Update on clinical management of *C. difficile* infection (CDI)

Professor Mark Wilcox

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Health Protection Agency

CDI key control measures

- An early warning system to identify changes in local epidemiology: this needs accurate diagnosis
- Increased emphasis on investigation of cases (RCAs) and especially clusters (ribotyping, MLVA)
- Reduce risk of transmission by rapid isolation or cohorting of suspected cases
- Introduction of CDI treatment pathways
- Environmental cleaning using chlorine containing disinfectants
- Hand (and skin) hygiene with soap & water
- Optimised/reduce overall antibiotic use, including restricting high risk agents in high risk patients

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Current CDI treatment issues

- Inadequate choice of therapeutics
- Poor sustained response/cure
- Efficacy vs virulent strains
- Poor predictive tools for severity / treatment response
- Unproven options in life-threatening CDI
- Increasing dependence on vancomycin
- Reduced susceptibility to metronidazole
- Poor evidence base for use of probiotics
- New treatment options needed

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Unmet CDI treatment needs

- *Reduced recurrence*
- *Improved sustained cure rate*

- Time to resolution of symptoms
- Severe CDI
- Prediction tools to optimise treatment options
- Reduced mortality

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How is CDI currently managed?

- Until now treatments have included metronidazole and vancomycin but these are sub-optimal
  - Failure in ~10-20% of cases[1]
  - According to severity of infection
  - Recurrence occurs in ~20% of cases

    & ~45% subsequently recur again[1]
  - Death

    17% 30-day mortality (~7% attributable)[2]

    24-48% mortality rate from severe CDI[3]

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1. Kelly and LaMont. N Engl J Med 2008;359:1932–40
2. Planche TD et al. 52nd ICAAC, 2012. Abstract D-160.
3. Health Protection Agency. Mandatory Surveillance of Healthcare Associated Infections

Severe CDI

- The 3 most frequently recognised risk factors for severe CDI are age, peak leukocytosis and creatinine
- However, such observations are retrospective
- Age is too non-specific for use as a severity predictor
- No single parameter is highly predictive of severe CDI, with possible exception of very high WCCs
- Definitions of severe CDI based on number of diarrhoeal stools have clear drawbacks
- A prospectively validated severity score is needed

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Pépin et al., 2004; Loo et al., 2005; Pépin et al., 2007

Definitions of severe CDI

Zar FA et al. Clin Infect Dis. 2007;45:302

- **PMC, treatment in ICU, or 2 of the following:**
- **Age >60, T>38.3°C, albumin <2.5/dL, WBC >15 x10^9/L**

Louie T et al ICAAC; 2007; Abst 3826

- **≥10 bowel movements/day or**
- **WBC >20 x10^9/L or**
- **Severe abdominal pain**

Cohen SH et al. ICHE. 2010;31:431

- **WBC >15 x10^9/L or**
- **Creatinine >1.5x baseline**

DoH/HPA (England), 2009

- **WBC >15 x10^9/L or**
- **Acutely rising creatinine (eg, >1.5x baseline) or**
- **T>38.3°C or**
- **Evidence of severe colitis (abdominal signs, radiology)**

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Lahue BJ, Davidson DM. Metronidazole and vancomycin outcomes for CDAD in a US hospital database. ECCMID Munich, 2007. Abstract O331.

Zar *et al*. A comparison of vancomycin and metronidazole for the treatment of CDAD, stratified by disease severity. *Clin Infect Dis* 2007; 45: 302-7.

Bouza E, *et al*. Results of a phase III trial comparing tolevamer, vancomycin and metronidazole in patients with Clostridium difficile-associated diarrhoea. 18th ECCMID 2008. Abstract O464).

Louie T, *et al*. Results of a Phase III Trial Comparing Tolevamer, Vancomycin and Metronidazole in Patients with *Clostridium difficile*-Associated Diarrhea. *ICAAC* 2007; L-3 abstract 3826.

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- Nassir WN, Sethi AK, Nerandzic MM, Bobulsky GS, Jump RL, donskey CJ. Comparison of clinical and microbiological response to treatment of *Clostridium difficile*-associated disease with metronidazole and vancomycin. *Clin Infect Dis* 2008;47:56-62.

- Kuijper EJ, Wilcox MH. Decreased effectiveness of metronidazole for the treatment of *Clostridium difficile* infection? *Clin Infect Dis* 2008;47:63-5).

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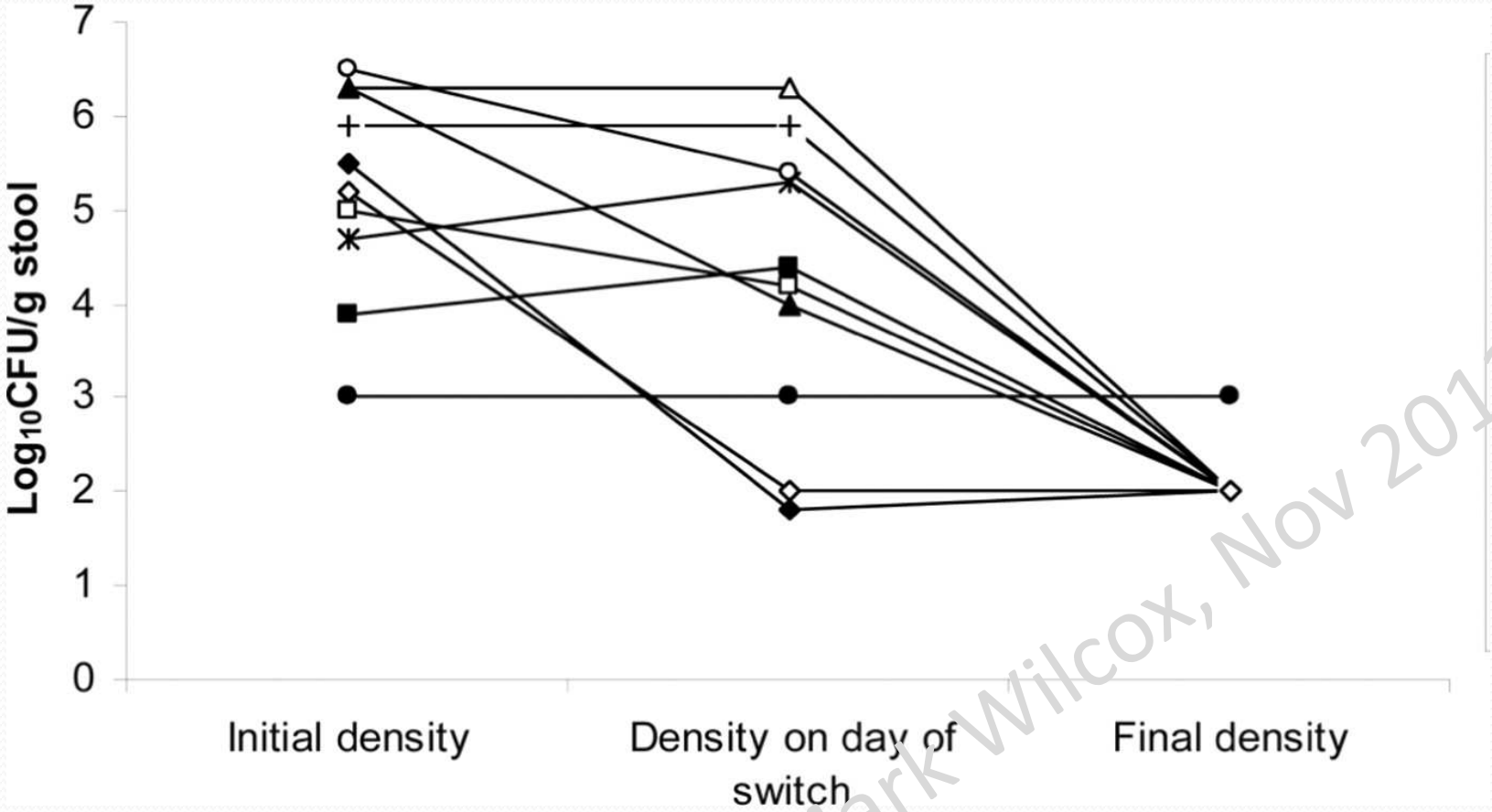
Concentration of *Clostridium difficile* in stool of 10 patients whose therapy was changed from metronidazole to vancomycin



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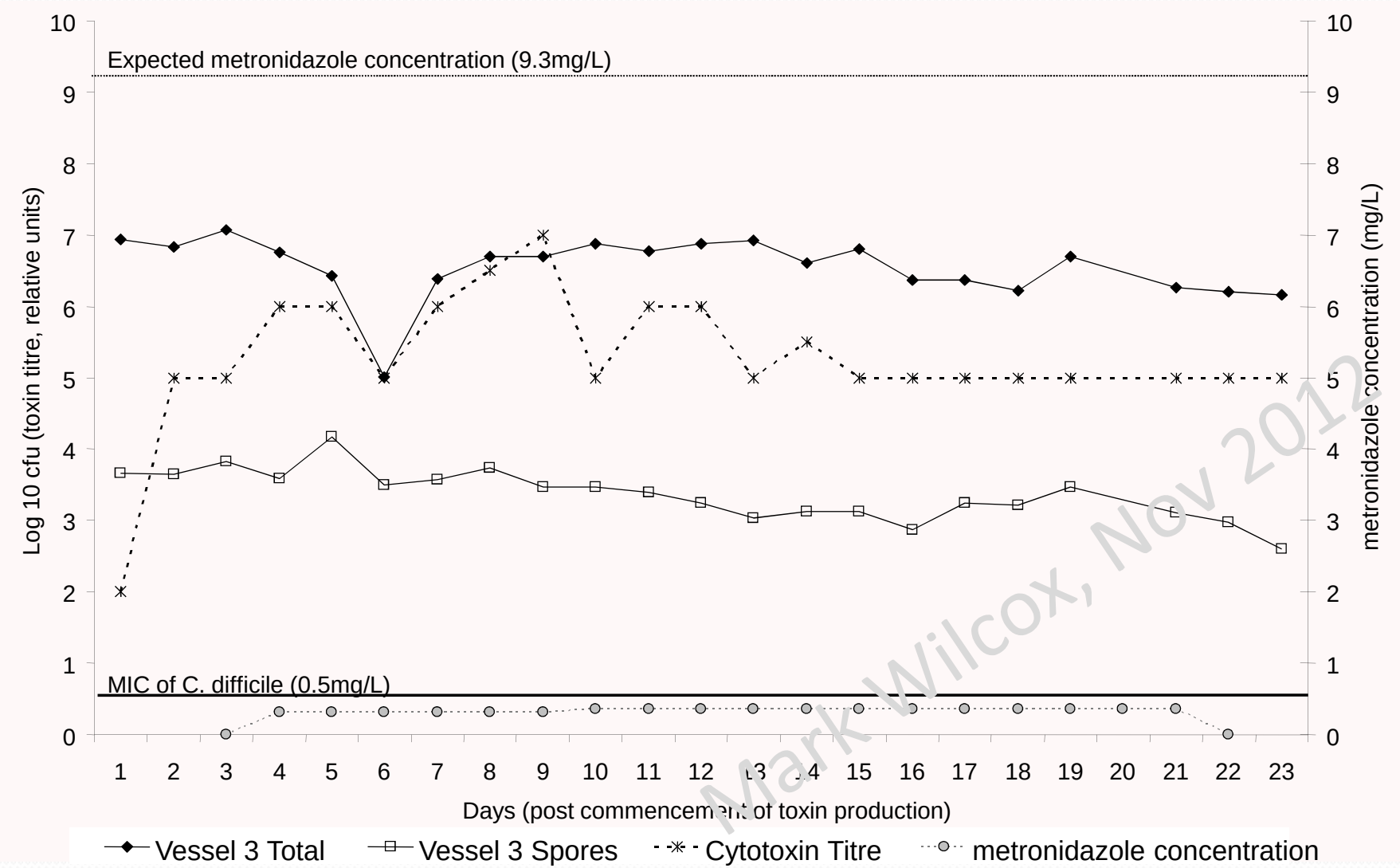
Al-Nassir W N et al. Clin Infect Dis. 2008;47:56-62

Activity of metronidazole against *C. difficile* ribotype 027 in gut infection model

Baines, Freeman, Wilcox. *J Antimicrob Chemother* 2007.



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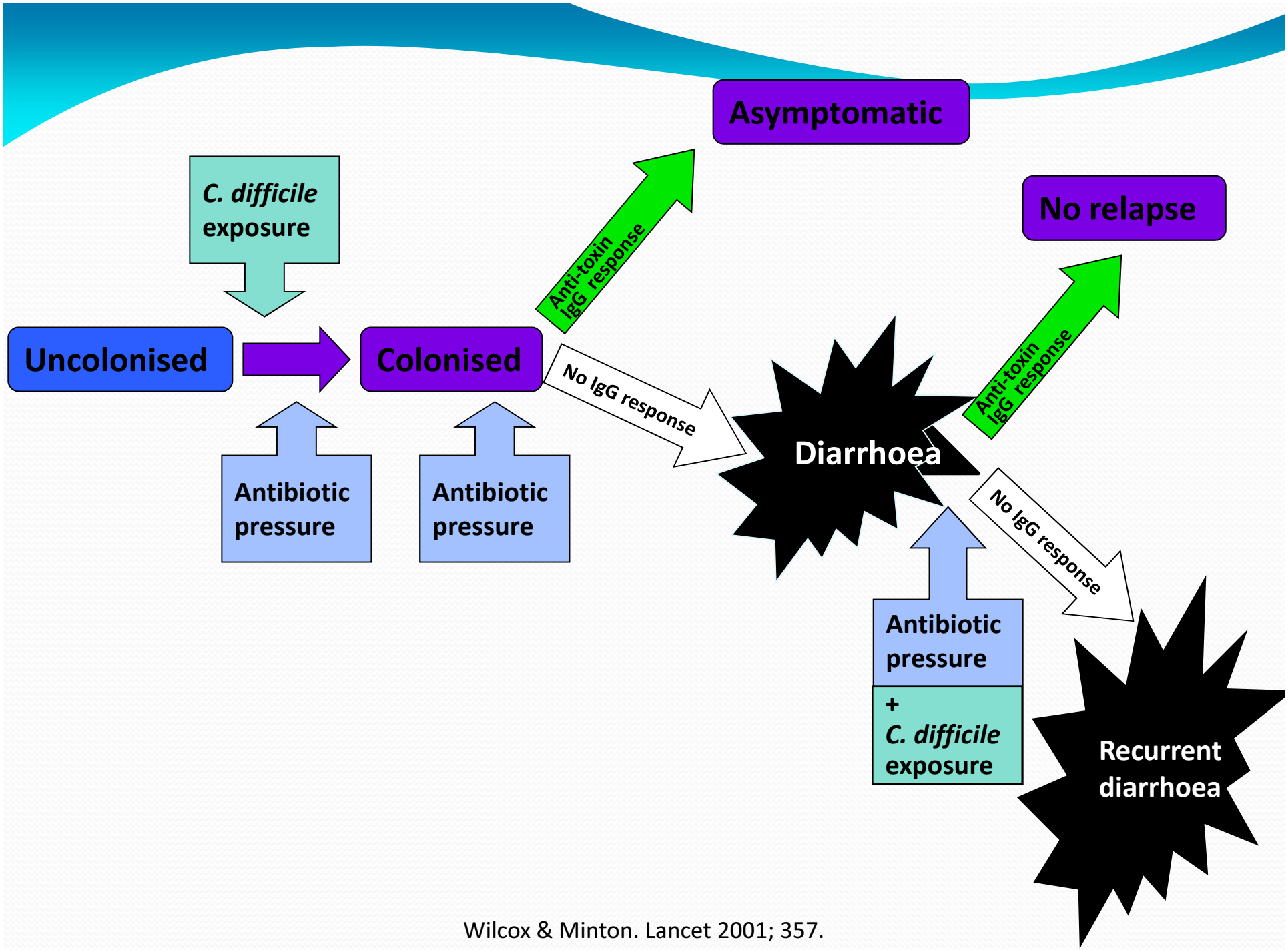

Wilcox & Minton. Lancet 2001; 357.

Determinants of recurrence risk

- Flora inhibition (antibiotics)
- Spore persistence
- Antibody deficit
- Previous recurrence
- Strain type
- Host biomarkers e.g. albumin
- Age
- Co-morbidities

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Gastroenterology. 2009 Apr;136(4):1206-14. Epub 2008 Dec 13.

Prospective derivation and validation of a clinical prediction rule for recurrent Clostridium difficile infection.

Hu MY, Katchar K, Kyne L, Maroo S, Tummala S, Dreisbach V, Xu H, Leffler DA, Kelly CP.

Division of Gastroenterology, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts 02215, USA.

Abstract

BACKGROUND & AIMS: Prevention of recurrent Clostridium difficile infection (CDI) is a substantial therapeutic challenge. A previous prospective study of 63 patients with CDI identified risk factors associated with recurrence. This study aimed to develop a prediction rule for recurrent CDI using the above derivation cohort and prospectively evaluate the performance of this rule in an independent validation cohort.

METHODS: The clinical prediction rule was developed by multivariate logistic regression analysis and included the following variables: age>65 years, severe or fulminant illness (by the Horn index), and additional antibiotic use after CDI therapy. A second rule combined data on serum concentrations of immunoglobulin G (IgG) against toxin A with the clinical predictors. Both rules were then evaluated prospectively in an independent cohort of 89 patients with CDI.

RESULTS: The clinical prediction rule discriminated between patients with and without recurrent CDI, with an area under the curve of the receiver-operating-characteristic curve of 0.83 (95% confidence interval [CI]: 0.70-0.95) in the derivation cohort and 0.80 (95% CI: 0.67-0.92) in the validation cohort. The rule correctly classified 77.3% (95% CI: 62.2%-88.5%) and 71.9% (95% CI: 59.2%-82.4%) of patients in the derivation and validation cohorts, respectively. The combined rule performed well in the derivation cohort but not in the validation cohort (area under the curve of the receiver-operating-characteristic curve, 0.89 vs 0.62; diagnostic accuracy, 93.8% vs 69.2%, respectively).

CONCLUSIONS: We prospectively derived and validated a clinical prediction rule for recurrent CDI that is simple, reliable, and accurate and can be used to identify high-risk patients most likely to benefit from measures to prevent recurrence.

Effect of CA on outcome after treatment of CDI with fidaxomicin or vancomycin

	No CA	CA	p value
Clinical cure (%)			
CA during treatment*	93%	84%	<0·001
Recurrence (%)			
CA during treatment*	18%	24%	0·11
CA during follow-up†	18%	25%	0·06
CA at any time‡	18%	23%	0·08
Sustained response (%)			
CA at any time‡	75%	66%	0·005
Median time to resolution of diarrhoea (h)			
CA during treatment*	54	97	<0·001

CA=concomitant antibiotics. *Days 1–10. †Days 11–40. ‡Days 1–40.

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Mullane KM, *et al*. *Clin Infect Dis* 2011;53:440-7.
Wilcox MH. Lancet Infect Dis 2012.

Fidaxomicin vs Vancomycin Phase 3 CDI Studies

Per Protocol (microbiologically evaluable)	OPT-80 (200mg bid)	Vancocin® capsules (125mg qid)	p-value	95% Confidence Interval
Clinical Cure	92.1% (244/265 pts) 91.7%	89.8% (254/283 pts) 90.6%	NA	(-2.6,)*
Recurrence	13.3% (28/211) 12.8%	24.0% (53/221) 25.3%	0.004 0.002	(-17.9, -3.3)
Global Cure	77.7% (206/265) 79.6%	67.1% (190/283) 65.5%	0.006 0.001	(3.1, 17.9)
Modified Intent-to-Treat (mITT)	**OPT-80 (200mg bid)**	**Vancocin® capsules (125mg qid)**	**p-value**	**95% Confidence Interval**
Clinical Cure	88.2% (253/287 patients)	85.8% (265/309 patients)	NA	(-3.1,)*
Recurrence	15.4% (39/253)	25.3% (67/265)	0.005	(-16.6, -2.9)
Global Cure	74.6% (214/287)	64.1% (198/309)	0.006	(3.1, 17.7)

* one-sided 97.5% CI

NA= Not Applicable (trial met non-inferiority endpoint)

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http://www.optimerpharma.com/news.asp?news_story=69&page_num=11.10.2008 SAN DIEGO, CA

http://www.optimerpharma.com/pipeline.asp?pipeline=1

Fidaxomicin (OPT-80, PAR-101, Difimicin)

- Reduced recurrence by ~50%
- Less effective against CD 027
- Some resistance emergence in VRE (not in CD)
- No fidaxomicin resistance in CD, but one isolate (cure patient) MIC = 16 mg/L
- Concomitant antibiotics

COST

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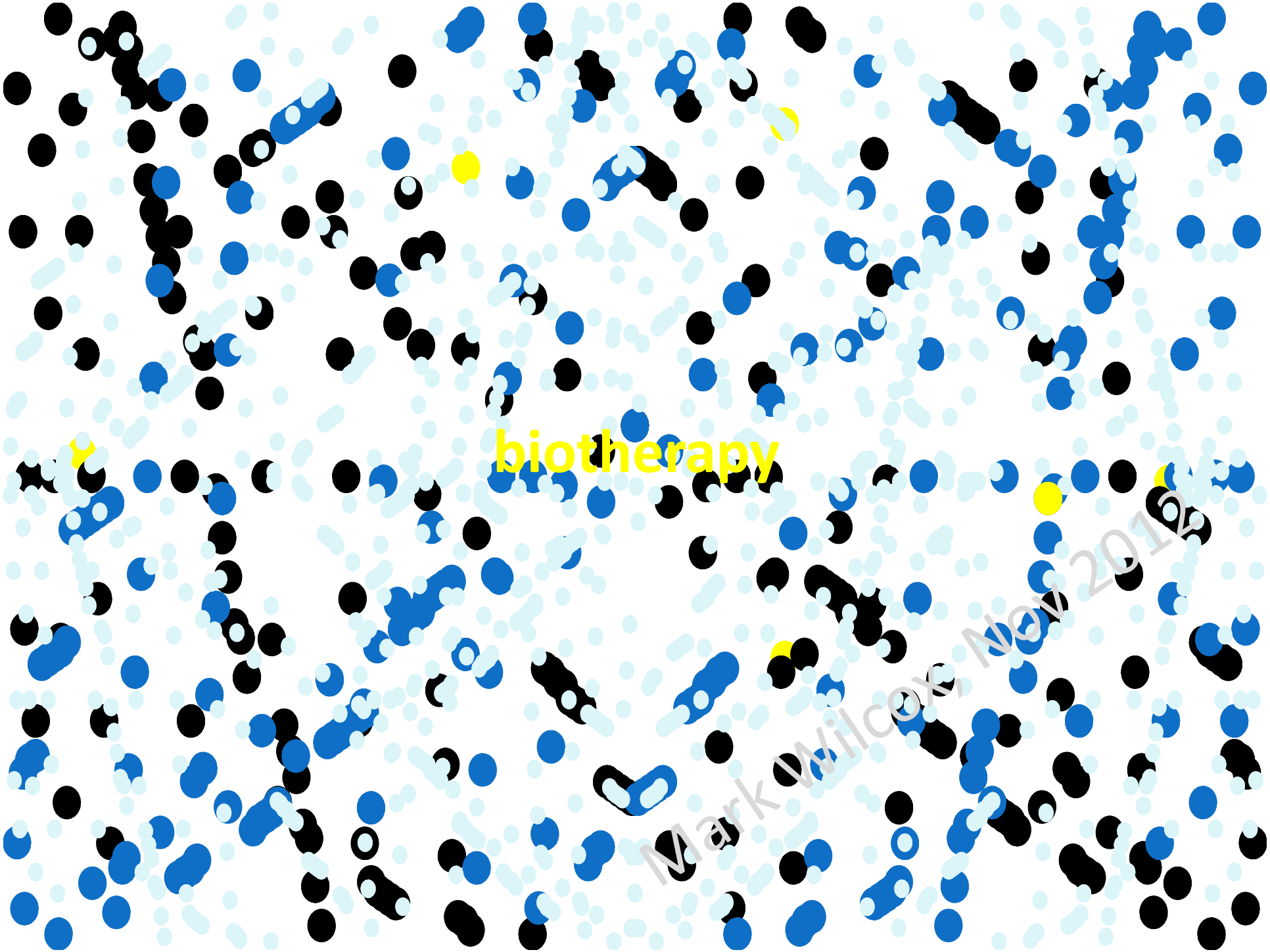
Weak evidence base for probiotics


biotherapy
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Randomized controlled trials of non-antibiotic treatment of initial CDI

Trial	Treatment	Number of patients	Cure (%)	Relapse (%)
Probiotics				
McFarland *et al.* [33]	Vancomycin or metronidazole + *Saccharomyces boulardi* 2×10^{10} CFU/day, 4 weeks	31	–	19
	Vancomycin or metronidazole + placebo	33	–	24
	Double-blind. No control for type, duration or dose of antibiotic. Unclear definition of relapse. Follow-up 8 weeks after start of treatment. p 0.86 for comparison of relapse rates			
Toxin-binding resins and polymers				
Louie *et al.* [17]	Tolevamer 1 g tid, 14 days + placebo	94	60	16
	Tolevamer 2 g tid, 14 days + placebo	91	79	7
	Vancomycin 125 mg qid, 10 days + placebo	94	91	19
	Non-inferiority trial. Patients with stool frequency >12 per day or abdominal pain were excluded. Tolevamer could be prolonged when inciting antibiotic could not be stopped. Double-blind. 23% drop-out. Per-protocol analysis. Cure rate of tolevamer 2 g non-inferior in comparison with vancomycin (Chow-test p 0.03). Non-inferiority of tolevamer 1 g compared with vancomycin could not be demonstrated. p 0.05 for comparison of relapse rates of tolevamer 2 g with vancomycin. Relapse rates of tolevamer 1 g and vancomycin not statistically different. Follow-up 6–8 weeks			
Louie *et al.* [34]	Tolevamer 3 g tid, 14 days	266	47	3
	Vancomycin 125 mg qid, 10 days	134	81	23
	Metronidazole 375 mg qid, 10 days	143	72	27
	Unpublished trial			
Bouza *et al.* [35]	Tolevamer 3 g tid, 14 days	268	42	6
	Vancomycin 125 mg qid, 10 days	125	81	18
	Metronidazole 375 mg qid, 10 days	135	73	19
	Unpublished trial			
Immunotherapy				
Lowy [36]	MDX-066 and MDX-1388 (intravenously administered monoclonal antibodies against TcdA and TcdB) after standard antimicrobial therapy	101	–	7
	Placebo after standard antimicrobial therapy	99	–	25
	Unpublished trial. Follow-up 12 weeks			

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From: Bauer MP, et al (ESCMID) Clin Microbiol Infect 2009;15:1067–79

Randomised controlled studies of recurrent CDI treatment

Trial	Treatment	Number of patients	Failure[a] (%)
Probiotics			
McFarland *et al.* [33]	Vancomycin or metronidazole + *Saccharomyces boulardii* 2×10^{10} CFU/day, 4 weeks	26	35
	Vancomycin or metronidazole + placebo	34	65
	Double-blind. No control for type, duration or dose of antibiotic. Unclear definition of relapse. Follow-up 8 weeks after start of treatment. p 0.04 for comparison of failure rates		
Surawicz *et al.* [49]	Vancomycin 500 mg qid, 10 days, followed by *Saccharomyces boulardii* 2×10^{10} CFU/day, 4 weeks	18	17
	Vancomycin 500 mg qid, 10 days, followed by placebo	14	50
	Vancomycin 125 mg qid, 10 days, followed by *Saccharomyces boulardii* 2×10^{10} CFU/day, 4 weeks	45	51
	Vancomycin 125 mg qid, 10 days, followed by placebo	38	45
	Metronidazole 1 g/day, 10 days, followed by *Saccharomyces boulardii* 2×10^{10} CFU/day, 4 weeks	27	48
	Metronidazole 1 g/day, 10 days, followed by placebo	26	50
	Follow-up 5 months after completion of study drug. p 0.05 for the comparison of failure rates in patients who received 500 mg of vancomycin qid. Drop-out was 22%. No further statistically significant differences		
Wullt *et al.* [50]	Metronidazole 400 mg tid, 10 days + *Lactobacillus plantarum* 299v 5×10^{10} CFU/day, 38 days	12	42
	Metronidazole 400 mg tid, 10 days + placebo	9	67
	Double-blind. 28% cent drop-out. Follow-up 70 days. Difference not statistically significant		
Lawrence *et al.* [51]	Vancomycin or metronidazole followed by *Lactobacillus* GG 6×10^{11} CFU/day, 21 days	8	38
	Vancomycin or metronidazole followed by placebo	7	14
	Patients blinded. No control for type, duration or dose of antibiotic. Follow-up 60 days after completion of antibiotic. Difference not statistically significant		
Passive immunotherapy with immune whey			
Mattila *et al.* [52]	Colostral immune whey 200 mL tid + placebo, 14 days	18	44
	Metronidazole 400 mg tid + placebo, 14 days	20	45
	Double-blind. Multi-centre trial. Follow-up 70 days. Difference not statistically significant.		

[a]Non-response or relapse.

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From: Bauer MP, et al (ESCMID) Clin Microbiol Infect 2009;15:1067–79

Faecal transplantation

- the ultimate probiotic?

- Eiseman et al 1958, pts with severe AAD
- 160 cases (largest n=18), 15 failures i.e. 90% success
- Aas *et al*. *Clin Infect Dis* 2003;36:580-5.
- Randomised, sham-procedure-controlled clinical trial in the Netherlands
- **Cost ???**

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Clin Infect Dis. 2011 Nov;53(10):994-1002.

Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent Clostridium difficile infection.

Gough E, Shaikh H, Manges AR.

Department of Epidemiology Biostatistics and Occupational Health, McGill University, 1020 Pine Avenue West, Montreal, Quebec, Canada.

Abstract

Clostridium difficile infection (CDI) is a gastrointestinal disease believed to be causally related to perturbations to the intestinal microbiota. When standard treatment has failed, intestinal microbiota transplantation (IMT) is an alternative therapy for patients with CDI. IMT involves infusing intestinal microorganisms (in a suspension of healthy donor stool) into the intestine of a sick patient to restore the microbiota. However, protocols and reported efficacy for IMT vary. We conducted a systematic literature review of IMT treatment for recurrent CDI and pseudomembranous colitis. In 317 patients treated across 27 case series and reports, IMT was highly effective, showing disease resolution in 92% of cases. Effectiveness varied by route of instillation, relationship to stool donor, volume of IMT given, and treatment before infusion. Death and adverse events were uncommon. These findings can guide physicians interested in implementing the procedure until better designed studies are conducted to confirm best practices.

Investigational therapeutic approaches for CDI

- {Ramoplanin}

- Anti-toxin monoclonal antibodies (Merck)
- Lipopeptide CB-183,315 (Cubist)

- LFF571 (Novartis)
- Vaccine – primary/secondary prevention (San-Pasteur)
- Cadazolid (Actelion)
- Non-Toxigenic CD strain (Viropharma)

- Novacta (lantibiotic), Summit, Oritavancin
- 'Tailored bacteritherapy'

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Anti-toxin antibodies

- CDI recurrence significantly less frequent in Mab pts
  - mean day of receipt of Mab = day 3, 90% by day 5

    7% vs. 25%, 95% CI, 7 to 29, **(P<0.001)**
  - 73% overall reduction in recurrence
  - 14% vs 25% in-patients, p=0.21
  - 0% vs 26% in out-patients, p<0.001
- Recurrence rates in NAP1/027 cases

  8% *vs* 32% **(P=0.06)**
- Recurrence in cases with >1 previous episode of CDI

  7% *vs* 38% **(P=0.006)**

Louie T, *et al*. *NEJM* 2010.

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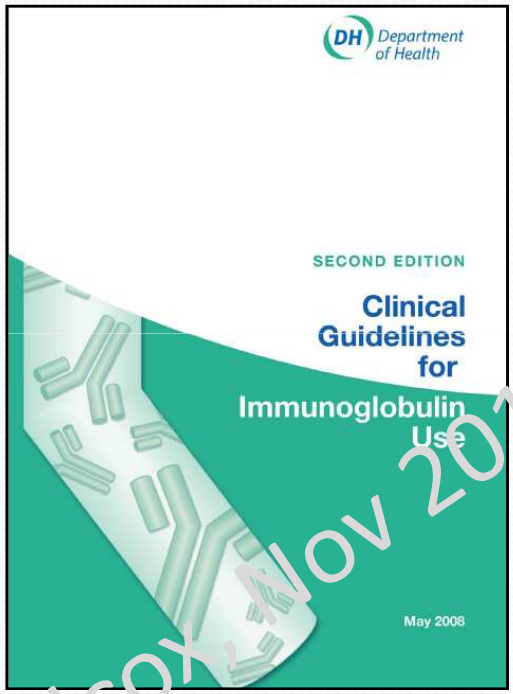
Other therapeutic approaches for CDI

- **Immunoglobulin therapy**

Condition	Recommend?		Recommendation/ Evidence grade	Alternatives
	Short-term	Long-term		
Infectious diseases				
Severe invasive group A streptococcal disease	SELECTED	NO	B, Ib	Activated protein C, antibiotics
Staphylococcal toxic shock syndrome	SELECTED	NO	C, III	Antibiotics
Necrotising (PVL-associated) staphylococcal sepsis	SELECTED	NO	C, III	Activated protein C, antibiotics
Severe or recurrent *Clostridium difficile* colitis	SELECTED	NO	C, III	Antibiotics, colectomy



- **Nitazoxanide**
- **Rifaximin**
- **Tigecycline**

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Case	Sex	Age, years	Symptoms	Method of diagnosis[a]	Duration of previous standard therapy[a]	Duration of tigecycline therapy[a]	Date of relief of symptoms after start of tigecycline therapy	Date of negative toxin EIA result after start of tigecycline therapy	Relapse within 3 months?
1	Male	60	Diarrhea >6 times per day; temperature >38.5°C; hypovolemic shock; pseudomembranes; bloody stools	Toxin EIA (day 16); culture positive for ribotype 159	Mtz (days 16–20); Vm (days 21–25); Vm and Mtz (days 26–57)	3 weeks, in combination with Vm (days 58–78)	Day 3	Day 3	No
2	Female	36	Ileus; temperature >38.5°C; hypovolemic shock; pseudomembranes	Toxin EIA (day 22); culture	Vm (day 22–26); Vm and Mtz (days 27–35)	15 days (days 36–50)	Day 5	Day 6	No
3	Male	36	Diarrhea >6 times per day; temperature >38.5°C; hypovolemic shock	Toxin EIA (day 36); culture positive for ribotype 078	No standard therapy	7 days (days 38–42), followed by 4 weeks of Vm (days 43–70)	Day 5	Day 13	No
4	Female	82	Diarrhea >6 times per day; temperature >38.5°C; hypovolemic shock; pseudomembranes; bloody stools	Toxin EIA (day 6); culture positive for ribotype 087	Mtz (days 6–16); Vm (days 17–27)	24 days (days 28–51), then 2 courses of pulse therapy[b] (days 59–65 and 73–79)	Day 7	Day 4	No

NOTE. EIA, enzyme immunoassay; Mtz, metronidazole; Vm, vancomycin.

[a] The day (after hospital admission) on which the toxin EIA result was positive or the day (after hospital admission) on which therapy was started is given in parentheses.

[b] After 24 days, 2 additional weeks of treatment were interspersed with 1 treatment-free week.

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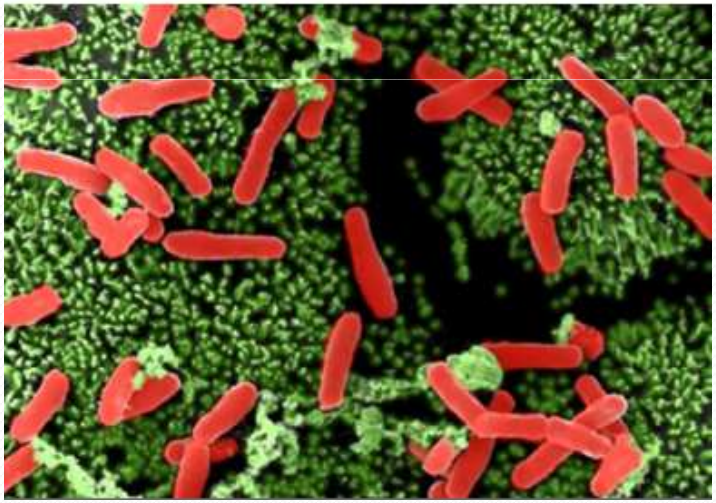
Herpers BL, *et al*. *Clin Infect Dis* 2009;48:1732-5.

Health Protection Agency

DH Department of Health

Clostridium difficile infection:

How to deal with the problem



INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY MAY 2010, VOL. 31, NO. 5

SHEA-IDSA GUIDELINE

Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA)

Stuart H. Cohen, MD; Dale N. Gerding, MD; Stuart Johnson, MD; Ciaran P. Kelly, MD; Vivian G. Loo, MD; L. Clifford McDonald, MD; Jacques Pepin, MD; and Mark H. Wilcox, MD

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Health Protection Agency http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1232006607827

Cohen S et al. ICHE 2010;31:on line.

Bauer MP, et al (ESCMID) Clin Microbiol Infect 2009;15:1067-79.

1st/2nd episode of *Clostridium difficile* infection (CDI)

Diarrhoea AND one of the following:
Positive *C. difficile* toxin test OR Results of *C. difficile* toxin test pending AND clinical suspicion of CDI

▼

Ideally discontinue non-*C. difficile* antibiotics to allow normal intestinal flora to be re-established

Suspected cases must be isolated

▼

Symptoms/signs not severe CDI

Oral metronidazole
400 or 500mg tds 10-14 days

▼

DAILY ASSESSMENT

▼

Symptoms improving

Diarrhoea should resolve in 1-2 weeks

Recurrence occurs in ~20% after 1st episode; 50-60% after 2nd episode

▼

Symptoms/signs severe CDI

WCC >15, acute rising creatinine and/or signs/symptoms of colitis

Oral vancomycin 125 mg qds 10-14 days

▼

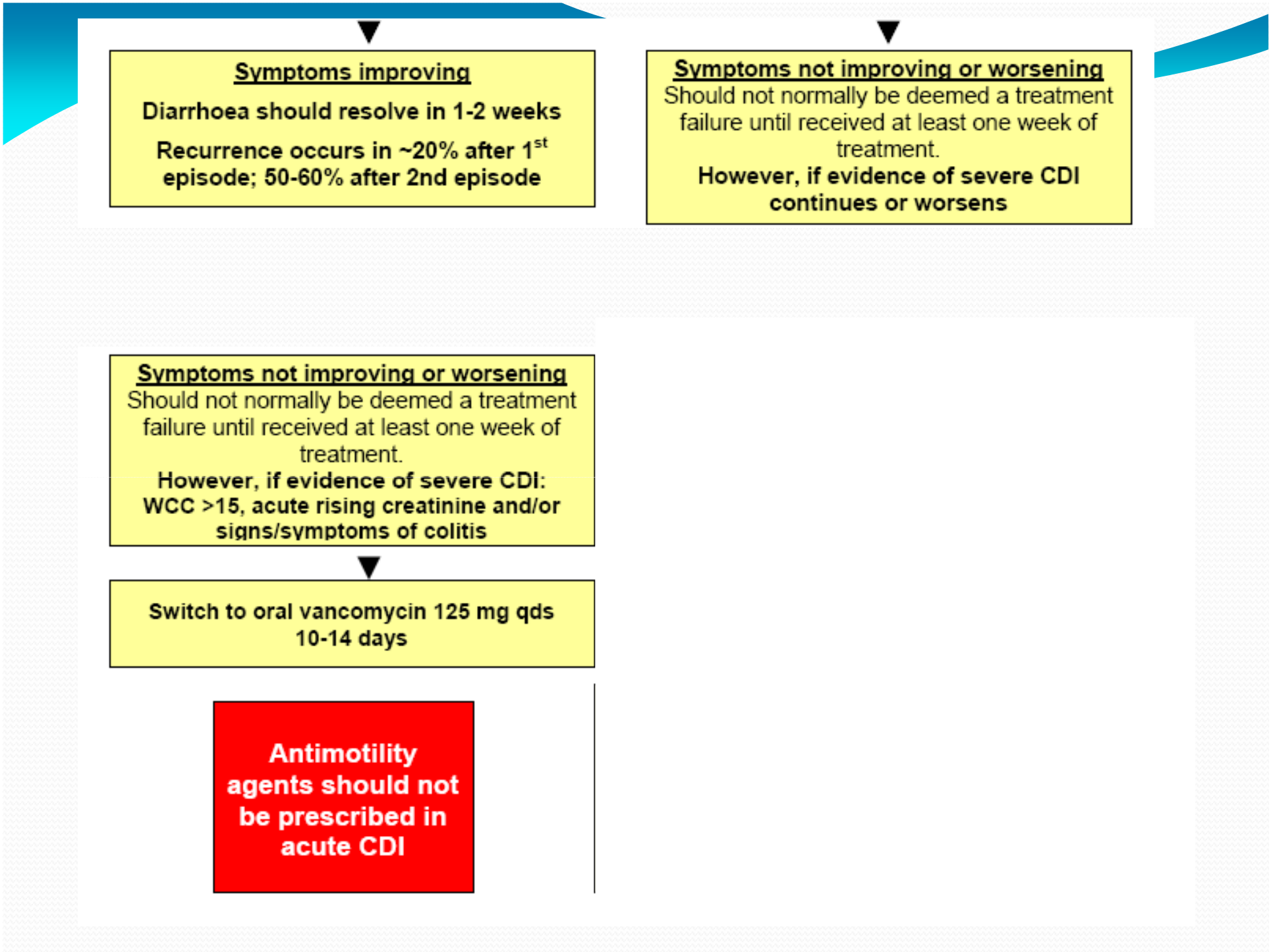
DAILY ASSESSMENT

▼

Symptoms not improving or worsening

Should not normally be deemed a treatment failure until received at least one week of treatment.

However, if evidence of severe CDI continues or worsens


Symptoms improving
Diarrhoea should resolve in 1-2 weeks
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Symptoms not improving or worsening
Should not normally be deemed a treatment failure until received at least one week of treatment.
However, if evidence of severe CDI continues or worsens
Symptoms not improving or worsening
Should not normally be deemed a treatment failure until received at least one week of treatment.
However, if evidence of severe CDI:
WCC >15, acute rising creatinine and/or signs/symptoms of colitis
Switch to oral vancomycin 125 mg qds 10-14 days
Antimotility agents should not be prescribed in acute CDI

DAILY ASSESSMENT

Symptoms not improving or worsening
Should not normally be deemed a treatment failure until received at least one week of treatment

However, if evidence of severe CDI continues or worsens

Surgery/GI/micro/ID consultation

AND, depending on degree of ileus, vancomycin 125–500 mg PO/NG qds, +/- metronidazole 500 mg iv tds 10 days

PLUS CONSIDER intracolonic vancomycin (500 mg in 100–500 ml saline 4–12-hourly) given as retention enema: 18 gauge Foley catheter with 30 ml balloon inserted per rectum; vancomycin instilled; catheter clamped for 60 minutes; deflate and remove (Apisarnthanarak et al., 2002)

Further surgery/GI/micro/ID consultation
Depending on choice of therapy (see above), consider:

1. high-dose oral/NG vancomycin (500 mg PO qds) ± rifampicin 300 mg PO bd
2. IV immunoglobulin 400 mg/kg, one dose, and consider repeating (Wilcox, 2004)

There is no robust evidence for the effectiveness of these approaches in severe CDI

Recurrent *Clostridium difficile* diarrhoea
≥ 3rd episode

Diarrhoea AND one of the following:
Positive *C. difficile* toxin test OR Results of *C. difficile* toxin test pending AND clinical suspicion of CDI

▼

Must discontinue non- *C. difficile* antibiotics if at all possible to allow normal intestinal flora to be re-established

Review all drugs with gastrointestinal activity or side effects (stop PPIs unless required acutely)

Suspected cases must be isolated

▼

Oral fidaxomicin
200 mg bd for 10-14 days

▼

Daily Assessment
(include review of severity markers, fluid/electrolytes)

▼

If severe CDI suspected/ documented ***see algorithm for 1st / 2nd episode of CDI***

Symptoms improving

Diarrhoea should resolve in 1-2 weeks

Recurrence occurs in ~20% after 1st episode; 40-60% after 2nd/3rd episode

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IF MULTIPLE RECURRENCES ESPECIALLY IF EVIDENCE OF MALNUTRITION, WASTING, etc.

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1. **Review ALL antibiotic and other drug therapy (consider stopping PPIs and/or other GI active drugs)**
2. **Consider supervised trial of anti-motility agents alone (no abdominal symptoms or signs of severe CDI)**

Also consider:

3. **Vancomycin tapering/pulse therapy (4-6 week regimen)** *(Am J Gastroenterol 2002;97:1769-75)*
4. **Oral vancomycin 125 mg qds + oral rifampicin 300 mg bd for 2 weeks** (no robust evidence for effectiveness)
5. **IV immunoglobulin, especially if worsening albumin status** *(J Antimicrob Chemother 2004:53:882-4)*
6. **Donor stool transplant** *(Clin Infect Dis 2003;36:580-5)*

Summary CDI treatment issues

- **Need to identify patients**
  - with severe infection
  - at risk of recurrence
- **Detrimental effect of concomitant antibiotics**
- **Multiple new drugs / interventions under investigation**
- **Antibiotics *vs* others**
- **Need to improve evidence base for when to use different CDI treatment options**
- **Can new treatment options reduce mortality?**

Mark Wilcox, Nov 2012