XI congresso nazionale

simeu

ROMA 24-26 MAGGIO 2018

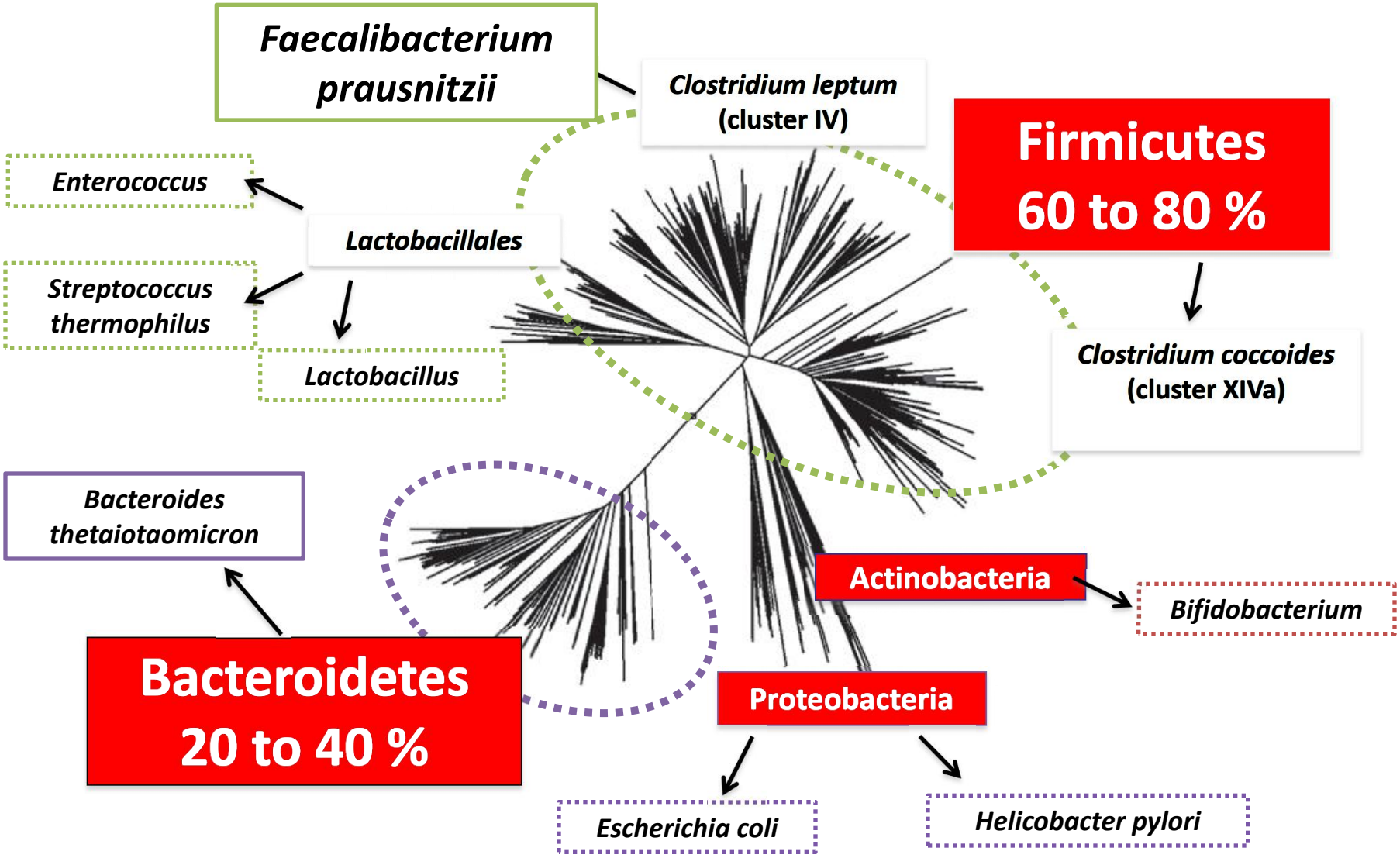
Gestione del paziente con Clostridium difficile in PS

F. Franceschi

Fondazione Policlinico Universitario A. Gemelli, Università Cattolica, Roma

THE ANATOMO-MICROBIOLOGICAL GUT BARRIER

Phylogenetic Diversity of Gut Bacteriome



2 major phyla: Firmicutes and Bacteroidetes (>70%)

Dethlefsen et al., Nature, 2007 18;449(7164):811-8 Ley et al., Science, 2008, 20;320(5883):1647-51
Tap et al., Environ Microbiol, 2009, 11(10):2574-84

EUBIOSIS

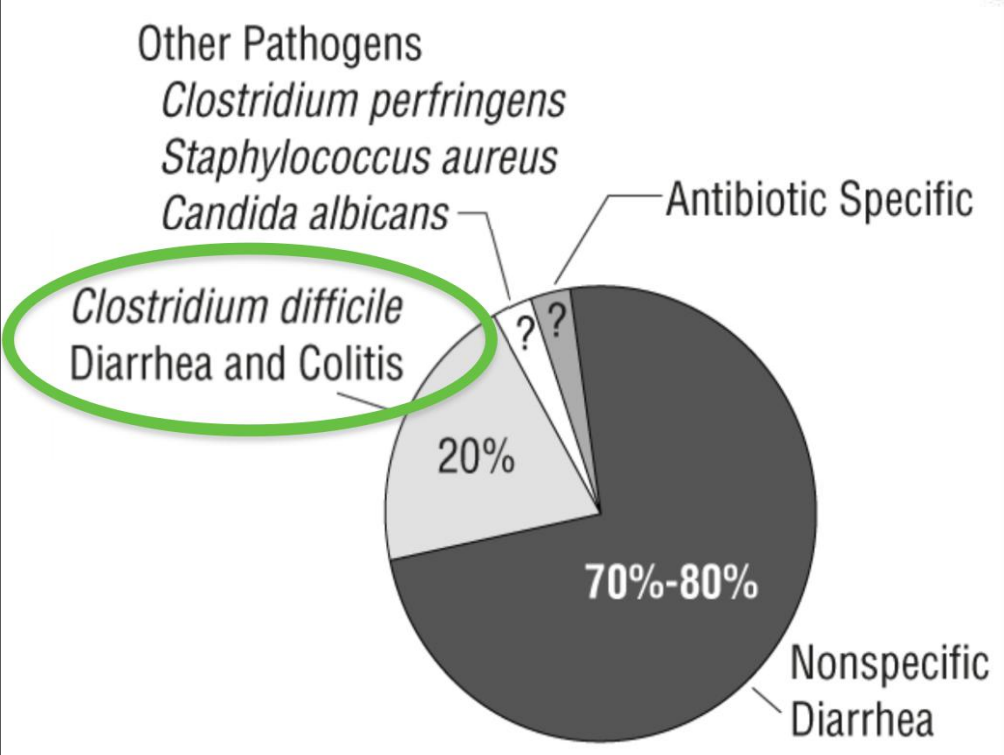
Failure of HOST-MICROBIOTA equilibrium

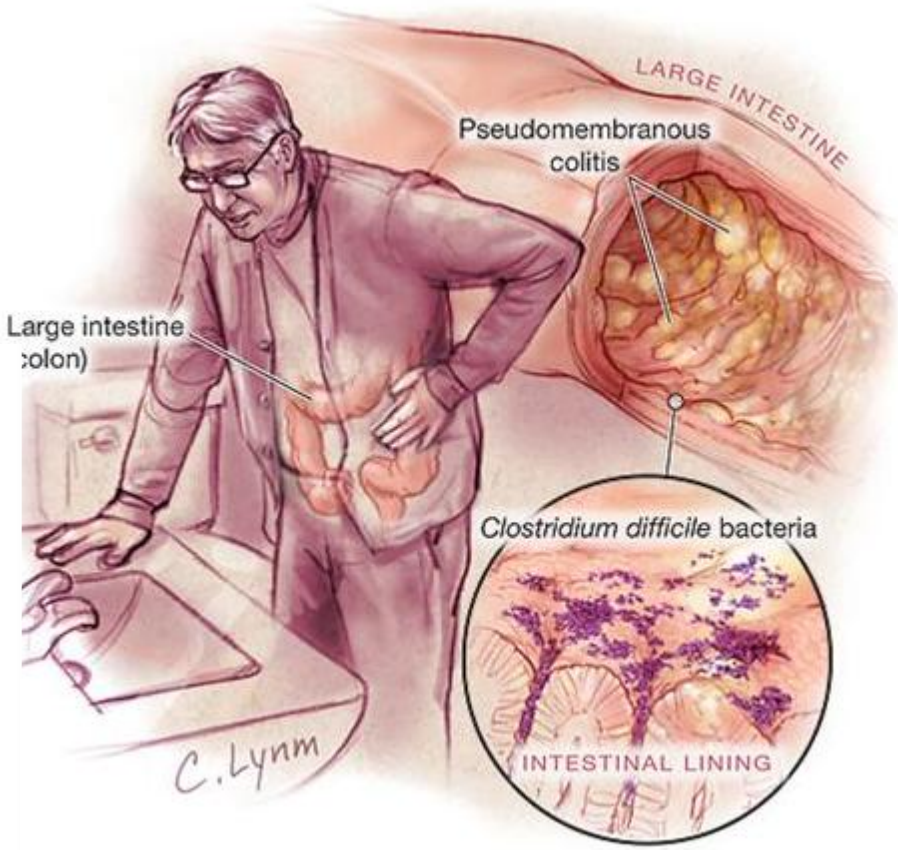
Quali-quantitative alterations of oral, esophageal, gastric, small bowel and/or colonic microbiota

DYSBIOSIS

Digestive and extradigestive diseases

Antibiotics, *C. difficile* and diarrhoea

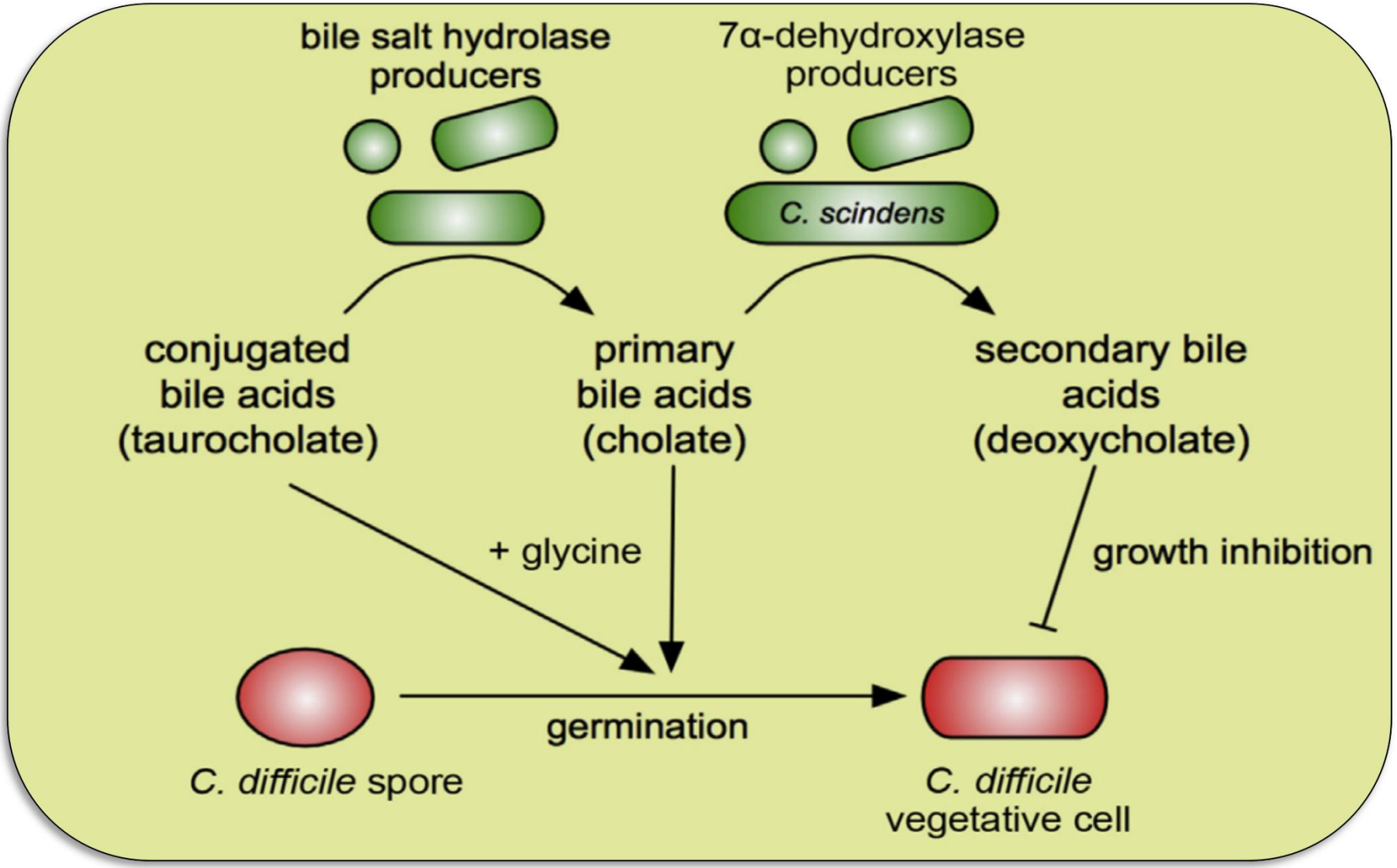




Hurley B JAMA 2002

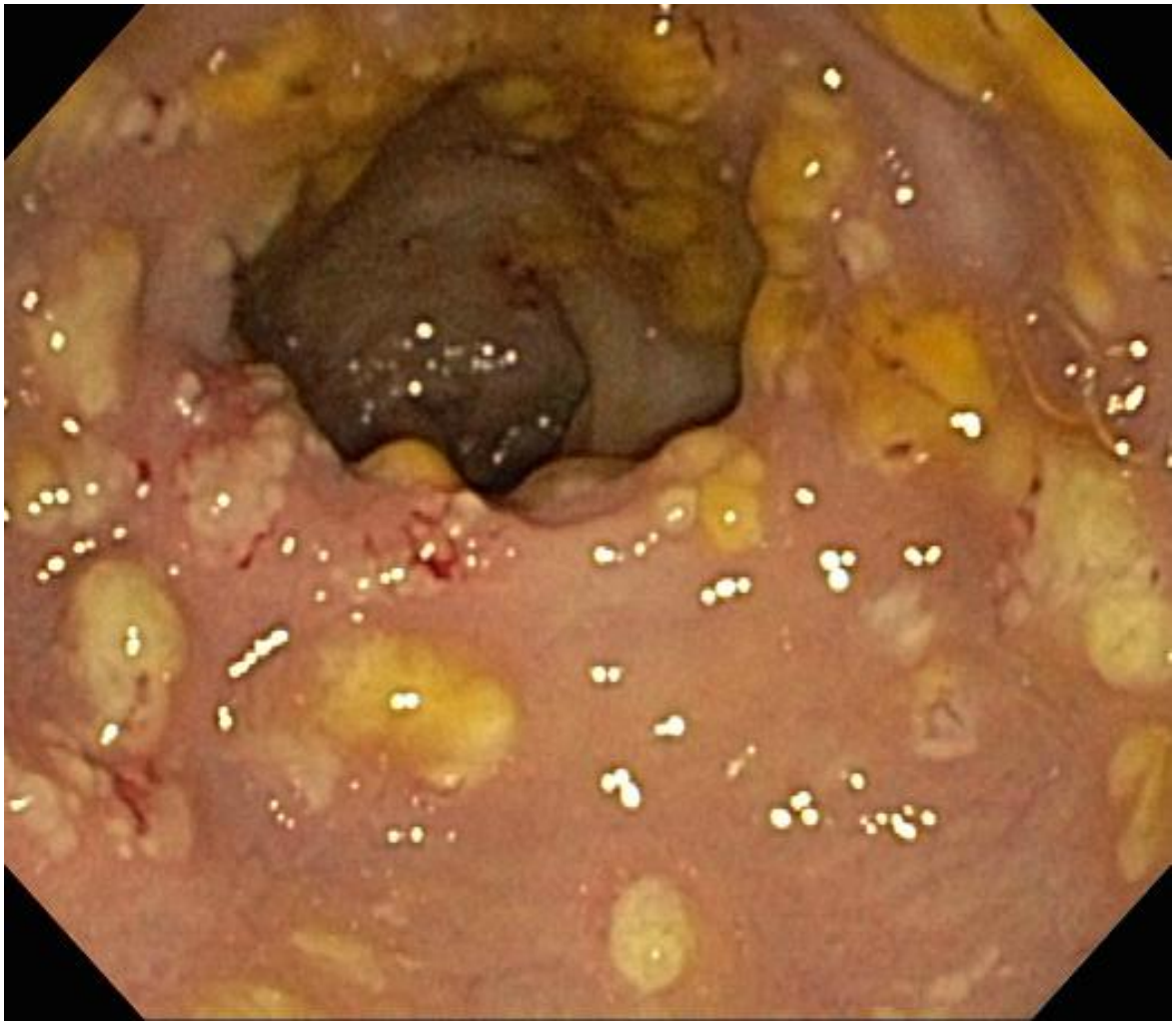
ANTIBIOTIC-DRIVEN DYSBIOSIS

The model of *C. difficile* infection



Vogt SL et al. Anaerobes 2015

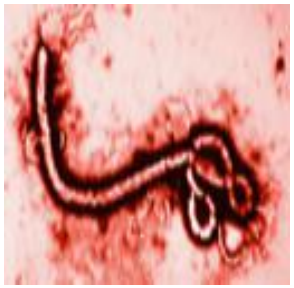
Colite pseudomembranosa



C DIFF INFECTION
Socio-economic burden in US -

Community acquired 52/100.000 159.700 cases ➡ 1,3% 30d-death

Health-care associated 93/100.000 293.300 cases ➡ 9,3% 30d-death



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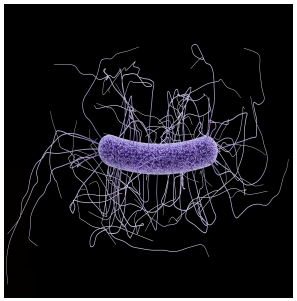


453.000 total cases

29.000 deaths

< 12.000 deaths since 2014 Ebola outbreak in W.Africa

4.800.000.000 $ (partial)

Quite similar to whole Sierra Leonean GDP

Lessa et al. N Engl J Med 2015

C DIFF INFECTION
Socio-economic burden in EU

	C difficile infection-positive samples per 10 000 patient bed-days			
	Reported rate, 2011–12 (n=458)	Measured rate, winter sampling (n=396)	Reported rate, 2012–13 (n=458)	Measured rate, summer sampling (n=396)
Austria	4·4	8·5	4·1	5·9
Belgium	5·5	7·6	4·0	3·1
Bulgaria	0·8	51·5	0·7	12·9
Czech Republic	4·4	33·0	6·2	4·8
Finland	14·9	16·3	28·7	8·8
France	3·9	4·6	3·3	2·9
Germany	10·2	27·9	11·0	21·7
Greece	3·4	3·1	3·9	3·8
Hungary	12·3	9·6	15·5	25·8
Ireland	4·8	12·2	9·1	0·0
Italy	9·5	9·4	7·2	14·3
Netherlands	7·4	0·0	5·3	12·1
Poland	8·6	29·4	8·2	48·3
Portugal	2·9	19·3	3·0	14·7
Romania	3·9	92·3	7·4	94·4
Slovakia	5·3	9·6	1·2	24·1
Spain	3·5	11·0	3·2	9·8
Sweden	16·2	9·7	13·3	14·1
UK	3·8	6·2	3·7	5·1
Europe	6·6	19·0	7·3	17·2

European point-prevalence

- **190 per 100.000 patient bed-days during winter**
- **172 per 100.000 patient bed days during summer**

Davies, KA, Longshaw CM et al., Lancet Infect Dis 2014

Quale è la prevalenza del
C. Diff nel DEA?

Clostridium difficile Infection Among US Emergency Department Patients With Diarrhea and No Vomiting

Fredrick M. Abrahamian, DO*; David A. Talan, MD; Anusha Krishnadasan, PhD; Diane M. Citron, BS; Ashley L. Paulick, BS; Lydia J. Anderson, PhD; Ellie J. C. Goldstein, MD; Gregory J. Moran, MD; for the EMERGEncy ID NET Study Group†

- Prospective study done in 10 US EDs on CDI among patients accessing the ER for diarrhea
- CDI was found in about 10% of those patients
- 44,2% reported a healthcare exposure

Table 2. Enrollment rates and *C difficile* prevalence among patients with diarrhea at 10 US EDs.

Site	Number Enrolled	*C difficile* Prevalence (%)*
New York, NY	25	2 (8.0)
Minneapolis, MN	56	1 (1.8)
Baltimore, MD	22	2 (9.1)
Kansas City, MO	23	1 (4.3)
Phoenix, AZ	52	7 (13.5)
Charlotte, NC	7	2 (28.6)
Albuquerque, NM	17	5 (29.4)
Portland, OR	67	7 (10.4)
Los Angeles, CA	100	13 (13.0)
Philadelphia, PA	53	3 (5.7)
Total	422	43 (10.2)

*Percentages reflect prevalence of *C difficile* by study site.

Disponible en ligne sur
ScienceDirect
www.sciencedirect.com
Elsevier Masson France
EM|consulte
www.em-consulte.com
Médecine et maladies infectieuses
ELSEVIER
Médecine et maladies infectieuses 46 (2016) 372–379

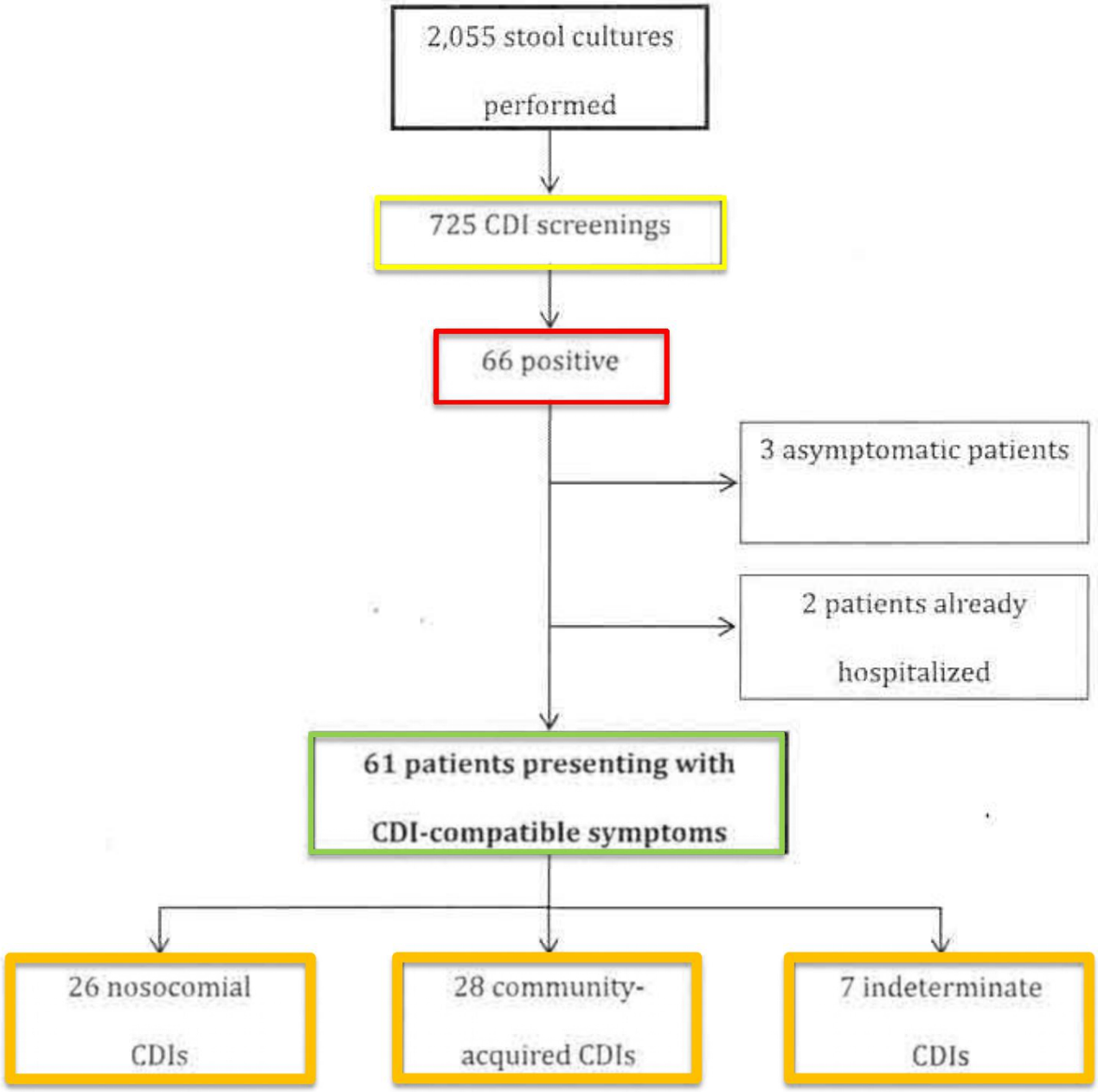
Original article

Community-acquired *Clostridium difficile* infections in emergency departments

Infections communautaires à Clostridium difficile dans les services d'urgence

D. Lefevre-Tantet-Etchebarne [a], V. Sivadon-Tardy [b], B. Davido [a,c], F. Bouchand [d], J. Grenet [e], E. Farfour [f], R. Getti [g], C. Duran [a], M. Chéron [h], E. Mathieu [i], J. Salomon [a], A. Dinh [a,c,*]

- Multicenter retrospective study over a 3 year-period of observation of both noscomial and community acquired CDI accessing the ER in France


2,055 stool cultures performed
725 CDI screenings
66 positive
3 asymptomatic patients
2 patients already hospitalized
61 patients presenting with CDI-compatible symptoms
26 nosocomial CDIs
28 community-acquired CDIs
7 indeterminate CDIs

Quali sono i fattori di rischio?

Table 3. Prevalence of *C difficile* among participants with and without traditional risk factors and other clinical features.

Clinical Features	Prevalence of Clinical Feature (%)	Prevalence of *C difficile* Infection (%)		Relative Risk (95% CI)
		Clinical Feature Present	Clinical Feature Absent	
Traditional risk factors				
Antibiotics in past* 3 mo	109/421 (25.9)	24/109 (22.0)	19/312 (6.1)	3.6 (2.0–6.6)
Overnight health care stay† in past* 3 mo	113/420 (26.9)	19/113 (16.8)	24/307 (7.8)	2.2 (1.2–3.9)
History of *C difficile* infection	14/421 (3.3)	4/14 (28.6)	39/407 (9.6)	3.0 (1.0–6.6)
Any traditional *C difficile* infection risk factor	171/419 (40.8)	26/171 (15.2)	17/248 (6.9)	2.2 (1.2–4.2)
Other clinical features				
≥65 y	59/422 (14.0)	8/59 (13.6)	35/363 (9.6)	1.4 (0.6–2.9)
≥10 episodes of diarrhea in past* 24 h	183/422 (43.4)	19/183 (10.4)	24/239 (10.0)	1.0 (0.6–1.9)
History of the following conditions				
IBD	16/422 (3.9)	1/16 (6.3)	42/406 (10.3)	0.6 (0.0–3.3)
HIV	15/422 (3.6)	2/15 (13.3)	41/407 (10.1)	1.3 (0.2–4.4)
Abdominal surgery	24/422 (5.7)	3/24 (12.5)	40/398 (10.1)	1.2 (0.3–3.6)
Pregnant	4/422 (1.0)	0/4	43/418 (10.3)	0.0 (0.0–6.2)
Gastric acid suppression‡	104/377 (27.6)	9/104 (8.7)	29/273 (10.6)	0.8 (0.4–1.7)
Health care worker	25/420 (6.0)	4/25 (16.0)	39/395 (9.9)	1.6 (0.5–4.1)

IBD, Inflammatory bowel disease.

*Past means before participant's ED visit.

†Overnight health care stay included hospitalized in the past 3 months (103/420; 24.5%), nursing home stay in the past 3 months (26/422; 6.2%), and currently in a nursing home (19/422; 4.5%).

‡Gastric acid suppression agents include use of antacids, H_2 blockers, or proton-pump inhibitors in the last month before onset of illness.

Abrahamian et al, Ann Emerg Med 2017

Table 2
Characteristics of community-acquired, indeterminate, and nosocomial CDI case patients managed at the emergency department.
Caractéristiques des cas d'ICD communautaires, indéterminées et nosocomiales consultant au service d'accueil des urgences.

	Community-acquired CDIs	Indeterminate CDIs	Nosocomial CDIs	*P* value[a]
Risk factors for CDI *n* patients (%)				
Aged > 65 years	12 (42.3)	5 (71.4)	19 (73.1)	0.030
History of CDI (in the previous 3 months)	1 (3.6)	1 (4.3)	4 (15.4)	NS[a]
Previous treatment increasing the risk of CDI occurrence	23 (82.1)	6 (85.7)	23 (88.5)	NS[a]
Antibiotic therapy (in the previous four weeks)	22 (78.6)	4 (57.1)	16 (61.5)	NS[a]
Chemotherapy (in the previous two months)	0	1 (4.3)	3 (11.5)	NS[a]
Immunosuppressant drugs (in the previous four weeks)	1 (3.6)	2 (28.6)	2 (7.7)	NS[a]
Proton pump inhibitor (in the previous four weeks)	6 (21.4)	4 (57.1)	13 (50)	0.045
Potential risk factors for CDI *n* patients (%)				
Contact with a hospitalized patient	0	1 (4.3)	Not looked for	
Outpatient consultation[b]	10 (35.7)	5 (71.4)	Not looked for	
Outpatient surgery in the previous 12 weeks	0	4 (57.1)	Not looked for	
Recent travel	4 (14.3)	4 (57.1)	Not looked for	
A family member working in a healthcare facility[c]	1 (3.6)	3 (42.9)	Not looked for	

Lefebre-Tantet-Etchebarne et al, Med Mal Inf 2016

MAEDICA – a Journal of Clinical Medicine
2015; 10(2): 163-169

MÆDICA - a Journal of Clinical Medicine

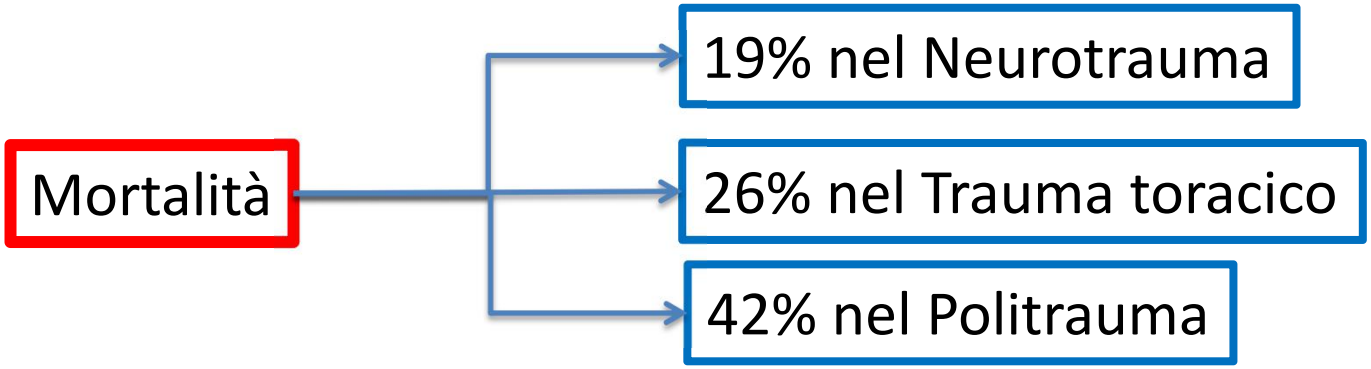
STATE OF THE ART

Clostridium Difficile Colitis in Trauma Patients – a Global Step by Step Review

Silviu MORTEANU[a,b]; Georgiana CHIRT[b]; Mircea BEURAN[a,b]

[a] "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[b] Department of Surgery, Emergency Clinical Hospital, Bucharest, Romania

- Il rischio di acquisire la CDI raddoppia nel pz con trauma



Come si esegue la diagnosi?

Test fecale

INFEZIONI GASTROENTERICHE E PARASSITARIE

Materiale: Feci

Assoluto campione: **110008090632** [Accettazione campione: 24/05/2017 14:24]

Clostridium difficile RG2

Antigene Glutammato Deidrogenasi (GDH) **POSITIVO**

(Test Immunoenzimatico)

Tossina A/B (tcdA/B) **POSITIVO**

SOLO LA POSITIVITA' AD ENTRAMBI ITEST E' INDICE DI PRESENZA DI C. DIFFICILE TOSSIGENO

(Test Immunoenzimatico)

Segure la procedura aziendale
(http intranet.policlinicogemelli.it radioprotezione-e-igiene-ospedaliera ?cp=3)

Validato da:

RG2 - [redacted]

European Review for Medical and Pharmacological Sciences 2015; 19: 3169-3172

A bedside test for *Clostridium Difficile* infection: an Emergency Department use. Preliminary results

D. MARSILIANI, G. DE MARCO, C. PETRUZZIELLO, G. MERRA, F. FRANCESCHI, V. OJETTI

Department of Emergency Medicine, Catholic University of the Sacred Heart, "A. Gemelli" Hospital, Rome, Italy

Tempo di esecuzione: 5 minuti

% Concordanza: 86%

Quali cautele utilizzare?

Quali cautele utilizzare?

1. Isolamento da contatto del paziente possibilmente in un box singolo e con bagno dedicato
2. In caso di mancanza di bagno dedicato utilizzare padelle monouso o dedicate e/o pannoloni da smaltire come rifiuti infetti
3. Il paziente deve evitare di toccare il personale non protetto, i familiari o accompagnatori e gli altri pazienti
4. Utilizzare materiale sanitario ed igienico monouso

Chiunque entri in contatto con il paziente con CDI deve indossare i seguenti DPI

2. Non toccarsi il viso o il cavo orale durante i contatti con il paziente
3. Favorire la frequente igiene del paziente
4. Smaltire i DPI tra i rifiuti ad alto rischio infettivo

Che terapia eseguire in PS?

Colite fulminante ⟶ Colectomia

Da eseguire quando compaiono segni di tossicità sistemica

FATTORI DI RISCHIO

- Old age (>70 years)
- prior CDI
- profound leukocytosis (>18,000/mm3)
- hemodynamic instability
- use of antiperistaltic medications,
- clinical triad of increasing abdominal pain, distention and diarrhea.

Sartelli et al. World Journal of Emergency Surgery (2015)

European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for *Clostridium difficile* infection

S. B. Debast[1], M. P. Bauer[2], E. J. Kuijper[3], on behalf of the Committee*

1) Department of Medical Microbiology, Radboud University Medical Center, Nijmegen, Departments of 2) Infectious Diseases and 3) Medical Microbiology, Centre for Infectious Diseases, Leiden University Medical Centre, Leiden, the Netherlands

Recommendations on oral antibiotic treatment of initial CDI: non-severe disease

Treatment	SoR	QoE	Ref(s)	Comment(s)
Metronidazole, 500 mg three times daily 10 days	A	I	[77,84–88]	No statistically significant difference in cure rate between metronidazole and vancomycin or teicoplanin. Statistically significant difference in sustained clinical cure between metronidazole and vancomycin in favour of vancomycin in one study [2,88] (and pooled results of two randomized controlled trials published only in abstract form [92,123,124]).
Vancomycin, 125 mg four times daily 10 days	B	I	[70,76,78,80,82,84,88,90,91]	Cochrane analysis: teicoplanin significantly better than vancomycin for bacteriological cure and borderline superior in terms of symptomatic cure [2].
Fidaxomicin, 200 mg twice daily 10 days	B	I	[70,89,91]	Evidence limited to two Phase III studies. Fewer recurrences as compared to vancomycin, except for *C. difficile* PCR ribotype 027 [91].
Vancomycin, 500 mg four times daily 10 days	C	I	[77,79–82,84]	Vancomycin: Equal cure rate 500 mg four times daily orally compared with 125 mg four times daily orally [80].
Stop inducing antibiotic(s) and observe the clinical response for 48 h	C	II	[116,117]	Rate of spontaneous resolution unknown in mild CDI. Studies performed before increased incidence of hypervirulent strains.

Debast SB, Clin Microbiol Infect 2014

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1) Department of Medical Microbiology, Radboud University Medical Center, Nijmegen, Departments of 2) Infectious Diseases and 3) Medical Microbiology, Centre for Infectious Diseases, Leiden University Medical Centre, Leiden, the Netherlands

Recommendations on oral antibiotic treatment of initial CDI: severe disease

Treatment	SoR	QoE	Ref(s)	Comment(s)
Vancomycin, 125 mg four times daily for 10 days	A	I	[70, 88, 90, 91]	Cure rate higher as compared with metronidazole in severe CDI [88][a]
Vancomycin 500 mg four times daily for 10 days	B	III (I[a])	[80]	Randomized controlled trial on dose effectiveness: no significant differences in measurable responses of high-dose compared to low-dose regiment. However: results not stratified for severity of illness [80][a].
Fidaxomicin 200 mg twice daily for 10 days	B	I	[70,89,91]	Evidence limited to two Phase III studies [70,91]. Fewer recurrences compared with vancomycin 125 mg four times daily in severe disease (except for PCR ribotype 027). No data on the efficacy in severe life-threatening disease and/or toxic megacolon: excluded from both studies.
Metronidazole, 500 mg three times daily for 10 days	D	I	[88]	Cure rate lower as compared with vancomycin in severe CDI [88]. Intention to treat analysis not reported. Extremely severe CDI excluded[b]. Differences in symptomatic cure of metronidazole versus vancomycin not statistically significant in a pooled analysis [2]. ICU admission and hypoalbuminaemia (= disease severity) predictors of metronidazole failure [119].

[a]Two studies reported in abstract form confirm the superiority of vancomycin over metronidazole for treatment of (severe) CDI [92,124,125].

Debast SB, Clin Microbiol Infect 2014

European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for *Clostridium difficile* infection

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1) Department of Medical Microbiology, Radboud University Medical Center, Nijmegen, Departments of 2) Infectious Diseases and 3) Medical Microbiology, Centre for Infectious Diseases, Leiden University Medical Centre, Leiden, the Netherlands

Recommendations on oral antibiotic treatment of mild/moderate initial CDI with risk for recurrent CDI or first recurrence

Treatment	SoR	QoE	Ref(s)	Comment(s)
Vancomycin, 125 mg four times daily for 10 days	B	I	[70,82,90,91]	No statistically significant difference in recurrence rate between vancomycin and teicoplanin [2,82,84].
Fidaxomicin, 200 mg twice daily for 10 days	B	I	[70,89,91]	Evidence limited to two Phase III studies [70,91]. Retrospective subset analysis: fewer secondary recurrences with fidaxomicin (n = 16/79 patients) as compared with vancomycin (n = 26/80 patients) after treatment of a first recurrence [144]. Fidaxomicin was not associated with fewer recurrences in CDI due to PCR ribotype 027 as opposed to non-027 [70].
Metronidazole, 500 mg three times daily for 10 days	C	I	[27,88]	Recurrence rate: metronidazole not inferior to vancomycin for treatment of mild primary CDI [2,82,88] or after a first recurrence [27]. Vancomycin significantly more effective in bacteriological cure than metronidazole in recurrent CDI [69].
Vancomycin, 500 mg four times daily for 10 days	C	III	[80]	One randomized controlled trial on dose effectiveness in primary CDI: no significant differences in responses of high-dose compared with low-dose regimens vancomycin. However, results not stratified for recurrent CDI [80].

Debast SB, Clin Microbiol Infect 2014

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S. B. Debast[1], M. P. Bauer[2], E. J. Kuijper[3], on behalf of the Committee*

1) Department of Medical Microbiology, Radboud University Medical Center, Nijmegen, Departments of 2) Infectious Diseases and 3) Medical Microbiology, Centre for Infectious Diseases, Leiden University Medical Centre, Leiden, the Netherlands

Recommendations on oral antibiotic treatment of multiple recurrent CDI (more than one relapse)

Treatment	SoR	QoE	Ref(s)	Comment(s)
Vancomycin, 125 mg four times daily for 10 days, followed by pulse regimen (125–500 mg/day every 2–3 days) for at least 3 weeks.	B	Ik	[69,150]	Retrospective case cohort of two placebo/antibiotic trials [69]; [126,146]. Observational study: [150]. Expert opinion [3].
Vancomycin, 125 mg four times daily for 10 days, followed by taper regimen: gradually decreasing the dose to 125 mg per day.	B	Ik	[69,150]	Retrospective case cohort of two placebo/antibiotic trials [69]; [125,146]. Observational study: [150]. Expert opinion [3].
Fidaxomicin, 200 mg twice daily for 10 days	B	IIrt	[75,144]	Evidence limited to two Phase III studies [70,91]. Retrospective subset analysis: fewer recurrences as compared to vancomycin treatment after first recurrence [144]. Systematic review: [75]. Efficacy after multiple recurrences was not investigated [144].
Vancomycin, 500 mg four times daily for 10 days	C	IIrt	[69,75]	Retrospective case cohort of two placebo/antibiotic trials: [126,146]. Trend for lower recurrence frequency for high-dose vancomycin [69]. Systematic review: [75].
Metronidazole, 500 mg three times daily for 10 days	D	IIrt	[69,75]	Retrospective case cohort of two placebo/antibiotic trials: [126,146]. Trend for lower recurrence frequency for high-dose vancomycin and low-dose metronidazole [69]. Systematic review: [75].

Debast SB, Clin Microbiol Infect 2014

Esistono terapie alternative?

FMT: route of administration

- Until 1989 enema was the most common technique

- Alternative methods carried out over the years:
  - *Nasogastric/Nasoduodenal tube*
  - *Gastroscopy*
  - *Colonoscopy*
  - *Enema*

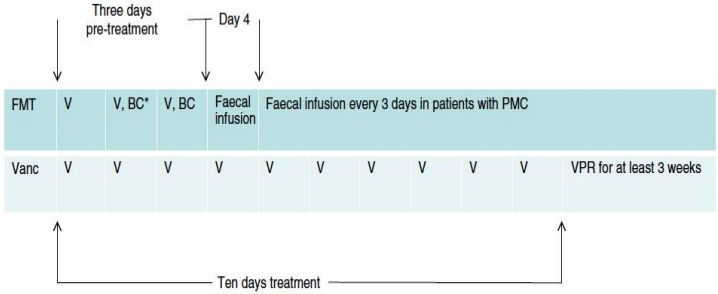
- Colonoscopic approach is favored over fecal enema (reaching of entire colon)

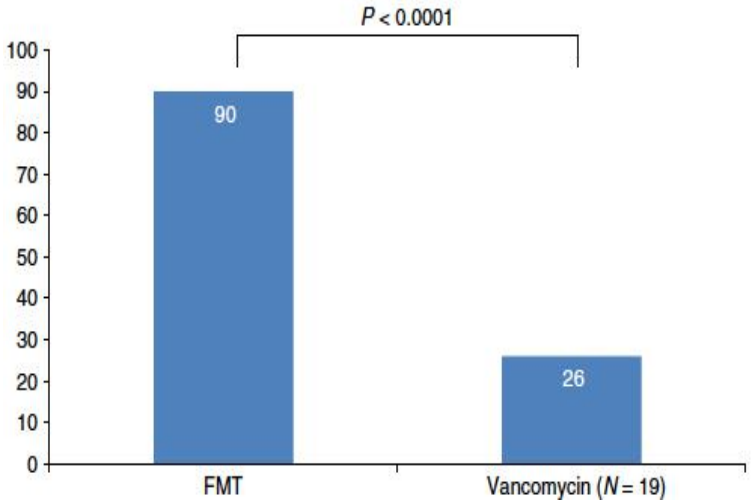
Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent *Clostridium difficile* infection

G. Cammarota*, L. Masucci†, G. Ianiro*, S. Bibbò*, G. Dinoi*, G. Costamagna‡, M. Sanguinetti† & A. Gasbarrini*

RCT: FMT colonoscopy

- ★ **Short vanco+FMT vs Standard vanco**
- ★ **Study stop after a 1-year interim analysis**
- ★ **Resolution of CDAD**
  - FMT group (n=20): 90%
  - Vancomycin group (n=19): 26%
- ★ **5/7 pts with severe disease (PMC): progressive disappearance of PMC and resolution of CDAD after multiple FMT**
- ★ **No significant adverse events**





Cammarota et al – APT 2015

European Consensus Conference on Faecal Microbiota Transplantation in Clinical Practice

FMT for recurrent *Clostridium difficile* infection

Statement: FMT is recommended as a highly effective and safe treatment option for both mild and severe rCDI. Its implementation in clinical practice is recommended

Quality of evidence: high **Strength of recommendation:** strong

FMT for refractory *Clostridium difficile* infection

Statement: FMT can be considered as a treatment option for refractory CDI

Quality of evidence: high **Strength of recommendation:** strong

FMT for the first episode of *Clostridium difficile* infection

Statement: There is insufficient evidence to recommend FMT as a treatment for the first episode of CDI. Additional studies are needed to determine if FMT could have an advantage over antibiotics for this indication

Quality of evidence: low **Strength of recommendation:** weak

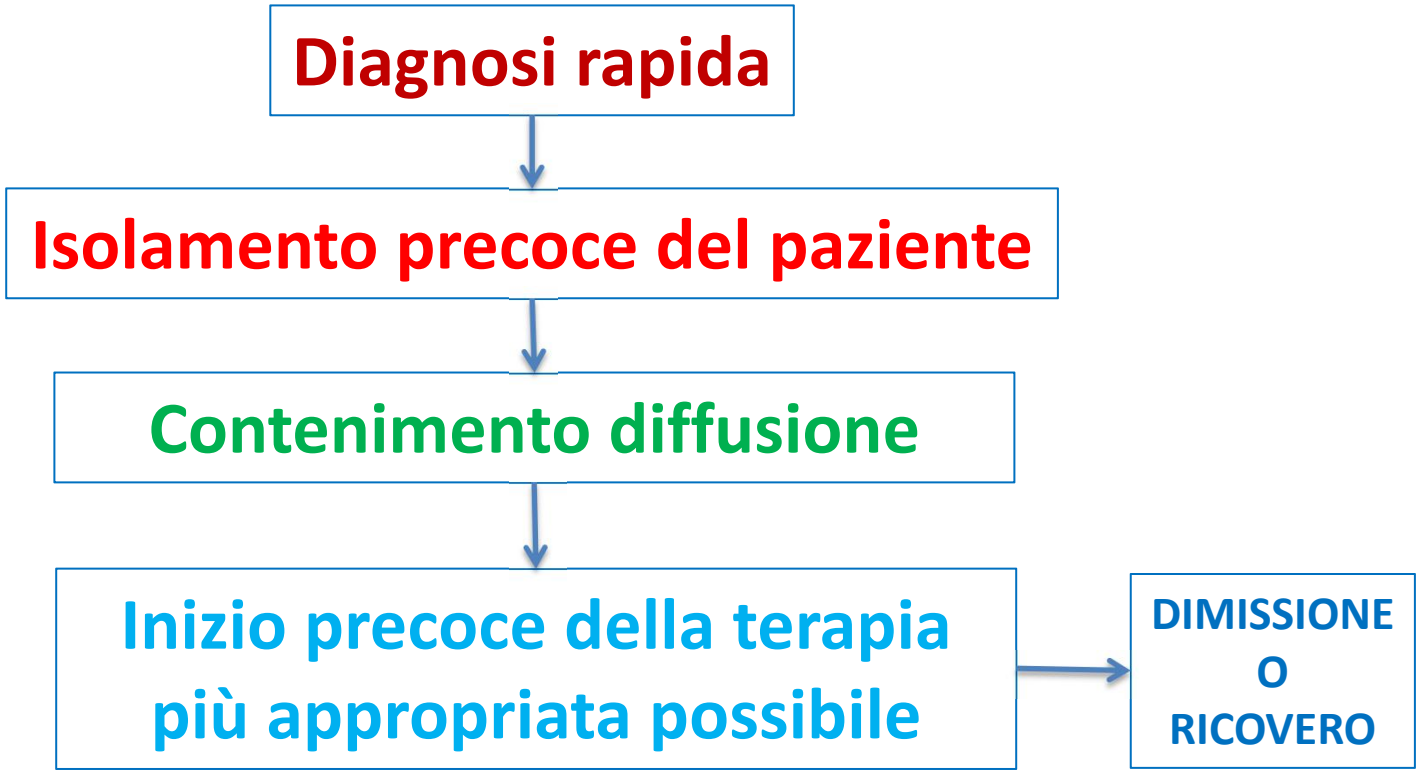
Cammarota et al – Under submission

Take Home Messages

- La CDI è divenuta una condizione sempre più frequente nei pazienti che accedono ai DEA
- La diarrea è sicuramente il sintomo di allarme più caratteristico riportato dai pazienti
- Occorre conoscere bene tutti i fattori di rischio

Take Home Messages

★Gli obiettivi da raggiungere su questi pazienti sono molteplici:



ISCRIZIONE GRATUITA CON CREDITI ECM

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Thanks!