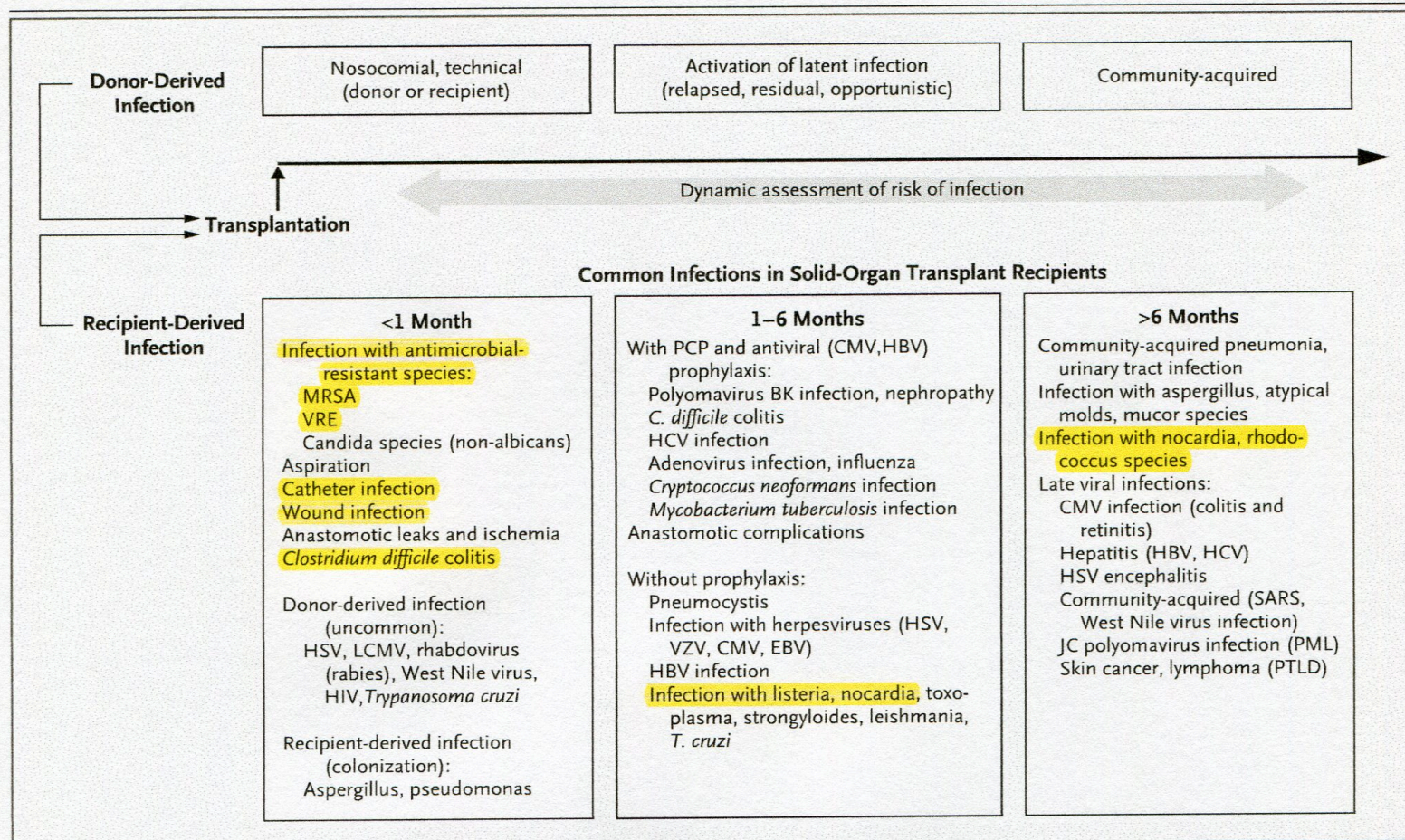


# Le infezioni da Gram + nel trapianto di organo solido

Prof. Ercole Concia

Università degli Studi di Verona





**Figure 4. Changing Timeline of Infection after Organ Transplantation.**

Infections occur in a generally predictable pattern after solid-organ transplantation. The development of infection is delayed by prophylaxis and accelerated by intensified immunosuppression, drug toxic effects that may cause leukopenia, or immunomodulatory viral infections such as infection with cytomegalovirus (CMV), hepatitis C virus (HCV), or Epstein–Barr virus (EBV). At the time of transplantation, a patient's short-term and long-term risk of infection can be stratified according to donor and recipient screening, the technical outcome of surgery, and the intensity of immunosuppression required to prevent graft rejection. Subsequently, an ongoing assessment of the risk of infection is used to adjust both prophylaxis and immunosuppressive therapy. MRSA denotes methicillin-resistant *Staphylococcus aureus*, VRE vancomycin-resistant *Enterococcus faecalis*, HSV herpes simplex virus, LCMV lymphocytic choriomeningitis virus, HIV human immunodeficiency virus, PCP *Pneumocystis carinii* pneumonia, HBV hepatitis B virus, VZV varicella–zoster virus, SARS severe acute respiratory syndrome, PML progressive multifocal leukoencephalopathy, and PTLD post-transplantation lymphoproliferative disorder. Modified from Fishman and Rubin<sup>1</sup> and Rubin et al.<sup>45</sup>



# VAD-Specific Infections

| Site of infection | Distribution of organisms                                                                                                                                                                                                                                      |
|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Driveline         | <i>Staphylococcus aureus</i> 30–44%<br><i>Pseudomonas aeruginosa</i> 10–28%<br>Enteric gram-negative bacteria 13–30%<br>Coagulase negative staphylococci 7–20%<br><i>Enterococcus spp</i> 5–15%<br><i>Corynebacterium spp</i> 2–15%<br><i>Candida spp</i> 0–8% |
| Pocket            | Coagulase negative staphylococci 15–40%<br><i>S. aureus</i> 20–30%<br><i>Enterococcus spp</i> 20–24%<br>Enteric gram-negative bacteria 5–25%<br><i>P. aeruginosa</i> 5–19%<br><i>Candida spp</i> 10%                                                           |
| Pump/cannula      | Coagulase negative staphylococci 20–40%<br><i>S. aureus</i> 20%<br><i>P. aeruginosa</i> 8–20%<br><i>Corynebacterium spp</i> 8–20%<br>Enteric gram-negative bacteria 0–15%<br><i>Enterococcus spp</i> 0–30%                                                     |



# Stafilococco Aureo Meticillino Resistente

**MRSA**

MRSA is a versatile, well equipped pathogen with the potential to evolve and adapt to its host as well as to the treatments developed to control its invasive damage.

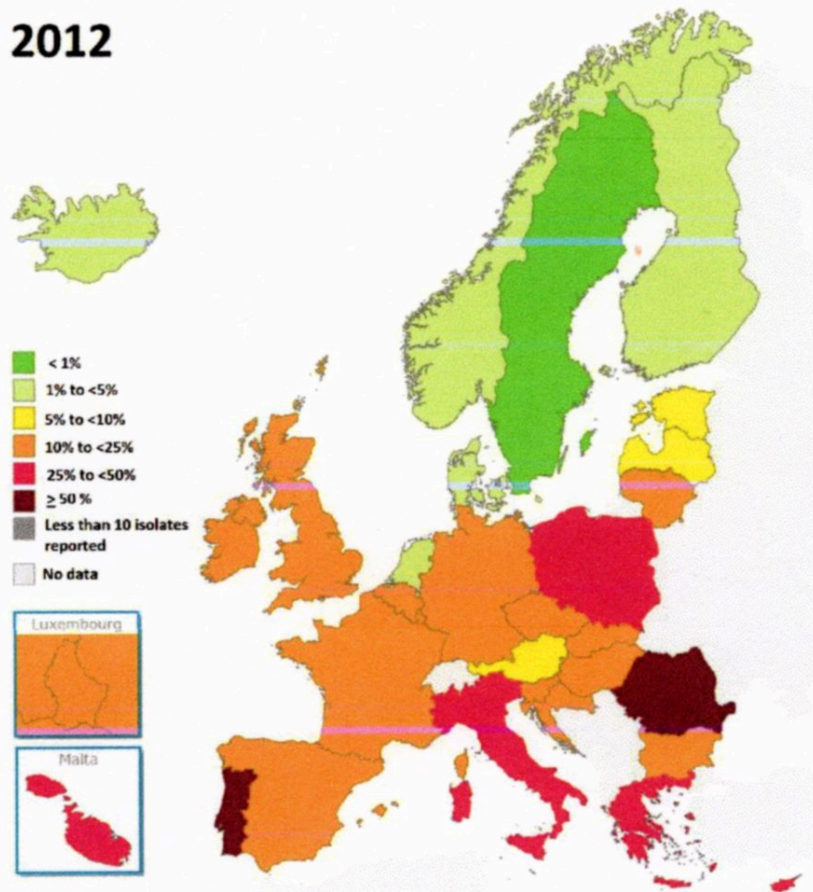
US : MRSA causes approximately 95.000 invasive infections and 19.000 deaths per year.

This mortality number is higher than the rates of deaths produced by HIV, viral hepatitis, Tbc and influenza combined.

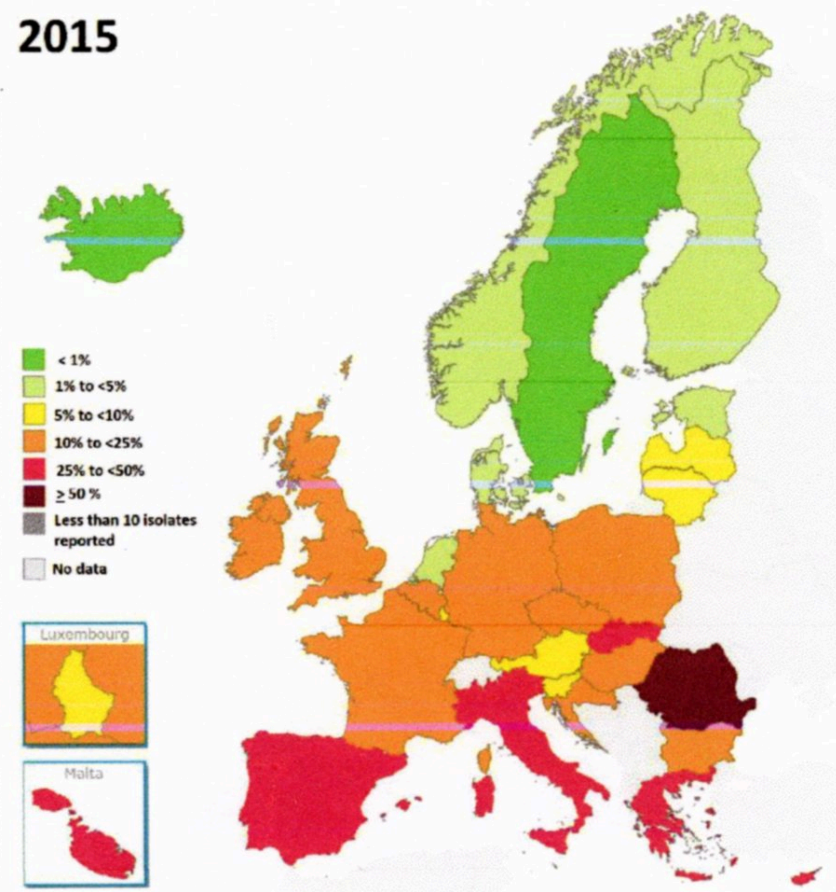


**Figure 7. *Staphylococcus aureus*: percentage of invasive isolates with resistance to meticillin (MRSA), EU/EEA, 2012 (left), 2015 (right)**

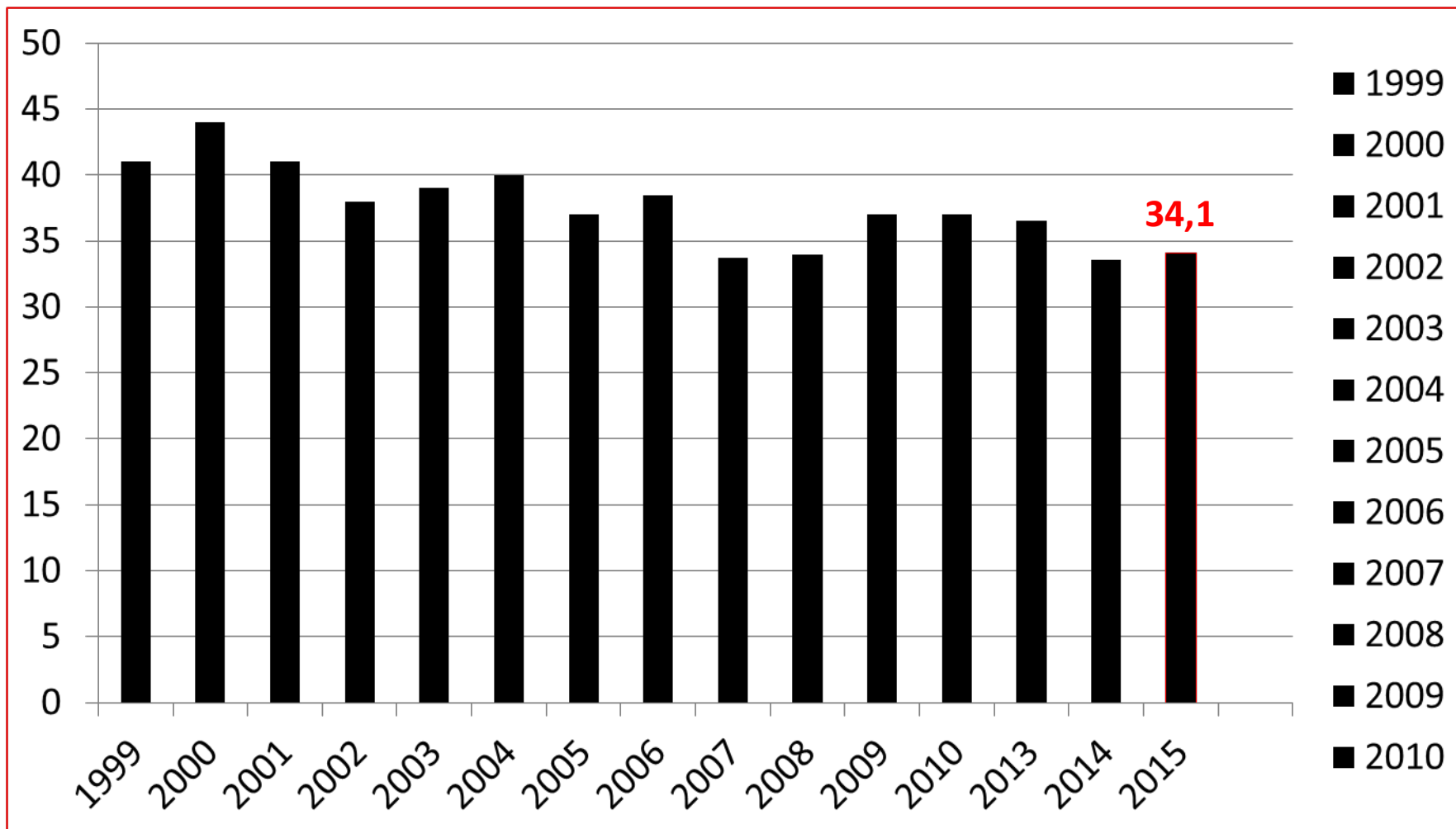
2012



2015



## MRSA IN ITALIA 1999 - 2015



# Vancomicina “MIC creep”

## Aumento delle MICs della vancomicina tra i ceppi di *Staphylococcus aureus* sensibili alla vancomicina

- E' presente in alcune istituzioni (ma non in tutte ...)
- Ritardata risposta alla terapia antibiotica
- Aumentata mortalità
- Aumentata percentuale di ricadute
- Prolungata ospedalizzazione
- Costo di ospedalizzazione totale aumentato
- Coinvolge sia gli MRSA che i MSSA



# Vancomycin MIC “creep” – USA data

|             | MIC <sub>50</sub> | MIC <sub>90</sub> |
|-------------|-------------------|-------------------|
| 1985 MSSA   | 0.06              | 0.12              |
| 2004 MSSA   | 2.0               | 2.0               |
| 1985 MRSA → | 0.12              | 0.25              |
| 2004 MRSA → | 2.0               | 2.0               |

**BREAKPOINT = 2**

\* P< 0.0001 - Kapadia M. et al 45° ICAAC abs E-807

# MIC per vancomicina e % di eradicazione

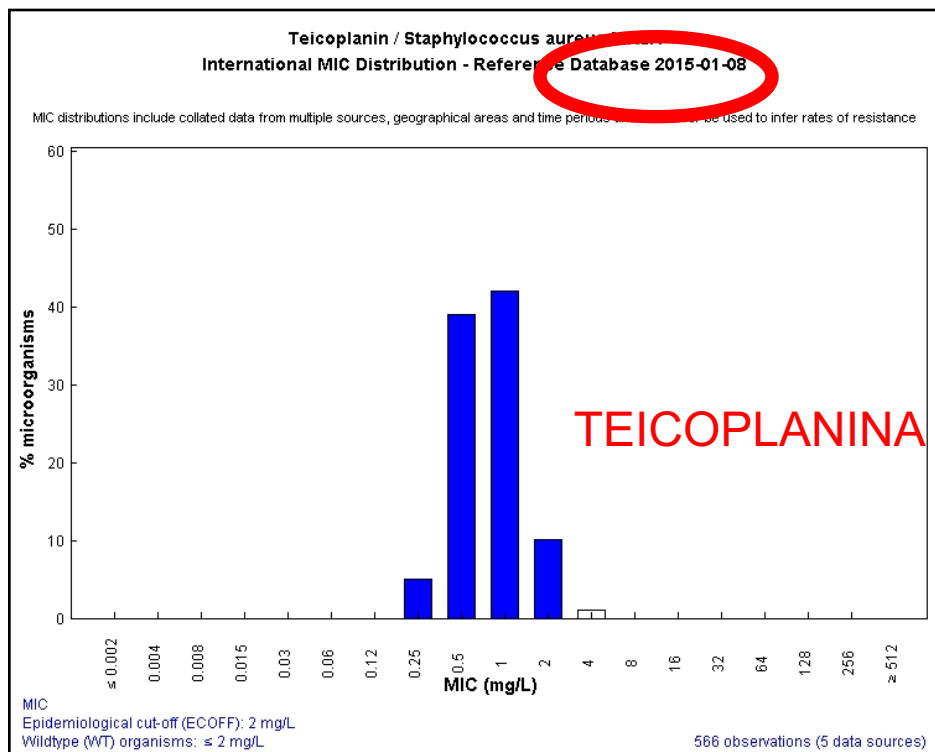
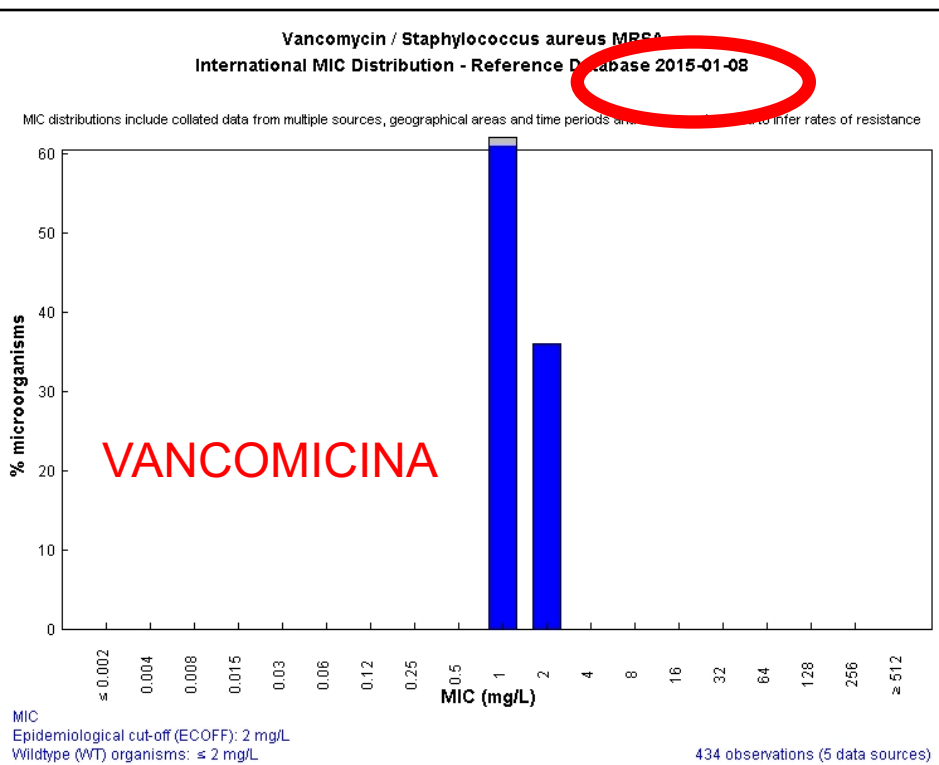
TABLE 2. Vancomycin MIC versus eradication rates

| Vancomycin MIC ( $\mu\text{g/ml}$ ) | No. of isolates | Median DTE <sup>a</sup> | Median duration of vancomycin therapy (days) | Eradication rate by EOT <sup>b</sup> | Median reduction in log <sub>10</sub> CFU/ml |
|-------------------------------------|-----------------|-------------------------|----------------------------------------------|--------------------------------------|----------------------------------------------|
| 0.5                                 | 13              | 6.0                     | 13.0                                         | 10/13 (77)                           | 3.06                                         |
| 1.0                                 | 7               | 9.5                     | 17.0                                         | 5/7 (71)                             | 3.09                                         |
| 2.0                                 | 14              | >15.0 <sup>c</sup>      | 18.5                                         | 3/14 (21)                            | 2.75                                         |

<sup>a</sup> DTE, day to eradication.

<sup>b</sup> EOT, end of treatment. The eradication rate data represent the number of patients from the organism was eradicated/total number of patients in the group (percent).

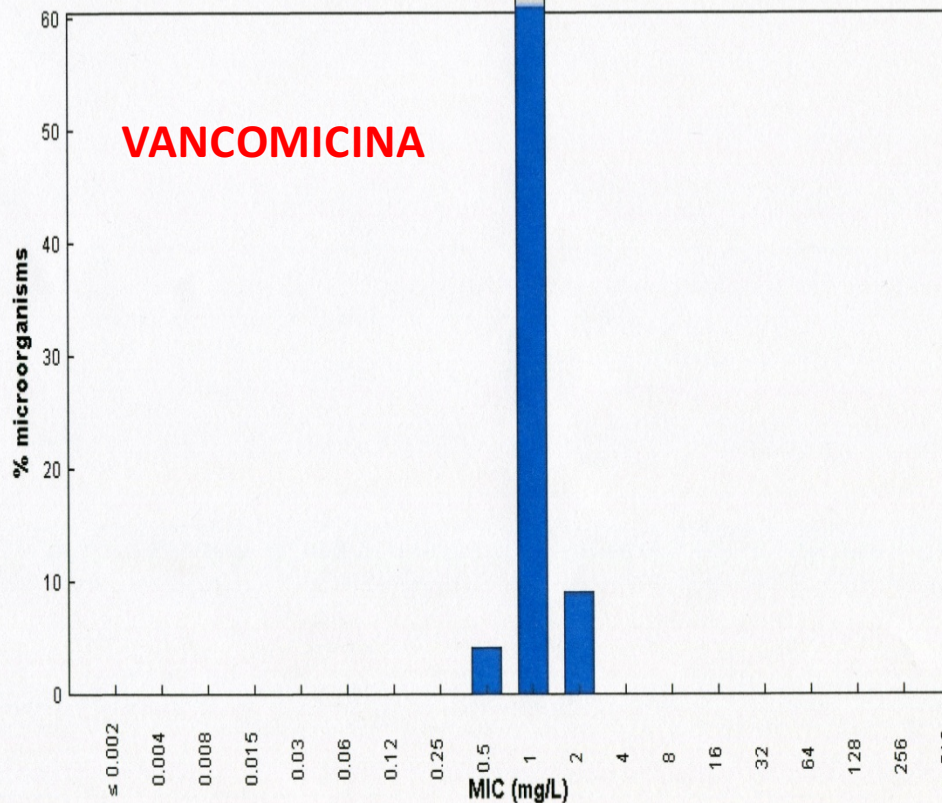
<sup>c</sup> The median time to eradication is greater than 15 days, as only 21% of patients showed clearance of bacteremia.



**MRSA**

**Vancomycin / Staphylococcus aureus MRSA**  
**International MIC Distribution - Reference Database 2017-05-03**

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance

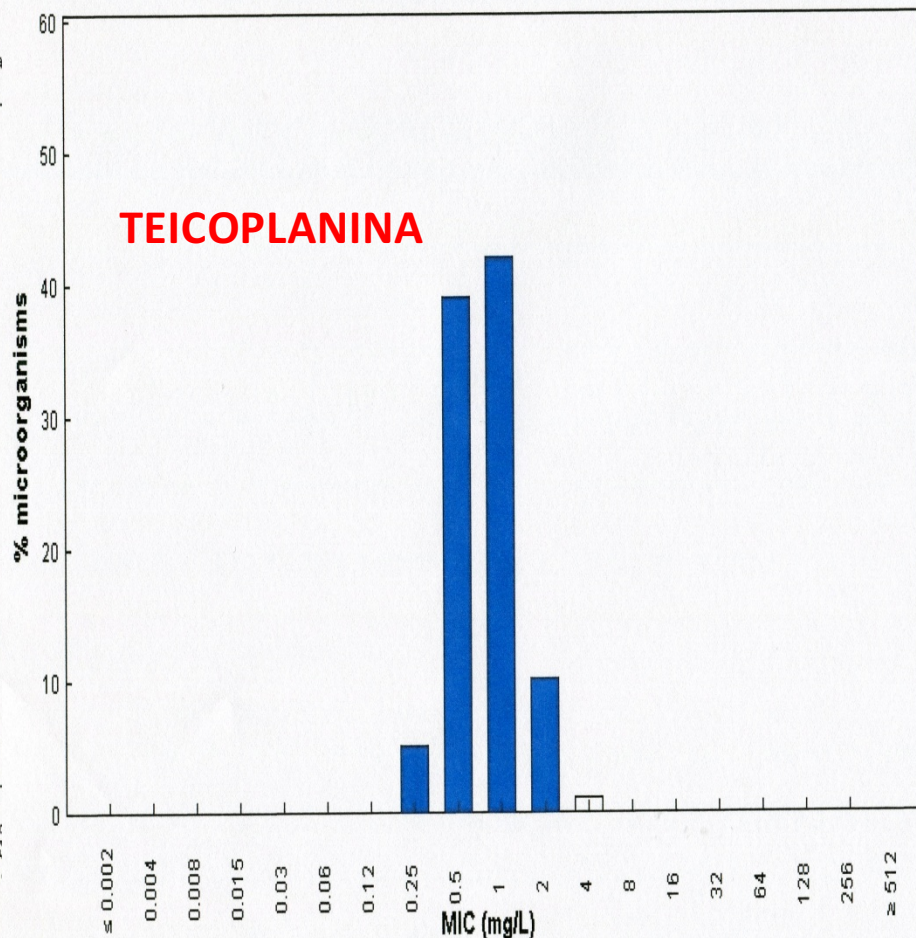


MIC  
 Epidemiological cut-off (ECOFF): 2 mg/L  
 Wildtype (WT) organisms: ≤ 2 mg/L

2574 observations (6 data sources)

**Teicoplanin / Staphylococcus aureus MRSA**  
**International MIC Distribution - Reference Database 2017-05-03**

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



MIC  
 Epidemiological cut-off (ECOFF): 2 mg/L  
 Wildtype (WT) organisms: ≤ 2 mg/L

566 observations (5 data sources)



# The Clinical Significance of Vancomycin Minimum Inhibitory Concentration in *Staphylococcus aureus* Infections: A Systematic Review and Meta-analysis

S. J. van Hal,<sup>1,2</sup> T. P. Lodise,<sup>3</sup> and D. L. Paterson<sup>4</sup>

<sup>1</sup>Department of Microbiology and Infectious Diseases, Sydney South West Pathology Services–Liverpool, South Western Sydney Local Health Network, New South Wales; <sup>2</sup>Antibiotic Resistance and Mobile Elements Group, Microbiology and Infectious Diseases Unit, School of Medicine, University of Western Sydney, Australia; <sup>3</sup>Albany College of Pharmacy and Health Sciences, New York; and <sup>4</sup>University of Queensland Centre for Clinical Research, Royal Brisbane and Womens Hospital Campus, Australia.

---

(See the Editorial Commentary by Deresinski, on pages 772–4.)

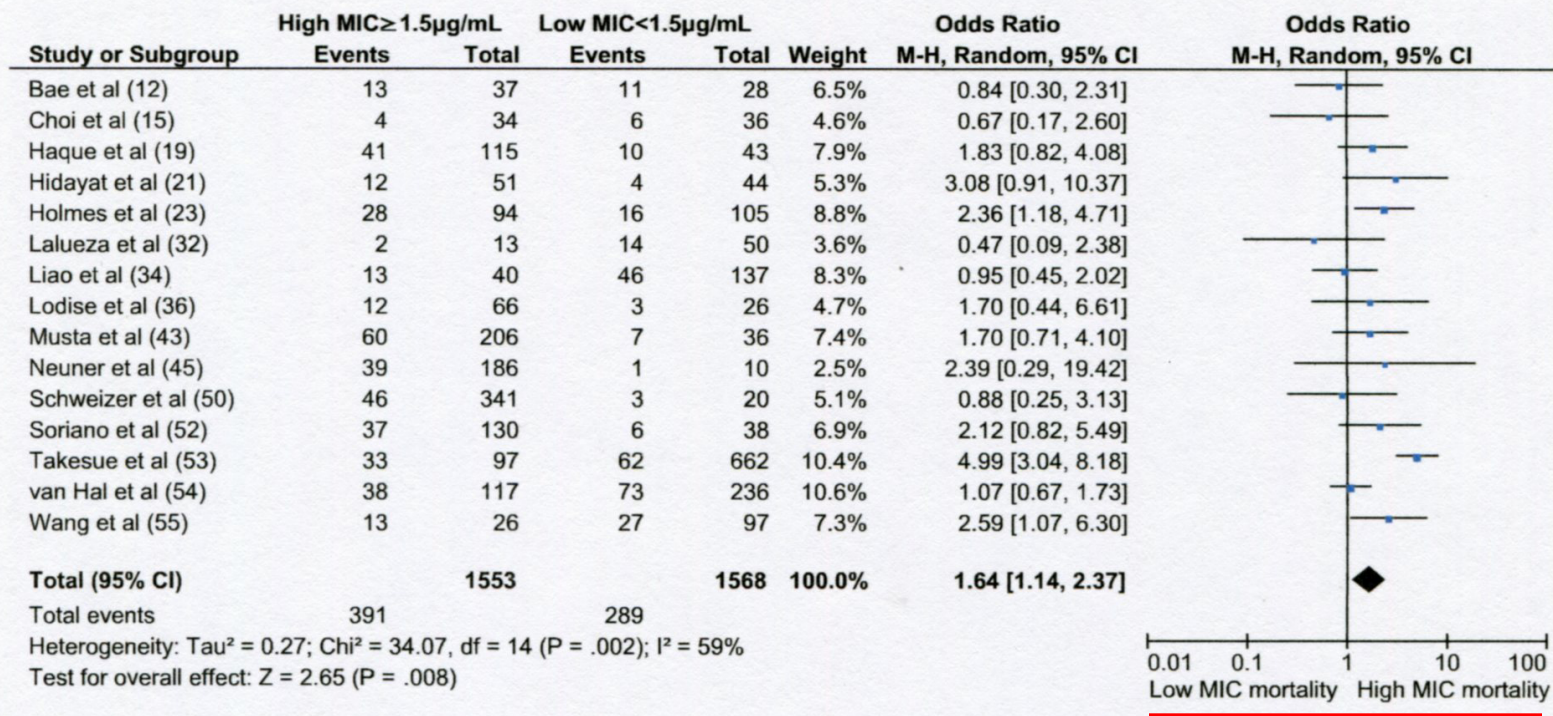
**Background.** Emerging data suggest that vancomycin may be less effective against serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections with minimum inhibitory concentration (MIC) values at the higher end of the susceptibility range. The purpose of this review is to examine the strength of these associations.

**Methods.** All relevant studies pertaining to treatment outcomes or mortality associated with vancomycin MIC were retrieved from the medical literature from January 1996 through August 2011 and analyzed according to Cochrane guidelines.

**Results.** Of the 270 studies identified, 48 studies were reviewed, with 22 studies included in the final meta-analysis. Vancomycin MIC was significantly associated with mortality for MRSA infection irrespective of the source of infection or MIC methodology (odds ratio [OR], 1.64; 95% confidence interval [CI], 1.14–2.37;  $P < .01$ ). This mortality association was predominantly driven by bloodstream infections (BSIs; OR, 1.58; 95% CI, 1.06–2.37;  $P = .03$ ) and isolates with a vancomycin MIC of 2 µg/mL by Etest (OR, 1.72; 95% CI, 1.34–2.21;  $P < .01$ ). Vancomycin MIC was significantly associated with treatment failure irrespective of source of infection or MIC methodology (OR, 2.69; 95% CI, 1.60–4.51;  $P < .01$ ).

**Conclusion.** High vancomycin MIC was associated with a higher mortality rate in MRSA BSI. Thus, institutions should consider conducting Etest MICs on all MRSA BSI isolates. Although these data highlight concerns about vancomycin, currently, there are no data to support better survival rates with alternative antibiotics. Data are sorely needed to determine whether other agents can remedy these outcomes observed with vancomycin for MRSA infections with elevated vancomycin MIC values.





**Figure 2.** Forest plot (using Mantel-Haenszel analysis) of events denoting methicillin-resistant *S. aureus* mortality (irrespective of source of infection and minimum inhibitory concentration [MIC] methodology used) comparing high vancomycin MIC ( $\geq 1.5 \mu\text{g/mL}$ ) with low MIC ( $< 1.5 \mu\text{g/mL}$ ) infections. Squares indicate point estimates, and the size of the square indicates the weight of each study. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel; MIC, minimum inhibitory concentration.

# Association Between Vancomycin Minimum Inhibitory Concentration and Mortality Among Patients With *Staphylococcus aureus* Bloodstream Infections

## A Systematic Review and Meta-analysis

Andre C. Kalil, MD, MPH; Trevor C. Van Schooneveld, MD; Paul D. Fey, PhD; Mark E. Rupp, MD

**IMPORTANCE** *Staphylococcus aureus* bacteremia (SAB) is a worldwide problem. It is unclear whether higher-vancomycin minimum inhibitory concentration (MIC) is associated with mortality. This potential association has direct consequences for patients and public health.

**DATA SOURCES** PubMed, Embase, the Cochrane Library, Evidence-based Medicine BMJ, and the American College of Physicians Journal Club were searched from inception through April 2014.

**STUDY SELECTION** Studies reporting mortality and vancomycin MIC in patients with SAB were included.

**DATA EXTRACTION AND SYNTHESIS** Two authors performed the literature search and the study selection separately. Random-effects modeling was used for all analyses.

**MAIN OUTCOMES AND MEASURES** All-cause mortality.

**FINDINGS** Among 38 included studies that involved 8291 episodes of SAB, overall mortality was 26.1%. The estimated mortality was 26.8% among SAB episodes ( $n = 2740$ ) in patients with high-vancomycin MIC ( $\geq 1.5$  mg/L) compared with 25.8% mortality among SAB episodes ( $n = 5551$ ) in patients with low-vancomycin MIC ( $< 1.5$  mg/L) (adjusted risk difference [RD], 1.6% [95% CI, -2.3% to 5.6%];  $P = .43$ ). For the highest-quality studies, the estimated mortality was 26.2% among SAB episodes ( $n = 2318$ ) in patients with high-vancomycin MIC compared with 27.8% mortality among SAB episodes ( $n = 4168$ ) in patients with low-vancomycin MIC (RD, 0.9% [95% CI, -2.9% to 4.6%];  $P = .65$ ). In studies that included only methicillin-resistant *S aureus* infections ( $n = 7232$ ), the mortality among SAB episodes ( $n = 2384$ ) in patients with high-vancomycin MIC was 27.6% compared with mortality of 27.4% among SAB episodes ( $n = 4848$ ) in patients with low-vancomycin MIC (adjusted RD, 1.6% [95% CI, -2.3% to 5.5%];  $P = .41$ ). No significant differences in risk of death were observed in subgroups with high-vancomycin MIC vs low-vancomycin MIC values across different study designs, microbiological susceptibility assays, MIC cutoffs, clinical outcomes, duration of bacteremia, previous vancomycin exposure, and treatment with vancomycin.

**CONCLUSIONS AND RELEVANCE** In this meta-analysis of SAB episodes, there were no statistically significant differences in the risk of death when comparing patients with *S aureus* exhibiting high-vancomycin MIC ( $\geq 1.5$  mg/L) to those with low-vancomycin MIC ( $< 1.5$  mg/L), although the findings cannot definitely exclude an increased mortality risk. These findings should be considered when interpreting vancomycin susceptibility and in determining whether alternative antistaphylococcal agents are necessary for patients with SAB with elevated but susceptible vancomycin MIC values.

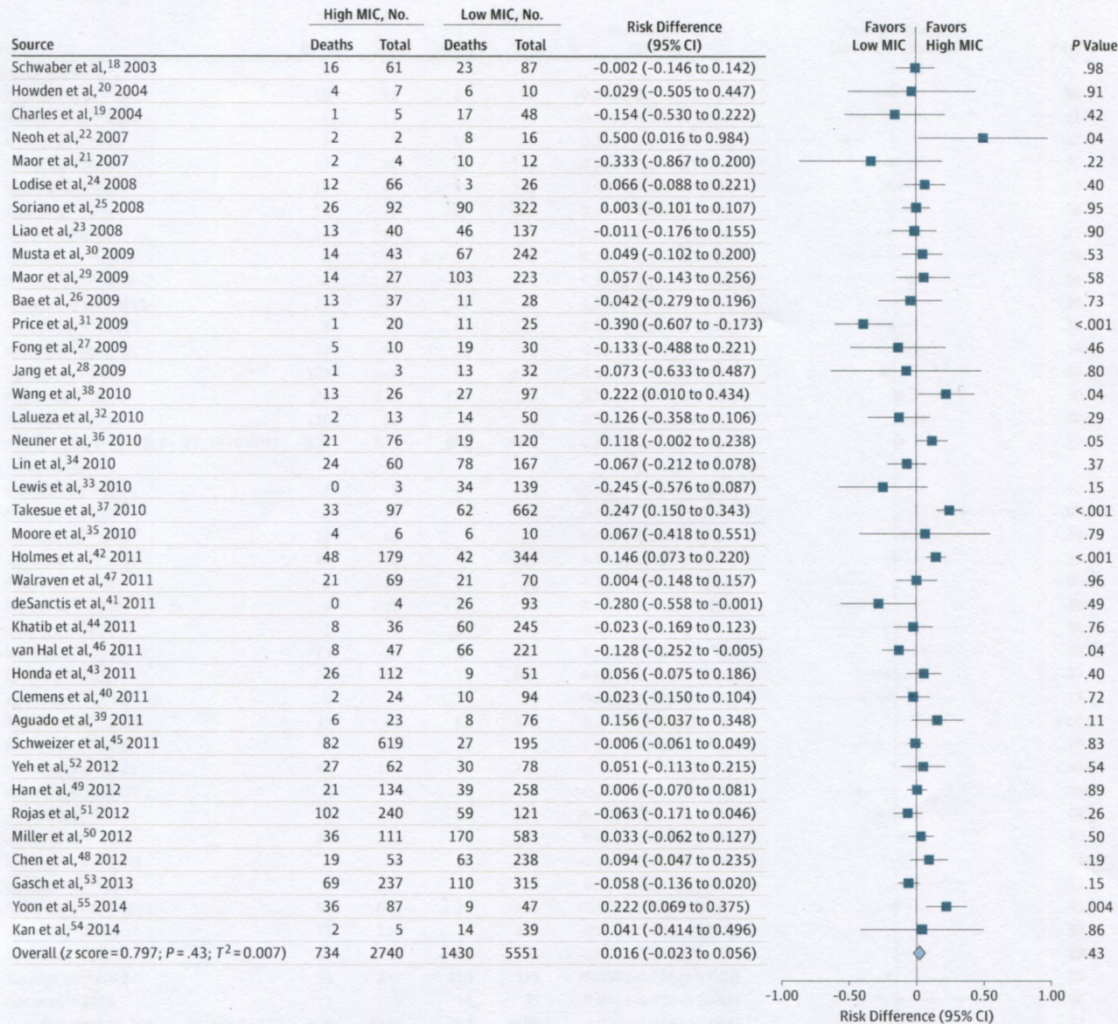
 Supplemental content at [jama.com](http://jama.com)

**Author Affiliations:** Department of Internal Medicine, Division of Infectious Disease, University of Nebraska Medical Center, Omaha (Kalil, Van Schooneveld, Rupp); Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha (Fey).

**Corresponding Author:** Andre C. Kalil, MD, MPH, Department of Internal Medicine, Division of Infectious Disease, University of Nebraska Medical Center, 985400 Nebraska Medical Center, Omaha, NE 68198-5400 ([akalil@unmc.edu](mailto:akalil@unmc.edu)).



Figure 2. Risk Difference for Overall Mortality for High-Vancomycin MIC vs Low-Vancomycin MIC



High-vancomycin minimum inhibitory concentration (MIC) was defined as greater than or equal to 1.5 ug/mL. The size of each data marker indicates the relative weight of each study.

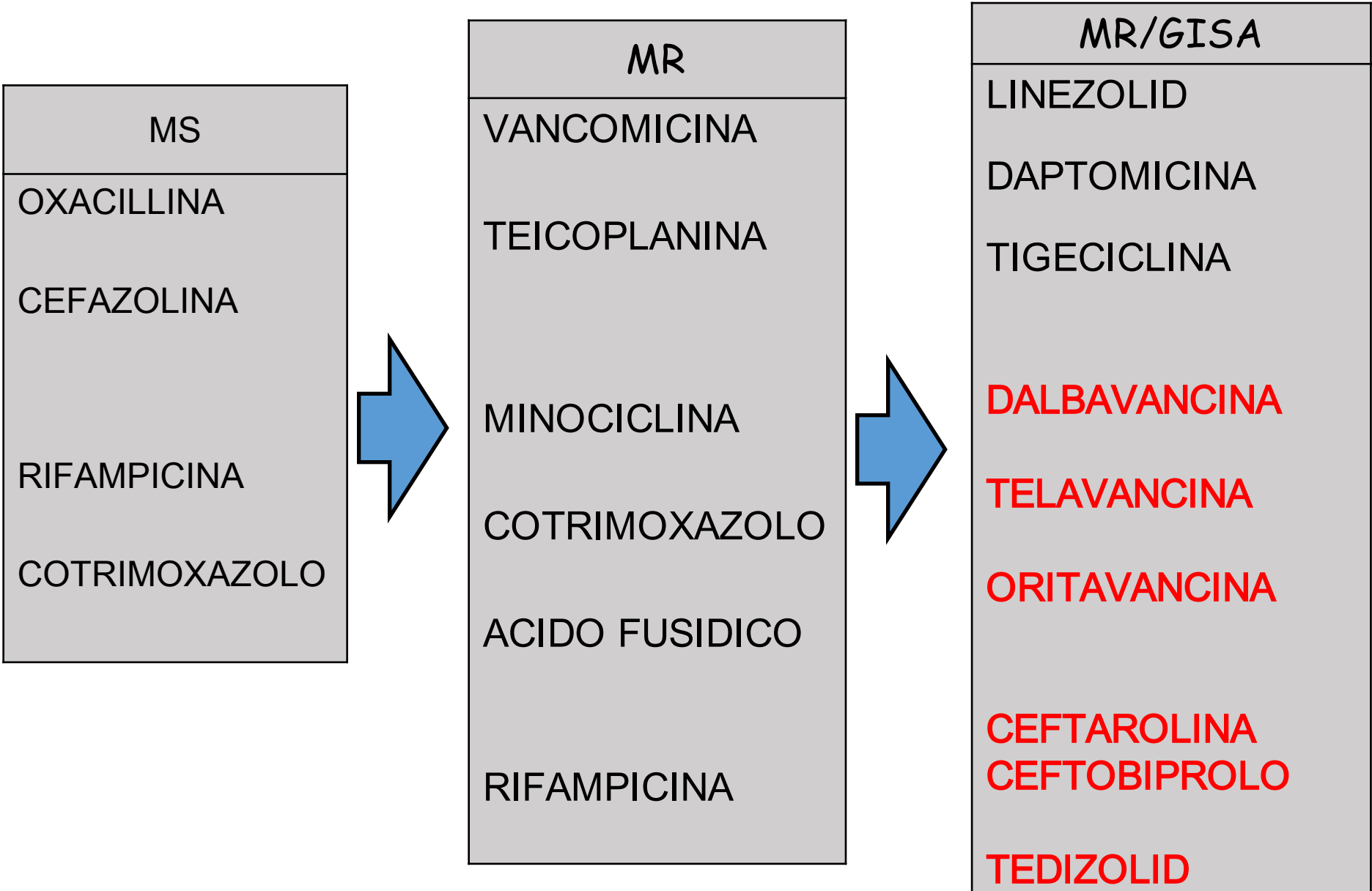


**Table 1**Antibiotic consumption and MIC<sup>a</sup> to vancomycin, daptomycin and linezolid

|                                                   | 2010           | 2011           | 2012           | 2013           | 2014           | p <sup>b</sup> |
|---------------------------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Total <i>Staphylococcus aureus</i> bacteraemia, n | 32             | 31             | 41             | 42             | 63             | -              |
| DDD/100 patients-day (Total DDD)                  |                |                |                |                |                |                |
| Vancomycin                                        | 1.37 (4296)    | 1.32 (3677)    | 0.92 (2648)    | 1.63 (4558)    | 1.55 (4345)    | 0.806          |
| Teicoplanin                                       | 1.02 (2917)    | 1.09 (3048)    | 0.75 (2155)    | 0.71 (1981)    | 0.47 (1484)    | 0.086          |
| Linezolid                                         | 4.30 (13 526)  | 4.04 (11 224)  | 3.13 (9006)    | 5.52 (15 443)  | 5.77 (16 154)  | 0.462          |
| Daptomycin                                        | 0.36 (1129)    | 0.50 (1386)    | 0.64 (1849)    | 1.55 (4342)    | 2.49 (6970)    | 0.023          |
| Cloxacillin                                       | 0.24 (759)     | 0.32 (879)     | 0.53 (1534)    | 0.87 (2441)    | 1.36 (3797)    | 0.015          |
| Quinolones                                        | 10.37 (32 593) | 11.65 (27 526) | 13.08 (37 698) | 21.77 (60 862) | 21.39 (61 502) | 0.029          |
| Antibiotic resistance                             |                |                |                |                |                |                |
| % MRSA                                            | 25.0           | 29.0           | 29.0           | 14.0           | 26.2           | 0.759          |
| Vancomycin MIC, mean (SD)                         | 2.12 (0.73)    | 1.62 (0.59)    | 1.47 (0.46)    | 1.16 (0.33)    | 1.16 (0.35)    | <0.001         |
| % <i>S. aureus</i> vancomycin MIC >1.0 (n)        | 100.0 (31)     | 66.7 (30)      | 67.5 (40)      | 33.3 (39)      | 50.0 (58)      | <0.001         |
| % <i>S. aureus</i> vancomycin MIC >1.5 (n)        | 100.0 (31)     | 53.3 (30)      | 32.5 (40)      | 7.7 (39)       | 6.9 (58)       | <0.001         |
| Daptomycin MIC, mean (95% CI)                     | 0.28 (0.18)    | 0.28 (0.18)    | 0.42 (0.29)    | 0.55 (0.32)    | 0.52 (0.23)    | 0.986          |
| % <i>S. aureus</i> daptomycin MIC >0.25 (n)       | 30.0 (20)      | 20.0 (5)       | 60.7 (28)      | 46.0 (39)      | 40.0 (60)      | 0.807          |
| Linezolid                                         |                |                |                |                |                |                |
| % <i>S. aureus</i> with linezolid MIC >2.0        | 6.00           | 0.00           | 0.00           | 0.00           | 1.59           | 0.309          |

Abbreviations: DDD, Defined Daily Doses; MRSA, methicillin-resistant *S. aureus*.<sup>a</sup> MIC in mg/L.<sup>b</sup> p-value for Kendall correlation test.

# ANTIBIOTICI AD ATTIVITA' ANTISTAFILOCOCCICA



E test E Microscan tendono a SOVRASTIMARE la MIC  
(una diluizione nel 60%)

Phoenix e Vitek tendono a SOTTOSTIMARE la MIC  
(una diluizione nel 27 %)



# TERAPIA DELLE INFEZIONI DA MRSA

(nelle infezioni da MSSA la terapia d'elezione è l'oxacillina)

CMI VANCOMICINA

$\leq 1$



VANCOMICINA  
TEICOPLANINA

BATTERIEMIE  
SEPSI  
ENDOCARDITI



DAPTOMICINA

CMI VANCOMICINA

$\geq 1$



POLMONITI  
INFEZIONI SNC



LINEZOLID\*  
CEFTOBIPROLO

SSSI



TIGECICLINA  
DAPTOMICINA  
LINEZOLID  
CEFTAROLINA

OSTEOMIELITI



DAPTOMICINA\*  
LINEZOLID\*

\* Indicazioni off label per le osteomieliti e per le infezioni del SNC

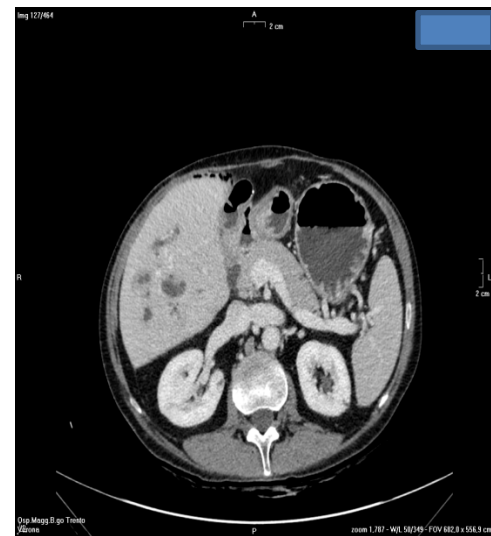
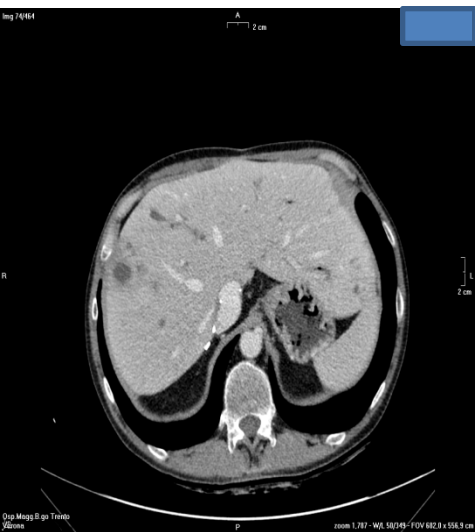
**ENTEROCOCCHI**

**M.G.**

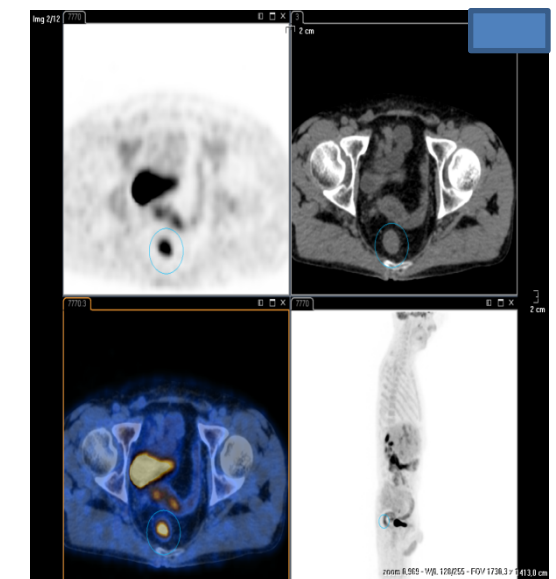
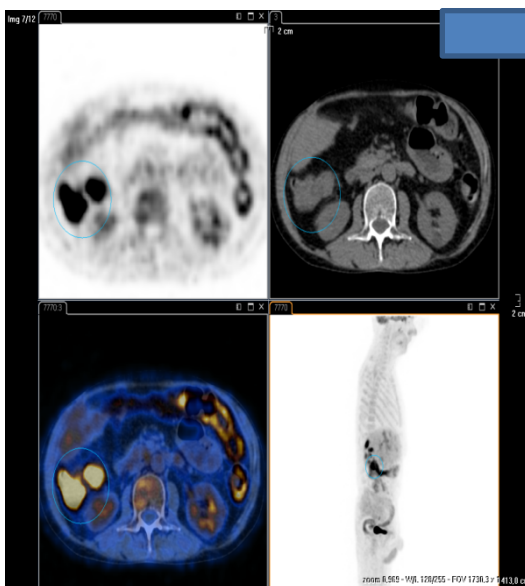
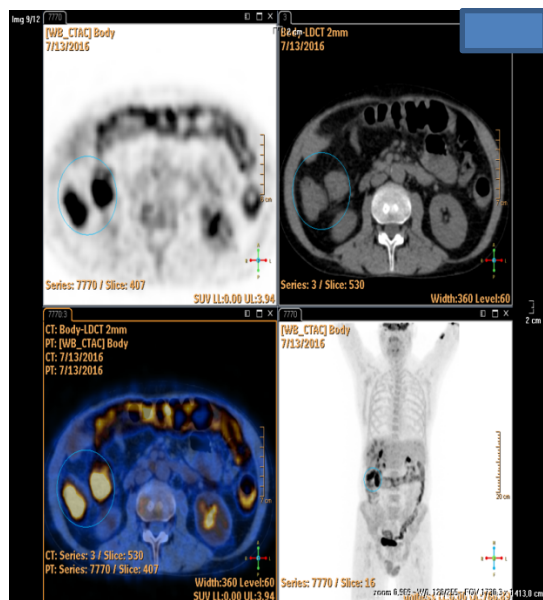
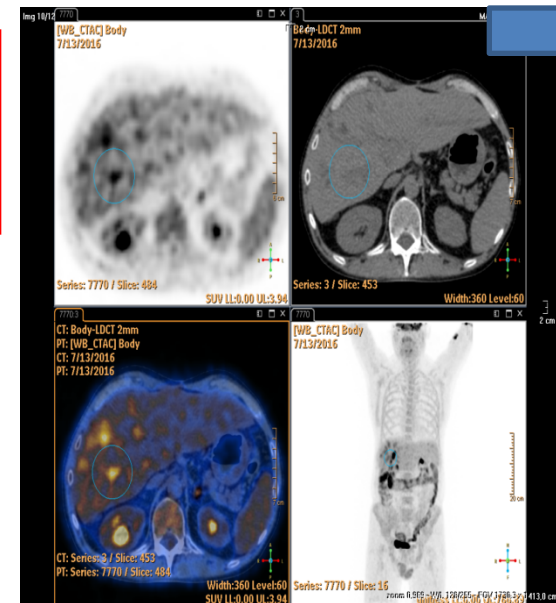
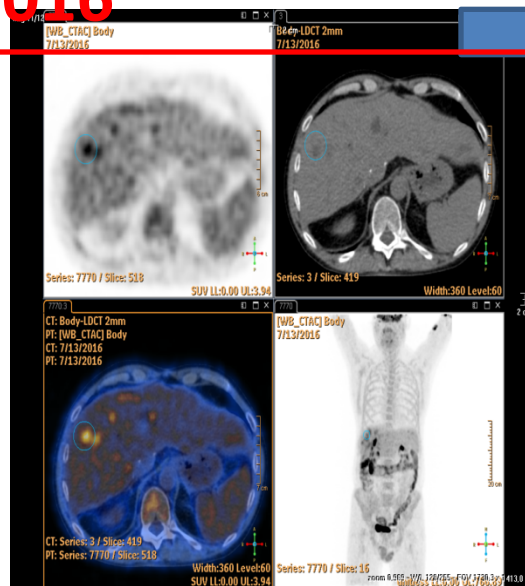
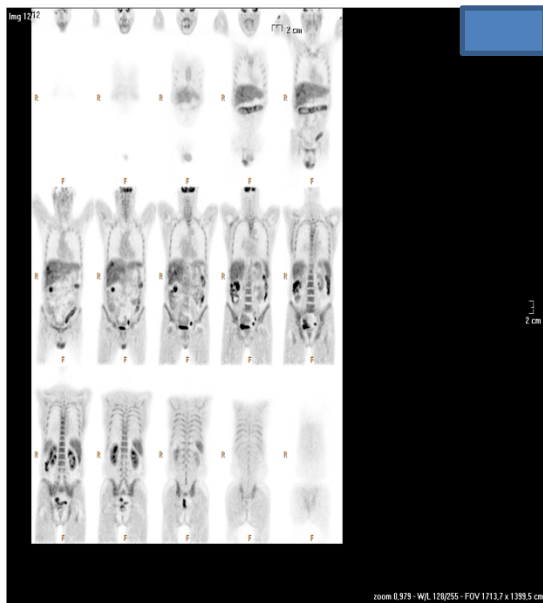
- **Paziente di 55 anni**
- **Dall'anamnesi emergono colangite sclerosante primitiva e malattia di Crohn**
- **Nel 2003 OLT**
- **Nel 2013 epaticodigiunostomia**
- **Nel 2014 re-OLT**



# TC-addome del 5 luglio 2016



# PET-TC del 13 luglio 2016

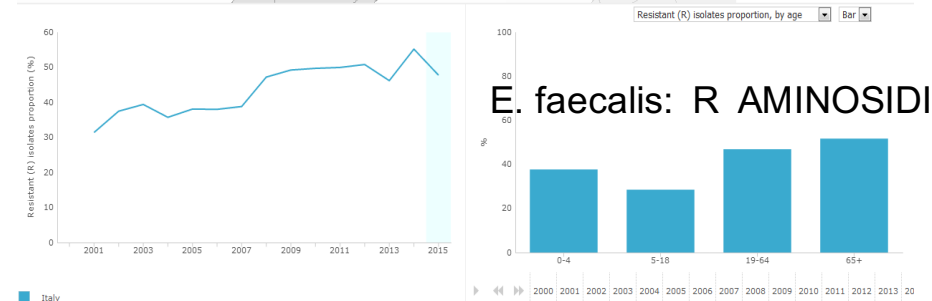
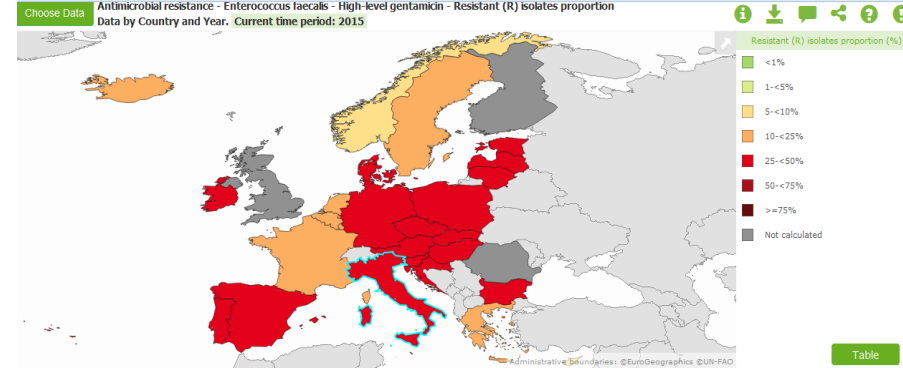
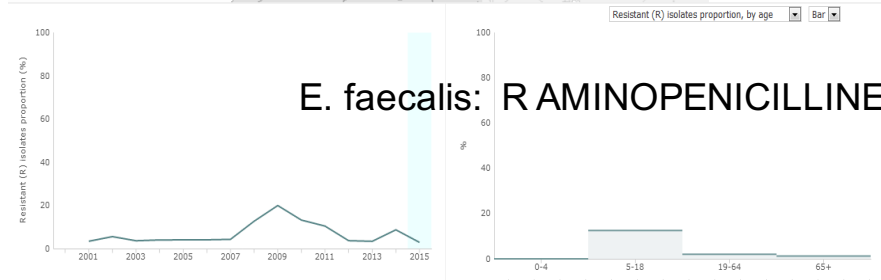
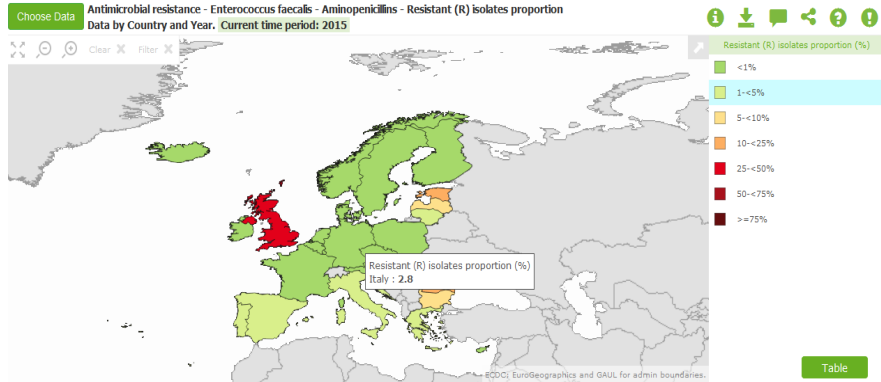


**...dalla coltura del materiale  
drenato vengono isolati Candida  
albicans  
+ Enterococcus faecalis**

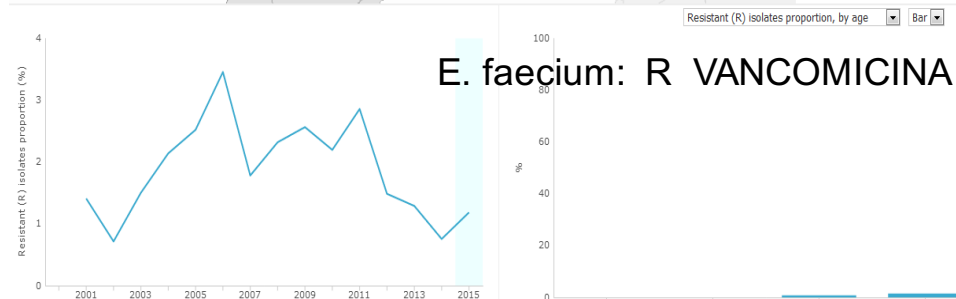
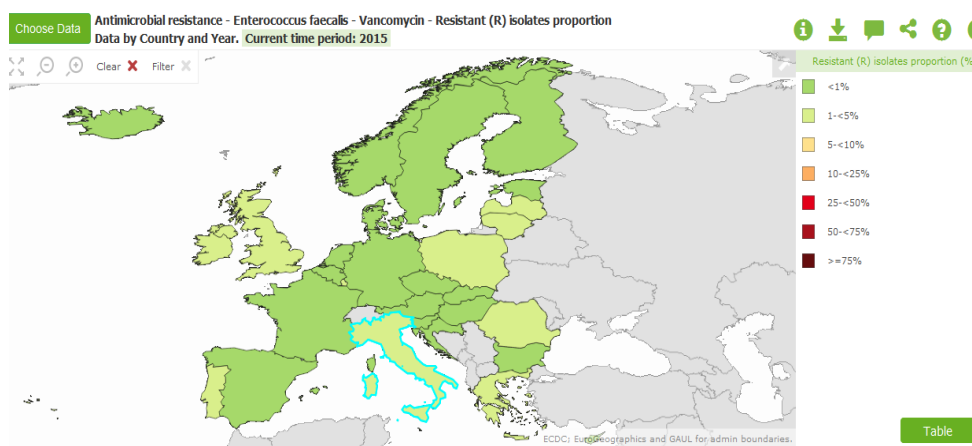
**La terapia antibatterica viene sostituita con  
PIPERACILLINA-TAZOBACTAM 4,5g x 4 al dì  
Viene iniziata terapia con:**

**ANIDULAFUNGINA 100 mg al dì dopo carico di  
200mg**

**Nonostante le emocolture negative il paziente viene  
sottoposto a nuovo ecocardiogramma e ad esame del  
fondo dell'occhio ed entrambi gli accertamenti  
risultano negativi**

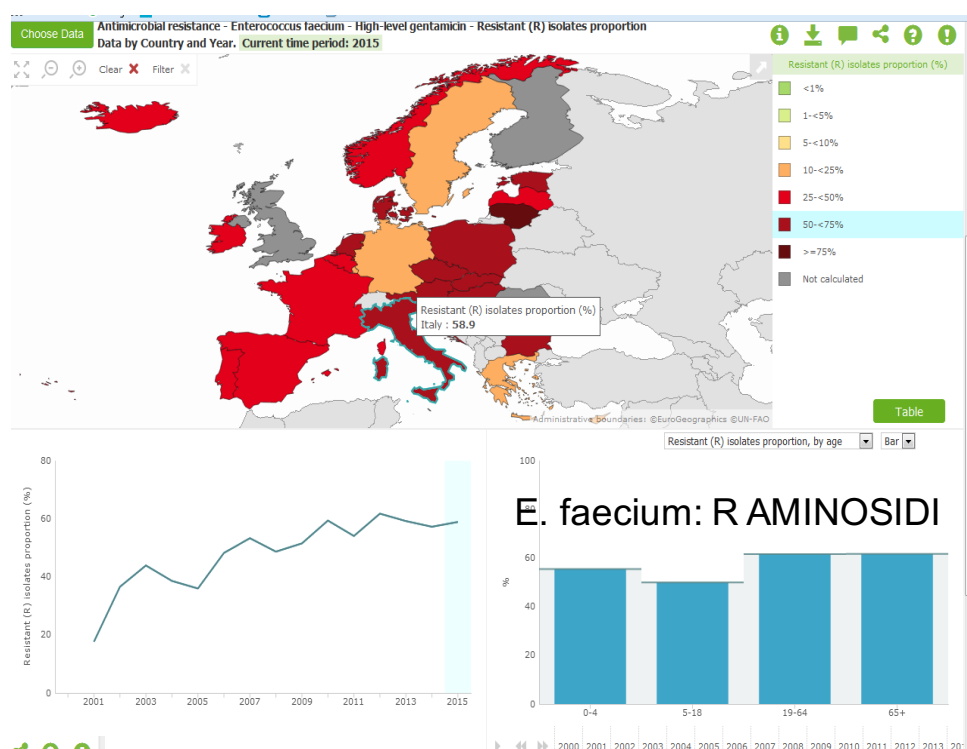
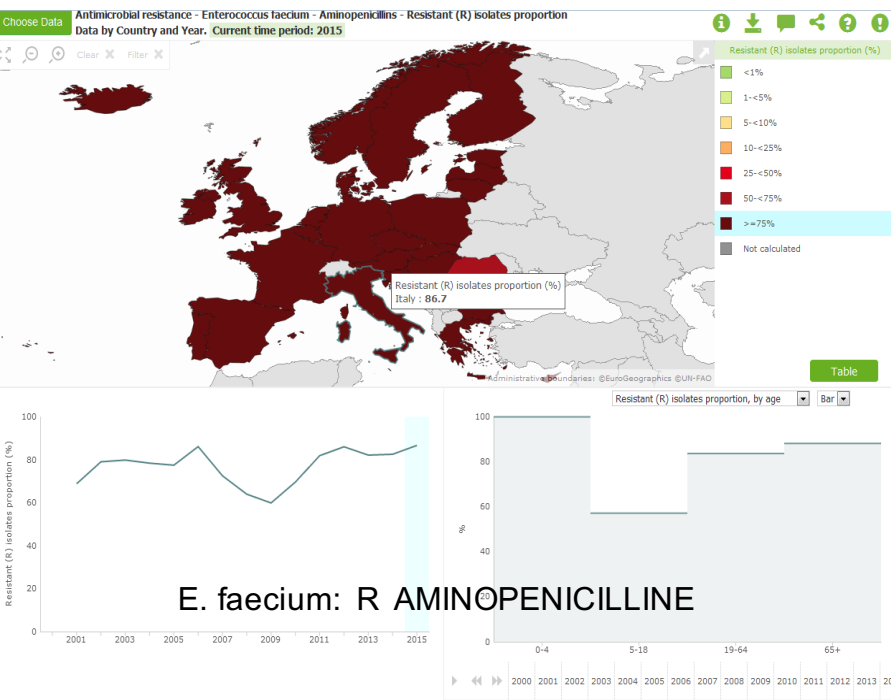


**Enterococcus faecalis**

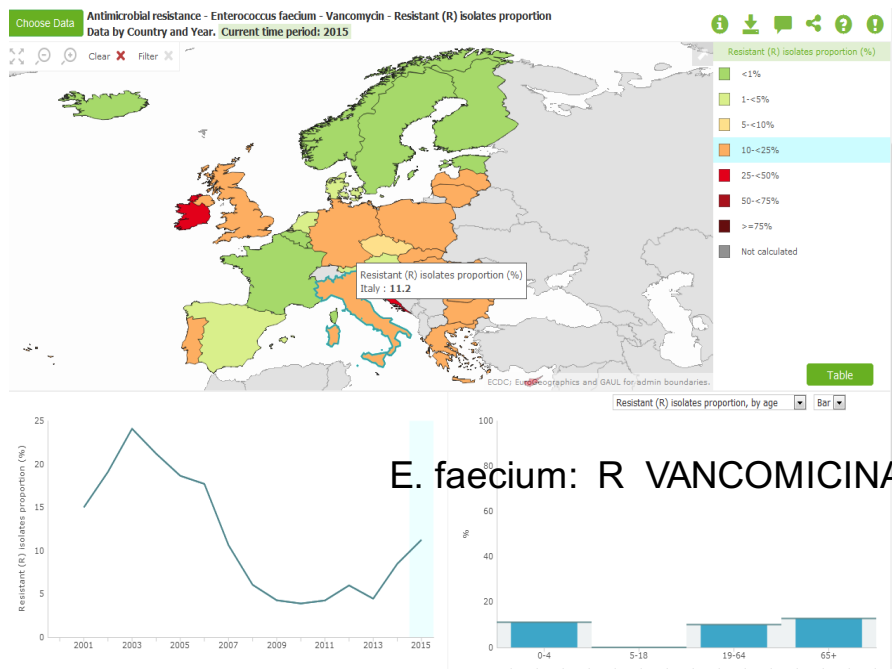


**ECDC 2015**





**Enterococcus faecium**



**ECDC 2015**

# 2016

|     | ITALIA | ARS Toscana   |
|-----|--------|---------------|
| VRE | 11 %   | 21 % (0-72 %) |
| KPC | 34 %   | 37 % (6-60 %) |



**Ampi-S**

**Ampicillina, Vancomicina, Linezolid, Daptomicina, Tigeciclina**

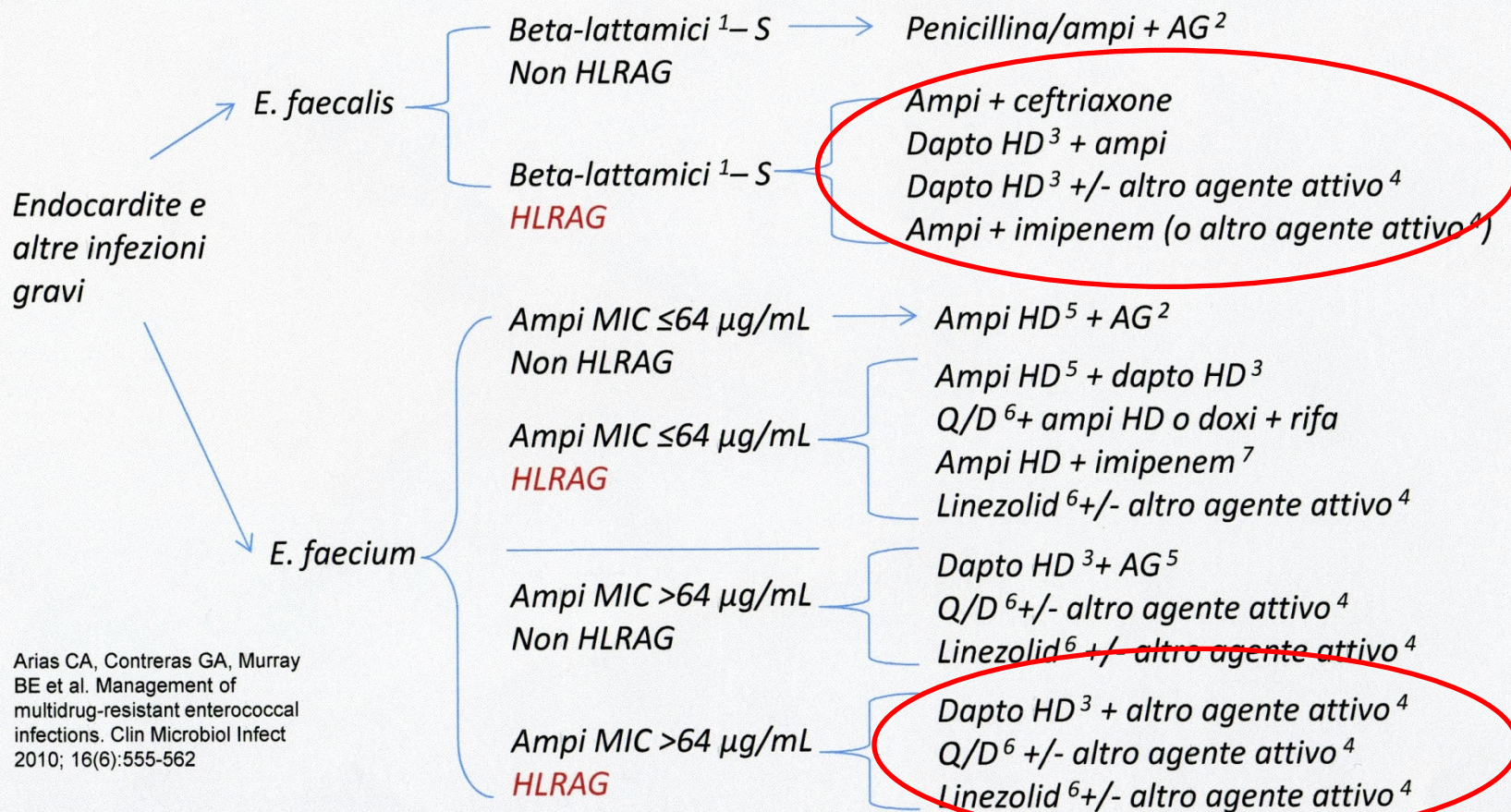
**Ampi-R**

**Vancomicina, Teicoplanina, Linezolid, Daptomicina, Tigeciclina**

**VRE**

**Linezolid, Daptomicina, Tigeciclina**

## Sintesi e algoritmo terapeutico nei VRE



Arias CA, Contreras GA, Murray BE et al. Management of multidrug-resistant enterococcal infections. Clin Microbiol Infect 2010; 16(6):555-562

1: se BL, ampi/sulbactam 12-24 g/die; 2) genta o strepto; 3) 8-12 mg/kg/die; 4) includono: tige, doxi con rifa o fluorochinoloni (se suscettibili per singolo agente); 5) fino a 30 g/die; 6) quinupristin/dalfopristin sono raccomandati da AHA, Linezolid è stato usato per meningiti; 7) se imipenem MIC <32 mg/L. **NOTA: MIC SECONDO CLSI**



**Table 3.** Antimicrobial therapy for vancomycin-resistant *Enterococcus* species.

| Infection                  | Regimen                                                                                       | Comments                                                                                                            |
|----------------------------|-----------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|
| UTI                        | Amoxicillin                                                                                   | Amoxicillin or ampicillin in susceptible <i>E. faecalis</i> and <i>E. faecium</i>                                   |
|                            | Ampicillin                                                                                    | Nitrofurantoin and fosfomycin should be used for cystitis if susceptible                                            |
|                            | Nitrofurantoin                                                                                | Linezolid and daptomycin can be used for complicated UTIs                                                           |
|                            | Fosfomycin                                                                                    |                                                                                                                     |
|                            | Linezolid                                                                                     |                                                                                                                     |
|                            | Daptomycin                                                                                    |                                                                                                                     |
| Intra-abdominal infections | Ampicillin                                                                                    | $\beta$ -Lactams are preferred for susceptible organisms                                                            |
|                            | $\beta$ -Lactam/ $\beta$ -lactamase inhibitor (ampicillin/sulbactam, piperacillin/tazobactam) | $\beta$ -Lactamase inhibitors or carbapenems for $\beta$ -lactamase-producing organisms or polymicrobial infections |
|                            | Carbapenems (imipenem)                                                                        | Linezolid and daptomycin are used for susceptible VRE <i>faecium</i> isolates                                       |
|                            | Linezolid                                                                                     | Tigecycline can be used in susceptible VRE <i>faecium</i> with polymicrobial infection                              |
|                            | Daptomycin                                                                                    | Drain abscess for source control                                                                                    |
|                            | Tigecycline                                                                                   | Linezolid is not approved or recommended for catheter-related infections                                            |
| Bacteremia                 | Ampicillin                                                                                    |                                                                                                                     |
|                            | Linezolid                                                                                     |                                                                                                                     |
| Meningitis                 | Daptomycin                                                                                    |                                                                                                                     |
|                            | Ampicillin <i>plus</i> gentamicin or streptomycin                                             | Daptomycin has been used with linezolid and gentamicin when susceptible                                             |
|                            | Linezolid                                                                                     | Consider intrathecal Q/D                                                                                            |
|                            | High-dose daptomycin <i>with</i> combination therapy                                          | Q/D <i>plus</i> daptomycin or linezolid for VRE <i>faecium</i>                                                      |
| Endocarditis               | Q/D <i>with</i> combination therapy                                                           | Remove or replace indwelling CNS device                                                                             |
|                            | Ampicillin <i>plus</i> aminoglycosides or ceftriaxone                                         | Ampicillin <i>plus</i> aminoglycoside is preferred in susceptible isolates for 4–6 weeks                            |
|                            | High-dose daptomycin <i>plus</i> aminoglycoside, ampicillin or ceftaroline                    | Daptomycin 8 mg/kg/24 hours for 6–8 weeks                                                                           |
|                            | Q/D <i>plus</i> another agent ( <i>E. faecium</i> only)                                       |                                                                                                                     |

Q/D: quinupristin/dalfopristin; VRE: vancomycin-resistant *Enterococcus*.



# *Nocardia*

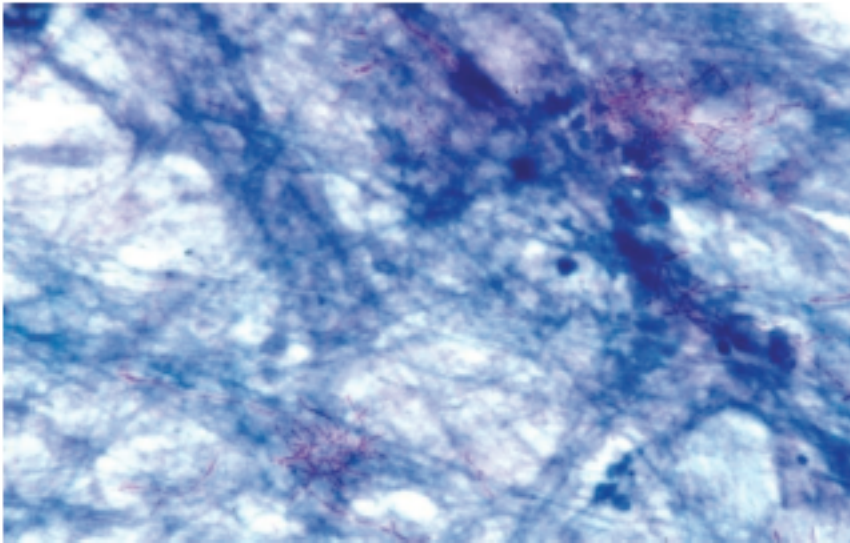


FIG. 3. *N. asteroides* filaments in a direct smear of sputum stained by the modified Kinyoun acid-fast method. Magnification,  $\times 1,000$ .

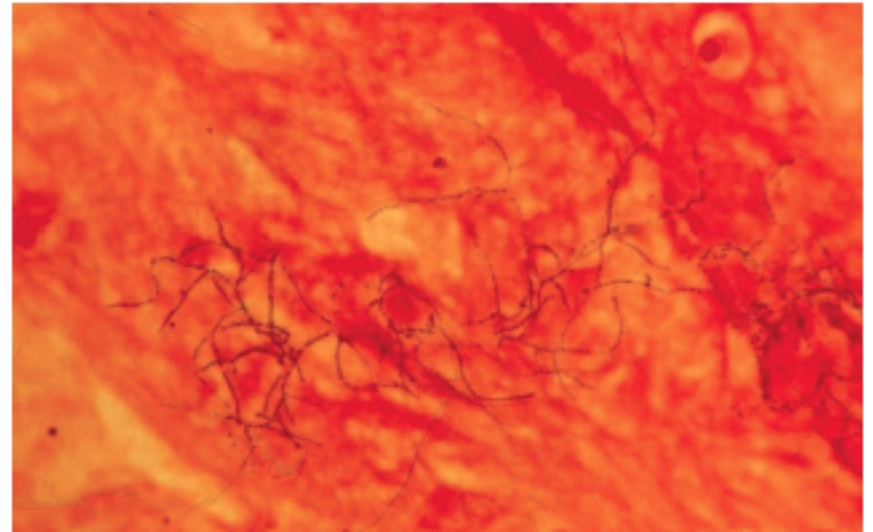
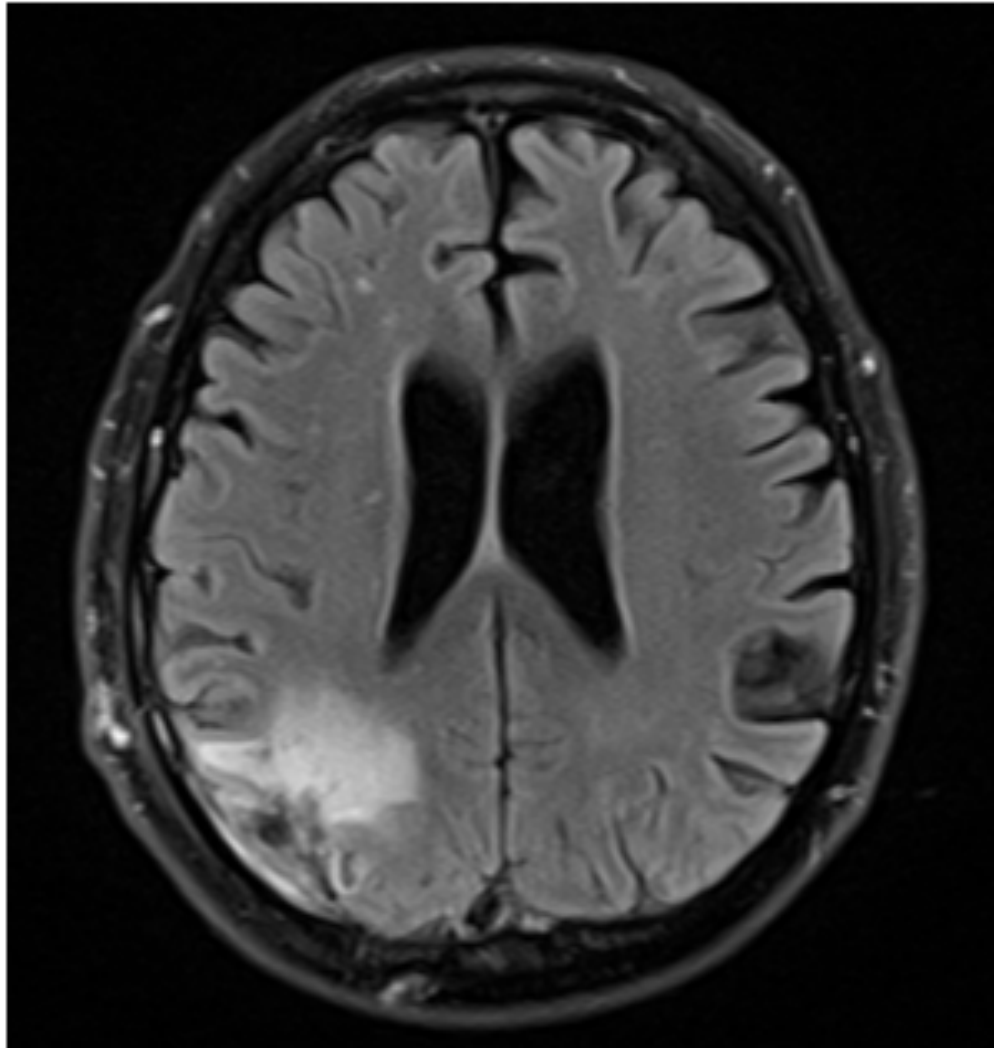


FIG. 2. Gram-positive beaded branching filaments of *N. asteroides* in a smear of sputum. Magnification,  $\times 1,000$ .

- Paziente maschio di anni 60 trapiantato di cuore
- Condotta in PS a Peschiera d/G per crisi comiziale. Qui esegue RM encefalo che documenta lesione sospetta per ascesso intraparenchimale parieto-occipitale;
- Viene trasferito presso il reparto di NCH di Verona, dove viene eseguita rachicentesi con ricerca di (1-3) - Beta -d- Glucano, risultato POSITIVO;





- Nel sospetto di eziologia fungina della lesione si procede a biopsia con drenaggio della raccolta asessuale;
- Da tale materiale viene tuttavia isolata

*Nocardia abscessus!*

## -- ESAMI BATTERIOLOGICI --

### Ricerca micobatteri su biopsia

|                                     |          |
|-------------------------------------|----------|
| Esame microscopico                  | Negativo |
| Coltura terreno solido L J          | Negativo |
| Coltura t. liquido non radiomarcato | Negativo |

### Materiali purulenti

|                              |                                                                             |
|------------------------------|-----------------------------------------------------------------------------|
| Nota                         | PARIETALE INTRACEREBRALE +RIC MICETI                                        |
| Esame microscopico           | leucociti polimorfonucleati ++; Bacilli sottili, filamentosi e ramificati . |
| Esame colturale in aerobiosi | Nocardia spp; Nocardia abscessus                                            |

#### **Actinomyces**

Nocardia spp

|                |   |            |
|----------------|---|------------|
| AMIKACINA      | R | MIC 32;    |
| CEFTRIAXONE    | S | MIC 0.19;  |
| MEROPENEM      | S | MIC 0.032; |
| TRIM.+SULFAMET | S | MIC 0.25;  |

|                                |                                  |
|--------------------------------|----------------------------------|
| Esame colturale in anaerobiosi | Nessuno sviluppo                 |
| Esame colturale per lieviti    | Nessuno sviluppo                 |
| Commento all'analisi           | Antibiogramma non standardizzato |

- Alla luce di tale risultato viene impostata terapia specifica con Trimetoprim/sulfametoxazolo + Meropenem;
- Ai controlli successivi buone condizioni generali con progressivo riassorbimento della raccolta precedentemente nota.



*Nocardia* infections appear to have increased in the last two decades, likely due to the expanding immunocompromised host population as well as better detection and identification procedures (2). The frequency of nocardial infections in solid organ transplant recipients varies between 0.7% and 3.5%, and in the past these infections were mostly reported in heart, kidney and liver transplant recipients, and

less frequently in lung transplantation (11–13). However, a review of 5126 organ transplant recipients noted that lung transplant recipients had a greater rate of nocardial infection (3.5%) than heart, intestine, kidney or liver recipients (2.5%, 1.3%, 0.2% and 0.1%, respectively) (13) and a recent retrospective study of 577 lung transplant recipients noted an incidence of 1.9% (14). Regarding species prevalence in organ transplant recipients with nocardiosis, in the series by Peleg et al. noted earlier, *N. nova* was the most common species isolated from 35 patients and was identified in 49% of cases, followed by *Nocardia farcinica* in 28%, *Nocardia asteroides* in 23% and *Nocardia brasiliensis* in 3% (13).



# *Nocardia* Infection in Solid Organ Transplant Recipients: A Multicenter European Case-control Study

Julien Coussement,<sup>1,a</sup> David Lebeaux,<sup>2,a</sup> Christian van Delden,<sup>3,4</sup> Hélène Guillot,<sup>5</sup> Romain Freund,<sup>6,7</sup> Sierk Marbus,<sup>8</sup> Giovanna Melica,<sup>9</sup> Eric Van Wijngaerden,<sup>10</sup> Benoit Douvry,<sup>11</sup> Steven Van Laecke,<sup>12</sup> Fanny Vuotto,<sup>13</sup> Leïla Tricot,<sup>14</sup> Mario Fernández-Ruiz,<sup>15</sup> Jacques Dantal,<sup>16</sup> Cédric Hirzel,<sup>4,17</sup> Jean-Philippe Jais,<sup>6,7</sup> Veronica Rodriguez-Nava,<sup>18</sup> Olivier Lortholary,<sup>2,b</sup> and Frédérique Jacobs<sup>1,b</sup>; for the European Study Group for *Nocardia* in Solid Organ Transplantation<sup>c</sup>

<sup>1</sup>Department of Infectious Diseases, CUB-Hôpital Erasme, Université Libre de Bruxelles, Brussels; <sup>2</sup>Université Paris Descartes, Sorbonne Paris Cité, AP-HP, Hôpital Necker Enfants Malades, Centre d'Infectiologie Necker-Pasteur and Institut Imagine, France; <sup>3</sup>Transplant Infectious Diseases Unit, Hôpitaux Universitaires de Genève, and <sup>4</sup>Swiss Transplant Cohort Study, Switzerland; <sup>5</sup>Service des Maladies Infectieuses et Tropicales, Sorbonne Universités, UPMC Université Paris 06, AP-HP, Hôpital Pitié-Salpêtrière, <sup>6</sup>Université Paris Descartes, INSERM UMRs 1138 Team 22, and <sup>7</sup>Biostatistics Unit, AP-HP, Hôpital Necker Enfants Malades, Paris, France; <sup>8</sup>Department of Infectious Diseases, Leiden University Medical Center, The Netherlands; <sup>9</sup>Immunologie Clinique et Maladies Infectieuses, AP-HP, Hôpital Henri Mondor, Créteil, France; <sup>10</sup>Department of General Internal Medicine, University Hospitals Leuven, Belgium; <sup>11</sup>Service de Pneumologie et de Transplantation Pulmonaire, Hôpital Foch, Suresnes, France; <sup>12</sup>Renal Division, Ghent University Hospital, Belgium; <sup>13</sup>Infectious Diseases Unit, Huriez Hospital, CHRU Lille, and <sup>14</sup>Service de Néphrologie–Transplantation Rénale, Hôpital Foch, Suresnes, France; <sup>15</sup>Unit of Infectious Diseases, University Hospital 12 de Octubre, Instituto de Investigación Hospital "12 de Octubre" (i+12), Madrid, Spain; <sup>16</sup>Institut de Transplantation, d'Urologie et de Néphrologie, CHU Nantes, France; <sup>17</sup>Department of Infectious Diseases, Bern University Hospital, University of Bern, Switzerland; and <sup>18</sup>Research Group on Bacterial Opportunistic Pathogens and Environment UMR5557 Écologie Microbienne, French Observatory of Nocardiosis, Université de Lyon 1, CNRS, VetAgro Sup, France

**Background.** Nocardiosis is a rare, life-threatening opportunistic infection, affecting 0.04% to 3.5% of patients after solid organ transplant (SOT). The aim of this study was to identify risk factors for *Nocardia* infection after SOT and to describe the presentation of nocardiosis in these patients.

**Methods.** We performed a retrospective case-control study of adult patients diagnosed with nocardiosis after SOT between 2000 and 2014 in 36 European (France, Belgium, Switzerland, the Netherlands, Spain) centers. Two control subjects per case were matched by institution, transplant date, and transplanted organ. A multivariable analysis was performed using conditional logistic regression to identify risk factors for nocardiosis.

**Results.** One hundred and seventeen cases of nocardiosis and 234 control patients were included. Nocardiosis occurred at a median of 17.5 (range, 2–244) months after transplant. In multivariable analysis, high calcineurin inhibitor trough levels in the month before diagnosis (odds ratio [OR], 6.11; 95% confidence interval [CI], 2.58–14.51), use of tacrolimus (OR, 2.65; 95% CI, 1.17–6.00) and corticosteroid dose (OR, 1.12; 95% CI, 1.03–1.22) at the time of diagnosis, patient age (OR, 1.04; 95% CI, 1.02–1.07), and length of stay in the intensive care unit after SOT (OR, 1.04; 95% CI, 1.00–1.09) were independently associated with development of nocardiosis; low-dose cotrimoxazole prophylaxis was not found to prevent nocardiosis. *Nocardia farcinica* was more frequently associated with brain, skin, and subcutaneous tissue infections than were other *Nocardia* species. Among the 30 cases with central nervous system nocardiosis, 13 (43.3%) had no neurological symptoms.

**Conclusions.** We identified 5 risk factors for nocardiosis after SOT. Low-dose cotrimoxazole was not found to prevent *Nocardia* infection. These findings may help improve management of transplant recipients.

**Keywords.** *Nocardia*; nocardiosis; organ transplant; opportunistic infections.



From: **Nocardia Infection in Solid Organ Transplant Recipients: A Multicenter European Case-control Study**

Clin Infect Dis. 2016;63(3):338-345. doi:10.1093/cid/ciw241

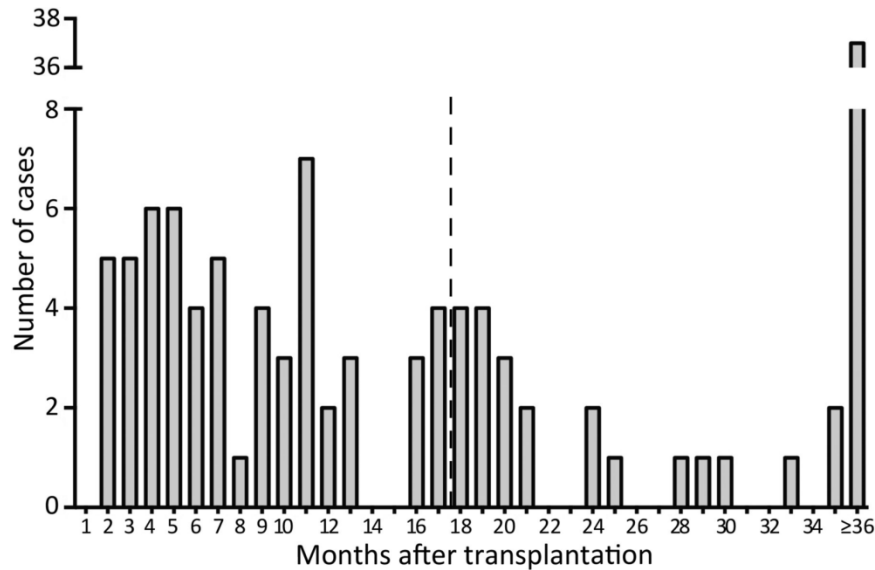
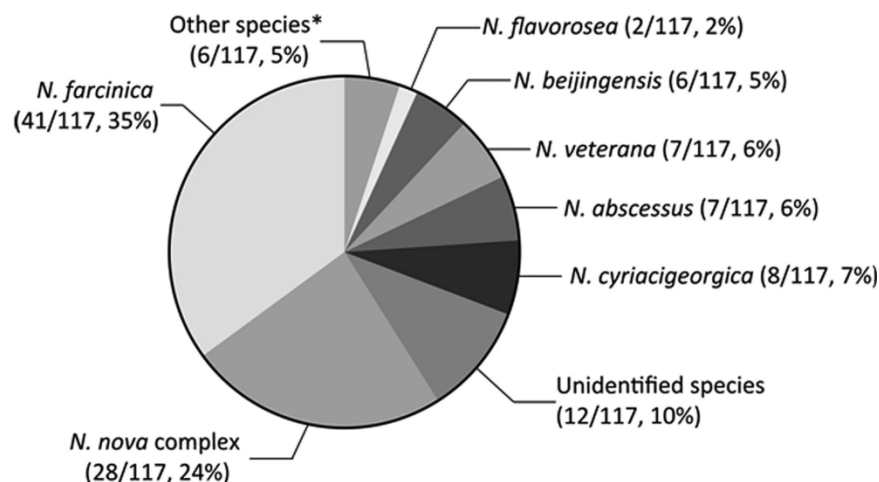


Figure Legend:  
Distribution of the time (in months) between solid organ transplant and the occurrence of nocardiosis in the 117 cases. Dashed line represents the median time point (17.5 months).

# From: **Nocardia Infection in Solid Organ Transplant Recipients: A Multicenter European Case-control Study**

Clin Infect Dis. 2016;63(3):338-345. doi:10.1093/cid/ciw241



## Figure Legend:

Distribution of the various *Nocardia* species identified using molecular biology in the 117 cases of posttransplant nocardiosis.  
\*Other species include *N. otitidiscaviarum* (n = 1), *N. brevicatena/paucivorans* complex (n = 1), *N. cerradoensis* (n = 1), *N. pseudobrasiliensis* (n = 1), *N. anaemiae* (n = 1), *N. takedensis* (n = 1).



## Description of Cases of Posttransplant Nocardiosis at Diagnosis

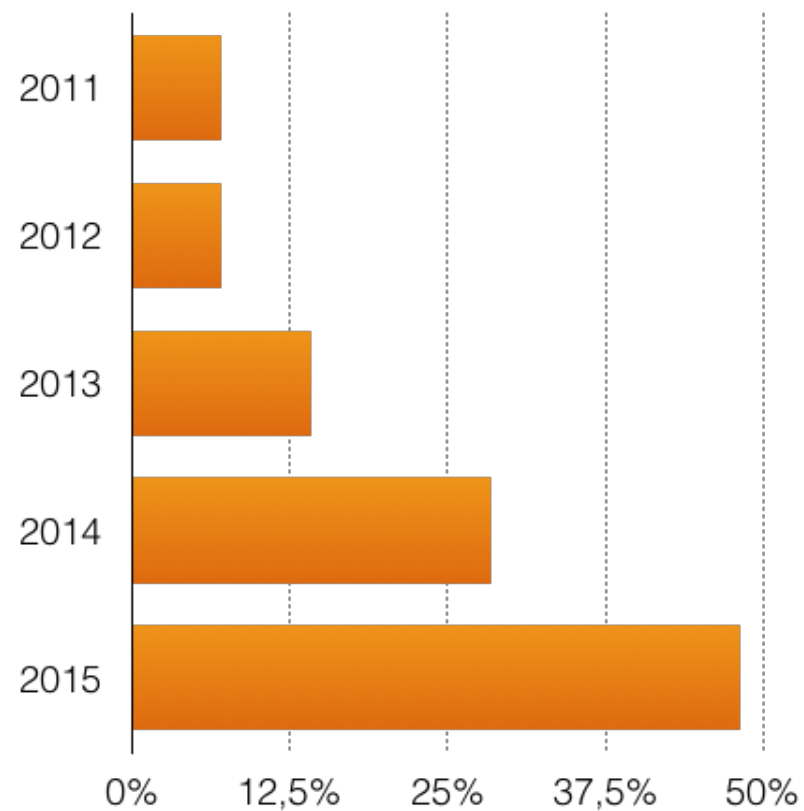
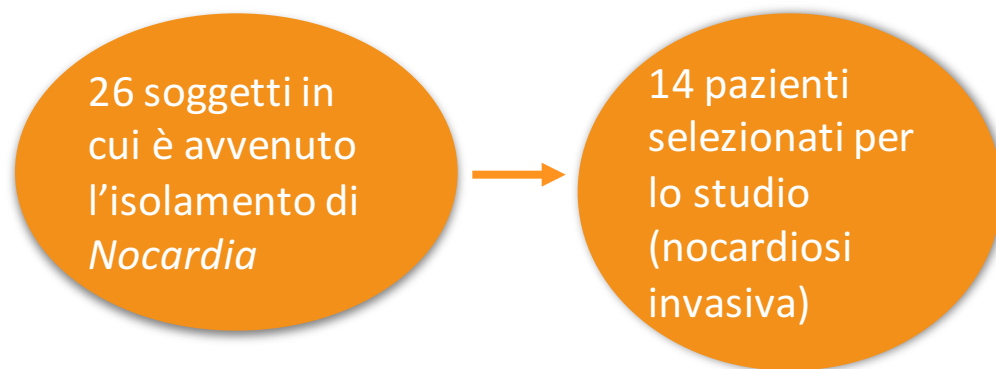
| Characteristics                                             | N = 117      |
|-------------------------------------------------------------|--------------|
| Clinical characteristics                                    |              |
| Time from onset of symptoms to diagnosis, d, median (range) | 19.5 (1–139) |
| Involved organs                                             |              |
| Lung                                                        | 101 (86.3)   |
| Skin and soft tissue                                        | 37 (31.6)    |
| Skin and soft tissue as the only site of infection          | 8 (6.8)      |
| Brain                                                       | 30 (25.6)    |
| Joint(s) or bone(s)                                         | 3 (2.5)      |
| Disseminated infection                                      | 50 (42.7)    |

**Table 3.**

Risk Factors for Nocardiosis in 117 Cases Compared With 234 Controls After Multivariable Analysis by Conditional Logistic Regression

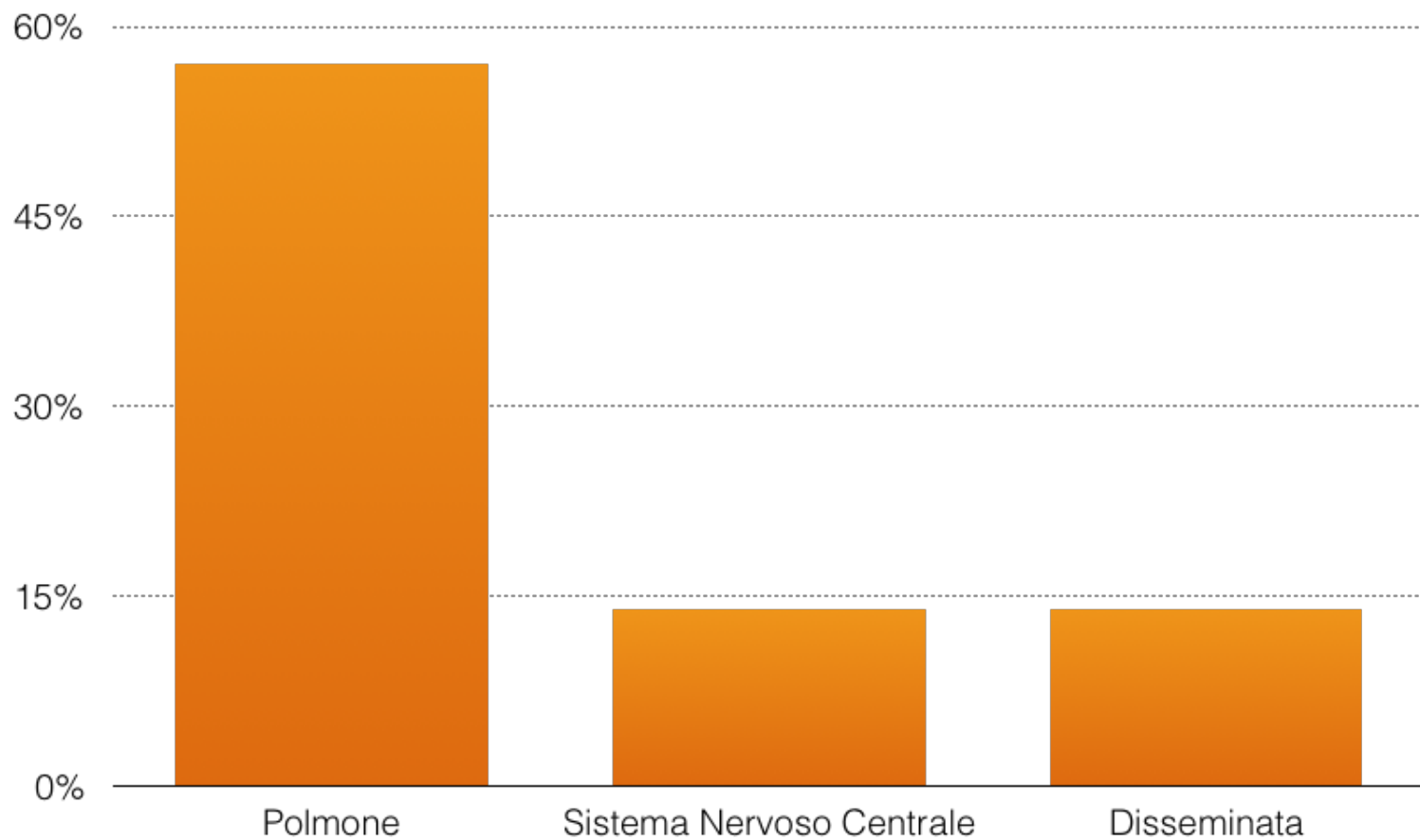
| Characteristic                                                   | OR (95% CI)          | P Value |
|------------------------------------------------------------------|----------------------|---------|
| High calcineurin inhibitor level in the month before nocardiosis | 6.11<br>(2.58–14.51) | <.001   |
| Use of tacrolimus at diagnosis                                   | 2.65 (1.17–6.00)     | .015    |
| Corticosteroid dose at diagnosis (per mg <sup>a</sup> )          | 1.12 (1.03–1.22)     | .002    |
| Age at diagnosis (per year)                                      | 1.04 (1.02–1.07)     | <.001   |
| Length of first ICU stay after transplant (per day)              | 1.04 (1.00–1.09)     | .049    |

## POPOLAZIONE IN STUDIO



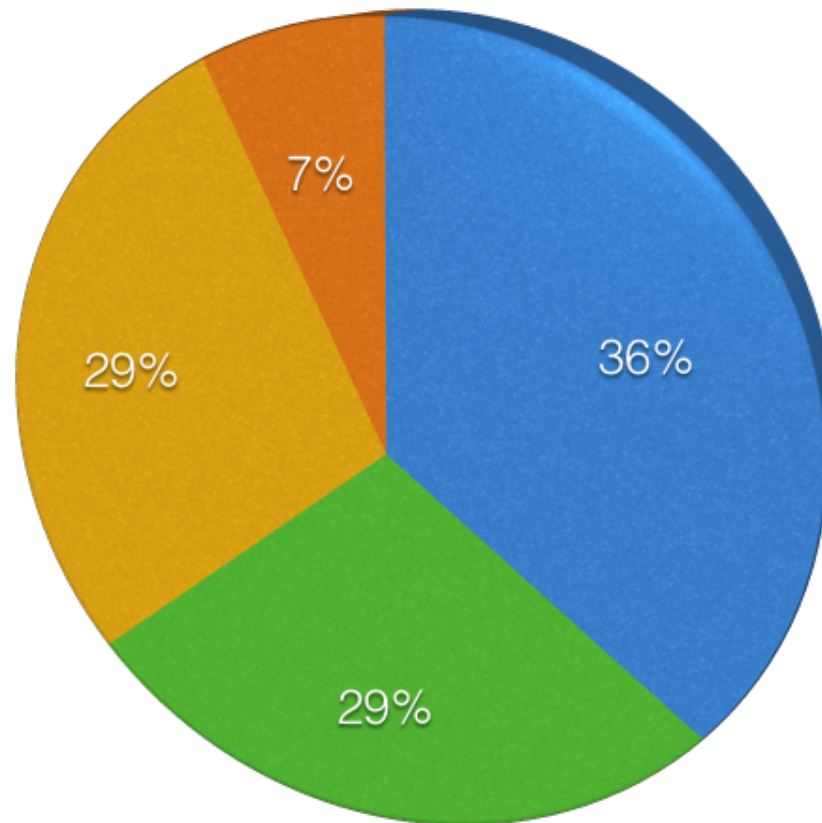


## SEDI MAGGIORMENTE INTERESSATE



## SPECIE DI NOCARDIA ISOLATE: AOUI VERONA 2011-2016

- N.abscessus
- N.farcinica
- N.cyriacigeorgica
- Non identificata



# classificazione e sensibilità antibiotica

TABLE 1 Antimicrobial nonsusceptibility for 1,299 *Nocardia* strains isolated over a 6-year period

| Organism (n)                           | % of strains with result <sup>a</sup> |       |         |         |         |       |         |         |         |         |             |
|----------------------------------------|---------------------------------------|-------|---------|---------|---------|-------|---------|---------|---------|---------|-------------|
|                                        | TMP-SXT R                             | AMK R | IMI R/I | CTR R/I | AUG R/I | LZD R | CIP R/I | CLA R/I | MIN R/I | TOB R/I | MXF R/I (n) |
| <i>N. abscessus</i> complex (110)      | 0                                     | 0     | 69      | 2       | 22      | 0     | 100     | 71      | 15      | 0       | 92 (39)     |
| <i>N. amamiensis</i> (2)               | 0                                     | 0     | 0       | 0       | 50      | 0     | 100     | 100     | 0       | 0       | 100 (1)     |
| <i>N. amikacinintolerans</i> (7)       | 0                                     | 57    | 28      | 43      | 0       | 0     | 100     | 86      | 14      | 0       | 100 (5)     |
| <i>N. aobensis</i> (2)                 | 0                                     | 0     | 50      | 50      | 100     | 0     | 100     | 0       | 100     | 100     | 100 (2)     |
| <i>N. asteroides sensu stricto</i> (3) | 0                                     | 0     | 0       | 0       | 100     | 0     | 100     | 100     | 33      | 0       | 100 (2)     |
| <i>N. beijingensis</i> complex (30)    | 0                                     | 0     | 7       | 3       | 97      | 0     | 96      | 37      | 20      | 0       | 95 (18)     |
| <i>N. blacklockiae</i> (1)             | 0                                     | 0     | 100     | 0       | 0       | 0     | 100     | 0       | 100     | 100     | 0 (1)       |
| <i>N. brasiliensis</i> (148)           | 0                                     | 0     | 99      | 51      | 4.7     | 0     | 99      | 97      | 76      | 0       | 1 (88)      |
| <i>N. brevicatena</i> (1)              | 0                                     | 0     | 0       | 0       | 100     | 0     | 100     | 0       | 0       | 0       | 0 (0)       |
| <i>N. carnea</i> (2)                   | 0                                     | 0     | 0       | 0       | 100     | 0     | 0       | 50      | 100     | 0       | 0 (0)       |
| <i>N. cyriacigeorgica</i> (264)        | 0                                     | 0     | 57      | 12      | 97      | 0     | 100     | 99      | 94      | 0.8     | 96 (128)    |
| <i>N. exalbida</i> complex (4)         | 0                                     | 0     | 25      | 0       | 100     | 0     | 75      | 50      | 50      | 0       | 100 (1)     |
| <i>N. farcinica</i> (204)              | 0.5                                   | 0     | 67      | 97      | 24      | 0     | 57      | 99.5    | 95      | 99.5    | 21 (99)     |
| <i>N. flavorosea</i> (1)               | 0                                     | 0     | 0       | 0       | 100     | 0     | 0       | 100     | 0       | 0       | 0 (1)       |
| <i>N. grenadensis</i> (2)              | 0                                     | 0     | 100     | 0       | 100     | 0     | 0       | 100     | 50      | 0       | 0 (0)       |
| <i>N. higoensis</i> (2)                | 0                                     | 0     | 50      | 0       | 100     | 0     | 0       | 50      | 0       | 0       | 0 (0)       |
| <i>N. ignorata</i> (1)                 | 0                                     | 0     | 100     | 100     | 100     | 0     | 100     | 0       | 0       | 0       | 0 (1)       |
| <i>N. mexicana</i> (1)                 | 0                                     | 0     | 100     | 0       | 100     | 0     | 100     | 0       | 100     | 100     | 0 (0)       |
| <i>N. neocaledoniensis</i> (1)         | 0                                     | 0     | 0       | 0       | 100     | 0     | 100     | 100     | 100     | 0       | 100 (1)     |
| <i>N. niigatensis</i> (2)              | 0                                     | 0     | 100     | 100     | 100     | 0     | 0       | 0       | 100     | 0       | 0 (1)       |
| <i>N. niwae</i> (6)                    | 0                                     | 0     | 0       | 0       | 100     | 0     | 100     | 50      | 50      | 0       | 0 (0)       |
| <i>N. nova</i> complex (320)           | 0                                     | 0     | 1       | 53      | 91      | 0     | 99      | 3       | 88      | 87      | 98 (162)    |
| <i>N. nova</i> <sup>b</sup> (246)      | 0                                     | 0     | 2       | 50      | 92      | 0     | 99      | 0       | 90      | 88      | 99 (132)    |
| <i>N. otitidiscaviarum</i> (29)        | 0                                     | 0     | 93      | 100     | 100     | 0     | 93      | 93      | 55      | 38      | 65 (17)     |
| <i>N. paucivorans</i> (11)             | 0                                     | 0     | 0       | 0       | 90      | 0     | 9       | 18      | 9       | 0       | 0 (5)       |
| <i>N. pseudobrasiliensis</i> (13)      | 31                                    | 31    | 100     | 100     | 100     | 0     | 0       | 0       | 100     | 0       | 0 (7)       |
| <i>N. puris</i> (7)                    | 0                                     | 0     | 57      | 86      | 85      | 0     | 100     | 100     | 0       | 0       | 100 (1)     |
| <i>N. rhamnosiphila</i> (4)            | 0                                     | 0     | 25      | 0       | 100     | 0     | 0       | 100     | 100     | 0       | 0 (2)       |
| <i>N. takedensis</i> (1)               | 0                                     | 0     | 0       | 0       | 0       | 0     | 100     | 0       | 0       | 0       | 100 (1)     |
| <i>N. testacea</i> (1)                 | 0                                     | 0     | 0       | 0       | 100     | 0     | 0       | 100     | 100     | 0       | 0 (0)       |
| <i>N. thailandica</i> (1)              | 0                                     | 0     | 0       | 0       | 100     | 0     | 100     | 0       | 100     | 0       | 0 (1)       |
| <i>N. transvalensis</i> complex (83)   | 19                                    | 72    | 94      | 37      | 53      | 0     | 16      | 96      | 85      | 96      | 0 (41)      |
| <i>N. vermiculata</i> (1)              | 0                                     | 0     | 0       | 0       | 100     | 0     | 100     | 0       | 100     | 0       | 0 (0)       |
| <i>N. vinacea</i> (1)                  | 0                                     | 0     | 0       | 0       | 100     | 0     | 100     | 0       | 100     | 0       | 0 (0)       |
| <i>N. yamanashiensis</i> (1)           | 0                                     | 0     | 100     | 100     | 100     | 0     | 100     | 0       | 0       | 100     | 0 (1)       |
| <i>Nocardia</i> sp. (32)               | 0                                     | 3     | 44      | 31      | 72      | 0     | 50      | 53      | 50      | 19      | 6 (16)      |
| Total (1,299)                          | 2                                     | 5     | 51      | 44      | 63      | 0     | 83      | 67      | 78      | 45      | 60 (642)    |

<sup>a</sup> Percent of strains with resistant (R) or intermediate (I) interpretation are listed. Testing for moxifloxacin was only available for a subset of isolates; numbers of strains are indicated in the last column. TMP-SMT, trimethoprim-sulfamethoxazole; AMK, amikacin; IMI, imipenem; CTR, ceftriaxone; AUG, amoxicillin-clavulanic acid; LZD, linezolid; CIP, ciprofloxacin; CLA, clarithromycin; MIN, minocycline; TOB, tobramycin; MXF, moxifloxacin.

<sup>b</sup> Antimicrobial nonsusceptibility results for the species *N. nova* are provided independently from those for the larger *N. nova* complex.

**Table 2:** Suggested therapy for *Nocardia* infections in transplant patients

| Disease            | Primary therapy                                                                  | Alternative‡                                                                                                             |
|--------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
| Pulmonary-stable   | TMP-SMX**–15 mg/kg in 3–4 divided doses, either IV or PO [II-2]                  | Imipenem + amikacin [III] or minocycline [III] or linezolid [III]                                                        |
| Pulmonary-critical | Imipenem** (500 mg q6h) + amikacin** (10–15 mg/(kg day)) [III] or TMP-SMX [II-2] | Linezolid 600 mg q12h [III]                                                                                              |
| Cerebral*          | Imipenem† + amikacin [III] or TMP-SMX [II-2]                                     | Linezolid 600 mg [III] q12h or ceftriaxone [III] 2 g q12h or cefotaxime** [III] 2 g q8h or minocycline [III] 200 mg q12h |
| Disseminated*      | Imipenem + amikacin [III] or TMP-SMX [II-2]                                      | Ceftriaxone, cefotaxime, linezolid or minocycline [III] after initial therapy                                            |

\*Based on animal studies and numerous case reports (1,2,11,15,36,44,47–56,59,61–63,65–75).

\*\*Adjust therapeutic agents based on patient's renal function.

†Meropenem (1 gram q8h) may be an alternative agent depending on species. [III]

‡The use of alternative regimens should be governed by antimicrobial susceptibility testing. This table is only a guide and choice of treatment depends on antimicrobial susceptibility, severity of condition and immunosuppression of the patient and allergy history. Alternate agents, such as amoxicillin-clavulanate, ceftriaxone, fluoroquinolones and macrolides may be effective [III] but there is insufficient information to support their use as initial therapy. These agents should be considered only if standard therapy is ineffective.

*Note:* Sulfonamides may be substituted for TMP-SMX.



# Nocardiosi del SNC

Dopo trattamento e.v iniziale per **3-6 settimane**,  
proseguire per via orale:

## **Paziente immunocompetente**

- TMP/SMX almeno 3 mesi
- Minociclina
- Amoxicillina-clavulanato

## **Paziente immunodepresso**

- 2 molecole attive almeno 1 anno

Follow-up per almeno 1 anno dalla fine del trattamento

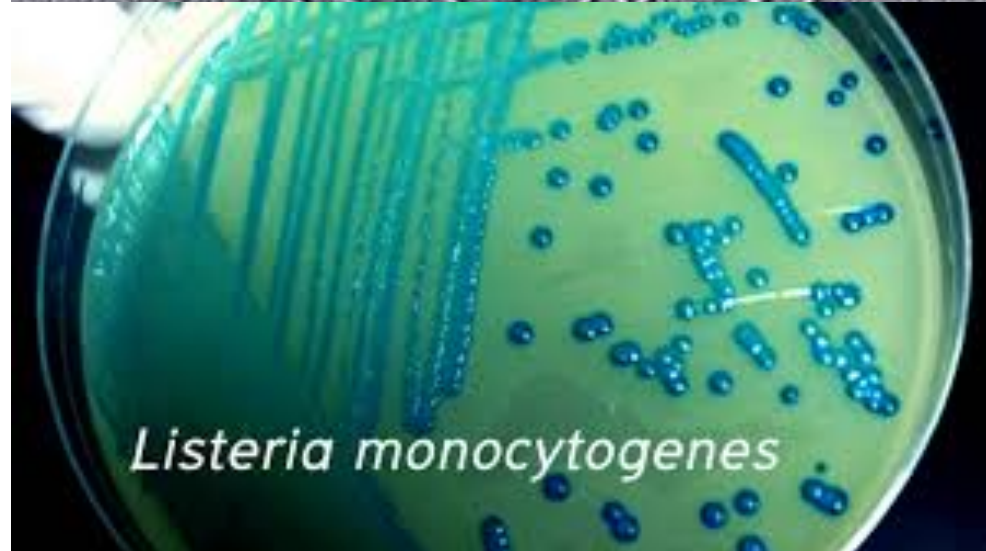
# Listeria spp.

- Anaerobio facoltativo
- Asporigeno
- Mobile e dotato di 1-6 flagelli polari
- Crescita ideale a 30° C-37° C, ma cresce anche a 4° - 10° C
- Terreni di coltura standard per isolamento da materiali sterili (sangue, LCR, liquido sinoviale)
- Necessari terreni selettivi per isolamento da materiali contenenti più specie batteriche: feci/alimenti

Agar blood-free + luce trasmessa a 45°  
(colorazione di Henry):

*Listeria* spp. blu-grigia

Altre specie giallognole-arancioni



# TRATTAMENTO “CLASSICO” SEPSI/MENINGITE/ENDOCARDITE

## I LINEA

AMPICILLINA 2 gr q 4h (batteriostatico)

PENICILLINA 4MU q 4h (batteriostatico)

+

AMINOGLICOSIDE

(gentamicina 5 mg/Kg/die)

da evitare nel I trim e nell'ultimo  
mese di gravidanza

## II LINEA

TMP-SMX 10-20 mg/Kg/die (TMP) div q 6-12h

+/-

AMPICILLINA 2 gr q 4h

Medicine (Baltimore). 1998;77(5):313

Clin Microbiol Rev. 1997;10(2):345

Infect Immun. 1994;62(6):2222

Clin Microbiol Infect. 2012 Jul;18(7):690-5.

# ANTIBIOTICI NON PIU'IN COMMERCIO

- PENICILLINA
- AMPICILLINA
- AMPICILLINA/SULBACTAM
- AMOXICILLINA/AC. CLAVULANICO ev
- OXACILLINA
- CEFUROXIME AXETIL
- TICARCILLINA/AC. CLAVULANICO
- STREPTOMICINA
- RIFAMPICINA ?



# ALTERNATIVE

- MEROPENEM 2 gr x3/die
- LINEZOLID 600 mg x2/die
- MACROLIDI e TETRACICLINE  
attivi in vitro ma batteriostatici

J Chemother. 2006;18(3):331

J Infect. 2006;52(3):e73.

Eur J Clin Microbiol Infect Dis. 2004;23(6):484

# *Rhodococcus equi*

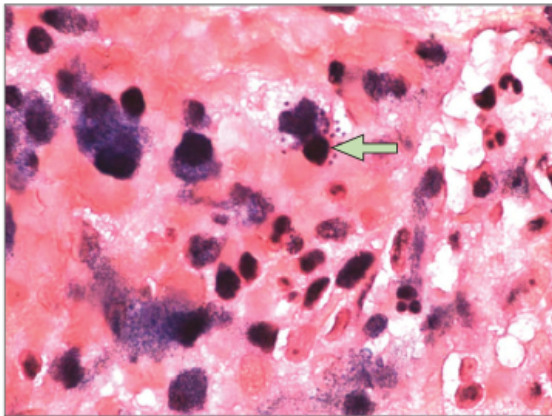


Figure 4: Lung tissue with intracellular coccobacillary forms  
Hucker's variation of tissue Gram stain.

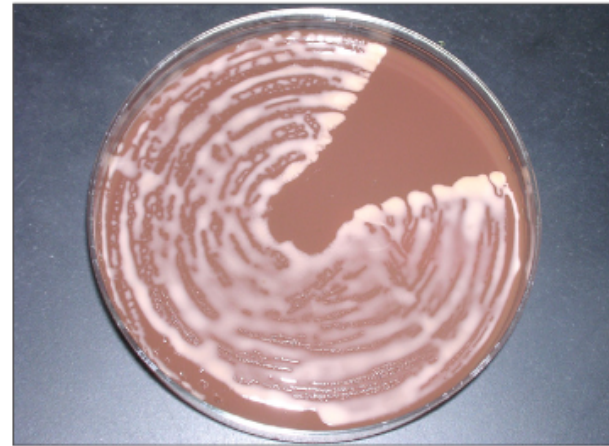


Figure 1: Coalescent, muroid, pink-tinged *Rhodococcus equi* colonies on  
chocolate agar plate

TABLE 1. MICs of AZI, CLR, and 20 other antimicrobial agents against gram-positive equine bacterial isolates

| Antimicrobial               | MIC ( $\mu\text{g/ml}$ ) |             |                   |
|-----------------------------|--------------------------|-------------|-------------------|
|                             | 90%                      | 50%         | Range             |
| <i>R. equi</i> (n = 64)     |                          |             |                   |
| Azithromycin                | 1                        | 0.5         | $\leq 0.12$ –2    |
| Clarithromycin              | 0.12                     | $\leq 0.06$ | $\leq 0.06$ –0.25 |
| Erythromycin                | $\leq 0.25$              | $\leq 0.25$ | $\leq 0.25$ –0.5  |
| Amikacin                    | 4                        | $\leq 2$    | $\leq 2$ –8       |
| Amoxicillin-clavulanic acid | 8                        | $\leq 2$    | $\leq 2$ –16      |
| Ampicillin                  | 4                        | 1           | $\leq 0.12$ –8    |
| Cefazolin                   | 16                       | $\leq 2$    | $\leq 2$ –>16     |
| Ceftazidime                 | >32                      | >32         | $\leq 0.25$ –>32  |
| Ceftiofur                   | 1                        | $\leq 0.5$  | $\leq 0.5$ –2     |
| Chloramphenicol             | 16                       | 8           | $\leq 4$ –32      |
| Clindamycin                 | >2                       | 2           | 1–>2              |
| Doxycycline                 | 1                        | 0.5         | $\leq 0.12$ –2    |
| Enrofloxacin                | 1                        | 0.5         | $\leq 0.25$ –2    |
| Florfenicol                 | >8                       | >8          | 2–>8              |
| Gentamicin                  | $\leq 1$                 | $\leq 1$    | $\leq 1$          |
| Imipenem                    | $\leq 1$                 | $\leq 1$    | $\leq 1$          |
| Nitrofurantoin              | 64                       | 64          | $\leq 32$ –128    |
| Oxacillin                   | >4                       | >4          | $\leq 2$ –>4      |
| Penicillin                  | 1                        | 0.25        | $\leq 0.12$ –2    |
| Rifampin                    | $\leq 0.5$               | $\leq 0.5$  | $\leq 0.5$ –>4    |
| Tetracycline                | 8                        | 4           | $\leq 2$ –16      |
| Trimethoprim-sulfadiazine   | 2                        | 1           | $\leq 0.25$ –2    |

Recommended: Two drugs: Azithro, Levo or Rif.

Alternative: Vanco or IMP + Azithro, Levo or Rif) Sanford 2017

# CLOSTRIDIUM DIFFICILE



## Urgent Threats

- *Clostridium difficile*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae*

## Serious Threats

- Multidrug-resistant *Acinetobacter*
- Drug-resistant *Campylobacter*
- Fluconazole-resistant *Candida* (a fungus)
- Extended spectrum  $\beta$ -lactamase producing Enterobacteriaceae (ESBLs)
- Vancomycin-resistant *Enterococcus* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant Non-typhoidal *Salmonella*
- Drug-resistant *Salmonella* Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant tuberculosis

## Concerning Threats

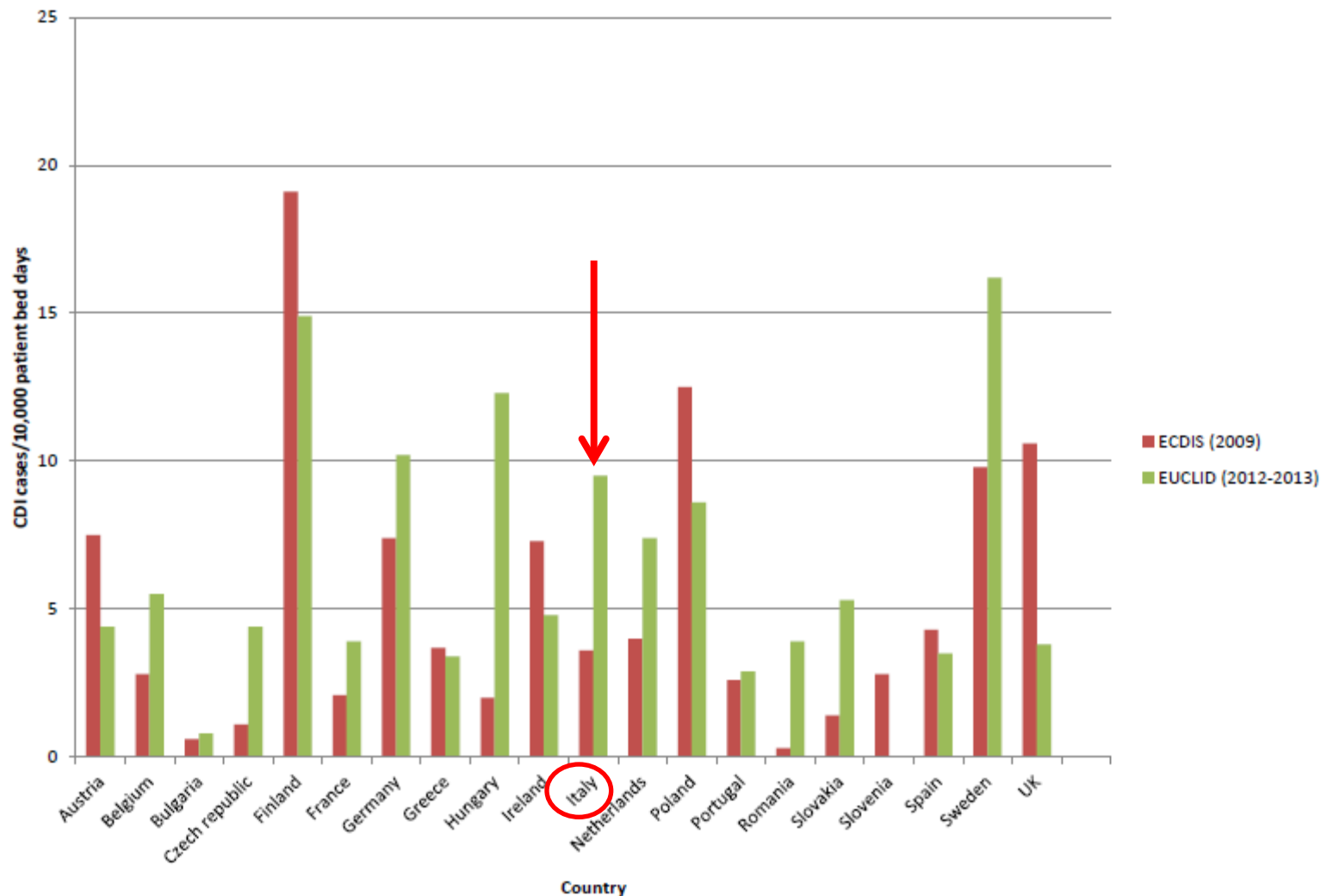
- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Erythromycin-resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*



U.S. Department of  
Health and Human Services  
Centers for Disease  
Control and Prevention

# CDI: Impact

|                                                                           | Number of annual cases | Cost     | Number of annual deaths |
|---------------------------------------------------------------------------|------------------------|----------|-------------------------|
| Hospital-onset, hospital acquired (HO-HA)                                 | 165,000                | \$ 1.3 B | 9000                    |
| Community-onset hospital acquired (CO-HA)<br>[4 weeks of hospitalization] | 50,000                 | \$ 0.3 B | 3000                    |
| Nursing home-onset                                                        | 263.000                | \$ 2.2 B | 16,500                  |



**Figure 2. Changing CDI incidence per country from 2008 to 2013**

**TABLE 1. Established and Emerging Risk Factors for *Clostridium difficile* Infection**

Age >65 y

Previous hospitalization and prolonged length of hospital stay

Nursing home or long-term care facility residence

Contact with active carriers

Antibiotic exposure

Increased risk with prolonged use or multiple antibiotics

Consumption of processed meat

Previous gastrointestinal surgery or endoscopic procedure

Presence of comorbid conditions

Malignancy and chemotherapy

Cystic fibrosis

Diabetes mellitus

Liver cirrhosis

Chronic kidney disease

Inflammatory bowel disease

Immunosuppression, immunodeficiency, or human immunodeficiency virus

Malnutrition

Hypoalbuminemia

Use of proton pump inhibitors

Solid organ or hematopoietic stem cell transplantation

Presence of gastrostomy or jejunostomy tube

**Mayo  
Clin  
Proc.  
Nov.  
2012**



**TABLE 2. Risk Factors for and Predictors of Severe *Clostridium difficile* Infection**

Age >65 y

Antiperistaltic or narcotic medication use

Underlying comorbid conditions

Immunosuppressive medication use

Acute kidney injury or chronic kidney disease

Chronic obstructive pulmonary disease

Altered mental status

Fever

Hypotension

Severe abdominal pain and/or distention

Ten or more bowel movements per day

Leukocytosis

Hypoalbuminemia

Ascites

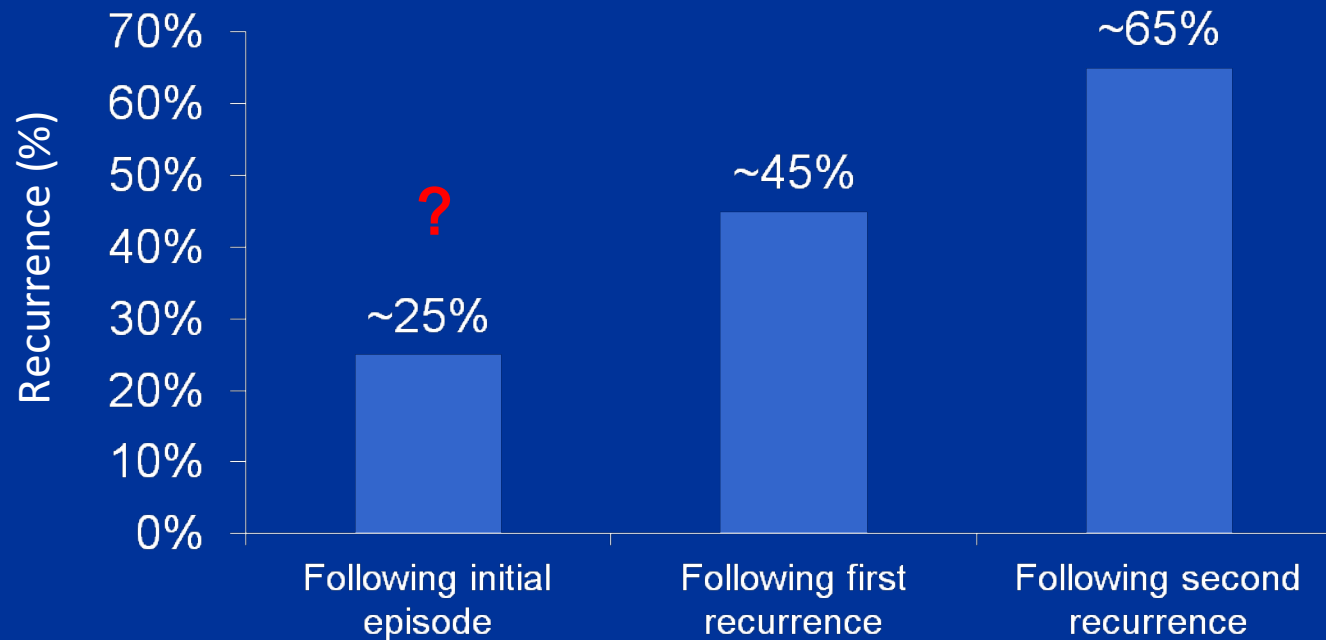
Ileus

Presence of pseudomembranes

**Mayo  
Clin  
Proc.  
Nov.  
2012**

# CDI RECURRENCE

## (within 30 days following treatment)



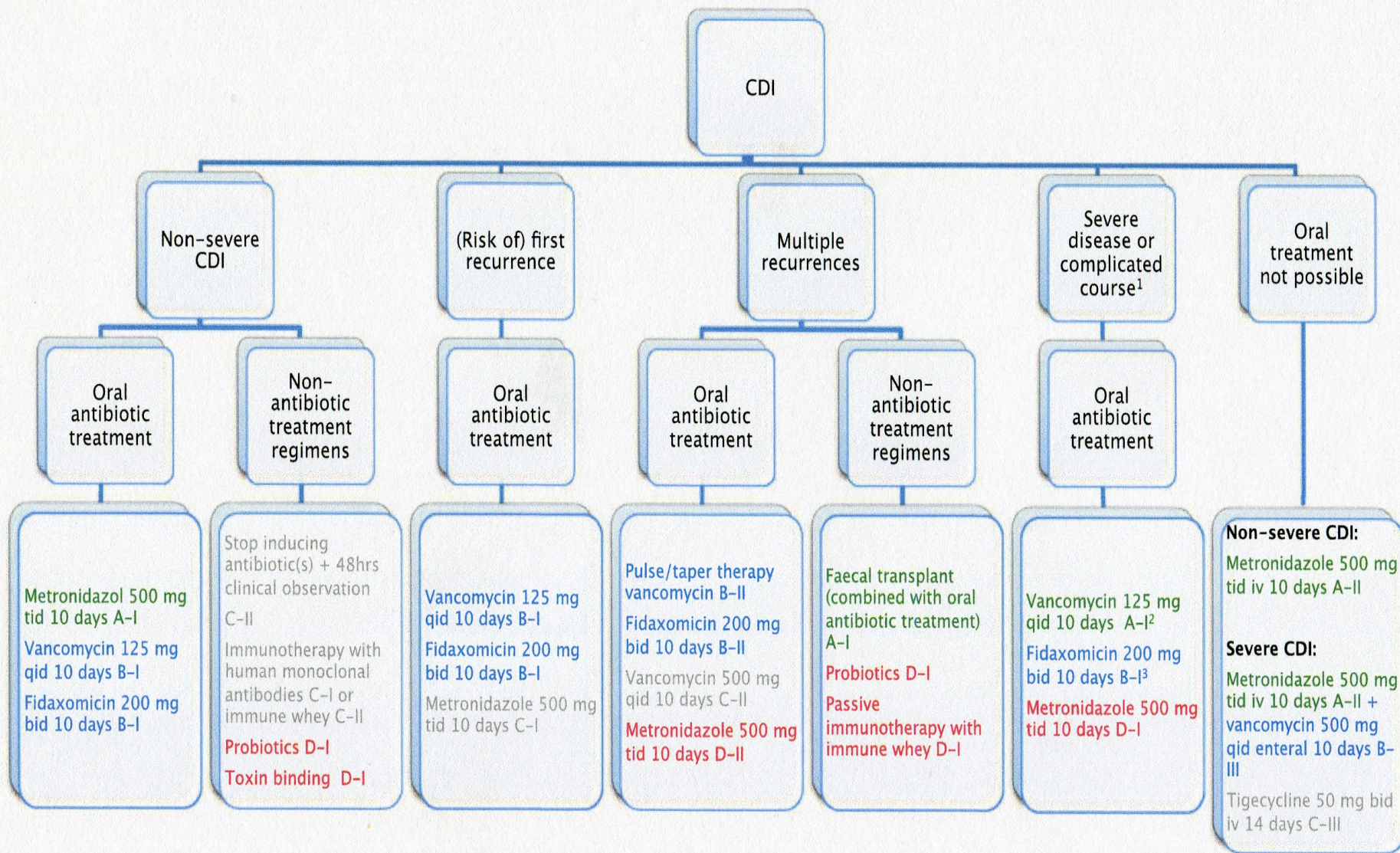
1. Louie et al. N Engl J Med 2011;364:422-31;
2. Lowy et al. N Engl J Med 2010;362:197-205;
3. Bouza et al. Clin Microbiol Infect 2008;14(Suppl 7):S103-4;

4. McFarland et al. Am J Gastroenterol 2002;97:1969-75;
5. McFarland et al. JAMA 1994;271:1913-8.
6. Pepin et al. Clin Infect Dis 2005;40:1591-7



in CDI incidence have been associated with the emergence of the North American pulsed field gel electrophoresis type 1 (NAP1) epidemic strain. The NAP1 strain is also associated with more severe CDI as well (3). CDI is a more frequently encountered problem in SOT recipients. The incidence of CDI is estimated to be 3–7% in liver recipients, 3.5–16% in kidney recipients, 1.5–7.8% in pancreas–kidney recipients, 9% in intestinal recipients, 15% in heart recipients and 7–31% in lung recipients (4). Fulminant colitis develops in up to 8% of immunocompetent patients and 13% of SOT recipients with CDI (5). The incidence of CDI in SOT recipients is highest within the first 3 months after the procedure probably because of more frequent antimicrobial exposure, intense immunosuppression and increased exposure to the healthcare setting (6). Late-onset CDI occurs months to years after the transplant and is usually associated with either antimicrobial exposure or intensified immunosuppression to treat graft rejection (6). It is not known how the NAP1 strain has impacted the incidence and severity of CDI in SOT recipients relative to the general hospital population.







## Algoritmo terapeutico delle coliti da *Clostridium difficile*

- **I° episodio**
- Vancomicina o metronidazolo
- **Pazienti intolleranti ai due farmaci :**
- Fidaxomicina
- **Pazienti ad alto rischio di recidiva\*:**
- Fidaxomicina

- **Recidiva**
- Fidaxomicina

# Pazienti ad alto rischio di recidiva:

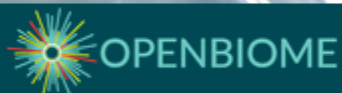
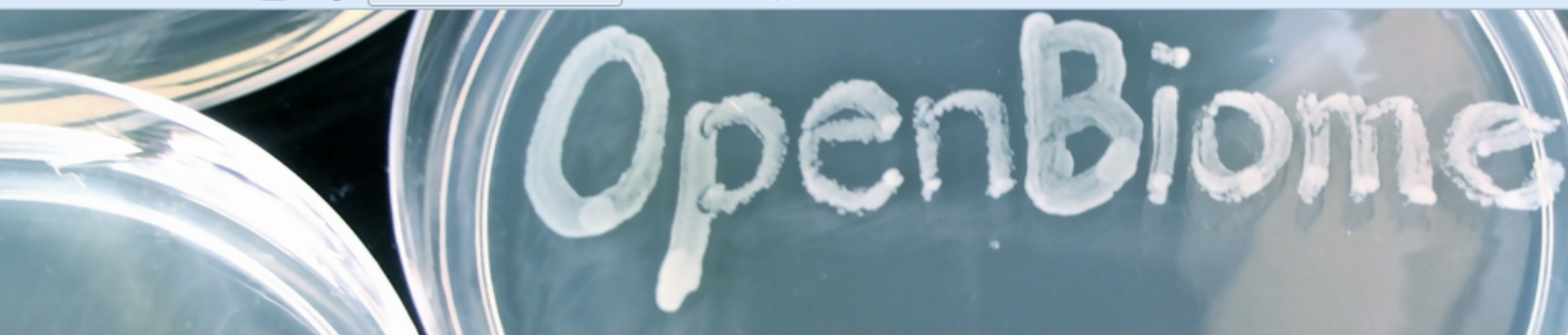
- Trapiantati
- Soggetti in chemioterapia antitumorale
- HIV/AIDS
- Altre immunodeficienze
- Pregressi episodi di infezione da *C. difficile*
- Presenza di comorbidità (malattie infiammatorie intestinali, cirrosi, cancro del colon, pregressa chirurgia addominale, grave ipoalbuminemia, grave insufficienza renale, uso prolungato di antibiotici e inibitori di pompa)

# FECAL BACTERIOTHERAPY

**Table 2 Modified Amsterdam Protocol for fecal microbiota transplantation (FMT) (11, 59)**

| Donor selection and screening                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Patient selection and preparation                                                                                                                                                                                                                                                              |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>1. Initial screening:</p> <p>Questionnaire addressing risk factors for potentially transmittable disorders</p> <p>Other exclusion criteria are recent antibiotic use (&lt;3 months), gastrointestinal symptoms (diarrhea or constipation or irritable bowel syndrome-like symptoms), recent travel to endemic areas of gastrointestinal pathogens, inflammatory bowel disease, gastrointestinal malignancy or polyposis</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <p>1. Indication for FMT?</p> <p>At least two recurrences of CDI or severe, therapy-resistant CDI</p>                                                                                                                                                                                          |
| <p>2. Basic laboratory test for potentially transmittable diseases<sup>a</sup></p> <p><i>Blood tests/serology:</i></p> <p>Hepatitis A (total antibodies, and if positive also Hepatitis A IgM)</p> <p>Hepatitis B (HbsAg, antiHbsAg, antiHBcore)</p> <p>Hepatitis C (antiHCV)</p> <p>HIV types 1 and 2</p> <p>Treponema pallidum assay</p> <p><i>Feces:</i></p> <p><i>Helicobacter pylori</i> antigen test</p> <p>Bacteriological evaluation by local standards, including the assessment of <i>Salmonella</i>, <i>Shigella</i>, <i>Yersinia</i>, and <i>Campylobacter</i></p> <p>Parasitological evaluation by local standards, including the assessment of <i>Giardia</i>, <i>Cryptosporidium</i>, <i>Cyclospora</i>, <i>Isospora</i>, and ova and parasites<sup>b</sup></p> <p>Test for presence of <i>Clostridium difficile</i> (culture or PCR)</p> <p>3. One day before donation of feces</p> <p>Questionnaire addressing recent health-related issues: stool frequency and pattern, general health, use of antibiotics, travel history, sexual behavior</p> | <p>2. Pretreatment of the patient</p> <p>Initiate vancomycin 125 mg q.i.d. for at least 4 days</p> <p>Bowel lavage using at least 2 L of a macrogol solution on day before infusion</p> <p>Stop vancomycin on day before infusion</p> <p>Placement of nasoduodenal tube on day of infusion</p> |
| Preparation of donor feces                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Infusion of donor feces                                                                                                                                                                                                                                                                        |
| <p>Dilute &gt;50 g fresh feces in ~400 cc sterile saline (NaCl 0.9%). Stir with spatulas</p> <p>Strain the supernatant through two unfolded gauzes</p> <p>Collect the solution in a closed bottle</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <p>Infuse donor feces solution through nasoduodenal tube (2–3 min per 50 ml)</p> <p>Flush the nasoduodenal tube with water after infusion of donor feces solution</p> <p>Remove tube 30 min after infusion</p> <p>Offer lemonade to patient immediately after removal of tube</p>              |





[WELCOME](#)
[FOR CLINICIANS](#)
[FOR PATIENTS](#)
[FOR EVERYONE](#)
[ABOUT](#)

## Welcome to OpenBiome.

### What we do

We work with clinicians to make [Fecal Microbiota Transplantation](#) (FMT) easier, cheaper, safer and more widely available. We do so by providing hospitals with screened, filtered, and frozen material ready for clinical use. This service eliminates the time, staff, protocols, and facilities needed to screen and prepare material from new donors for each treatment. With OpenBiome, all that's needed to deliver FMT is a doctor and an endoscope.

### Why we're here

We founded OpenBiome, a nonprofit 501(c)(3) organization, after watching a friend and family member suffer through 18 months of [C. difficile](#) and 7 rounds of vancomycin before finally receiving a successful, life-changing FMT. The remarkable efficacy of this treatment and the great lengths required to receive it convinced us that we needed to help expand access. After many discussions with local clinicians and the FDA, we launched OpenBiome in 2012 to make FMT faster and easier for patients and doctors alike.



### Fecal Microbiota Preparation

Ingredients: Human feces (dried to 330 microns, Sodium Chloride 0.5%), Glycerol (12.5%), Water.

Uses: For use in fecal microbiota transplantation.

Other information: • Store immediately at -20°C. • Thaw either for room temperature or overnight at -20°C. • Thawing temperature, samples may remain refrigerated for up to 8 hours. • Thawing and refreezing may affect quality metrics for

Warnings: • Do not use if the container is damaged or the seal is broken. • Do not use if the container is expired.

Expiry Date

### Fecal Microbiota Preparation

Ingredients: Human feces (dried to 330 microns, Sodium Chloride 0.5%), Glycerol (12.5%), Water.

Uses: For use in fecal microbiota transplantation.

Other information: • Store immediately at -20°C. • Thaw either for room temperature or overnight at -20°C. • Thawing temperature, samples may remain refrigerated for up to 8 hours. • Thawing and refreezing may affect quality metrics for

Warnings: • Do not use if the container is damaged or the seal is broken. • Do not use if the container is expired.

Expiry Date

### Fecal Microbiota Preparation

Ingredients: Human feces (dried to 330 microns, Sodium Chloride 0.5%), Glycerol (12.5%), Water.

Uses: For use in fecal microbiota transplantation.

Other information: • Store immediately at -20°C. • Thaw either for room temperature or overnight at -20°C. • Thawing temperature, samples may remain refrigerated for up to 8 hours. • Thawing and refreezing may affect quality metrics for

Warnings: • Do not use if the container is damaged or the seal is broken. • Do not use if the container is expired.

Expiry Date

### Fecal Microbiota Preparation

Ingredients: Human feces (dried to 330 microns, Sodium Chloride 0.5%), Glycerol (12.5%), Water.

Uses: For use in fecal microbiota transplantation.

Other information: • Store immediately at -20°C. • Thaw either for room temperature or overnight at -20°C. • Thawing temperature, samples may remain refrigerated for up to 8 hours. • Thawing and refreezing may affect quality metrics for

Warnings: • Do not use if the container is damaged or the seal is broken. • Do not use if the container is expired.

Expiry Date

### Fecal Microbiota Preparation

Ingredients: Human feces (dried to 330 microns, Sodium Chloride 0.5%), Glycerol (12.5%), Water.

Uses: For use in fecal microbiota transplantation.

Other information: • Store immediately at -20°C. • Thaw either for room temperature or overnight at -20°C. • Thawing temperature, samples may remain refrigerated for up to 8 hours. • Thawing and refreezing may affect quality metrics for

Warnings: • Do not use if the container is damaged or the seal is broken. • Do not use if the container is expired.

Expiry Date

OpenBiome  
01-047-A

OpenBiome  
01-046-D

OpenBiome  
01-046-E

OpenBiome  
01-047







OPENBIOME

## OpenBiome | Order Form

### Partner Information

|                                            |                                                                                                                      |             |
|--------------------------------------------|----------------------------------------------------------------------------------------------------------------------|-------------|
| <b>A. HOSPITAL / CLINIC INFORMATION</b>    |                                                                                                                      |             |
| 1. Name of hospital or clinic              | 2. Customer ID (if known)                                                                                            |             |
| 3. Date                                    | 4. Purchase order number (PO#) (optional) <input type="checkbox"/> I certify that my facility does not require a PO# |             |
| 5. Shipping Address                        |                                                                                                                      |             |
| 6. City                                    | 7. State                                                                                                             | 8. Zip Code |
| <b>B. AUTHORIZED PURCHASER INFORMATION</b> |                                                                                                                      |             |
| 9. Name of Buyer                           | 10. Email Address of Buyer                                                                                           |             |
| 11. Phone Number of Buyer                  | 12. Email for Shipping Confirmation (if different from #10 above)                                                    |             |
| <b>C. BILLING CONTACT INFORMATION</b>      |                                                                                                                      |             |
| 13. Name of Billing Contact                | 14. Phone Number of Billing Contact                                                                                  |             |
| 15. Email Address of Billing Contact       | 16. Email Address for Electronic Invoice                                                                             |             |
| <b>D. SPECIAL INSTRUCTIONS OR COMMENTS</b> |                                                                                                                      |             |
| 17. Special Instructions or Comments       |                                                                                                                      |             |

### Order Information

| E. ORDER INFORMATION |                                                                                             |                  |          |       |
|----------------------|---------------------------------------------------------------------------------------------|------------------|----------|-------|
| ITEM                 | DESCRIPTION                                                                                 | UNIT PRICE       | QUANTITY | TOTAL |
| FMP250               | FMT Lower Delivery                                                                          | \$385            |          |       |
| FMP30                | FMT Upper Delivery                                                                          | \$385            |          |       |
| FMPCapG3             | FMT Capsule G3 (physician orientation required before first order)                          | \$535            |          |       |
| Standard S&H         | Flat Shipping & Handling fee per shipment, waived on orders of 10 units or more             | \$150            |          |       |
| Same-day Shipping    | Order must be received before 3pm ET Mon-Thur. Availability not guaranteed                  | Additional \$50  |          |       |
| First Overnight      | Approximate 8am local delivery time, compared to approximate 10:30am Standard delivery time | Additional \$100 |          |       |
|                      |                                                                                             |                  |          |       |

### Dosage and Delivery

The recommended dose for treatment of rCDI is 30 capsules, swallowed consecutively in a single session.

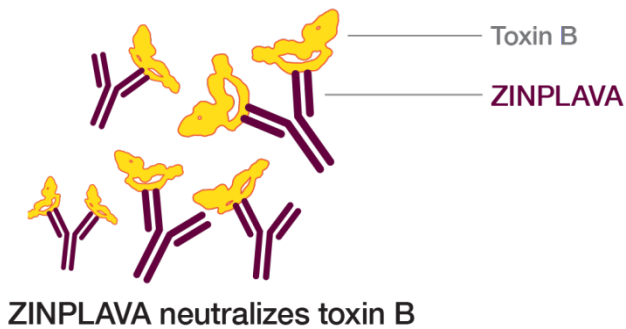


**Table 1.** Summary of the role of host immunity in CDI, and current and emerging treatment and prevention and strategies

| CDI host defence                                     | CDI treatment             |                                                                                                                            | CDI primary prevention <sup>a</sup> |                                         | Secondary prevention (of recurrence)                          |                                                                                                                                       |
|------------------------------------------------------|---------------------------|----------------------------------------------------------------------------------------------------------------------------|-------------------------------------|-----------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|
|                                                      | Current therapy           | Current use                                                                                                                | Vaccines                            | Stage of development <sup>b</sup>       | Passive immunization                                          | Stage of development <sup>b</sup>                                                                                                     |
| <b>Innate immunity</b>                               |                           |                                                                                                                            |                                     |                                         |                                                               |                                                                                                                                       |
| Host intestinal microbiota (colonization resistance) | Metronidazole             | In widespread routine use                                                                                                  | Sanofi Pasteur                      | Phase III ongoing                       | Bezlotoxumab                                                  | Phase III                                                                                                                             |
| Mucosal immunity (cytokines and chemokines)          | Vancomycin                | In widespread routine use                                                                                                  | Pfizer                              | Phase II                                | Intravenous immunoglobulin                                    | RCT                                                                                                                                   |
|                                                      | Fidaxomicin               | Usage variable by region/healthcare provider (especially for patients at high risk of recurrence and/or for recurrent CDI) | Valneva                             | Phase II                                |                                                               |                                                                                                                                       |
| <b>Adaptive immunity</b>                             | <b>New antimicrobials</b> | <b>Stage of development<sup>b</sup></b>                                                                                    | <b>Other agents</b>                 | <b>Stage of development<sup>b</sup></b> | <b>Biotherapeutics</b>                                        | <b>Stage of development<sup>b</sup></b>                                                                                               |
| Anti-TcdA (antitoxin A antibody)                     | Surotomycin               | Phase III                                                                                                                  | Ribaxamase (beta-lactamase)         | Phase II                                | Faecal microbiota transplantation—fresh, frozen, encapsulated | Considered to be investigational by FDA. Usage variable by region/healthcare provider (for patients with multiple recurrences of CDI) |
| Anti-TcdB (antitoxin B antibody)                     | Cadazolid                 | Phase III (ongoing)                                                                                                        | DAV132 (antibiotic adsorbent)       | Phase I                                 | Nontoxigenic <i>C. difficile</i>                              | Phase II                                                                                                                              |
| Antibodies against surface proteins                  | Ridinilazole              | Phase II                                                                                                                   |                                     |                                         | RBX2660                                                       | Phase II                                                                                                                              |
| Antibodies against adhesion molecules                |                           | Nonrandomized trial                                                                                                        |                                     |                                         | SER-109                                                       | Phase II                                                                                                                              |

CDI, *Clostridium difficile* infection; FDA, Food and Drug Administration.<sup>a</sup>The role of vaccination in secondary prevention is yet to be established.<sup>b</sup>Stage of development<sup>b</sup> refers to completed trials unless stated.

# INTRODUCING **BEZLOTOXUMAB**



**BEZLOTOXUMAB** is indicated for the prevention of *Clostridium difficile* infection (CDI) recurrence in patients 18 years or older receiving antibiotic therapy for CDI.

- Specific human monoclonal antibody
- Binds with high affinity to *C difficile* toxin B and neutralizes its activity by preventing it from binding to host cells



# The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

JANUARY 26, 2017

VOL. 376 NO. 4

## Bezlotoxumab for Prevention of Recurrent *Clostridium difficile* Infection

M.H. Wilcox, D.N. Gerding, I.R. Poxton, 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\*

### ABSTRACT

#### BACKGROUND

*Clostridium difficile* is the most common cause of infectious diarrhea in hospitalized patients. Recurrences are common after antibiotic therapy. Actoxumab and bezlotoxumab are human monoclonal antibodies against *C. difficile* toxins A and B, respectively.

#### METHODS

We conducted two double-blind, randomized, placebo-controlled, phase 3 trials, MODIFY I and MODIFY II, involving 2655 adults receiving oral standard-of-care antibiotics for primary or recurrent *C. difficile* infection. Participants received an infusion of bezlotoxumab (10 mg per kilogram of body weight), actoxumab plus bezlotoxumab (10 mg per kilogram each), or placebo; actoxumab alone (10 mg per kilogram) was given in MODIFY I but discontinued after a planned interim analysis. The primary end point was recurrent infection (new episode after initial clinical cure) within 12 weeks after infusion in the modified intention-to-treat population.

#### RESULTS

In both trials, the rate of recurrent *C. difficile* infection was significantly lower with bezlotoxumab alone than with placebo (MODIFY I: 17% [67 of 386] vs. 28% [109 of 395]; adjusted difference, -10.1 percentage points; 95% confidence interval [CI], -15.9 to -4.3;  $P<0.001$ ; MODIFY II: 16% [62 of 395] vs. 26% [97 of 378]; adjusted difference, -9.9 percentage points; 95% CI, -15.5 to -4.3;  $P<0.001$ ) and was significantly lower with actoxumab plus bezlotoxumab than with placebo (MODIFY I: 16% [61 of 383] vs. 28% [109 of 395]; adjusted difference, -11.6 percentage points; 95% CI, -17.4 to -5.9;  $P<0.001$ ; MODIFY II: 15% [58 of 390] vs. 26% [97 of 378]; adjusted difference, -10.7 percentage points; 95% CI, -16.4 to -5.1;  $P<0.001$ ). In prespecified subgroup analyses (combined data set), rates of recurrent infection were lower in both groups that received bezlotoxumab than in the placebo group in subpopulations at high risk for recurrent infection or for an adverse outcome. The rates of initial clinical cure were 80% with bezlotoxumab alone, 73% with actoxumab plus bezlotoxumab, and 80% with placebo; the rates of sustained cure (initial clinical cure without recurrent infection in 12 weeks) were 64%, 58%, and 54%, respectively. The rates of adverse events were similar among these groups; the most common events were diarrhea and nausea.

#### CONCLUSIONS

Among participants receiving antibiotic treatment for primary or recurrent *C. difficile* infection, bezlotoxumab was associated with a substantially lower rate of recurrent infection than placebo and had a safety profile similar to that of placebo. The addition of actoxumab did not improve efficacy. (Funded by Merck; MODIFY I and MODIFY II ClinicalTrials.gov numbers, NCT01241552 and NCT01513239.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Wilcox at the Division of Microbiology, Old Medical School, Leeds General Infirmary, Leeds LS1 3EX, United Kingdom, or at mark.wilcox@nhs.net.

\*A complete list of investigators in the MODIFY I and MODIFY II trials is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2017;376:305-17.

DOI: 10.1056/NEJMoa1602615

Copyright © 2017 Massachusetts Medical Society.

**Table 2. Clinical Adverse Events in the As-Treated Population in Both Trials.**

| Time Period and Event                         | Actoxumab plus<br>Bezlotoxumab<br>(N = 777) | Bezlotoxumab<br>(N = 786) | Actoxumab<br>(N = 235) | Placebo<br>(N = 781) |
|-----------------------------------------------|---------------------------------------------|---------------------------|------------------------|----------------------|
| <i>number of participants (percent)</i>       |                                             |                           |                        |                      |
| During the 24 hours after infusion            |                                             |                           |                        |                      |
| Infusion-specific reaction*                   | 62 (8.0)                                    | 81 (10.3)                 | 26 (11.1)              | 59 (7.6)             |
| Treatment stopped because of an adverse event | 0                                           | 1 (0.1)                   | 1 (0.4)                | 0                    |
| During the 4 weeks after infusion             |                                             |                           |                        |                      |
| One or more adverse events                    | 455 (58.6)                                  | 485 (61.7)                | 158 (67.2)             | 478 (61.2)           |
| Serious adverse event                         | 123 (15.8)                                  | 156 (19.8)                | 65 (27.7)              | 167 (21.4)           |
| Death                                         | 28 (3.6)                                    | 32 (4.1)                  | 14 (6.0)               | 32 (4.1)             |
| Drug-related adverse event†                   | 50 (6.4)                                    | 59 (7.5)                  | 17 (7.2)               | 46 (5.9)             |
| Serious drug-related adverse event‡           | 5 (0.6)                                     | 4 (0.5)                   | 3 (1.3)                | 2 (0.3)              |
| Most common adverse events§                   |                                             |                           |                        |                      |
| Abdominal pain                                | 32 (4.1)                                    | 34 (4.3)                  | 15 (6.4)               | 34 (4.4)             |
| Diarrhea                                      | 46 (5.9)                                    | 47 (6.0)                  | 13 (5.5)               | 45 (5.8)             |
| Nausea                                        | 47 (6.0)                                    | 52 (6.6)                  | 28 (11.9)              | 39 (5.0)             |
| Vomiting                                      | 24 (3.1)                                    | 31 (3.9)                  | 10 (4.3)               | 21 (2.7)             |
| Fatigue                                       | 21 (2.7)                                    | 18 (2.3)                  | 11 (4.7)               | 12 (1.5)             |
| Pyrexia                                       | 31 (4.0)                                    | 36 (4.6)                  | 11 (4.7)               | 27 (3.5)             |
| <i>C. difficile</i> infection¶                | 27 (3.5)                                    | 23 (2.9)                  | 20 (8.5)               | 48 (6.1)             |
| Urinary tract infection                       | 24 (3.1)                                    | 32 (4.1)                  | 13 (5.5)               | 35 (4.5)             |
| Headache                                      | 33 (4.2)                                    | 35 (4.5)                  | 14 (6.0)               | 24 (3.1)             |
| During the 12 weeks after infusion            |                                             |                           |                        |                      |
| Serious adverse event                         | 212 (27.3)                                  | 231 (29.4)                | 104 (44.3)             | 255 (32.7)           |
| Death                                         | 51 (6.6)                                    | 56 (7.1)                  | 27 (11.5)              | 59 (7.6)             |

\* The adverse events reported on the day of or day after infusion that might have been a sign of an acute hypersensitivity reaction were nausea, vomiting, chills, fatigue, feeling hot, infusion-site conditions, pyrexia, arthralgia, myalgia, dizziness, headache, dyspnea, nasal congestion, pruritus, rash, urticaria, flushing, hot flush, hypertension, and hypotension.

† Causality was assessed by the investigator, who was unaware of the study-group assignments.

‡ A list of serious drug-related events is provided in Table S12 in the Supplementary Appendix.

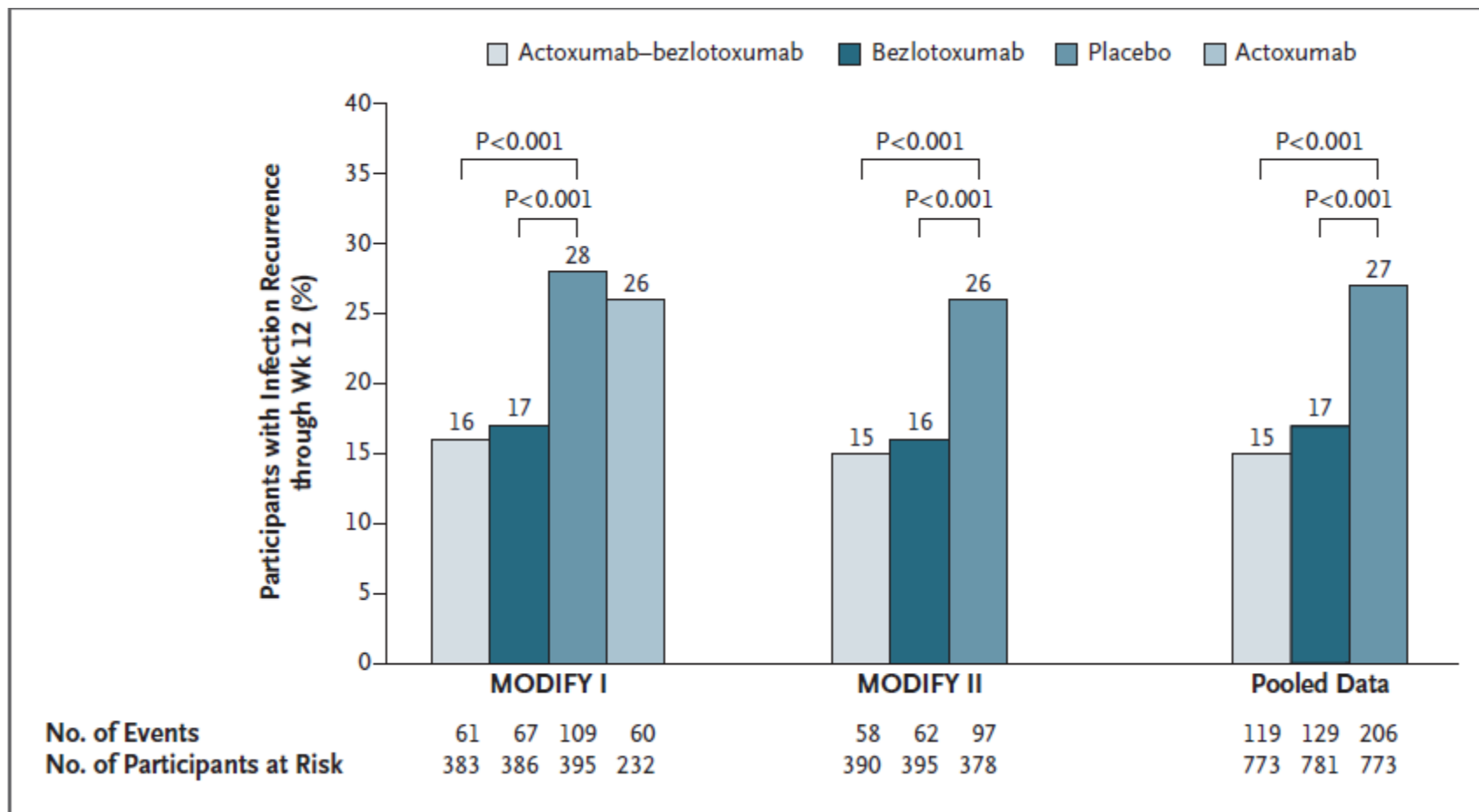
§ This category includes events with an incidence of at least 4% in at least one study group reported during the first 4 weeks after infusion.

¶ *C. difficile* infection (the primary efficacy end point) was to be reported as an adverse event only if it was serious.

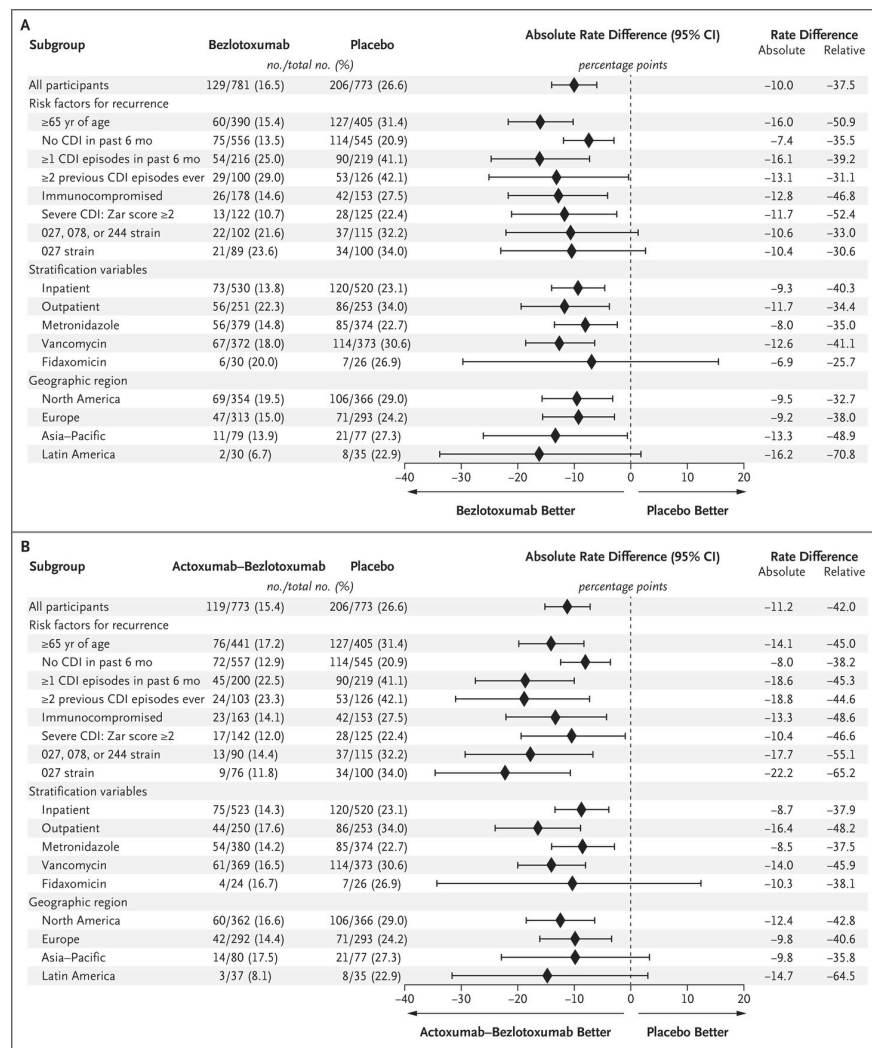
|| A summary of serious adverse events is provided in Table S13 in the Supplementary Appendix.



## Participants with Recurrent *Clostridium difficile* Infection during the 12-Week Follow-up Period



## C. difficile Infection Recurrence According to Subgroup.



22 November 2016  
EMA/CHMP/714398/2016  
Committee for Medicinal Products for Human Use (CHMP)

#### Summary of opinion<sup>1</sup> (initial authorisation)

## Zinplava bezlotoxumab

On 22 November 2016, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion via written procedure, recommending the granting of a marketing authorisation for the medicinal product Zinplava, intended for the prevention of recurrence of *Clostridium difficile* infection (CDI). The applicant for this medicinal product is Merck Sharp & Dohme Limited.

Zinplava will be available as a 25 mg/ml concentrate for solution for infusion. The active substance of Zinplava is bezlotoxumab, a human monoclonal antitoxin antibody that binds with high affinity to *C. difficile* toxin B and neutralizes its activity (ATC code: J06BB21).

The benefits with Zinplava are its ability to prevent the recurrence of *C. difficile* infection diarrhoea episodes in the 12 weeks after treatment. The most common side effects following infusion are nausea, pyrexia and headache.

The full indication is:

"Zinplava is indicated for the prevention of recurrence of *Clostridium difficile* infection (CDI) in adults at high risk for recurrence of CDI (see sections 4.2, 4.4 and 5.1)."

Detailed recommendations for the use of this product will be described in the summary of product characteristics (SmPC), which will be published in the European public assessment report (EPAR) and made available in all official European Union languages after the marketing authorisation has been granted by the European Commission.

<sup>1</sup> Summaries of positive opinion are published without prejudice to the Commission decision, which will normally be issued 67 days from adoption of the opinion



## TETRACICLINE

Eravaciclina  
Omadaciclina

## KETOLIDI

Cetromicina  
Solitromicina

## CHINOLONI

Nemonoxacina  
Delafloracina  
Finafloracina  
Zobofloraclina  
Chinafloracina  
Ozenoxacina  
JNJ-Q2  
DS-8587  
KPI-10  
GSK2140944  
ACH-702

## MONOBATTAMI

BAL30072

## OXAZOLIDINONI

Tedizolid  
Radezolid  
Posizolid  
MRX-1  
LCB01-0371

## INIBITORI ENZIMATICI COMBINAZIONI

Ceftolozane-  
Tazobactam  
Ceftazidime-Avibactam  
Ceftarolina-Avibactam  
Aztreonam-Avibactam  
Imipenem-MK-7655  
Biapenem-RPX7009

## AMINOGLICOSIDI

Plazomicina

## POLIMIXINE

CB-182,804

## CARBAPENEMI

Panipenem  
Biapenem  
Razupenem

## LIPOGLICOPEPTIDI

Telavancina  
Dalbavancina  
Oritavancina

## AGENTI ATTIVI SULLE MEMBRANE

Brilacidina  
POL7080  
ACHN-975

## COMPOSTI ANTI C. difficile

Surotomicina  
Cadazolid  
LFF571  
NVB302