# Does Antimicrobial Stewardship and Specific *Clostridium difficile* Antimicrobial Prophylaxis Prevent CDI?


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**BMBF 01KN1106**



**CECAD – Cluster of Excellence**

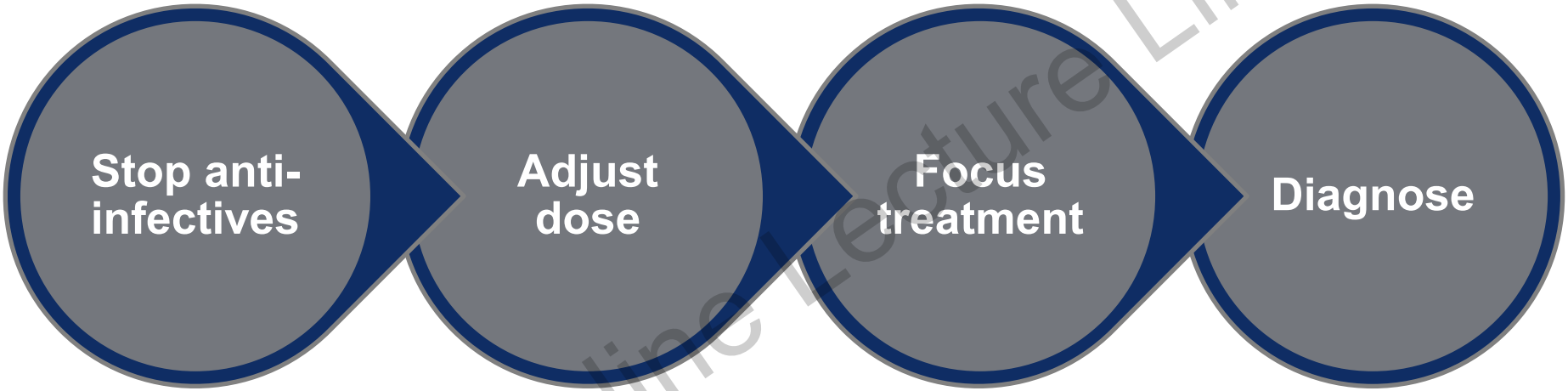
**University of Cologne**




# Transparency Declaration

- German Federal Ministry of Research and Education
  (BMBF 01KN1106, 01KN0706, 01GH1001E, 01EZ0931)
- German Research Foundation (DFG)
- German Center for Infection Research (DZIF)
- German José Carreras Leukaemia Foundation
- European Commission (FP7, IMI)
- European Organisation for Research and Treatment of Cancer (EORTC)
- European Society for Clinical Microbiology and Infectious Diseases (ESCMID)
- European Confederation of Medical Mycology (ECMM)
- Research Grants, Trial Design, or Speaker for:
  3M, Actelion, Astellas, Basilea, Bayer, Biocryst, Celgene, Cubist, F2G, Gilead, GSK, Menarini, Merck Serono, MSD, Miltenyi, Novartis, Optimer, Pfizer, Quintiles, Sanofi Pasteur, Viropharma

# Cologne ID Consulting Service
## Most Typical Advice




- Excessive coverage
- Combination tx for *P. aeruginosa*
- ICU: Empiric tx
- Haem/SCT: Antifungal combination tx
- Toxicity
- Tx duration accomplished

- Upon changing degree of renal failure
- According to Therapeutic drug monitoring

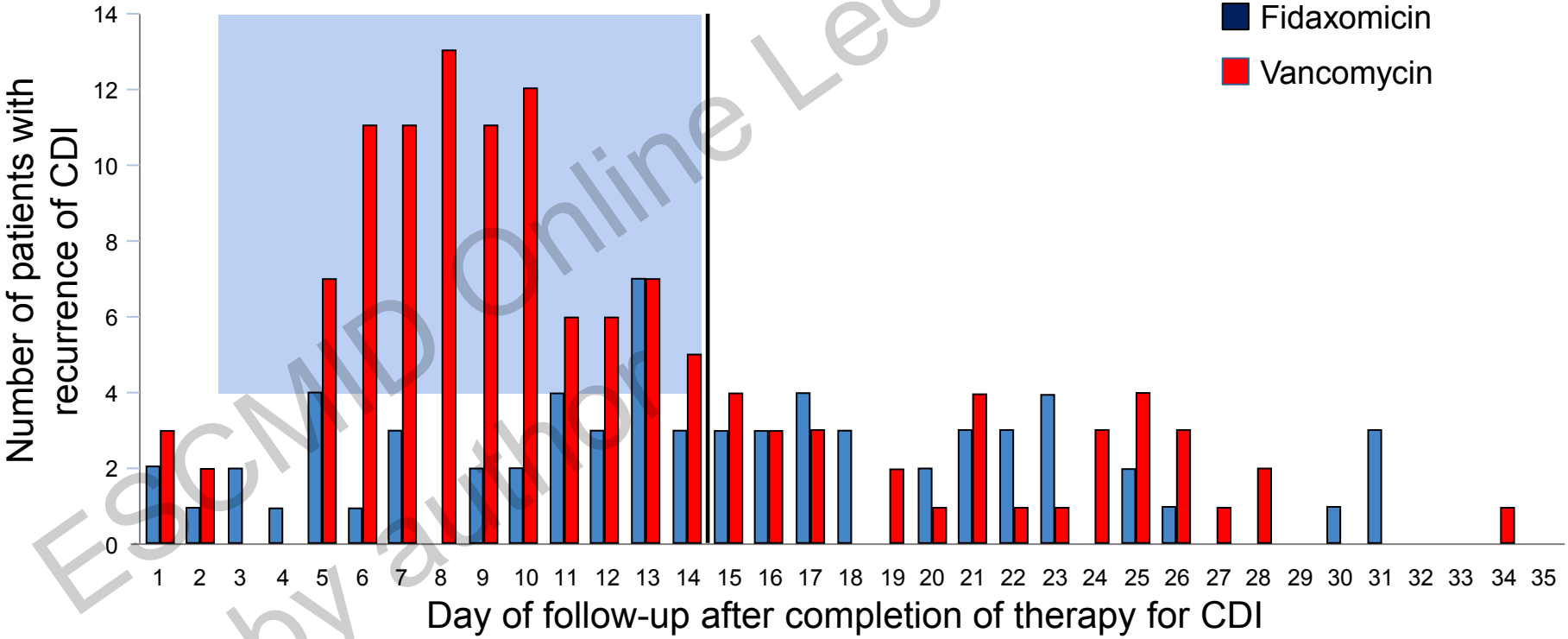
- Replace vancomycin with flucloxacillin in MSSA

- Collect more blood cultures
- Pursue biopsy

# Antimicrobial Stewardship could prevent too short courses of anti-CDI treatment

**Early recurrence (relapse):**
Fidaxomicin: 7.4%
Vancomycin: 19.3%

**Late recurrence (relapse/reinfection):**
Fidaxomicin: 6.6%
Vancomycin: 8.1%






Eur Public Assessment Report EMA 857570 2011.

# Avoid Proton Pump Inhibitors (PPI)

Administration of proton pump inhibitors in critically ill medical patients is associated with increased risk of developing *Clostridium difficile*–associated diarrhea

Lukas Buendgens, MD, Jan Bruensing, MD, Michael Matthes, Hanna Dückers, MD, Tom Luedde, MD, PhD, Christian Trautwein, MD, Frank Tacke, MD, PhD *,1, Alexander Koch, MD 1

*Department of Medicine III, RWTH-University Hospital Aachen, Pauwelsstrasse 30, 52074 Aachen, Germany*

- PPI prevent gastrointestinal bleeding ICU patients
- PPI increase risk of CDI in non-ICU in-patients
- Retrospective, single-center analysis, 1999-2010
- N= 3,286 critically ill patients
- **91% received stress ulcer prophylaxis**
  - 56% PPI
  - 6% H2 blockers
  - 10% sucralfate
  - 20% combinations

Buendgens L et al. J Crit Care 2014; epub.

# Avoid Proton Pump Inhibitors (PPI)

- 1% developed GI bleeding, independent of prophylaxis
- 3.3% developed CDI, associated with
- Independent risk factors for CDI by multivariate analysis
  - Fluoroquinolones (odds ratio 1.9)
  - 3rd generation cephalosporins (OR 1.8)
  - **PPI (OR 3.1)**
- Risk adjusted PPI use should be investigated
  - Mechanical ventilation
  - Coagulopathy



Buendgens L et al. J Crit Care 2014; epub.

# Long-Term Care Facilities (LTCF)

- Setting: 160-bed LTCF attached to a hospital
- Initiation of an ID consulting service
- Comparison of systemic antimicrobial use & *C. difficile* tests before and after



Jump R et al. Infect Control Hosp Epidemiol 2012; 33: 1185-1192.

# Long-Term Care Facilities (LTCF)

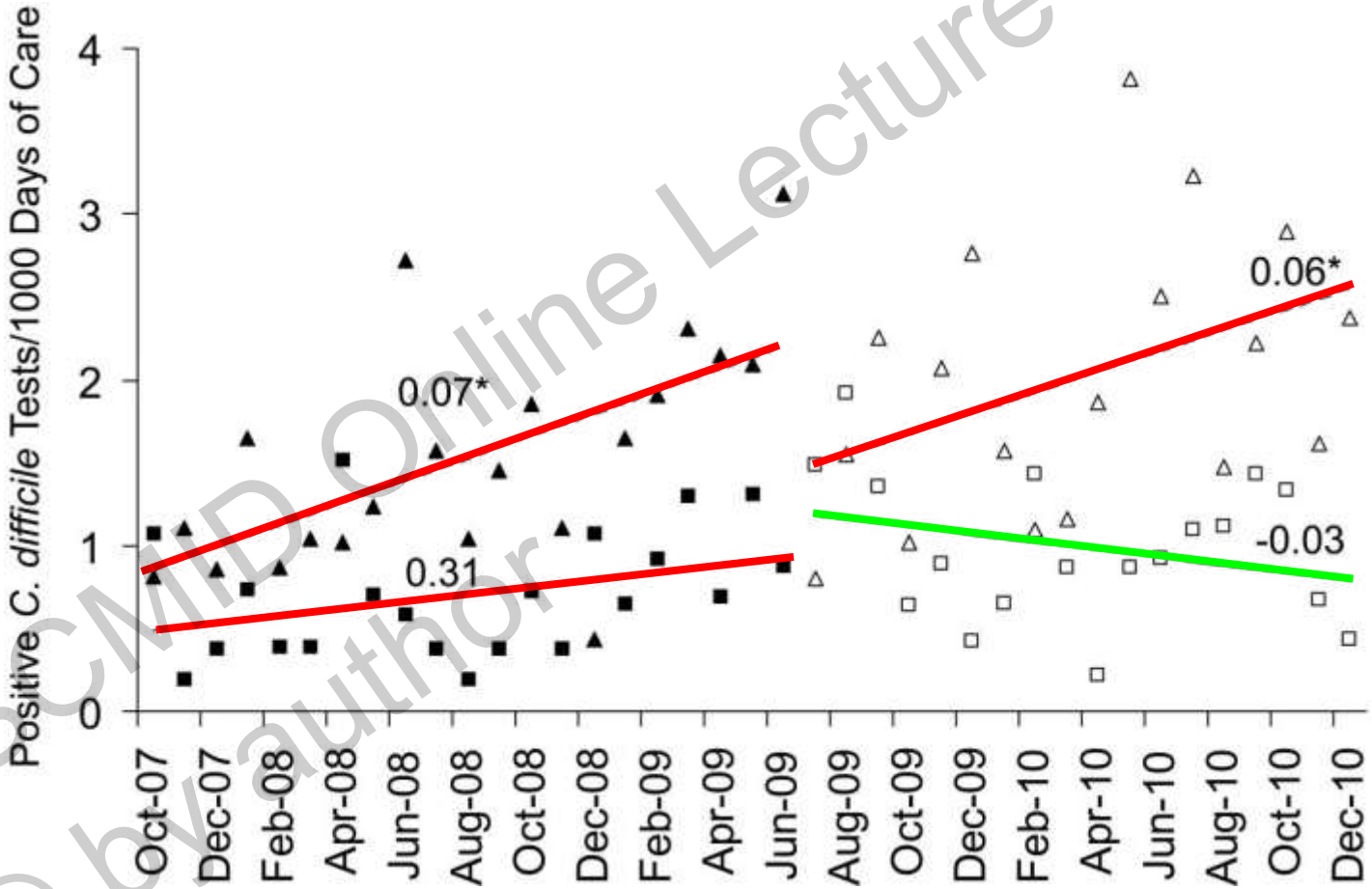
- Total systemic antibiotic use decreased by 30%
  - -32% reduction in oral
  - -25% reduction in i.v.
  - -64% for tetracyclines
  - -61% for clindamycin
  - -38% for sulfamethoxazole/trimethoprim
  - **-38% for fluoroquinolones**
  - -28% for ß-lactam/ß-lactamase inhibitor combinations
- The rate of positive *C. difficile* tests declined



Jump R et al. Infect Control Hosp Epidemiol 2012; 33: 1185-1192.

# Long-Term Care Facilities (LTCF)

- Positive *C. difficile* Tests – "Trend reversed"





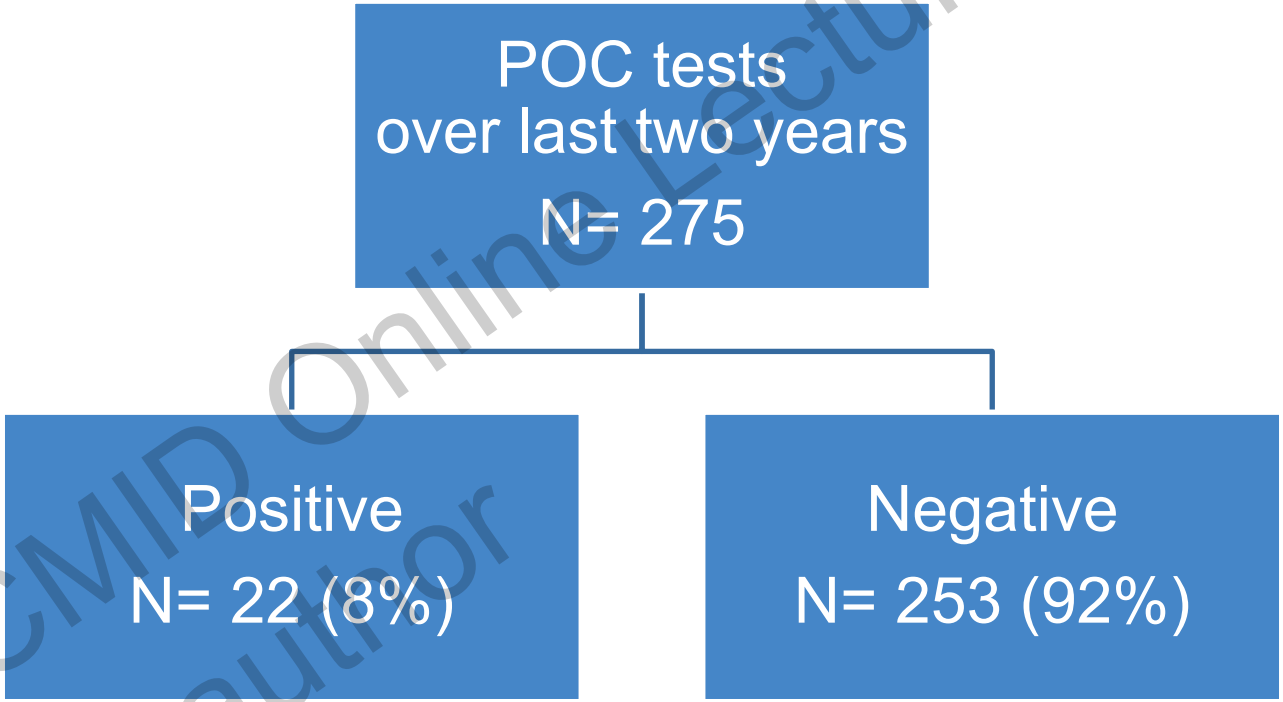

Jump R et al. Infect Control Hosp Epidemiol 2012; 33: 1185-1192.

# Antimicrobial Stewardship – POC Testing




Techlab® ‘C.DIFF QUIK CHEK COMPLETE’.

## Bedside CDI testing prevents empiric treatment





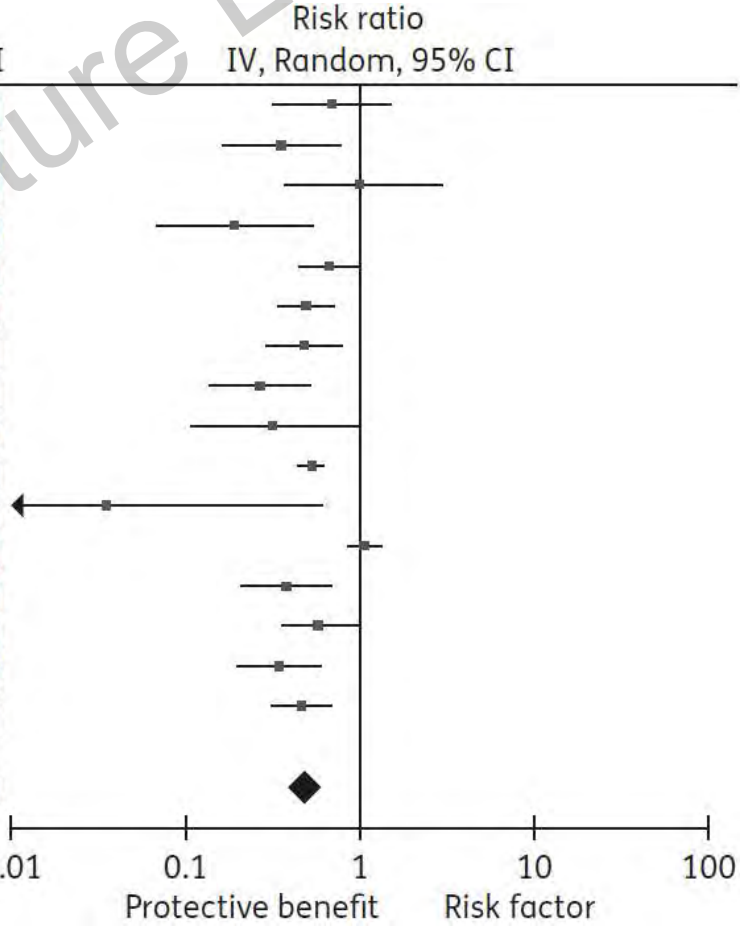

Cornely O, data on file.

# Effect of Antimicrobial Stewardship on CDI Incidence – A Meta-Analysis

## Saturday, May 10, 14:18 Hall G

| Study of subgroup | log [Risk ratio] | SE | Weight | Risk ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Elligson 2012 | −0.37 | 0.393 | 5.0% | 0.69 [0.32, 1.49] |
| Fowler 2007 | −1.05 | 0.372 | 5.3% | 0.35 [0.17, 0.73] |
| Frank 1997 | 0.029 | 0.522 | 3.6% | 1.03 [0.37, 2.86] |
| Gulihar 2009 | −1.65 | 0.522 | 3.6% | 0.19 [0.07, 0.53] |
| Jones 1997 | −0.4 | 0.205 | 8.1% | 0.67 [0.45, 1.00] |
| Ludlam 1999 | −0.721 | 0.177 | 8.7% | 0.49 [0.34, 0.69] |
| Malani 2013 | −0.755 | 0.257 | 7.2% | 0.47 [0.28, 0.78] |
| Miller 2009 | −1.341 | 0.341 | 5.8% | 0.26 [0.13, 0.51] |
| O'Cornor 2004 | −1.164 | 0.567 | 3.2% | 0.31 [0.10, 0.95] |
| Price 2010 | −0.661 | 0.082 | 10.1% | 0.52 [0.44, 0.61] |
| Reinoso 2002 | −3.372 | 1.438 | 0.7% | 0.03 [0.00, 0.57] |
| Schön 2011 | 0.034 | 0.103 | 9.8% | 1.03 [0.85, 1.27] |
| Starks 2008 | −0.984 | 0.309 | 6.3% | 0.37 [0.20, 0.68] |
| Stone 1998 | −0.546 | 0.251 | 7.3% | 0.58 [0.35, 0.95] |
| Talpaert 2011 | −1.079 | 0.272 | 6.9% | 0.34 [0.20, 0.58] |
| Thomas 2002 | −0.78 | 0.19864 | 8.3% | 0.46 [0.31, 0.68] |
| Total (95% CI) | | | 100.0% | 0.48 [0.38, 0.62] |

Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 61.27$, df = 15 ($P < 0.00001$); $I^2 = 76\%$
Test for overall effect: $Z = 5.94$ ($P < 0.00001$)



# Many of Our Patients are at Risk of CDI

- >65 years[1,2]
- Chronic underlying diseases[3]
- Antibiotics use[2,4]
- Immunosuppressants[5]
  - AML[7]
  - HSCT[7]
- Surgical procedures[6]
- Previous CDI episode[2]



1. Loo et al. N Engl J Med 2005; 353: 2442–9;
2. Bauer et al. Lancet 2011; 377: 63–73;
3. Wilson et al. Clin Infect Dis 2010; 50: e77-e81;
4. Shah et al. J Trauma 2012; 72: 691–5;
5. Ali et al. Liver Transpl 2012; 18: 972–8;
6. Zerey et al. Surg Infect 2007; 8: 557–66;
7. Vehreschild et al. Biol Blood Marrow Transplant. Epub ahead.

# Specific Prophylaxis – Challenges

- Whose the target population?
  - ➢ At Cologne University screening of all CDI cases for clinical trial inclusion since 2006
  - ➢ No CDI clusters
  - ➢ No two CDI patients on the same ward at the same time

# CDI in AML and in HSCT Patients

**Sunday, May 11, 13:30**

| Denominator | Incidence in AML | Incidence in HSCT |
|---|---|---|
| Hospitalisations | 19/310 (6.1%) | 28/223 (12.6%) |
| **Patients** | **18/153 (11.8%)** | **30/229 (13.1%)** |
| 10,000 patient days | 17.9 | 27.4 |

Of note, 23/28 (82%) CDI episodes occurred within one month after allogeneictransplantation.



Vehreschild MJGT et al. Biol Blood Marrow Transplant epub ahead. ECCMID 2014; Poster P0784.

# Specific Prophylaxis

- Safety and efficacy of fidaxomicin for prophylaxis against CDI
- Hematopoietic stem cell transplantation
- RCT, placebo-controlled, N=350
- Recruiting



ClinicalTrials.gov
A service of the U.S. National Institutes of Health

NCT01691248.

# Specific Prophylaxis with Metronidazole?

## Risk of *Clostridium difficile* Infection in Hospitalized Patients Receiving Metronidazole for a Non–*C difficile* Infection

Sandra Rodriguez,* Marlow B. Hernandez,* Giorgio Tarchini,‡ Megan Zaleski,* Marjon Vantanchi,* Lyssette Cardona,‡ Fernando Castro-Pavia,§ and Alison Schneider§

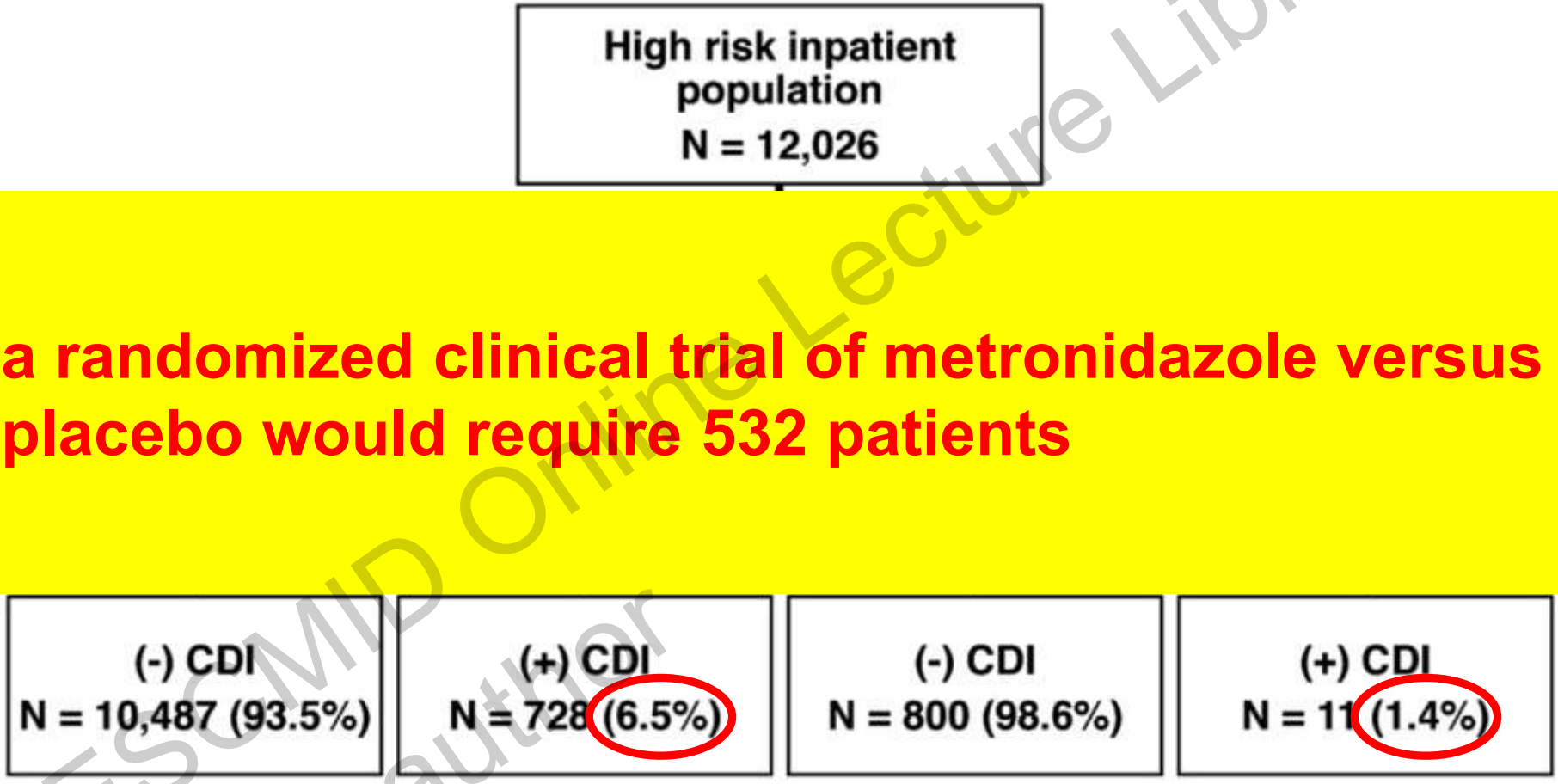
*Department of Internal Medicine, ‡Department of Infectious Disease, and §Department of Gastroenterology and Hepatology, Cleveland Clinic Florida, Weston, Florida

- Does prophylactic metronidazole – before patients receive other antibiotics – reduce the risk of CDI?
- Retrospective cohort analysis
- N= 12,026 high-risk patients (2008-2012)



Rodriguez S et al. Clin Gastroent Hepatol 2014; epub.

# Specific Prophylaxis with Metronidazole?




**80% reduction (OR 0.2; 95% CI, 0.11–0.38) adjusted for age, sex, and comorbidities.**

Rodriguez S et al. Clin Gastroent Hepatol 2014; epub.

# Not so Specific Prophylaxis – Probiotics

## Probiotics for the Prevention of *Clostridium difficile*–Associated Diarrhea

### A Systematic Review and Meta-analysis

Bradley C. Johnston, PhD; Stephanie S.Y. Ma, MD; Joshua Z. Goldenberg, BSc; Kristian Thorlund, PhD; Per O. Vandvik, MD, PhD; Mark Loeb, MD; and Gordon H. Guyatt, MD

- To assess efficacy & safety of probiotics for prevention of CDI
- 20 trials from 1989 - 2011
- N=3,818
- Moderate-quality evidence suggests that probiotic prophylaxis results in a large reduction in CDAD without increase in important adverse events



Johnston BC et al. Ann Intern Med 2012; 157: 878-888.

# Prophylaxis of Recurrence – MoAbs

- MK-6072 and MK-3415A in CDI (MODIFY I)
- RCT, placebo-controlled, N=1200
- Recruiting

- MK-3415, MK-6072, and MK-3415A in CDI (MODIFY II)
- RCT, placebo-controlled, N=1600
- Recruiting



ClinicalTrials.gov
A service of the U.S. National Institutes of Health NCT01241552 & NCT01513239.

# Prophylaxis of Recurrence – Strategies

- Vaccines
- Non-toxigenic *C. difficile*

# Current Approach

1. Diagnose CDI on the first day of diarrhoea
2. Treat along the ESCMID guidelines
3. Explain CDI to physicians, patients, relatives
   - e.g. ECDC fact sheets
4. ID consult when high risk of recurrence
   - e.g. continued antibacterial use

# Outlook

- What might be used tomorrow
  - New antibiotics are coming
  - Other therapeutic principles
  - Primary prophylaxis
    if we identify a population at high enough risk

- What can be used today
  - Antimicrobial stewardship
  - Prophylaxis of recurrence with FDX