CDI and CRE in LTC:

An Alphabet Soup of Gut Bacteria

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Speaker Disclosures

Dr. Jump has no direct conflicts of interest related to this presentation.

Dr. Jump has current research support from Steris. She has previously consulted for GOJO and Pfizer and has previous grant support from Pfizer, Merck and ViroPharma.

The opinions presented herein are my own and do not represent those of the Veterans Affairs system or the federal government.



Learning Objectives

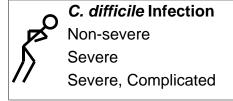
By the end of the session, participants will be able to:

- Articulate risk factors for developing *C. difficile* infection
- Describe infection control interventions to reduce the risk of acquiring *C. difficile*
- Recognize carbapenem-resistant
 Enterobacteriaceae (CRE) and describe
 infection prevention strategies for these
 bacteria

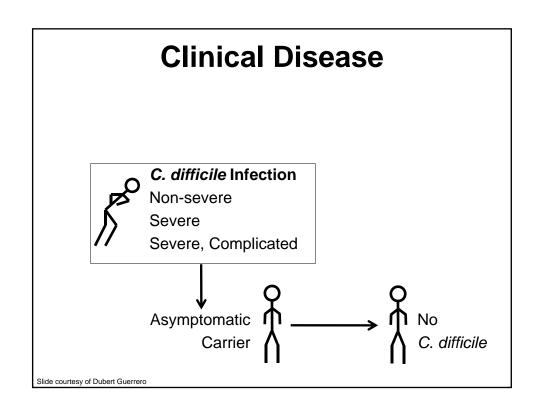


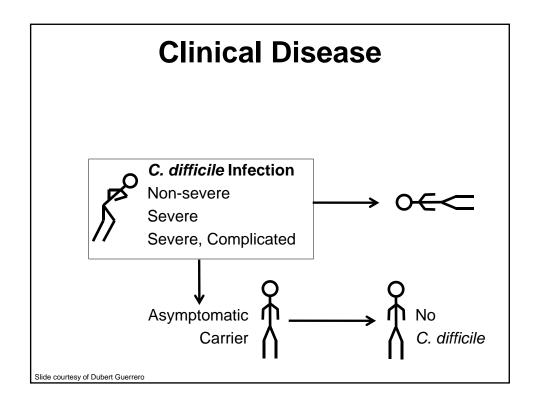
Pathophysiology

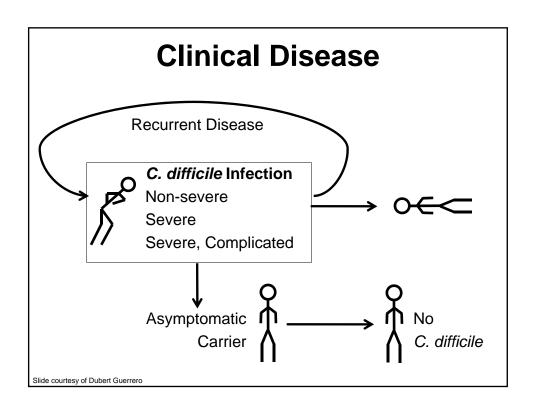
Clinical Disease

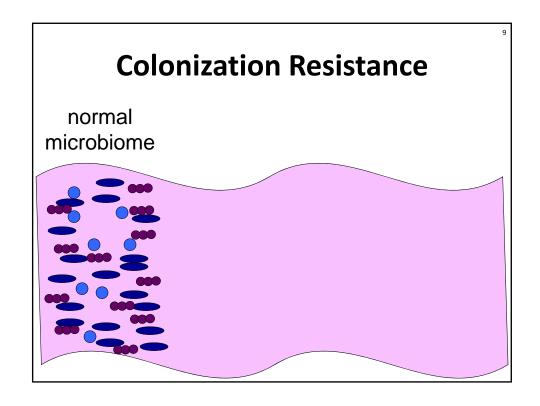


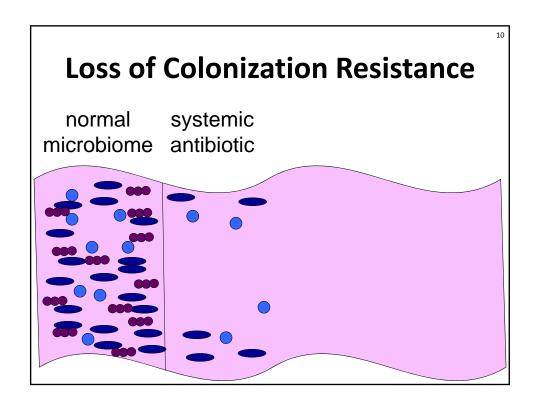
Slide courtesy of Dubert Guerrero

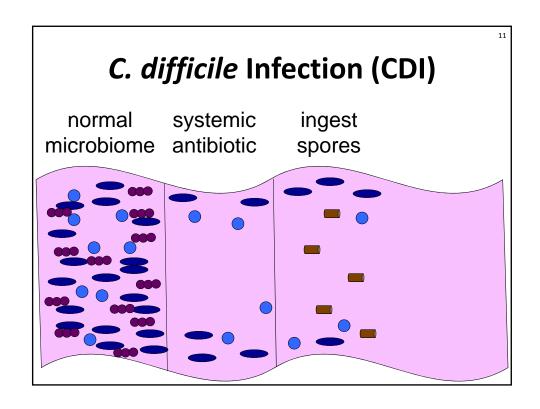


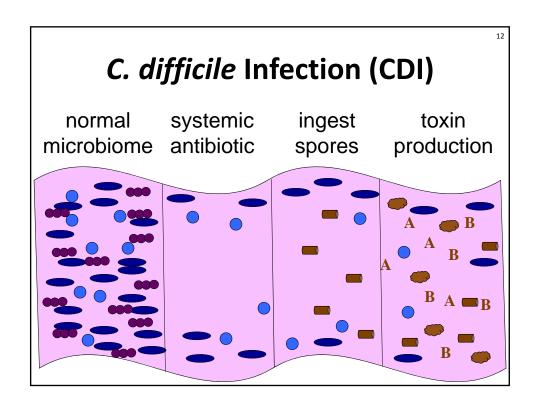


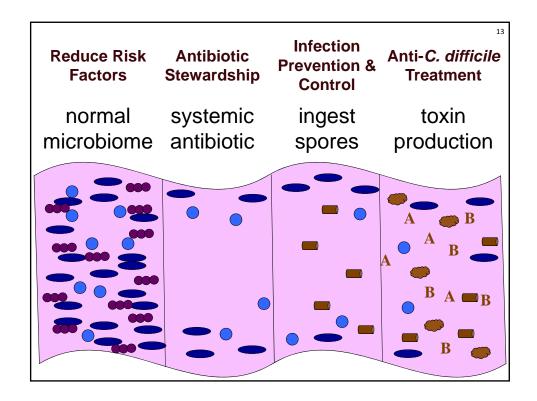










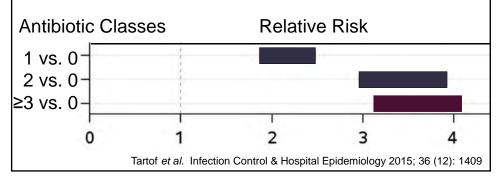


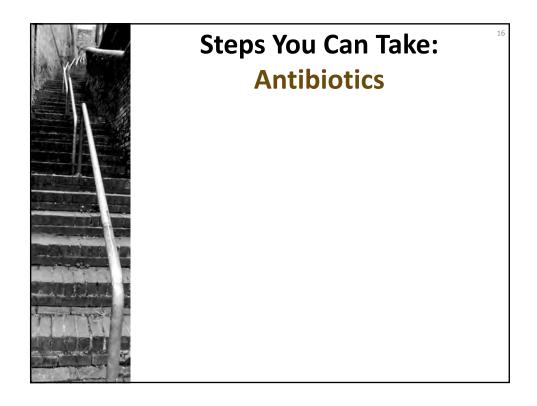


Antibiotics
are the most
important risk
factor for
developing
C. difficile
infection.

More Antibiotic Classes Increases the Risk of *C. difficile* Infection

- ~400,000 adults admitted to 14 hospitals in 2011-2012
- ~2,600 with CDI (0.7%)







Steps You Can Take: Antibiotics

Avoid antibiotics when possible

Active monitoring
Promote watchful waiting

When you must use antibiotics...

Use shorter courses (≤ 7 days)

Choose narrow spectrum agents

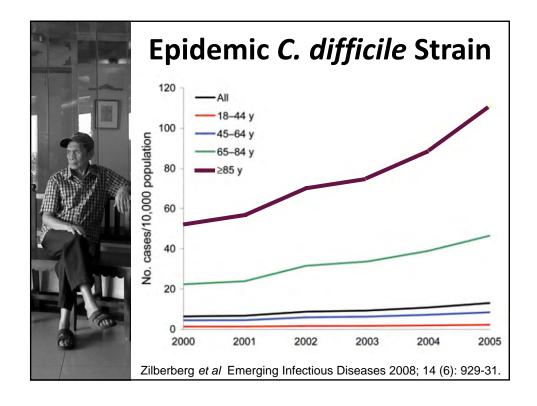
Choose agents with less excretion into the GI tract



Advanced Age

is the second most important risk factor for developing

C. difficile infection.





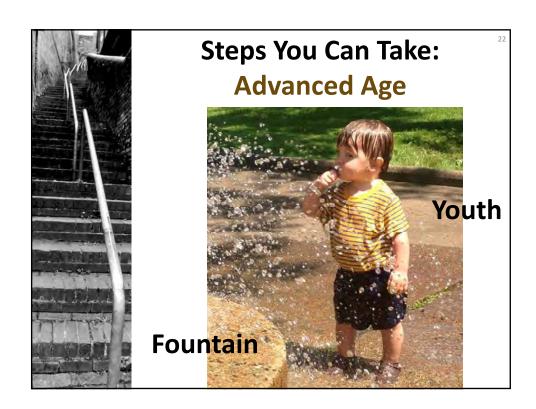
Age-Related Vulnerability

- In 2010, >90% of deaths due to CDI were in people ≥ 65 years.
- Aging leads to immune senescence.
- A poor antibody response to *C. difficile* correlates with infection.
- Older adults have a less diverse and less resilient gut microbiome.

Kelly Clin Microbiol Infect 2012; 18 Suppl 6:21-7
Biagi et al. PLoS ONE 2010; 5: e10667;
Rea et al. J Clin Micro 2012; 50(3):867-75
Death: Preliminary Data for 2010. National Vital Statistic Reports 2012.



Steps You Can Take: Advanced Age





Other Risk Factors

- Previous hospitalization
- Resident at a long-term care facility
- Underlying disease severity
- Albumin ≤ 3.5 g/dL
- Gastric acid suppression

McDonald *et al.* MMWR **2012**; 61(9):157-62 Dial *et al.* JAMA 2005; 294: 2989-2995 Kyne *et al.* Age & Ageing 1999; 28: 107-113 Dubberke *et al.* Clin Infec Dis 2007; 45: 1542-49 Bobulsky *et al.* Clin Infect Dis. 2008;46(3):447-50



Risk Factors for Recurrent Disease

Predictor	Adjusted Hazard Ration	
Age > 75 years	1.5 (1.1 – 2.0)	
PPI* Use	1.5 (1.1 – 2.0)	
Antibiotic re-exposure	1.3 (0.9 – 1.7)	
Length of Stay, per day	1.003 (1.002 – 1.004)	

Indication for PPI Use	No. (%) (n = 191)
No indication	101 (53%)
Age > 60 y w/ 2 other risk factors	39 (20%)
Upper GI bleeding	17 (9%)
GERD in previous 90 days	15 (8%)

*PPI = proton pump inhibitor McDonald *et al.* JAMA Internal Med 2015; (online 3/2/15)



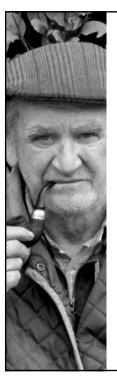
Types of Tests		
Common Name (No. tests)	Type of Test	Results
GDH (4)	Enzyme Immunoassay (EIA) for Glutamate dehydrogenase (GDH)	C. difficile (sensitive)
EIA (9)	EIA for toxin	Toxins B & A (specific)
NAAT or PCR (11)	Nucleic Acid Amplification Test (NAAT) Crobach et al. Clin Micro and	Toxin B (& A); epidemic strain (sensitive)



Principles of Testing

- Enable nurses to initiate tests for C. difficile
- Sample should take the shape of the container, i.e. unformed stool
- If there is a concern for an ileus, send a rectal swab*
- No need for repeat tests
- NO TESTS OF CURE!

*rectal swabs can be tested using GHD EIA or NAAT

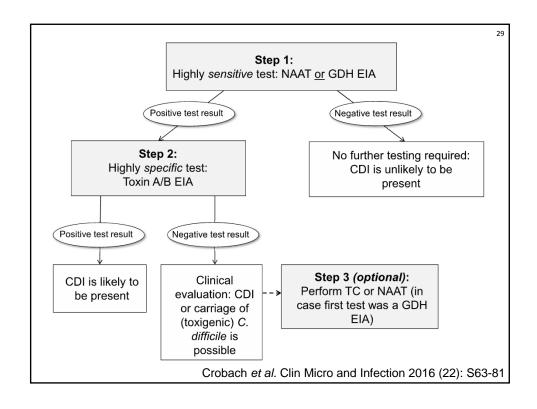


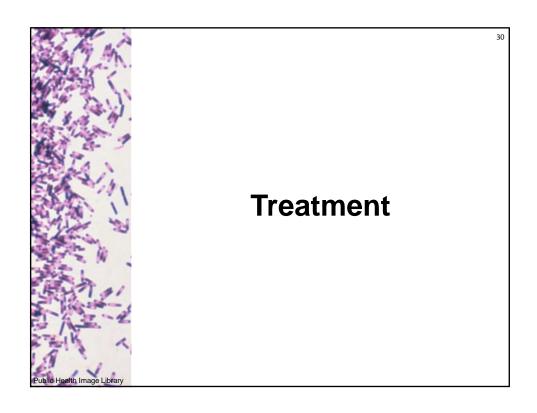
Testing Algorithm*

- No single commercial test is sufficient as a stand-alone test
- 2-step approach
 - 1. High negative predictive value, *i.e.* sensitive test to rule-out
 - 2. High positive predictive value, *i.e.* specific test to conform

*European Society of Clinical Microbiology and Infectious Disease; Crobach et al. Clin Micro and Infection 2016 (22): S63-81

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2010

Treatment of Non-Severe *C. difficile* Infections

- Diarrhea; 3 or more unformed stools in <24 hours
- Stool tests positive for toxigenic C. difficile

Recommendation	Strength
Stop the inciting antibiotics	A-II
Oral metronidazole	A-I
If on warfarin, oral	A-I
vancomycin	

Cohen et al. Infec Control Hosp Epi 2010; 31:431-55

2010

Treatment of Severe C. difficile Infections

- Severe infection
 - WBC >15K, Cr >1.5 x baseline

Recommendation	Strength
Oral vancomycin	B-I

- IV metronidazole and oral vancomycin together associated with reduced mortality (16%) compared to oral vancomycin alone (36%).
- · Single center, retrospective study.

Cohen *et al.* Infec Control Hosp Epi 2010; 31:431-55 Rokas *et al.* CID 2015; 61: 934-41

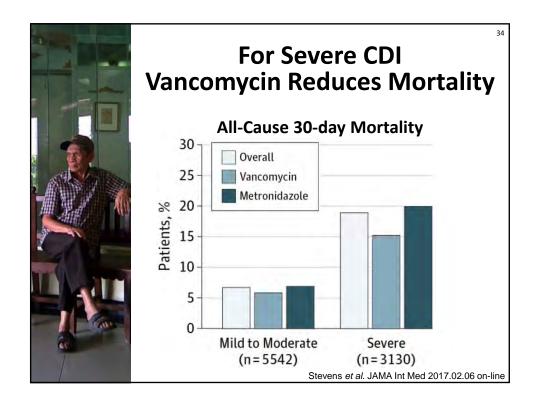


Vancomycin vs. Metronidazole

Retrospective cohort study of ~47,000
 Veterans with C. diff infection (2005 – 2012)

- Of those, ~4% treated with oral vancomycin
- Matched these to those treated with metronidazole, stratified by disease severity
- No difference in rate of recurrence

Stevens et al. JAMA Int Med 2017.02.06 on-line



2010

Treatment of Severe *C. difficile* Infections

- Severe infection
 - WBC >15K, Cr >1.5 x baseline
- Severe & Complicated
 - Unstable, Ileus, Toxic Mega-colon

Recommendation	Strength
-Oral vancomycin (high dose) -(If ileus, consider rectal instillation) -Consider IV metronidazole	C-III
Monitor serum lactate, WBC	B-II

Consult Surgery & Infectious Disease

Cohen et al. Infec Control Hosp Epi 2010; 31:431-55

2010

Treatment, Recurrent Disease

No tests of cure!

Cohen et al. Infec Control Hosp Epi 2010; 31:431-55; Garey et al. J Antimicrob Chemo 2011 66(12):2850-5 Surawicz et al. Am J. Gastroenterology 2013; 108:478-498

2010

Treatment, Recurrent Disease

No tests of cure!

Recurrence	
Any	Stop the inciting antibiotics
First	Repeat metronidazole
Second	Oral vancomycin
>2nd	oral vancoor

Cohen et al. Infec Control Hosp Epi 2010; 31:431-55; Garey et al. J Antimicrob Chemo 2011 66(12):2850-5 Surawicz et al. Am J. Gastroenterology 2013; 108:478-498



Fidaxomicin

- Active against *C. difficile* but spares other members of gut microbiome
- Treatment outcomes = vancomycin
- Reduces the risk of recurrent disease

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Cost Comparison

Fidaxomicin (10 days) \$ 3300 Vancomycin (capsules; 14 days) \$ 2000 Vancomycin (compounded) \$ 40 Metronidazole \$ 30

Cruz; Pharmacy & Therapeutics, 2012 37(5):278-81



Preventing Recurrence?

- Risk of recurrent CDI ~20-30%
- ~1000-bed teaching hospital
- Retrospective cohort of people with history of CDI who went on to receive systemic antibiotics
- Of 203 patients, 71 received oral vancomycin while on systemic antibiotics
- Recurrent disease in 4% (3/71) of those on po vancomycin; 27% (35/102) of those not on po vanco

Van Hise et al Clin Infec Dis 2016;64:651-2



Preventing Recurrence?

• In general, risk of recurrent CDI ~20-30%

 Retrospective cohort of people with history of CDI who went on to receive systemic antibiotics

Group	Recurrent CDI
Systemic antibiotic	27% (35/102)
Systemic antibiotic & oral vancomycin*	4% (3/71)

*PO vanco for 0-6 days after end of systemic antibiotic

Risk of subsequent recurrence? Risk of VRE?

Van Hise et al Clin Infec Dis 2016;64:651-2

Fecal Microbiota Transplant (FMT)



- Administration of feces from a healthy donor
- Symptom resolution in 1-2 days
- 15/16 (93%) patients cured with 1-2 treatments
- In small series of 10 adults >80 years, 8 of 10 had symptom resolution

Van Nood et al NEJM 2013; 368:407-15; Rubin et al. 2009 JAGS;57:2386;

Fresh or Frozen?



- Randomized non-inferiority study
- 232 adults (~73 years) with refractory CDI
- Frozen → thawed FMT works as well as fresh FMT
- FMT is a cost-effective, well-tolerated strategy
- To start your own center...

see Costello et al. CID 2016:62 (908-14)

Lee et al. JAMA 2016;315(2):142-149 Konijeti et al. Clin Infect Dis 2014;58:1507-14 Drekonja et al. VA ESP Project #09-009;2014



Hecker et al. OFID 2016; 3(2): ofwo91 Youngster et al JAMA 2014; 312(17):1772-78 Khanna et al. J Inf Dis 2016 214:173-81 **Frozen stool.** Capsules stored at -80° C. Each treatment made from a single donor

A Variety of Poop Pills

- Trial on 20 patients, ages 7 90 with refractory/ recurrent CDI
- 15 capsules a day for 2 days
- 14 responded to first treatment; 4 to second treatment for 90% cure rate
- Spore capsules. Spores generated by ethanol-treatment of stool samples
- 30 patients (median age 65 yrs) with recurrent CDI
- 26 with clinical resolution
- 15 capsules a day for 2 days

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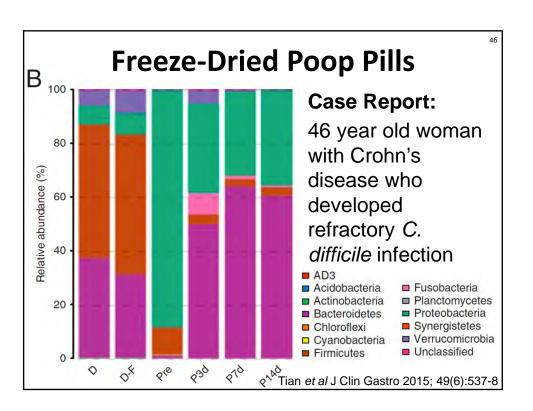
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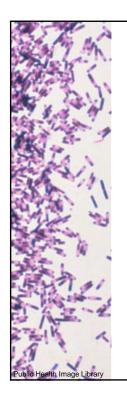
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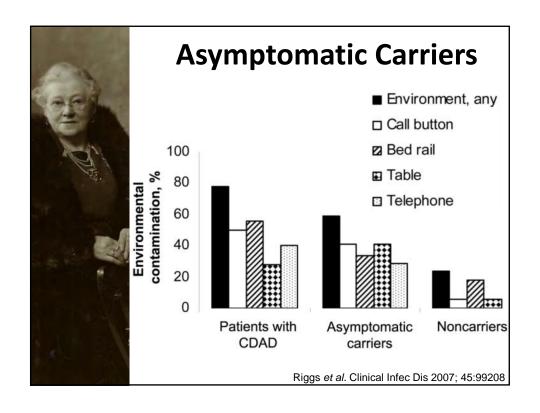
Infection Control & Prevention

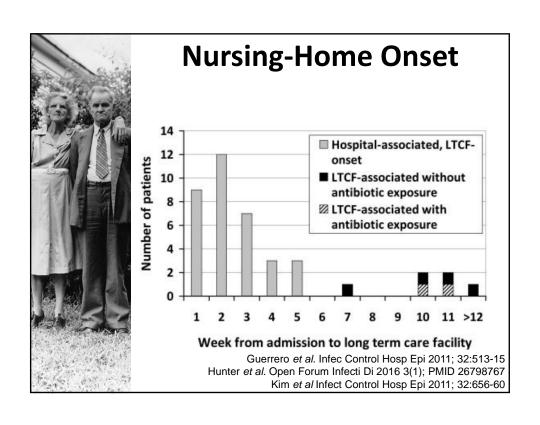


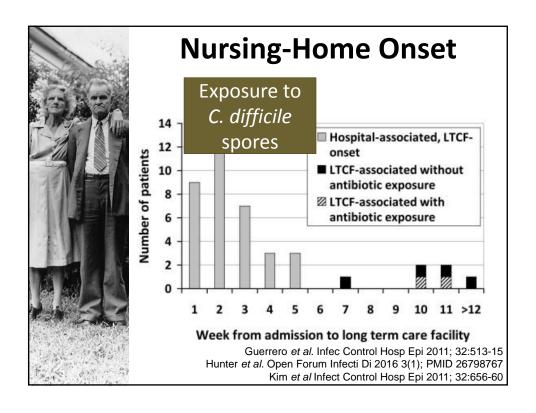
C. difficile Spores

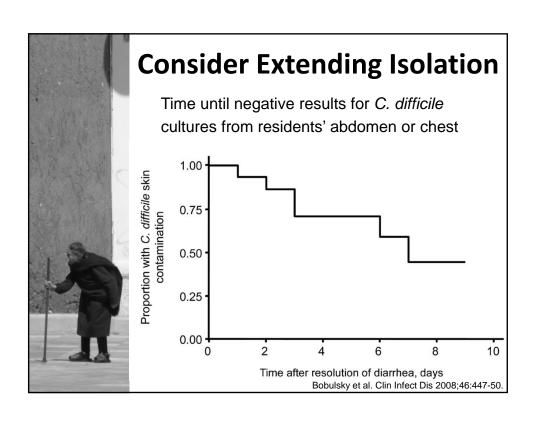
- May be recovered months after left on a surface
- Difficult to kill using routine cleaning agents
- Spores are shed onto skin and into the environment

Bobulsky *et al.* Clin Infect Dis. 2008;46(3):447-50 Kim *et al.* Jnl Hosp Infection 1981; 143(1) 43-50











There's no place like home...



...but how do we clean it?

Slide Courtesy of Curtis Donskey Sitzlar et al Infect Control Hosp Epi 2012: 33:534-36.



Steps You Can Take:

Infection Control

Minimize Transmission by Patients/Residents

Private rooms if know or suspect C. difficile infection*

Encourage hand hygiene

Extend isolation

Have them use common equipment at the end of the day

*Who moves?

Cohen et al. Infec Control Hosp Epi 2010; 31:431-55 Manian et al. Am J Infec Control 2013; 41(6):537-41 http://www.cdc.gov/HAI/prevent/prevention_tools.html#ltc



Steps You Can Take:

Infection Control

Minimize Transmission by Staff

Hand hygiene with soap & water

Single use/disposable equipment

Dedicated equipment (e.g., slings)

Mandatory education annually; more often for high-turnover staff

> Cohen et al. Infec Control Hosp Epi 2010; 31:431-55 Manian et al. Am J Infec Control 2013; 41(6):537-41

> http://www.cdc.gov/HAI/prevent/prevention_tools.html#ltc



Steps You Can Take:

Infection Control

Minimize Transmission by Staff

Contact precautions (gown, glove)

Make equipment available at the door

Designate someone on every shift to replenish supplies

Supply disinfectant wipes with bleach

Cohen et al. Infec Control Hosp Epi 2010; 31:431-55 Manian et al. Am J Infec Control 2013; 41(6):537-41



Steps You Can Take:

Infection Control

Minimize Environmental Reservoirs

Involve & educate housekeeping staff

Daily disinfection of high-touch surfaces

Assess adequacy of cleaning before changing to a new product

Cleaning & disinfection with sporicidal agent (i.e. bleach)

Cohen *et al.* Infec Control Hosp Epi 2010; 31:431-55 Manian *et al.* Am J Infec Control 2013; 41(6):537-41 http://www.cdc.gov/HAI/prevent/prevention_tools.html#ltc



Active Surveillance?

- Rectal swabs upon hospital admission to detect gene for Toxin B
- If positive, contact precautions during the hospitalization
- Of ~7600 admissions, 5% identified as carriers

Time Period	Rate of HA-CDI*
Epidemic period (8/04 – 7/07)	11.1
Pre-intervention period (7/07 – 11/13)	6.9
Intervention period (12/13 – 3/15)	3.0

*Healthcare-associated C. difficle infections/10,000 patient days

Longtin et al. JAMA Int Med. 2016 176(6);796-804



Steps You Can Take: Infection Prevention

Facility-wide Measures

Antimicrobial Stewardship Program

Surveillance for C. difficile infection

Avoid tests of cure

Laboratory-based alert system

 $\underline{http://www.cdc.gov/HAI/prevent/prevention_tools.html\#ltc}$



Steps You Can Take:

Infection Prevention

Early response to potential CDI

Define criteria to suspect CDI

Preemptive contact isolation

Standing orders to test for *C. difficile* (when criteria met)

http://www.cdc.gov/HAI/prevent/prevention_tools.html#ltc



Probiotics for Primary Prevention?

- Meta-analysis slightly favors probiotics
- Lactobacillus casei, L. acidophilus and L. rhamnosus in varying combinations
 - Above given as part of clinical trials
- Double-blind RCT of Sacromyces boulardii stopped for futility
- FDA-approved probiotics?

Johnson *et al.*, Int J Infect Dis. 2012; 16:e786-92 Evans & Johnson, Clin Infec Dis 2015:60 (s2)S122-8 Bakken. Clin Infec Dis 2014:59: 858-861 Ehrhardt *et al.* OFID on-line January 2016 **Bakken. CID 2014:59 (858-61)



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 - Yogurt
 - Kefir**

Johnson *et al.*, Int J Infect Dis. 2012; 16:e786-92 Evans & Johnson, Clin Infec Dis 2015:60 (s2)S122-8 Bakken. Clin Infec Dis 2014:59: 858-861 Ehrhardt *et al.* OFID on-line January 2016 **Bakken. CID 2014:59 (858-61)

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On the Horizon: Vaccines

- Tested in healthy adults 50-85 years old
- 3 dose regimen (0, 1 & 6 months)
- Generated antibodies against Toxins A & B lasting through (at least) 6 months post-vaccine
- Well-tolerated
- Efficacy studies pending

Sheldon et al., Vaccine. 2016(34) 2082-2091



Take Home Messages

- Antibiotic exposure is the main risk factor for C. difficile infection
- Metronidazole and oral vancomycin are the mainstays of treatment
- Fecal microbiota transplant is safe and effective
- More palatable options are becoming available



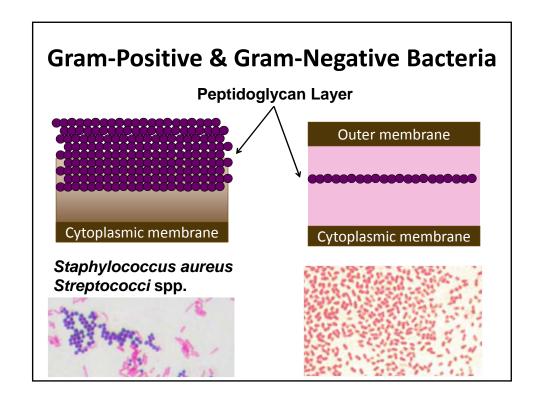
Together, we can wipe out *C. diff*

Let's doo it!



CRE

Carbapenem-Resistant Enterobacteriaceae





Gram Negative Bacteria

Enterobacteriaceae / Lactose-Fermenting

- Escherichia coli
- Klebsiella spp.
- Enterobacter spp.

Non-Lactose Fermenting

- Pseudomonas aeruginosa
- Acinetobacter baumaniix

http://www.cdc.gov/drugresistance/threat-report-2013/



Antibiotics Used Against Gram-Negative Bacteria

1st/2nd generation cephalosprins

Penicillins

Fluoroquinolones

Extended-spectrum cephalosporins

Beta-lactam inhibitor combinations

Carbapenems

Aminoglycosides

Tigecycline

Colistin

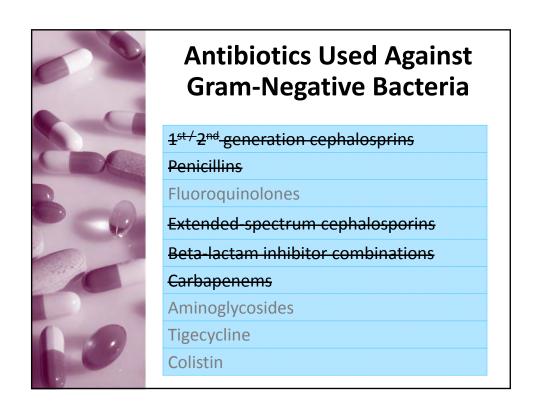


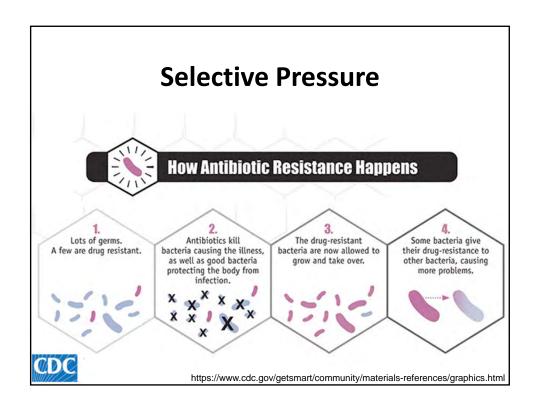
Alphabet Soup of MDR GN

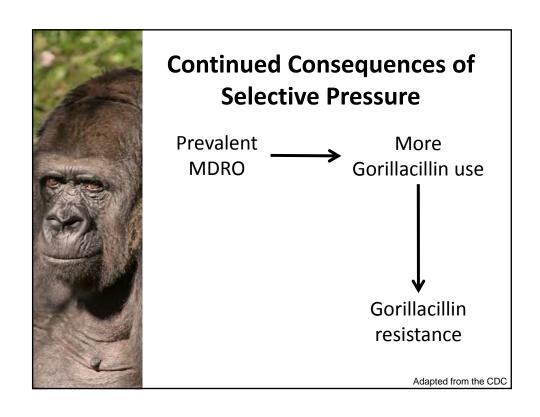
- Fluoroquinolone-resistant GN bacteria
- Extended-spectrum Beta-lactamase (ESBL) producing bacteria
 - Resistant to amp/sulbactam, piperacillin/tazobactam, ceftriaxone, ceftazidime, aztreonam
 - Carbapenems are treatment of choice
- Carbapenem-Resistant Enterobacteriaciae (CRE)
 - Klebsiella pneumoniae carbapenemase (KPC)
 - New Delhi Metallo-beta-lactamase (NDM)
 - Resistant to ertapenem, meropenem, imipenem/cilastin, doripenem
 - Sometimes tigecycline, usually colistin....

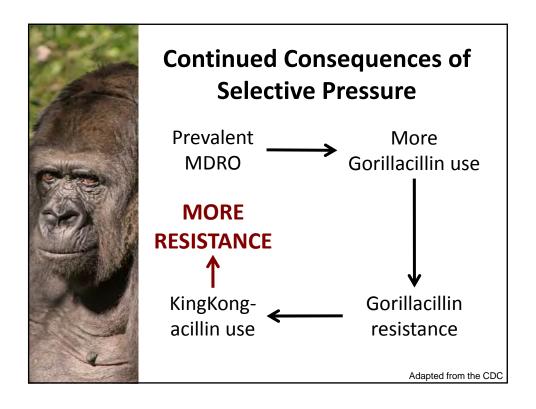
CDC's Guidance for Control of CRE - 2012 CRE Toolkit: http://www.cdc.gov/HAI/prevent/prevention-tools.html#ltc

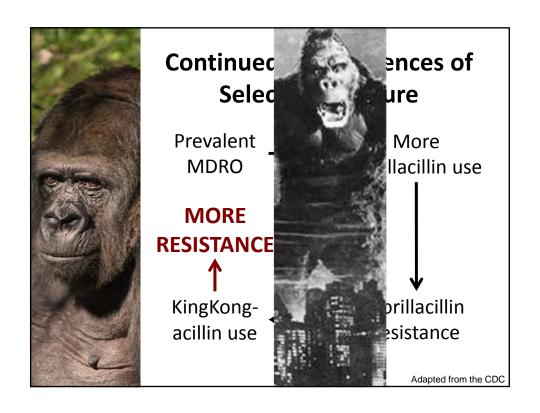






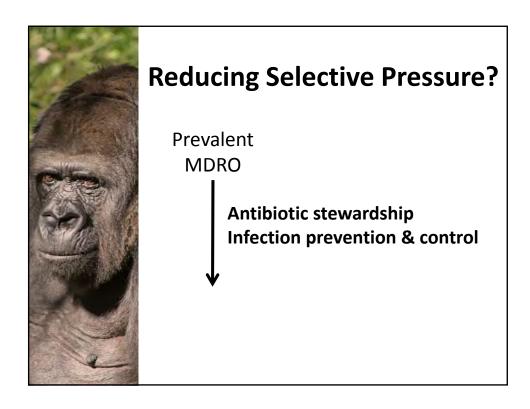


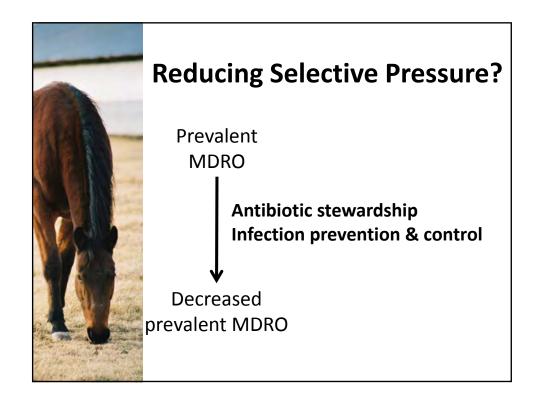


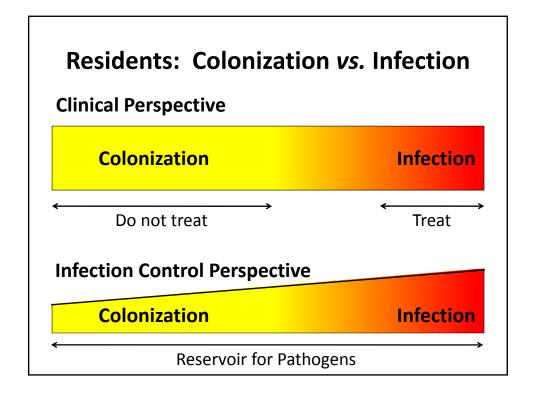














Nursing Homes as Reservoirs of MDROs

- Analysis of MDS data over 15 months
- Of ~4 million NH residents, 5% with MDRO infection
- For those infected with an MDRO during the study, 57% in NH, 41% in acute care
- Colonization rate unknown

Kahvecioglu et al. ICHE 2014 35(S3):S48-S55

Carbapenem-Resistant *Klebsiella* pneumoniae Outbreak



- Hospital reported an outbreak
- Cases investigated from April 2009 February 2011
- 19 cases identified
 - 16 admitted from a LTCF
 - 14 from LTCF A
- Genetic analysis >88% similarity among isolates

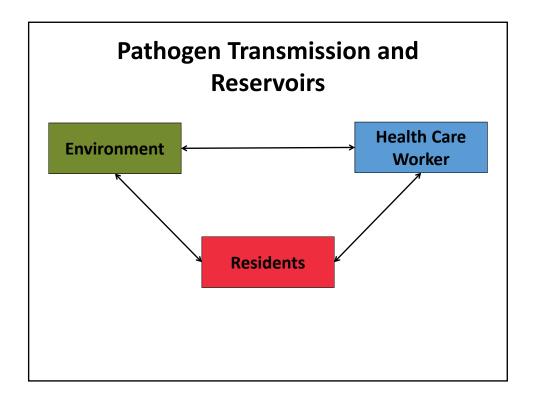
MMWR Oct 21, 2011 60(41) 1418- 20

Field Investigation of LTCF A



- No infection preventionist x 9 months
- Did not record MDRO status of residents
- Hand hygiene stations not conveniently located
- PPE supplies not available for those on contact precautions
- 11 of 118 resident samples (9%) with CRE; 8 previously undetected

MMWR Oct 21, 2011 60(41) 1418- 20



Pathogen Transmission in Nursing Homes

Transmission of MRSA to Healthcare Personnel Gowns and Gloves during Care of Nursing Home Residents

Mary-Claire Roghmann, MD, MS¹, J. Kristie Johnson, PhD², John D. Sorkin, MD, PhD³, Patricia Langenberg, PhD¹, Alison Lydecker, MPH¹, Brian Sorace, BS¹, Lauren Levy, JD, MPH¹, and Lona Mody, MD, MSc⁴

Glove contamination higher than gown contamination

Residents with skin breakdown had higher rates of transmission

High Risk Activities:

Dressing
Transferring
Hygiene
Changing Linens
Toileting

ICHE 2015 Sep 36(9):1050-1057



Isolation Precautions

١.				
	Standard Precautions (aka Universal Precautions)	Infection prevention practices that apply to all residents, regardless of diagnosis or presumed infection status		
	Transmission- based Precautions (aka Isolation Precautions)	Actions beyond Standard Precautions based on means of transmission (i.e., airborne, droplet & contact)		
	Contact Precautions	Measures to prevent transmission of infectious agents spread by direct or indirect contact with the resident or their environment		
	2007 Guideline for Isolation Precautions (CDC HICPAC)			



Colonization with MDR GN in Nursing Home Residents

Gram-negative bacteria may last hours to days to months on inanimate surfaces

Colonization with FQ-resistant GNR on average 76 days (\pm 66d) after admission

- Average length of stay is 463 days
- Up to 50% with quinolone-resistant Gramnegatives
- 17% with ESBL
- 1% with CRE

ESBL transmission rate of nearly 10% in a longterm care unit without contact precautions

Kramer et al. 2006 BMC Infectious Diseases 6:130; Tschudin-Sutter et al. 2016 22(6): 1094-1097 Reviewed in Dumyati et al. 2017. Current Infectious Disease Reports (in press)



Sites & Duration of Colonization with MDR GN

- May colonize stool
- May also colonize urine, devices, wounds, skin
- No protocols for declonization
- May continue to harbor organisms for months.
- Duration of contact precautions
 - ? Forever
 - ? 6 months without hospitalizations, antimicrobial therapy, and invasive devices before reculturing patients to document clearance of carriage

 $Siegal~\it et~al.~2007~http://www.cdc.gov/ncidod/dhqp/pdf/isolation 2007.pdf$

MDR GNB* Core Prevention Strategies

- Hand hygiene
- Contact Precautions
- Recognize previously colonized patients
- Rapidly report ESBL & CRE lab results
- Provide ESBL & CRE education for healthcare providers
- Minimize use of devices
- Screen for ESBL & CRE

Adapted from the CDC



Risk Factors for Multi-Drug Resistant Organisms in NHs

- Recent antibiotic exposure (4 months)
- Dependence for assistance with ADLs
- Indwelling medical devices, decubitus ulcers, other wounds, urinary and fecal incontinence

Reviewed in Dumyati et al. 2017 Current Infectious Disease Reports (in press)



Contact Precautions for In-Room Care

- Hand hygiene
- Gowns, gloves upon entry
- Removal of gowns, gloves at exit
- Hand hygiene
- Single use equipment
- Dedicate equipment to individual resident when possible
- Clean/disinfect between individuals

The burden is on healthcare workers



Socialization & Other Ideas

- Encourage resident hand hygiene
- Clean
- Contained
- Cooperative

May cohort with a "low risk roommate"

- No (major) wounds.
- No invasive devices.
- Not immunocompromised.
- No recent antibiotic exposure (?)

Designate someone to restock PPE on every shift



Targeted Infection Prevention Study

For residents with urinary catheters or feeding tubes

- Hand hygiene before/after care
- Gown & glove use during morning/evening care, device care
- Staff education (intensive!)
- Active surveillance for MDROs

Mody et al. JAMA Int Med. 2015 175(5);714-723



Targeted Infection Prevention Study

418 residents enrolled; >6000 samples

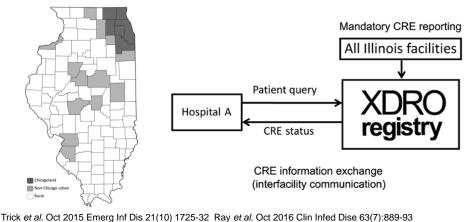
Outcome	Rate Ratio
MDRO prevalence	0.77
New MRSA acquisitions	0.78
Risk of first CAUTI	0.54
Risk of all CAUTI	0.69

No change in GNR acquisition, feedingtube associated pneumonia or skin/soft tissue infections

Mody et al. JAMA Int Med. 2015 175(5);714-723

Regional Approach to Infection Control

- Automated, regional sharing of information about CRE
- In 1 year, ~1500 reports of CRE from 115 hospitals, 5 LTACHs, 46 long-term care facilities and 7 reference laboratories





Take Home Messages

- Balance between resident safety and individual liberty
- Any resident with an MDRO is a reservoir for that organism
- Activities most linked to transmission involve a health care workers (i.e., not resident-toresident)
- For MDROs, transmission-based precautions based on resident risk factors may be most rational, feasible strategy
- Coordinated, regional approaches feasible, helpful and necessary

