Clostridium difficile 027, A Southern Hemisphere Perspective

Dr. David Hammer, Medlab South, New Zealand

A Webber Training Teleclass

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Hosted by Jane Barnett
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THE PRESS 6 July 2006

Total Annual Cost of Nosocomial Infection

- USA US$ 7 000 000 000
- UK £ 1 000 000 000
- NZ NZD 136 000 000

C. difficile – more than just a little diarrhoea …

- 7 – 64% mortality rate
- US $ 1 000 000 000 / year
- EU € 300 000 000 / year
- UK £ 2000 (extra cost per case)
  and 10 day increase in length of stay
  > 43 000 cases reported in UK 2004
  (2000 x 43000 = £ 86 000 000)

Declaration of personal interest

- Harry (an elderly family friend)
- Routine shoulder operation – UK NHS
- Acquired *C. difficile*
- Died in hospital
- Undignified and painful death
- Personal interest in preventing further such tragedies

Epidemiology

- Up to 50% neonates → < 3% 2 year olds
- Isolated in 3% of healthy adults who usually have high antibody levels to toxin A
- Mostly acquired from environment
  - Lower incidence single vs double rooms
  - Possible food sources in studies on meat
- Person to person spread well documented
  - 60% HCW's hands (in those caring for carriers)
- Occasionally endogenous
- Sexual transmission described

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Not just patients

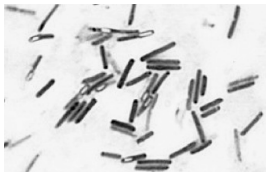
- Documented infections in
  - HCWs
  - Lab workers CID 2008:47;1Dec:1493

Why don't people get *C difficile*?

- Protective factors
  - IgG
  - Non-toxigenic carriage protective
  - Bowel flora (10^{12} bacteria/g stool)
    - Bacterial interference
    - Bowel flora changes with age
    - Bowel flora can be affected by antibiotics, chemo or surgery
- Neonates
  - high colonisation but low disease
  - probable lack of toxin receptors

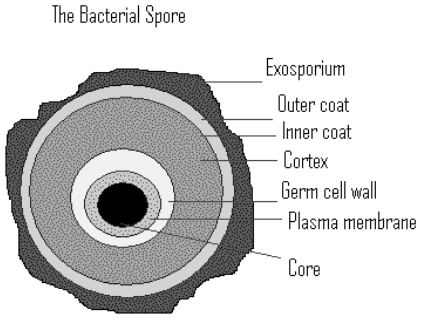
The Bug

- Gram positive anaerobic bacillus
- Spores



Pathogenicity of *C. difficile*

- Spores
  - Tough outer layers enable prolonged and tenacious environmental survival
- Toxins
  - A number of poisons produced by the bacterium wreak havoc on human tissue



Implications of spores

- Potentially survive for decades in the environment
- Difficult to eradicate without extreme measures (eg. bleach or autoclave)

Group	Disinfection
Prions	Very difficult
Spores	
Cryptosporidia	
Mycobacteria	
Non-enveloped viruses	
Fungi	
Vegetative bacteria	
Enveloped viruses	Easy

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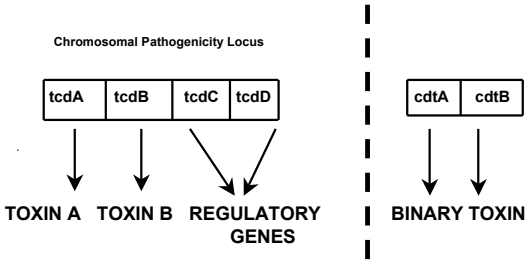
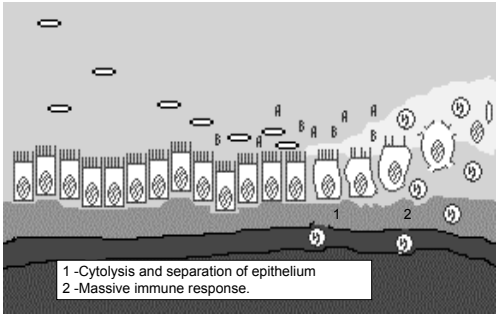
Toxins

- *C. difficile* disease is toxin based
- Toxin A (enterotoxin)
  - Also causes inflammatory response
- Toxin B (cytotoxin) 10 x more toxic than A!
- Both damage cytoskeleton
- Binary toxin attacks actin filaments in cell causing cell death

Toxins Genes



Colonic disease



Clinical manifestations

- Usually within 5 – 10 days of antibiotics
- 2/3 Asymptomatic
- Profuse watery diarrhoea (± blood)
- 50% have fever & ↑ WBC
- 1/3 abdominal pains
- Rarely
  - bacteraemia
  - osteomyelitis
  - splenic abscess
- Reactive arthritis described

Complications

- Perforation/ Acute abdomen
  - mimics appendicitis
- Toxic megacolon
  - mimics Inflammatory Bowel Disease
  - 64% mortality
- Beware the 'known colitic' patient!

Diagnosis of *C. difficile*

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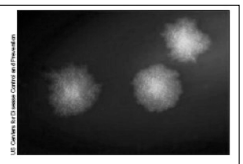
Diagnosis - Culture



- The 'difficult' bacterium
- Non-haemolytic, yellow-white ground- glass colonies with rhizoid margins
- p-cresol (horse manure) odour
- Fluoresces chartreuse under UV
- CCFA media – selective but
  - not sensitive for spores (unless bile salts added)
  - non-specific (25% non-toxigenic strains)

Diagnosis – other modalities

- Neutralisation assay
  - Culture and neutralisation of toxins
  - Gold standard but slow & expensive
- ELISA
  - sensitivity 64 – 94%; specificity 75 – 100%
  - Issues with detection of A- B+ strains in older systems
- PCR only recently available for direct diagnosis
- Endoscopy reserved for special situations

The 'new' outbreak strain

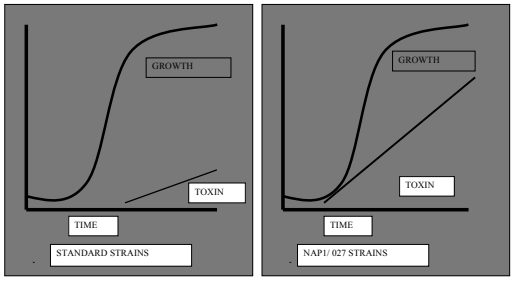
'New' outbreak strain

- Restriction endonuclease analysis BI/ PFGE NAP1, toxintype III, Ribotype 027
- Originally described in 1994
- Historically rare (5%)
  - Past, sensitive to F/Qs (gati- & moxifloxacin)
  - Current epidemic isolates all resistant to F/Qs

027 pathogenesis

- Toxins: A + B + binary toxin + deletion tcdC
- Toxin levels ± 20 x higher than standard strains
  - More virulent
- Increased sporulation
  - Better spread

Toxin & spore production



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US

- New strain identified in US since 2001
- CDC data showed a rise of 26% in discharge diagnosis of *C. difficile* between 2000 and 2001

Canada

- Identified in 2002 – 2003
- Epidemic detected because of increased colectomies!
- Quebec: 1995 3.6/10 000 pt days
  2005 >15/10 000 pt days
- Death in 22/132 cases of epidemic strain vs 0/25 infected with other strains

UK

- Incidence of CDAD doubled between 2001 and 2004
- National incidence of 678/ 100 000 in people over 75
- 43 672 cases of *C. difficile* in 2004
  - notification now mandatory

027 in the EU and beyond

- 2005
  - Netherlands
- 2006
  - Austria, Denmark, France, Switzerland, Scotland
- 2007
  - Belgium, Germany, Ireland, Norway, Spain, Japan
- 2008
  - Sweden

New Zealand/ Oceania

- Current situation
  - Anecdotally *C. difficile* is not a major problem
- But
  - NOT a notifiable disease
  - No co-ordinated screening program
  - No 027 specific surveillence
- It's just a matter of time before it arrives!
- Are we ready for it?
  - Probably not

Treatment

- Stop offending antibiotic cures ± 20%
- Supportive therapy
  - Fluids and electrolytes
- Avoid antiperistaltic agents
  - These may make disease worse
- Do not treat asymptomatic carriers

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Antibiotic Therapy – Metronidazole

- Oral metronidazole
  - Cheap
  - Recommended for first line use in mild disease
- IV metronidazole
  - some efficacy in NBM patients

Antibiotic Therapy - Vancomycin

- Oral vancomycin
  - Very expensive
  - Recommended for first line use in severe disease
    - WBC > 20 000/ml
    - Creatinine > 200 micromol/L
    - Age > 70
    - CT evidence of inflammation EID 2009 Mar;15(3):415-22.
  - use 2nd line in mild disease

Antibiotic Therapy

- Both metronidazole & vancomycin have
  - ± 90% cure
  - ± 15% relapse
  - Some in vitro resistance described
  - Possible risk of increased VRE

Other treatments

- Limited data available for
  - Teicoplanin
  - Rifamycins
  - Fusidic acid
  - Bacitracin
  - Nitazoxanide
- Anion-exchange resins
- Intravenous Immunoglobulins
  - Very expensive
  - Successful case reports
- Stool infusions reported successful
  - the domain of the desperate!

Recurrence

- Well-described
- May be multiple
- Up to 50% are different strain
  - Resistance is NOT usually a feature
- Re-treat with initial antibiotic used
  - May try tapering/ pulsed doses to eradicate germinating spores
- Role of probiotics is uncertain
  - *Saccharomyces boulardii* & *Clostridium coccoides* show some potential
  - No convincing evidence yet
  - Risk of nosocomial disease in immune compromised

Prevention & Control

Incorporating standard precautions

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Case management

- Contact/ Enteric isolation of cases
  - Own toilet
- Gloves
- Gowns
  - Especially dealing with soiled material

Hand hygiene

- Good handwashing technique essential
  - Washing is the preferred method of hand hygiene in the setting of *C. difficile*
- NB – Alcohol does not kill spores!
- However, no studies have shown increased infections in units with use of alcohol hand rub

Environmental factors

- Good bed: toilet ratios CMAJ Oct 2005;1049-50
- Environmental disinfection is vital
  - Hypochlorites, peracetic acid, peroxide
  - CDC recommends hypochlorites
  - Adequate cleaning job necessary BMC ID 2007;7:61
  - Non-isolation areas also important Am J Inf Cntrl 2009 Feb;37(1):15-9
- Potential for increased sporulation with
  - Non-sporicidal agents Lancet 2000 Oct 14; 356:1324
  - Diluted concentrations of sporicides
- Disinfectant vaporisers being tested
- Cleaning of bed pans a problem Am J Inf Cntrl 2008 Feb;36(1)5-11

Caveat emptor

- Beware of claims of increased efficacy of alcohol or chlorhexidine hand disinfectants against *C. difficile* as these are based on vegetative form, not spores John Boyce SHEA 2009
- Same caution should be applied to some claims concerning environmental disinfectants!

Identifying at risk patients

- Age, comorbidities, antibiotics, PPIs
- Waterlow score >20 could be used to identify high risk patients
  - Sensitivity 70%
  - Specificity 95%

Journal of Hospital Infection March 2009;71,239-244

Patient hygiene

- Growing evidence of carriage of *C. difficile* on skin of asymptomatic and symptomatic patients (even after symptom resolution)

CID 2007;45:992–998 & 2008;46:447–450

- Raises the question of the role of patient cleaning

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Rationalise antibiotic use

- Well documented association with CDAD &
  - Clindamycin
  - Cephalosporins
  - Fluoroquinolones
- Generally believed that 50% of antibiotics are unnecessary
- Some studies show reduced *C. difficile* infection rates with better antibiotic stewardship

CID 2007 Sept1; Suppl2:S112-21

SHEA/ IDSA guidelines

- www.shea-online.org/evidence-based-guidelines.cfm
- Contact precautions
- Proper environmental cleaning
- Hand hygiene
- Lab based notification system
- Surveillance of CDI rates
- Education of clinicians, management, patients & visitors
- Antimicrobial stewardship

Experimental work

- Vaccine under development

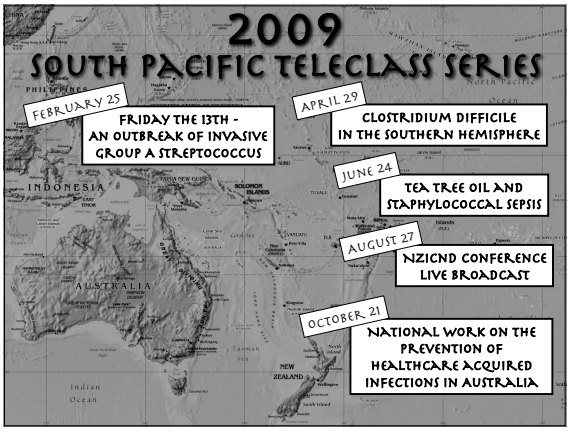
In Conclusion

- The Infection Control message remains the same:

  "Wash your hands, you sinners…" - James 4:8

- Perhaps there are too many saints in healthcare?

- Thank you for your attention
- Any questions?



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