Prevenzione e terapia delle infezioni da C.difficile

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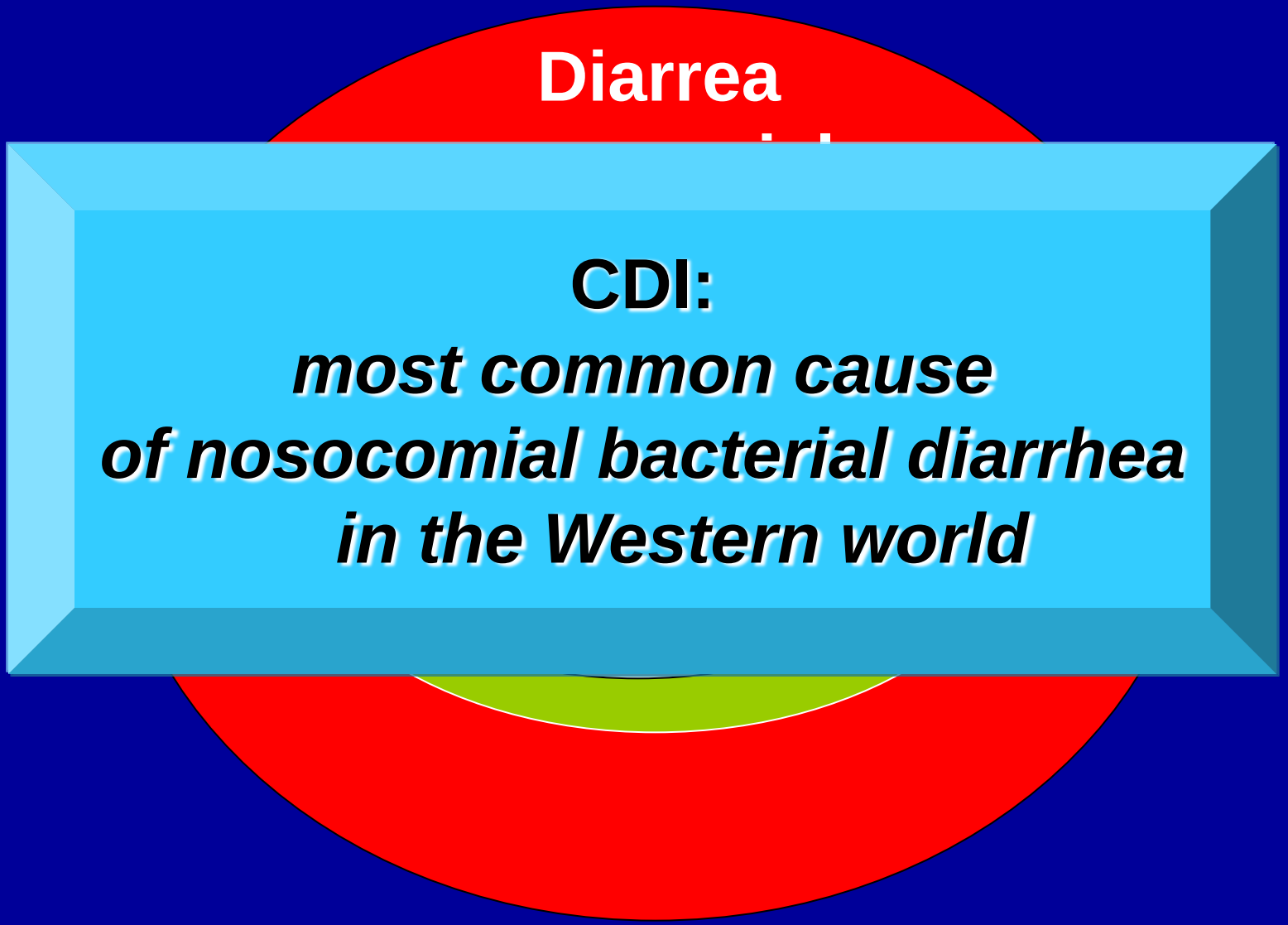
6° INFECTO
Paestum
16 maggio 2014

CDI: diarrea infettiva nosocomiale



CDI: clinical syndromes and *complications*

- **Col**
- **Fro**
- **Col**
- ***Tox***
- ***Col***
- ***Sep***

CDI: *a substantial cause of unexplained nosocomial leukocytosis*

Domande

1.
2.
3.
4.

Risposte:
tra opinioni ed evidenze !!

Q1 terapia empirica

- **Diagnosi rapida: una necessita' realizzabile**
- **Requisito per accreditamento laboratorio microbiologia: 24/7/365**
- **Realizzabile "al letto del malato" (test rapido)**
- **Ricerca della tossina A/B: limiti del test se utilizzato da solo**

UPDATED GUIDANCE ON THE DIAGNOSIS AND REPORTING OF *CLOSTRIDIUM DIFFICILE*

Department of Health

6 March 2012

STEP 2: Testing

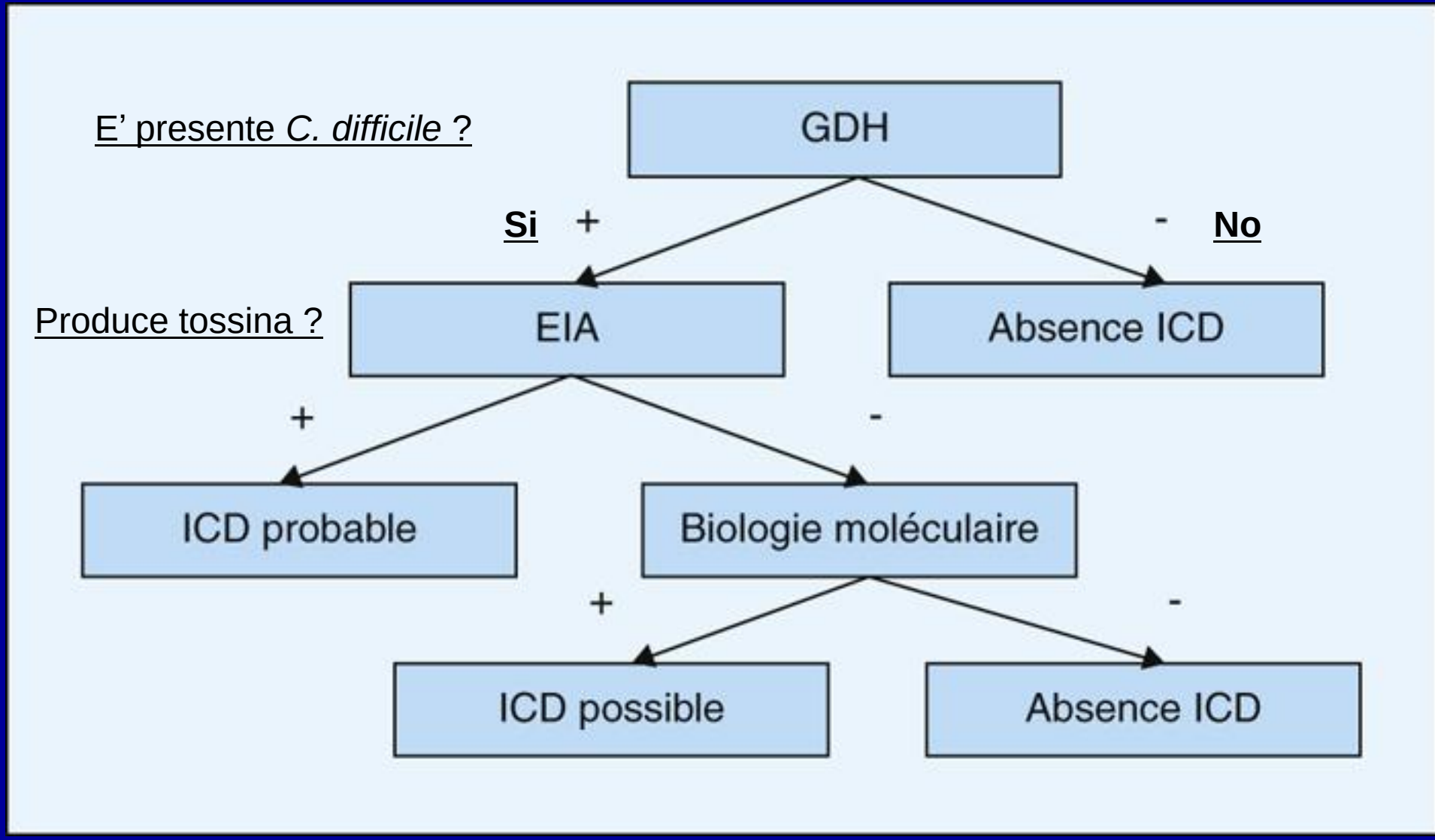
C. difficile toxin EIAs are **not suitable as stand alone tests** for the diagnosis of CDI or detection of *C. difficile*.

The Department and ARHAI advise that organisations adhere to a two stage testing approach which consists of a GDH EIA (or a NAAT or PCR) test to screen samples, followed by a sensitive toxin EIA test (or a cytotoxin assay[1]). If the first test (GDH or NAAT) is negative, the second test (sensitive toxin EIA) does NOT need to be performed[2].

[1]Note: a cytotoxin assay (the reference method) yields slower results and this needs to be taken into account when making management and infection control decisions.
[2]Note: To further clarify samples from potential C. difficile excretors, colleagues may wish to add an optional third test (e.g. NAAT or PCR).

NHS

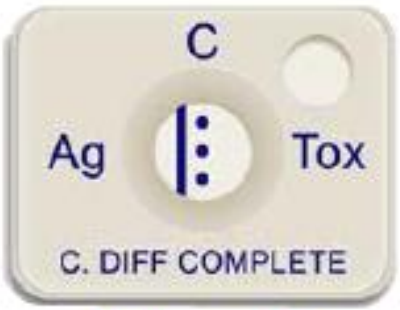
ALGORITMO DIAGNOSTICO



TEST RAPIDO COMBINATO

Alere™

C. diff Quik Chek Complete™



C. difficile could be present, potential *C. difficile* excretor

C. difficile most likely present with a possible poor outcome

C. difficile negative

Rapid Detection of C. diff antigen (GDH) & Toxins A/B

Terapia empirica x CDI

- **Se test rapido NON disponibile valutare:**

1. **Fattori di rischio specifici:**

- **Antibiotics (clindamycin, penicillins, FQs) and**
- **Using 3 or more antibiotics at one time (SoR: B1)**
- **Proton-pump inhibitors: (SoR: B1)**
- **Hospital risk factors: proximity to other patients with *C difficile* and longer length of stay (SoR: B)**
- **Patient risk factors: advanced age and comorbid conditions (SoR: B)**

Terapia empirica x CDI

2. **Criteri clinici:**

- **entità della diarrea**
- **Ipotensione, shock settico**
- **megacolon, ileo**
- **Leucocitosi (> 15.000/mmc)**
- **Incremento creatinina (> 1. 5 VB)**

Terapia empirica x CDI

3. Criteri epidemiologici:

- **epidemia in corso**
- **prevalenza ceppo BI/NAP1/027 (Torino 2009, Italia centrale 2010-2012, Roma 2013)**

Quale terapia empirica x CDI ?

Clinical definition	Supportive clinical data	Recommended Therapy	SoR
Initial epi mild or mo			AI
Initial epi sever			BI
Initial epi sever complica			CIII
	Ileus	As above, + Vanco rectal instillations	

Approccio da rivedere considerando opzione fidaxomicina

SHEA-IDSA Guideline ICHE, 2010; 31:433-455

Q 2 Nuove opzioni terapeutiche

- **20%-30% of pts who initially respond to treatment will have a recurrence up to 8 weeks after completion of treatment (most of the recurrences within the first 14 days)**
- ***Rates of recurrence similar between pts initially treated with vancomycin or metronidazole***
- **Insufficient data on:**
  - **CDI caused by strain BI/NAP1/027**
  - **Impact of concomitant antibiotic use**

Drawbacks of current recommendations for CDI treatment

Recurrent *Clostridium difficile* infection: A review of risk factors, treatments, and outcomes

Stuart Johnson [a,b,*]

Table 1 Important risk factors for the development of recurrent *Clostridium difficile* infection.

- Inadequate antitoxin antibody response
- Persistent disruption of the colonic flora
- Advanced age
- Continuation of non-*C. difficile* antimicrobial therapy following a first episode of CDI
- Long hospital stays
- Concomitant receipt of antacid medications

CDI, *Clostridium difficile* infection.

Journal of Infection (2009) **58**, 403–410

Drawbacks of antibiotics currently used for CDI

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-
-
-

There is a strong need for new agent and/or new treatment modalities

Fidaxomicin

- N
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- N
- R
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- M
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  ri

First antimicrobial agent approved by FDA for CDI in adults over the last 25 years

In vitro susceptibility of *C.difficile* strains to fidaxomicin, vancomycin, metronidazole

Table 2. In Vitro Susceptibilities of 525 Historical Clinical *Clostridium difficile* Isolates

			No. of Strains With MIC µg/mL of:								
Study	Susceptibility Testing Method	Drug	≤0.03	0.06	0.125	0.25	0.5	1	2	4	≥8
Ackermann et al [27]	Broth microdilution	FDX	204	3	…	…	…	…	…	…	…
		VAN	1	3	7	81	115	…	…	…	…
		MTZ	25	39	138	3	2	…	…	…	…
Hecht et al [28]	Agar dilution	FDX	20	29	50	11	…	…	…	…	…
		VAN	…	2	…	…	34	68	5	1	…
		MTZ	2	3	70	32	3	…	…	…	…
Karlowsky et al [29]	Agar dilution	FDX	…	2	73	65	51	17	…	…	…
		VAN	…	…	…	25	102	67	13	1	…
		MTZ	…	…	…	…	120	81	6	1	…

Clinical Infectious Diseases 2012;54(4):568–74

In vitro susceptibilities of Fidaxo, Vanco and Metronidazole against selected aerobic and anaerobic organisms

Table 1. In Vitro Susceptibilities of Fidaxomicin, Vancomycin, and Metronidazole Against Selected Aerobic and Anaerobic Organisms (μg/mL)

Organism	Drug	Range	MIC_{50}	MIC_{90}
Bacteroides fragilis [22–24]	FDX	64 – >128	>128	>128
	VAN	>16	>16	>16
	MTZ	0.25–1.0	1.0	1.0
Non-*fragilis B. fragilis* group [22–24]	FDX	64 – >128	>128	>128
	VAN	>16	>16	>16
	MTZ	0.25–16	…	…
Other anaerobic gram-negative rods[a] [23]	FDX	0.06 – >1024	1024	>1024
	VAN	0.5 – >1024	512	1024
	MTZ	0.25 – >128	0.25	4
Clostridium perfringens [22, 23]	FDX	≤0.016–0.06	…	…
	VAN	0.25–2	…	…
	MTZ	≤0.125–2	…	…
Other *Clostridium* species[b] [22]	FDX	≤0.016–0.06	≤0.016	0.03
	VAN	0.5–2	1	2
	MTZ	≤0.125–1	0.5	0.5
Enterococcus species[c] [23]	FDX	2–16	8	8
	VAN	0.5–4	1	4
	MTZ	>1024	>1024	>1024
Staphylococcus species[d] [23]	FDX	0.25–2	0.5	2
	VAN	1–4	2	4
	MTZ	128 – >1024	256	>1024

Clinical Infectious Diseases 2012;54(4):568–74

Fidaxomicin versus Vancomycin for *Clostridium difficile* Infection

Table 1. Demographic and Baseline Clinical Characteristics of the Patients in the Modified Intention-to-Treat and Per-Protocol Populations.*

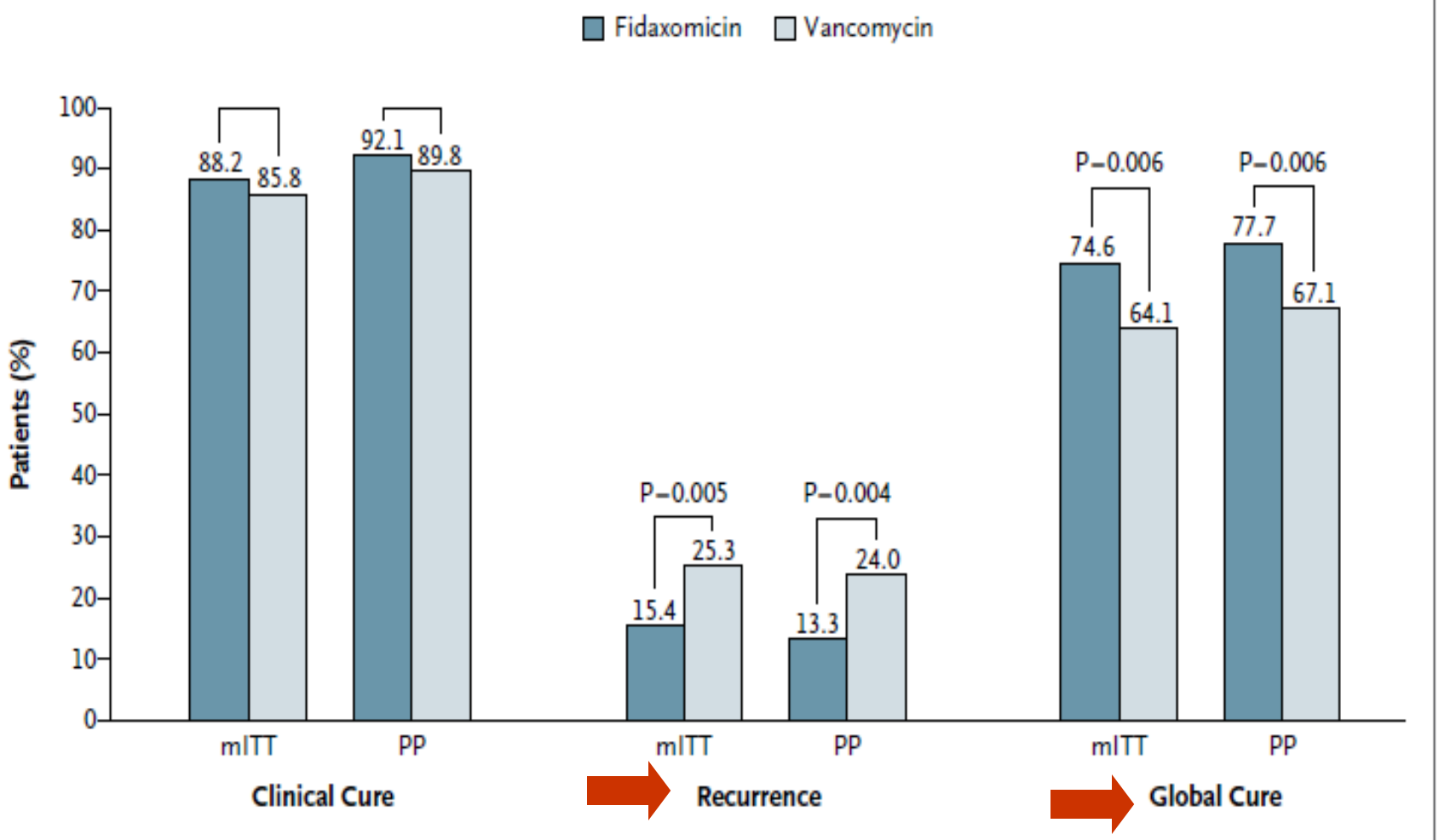
Characteristic	Modified Intention-to-Treat Population			Per-Protocol Population		
	Fidaxomicin (N=287)	Vancomycin (N=309)	Total (N=596)	Fidaxomicin (N=265)	Vancomycin (N=283)	Total (N=548)
Age (yr)	60.3±16.9	62.9±16.9	61.6±16.9	59.9±17.1	62.7±17.0	61.3±17.1
Female sex (%)	57.1	54.7	55.9	57.4	54.8	56.0
Unformed stools per day (no.)	8.1±4.2	8.3±5.4	8.2±4.8	8.2±4.3	8.4±5.5	8.3±4.9
Inpatient (%)	58.2	60.5	59.4	55.1	57.2	56.2
Lack of response to metronidazole (%)	4.5	5.5	5.0	4.9	5.7	5.3
Treatment for *C. difficile* infection in previous 24 hr (%)	38.3	39.8	39.1	37.4	38.5	38.0
Previous episode of *C. difficile* infection (%)	16.7	17.5	17.1	16.2	17.0	16.6
BI/NAP1/027 strain (%)†	37.5	38.6	38.1	35.3	36.4	35.9

OPT 80-003

Thomas J. Louie, N Engl J Med 2011;364:422-31.

Fidaxomicin versus Vancomycin for *Clostridium difficile* Infection

OPT 80-003



N Engl J Med 2011;364:422-31.

OPT 80-003 conclusions

- ***Fidaxomicin 200 mg bid* and *vancomycin 125 mg qid* orally have similar effectiveness with respect to the *clinical resolution of acute diarrheal disease* due to C.difficile after 10 days of treatment**
- **More *sustained or durable resolution of disease (global cure)* is achieved with fidaxomicin (clinical cure without recurrence 25 days after treatment completion)**

N Engl J Med 2011;364:422-31.

Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial

Oliver A Cornely, Derrick W Crook, Roberto Esposito, André Poirier, Michael S Somero, Karl Weiss, Pamela Sears, Sherwood Gorbach, for the OPT-80-004 Clinical Study Group

	Fidaxomicin (n=252)	Vancomycin (n=257)	All patients (n=509)	Europe (n=198)	USA and Canada (n=311)
Age (years)	64·3 (17·9)	62·5 (18·4)	63·4 (18·1)	66·9 (16·9)	61·2 (18·6)
Female	148 (58·7%)	162 (63·0%)	310 (60·9%)	108 (54·5%)	202 (65·0%)
UBM per day					
Mean	7·5 (4·4)	7·5 (4·3)	7·5 (4·4)	6·9 (4·2)	7·8 (4·4)
Median	6 (4–9)	6 (4–10)	6 (4–9)	5 (4–8)	6 (5–10)
Inpatient	174 (69·0%)	173 (67·3%)	347 (68·2%)	167 (84·3%)	180 (57·9%)
Severe infection*	63 (25·0%)	61 (23·7%)	124 (24·4%)	50 (25·3%)	74 (23·8%)
24 h pretreatment	97 (38·5%)	98 (38·1%)	195 (38·3%)	79 (39·9%)	116 (37·3%)
Previous infection	40 (15·9%)	36 (14·0%)	76 (14·9%)	20 (10·1%)	56 (18·0%)
NAP1/BI/027 strain†	65 (33·2%)	60 (33·1%)	125 (33·2%)	14 (10·4%)	111 (45·9%)
Concomitant antibiotics					
At any time (day 1–40)	83 (32·9%)	69 (26·8%)	152 (29·9%)	69 (34·8%)	83 (26·7%)
During treatment (day 1–10)	51 (20·2%)	45 (17·5%)	96 (18·9%)	40 (20·2%)	56 (18·0%)
During follow-up (day 11–40)	64 (25·4%)	58 (22·6%)	122 (24·0%)	60 (30·3%)	62 (19·9%)

Lancet Infect Dis 2012; 12: 281-89

Fidaxomicin versus Vancomycin for *Clostridium difficile* Infection

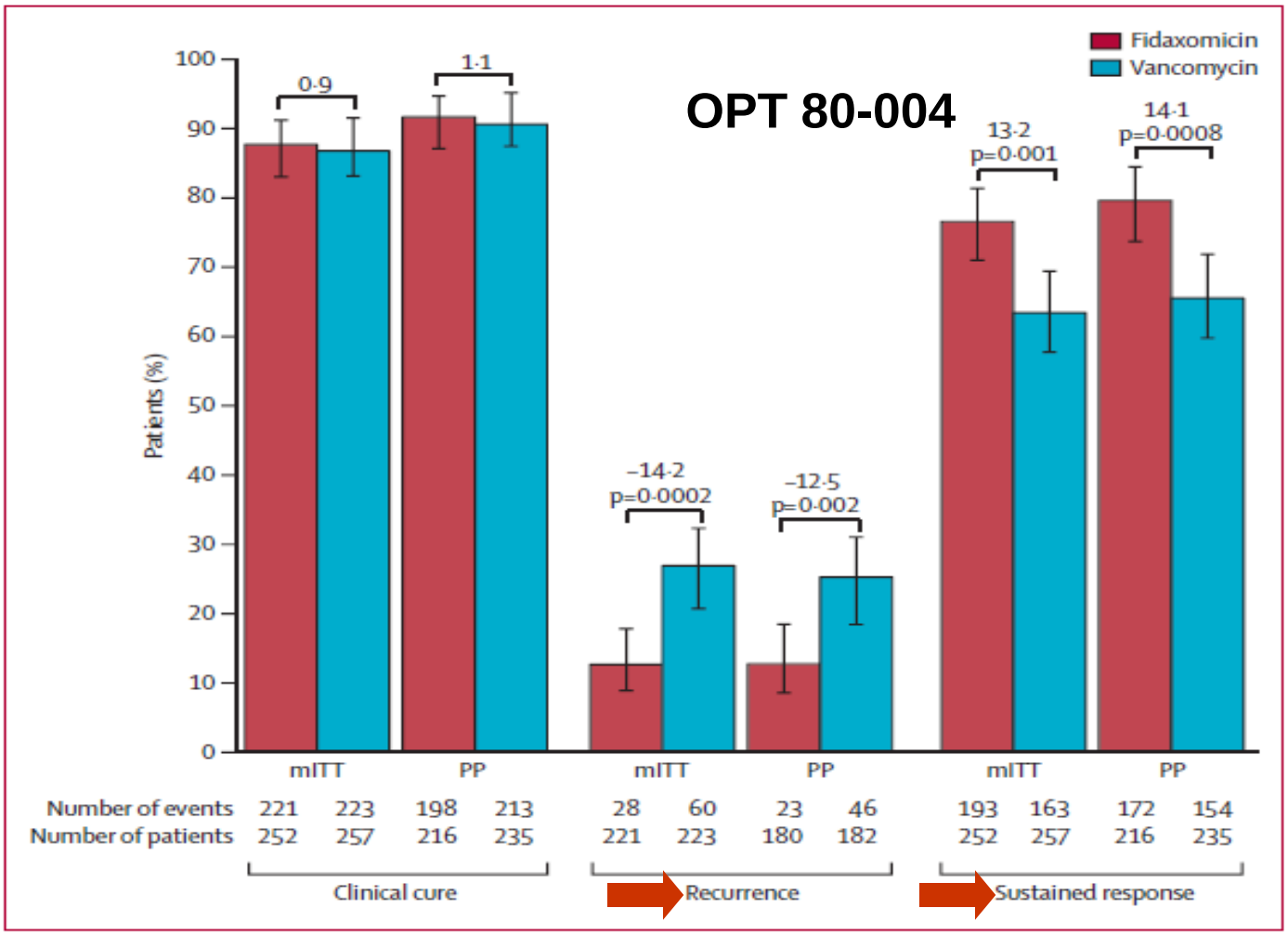


Figure 2: **Clinical outcomes by treatment group**

Lancet Infect Dis 2012; 12: 281-89

OPT 80-004 conclusions

- *Fidaxomicin non-inferior to vancomycin in initial clinical response*
- *Pts succesfully treated with fidaxomicin were less likely to have recurrence within 4 weeks after treatment completion, traslating to a superior sustained response (difference: 14%)*
- *Clinical cure rate for pts receiving concomitant antibiotics better for fidaxomicin: 46/51 (90,2%) vs 33/45 (72,3%) (p= 0.031)*

Lancet Infect Dis 2012; 12: 281-89

Efficacy of Fidaxomicin Versus Vancomycin as Therapy for *Clostridium difficile* Infection in Individuals Taking Concomitant Antibiotics for Other Concurrent Infections

OPT 80-003/004

- **CAs concurrent with CDI treatment (fidaxomicin or vancomycin) associated with lower cure rate (84.4% vs 92,6%; P>0.001) and extended time to resolution of diarrhea (97 vs 54 hrs; P<0.001)**
- ***With concurrent CAs, cure rate was 90% for fidaxomicin and 79.4% for vancomycin (P=0.04)***
- ***In pts receiving CAs during treatment and/or FU, fidaxomicin theray was associated with 12.3% fewer recurrences (16.9% vs.29.2%; P = .048)***
- **Fidaxomicin was significantly more effective than vancomycin in achieving clinical cure in the presence of CAs therapy and in preventing recurrence regardless of CAs use**

Mullane et al. Clinical Infectious Diseases 2011; 53 (5):440-447

Decreased Cure and Increased Recurrence Rates for *Clostridium difficile* Infection Caused by the Epidemic *C. difficile* BI Strain

OPT 80-003/004

Laurica A. Petrella,[1] Susan P. Sambol,[1,2] Adam Cheknis,[1] Kristin Nagaro,[1] Yin Kean,[3] Pamela S. Sears,[3] Farah Babakhani,[3] Stuart Johnson,[1,2] and Dale N. Gerding[1,2]

- **Clinical cure rate for pts infected with epidemic BI strain of *C. difficile* are significantly reduced in comparison with CDI caused by other strains, independent of the treatment agent used (fidaxomicin or vancomycin).**
- **by multivariate analysis increased recurrence rates of CDI were also related to: infection with BI strain, prior history of CDI, and concomitant use of other antimicrobials**

Clinical Infectious Diseases Advance Access published May 21, 2012

18-

DIFICLIR è indicato per il trattamento negli adulti delle infezioni da *Clostridium difficile* (CDI - *Clostridium difficile infections*) note anche come diarrea associata a C. difficile (*CDAD - C. Difficile - associated diarrhoea*). Può essere prescritto da centri ospedalieri e territoriali del SSN in pazienti con diagnosi microbiologica di CDI/CDAD (GDH positivo *oppure* con tossina A e/o B positiva) per il trattamento:

☐ **Del primo episodio** in:

- Pazienti intolleranti o che non rispondono alla terapia di prima scelta (vancomicina e metronidazolo) *oppure*
- Pazienti ad alto rischio di recidiva come:
  - Paziente immunocompromesso (trapiantato, sotto chemioterapia antritumorale, HIV positivo/AIDS, altre immunodeficienze), *oppure*
  - Paziente con altre gravi patologie concomitanti. In questo caso, specificare

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☐ **Degli episodi successivi al primo:**

- Trattamenti delle infezioni ricorrenti da CD.

Dose e durata del trattamento	
☐ Dose/die: **200 mg x 2/die**	Durata prevista del trattamento: **10 giorni**

FUTURE PHARMACOTHERAPY OF CDI : DRUGS UNDER DEVELOPMENT

LFF 571 (Novartis)

semisynthetic thiopeptide with high and selective in vitro activity

Phase II trials undergoing

Surotomycin (Cubist)

novel lipopeptide structurally related to daptomycin

Phase III trials undergoing

SMT 19969

bis-benzimidazole tetrahydrate compound with minimal growth inhibition against a large panel of isolates from the gut flora

Cadazolid (Actelion)

non-absorbable oxazolidinone with very selective actitvity

Scheduled for Phase II trials

Oritavancin

Lipoglycopeptide fourfold more active in vitro than vanco and metro

Strong activity against ribotype 027 in a human gut model

CamSA

bile salt analog, inhibits *C. difficile* spore germination in vitro. In a murine model study a single dose of prevented CDI without any toxicity suggesting a possible new approach for prevention of CDI

A New Strategy for the Prevention of *Clostridium difficile* Infection

Amber Howerton, Manomita Patra, and Ernesto Abel-Santos

Department of Chemistry, University of Nevada, Las Vegas

(See the editorial commentary by Armstrong et al on pages 1484–6.)

Background. *Clostridium difficile* infection (CDI) is a leading cause of antibiotic-associated diarrhea. The infective form of *C. difficile* is the spore, but the vegetative bacterium causes the disease. Because *C. difficile* spore germination is required for symptomatic infection, antigermination approaches could lead to the prevention of CDI. We recently reported that CamSA, a bile salt analog, inhibits *C. difficile* spore germination in vitro.

Methods. Mice infected with massive inocula of *C. difficile* spores were treated with different concentrations of CamSA and monitored for CDI signs. *C. difficile* spore and vegetative cells were counted in feces from infected mice.

Results. A single 50-mg/kg dose of CamSA prevented CDI in mice without any observable toxicity. Lower CamSA doses resulted in delayed CDI onset and less severe signs of disease. Ingested *C. difficile* spores were quantitatively recovered from feces of CamSA-protected mice.

Conclusions. Our results support a mechanism whereby the antigermination effect of CamSA is responsible for preventing CDI signs. This approach represents a new paradigm in CDI treatment. Instead of further compromising the microbiota of CDI patients with strong antibiotics, antigermination therapy could serve as a microbiota surrogate to curtail *C. difficile* colonization of antibiotic-treated patients.

The Journal of Infectious Diseases 2013;207:1498–504

Systematic Review of Intestinal Microbiota Transplantation (Fecal Bacteriotherapy) for Recurrent *Clostridium difficile* Infection

Intestinal Microbiota Transplantation (IMT) for recurrent CDI and PMC

Systematic review of 317 pts treated across 27 case series and reports

IMT highly effective, disease resolution in 92% of cases

Effectiveness varied by route of instillation, relationship to stool donor, volume of IMT given, and treatment before infusion

Deaths and adverse events uncommon

Better designed studies should be performed

Clinical Infectious Diseases 2011;53(10):994–1002

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 21, 2010 VOL. 362 NO. 3

Treatment with Monoclonal Antibodies against *Clostridium difficile* Toxins

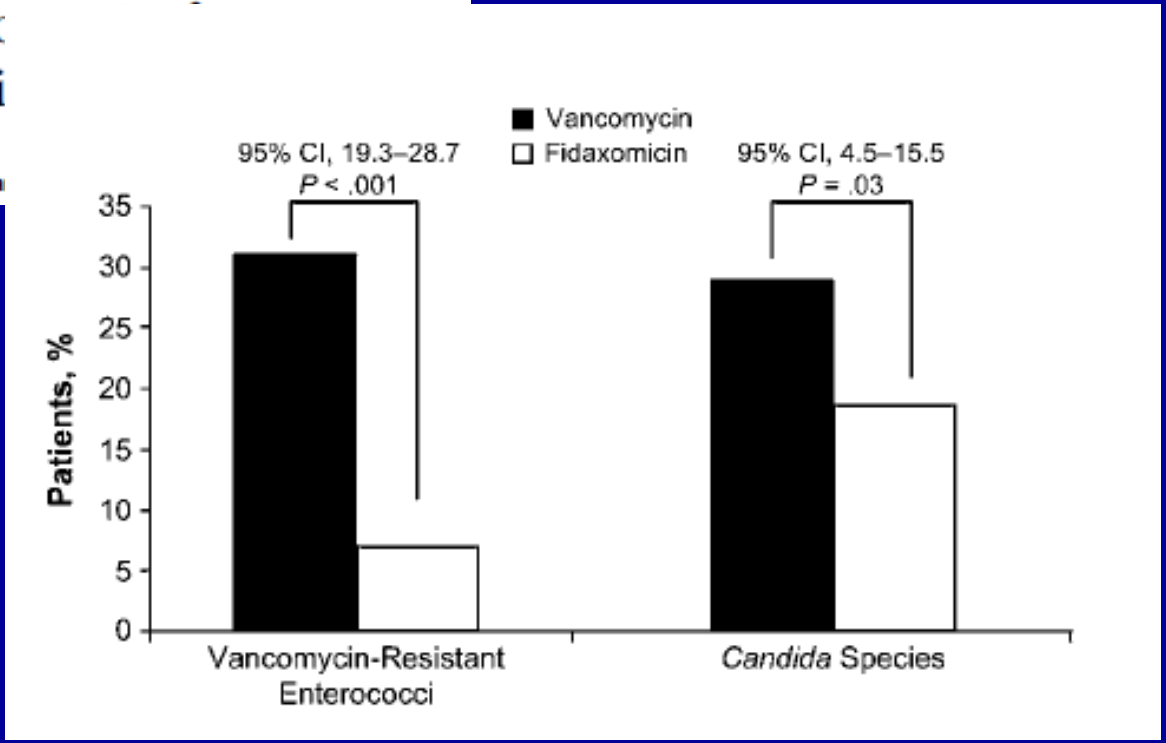
Israel Lowy, M.D., Ph.D., Deborah C. Molrine, M.D., M.P.H., Brett A. Leav, M.D., Barbra M. Blair, M.D., Roger Baxter, M.D., Dale N. Gerding, M.D., Geoffrey Nichol, M.B., Ch.B., William D. Thomas, Jr., Ph.D., Mark Leney, Ph.D., Susan Sloan, Ph.D., Catherine A. Hay, Ph.D., and Donna M. Ambrosino, M.D.

Treatment with monoclonal antibodies against *C. difficile* toxins A and B, in addition to metronidazole or vancomycin, reduced the rate of recurrence of infection, as compared with placebo (7% vs. 25%)

Q 3
Possibile relazione tra vanco e rischio VRE & *Candida* spp.: quale prevenzione ?

Reduced Acquisition and Overgrowth of Vancomycin-Resistant Enterococci and *Candida* Species in Patients Treated With Fidaxomicin Versus Vanco *Clostridium difficile* Infecti

Michelle M. Nerandzic,[1] Kathleen Mullane,[2] Mark A. Miller,[3] Fa



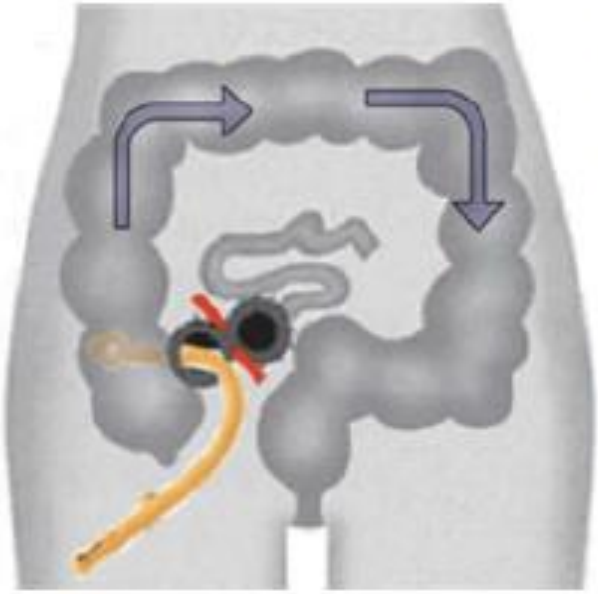
Clinical Infectious Diseases 2012;55(S2):S121–6

Q 4
Indicazioni, timing e tipo di chirurgia

- **Megacolon**
- **Colonic perforation**
- **Acute abdomen**
- **Septic shock (selected cases)**
- ***Emergency colectomy for fulminant CDI caused by ribotype 027: mostly beneficial in pts with age > 65 years, immunocompetent, WBC> 20.000 cmm, lactate 2,2-4,9 mmol/l ****

*** Lamontagne F. et al. Ann Surg 2007; 245: 267-72**

Diverting loop ileostomy & colonic lavage



1. Creation of diverting loop ileostomy.
2. Intraoperative antegrade colonic lavage with 8 liters of warmed PEG3350/electrolyte solution via ileostomy.
3. Postoperative antegrade colonic enemas with vancomycin (500 mg in 500 mL X 10 days) via ileostomy.

FIGURE 1. Operative treatment strategy for loop ileostomy and colonic lavage for severe, complicated *C. difficile*-associated disease. When possible laparoscopic exploration of the colon and abdominal cavity is performed and a diverting loop ileostomy is created. The colon is then lavaged in an antegrade fashion through the ileostomy with a high volume (8 L) of polyethylene glycol 3350 or balanced electrolyte solution and the effluent is collected via a rectal drainage tube. A catheter is placed in the efferent limb of the ileostomy to deliver vancomycin flushes in an antegrade fashion in the postoperative period.

TABLE 2. Demographics and Outcomes in Patients with Severe, Complicated CDAD Treated with Ileostomy or Colonic Lavage Versus Colectomy

	Ileostomy/Lavage	Colectomy	*P*
Age, y	65.3 ± 13	62.1 ± 14	0.28
Sex	45% women	45% women	1.0
APACHE-II (mean ± SD)	29.7 ± 5.5	28.5 ± 7.1	0.39
While blood cell count (mean ± SD)	25.4 ± 12.1	27.1 ± 13.2	0.54
Band count (mean ± SD)	21.4 ± 12.2	21.3 ± 12.9	0.97
Albumin (mean ± SD)	2.0 ± 0.8	2.2 ± 0.8	0.26
Intensive care unit	38/42 (90%)	38/42 (90%)	0.64
Intubated	27/42 (64%)	26/42 (62%)	0.82
Vasopressors	31/42 (74%)	32/42 (76%)	0.81
Immunosuppression	19/42 (45%)	17/42 (40%)	0.66
Postoperative death	8/42 (19%)	21/42 (50%)	0.006*

*Odds ratio = 0.24 (0.09–0.63).

Conclusions

- **CDI: increasing incidence and cost**
- **Fidaxomicin: a safe and well-tolerated new antibiotic for CDI**
- **A susbstantial progress in CDI treatment: lower recurrence rate and higher sustained clinical response for pts with mild to moderate diarrhoea and those receiving concurrent CAs**
- **A 10-day course of fidaxomicin will cost over $ 2000: a cost-benefit analysis will be needed**
- **Unmeet clinical needs: treatment for severe case and BI/NAP1/027 strain**

Conclusions

- **Probiotics, IVIG: probably unuseful**
- **Fecal transplantation: useful in selected case**
- **Monoclonal antibodies and toxoid vaccine: the next future**
- ***Don’t forget: antimicrobial stewardship, isolation and case notification, hygienic precautions (bleach !)***