megacolon
    - Perforation / peritonitis
  - Mortality - 24-38%

# Case Definition

Acute onset diarrhea:

> 3 loose stools within 24 hrs x 2 days, no other etiology

AND

Laboratory confirmation of toxin production

OR

Diagnosis of typical pseudomembranes on sigmoidoscopy or histological/pathological diagnosis of CDAD

OR

Diagnosis of toxic megacolon

# Recurrent Disease

- 20 - 30% ( 5-40%)
- After 1st recurrence →
  Further recurrences up as high as 65%
- Occurs - median 8 days ( 1- 42 days)

*McFarland et al* 1999

- Cost $10,970 per patient

## Cause

- Persistence of *C difficile* spores - 64%
  – Metronidazole/vancomycin have no activity
- Reinfection - 32%
- Not antibiotic resistance

# Recurrent Disease

- Risk
- Female sex
- Chronic renal failure
- Recent abdominal surgery
- Increasing age
- Exposure to additional antibiotics

Response rate to retreatment- 90% ( 60-70%)

# Diagnosis

WBC

- May precede diarrhea/abdominal pain
- ↑ 50-60%
  - ↑ bands ( 47%)

*Wahanita et* al CID 2002

- Mean WBC 15,800/$mm^3$
- 26% - > 20,000/$mm^3$
- 6% - > 30,000/$mm^3$
  - >30,000/$mm^3$ /no hematologic malignancy
    - 25% CDAD
- 58% unexplained leucocytosis - CDAD

Hypoalbuminemia

- Protein losing enteropathy

# Diagnosis

## Cytotoxin assay

- Gold standard
  - Centrifuge stool samples
  - Remove bacteria by membrane extraction
  - Expose fibroblast monolayers to stool filtrates
    - With/without neutralizing antibody
  - Observe for cytotoxicity at 48-72 hours

→ Cytopathic effect neutralized by specific antibody

- Sensitivity 80-85% / specificity 99%
- Difficult to perform

# Diagnosis

## Culture

- Requires specialized media
  - CCFA- cycloserine-cefoxitin-fructose-eggyolk agar
  - Strict anaerobic conditions

  Not specific for pathogenic toxin producing strains

→ Must test for toxin genes by:

- PCR
- Toxin production by cell culture assay of culture broth

Time to result - 48-72 hours

High Complexity

Advantages

- Highest sensitivity(95%)/specificity(>99%)
- Provides organism for typing/virulence testing

# Diagnosis

## Enzyme Immunoassay

- Detects Toxins A & B

- Rapid test – result in 2-6 hours
- Sensitivity - 63-99% ( majority-85-95%)
- Specificity – 93-100%

## Single negative test does not rule out CDAD

- Repeat if clinical suspicion
- Alternate method if clinical suspicion high

# Diagnosis

## Combination Immunoassay

- Detects *C difficile* common antigen (glutamate dehydrogenase )
  - sensitivity 97%

- Detects Toxins A & B
  - specificity 97-99%

- Rapid test – result same day
- High negative predictive value
- Low specificity – detection of nonpathogenic strains
- Antigen (+) / Toxin (-) - need alternate method

# Diagnosis

## Nucleic Acid Amplification (PCR)

- Direct detection of *C difficile* toxin from stool
  - higher sensitivity/specificity
  - require specialized testing
  - now available at KGH

# Rejection Criteria

- Formed stool
  - Soft/liquid / takes the shape of the container
  - Rectal swabs unacceptable

- Patients < 2 years old – requires specialized testing

- Patient tested positive in previous 14 days
  - Must NOT be used as a test of cure. Toxin may be detected in stool for weeks/months after treatment.

# Management

- Discontinue antibiotic is possible
  - 20-25% mild disease resolve spontaneously
  - Use low risk antibiotics
- Do not use antidiarrheal agents

1st episode (mild – moderate)

- Metronidazole 500 mg po tid x 10-14 days

1st relapse

- Metronidazole 500 mg po tid x at least 14 days

2nd relapse (or 1st episode severe)

- Vancomycin 125 mg po qid x 10-14 days

Note: metronidazole not recommended after 2 courses or for prolonged duration-cummulative risk of toxicity

# Management

## Severe CDI:

- Serum creatinine 1.5 X pre-morbid  level
- WBC > 15,000 cells/$mm^3$
- hypotension
- ICU admission
- toxic megacolon
- ileus

# Management:

## Metronidazole

Historically – similar to vancomycin

- Cure rate - 95%
- Relapse – 5 -15%
- Failure rate – 2%

Since 2000 – increased failure rates:

- 18.2% *(Kelly CP, LaMont JT, NEJM, 2008; 359:18)*
- 26% Quebec – *(Pepin et all CID 2005;40:1591-7)*

- up to 6.3% resistance rates
  - not linked to clinical failure

# Management

## Vancomycin

- Minimal absorption - high stool concentrations
- Cure rates – 86-99%
- Relapse – 15 -33%

*Zar et al CID 2007;45:302-7*

- 172 pts - response rates
- metronidazole(250mg qid) vs vancomycin(125 mg qid)
- similar efficacy in mild cases (M-90% vs V-98%)
- superior for severe cases ( M-76% vs V-97%)

# Management

## Vancomycin

Markers for severe *C difficile:*

- Pseudomembranous colitis
- Marked peripheral leucocytosis
- Acute renal failure
- Hypotension

Coexisting ileus/toxic megacolon:

- IV metronidazole + vancomycin ( NG/enema)

Recurrent disease

- Tapering vancomycin doses

# Management

## Other antibiotic therapies

- Bacitracin
- Teicoplanin
- Vancomycin + Rifampin

  *Johnson et al CID 2007;44:846-8*
- Tolevamer (high molecular weight inert polymer)

  *Louie et al. CID 2006;43:411-20*
  - Inferior in initial therapy
  - Recurrent infection less common
- Cholestyramine +/- vancomycin
  - 4 gm packet tid x 5-10 days
  - Binds toxin (also vancomycin)

# New Dugs

## Nitazoxanide

- Related to metronidazole- similar clinical outcomes
- Better pharmacokinetics – some success in relapses
- Only available in US (Special Access in Canada)
- 500mg bid x 10 days

## Fidaxomicin

- New class
  - Macrocyclic antibiotic
- 8X more active than vancomycin
  - long post antibiotic effect
  - 200 mg bid x 10 days
- Clinical trial –(1/3 NAP1 strain)
  - equivalent to vancomycin
  - up to 45% less recurrences
    - at 28 days- 13.3% versus 24%

# Management

## Non antibiotic approaches

- Passive immunization
  - Anti-toxin A and B monoclonal antibodies
    - Phase II trial 7% vs 38% recurrence
  - Intravenous Immunoglobulin (400 mg/kg)
    - Some favorable results in recurrent disease
    - Unproven efficacy- no randomized control trials
- Active immunization
  - *C difficile* vaccine ( inactivated toxoid A & B)
    - Immunogenic healthy volunteers
    - 3 patients with recurrent disease- no relapses

*Gastroenterology 2005;128:764-70*

# Management

## Probiotics:

- *Saccharomyces boulardii*
  - 500 mg bid x 4 weeks
  - produces protease that blocks toxin attachment
- Lactobacillus
  - inhibitory for *C difficile*
  - 1 gm packet qid

## Results:

- some efficacy in reducing incidence of simple AAD
- inconsistent data in preventing CDAD
- not effective as solo therapy

# Management

## Non antibiotic approaches

- Administration of non toxigenic strain of *C difficile*
  *( JID 2002;186:1781-9)*
- Fecal transplants
  - Calgary
    - Since 1996, 48 patients
    - 96% success rate
    - Candidates- failed tapering vancomycin and probiotics

# Management

## Fecal transplants

### Donor

- First degree relative
  - No antibiotics in previous 6 months
  - Screened for Hepatitis B, C, HIV
  - Ova and Parasites
  - *C difficile* culture
- Stool collected for 3 days in refrigerated sealed plastic container
- Mixed with phosphate buffered saline + cysteine
- Infused using barium enema set up- 15-45 minutes
- Removes about half of 1500 ml infused

## Prevention

- Spores can persist months –years
  - Hospital room contamination
    - symptomatic pts - 49%
    - asymptomatic pts – 29%
  - Up to 59% HCWs caring for CDAD pts

    → culture + ( 75% physicians!!)

## Measures

- Private rooms
- Use of gloves- ↓ incidence
- Surface decontamination – hypochlorite solution
- Proper decontamination of endoscopes

# Prevention

## Reduction of High Risk Antibiotics

- *Valiquette et al* CID 2007

  2003-2004/ 2005-2006

- Decreased targeted antibiotics 23% / 54%

→ Decreased nCDAD by 60%

- Inefficacy of infection control measure
  - Implementation too late in epidemic
  - Environmental contamination with spores