The Elusive *Clostridium difficile*: What We Know and What We Don’t Know

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No Disclosures
No Conflicts of Interest
The Scenario

Subtitle: The questions change, but the answer is always money
A Visit from the California Department of Public Health

National Healthcare Safety Network
SIR - CDI FacwideIN LabID Data (2010-2011 Baseline)
As of: August 30, 2017 at 2:52 PM
Date Range: BS1_LABID_RATE CDIF summaryYr 2014 to 2016

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<td>1.305</td>
<td>0.0103</td>
<td>1.072, 1.575</td>
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Well?
**Clostridium difficile** Infection
Standardized Infection Ratio (SIR)*

<table>
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<tr>
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<tr>
<td>Pre-Intervention</td>
<td>1.28**</td>
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<td>(Apr 2014 - Mar 2015)</td>
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<tr>
<td>Intervention (Washout)</td>
<td>1.17</td>
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<tr>
<td>(Apr 2015 - Mar 2016)</td>
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<tr>
<td>Post-Intervention</td>
<td>0.86**</td>
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<td>(Apr 2016 - Mar 2017)</td>
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* National Healthcare Safety Network LabID Event Surveillance Definition (2010 - 2011 Baseline)
** Decrease between pre-intervention and post-intervention SIRs ($P = 0.0228$)
Ride the Epidemiologic Rocket to Glory!
Objectives

- Describe one institution's quality improvement efforts to reduced hospital-onset CDI
- Outline the ongoing challenges in the containment of CDI
- Review the debate regarding the optimal test for the detection of CDI and the impact of handsfree (“no touch”) disinfectant strategies in controlling CDI
2014

CDC Emerging Infections Program: ~ 450,000+ cases in US per year; > 29,000 deaths; > 150,000 represent community onset infection;
Action Items:

- Targeted units with high numbers of CDI
- Enhanced environmental cleaning
- Provided education to all services
- Removed proton pump inhibitors from order sets
- Targeted reduction of high risk antimicrobial agents: quinolones, clindamycin
- Promoted patient hygiene - bathing
And the Spores Keep On Shedding…Persistence of *C. difficile* Contamination after Treatment

Even after resolutions of infection (diarrhea), patients will continue to shed spores and contaminate the environment, albeit not in the same magnitude as during active infection.
Antimicrobials and Associated Risks for CDI

- Cumulative antibiotic exposures are associated with risk for CDI
- Increased odds ratio of CDI for 3 months following exposure

**High Risk**
- Clindamycin
- Quinolones (levofloxacin, ciprofloxacin)
- 2nd or 3rd generation cephalosporins (e.g. cefuroxime, ceftriaxone)

**Medium Risk**
- Augmentin®, Unasyn®, Zosyn®, carbapenems (e.g., meropenem)

**Low Risk**
- Metronidazole, vancomycin (IV), aminoglycosides, nitrofurantoin, fosfomycin, sulfonamides, tetracyclines

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Hospital Ward Antibiotic Prescribing and the Risks of CDI

Acid Suppressive Therapy, Proton Pump Inhibitors (PPIs) and CDI

Order of increasing risk: histamine type 2 receptor antagonists (H₂RA, e.g. famotidine [Pepcid®]) < PPI (e.g. Protonix®) < more frequent dosing of PPI’s

- PPIs are associated with a 3.6x greater risk of CDI
- H₂RAs are associated with 1.4x greater risk of CDI

- PPIs and H₂RAs are available over the counter (OTC)
- PPI increases risk of recurrent CDI

**Clostridium difficile Infection (CDI)** Rapid Process Improvement:
- Identify education opportunities; provide guidance on when to test; ensure compliance with contact precautions and hand hygiene; ensure environmental cleanliness, promote patient hygiene, engage patient and family; increase laboratory support, and enhance Antimicrobial Stewardship Program.

- Enhanced administrative support and designated as an institution priority
- Formation of CDI Steering Committee
- Perform root cause analysis on every healthcare facility-onset CDI case

**Revision of Nursing Standardized Procedure and development of CDI testing algorithm**

**Development of education modules for nursing and physicians**

- Remove proton pump inhibitors from orders sets
- Provide education to all patient care units and other healthcare providers
- Intensify efforts in patient care areas with high CDI rates
- Initiate discussion on chlorhexidine bathing and CDI reduction

**Notification of MDs regarding CDI rates**
- Positive cases shared at Daily Reliability Huddles

**ASP: Intensify efforts to decrease house-wide quinolone use**
Effect of Hospital-Wide Chlorhexidine Patient Bathing on Healthcare-Associated Infections

- Three phases:
  - Bathing 3 days per week, followed by
  - Daily bathing, followed by
  - A 4-month post-intervention washout period returning to standard soap-and-water bathing

- CDI rates during the 3-day-per-week: (relative risk [RR], 0.71; $P = .003$); **daily bathing** (RR, 0.41, $P < .01$); most reduction was among a cohort of adult and pediatric critical care patients (RR, 0.30, $P < .001$) during daily bathing.

- Correspondingly, CDI rates significantly increased during the 4-month post-intervention soap-and-water period,
Environmental Cleanliness

Staff Education “5 at 5”

To help in maintaining cleanliness of the high touch/contaminated surfaces, staff offered to implement cleaning 5 surfaces twice daily.

Ancillary staff have also offered to help with Wiping down surfaces
The percentage of surfaces cleaned by EVS with passing scores has steadily increased. Areas with the most opportunity for improvement were: patient call lights (61% passing) side rails (75% passing), inside door handles (76%), over bed tables (75% passing), patient phones (77%).
*Unexplained diarrhea* is defined as diarrhea in the absence of a laxative or bowel stimulant in the past 48 hours.

**DO NOT** test for *C. difficile:*

1. When a negative *C. difficile* test has been completed in the past 7 days;
2. When patient has had diarrhea in the setting of a laxative or a bowel stimulant in the previous 48 hours.
3. **DO NOT conduct a “Test of Cure”** (defined as a repeat *C. difficile* test in a patient who has had a clinical response to therapy and resolution of symptoms).
4. If the patient has a history of CDI and does not have diarrhea

**Contact Precautions for CDI** may be stopped when:

1. The patient has been treated with at least 5 days of appropriate antibiotic, AND
2. The patient is symptom free (no diarrhea or abdominal pain), AND
3. The patient is not on any antibiotics
4. Infection Prevention has approved removal

**Bristol Stool Chart:** Types 5-7 are the ONLY acceptable stool specimens to send for testing

- **Type 5** - Soft blobs with clear-cut edzes (passed easily)
- **Type 6** - Fluffy pieces with ragged edges, a mushy stool
- **Type 7** - Watery, no solid pieces. Entirely Liquid

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**Note:** If patient develops unexplained diarrhea at any point during admission, please start this process over.

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Updated 2/8/17
**Clostridium difficile** Infection (CDI) Testing:
A Comparison of Three Time Periods

- **Pre-Intervention**
  - April 2014 - March 2015
  - Number of CDI Tests Submitted: 2241

- **Intervention**
  - April 2015 - March 2016
  - Number of CDI Tests Submitted: 2027

- **Post-Intervention**
  - April 2016 - March 2017
  - Number of CDI Tests Submitted: 1327

*Number of (+) Healthcare Facility-Onset CDI Tests:
- Pre-Intervention: 137
- Intervention: 130
- Post-Intervention: 85

* Per National Healthcare Safety Network LabID Event Surveillance Definition
Percentage of Total Number of Specimens Submitted

<table>
<thead>
<tr>
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<th>Pre-Intervention</th>
<th>Intervention</th>
<th>Post-Intervention</th>
</tr>
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<tbody>
<tr>
<td>% &lt; 3days</td>
<td>50</td>
<td>53</td>
<td>52</td>
</tr>
<tr>
<td>% &gt; 3days</td>
<td>45</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td>% + toxin</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>% - toxin</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>% discordant</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Total number of samples submitted:
Pre-intervention: 2241
Intervention: 2027
Post-intervention: 1327
Total number of CDI LabID
Pre-intervention: 275
Intervention: 348
Post-intervention: 244
Does Control of HO-CDI Control CDI?
Transmission of CDI from symptomatic patients accounted for slightly more than a third of such cases…. Suggests that many cases arise from genetically diverse sources…..

CONCLUSIONS
Over a 3-year period, 45% of *C. difficile* cases in Oxfordshire were genetically distinct from all previous cases. Genetically diverse sources, in addition to symptomatic patients, play a major part in *C. difficile* transmission. (Fund by the U.K. Clinical Research Collaboration Translational Infection Research Initiative and others.)
Community Antibiotic Prescriptions per 1,000 Population by State — 2014

At least 30% of antibiotics prescribed in doctors’ offices, emergency departments and hospital clinics are unnecessary.*

Data source: IMS Health Xponent 2014.
The Magnitude of Antimicrobial Use

• In 2014, 266.1 million courses of antibiotics are dispensed to outpatients in U.S. community pharmacies. This equates to more than 5 prescriptions written each year for every 6 people in the US.\(^1\)
• At least 30% of antibiotics prescribed in the outpatient setting are unnecessary, meaning that no antibiotic was needed at all.\(^2\)
• Total inappropriate antibiotic use 50% of all outpatient antibiotic use.\(^3,4,5\)
• Local outpatient prescribing practices contribute to local resistance patterns.\(^7\)
• An estimated 80-90% of the volume of human antibiotic use occurs in the outpatient setting.\(^10,11\)

https://www.cdc.gov/getsmart/community/improving-prescribing/outpatient-stewardship.html
Lawsuits among Physicians and MRSA

• Correlation between the prevalence of MRSA both antibiotic prescriptions per capita and density of attorneys in countries in Europe and North America

• No correlation between prevalence of MRSA and physician density.

• Fear of lawsuits and attorney density may be a crude surrogate marker of antibiotic prescription practices that contribute to the emergence of antimicrobial resistance among virulent pathogens.
Food and *C. difficile*
<table>
<thead>
<tr>
<th>Country (region), product</th>
<th>No. of positive samples/ total no. cultured (%)</th>
<th>PCR ribotype</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
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<td></td>
<td></td>
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<tr>
<td>Ground beef</td>
<td>13/26 (50.0)</td>
<td>027, 078</td>
<td></td>
</tr>
<tr>
<td>Summer sausage</td>
<td>1/7 (14.3)</td>
<td>027</td>
<td></td>
</tr>
<tr>
<td>Ground pork</td>
<td>3/7 (42.9)</td>
<td>027, 078</td>
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<tr>
<td>Braunschweiger</td>
<td>10/16 (62.5)</td>
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<td>Chorizo</td>
<td>3/10 (30)</td>
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<tr>
<td>Pork sausage</td>
<td>3/13 (23.1)</td>
<td>027, 078</td>
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<tr>
<td>Ground turkey</td>
<td>4/9 (44.4)</td>
<td>078</td>
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<tr>
<td>Canada (Ontario, Quebec)</td>
<td></td>
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<td>[11]</td>
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<tr>
<td>Ground beef</td>
<td>11/53 (20.8)</td>
<td>077, M31, 014, M26</td>
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<tr>
<td>Ground veal</td>
<td>1/7 (14.3)</td>
<td>M31</td>
<td></td>
</tr>
<tr>
<td>Canada (nationwide)</td>
<td></td>
<td></td>
<td>[12]</td>
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<td>10/149 (6.7)</td>
<td>M26, 077, J, 014, C, F, H</td>
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<td>3/65 (4.6)</td>
<td>M26, J, K</td>
<td></td>
</tr>
<tr>
<td>Canada (British Columbia, Saskatchewan, Ontario, Quebec)</td>
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<td>[13]</td>
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<tr>
<td>Ground beef</td>
<td>14/115 (12.2)</td>
<td>078, 027, C</td>
<td></td>
</tr>
<tr>
<td>Ground pork</td>
<td>14/115 (12.2)</td>
<td>078, 027, C, E, Y</td>
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<tr>
<td>Scotland</td>
<td></td>
<td></td>
<td>[14]</td>
</tr>
<tr>
<td>Salad</td>
<td>3/40 (7.5)</td>
<td>017, 001</td>
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**NOTE.** PCR, polymerase chain reaction.
Prevalence and Risk Factors for *C. difficile* Colonization in Dogs and Cats in an ICU

- Veterinary ICU in Canada
- 402 animals studied: rectal swabs on admit and every 3 days until death or discharge
- Isolated 73 (18%): 53% (39/73) were CA-CDI or 11% of total
- 69% of isolates: toxigenic
- Risk factors: antimicrobials before admit, immunosuppressives during stay were associated with HA colonization
- Acquisition during hospital admission = diarrhea
Which is the Better Test to Diagnose CDI
Ferric Fang, M.D.: PCR more sensitive and will not miss cases of CDI.

Chris Polage, M.D.: Toxin test; discordant cases represent colonization.
Overdiagnosis of *Clostridium difficile* Infection in the Molecular Test Era

**Objective** To determine the significance of toxin negative and PCR positive (Toxin−/PCR+) for CDI.

**Design, Setting, and Participants** Prospective observational cohort study at a single academic medical center among 1416 hospitalized adults tested for *C difficile* toxins 72 hours or longer after admission between December 1, 2010, and October 20, 2012.

**Main Outcomes and Measures** Toxin results were reported clinically. PCR results were not reported. The main study outcomes:
- duration of diarrhea during up to 14 days of treatment,
- rate of CDI-related complications (ie, colectomy, megacolon, or intensive care unit care)
- CDI-related death within 30 days

Polage CR. *JAMA Intern Med* 2015;175:1792-1801
Overdiagnosis of *Clostridium difficile* Infection in the Molecular Test Era

Conclusions and Relevance

- Among hospitalized adults with suspected CDI, virtually all CDI-related complications and deaths occurred in patients with positive toxin immunoassay test results.
- Patients with a positive molecular test result and a negative toxin immunoassay test result had outcomes that were comparable to patients without *C difficile* by either method.
- Exclusive reliance on molecular tests for CDI diagnosis without tests for toxins or host response is likely to result in overdiagnosis, overtreatment, and increased health care costs.
The addition of clinical information decreases the specificity of the PCR from 98% to 89% with a positive predicted value of only 60%.

"Clostridium difficile infection is a clinical diagnosis…you need appropriate signs and symptoms of CDI, then you have a positive test…"

Erik Dubberke, M, MSPH
Can Enhanced Hospital Disinfection Prevent *Clostridium difficile*?

12 month study of enhanced cleaning with use of fluorescent marker in 15 hospitals

Sustained improvement documented with decrease in environmental cultures from 13%-3%

HOWEVER, the incidence of HA-CDI was unchanged, before, during, and after the study

**CONCLUSION**: Multiple interventions are necessary to decrease HA-CDI
**Clostridium difficile** Infection
Standardized Infection Ratio (SIR)*

<table>
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<tr>
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<th>Intervention (Washout)</th>
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** Decrease between pre-intervention and post-intervention SIRs ($P = 0.0228$)
Handsfree Disinfection Technology
# Handsfree Disinfection Systems

<table>
<thead>
<tr>
<th>Type of Disinfection</th>
<th>Comments</th>
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<tbody>
<tr>
<td><strong>Aerosolized-Vapor Generating Systems</strong></td>
<td></td>
</tr>
<tr>
<td>Aerosolized H2O2 systems</td>
<td>5-6% H2O2 and &lt; 50 ppm silver, converted to harmless water and oxygen. Cycle time is 2 hours; multiple cycles necessary; vents have to be sealed; distribution may not be uniform</td>
</tr>
<tr>
<td>Vaporized H2O2 systems</td>
<td>Requires 2 units: generator and an aeration unit; cycle times 1.5 hours; vents have to be sealed</td>
</tr>
<tr>
<td><strong>Utraviolet C radiation (UVC)</strong></td>
<td></td>
</tr>
<tr>
<td>Mercury-based UVC</td>
<td>Multiple units needed; pathogen specific dosing requirements; operator dependent; Incomplete deactivation of pathogens</td>
</tr>
<tr>
<td>Pulsed-xenon UV</td>
<td>Machine cycle must be run in multiple room locations Short cycle time 5-10 minutes</td>
</tr>
<tr>
<td><strong>Chemical (fogging systems)</strong></td>
<td>No compelling studies</td>
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The Benefits of Enhanced Terminal Room (BETR) Disinfection Study

A Cluster Randomized, Multicenter Crossover Study with 2x2 Factorial Design to Evaluate the Impact of Enhanced Terminal Room Disinfection on Acquisition and Infection Caused by Multidrug-Resistant Organisms
## BETR Disinfection Study

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<th>UV-C</th>
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<tr>
<td>Quat*</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Bleach</td>
<td>C</td>
<td>D</td>
</tr>
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</table>

*NOTE: Bleach always used in rooms of patients with suspected or confirmed C. difficile*

Anderson D et al. IDWeek 2015
Conclusions

• Successfully implemented environmental disinfection trial: 28 months, 9 hospitals
• 90% compliance in > 20,000 room observations
• Appears that enhanced disinfection is more effective in controlling non-spore forming microorganisms than when quats are used alone
• Bleach alone appears to be as effective compared to bleach with enhanced environmental disinfection in CDI
Results: 210 CDI patients were identified, resulting in 351 opportunities for room disinfection at discharge or patient transfer, of which 207 (59%) were treated with PX-UV. Compliance with CDI room treatment did not differ by time of day or day of week (weekday compliance was 60% vs. 55% on weekends; p=0.47; day shift compliance was 61% vs. 53% on night shift; p=0.21). Compliance with PX-UV in CDI rooms was higher during the first half versus the second half of the study (70% vs. 59%, p <0.01). Of the 3032 patients discharged from the 4 high CDI rate units, 1771 (58%) rooms were treated with PXUV.

Hospital-wide CDI rates were not statistically different between the study periods [475 cases of hospital-acquired CDI/631,008 patient days (rate = 0.75 cases/1000 pt days) pre-intervention vs. 134 cases/ 210,191 patient days (rate = 0.63) post-intervention; incidence rate ratio (IRR) = 0.85; p = 0.09; Figure] or on the 4 patient care areas with high CDI rates (154 cases, rate = 2.15 cases/1000 pt days pre-intervention vs. 43 cases, rate = 1.61 post intervention; IRR = 0.75, p = 0.09).

Conclusion: Overall compliance with use of the PX-UV system was 60%. Compliance with use was decreased in the second half of the study. There was no significant difference in CDI infection rates with use of the PX-UV light disinfection system.
C. DIFF CONTROLLED STUDY IN 6 ICUS

- 39% decrease in CDI incidence on Xenex Units (p=0.03)
- 42% increase in CDI in control units

Xenex is now the standard of care
Outcomes with Xenex Technology

Influence of a total joint infection control bundle on surgical site infection rates.

Quality improvement initiatives combined with pulsed xenon ultraviolet room disinfection were implemented to reduce surgical site infections (SSIs) in patients undergoing total joint procedures. After 12 months, knee SSIs were reduced from 4 to 0 ($P = .03$) and hip SSIs were reduced from 3 to 0 ($P = .15$) for a combined prevention of 7 SSIs ($P = .01$) and a savings of $290,990.
STOP-SSI

- Pragmatic intervention trial
- 20 centers, 42K surgeries
- Targeted decolonization and prophylaxis, based upon nasal S. aureus carrier status
- Primary outcome is complex S. aureus SSIs

**S. aureus** screening, decolonization, targeted prophylaxis, reduced complex **S. aureus** SSIs > 40%

Utilization and Impact of a Pulsed-Xenon Ultraviolet Room Disinfection System and Multidisciplinary Care Team on *Clostridium difficile* in a Long-term Acute Care Facility
Sharp Coronado, Long-term Care Facility and C. difficile Infection

CDI rate per 10,000 patient days was reduced from 6.1 (average rate 2008-2010) to 1.1 (average rate 2011-2014) 6 cases in 2015 (3 acute care, 3 LTC)

Newer Agents for Treatment and Prevention of CDI

The poop pill
Fidaxomicin
Bezlotoxumab
Non-toxic *C. difficile* spores (NTCD-M3)
*C. difficile* vaccine
“There are known knowns; there are things we know we know.”

“We also know there are known unknowns; that is to say we know there are some things we do not know.”

“But there are also unknown unknowns – there are things we do not know we don’t know.”

Donald Rumsfield
February 12, 2002
Summary

- Administrative support is critical
- A multi-pronged approach is necessary to contain CDI
- Sustainability of strategies is an ongoing challenge
- Reduction of CDI requires strategies to improve antibiotic therapy in the outpatient setting
- Recognition of the limitation of CDI testing is critical since CDI is a clinical diagnosis
- Handsfree disinfectant technology may be helpful in the control of CDI
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Questions?