GASTROINTESTINAL DISEASE IN THE HEALTHCARE SETTING: CLOSTRIDIUM DIFFICILE AND NOROVIRUS

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DISCLOSURES

Nothing to Disclose





Diarrheal Disease in Hospital: Response



Diarrheal Disease in Hospital: Response



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Diarrheal Disease in the Hospital: Hospital Epidemiologist

- Any infectious diarrhea can be hospital-acquired
 - Foodborne
 - Patient-to-patient (or HCW-to-patient)
- Common etiologies
 - · Clostridium difficile and Norovirus
 - Rotovirus, Salmonella, Cryptosporidium
- Response
 - · C. difficile: Contact Precautions for duration of illness
 - Rotovirus: CP/DOI; mask if aerosol
 - All others: Standard precautions
 - EXCEPT: Contact, if diapered/incontinent or outbreak

Overview

C. difficile	Norovirus
 Epidemiology Pathogenesis Clinical presentations Diagnosis Treatment Prevention 	 Background Clinical features Immunity Epidemiology/Transmission Prevention







CLOSTRIDIUM DIFFICILE

"The difficult clostridium"

Case

CC: 48 yo man presented to ED with confusion, acute abdominal pain and diarrhea

HPI:

- Numerous non-bloody liquid stools x 2 d
- Acute diffuse abdominal pain x 1 day
- No associated N/V
- No F/C/sweats
- · On the DOA pt became disoriented; fiancée called 911

Case

- PMHx:
 - Depression
 - Chronic Back Pain
 - Tobacco use
- All: NKDA
- Meds:
 - Sertaline
 - NSAID
 - Percocet prn
 - Protonix

- SHx:
 - Lives w/ fiancée
 - Denies Etoh/IVDA
 - + Tobacco Use
- ROS:
 - Recently seen by PCP for upper respiratory symptoms and prescribed Moxifloxacin for "possible bronchitis vs. URI"

Case: PE/Lab Data

- 99.8 115 18 87/42 98% RA
- Moderate distress
- · Diffuse abdominal tenderness w/o guarding or rebound
- WBC = 68K
- HCT 45%
- Na+ 128, K+ 6.6, CO2 14
- Cr 5.8

Case: Initial Course

- IVF replacement
- Pressors initiated
- Admitted to the MICU
- Abdominal Imaging ...





Case: Course

- · IV Metronidazole was initiated
- Surgical consult
 - Emergent exploratory laparotomy
 - · Swollen edematous colon, pseudomembranes
 - Sub-total colectomy
- Patient died shortly after surgery

Clostridium difficile

- · Gram-positive, spore forming rod
- Obligate anaerobe
- Toxin A and Toxin B
 Required to cause disease
 - C. difficile infection (CDI)



Antibiotic exposure most important RF
Primarily healthcare-associated pathogen*

C. Difficile: Overview

- Epidemiology
- Pathogenesis
- Clinical presentations
- Diagnosis
- Treatment
- Prevention

C. difficile: Overview

Epidemiology

- Pathogenesis
- Clinical presentations
- Diagnosis
- Treatment
- Prevention



C. difficile: Epidemiology

	Annual Incidence	Deaths	Costs	
Hospital-Onset	165,000	9,000	1.3 billion	

Campbell et al. ICHE. 2009;; Dubberke et al. Emerg Infect Dis. 2008; Dubberke et al. CID 2008; Elixhauser et al. HCUP Statistical Brief #50. 2008

C. difficile: Epidemiology

	Annual Incidence	Deaths	Costs
Hospital-Onset	165,000	9,000	1.3 billion
LTCF-Onset	263,000	16,500	2.2 billion
Community- Onset	50,000	3,000	0.3 billion

Campbell et al. ICHE. 2009; Dubberke et al. Emerg Infect Dis. 2008; Dubberke et al. CID 2008; Elixhauser et al. HCUP Statistical Brief #50. 2008

C. difficile: Epidemiology



Campbell et al. ICHE. 2009;; Dubberke et al. Emerg Infect Dis. 2008; Dubberke et al. CID 2008; Elixhauser et al. HCUP Statistical Brief #50. 2008

C. difficile: Rising Incidence



C. difficile is prevalent

- In 2010 a Nationwide Inpatient Sample was performed to assess the prevalence and relative frequency of HAIs
 - 4% of all inpatients had an HAI
 - 12.1% of all HAIs were due to C. difficile

McGill et al. NEJM, 2014; 4:370

Research

Recherche

Clostridium difficile-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity

Jacques Pépin, Louis Valiquette, Marie-Eve Alary, Philippe Villemure, Anick Pelletier, Karine Forget, Karine Pépin, Daniel Chouinard

Fast-tracked article. Published at www.cmaj.ca on Aug. 4, 2004.

Pepin et al. CMAJ, 2004; 171:466



Fig. 1: Annual incidence (per 100 000 population) of *Clostridium difficile*-associated diarrhea (CDAD) in Sherbrooke, Que., 1991–2003.

C. difficile: Epidemic Strains

- FQ-resistant
- Increased virulence
- B1/NAP1
- Increased morbidity and mortality
- Increased severity of presentations

C. difficile: Epidemic Strains



C. difficile: Risk Factors

- Antimicrobial exposure
- Acquisition of C. difficile
- Advanced age
- Underlying illness
- Immunosuppression
- Tube feeds
- Gastric acid suppression/PPI

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Major modifiable risk factors



C. difficile: Overview

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Step #1: Disruption of normal colonic flora



Antimicrobials Predisposing to CDI

Very Commonly Related	Less Commonly Related	Uncommonly Related
Clindamycin	Other penicillins	Aminoglycosides
Ampicillin	Sulfonamides	Bacitracin
Amoxicillin	Trimethoprim	Metronidazole
Cephalosporins	Cotrimoxazole	Teicoplanin
Fluoroquinolones	Macrolides	Rifampin
	Carbapenems	Chloramphenicol
		Tetracyclines
		Daptomycin
		Tigecycline

Bouza E, et al. Med Clin North Am. 2006;90:1141-1163. Loo VG, et al. N Engl J Med. 2005;353:2442-2449.

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Bouza E, et al. Med Clin North Am. 2006;90:1141-1163. Loo VG, et al. N Engl J Med. 2005;353:2442-2449.

Step # 2: Exposure to C. difficile



Step # 2: Exposure to C. difficile



Exposure to *C. difficile*: From Where?

- May be different in...
 - outbreak versus endemic setting
 - Hospital versus community onset
- Transmission from patients with CDI
 - · May be less common than previously thought
 - Recent genotypic analysis, 45% of CDI patients with unique strains*
 - Infants
 - · Other asymptomatic colonizers?
 - Food?
 - Environment?
 - Animals?

Eyre et al. NEJM, 2013; 369:1195; Chitnis et al. JAMA IM 2013







C. difficile: Overview

- Epidemiology
- Pathogenesis
- Clinical presentations
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- Treatment
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C. difficile: Clinical Presentations

- Asymptomatic carriage
- Antibiotic-associated diarrhea
- Colitis without pseudomembranes
- Pseudomembranous colitis
- Recurrent disease (relapse vs. infection)
- Fulminant colitis

C. difficile: Asymptomatic Carriage

- > 50% of healthy neonates
- 1-2% of healthy adults
 - After antibiotic use, > 25%
 - Hospitalized, ~ 20%
 - Long-term care, ~ 50%



C. difficile: Asymptomatic Carriage

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Many People are Colonized Treatment NOT Effective



C. difficile: Overview

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C. difficile: Diagnostics

Test	Advantage(s)	Disadvantage(s)
Toxin testing		
Toxin Enzyme immunoassay (EIA)	Rapid, simple, inexpensive	Least sensitive method, some detect only toxin A, assay variability
Tissue culture cytotoxicity	More sensitive than toxin EIA, biologically active toxin	Labor intensive; requires 24–48 hours for a final result, special equipment;
Organism identification		
Glutamate dehydrogenase (GDH) EIA	Rapid, sensitive, possible screen for diagnostic algorithm	Not specific, toxin testing required to verify diagnosis; may not be 100% sensitive
PCR	Rapid, sensitive, detects presence of toxin gene	Cost, special equipment, may be "too" sensitive
Stool culture	Most sensitive test available when performed appropriately	Confirm toxin production; labor- intensive; requires 48–96 hours for results

C. difficile: Diagnosis, Key Points



Diagnosis: How many samples do I send?

- "C. diff x 3" based on single study
 - Assumed 100% specificity
- Prevalence of disease decreases with repeat testing
 - Positive predictive value (PPV) plummets
- Test based on index of suspicion

Manabe YC et al Ann Int Med. 1995; Litvin M, et al. ICHE. 2009



C. difficile: Optimize Testing

- Poor test ordering practices can lead to false positives
 - · Choose tests with high sensitivity/specificity
 - PCR
 - · GDH screen with toxin confirmation
 - Increase pre-test probability
 - Do NOT test formed stool
 - Do NOT repeat test w/in 5 days
 - Do NOT send test of cure
 - Do focus testing on patients with watery diarrhea; 3 or more unformed stools in 24 hours

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Recall: ~ 20% of hospitalized patients are colonized!

C. difficile: Diagnosis, Key Points



C. difficile: Overview

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Case/Board Question

- A 42 yo man is evaluated for recurrent diarrhea. Four weeks ago, the patient was diagnosed with mild *Clostridium difficle* infection and treated with a 14-day course of metronidazole, 500 mg orally every 8 hours, with resolution of his symptoms. He currently takes no medications.
- One week after his last dose of metronidazole, he develops recurrent watery stools without fever or other symptoms. There is no visible blood or mucus in the stools.
- Physical examination findings are noncontributory. Results of laboratory studies show a leukocyte count of 10.4 and a normal serum creatinine level. A stool sample tests positive for occult blood, and results of a repeat stool assay are again positive for *C. difficile* toxin.

Case/Board Question

- Which of the following is the most appropriate treatment at this time?
 - A. Oral metronidazole for 14 days
 - B. Oral metronidazole taper over 42 days
 - C. Oral vancomycin for 14 days
 - D. Oral vancomycin plus parenteral metronidazole for 14 days
 - E. Oral vancomycin taper over 42 days

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C. difficile: Treatment

Step #1: Stop Antibiotics (if possible)





C. difficile: Treatment Options

Metronidazole	<u>Vancomycin</u>
• PO/IV, TID-QID	• PO QID
O and a stable to see a	
Comparable to vanc	 Only FDA approved
Guidelines	 Gold standard
Low cost	
High recurrence	 High recurrence
 May be less effective 	Promote VRE?
in severe cases	 High cost

C. difficile: Treatment Options

Metronidazole • 250 mg PO/IV QID		Vancomycin • 125-250 PO QID	
• Compa			proved
• Guideli	Fidaxor	d	
 Low co 	Comparable to Vanc		
	Possibly less recurrence		
 High re 		ice	
• May be less effective Promote VRE			?
in severe cases		 High cost 	

Freatment of nonsevere Clostridium difficile associated diarrhea in adults
Initial episode
Mild disease: metronidazole 500 mg orally three times daily or 250 mg four times daily for 10 to 14 days
Severe disease: vancomycin 125 mg orally four times daily for 10 to 14 days
First relapse
Confirm diagnosis (see text)
If symptoms are mild, conservative management may be appropriate.
If antibiotics are needed, repeat treatment as in initial episode above. Alternative: fidaxomicin 200 mg orally twice daily for 10 days ^[4,5]
Second relapse ^[1,2]
Confirm diagnosis (see text)
Tapering and pulsed oral vancomycin (below), with or without probiotics (for example, Saccharomyces boulardii 500 mg orally twice daily) weeks in the absence of antibiotics.
125 mg orally four times daily for 7 to 14 days
125 mg orally twice daily for 7 days
125 mg orally once daily for 7 days
125 mg orally every other day for 7 days
125 mg orally every 3 days for 14 days
Alternative: fidaxomicin 200 mg orally twice daily for 10 days ^[4,5]
Subsequent relapse ^[3,4,5]
Confirm diagnosis (see text)
Fidaxomicin 200 mg orally twice daily for 10 days if not used previously
Fecal bacteriotherapy (fecal microbiota transplant)

C. difficile: Treatment Issues

- Inability to take PO
 - IV metronidazole
 - Vancomycin retention enema

- Surgical Consult
 - Critically ill or delayed response to therapy
 - Leukemoid reaction
 - Renal failure
 - Septic Shock
- Infection Control Measures



C. difficile: Treatment, recurrence

- Repeat initial treatment regimen (1st relapse)
- Oral vancomycin taper
- Fidaxomicin
- Probiotics
- IVIG
- Fecal transplant
- · 25% of patients may have recurrent disease

C. difficile: Fecal Transplant







Nood et al. NEJM 2013; 368:4073.

C. difficile: Diagnosis, Key Points



Table	1.	Laboratory	screening	protocol	for	donor	blood	and
stool	samp	oles obtained	before st	ool transp	lant	ation.		

Laboratory		
sample	Infectious agent	Laboratory test
Blood	HAV	HAV antibody (IgM and IgG)
	HBV	Antibody to hepatitis B surface antigen, antibody to hepati- tis B core antigen
	HCV	HCV antibody (RIBA-II)
	HIV-1 and HIV-2	EIA
	Treponema pallidum	Rapid plasma reagin test
Stool	Clostridium difficile	Toxin A or toxin B (cytotoxin) detection
	Enteric bacterial pathogens	Selective stool culture
	Ova and parasites	Light microscopy

NOTE. HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; RIBA-II, recombinant immunoblot assay, second generation test.

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 Table 1.
 Laboratory screening protocol for donor blood and stool samples obtained before stool transplantation.

NOTE. HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; RIBA-II, recombinant immunoblot assay, second generation test.

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- Epidemiology
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SUPPLEMENT ARTICLE: SHEA/IDSA PRACTICE RECOMMENDATION

Strategies to Prevent *Clostridium difficile* Infections in Acute Care Hospitals

Erik R. Dubberke, MD; Dale N. Gerding, MD; David Classen, MD, MS; Kathleen M. Arias, MS, CIC; Kelly Podgorny, RN, MS, CPHQ; Deverick J. Anderson, MD, MPH; Helen Burstin, MD; David P. Calfee, MD, MS; Susan E. Coffin, MD, MPH; Victoria Fraser, MD; Frances A. Griffin, RRT, MPA; Peter Gross, MD; Keith S. Kaye, MD; Michael Klompas, MD; Evelyn Lo, MD; Jonas Marschall, MD; Leonard A. Mermel, DO, ScM; Lindsay Nicolle, MD; David A. Pegues, MD; Trish M. Perl, MD; Sanjay Saint, MD; Cassandra D. Salgado, MD, MS; Robert A. Weinstein, MD; Robert Wise, MD; Deborah S. Yokoe, MD, MPH







http://www.shea-online.org/about/compendium.cfm

C. difficile: Basic IP Recommendations

Basic Recommendation	Grade
CP for pts with CDI until 48 hours after diarrhea resolves	Al gloves BIII gowns BIII for isolation
Ensure adequate disinfection of equipment/environment	BIII equipment BII environment
Alert system if patient diagnosed with CDI	BIII
CDI surveillance and feedback to units/ administrators	BIII
Educate HCP, housekeeping, and hospital administration	BIII
Measure HH and CP compliance	BIII

http://www.shea-online.org/GuidelinesResources/CompendiumofStrategiestoPreventHAIs.aspx

C. difficile: Prevention, Special Approach

Special Approach	Grade
Intensify efforts at HH and CP compliance	BIII
Preferentially use soap and water for HH	BIII
Place patients in CP while C. difficile testing is pending	BIII
Prolong CP until discharge	BIII
Assess the adequacy of room cleaning	BIII
Use bleach for environmental disinfection	BII
Initiate an antimicrobial stewardship program	All

http://www.shea-online.org/GuidelinesResources/CompendiumofStrategiestoPreventHAIs.aspx



C. difficile: Antimicrobial Stewardship

- ~ 50% antibiotic use is "inappropriate"
 - No need for antibiotics, 25%
 - Wrong antibiotic or duration, 25%
- Stewardship of all antibiotics is important
 - · Focused restrictions of clindamycin, cephalosporins and FQ





Hecker et al 2003, Werner et al 2011, Siegel et al 2007, Carling et al 2003, Khan et al 2003

C. difficile: Antimicrobial Stewardship



Fowler et al. J Antimicrob Chemother 2007;59:990-5.

C. difficile: Infection Prevention



C. difficile: Hand Hygiene

An essential tool in prevention of infection



C. difficile: Evidence for HH





Bobulsky et al. CID 2008;46:447.

C. difficile: HH, Which Method?



C. difficile: HH, Which Method?

Interventions compared		Mean log reduction (95% CI),
Intervention 1	Intervention 2	log ₁₀ CFU/mL
Warm water and plain soap	No hand hygiene	2.14 (1.74-2.54)
Warm water and plain soap	Alcohol-based handrub	2.08 (1.69-2.47)
Cold water and plain soap	No hand hygiene	1.88 (1.48-2.28)
Cold water and plain soap	Alcohol-based handrub	1.82 (1.43-2.22)
Warm water and plain soap	Antiseptic hand wipe	1.57 (1.18-1.96)
Warm water and antibacterial soap	No hand hygiene	1.51 (1.12-1.91)
Warm water and antibacterial soap	Alcohol-based handrub	1.46 (1.06-1.85)
Cold water and plain soap	Antiseptic hand wipe	1.31 (0.92-1.71)
Warm water and antibacterial soap	Antiseptic hand wipe	0.94 (0.55-1.34)
Warm water and plain soap	Warm water and antibacterial soap	0.63 (0.23-1.02)
Antiseptic hand wipe	No hand hygiene	0.57 (0.17-0.96)
Antiseptic hand wipe	Alcohol-based handrub	0.51 (0.12-0.91)
Cold water and plain soap	Warm water and antibacterial soap	0.37 (-0.03 to 0.76)
Warm water and plain soap	Cold water and plain soap	0.26 (-0.14 to 0.66)
Alcohol-based handrub	No hand hygiene	0.06 (-0.34 to 0.45)

Oughton et al. Infect Control Hosp Epidemiol 2009;30:939-44.

But...



FIGURE 1. Use of alcohol hand rub by healthcare workers, in liters per 1,000 patient-days, per quarter, 2000-2003.

Boyce JM et al. Infect Control Hosp Epidemiol 2006; 27:479-83.

But...



FIGURE 2. Number of patients with 1 or more tests positive for *Clostridium difficile* toxin per 1,000 patient-days, 2000-2003.

Boyce JM et al. Infect Control Hosp Epidemiol 2006; 27:479-83.

And...

Product	Log10 Reduction
Tap Water	0.76
4% CHG antimicrobial hand wash	0.77
Non-antimicrobial hand wash	0.78
Non-antimicrobial body wash	0.86
0.3% triclosan antimicrobial hand wash	0.99
Heavy duty hand cleaner used in manufacturing environments	1.21*

Edmonds, et al. Presented at: SHEA 2009; Abstract 43.

C. difficile: Hand Hygiene

- Still an essential measure
 - · Soap and Water generally recommended (outbreaks)
 - ETOH-based hand rubs may still be effective (don't discourage)
- · Spores may be difficult to eradicate with any method
- Emphasis on Isolation/Glove and Gown Use

C. difficile: Contact Precautions

- Private room
- Gown/Glove use
 - for contact with patient and environment
 - for duration of symptoms (CDC)



But...



Bobulsky et al. CID 2008;46:447.

And...

Recurrence is Common Up to 25% of Cases

C. difficile: Environmental Hygiene

- Common contaminant of near patient environment
- May persist up to 5 months on surfaces



C. difficile: Risk from Prior Room Occupant



Shaughnessy, et al. ICHE 2011, 32: 201

C. difficile: Environmental Hygiene

- · Bleach may be more effective
 - Sporicidal
 - · Benefit in "highly endemic" or outbreak settings
 - · Limited data on effect of transmission
- Ensure adequate cleaning



Board Question

- Which of the following is correct regarding *Clostridium difficle* toxin-mediated diarrhea (CDI) associated with antibiotic administration?
 - A. C. difficle toxin causes 80-90% of all antibiotic-associated diarrheal illness
 - B. C. diffile-negative antibiotic associated diarrhea is caused by enteropathogenic Escherichia coli
 - C. The anticipated relapse rate is as high as 20% after 10 days of recommended antibiotic therapy
 - D. The anticipated relapse rate is lower in patient treated with vancomycin than in those treated with metronidazole

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Norovirus



Noroviruses: Taxonomy

- ssRNA virus (small); Family Caliciviridae
- Non-enveloped
- 5 distinct genogroups
 - · GI, GII, GIV associated with human disease





MMWR 2011; 60(RR19):1-12

Noroviruses: Clinical Features

- · Estimated 23 million infections annually
- Incubation period: 12-72 hrs
- Onset: abrupt or gradual
- Duration: 12-72 hrs
- Symptoms
 - Children: Vomiting > diarrhea
 - Adults: Diarrhea > vomiting
 - Abdominal pain/cramping
 - Constitutional symptoms 30%: HA, fever, chills, myalgias, malaise
- Up to 30% may be asymptomatic

MMWR 2011; 60(RR19):1-12

Immunity

- Incompletely understood
- Pre-existing antibodies not protective
 - Protective effect may last only 8 weeks to 6 months
- Histo-blood group antigen expression
 - Lack of expression in intestinal cells protective
- · Evolves to escape adaptive and innate immunity

MMWR 2011; 60(RR19):1-12

Transmission

- · Humans only known reservoir
- Highly contagious
 - · As few as 18 viral particles infectious
 - 5 billion per gram feces at peak shedding
- Modes of transmission
 - Person-to-person
 - Food contamination
 - Aerosolized vomitus
 - Fomites



MMWR 2011; 60(RR19):1-12

Epidemiology

- 23 million cases/yr
 - 25% foodborne
- Year round
 - Outbreaks in winter
 - Evolution of GII-4
- 35.4% of outbreaks reported from LTCF



MMWR 2011; 60(RR19):1-12

Diagnosis

- Noroviruses CANNOT be cultured in the lab
 - Important when assessing prevention measures
- Electron microscopy
 - Need 10⁶-10⁷ virus particles/ml stool
- Nucleic acid hybridization/PCR
 - Broadly reactive
 - · PCR products can be sequenced for typing
 - · Can detect asymptomatic carriers
- Enzyme immunoassays
 - Sensitivity 36% to 80%
 - Type specific and requires high innoculum

MMWR 2011; 60(RR19):1-12

Prevention: Isolation/Cohorting

- Contact precautions
 - Until 24 to 72 hours after asymptomatic
 - Consider isolate exposed patients during incubation period
- Sick healthcare workers
 - Furlough until asymptomatic for 48 to 72 hrs
- Prolonged shedding in infants/young children
 - Extend duration?

MMWR 2011; 60(RR19):1-12

Prevention: Hand Hygiene

- Soap and water preferred
 - Removes 0.7 to 1.2 log₁₀ after 20 seconds
- · Alcohol-based hand rubs adjunct between hand washings
 - Alcohol based hand rubs no removal by PCR
 - Reduces viable FCV/MNV by 2.5 log₁₀

Prevention: Environment

- Clean surface with standard disinfectant to remove organic loads
- Follow with 1:10 to 1:50 dilution of household bleach
 - 4 log₁₀ reduction of FCV and MNV after 4 minutes

MMWR 2011; 60(RR19):1-12

Norovirus: Key Points

<image><image><image><image><image><image>

Key Points







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