Advances in C difficile Treatment: Clinical and Translational Strategies

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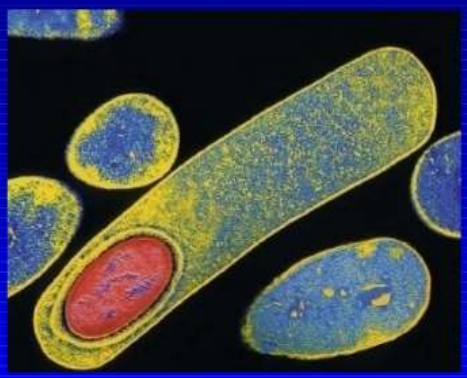
Clostridium difficile

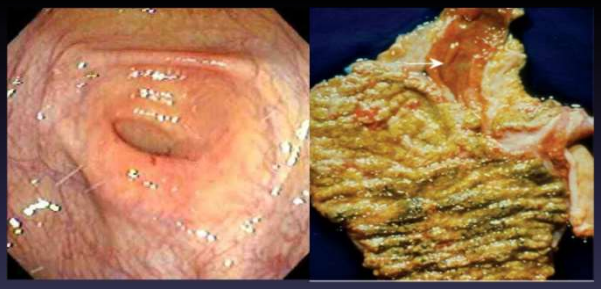
Spore-forming, anaerobic, gram-positive bacillus



Colored transmission electron micrograph of *C difficile* forming an endospore (red)

Aslam S, et al. *Lancet Infect Dis*. 2005;5:549-557.

C difficile: a commensal gone wild



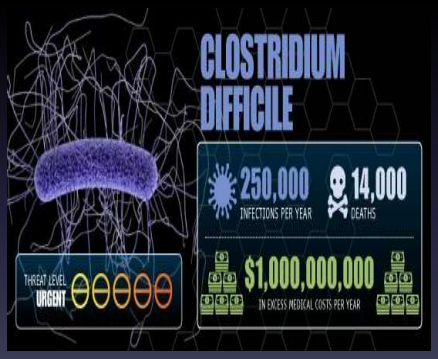
- Rates of colonization approach 50 percent in some high-risk populations
- General public may have 2-3% colonization rates
- Changes in microbiota of intestine allow proliferation and pathogenesis

Objectives of Seminar

- To review the impact of *C. difficile*
- To discuss emerging concepts in pathogenesis of *C. difficile*
- To review treatment algorithms for *C. difficile*
- To review non-antibiotic therapeutic options including antibody-based therapeutics
- Disclosure: Provisional Patent 2014-094 "Modification of Lactococcus lactis for Production of Therapeutic Proteins"

A Growing Epidemic

- Most common and costly healthcare associated infection
- Rapid spread in hospitals and community environments
- Pathogenesis closely linked to disruption of intestinal microbiota and natural defenses



Evolving Concepts in Epidemiology

Role of nosocomial transmission may have been overestimated

Community acquired infections on the rise

New strains, such as B1/NAP1/O27

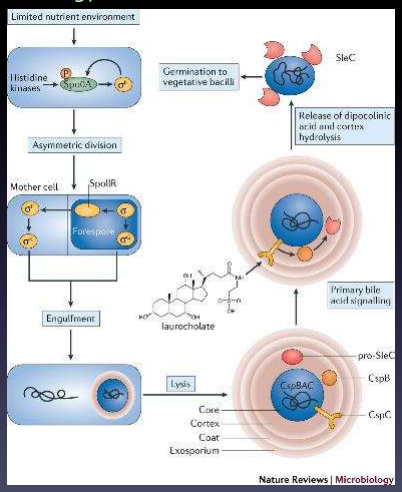
Environmental reservoirs may shed light on epidemiological risks

Oxfordshire, England study of genetic diversity of all C difficile isolates: 45% of all isolates over 3 years genetically distinct

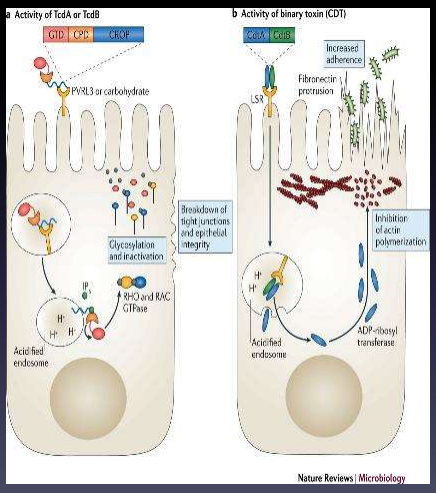
Pathogenesis

Abt et al Nature Reviews Microbiology: October 2016

- Tightly linked to spore formation, triggered by nutrient depletion
- Histidine kinases activate SpoOA. Negative mutants unable to sporulate.
- Signaling leads to forespore and lysis
- Bile acids trigger germination through CspC receptor
- Enzymatic degradation of cortex releases vegetative cell that can produce toxins



Virulence of Toxins



- Virulence primarily through toxins
- TcDA and TcDB encoded on pathogenicity locus
- Glucosyl transferase domains (GTD) inactivate GTPases in target epithelial cells
- Regulation by cysteine protease domain (CPD)
- CROP domain associated with binding to target cells
- Net effect: disruption of tight junctions, loss of epithelial integrity
- TcDB greater driver of virulence
- TcDR, TcDC and TcDE may regulate production and activity of other toxins
- Binary toxin (CDT) associated with worse patient outcomes, increased adherence

Treatment Algorithms

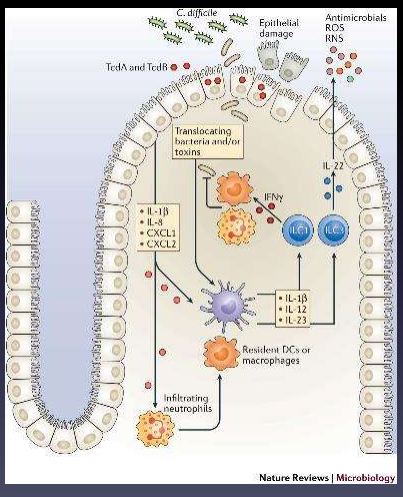
FIRST EPISODE

- If possible, remove offending antibiotic
- Vancomycin 125 mg po qid for 10 days
- Vancomycin is superior to metronidazole
- Fulminant CDI (shock, ileus, megacolon) may require urgent surgery or vancomycin 500 mg qid PLUS metronidazole 500 mg IV q8
- Vancomycin retention enemas may be used

SECOND EPISODE

- Approx 25% recurrence rate
- Approx 40% recurrence thereafter
- Advanced age, use of PPI, use of antibiotics, decreased CMI all associated with recurrence
- Fidaxomicin 200 mg po bid for 10 days may be used: about 15% lower rate of recurrence at 25 times the price
- Vancomycin for standard 10 day course, followed by slow taper of 125 mg po bid for 7 days, 125 mg po qd for 7 days, 125 mg qod for 2-8 weeks
- CDI prophylaxis

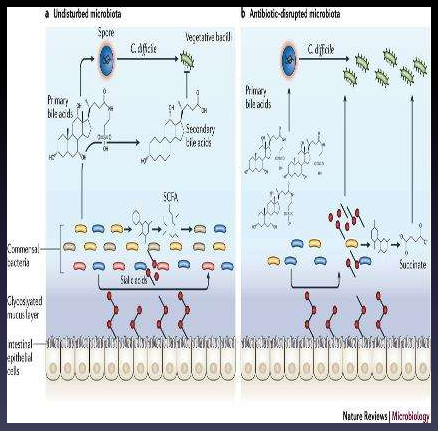
Host Responses



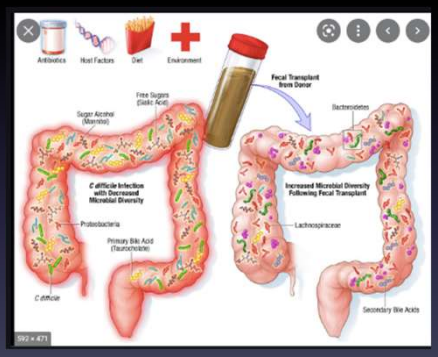
- Toxin-mediated damage allows bacterial translocation
- Pro-inflammatory cytokines released in response IL1beta, IL-12, IL-23
- Activation of neutrophils and ROS is generally ameliorating
- However, exaggerated responses reflect toxin levels and duration of infection
- Conflicting reports of role of toxemia and multi-organ effect in severe CDI

The Role of Microbiota

- Intestinal microbiota process bile acids to secondary forms: negative loop
- Sialic acids and SCFA's released as energy sources
- Antibiotic-depleted environment reduces secondary bile acids
- Absence of bacterial populations to consume sialic acids and SCFA's allows growth of *C. difficile* vegetative cells
- *C. scindens* mediates resistance to CDI
- Role of fecal microbiota transplant



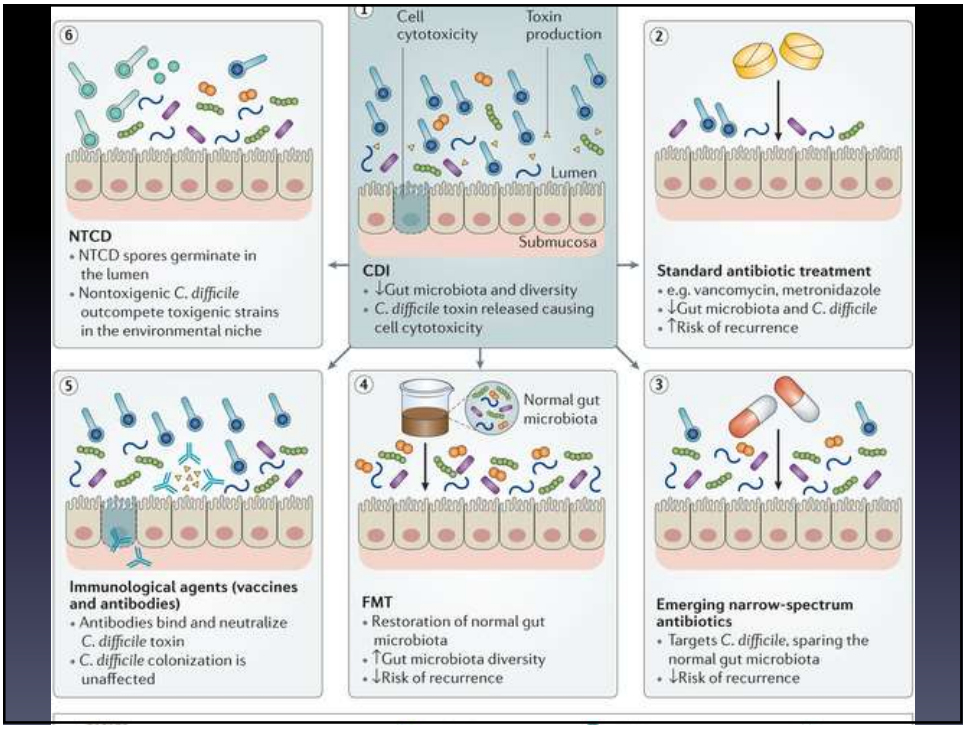
Fecal Microbiota Transplantation FMT



- Goal is to restore microbiome
- FMT is being used in other conditions such as IBD
- FDA approved after second relapse
- Cure rates as high as 93%
- Safe and tested in immunocompromised patients
- Growing evidence for FMT as first-line therapy

Why Are Antibiotics Such a Bad Idea?

- Vancomycin and metronidazole remain mainstay
- They further destroy Gotham
- Fidaxomycin may be more targeted
- Strategies that restore microbiota or target toxins may make more sense



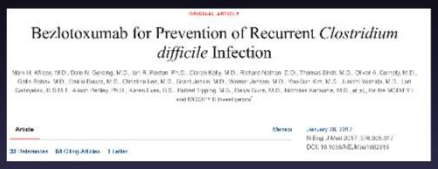
Antibody-based Strategies

Strong evidence exists for use of mAb's to TcdB as protection against CDI

Neutralization of binary toxin of unclear significance

Phase 3 studies of bezlotoxumab 10 mg/kg single infusion along with standard of care antibiotics: about 17% reduction in recurrence at 12 weeks compared to 28% placebo arm (p= 0.0003)

Promising therapeutic option,though this may be limited by costs


Bezlotoxumab for Prevention of Recurrent *Clostridium difficile* Infection

Human Paratransgenic Strategies to Control C difficile

- To develop lines of genetically modified probiotics, specifically *Lactococcus lactis*, that express neutralizing recombinant antibodies against TcdA and TcdB as a prophylactic and therapeutic approach against CDI
- To develop lines of genetically modified probiotics, specifically *Lactococcus lactis*, that express peptides such as alpha defensin 5 that modulate intestinal microbiome

Summary

- Infections with *C difficile* are a major public health concern
- Epidemiology may be more complex than originally suggested
- Complex pathophysiology related to alteration of intestinal microbiota
- "Smart" strategies needed: NOT more antibiotics
- Antibodies show promise
- Fingers crossed in my laboratory