

Prevention of Clostridium difficile Infection - What We Find in Guidelines
Dr. Walter Zingg and Dr. Maria Martin
A Webber Training Teleclass

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Prevention of Hospital Infections by Intervention & Training

Prevention of Clostridium difficile Infection - What We Find in Guidelines

Dr. Walter Zingg, MD
Dr. Maria Martin, MD, MPH

Hosted by Paul Webber
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March 26, 2015

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Outline

- PROHIBIT work package 2
- Guidelines in WP 2
- *C. difficile*
 - Studies and guidelines
 - Treatment
 - Summary

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- Identification and analysis of current guidelines for prevention of HAI (CDI, VAP, CABSI, SSI, UTI) in European countries
- Overview on current surveillance systems in European countries
- Overview of public reporting of HAI in European countries and consensus statement about benefits and challenges of public reporting

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Deliverables WP2

- Systematic review of guidelines and recommendations in European countries
- Report on surveillance programmes in European countries
- Report on public reporting of HAI in European countries

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Description WP2

- Countries enclosed: 27 EU member states plus Switzerland, Norway, Iceland and Croatia (total 34)
- Topics of interest:
 - CDI
 - SSI
 - VAP
 - CABSII
 - UTI

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Questionnaires

- 1st Q: sent out End of August 2010
 - Elements: basic questions on available guidelines, surveillance systems and practices in (public) reporting of HAI rates
 - Return rate 100% (last in April 2011)
- 2nd Q (decided in Berlin Dec. 2010): sent out in March 2011
 - Elements: financing of health care services with focus on HAI („pay for performance”); public interest in HAI prevention
 - Return rate 91%

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Guidelines

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Guidelines

- Extensive internet search according to specifications of NCPs or recontact
- Translation into English
- Development of matrices with QSR NVivo software (basis German and CDC guidelines)

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Challenges: „Where are the guidelines...?“



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Matrix for systematic review (NVivo software)

Name	Quoten	Referenzen	Erstellt am	Erstellt von	Erstellt am	Beantwortet
pneumonia	0	0	22.09.2010 14:28	SVS	22.09.2010 14:28	SVS
cough	0	0	12.10.2010 19:20	SVS	12.10.2010 19:20	SVS
fever	0	0	13.10.2010 11:39	SVS	13.10.2010 11:39	SVS
flu	0	0	13.10.2010 11:40	SVS	13.10.2010 11:40	SVS
strep	0	0	10.11.2010 17:19	SVS	10.11.2010 17:19	SVS
influenza	0	0	10.11.2010 17:20	SVS	10.11.2010 17:20	SVS
respiratory	0	0	10.11.2010 17:20	SVS	10.11.2010 17:20	SVS
bronchitis	0	0	10.11.2010 17:20	SVS	10.11.2010 17:20	SVS
asthma	0	0	13.10.2010 11:58	SVS	10.11.2010 17:19	SVS
infectious	0	0	13.10.2010 11:40	SVS	13.10.2010 11:40	SVS
infectious	0	0	13.10.2010 11:39	SVS	13.10.2010 11:39	SVS
infectious	0	0	13.10.2010 11:40	SVS	13.10.2010 11:40	SVS
infectious	0	0	13.10.2010 11:20	SVS	13.10.2010 11:20	SVS
infectious	0	0	13.10.2010 11:20	SVS	13.10.2010 11:20	SVS
infectious	0	0	13.10.2010 11:38	SVS	13.10.2010 11:41	SVS
infectious	0	0	13.10.2010 11:20	SVS	13.10.2010 11:20	SVS
infectious	0	0	12.10.2010 19:21	SVS	12.10.2010 19:21	SVS
infectious	0	0	13.10.2010 11:24	SVS	13.10.2010 11:24	SVS
infectious	0	0	10.11.2010 17:26	SVS	10.11.2010 17:26	SVS
infectious	0	0	10.11.2010 17:26	SVS	10.11.2010 17:26	SVS
infectious	0	0	13.10.2010 12:38	SVS	13.10.2010 12:38	SVS
infectious	0	0	13.10.2010 12:38	SVS	13.10.2010 12:38	SVS
infectious	0	0	13.10.2010 12:01	SVS	10.11.2010 17:26	SVS
infectious	0	0	13.10.2010 11:30	SVS	13.10.2010 11:30	SVS
infectious	0	0	10.11.2010 17:27	SVS	10.11.2010 17:27	SVS
infectious	0	0	10.11.2010 17:27	SVS	13.10.2010 11:48	SVS
infectious	0	0	13.10.2010 12:39	SVS	13.10.2010 12:40	SVS
infectious	0	0	13.10.2010 12:01	SVS	10.11.2010 17:27	SVS
infectious	0	0	13.10.2010 11:35	SVS	13.10.2010 11:35	SVS
infectious	0	0	13.10.2010 11:25	SVS	13.10.2010 11:27	SVS
infectious	0	0	13.10.2010 11:35	SVS	13.10.2010 11:35	SVS

Example: Pneumonia

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Matrix for systematic review (NVivo software)

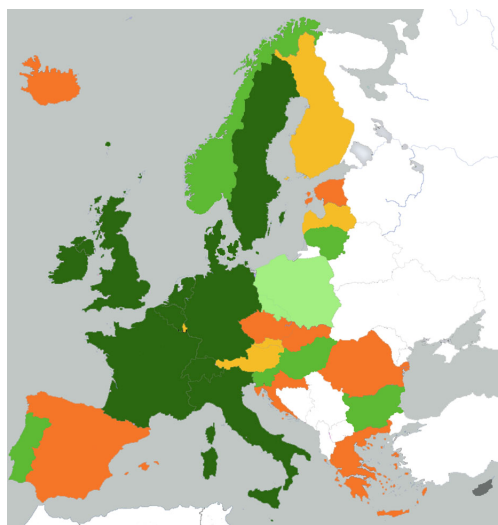
Name	Quellen	Relationen	Erstellt am	Erstellt von	Erdatzeiter an	Erdatzeiter von
blood stream infection (BSI)	1	1	25.06.2010 09:07	MM	05.07.2010 15:09	MM
antibiotic and pulmonary catheter	1	1	25.06.2010 16:16	MM	13.07.2010 14:25	MM
antibiotic use	0	0	25.06.2010 15:59	MM	25.06.2010 15:59	MM
antibiotic for hemodialysis	1	1	25.06.2010 16:17	MM	13.07.2010 14:47	MM
antibiotic catheter	1	1	25.06.2010 16:16	MM	13.07.2010 16:29	MM
antibiotic use and lumens	1	1	05.07.2010 11:16	MM	13.07.2010 16:32	MM
antibiotic site dressing	1	2	05.07.2010 17:27	MM	13.07.2010 14:11	MM
antibiotic or antibiotic for in	1	1	13.07.2010 14:15	MM	13.07.2010 14:17	MM
antibiotic use on open dress	0	0	05.07.2010 17:28	MM	05.07.2010 17:29	MM
frequency of dressing change	1	4	05.07.2010 17:29	MM	13.07.2010 14:14	MM
education of staff in IV teams	1	1	05.07.2010 11:14	MM	12.07.2010 16:30	MM
hand hygiene	1	1	07.07.2010 11:14	MM	13.07.2010 16:37	MM
insertion of central line catheter	1	1	25.06.2010 15:59	MM	13.07.2010 14:04	MM
maximal sterile barrier prece	1	2	05.07.2010 17:20	MM	12.07.2010 16:39	MM
skin antibiotic	1	1	12.07.2010 16:39	MM	12.07.2010 16:39	MM
no routine catheter replacem	1	2	05.07.2010 17:31	MM	13.07.2010 14:20	MM
infection of insertion site	1	1	05.07.2010 17:19	MM	13.07.2010 14:04	MM
use/absence of catheter site	1	2	07.07.2010 15:59	MM	13.07.2010 14:21	MM
systemic antibiotic prophylax	1	1	07.07.2010 13:56	MM	12.07.2010 16:36	MM
use of antibiotic or heparin lo	1	1	05.07.2010 17:39	MM	13.07.2010 14:22	MM
early or complete replacem	0	0	05.07.2010 17:16	MM	08.07.2010 17:15	MM
antibiotic catheters	1	1	25.06.2010 16:12	MM	12.07.2010 16:27	MM
antibiotic catheters (bandage)	0	0	25.06.2010 16:19	MM	25.06.2010 16:19	MM
antibiotic catheters	1	1	25.06.2010 16:19	MM	12.07.2010 16:13	MM
C. difficile infection (CDI)	0	0	25.06.2010 09:06	MM	25.06.2010 09:06	MM
antimicrobial (AMR)	1	1	25.06.2010 09:02	MM	25.06.2010 11:36	MM
hospital site infection (HSI)	0	0	25.06.2010 09:01	MM	25.06.2010 09:01	MM
urinary tract infection (UTI)	1	1	25.06.2010 09:03	MM	25.06.2010 14:06	MM

Example:
CABS1

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Guidelines in Europe



- No guidelines
- One guideline
- Two guidelines
- Three guidelines
- Four guidelines
- Five guidelines

In total: 101 national guidelines on the five topics of interest

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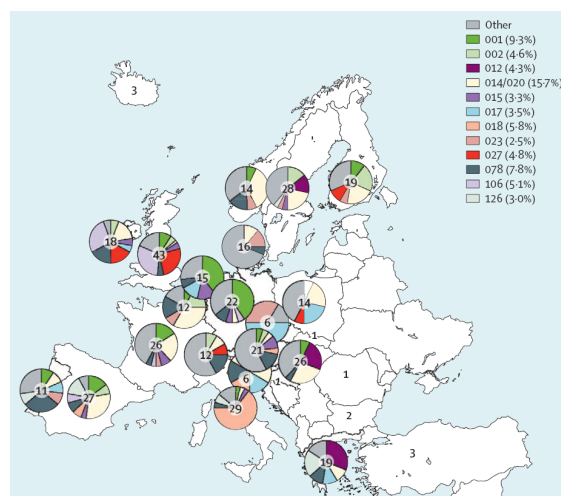
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Clostridium difficile

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C. difficile in Europe



Ribotype	n/n (%)
014/020*	61/389 (16%)
001	37/389 (10%)
078	31/389 (8%)
018	23/389 (6%)
106	20/389 (5%)
027	19/389 (5%)
002	18/389 (5%)
012	17/389 (4%)
017	14/389 (4%)
015	13/389 (3%)
126	12/389 (3%)
023	10/389 (3%)
046	8/389 (2%)
003	7/389 (2%)
011	6/389 (2%)
053	6/389 (2%)
056	6/389 (2%)

*reported together because of close relatedness

Bauer MP. *Lancet* 2011;377:63

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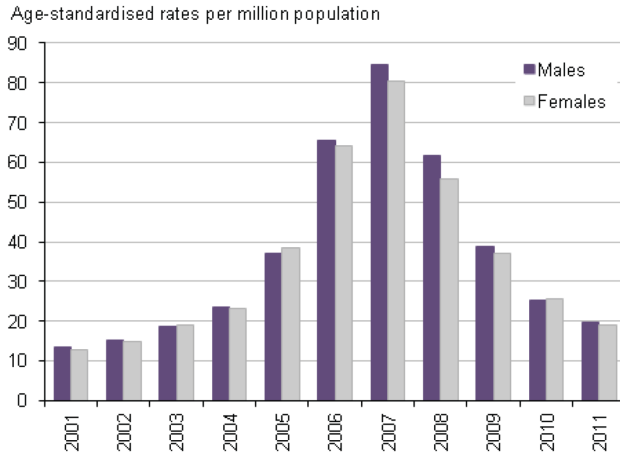
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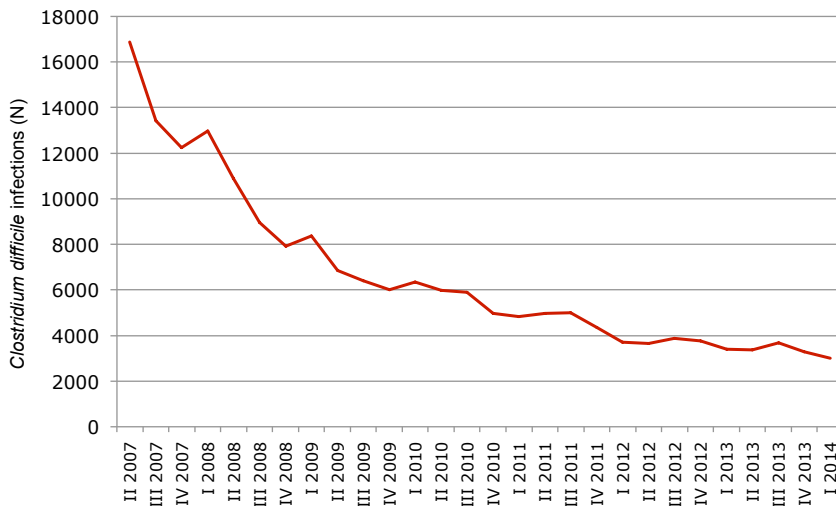
Mortality – England & Wales



UK Office for National Statistics

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Clostridium difficile infection by English NHS acute trusts



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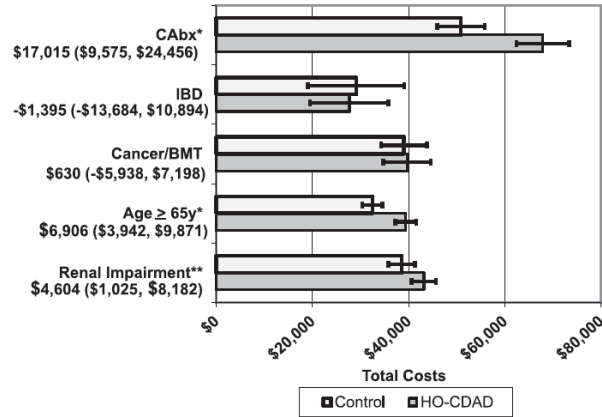
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Costs



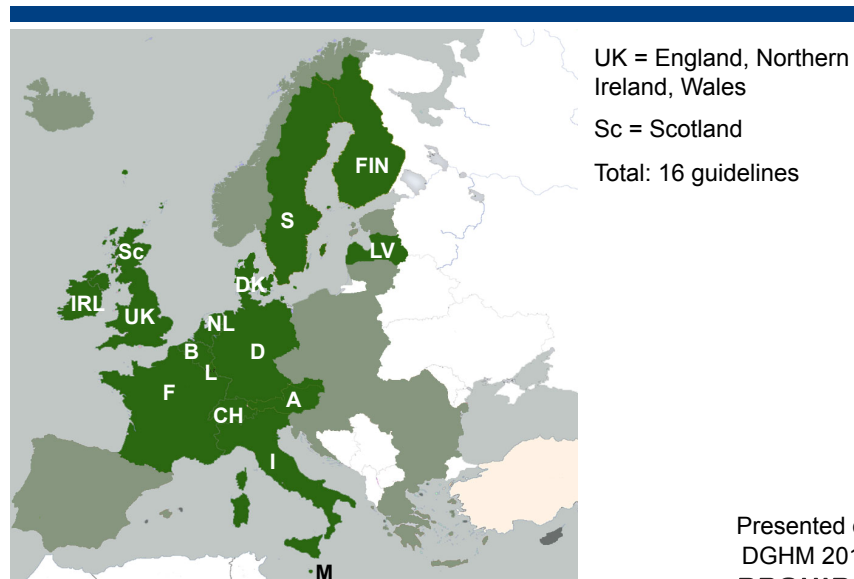
BMT: bone marrow transplant; CAbx, concomitant antibiotics; IBD, inflammatory bowel disease
 *p-value for difference < 0.001; **p-value for difference = 0.012.

Campbell R. *J Med Econ* 2013;16:440

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C. difficile guidelines



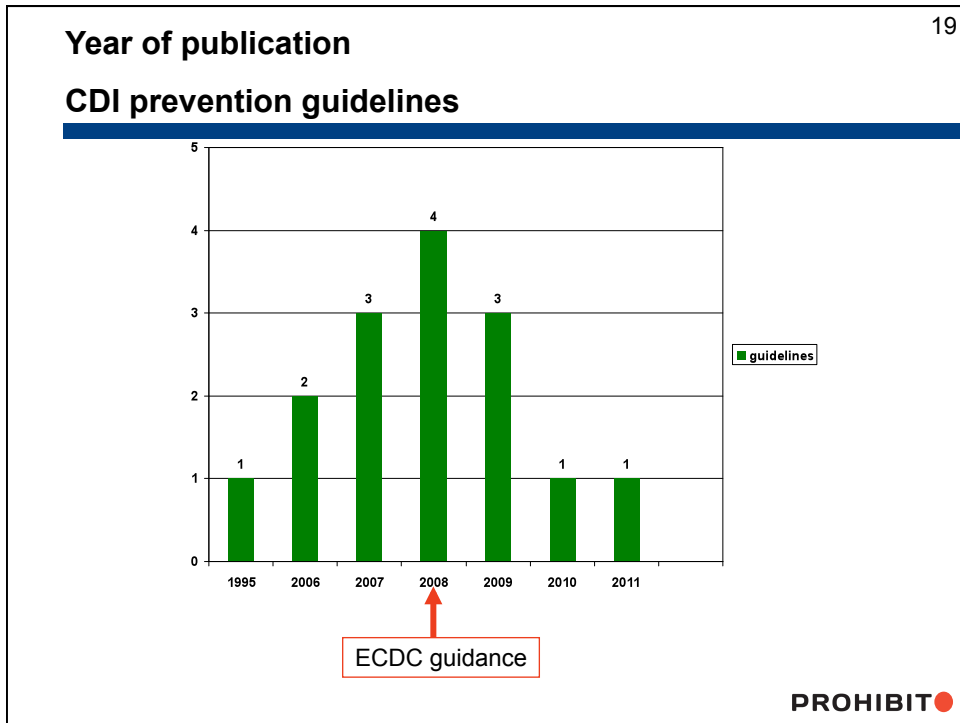
Presented on
 DGHM 2011
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Level of evidence

Table III
Categories of strength of recommendation and underlying levels of evidence in national European *Clostridium difficile* infection prevention guidelines (PROHIBIT study group)^a

Level of evidence	Country and category of strength														
	Malta (SHEA/IDSA)			ECDC, Austria, Scotland, Italy					England			Sweden			
	A	B	C	IA	IB	IC	II	UI	A	B	C	I	II	III	
Meta-analysis or systematic reviews															X
Randomized controlled trials	X			X											X
Well-designed studies	X	X		X								X		X	
Suggestive studies					X			X				X			X
Case-control and cohort studies			X		X							X			
Case reports; descriptive studies						X								X	
Theoretical rationale						X			X				X		X
Expert consensus			X									X	X		
Legal regulations							X					X			
Unresolved question									X						

PROHIBIT, Prevention of Hospital Infection by Intervention and Training; SHEA/IDSA, Society for Healthcare Epidemiology of America/Infectious Diseases Society of America; ECDC, European Centre for Disease Control and Prevention; UI, unresolved issue.
^a Table adapted from Cookson et al.²⁶

Martin M et al., JHI 2014

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Transmission and *C. difficile*

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Proximity is a risk for transmission

Likelihood of *C. difficile* transmission from CDI patients to roommates, direct neighbors or patients hospitalized at the same bed position sequentially

Setting	Transmission, n/n (%)	Risk, RR (95%CI)
Sequential patient	4/135 (3.0%)	1.21 (0.32-3.39)
Roommate	4/71 (5.6%)	2.37 (0.63-6.95)
Neighbor	16/249 (6.4%)	3.40 (1.95-5.94)

Chang VT. *Clin Infect Dis* 2000;31:717

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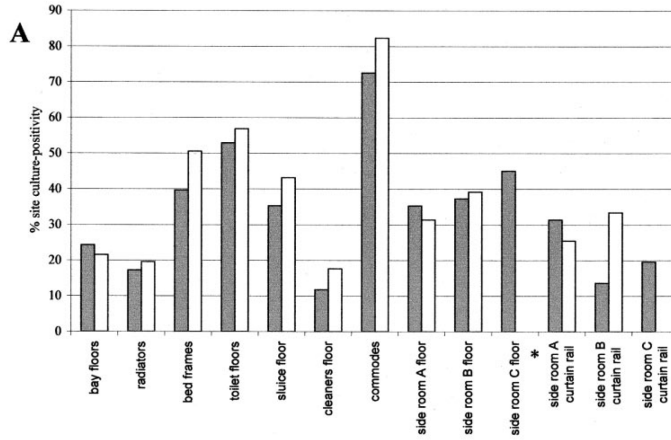
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C. difficile in the environment



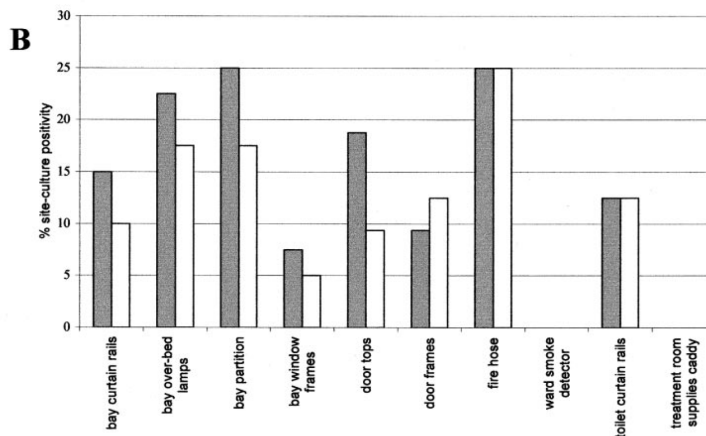
Department of Microbiology, Leeds Teaching Hospitals & University of Leeds

Fawley WN. *J Clin Microbiol* 2005;43:2685

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C. difficile in the environment



Fawley WN. *J Clin Microbiol* 2005;43:2685

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Colonization pressure

Systematic review; three studies about CDI-transmission in the hospital setting:

Colonization pressure* was significantly associated (OR 2.9-4) with *C.difficile* transmission

*measured as the presence of CDI-cases as a risk factor for *C. difficile* transmission

Ajao AO. *Infect Control Hosp Epidemiol* 2011;32:481

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Environmental disinfection (CDI)

→ ECDC:

- Regular disinfection, chlorine-based preferred - IB (Evidenz 2b (1), 2c (2), 4 (1))
- Frequently touched surfaces, at least 1x /d - IB (Evidenz 1b (1), 2a (1), 4 (1))
- Bathroom, toilets etc. clean scrupulously - IB (Evidenz 1b (1), 2a (1))

Martin M et al., JHI 2014

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Environmental disinfection (CDI)

Country (year)	agent	Frequently touched surfaces	Bathroom, toilet etc.
Austria (2007)	Sporicidal	1x d	2x d
Belgium (2008)	Chlorine based	1x d	Min. 1x d
Denmark (2011)	Chlorine based	1x d	1x d
Finland	Chlorine based	Min. 1x d	Min. 1x d
France (2010)	Chlorine based	Not specified	Not specified
Germany (2009)	H2O2 or chlorine	1x d	1x d
Ireland (2008)	Chlorine based	1x d	After each use
Italy (2009)	Chlorine based	Min. 1x d	Not specified
Latvia (2007)	Chlorine based	Not specified	Not specified
Luxembourg (2007)	Chlorine based	Min. 1x d	Min. 1x d
Malta (SHEA 2008)	Chlorine based	Not specified	Not specified
Netherlands (2006)	Not specified	Not specified	Not specified
Sweden (2006)	Peracetic acid	Not specified	Not specified
Switzerland (1995)	mechanic effect of cleaning	„Die kontinuierliche Reinigung...“	
GB (2008)	Chlorine based	Min. 1x d	After each use
Sc (2009)	Chlorine based	Min. 1x d	Not specified

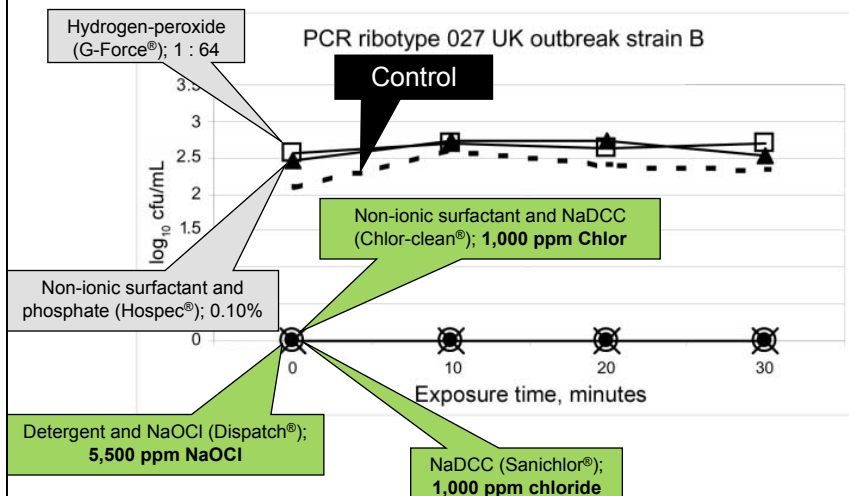
Martin M et al., JHI 2014

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Effectiveness of disinfectants

Spore germination after exposure to different disinfectants



Fawley WN. Infect Control Hosp Epidemiol 2007;28:920

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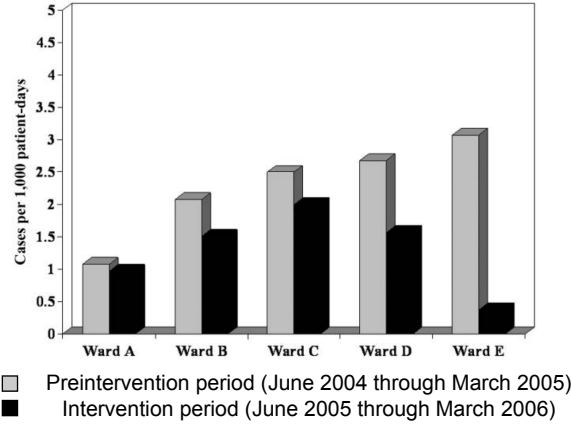
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Vaporized hydrogen-peroxide

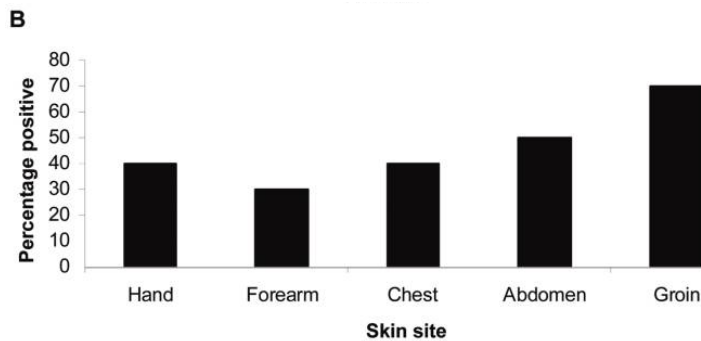


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Boyce JM. *Infect Control Hosp Epidemiol* 2008;29:723

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Contamination of healthcare worker's hands



Contamination of healthcare worker's hands after touching different skin areas of CDI-patients

Bobulsky GS. *Clin Infect Dis* 2008;46:447

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Hand hygiene (CDI)

→ ECDC: wearing of gloves for patient contact and immediate vicinity - IB (Evidenz 1b (2), 2b (2))

- **All** guidelines recommend wearing of gloves

- *Washing or disinfecting?*

→ ECDC: Hand washing with soap, alcohol-based hand rub not sufficient - IB (Evidenz 2a (2), 2b (3), 2c (1), 4 (1))

- Disinfecting, then washing (2): A, D
- Washing, then disinfecting (5): B, DK, F, GB, S
- Only washing (7): FIN, IRL, I, L, M, NL, Sc
- Latvia: washing or disinfecting with Chlorhexidine
- Switzerland: disinfecting or antiseptic soap

Martin M et al., JHI 2014

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Antibiotics and *C. difficile*

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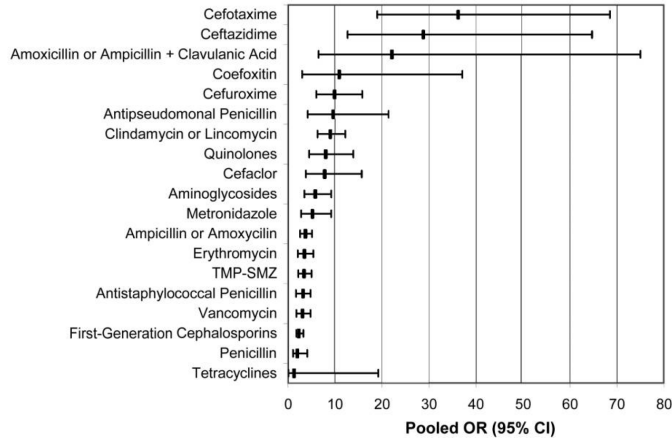
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Antibiotics and CDI: a meta-analysis



Owens RC. *Clin Infect Dis* 2008;46:S19

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Antibiotics and CDI

Low risk	Medium risk	High risk
Aminoglycosides	Co-amoxiclav	Second/third generation cephalosporins Clindamycin Fluoroquinolones
Vancomycin	Macrolides	
Trimethoprim	Amoxicillin/ampicillin	
Tetracyclines		
Piptazobactam		
Benzympenicillin		

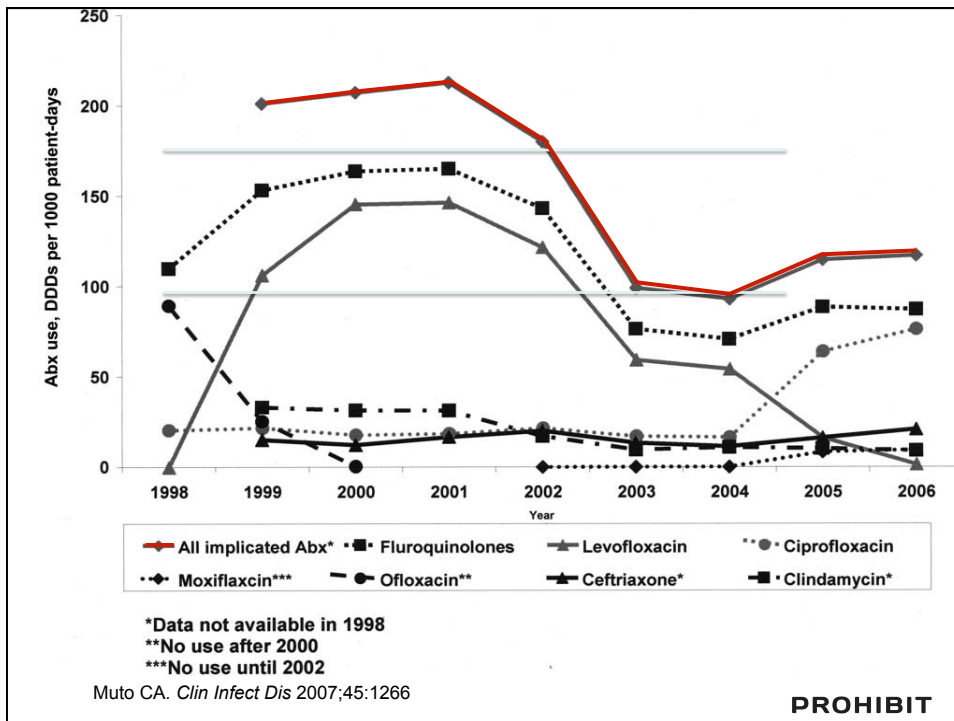
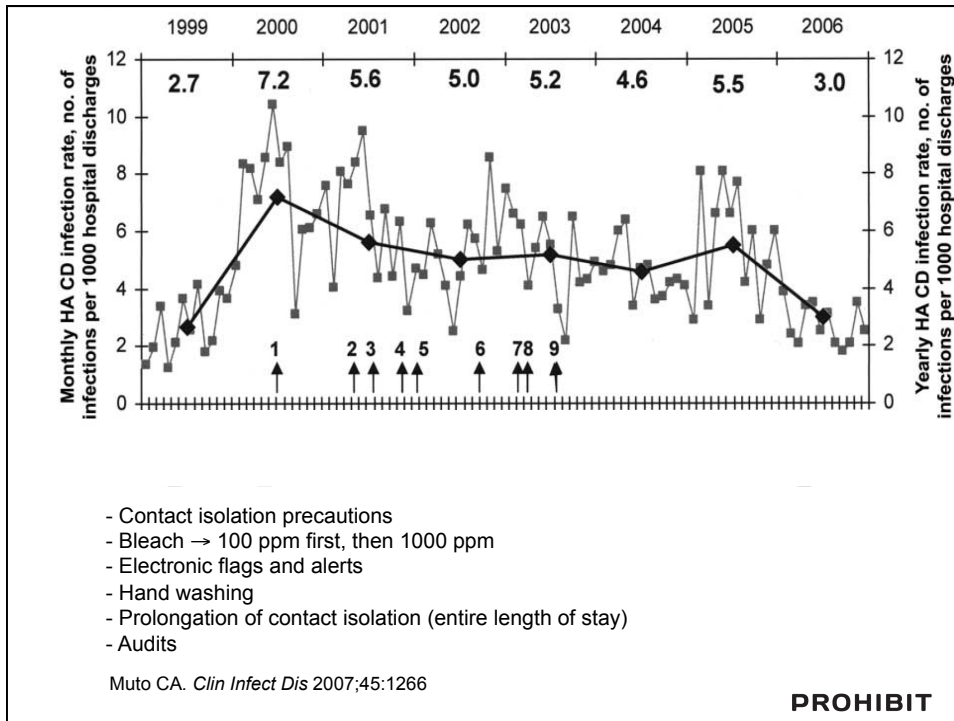
Monaghan T. *Postgrad Med J* 2009;85:152

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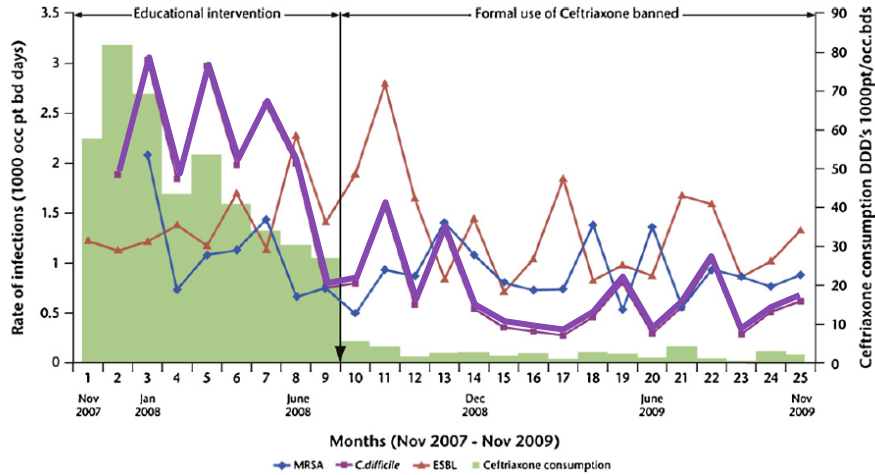
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Effects of a restrictive antibiotic policy on hospital-acquired *Clostridium difficile* – a district hospital



Dancer S. *Int J Antimicrob Agents* 2013;41:137

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Antibiotic Stewardship

→ ECDC: Stop antibiotic treatment - IA (Evidenz 1a (1))

- A, B, CH, FIN, GB und Sc, I, IRL, L (9)

→ ECDC: good antibiotic stewardship in outbreaks or in high endemic situations - IB (Evidenz 1a (1), 2b (5), 3b (9), 4 (4))

- according ECDC (2): B, M
- General recommendation for good antibiotic stewardship (8): A, B, D, GB und Sc, IRL, L, S

Martin M et al., JHI 2014

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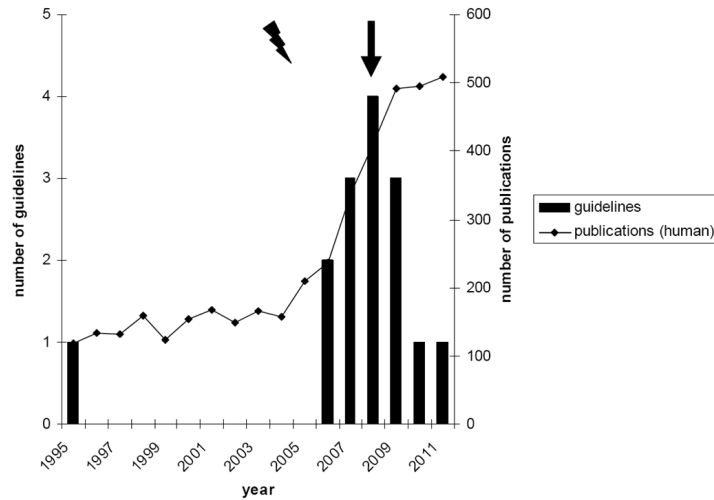
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Publications and Guidelines



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Guidelines - Conclusions

- Most national CDI guidelines published or revised in last 10 years
- Only about half of guidelines state evidence and strength of recommendations
- Guidelines vary in scope and detailing
- Heterogeneity in terminology

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ESCMID treatment guidelines

Teicoplanin/vancomycin > metronidazole

- Efficacy of teicoplanin may be superior to vancomycin
- Vancomycin concentration in the colon is largely superior to metronidazole, which is readily absorbed in the small intestines and is found in feces only in (very) low concentrations
- High dose vancomycin is not superior to low dose vancomycin: most likely due to its non-absorption

Treatment duration: 10 days

There are studies of 7 days treatment duration; however, data to justify shorter treatment are not sufficient yet

Bauer MP. *Clin Microbiol Infect* 2009;15:1067

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“Outside the box” CDI management

Intraluminal toxin-binders or neutralizers

Cholestyramine, cholestipol, tolevamer, whey protein in immunized cow's milk

Biotherapeutic agents to restore the protective microbiota

Probiotics, faecal transplants, nontoxigenic *C. difficile* strains, synthetic mixture of bacteria

Antibodies to improve CDI-immunity

Monoclonal antibodies, active vaccination

Anti-sporulation

CamSA, a bile salt analog, inhibits *C. difficile* spore germination in vitro

Gerding DN. *Clin Infect Dis* 2010;51:1306

Howerton A. *J Infect Dis* 2013; epub, ahead of print

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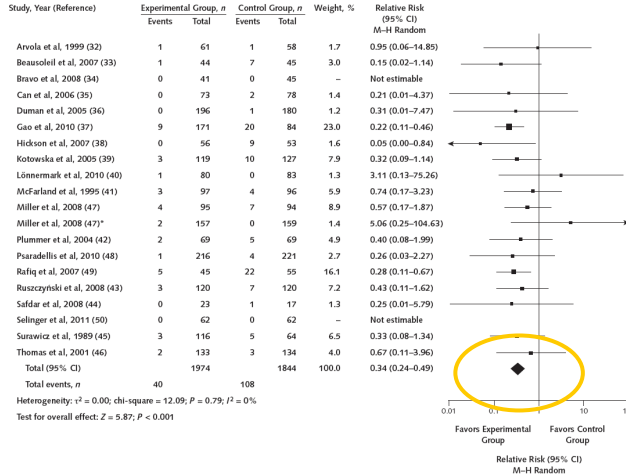
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Probiotics



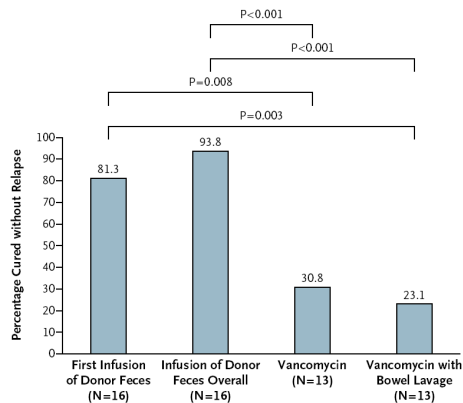
Johnston BC. *Ann Intern Med* 2012;157:878

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Fecal transplantation

RCT – 41 Adult patients with CDI relapse after at least one course of adequate antibiotic therapy (≥ 10 days of vancomycin or ≥ 10 days of metronidazole)



1. Vancomycin 4-5 days + bowel lavage (4 liters macrogol) + nasoduodenal infusion of donor feces
2. Standard vancomycin regimen for 14 days (500 mg orally four times per day)
3. Standard vancomycin regimen for 14 days + bowel lavage

Van Nood E. *New Engl J Med* 2013;368:407

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Cochrane: Antibiotic treatment for CDI

Uncertainty whether mild CDAD needs to be treated

Little evidence for antibiotic treatment of severe CDAD as many studies excluded these patients

Small numbers of patients were included in the studies and there was high risk of bias, especially related to dropouts

Most of the active comparator studies found no statistically significant difference in efficacy between vancomycin and other antibiotics including metronidazole, fusidic acid, nitazoxanide or rifaximin

Teicoplanin may be an attractive choice

Nelson RL. *Cochrane Database Syst Rev* 2011;9:CD004610

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Summary

Infection control measures

Contact precautions (gloves, gowns)

- Gloving is the most important measure of „hand hygiene“
- Use disposable gowns

Hand washing during outbreaks or increased CDI-rates

- Rinsing removes spores mechanically
- No advantage by using medicated products

Isolation/cohorting

- Given the high contamination of spores and patients moving in the room mixed accommodation of CDI and non-patients is a risk – isolate if possible!

Cleaning of the patient's environment

- Bleach (>1000 ppm)
- Daily cleaning of the patient's room

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Prevention measures

Antibiotic stewardship

- Treat as narrow as possible (improve diagnosis, local resistance data)
- Almost all antibiotic groups have been shown to be associated with CDI!

Surveillance

- Good surveillance detects problems in good time

Audits

- Implementation of infection control measures is complex and sometimes difficult – Audits help assure compliance

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Thank You !

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