

**Convegno Nazionale  
Terapia Antibiotica dei  
patogeni multiresistenti  
(MDRO):  
una sfida aperta**



**Cona (Fe) 15 giugno 2018**

**Nuovo "Arcispedale S. Anna"  
Aula Congressi**

# ***Clostridium difficile:* prevenzione e terapia**

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Divisione di Malattie Infettive



Ospedale  
di Cremona

Sistema Socio Sanitario



Regione  
Lombardia

ASST Cremona

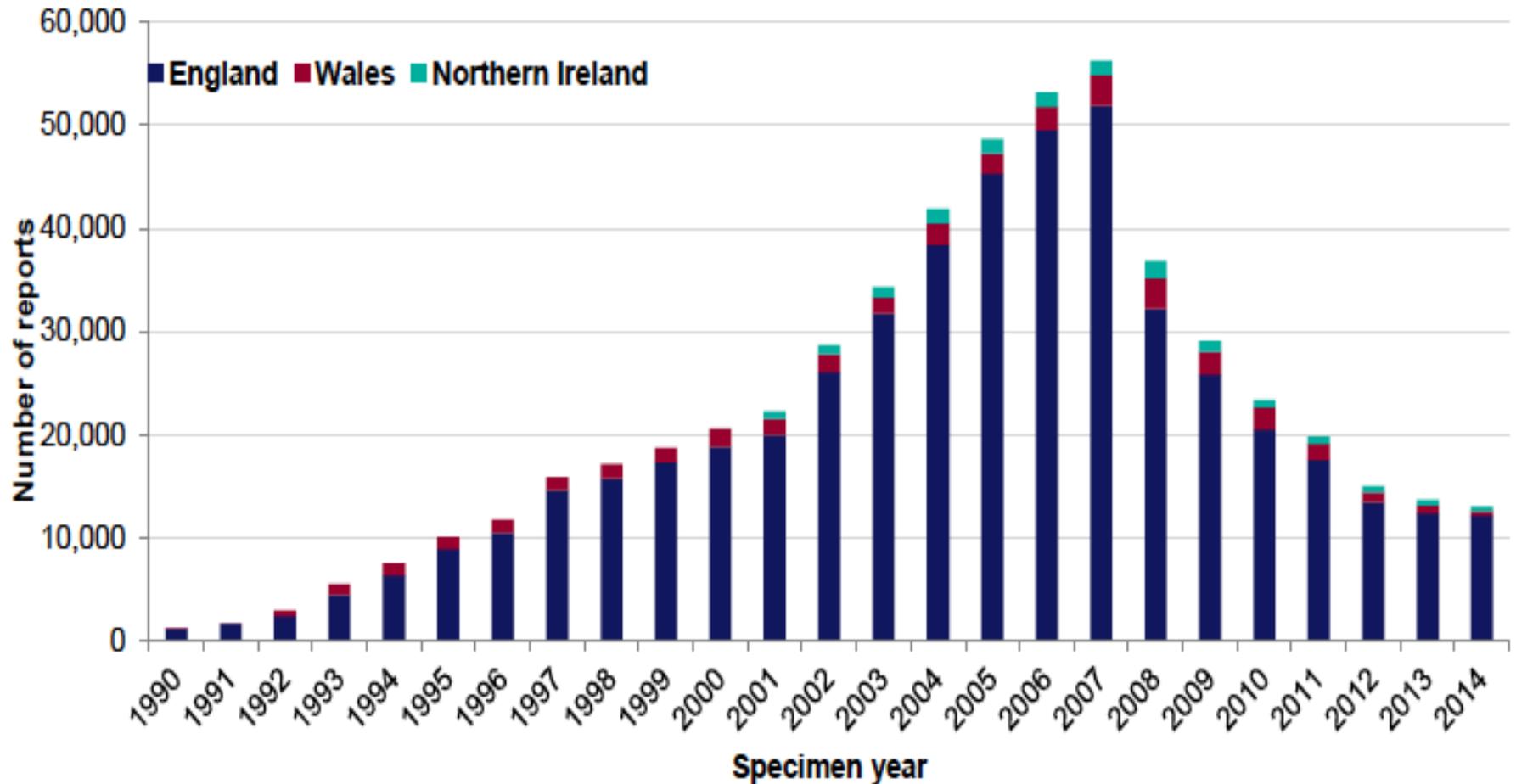
# Conflitti di interesse

- Progetti: CCM, SIMIT
- Relazioni a congressi: Pfizer
- Partecipazione a congressi: Angelini, Janssen, Merck, ViiV

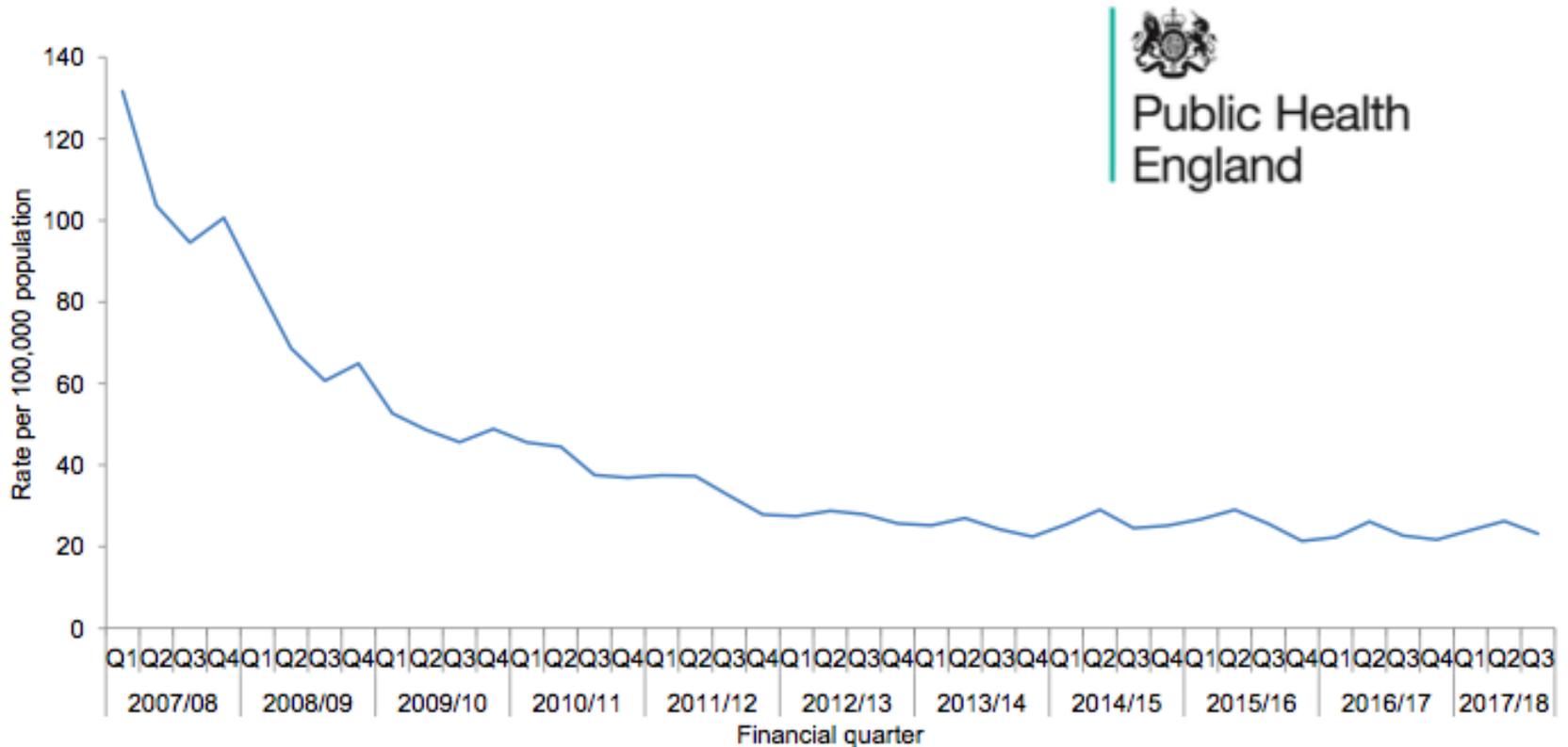
- Introduzione
- Terapia
- Prevenzione
- Un'esperienza personale
- Conclusioni

- **Introduzione**
- Prevenzione
- Terapia
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- Conclusioni

# 1a. Epidemiologia – Regno Unito



# 1b. Epidemiologia – Inghilterra



# Fattori di rischio

- Età >65 anni
- Terapia antibiotica
  - Cefalosporine di III generazione
  - Clindamicina
  - Fluorochinoloni
  - BLBLI
- Inibitore di pompa protonica (?)

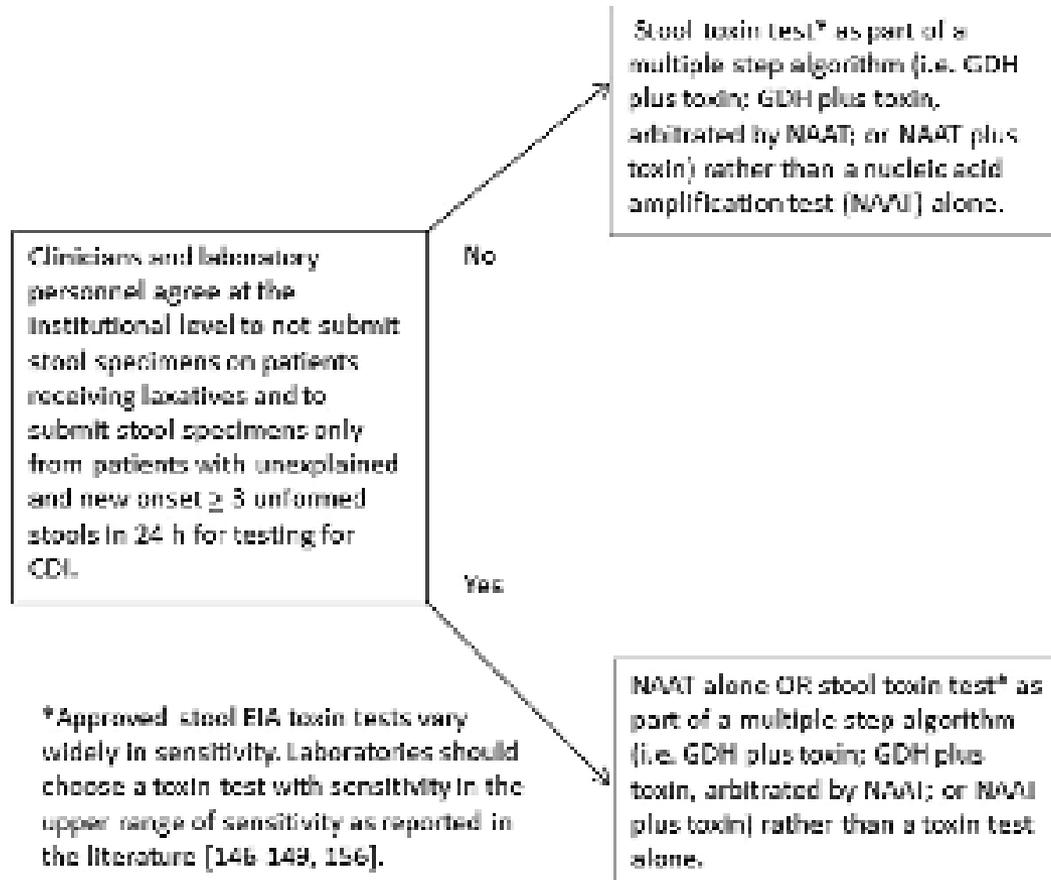
## 2. Classificazione delle infezioni da *Clostridium difficile* (CDI)

Tipo	Sigla	Tempi
CDI associato alle cure sanitarie	HA	- Dal 3° giorno di ricovero - In comunità, entro 4 settimane dal ricovero
CDI di comunità	CA	-In comunità e nessun contatto nelle 12 settimane precedenti -Nei primi 2 giorni di ricovero e nessun contatto con le strutture sanitarie nelle 12 settimane prec.
CDI di origine sconosciuta	U	-Un contatto con le strutture sanitarie 4-12 settimane prima del ricovero

## 3a. Diagnosi

- Eseguire la ricerca nelle persone che hanno  $\geq 3$  scariche di feci non formate in 24 ore
- Non ripetere l'indagine
- Non ripetere prima di 7 giorni nelle sospette recidive

# 3b. Diagnosis



# 3c. Diagnosi

## Recommendations

### Outbreak and endemic setting

Strong recommendation: A two-stage test (GDH or NAAT for toxin genes followed by a highly sensitive toxin test or GDH in combination with a toxin test) is recommended to diagnose CDI. In the case of a negative result of the toxin test, NAAT (if not already part of the first diagnostic step) or toxigenic culture can be performed based on clinical evaluation or local infection prevention requirements. (Moderate-quality evidence as defined by the European Society of Clinical Microbiology and Infectious Diseases: update of the diagnostic guidance document for *Clostridium difficile* infection [49]).

# 4a. Sorveglianza delle infezioni da *Clostridium difficile*

- Minimo sindacale: sorveglianza delle HO
- HA: casi per 10.000 giornate di degenza
- CA: casi per 1.000 ricoveri

# 4b. Sorveglianza

## Identificazione di un'epidemia

### Threshold to distinguish endemic and outbreak situations [62]

#### For wards/units $\geq 20$ beds:

3 cases of healthcare-associated CDI identified on 1 ward/unit within a 7-day period or 5 cases within a 4-week period

#### For wards/units $< 20$ beds:

2 cases of healthcare-associated CDI identified on 1 ward/unit within a 7-day period or 4 cases within a 4-week period

# 5. Restituzione dei dati

- Epidemia: fornire i tassi di infezione in modo tempestivo a livello sia di ospedale sia di reparto
- Endemia: fornire i tassi di infezione in modo tempestivo

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# Prevenzione

**Farmaci**



**Selezione**

**Mani**



**Trasmissione**

# Linee guida europee 1995 - 2011

Concordance of recommendations in national European guidelines with IA-ranked recommendations in the ECDC guidance (PROHIBIT study group)

Country (publication year)	No 'test of cure'	Education of staff	Information for visitors	Do not share thermometers (medical devices in general)	Avoid electronic thermometers with disposable sheaths	Stop AB treatment as soon as possible
ECDC (2008)	Rec. (IA; 1a)	Rec. (IA; 1a, 2b, 4, 5)	Rec. (IA; 1a, 2b, 4, 5)	Rec. (IA; 1b, 2b); (pat. specific IB)	Rec. (IA; 1b, 2b)	Rec. (IA; 1a)
Austria (2007)	Rec. (IA)	Rec. (IA)	Education in outbreak	Rec. IA [pat. specific (IB)]	Not explicitly mentioned	Rec. (IA)
Belgium (2008)			Rec.	Rec.	Not explicitly mentioned	Rec.
Denmark (2011)			Rec.	Avoid rectal thermometer (pat. specific)	Not explicitly mentioned	
Finland (2009)	Rec.	Rec.		Rec. (pat. specific)	Not explicitly mentioned	Rec.
France (2010)	Rec.		Rec.	Rec. (pat. specific)	Not explicitly mentioned	
Germany (2009)	Rec.	Rec.		Rec. (pat. specific)	Not explicitly mentioned	Rec.
Ireland (2008)	Rec.	Rec.	Rec.	Rec. (pat. specific)	Not explicitly mentioned	Rec.
Italy (2009)	Rec. (IA)	Rec. (IA)	Rec. (IA)	Rec. (IA) (pat. specific)	Rec. (IA)	Rec. (IA)
Latvia (2007)			Rec.	Rec. (pat. specific)	Not explicitly mentioned	
Luxembourg (2007)				(Pat. specific)	Not explicitly mentioned	Rec.
Malta (SHEA 2008)	Rec. (B-III)	Rec. (B-III)	Rec. (B-III)	Rec. (B-III) (pat. specific)	Not explicitly mentioned	
Netherlands (2006)				(Pat. specific)		
Sweden (2006)				(Pat. specific)		Rec.
Switzerland (1995)				(Pat. specific) (B)		Rec. (B)
UK – England (2008)		Rec. (B)	Rec. (A)	Rec. (IA) [single use (IB)]		
UK – Scotland (2009)	Rec. (IA)	Rec. (IA)	Rec. (IA)		Rec. (IA)	Rec. (IA)

# Linee guida europee 1995 - 2011

Country (publication year)	Placing of patients		Environmental disinfecting agent	Hand hygiene		Surveillance
	Single room isolation	Cohorting		Wearing of gloves	Washing or disinfecting	
ECDC (2008)	Rec. (IB; 1b, 2b)	Possible (IB; 1b, 4)	Chlorine-based (IB; 2b, 2c, 4)	Rec. (IB; 2a, 2b, 2c)	Washing (IB; 2a, 2b, 2c)	ec. (IB; 2b, 3b, 4, 5)
Austria (2007)	Rec. (IB)	Possible (IB)	Sporicidal (IA)	Rec. (IB)	Disinfecting then washing (IB)	ec. (IB)
Belgium (2008)	Rec.	Possible	Chlorine-based	Rec.	Washing then disinfecting	ec. (mandatory)
Denmark (2011)	Rec.	Possible	Chlorine-based	Rec.	Washing then disinfecting	
Finland (2009)	Rec.	Possible	Chlorine-based	Rec.	Washing then disinfecting	ec.
France (2010)	Rec.	Possible	Chlorine-based	Rec.	Washing then disinfecting	ec.
Germany (2009)	Rec.	Possible	H <sub>2</sub> O <sub>2</sub> or chlorine	Rec.	Disinfecting then washing	ec.
Ireland (2008)	Rec.	Possible	Chlorine-based	Rec.	Only washing	ec. (mandatory)
Italy (2009)	Rec. (IB)	Possible (IB)	Chlorine-based (IB)	Rec. (IB)	Only washing (IB)	ec. (IB)
Latvia (2007)	Rec.	Possible	Chlorine-based	Rec.	Washing or disinfecting with chlorhexidine	
Luxembourg (2007)			Chlorine-based	Rec.	Only washing	ec.
Malta (SHEA 2008)	Rec. (B-III)	Possible	Chlorine-based (B-I)	Rec. (A-I)	Only washing (B-III)	ec. B-III
Netherlands (2006)	Rec.	Possible	Not specified	Rec.	Only washing	
Sweden (2006)	Rec. (I)	Possible	Peracetic acid	Rec.	Washing then disinfecting (I)	
Switzerland (1995)	Rec.		Mechanics of cleaning more important	Rec.	Disinfecting or washing with antiseptic soap	
UK – England (2008)	Rec. (B)	Possible	Chlorine-based (B)	Rec. (B)	Washing then disinfecting (B)	ec. (B) (mandatory)
UK – Scotland (2009)	Rec. (IB)	Possible (IB)	Chlorine-based (IB)	Rec. (IB)	Only washing (IB)	ec. (IB) (mandatory)

# 1. Isolamento

- **Guanti**
- **Sovracamice**
- Igiene mani e corpo del paziente
- Materiale dedicato

# 2. Igiene delle mani

## Recommendations

No specific recommendations regarding the most effective technique/product for removal of *C. difficile* spores can be made.

## Outbreak setting

- Conditional recommendation: Switch from AHR to hand washing due to the lack of *in vitro* activity of AHR against spores (very low quality of evidence).
- Conditional recommendation: Initiate interventions to increase hand hygiene compliance (very low quality of evidence).

## Endemic setting

- Conditional recommendation: Do not switch from AHR to hand washing with soap and water to reduce the incidence of CDI (very low quality of evidence).
- Conditional recommendation: Initiate interventions to increase hand hygiene compliance (very low quality of evidence).

Lavaggio delle mani con **acqua e sapone:**

iperendemia, epidemia, aree cutanee contaminate

# SAVE LIVES



Clean **Your** Hands



#SafeHANDS

# 3. Stewardship degli antibiotici

## Recommendations

### Outbreak setting

- Strong recommendation: Restriction of antibiotic agents/classes is effective in reducing CDI rates (low quality of evidence).
- Strong recommendation: Reducing the duration of antibiotic therapy is effective in reducing CDI rates (very low quality of evidence).

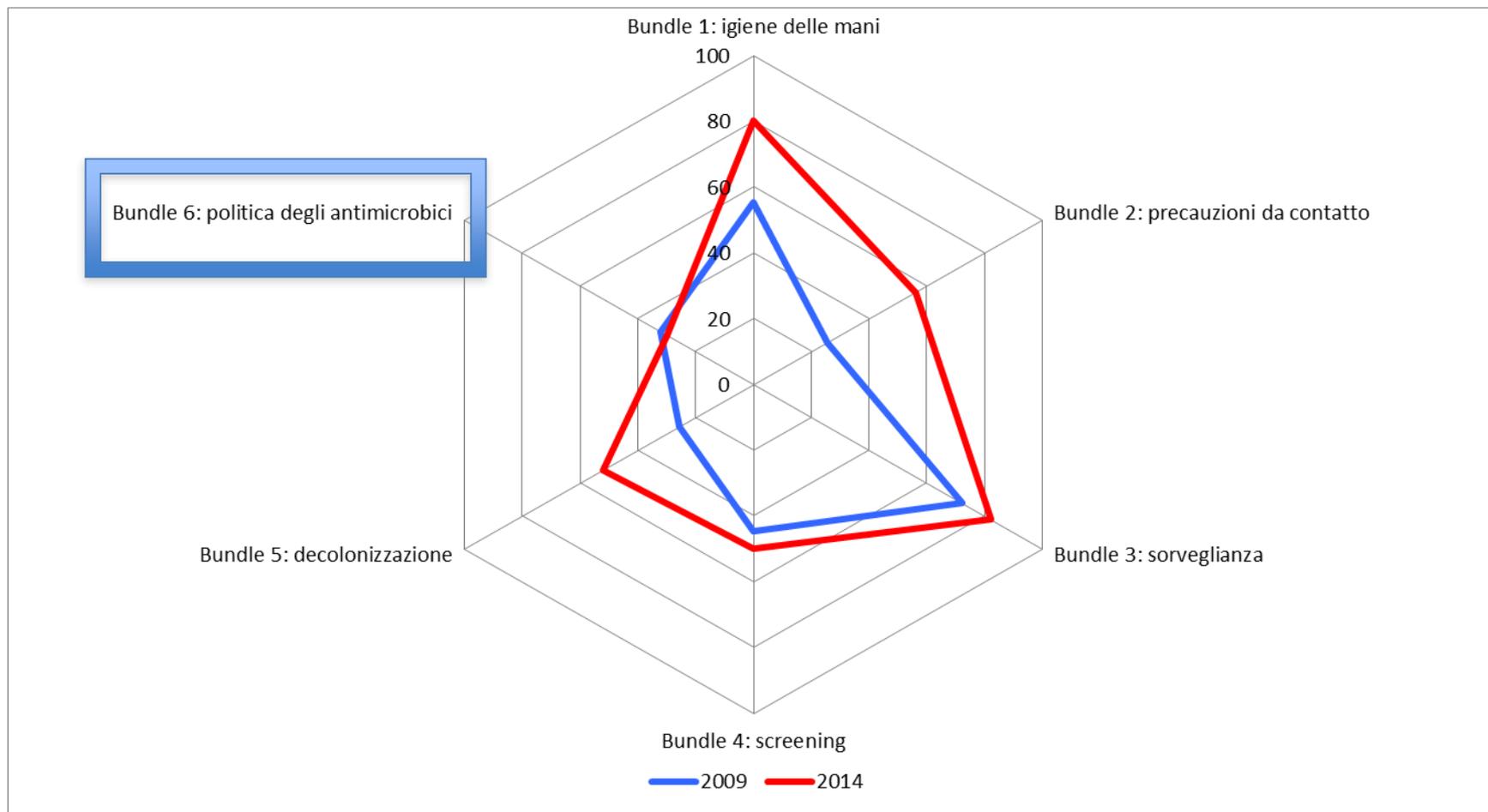
### Endemic setting

- Strong recommendation: Restriction of antibiotic agents/classes is effective in reducing CDI rates (moderate quality of evidence).
- Strong-recommendation: Reducing the duration of antibiotic therapy is effective in reducing CDI rates (very low quality of evidence).

# Programmi di stewardship antibiotica

## Progetto ProSA-2

50 ospedali, 16% dei ricoveri in Italia



# 4. Formazione

## Recommendations

### Outbreak setting

- **Strong recommendation:** Educate healthcare workers on prevention of CDI to enhance their knowledge and skills on prevention strategies.

Due to the lack of studies elucidating the impact of education of healthcare workers in outbreak settings formal grading of the evidence was not performed.

- **Conditional recommendation:** Implement intensified teaching in conjunction with other intervention measures to reduce CDI rates (very low quality of evidence)

### Endemic setting

- **Strong recommendation:** Educate healthcare workers on prevention of CDI to enhance their knowledge and skills on prevention strategies (very low quality of evidence).
- **Conditional recommendation:** Implement intensified teaching in conjunction with other intervention measures to reduce CDI rates (very low quality of evidence)

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# Quale terapia?

- Quale paziente?
- Definire la gravità

# Stadiazione della gravità

1–3 Points, Mild to Moderate Disease; 4–6 Points, Severe Disease; ≥7 Points, Severe Complicated Disease	
Criteria	Points
Immunosuppression and/or chronic medical condition	1
Abdominal pain and/or distention	1
Hypoalbuminemia (<3 g/dL)	1
Fever (>38.5°C)	1
ICU admission	1
CT scan with nonspecific findings of pancolitis, ascites, and/or bowel wall thickening	2
WBC count > 15,000 or <1,500 and/or band count > 10%	2
Creatinine 1.5-fold > baseline	2
Abdominal peritoneal signs	3
Vasopressors required	5
Mechanical ventilation required attributed to CDAD	5
Disorientation, confusion, or decreased consciousness	5

\*This scoring system is for patients with a diagnosis of CDAD and is not yet validated.  
CDAD: Clostridium difficile associated disease.

Variable	Odds Ratio	95% Confidence Interval	Points
Age > 70 y	3.80	1.14–13.68	2
WBC count ≥ 20,000/μL or ≤2,000/μL	1.81	0.54–6.05	1
Cardiorespiratory failure*	285	24–21,491	7
Diffuse abdominal tenderness	189	27–8,429	6

\*Cardiorespiratory failure: the need for mechanical ventilation or vasopressor support.

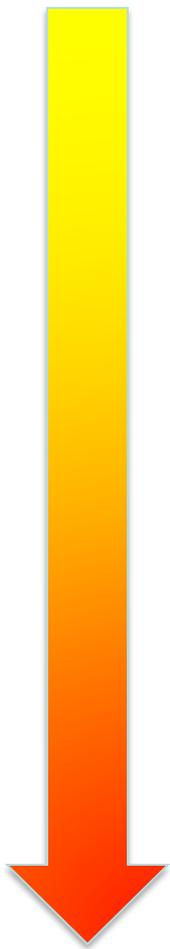
≥6 punti: grave

1-3 punti: lieve – moderato

4-6 punti: grave

≥7 punti: grave complicato/fulminante

# Stadiazione della gravità



CDI Disease Category	Clinical and Laboratory Signs	Associated Risk Factors
Mild to moderate	Diarrhea without systemic signs of infection, white blood cell count <15 000 cells/mL, and serum creatinine <1.5 times baseline <sup>15</sup>	Antibiotic use, previous hospitalization, longer duration of hospitalization, use of proton pump inhibitors, receipt of chemotherapy, chronic kidney disease, and presence of a feeding tube <sup>10-14</sup>
Severe	Systemic signs of infection, and/or white blood cell count ≥15 000 cells/mL, or serum creatinine ≥1.5 times the premorbid level <sup>15</sup>	Advanced age, infection with BI/NAP1/027 strain <sup>114,115</sup>
Severe, complicated	Systemic signs of infection including hypotension, ileus, or megacolon <sup>15</sup>	See above, <sup>a</sup> plus recent surgery, history of inflammatory bowel disease, and intravenous immunoglobulin treatment <sup>43</sup>
Recurrent	Recurrence within 8 weeks of successfully completing treatment for CDI <sup>16,20</sup>	Patient age ≥65 y, concomitant antibiotic use, presence of significant comorbidities, concomitant use of proton pump inhibitors, and increased initial disease severity <sup>16</sup>

# Sospensione del trattamento iniziale

**Antibiotic treatment for *Clostridium difficile* associated diarrhea in adults (Review)**

Nelson RL, Kelsey P, Leeman H, Meardon N, Patel H, Paul K, Rees R, Taylor B, Wood E, Malakun R

Efficacia 15%

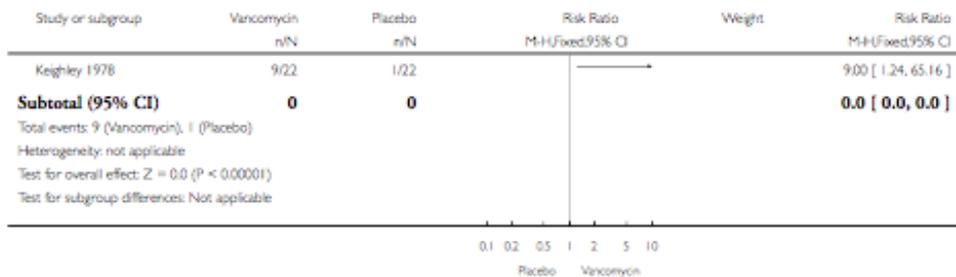
Usata un tempo

## Analysis 1.1. Comparison 1 Vancomycin versus Placebo, Outcome 1 Symptomatic Initial Response.

Review: Antibiotic treatment for *Clostridium difficile*-associated diarrhea in adults

Comparison: 1 Vancomycin versus Placebo

Outcome: 1 Symptomatic Initial Response

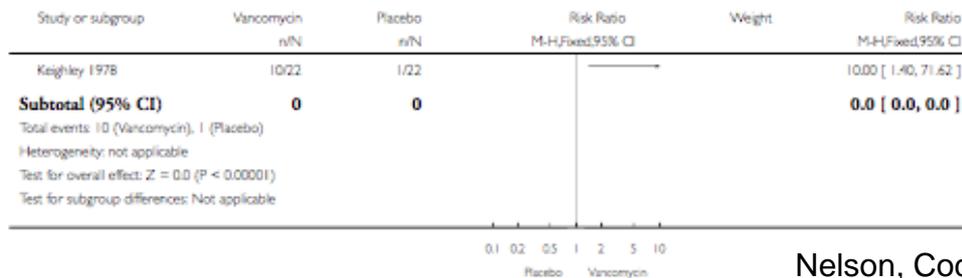


## Analysis 1.2. Comparison 1 Vancomycin versus Placebo, Outcome 2 Bacteriologic Initial Response.

Review: Antibiotic treatment for *Clostridium difficile*-associated diarrhea in adults

Comparison: 1 Vancomycin versus Placebo

Outcome: 2 Bacteriologic Initial Response



# Metronidazolo - Vancomicina

## Intervention: Metronidazole versus Vancomycin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Metronidazole versus Vancomycin				
Symptomatic cure with all exclusions treated as failures Follow-up: mean 4 weeks	792 per 1000 <sup>1</sup>	713 per 1000 (665 to 768)	RR 0.9 (0.84 to 0.97)	872 (4 studies)	⊕⊕⊕⊕ moderate <sup>2</sup>	
Bacteriologic cure Follow-up: mean 4 weeks	529 per 1000 <sup>1</sup>	449 per 1000 (328 to 619)	RR 0.85 (0.62 to 1.17)	163 (2 studies)	⊕⊕⊕⊕ very low <sup>2,3</sup>	
Cure (combined symptomatic and bacteriologic cure) - mild disease Follow-up: mean 4 weeks	841 per 1000 <sup>1</sup>	740 per 1000 (597 to 917)	RR 0.88 (0.71 to 1.09)	90 (1 study)	⊕⊕⊕⊕ very low <sup>3,4,5</sup>	
Cure (combined symptomatic and bacteriologic cure) - severe disease	711 per 1000 <sup>1</sup>	526 per 1000 (369 to 739)	RR 0.74 (0.52 to 1.04)	82 (1 study)	⊕⊕⊕⊕ very low <sup>3,4,5</sup>	

# Teicoplanina - Vancomicina

## Intervention: Teicoplanin versus Vancomycin

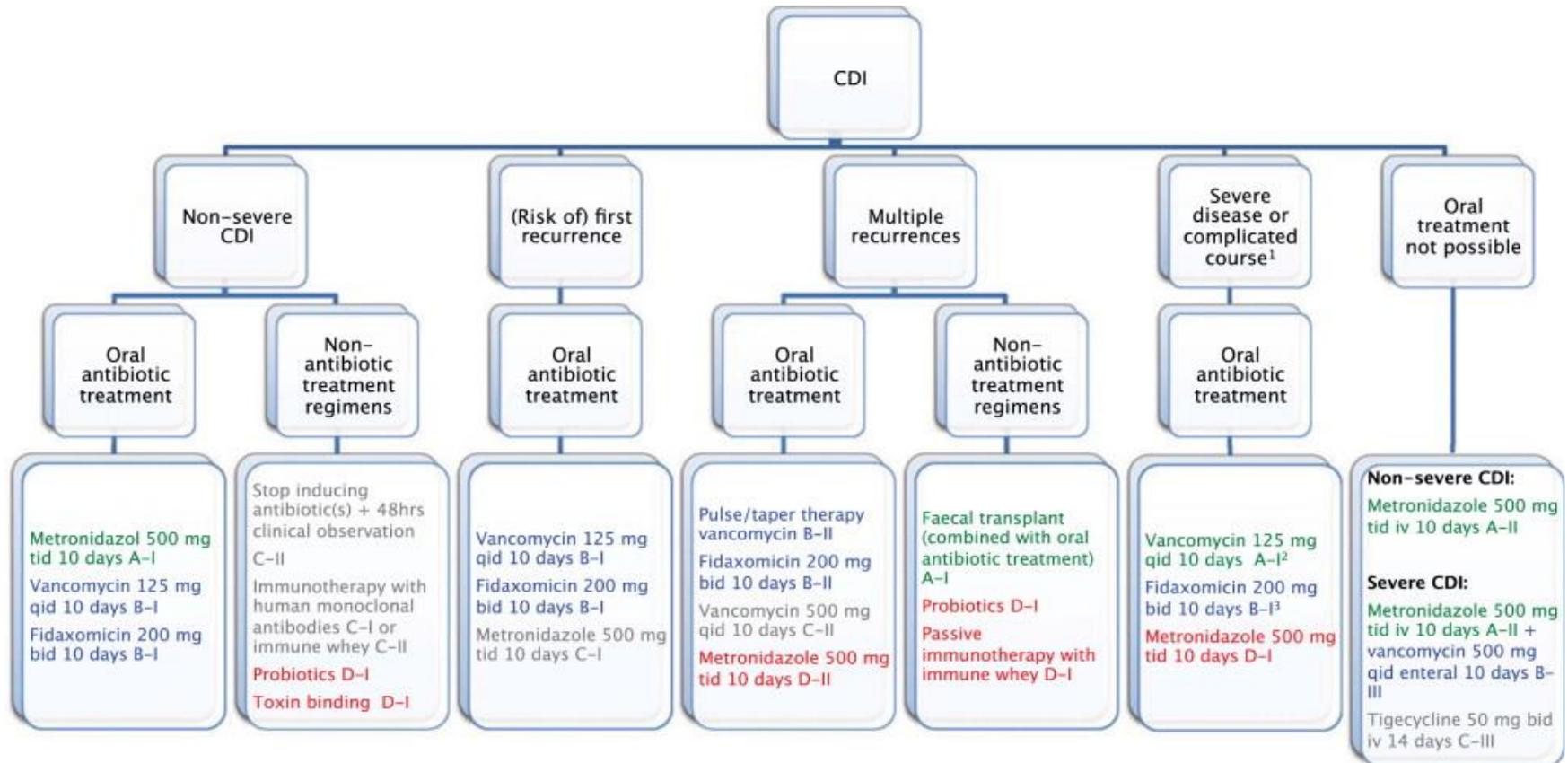
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Teicoplanin versus Vancomycin				
Symptomatic Cure Follow-up: mean 4 weeks	727 per 1000 <sup>1</sup>	880 per 1000 (727 to 1000)	RR 1.21 (1 to 1.46)	110 (2 studies)	⊕○○○ very low <sup>2,3</sup>	
Bacteriologic Cure Follow-up: mean 4 weeks	452 per 1000 <sup>1</sup>	822 per 1000 (537 to 1000)	RR 1.82 (1.19 to 2.78)	59 (1 study)	⊕○○○ very low <sup>2,4</sup>	

# Fidaxomicina - Vancomicina

Intervention: Fidaxomicin  
Comparison: Vancomycin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Vancomycin	Fidaxomicin				
Symptomatic Cure Follow-up: mean 4 weeks	610 per 1000 <sup>1</sup>	713 per 1000 (652 to 774)	RR 1.17 (1.07 to 1.27)	1164 (2 studies)	⊕⊕⊕○ moderate <sup>2</sup>	

# Terapia – ESCMID 2014



*Clinical Infectious Diseases*

**IDSA GUIDELINE**



# Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

L. Clifford McDonald,<sup>1</sup> Dale N. Gerding,<sup>2</sup> Stuart Johnson,<sup>2,3</sup> Johan S. Bakken,<sup>4</sup> Karen C. Carroll,<sup>5</sup> Susan E. Coffin,<sup>6</sup> Erik R. Dubberke,<sup>7</sup> Kevin W. Garey,<sup>8</sup> Carolyn V. Gould,<sup>1</sup> Claran Kelly,<sup>3</sup> Vivian Lee,<sup>10</sup> Julia Shaklee Sammons,<sup>6</sup> Thomas J. Sandora,<sup>11</sup> and Mark H. Wilcox<sup>12</sup>

# Terapia – primo episodio

Forma	Terapia	Durata (gg)
Lieve o moderata	Vancomicina 125 mg ogni 8 ore per os Fidaxomicina 200 mg ogni 12 ore per os  Se non disponibili: Metronidazolo 500 mg ogni 8 ore per os	10
Grave	Vancomicina 125 mg ogni 6 ore per os Fidaxomicina 200 mg ogni 12 ore per os	10 – 14
Fulminante	Vancomicina 500 mg ogni 6 ore per os + vancomicina rettale 250 mg ogni 12 ore + metronidazolo 500 mg ogni 8 ore ev	??

# Terapia - recidive

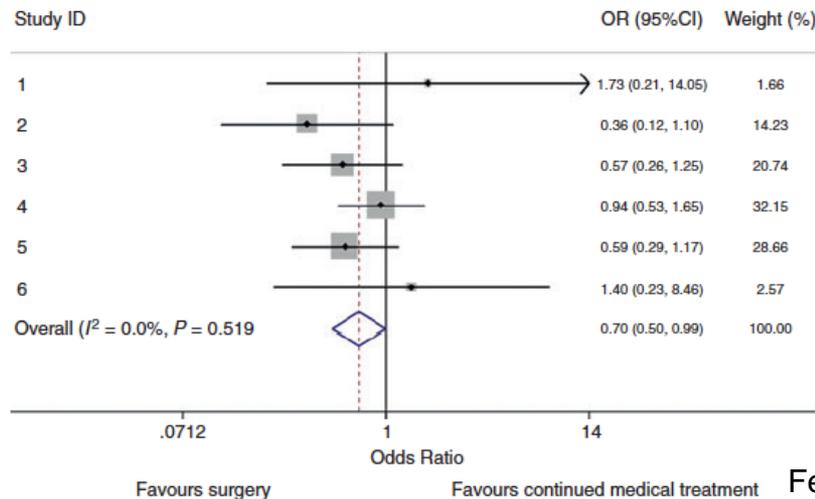
Recidiva	Terapia	Durata (gg)
Prima	Vancomicina 125 mg ogni 6 ore per os	10
	Fidaxomicina 200 mg ogni 12 ore per os (se vancomicina in prima linea)	10
	Vancomicina a scalare 125 mg ogni: 6 ore per 10-14 gg 12 ore per 7 giorni 24 ore per 7 giorni 2-3 giorni per 2 – 8 settimane	6-12 settimane
Seconda o più	Vancomicina a scalare	6-12 settimane
	Vancomicina 125 mg ogni 6 ore per os per 10 giorni, seguita da rifaximina 400 mg ogni 8 ore per 20 giorni	30
	Fidaxomicina 200 mg ogni 12 ore per os	10
	Trapianto di microbiota fecale	

# E la chirurgia?

La colectomia totale non aumenta la mortalità

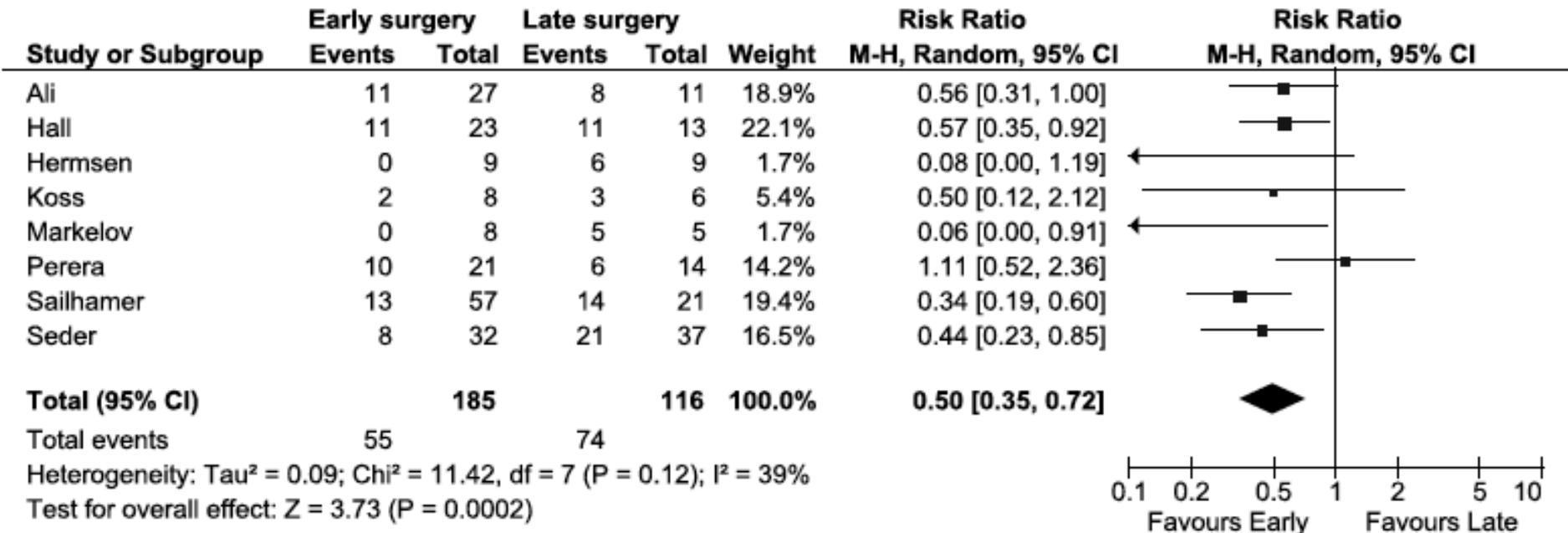
Indicazione: Colite fulminante - almeno 1 di:

- Ricovero in UTI
- Valutazione per chirurgia
- Morte per colite da *C. difficile*



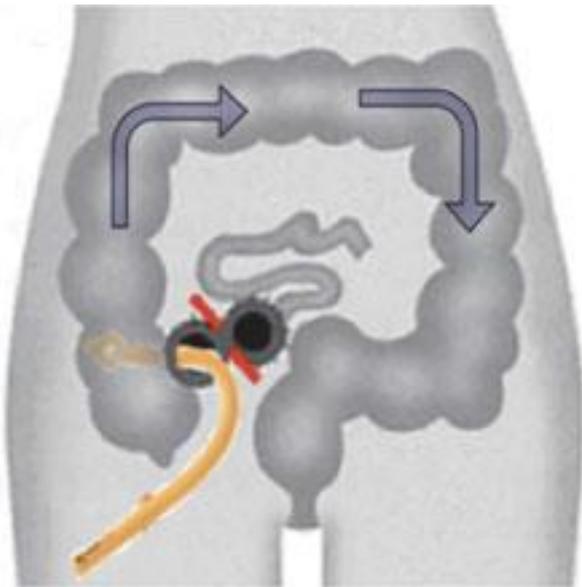
# Quando la chirurgia?

- Precoce meglio che tardiva
- Prima di shock o necessità di amine o insufficienza d'organo



# Quale intervento

- Subcolectomia con conservazione del retto (colectomia)
- Ileostomia con lavaggio colico
  - Mortalità ridotta (19% vs 50%,  $p=0,006$ )



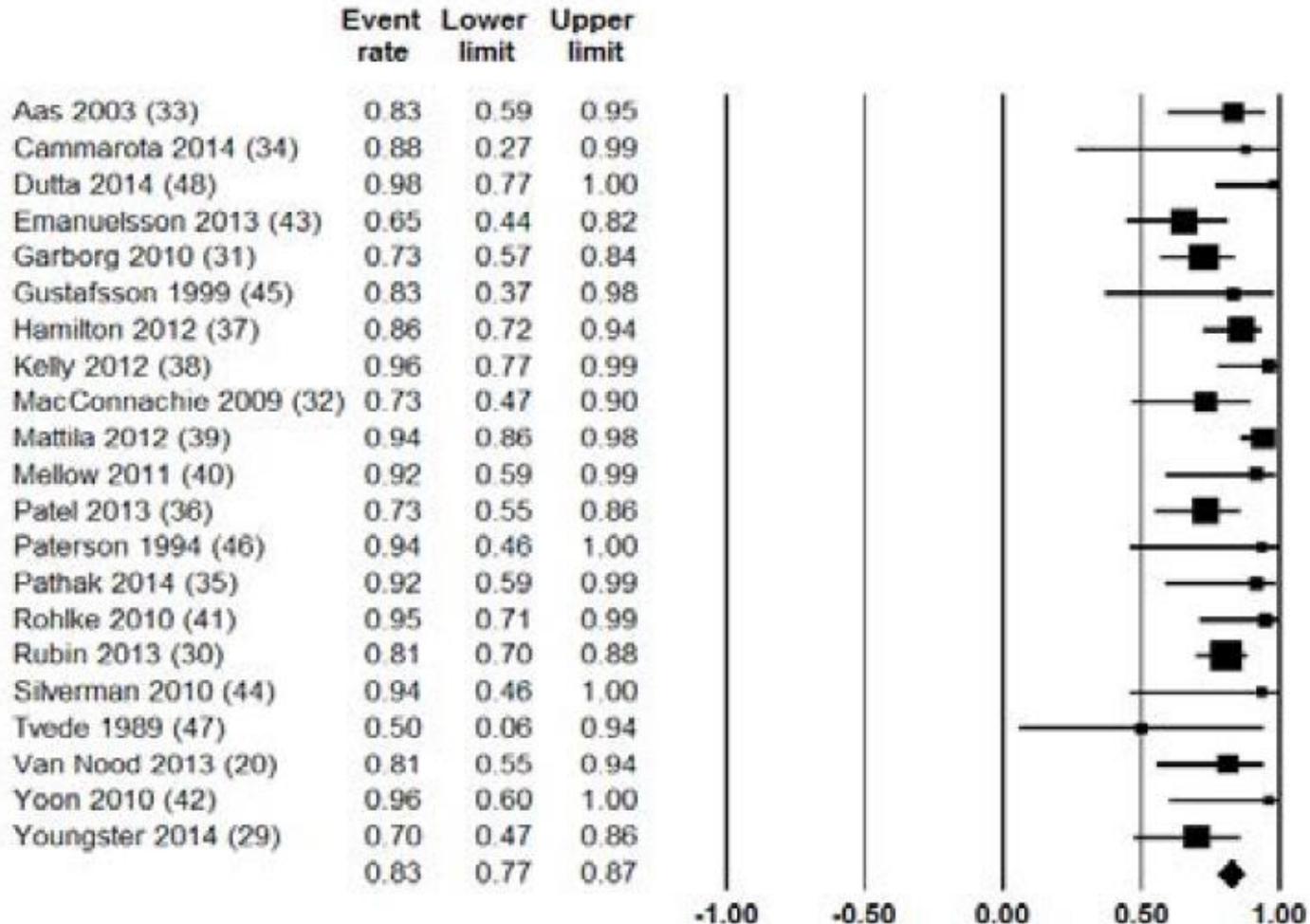
1. Creation of diverting loop ileostomy.
2. Intraoperative antegrade colonic lavage with 8 liters of warmed PEG3350/electrolyte solution via ileostomy.
3. Postoperative antegrade colonic enemas with vancomycin (500 mg in 500 mL X 10 days) via ileostomy.

zienti

# Trapianto di microbiota fecale

Study name

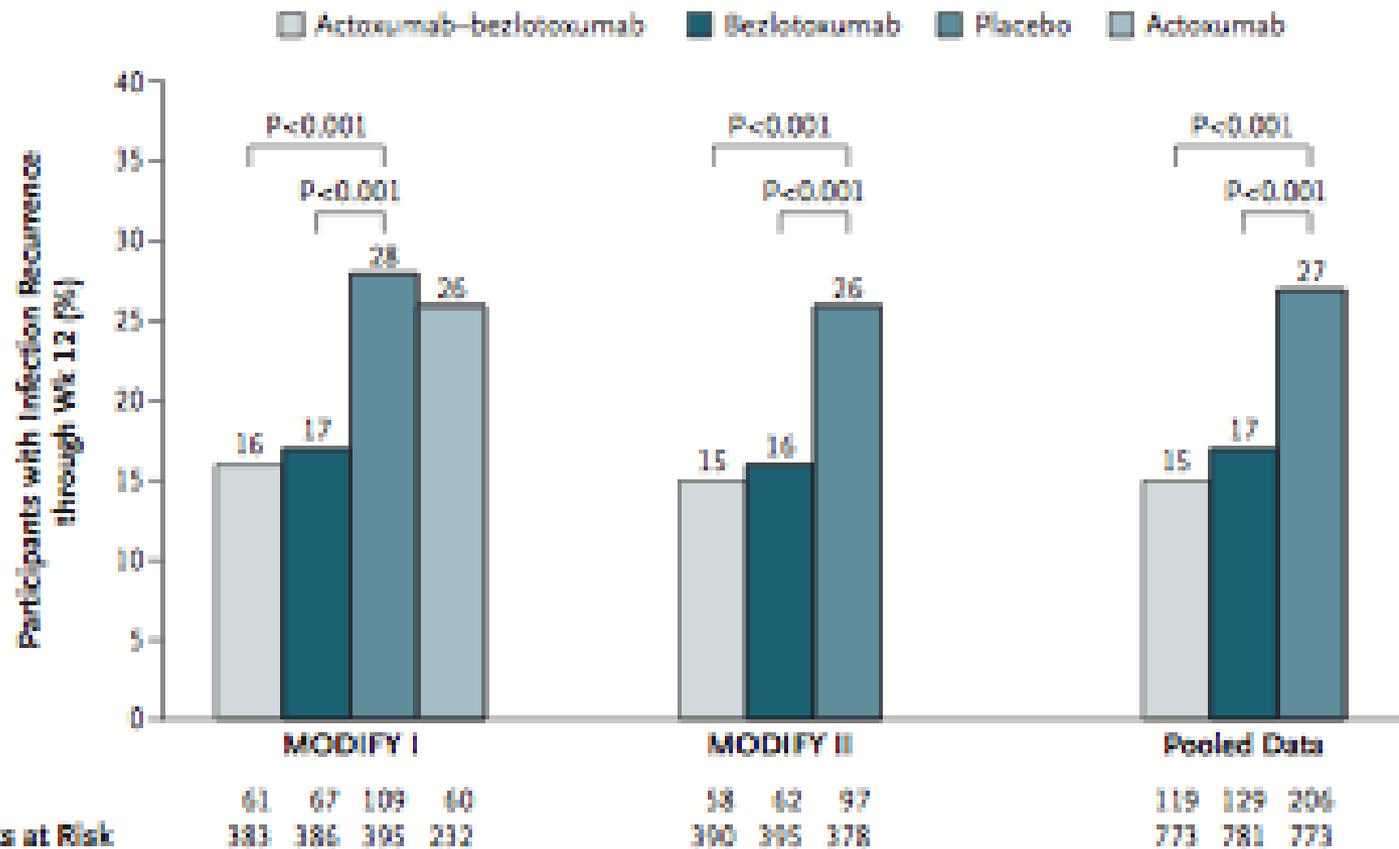
Event rate and 95% CI



Bezlotoxumab for Prevention of Recurrent *Clostridium difficile* Infection

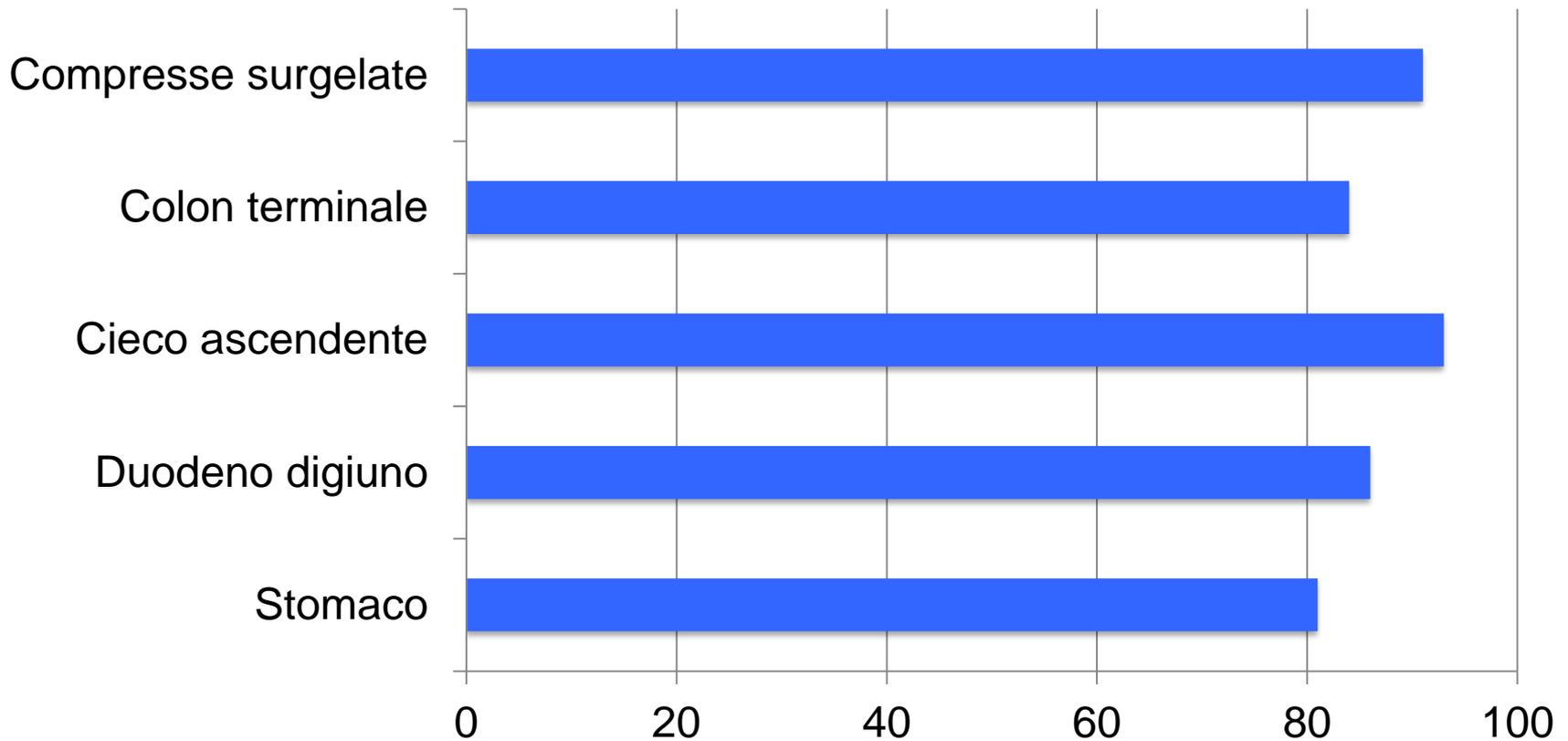
M.H. Wilcox, D.N. Gerding, I.R. Poston, C. Kelly, R. Nathan, T. Birch, O.A. Cornely, G. Rahav, E. Bouza, C. Lee, G. Jenkin, W. Jensen, Y.-S. Kim, J. Yoshida, L. Gabryelski, A. Pedley, K. Eves, R. Tipping, D. Guris, N. Kartsonis, and M.-B. Dorr, for the MODIFY I and MODIFY II Investigators\*

# Actoxumab & Bezlotoxumab



# Quale via di infusione?

## Efficacia



# Altre terapie

- Tigeciclina: studi in corso
- Surotomicina: studi in corso
- Cadazolid: studi in corso
  
- Colestipol e colestiramina: non efficaci
- Tolevamier: inferiore
- Acido ursodesossicolico
  
- Siero anti-tossina A: può proteggere
- Vaccino: studi in corso
- Pool di immunoglobuline: potenzialmente attivo
- Colostro di vitello

# Schematizzazione

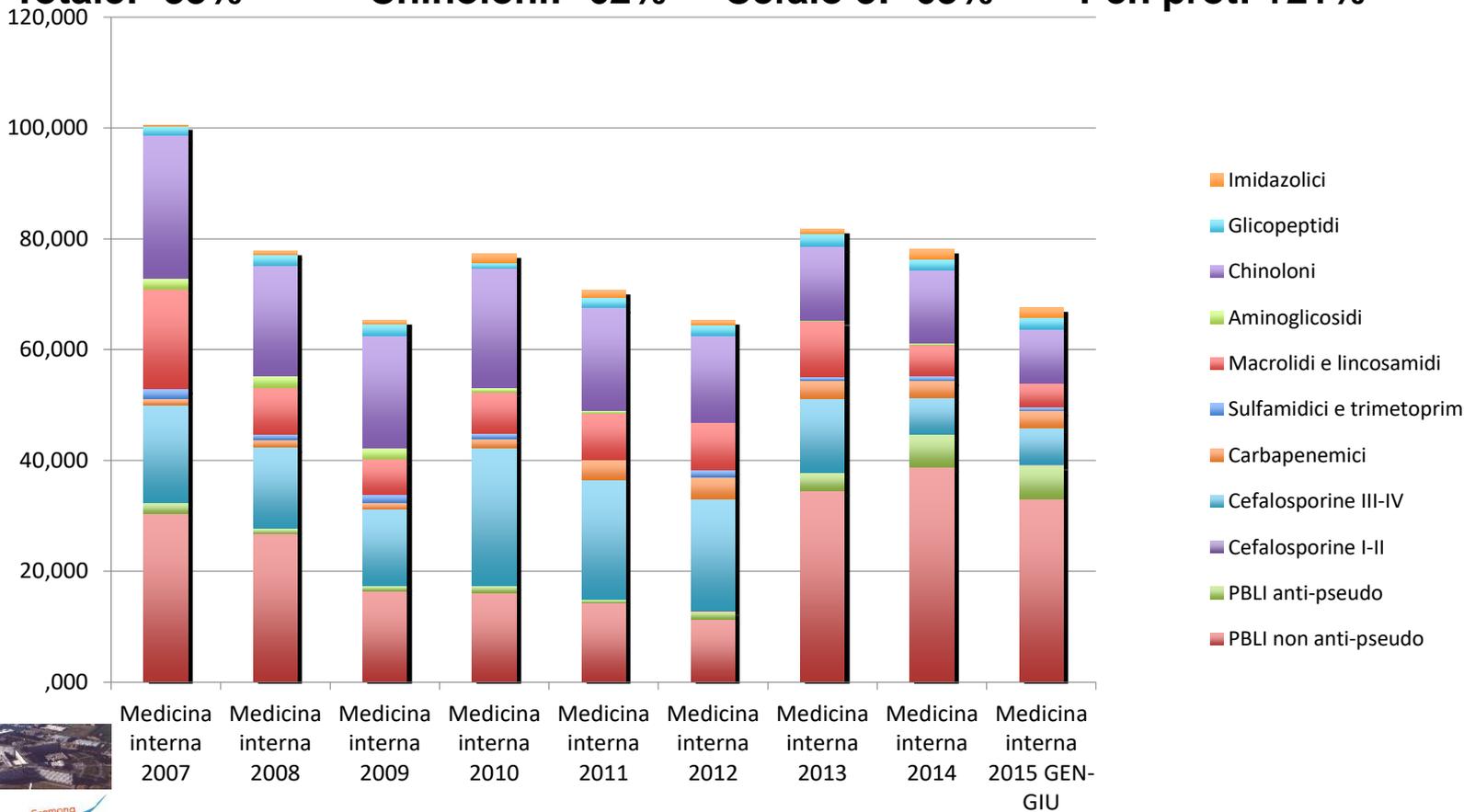
- Vancomicina= Juventus
- Fidaxomicina= Roma
- Metronidazolo= Napoli
- Tolevamer= Inter
- Mab= Real Madrid

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# Consumo di antibiotici in medicina

DDD/100 giorni paziente  
2007 – 2015

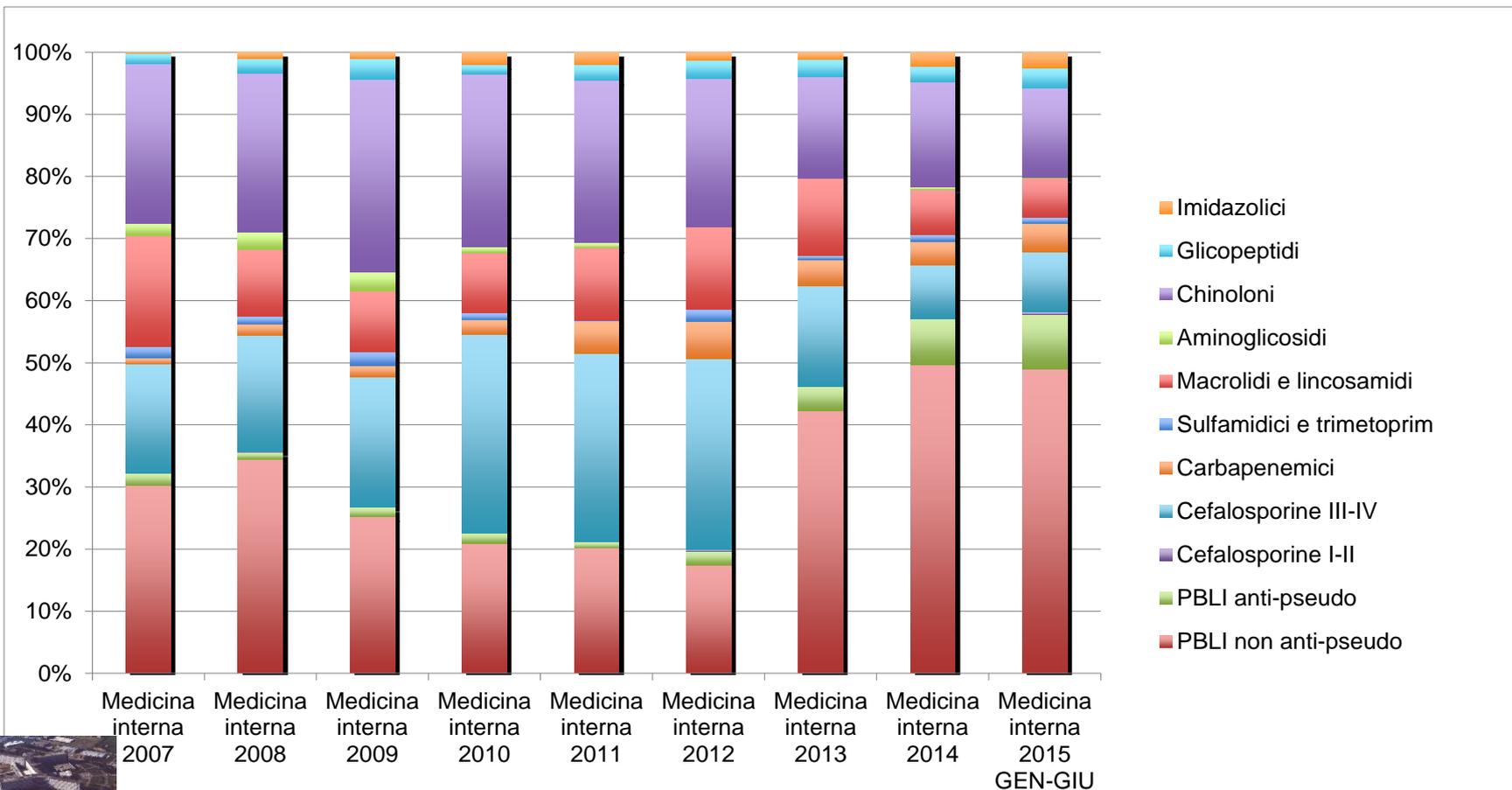
**Totale: -33%**      **Chinoloni: -62%**      **Cefalo 3: -63%**      **Pen prot: +21%**



# Consumo di antibiotici in medicina

## proporzioni delle prescrizioni per classe

### 2007 – 2015

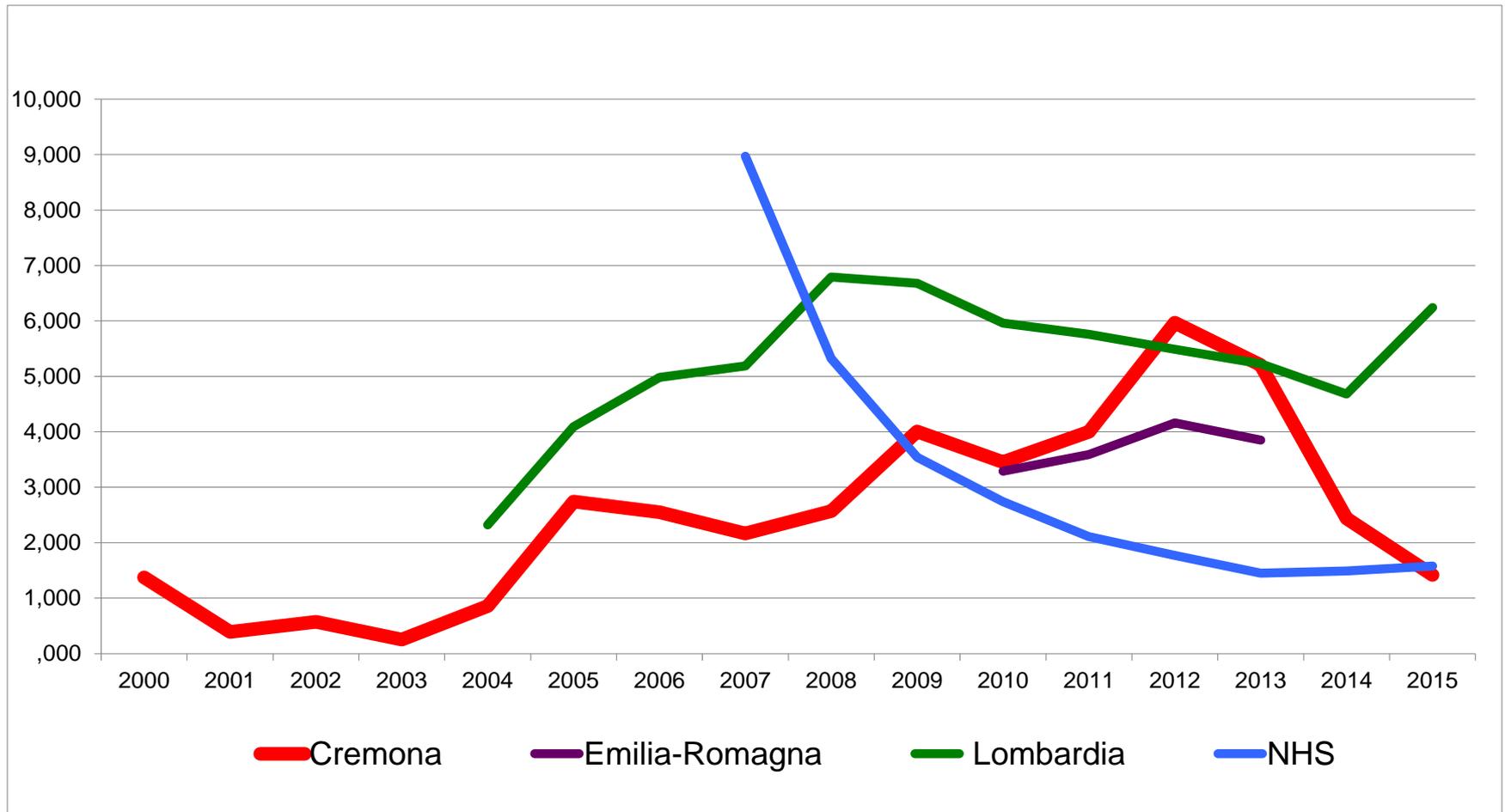




# Consumo di soluzioni idroalcoliche 2008-2017

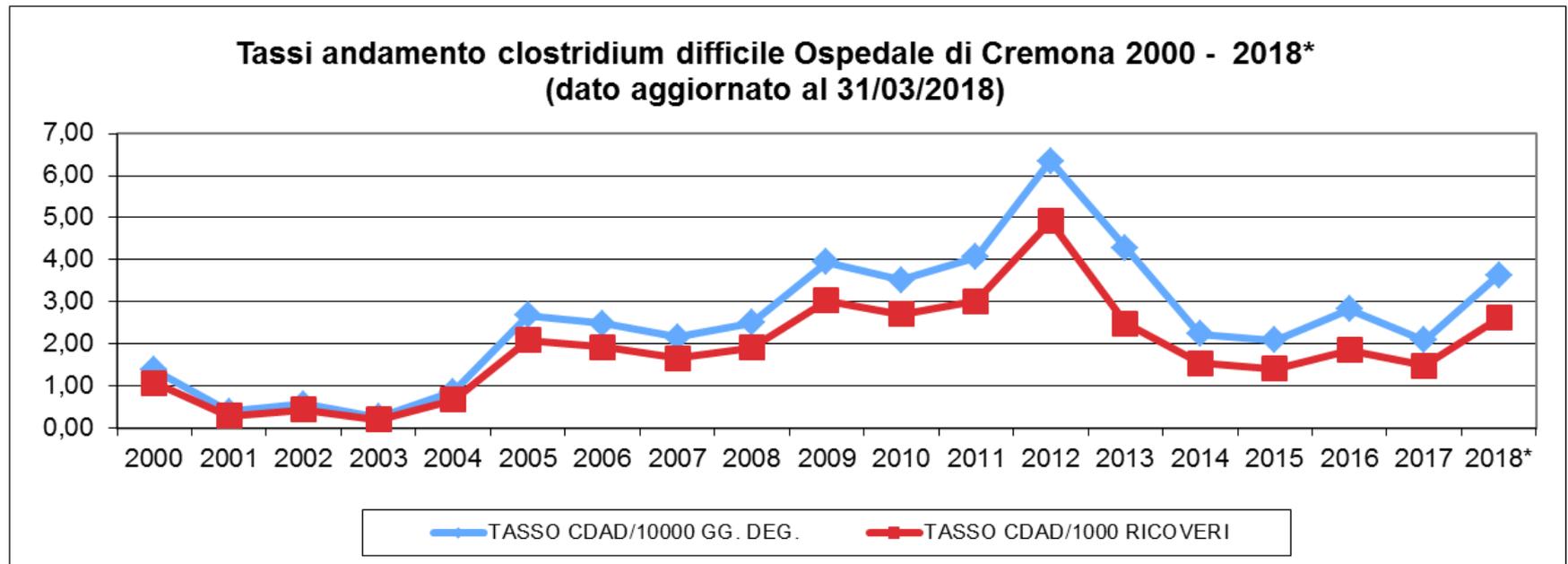


# Tasso di CDI per 10.000 giornate di degenza



# Isolamenti di Clostridium difficile

## Ospedale di Cremona 2000-2018



- Introduzione
- Terapia
- Prevenzione
- Un'esperienza personale
- **Conclusioni**

Recidive: 6%

Atteso: 20-35%

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Piero Manzoni, 1961

Prevenzione

Vancomicina

Trapianto di feci: da organizzare

Casi gravi: considerare con attenzione la chirurgia

Mettere in atto programmi di:

- politica degli antibiotici
- controllo delle infezioni
- igiene delle mani

Grazie