Recenti acquisizioni in antibioticoprofilassi e antibioticoterapia

Nicola Petrosillo

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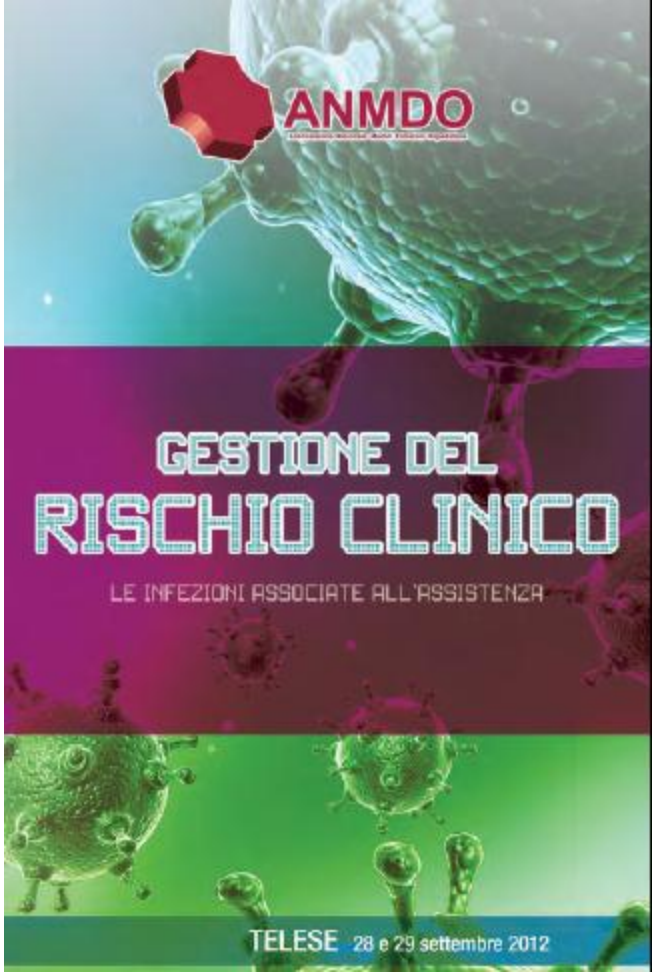


MULTA CORDA UNA CAUSA
Istituto di Ricovero e Cura a Carattere Scientifico
LAZZARO SPALLANZANI

The new resistance era

- **THE VANCO MIC CREEP OF MRSA**
- **THE PERSISTENT CHALLENGE OF *ENTEROCOCCUS SPP***
- **THE EXPLOSION OF ESBL *ENTEROBACTERIACEAE***
- **THE INCREASING CARBAPENEM and MDR RESISTANCE OF *P. aeruginosa***
- **THE OMINOUS EPIDEMIOLOGY OF MBL / KPC *ENTEROBACTERIACEAE***
- **THE MDR ACINETOBACTER REBUS**

Risk of death from a serious infection

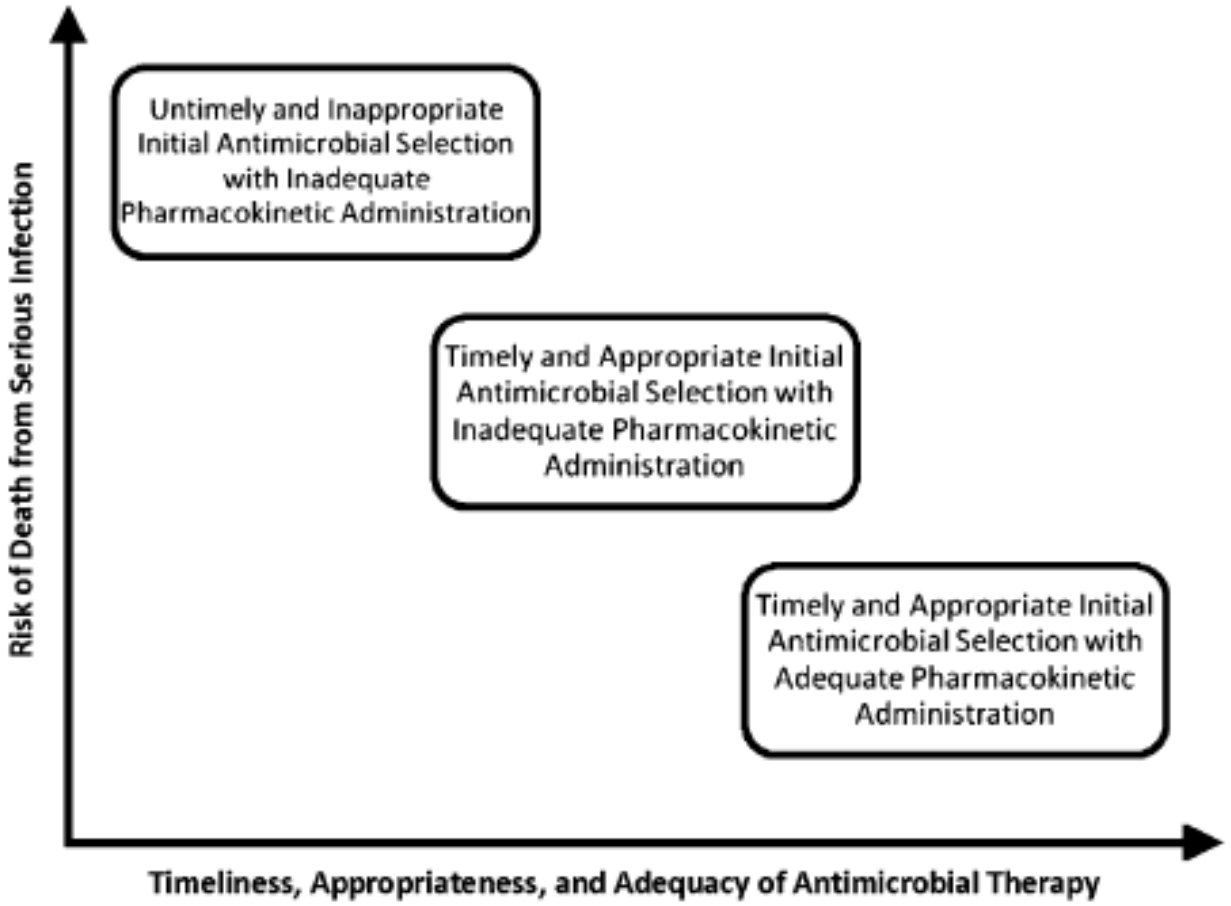


Figure 2. Risk of death from a serious infection as related to timeliness, appropriateness, and adequacy of antimicrobial therapy.

Lawrence KL et al. *Am J Respir Crit Care Med 2009; 179: 434–438.*

PREVENZIONE del RISCHIO INFETTIVO - Procedure essenziali

- Misure comportamentali
- Qualità dell'ambiente inanimato
- Controllo dei vettori /degli animali
- Igiene degli alimenti
- Misure di profilassi "coercitive" a tempo

Prevenzione Primaria

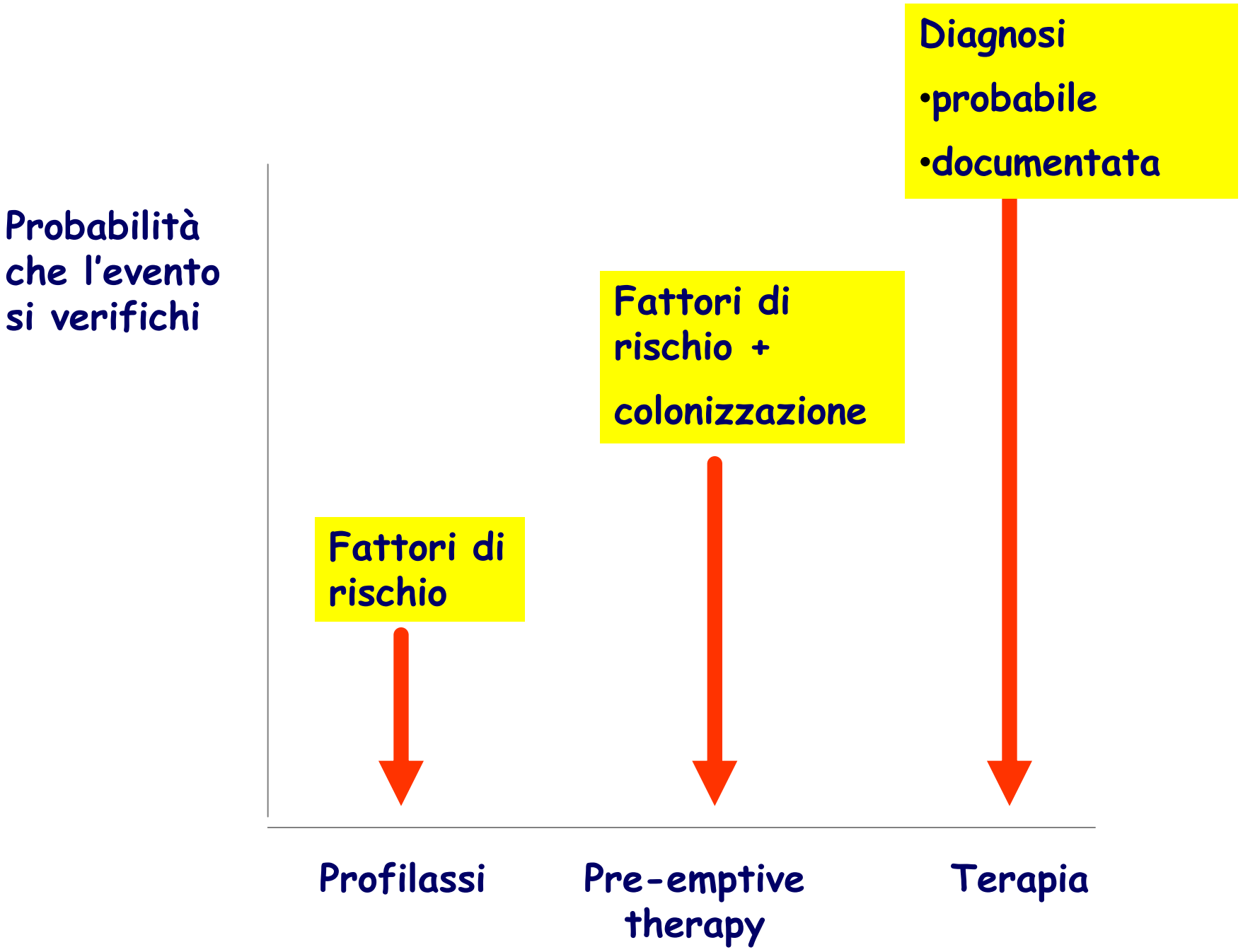
isolamento degli infetti
controllo dei portatori
controllo dei contatti

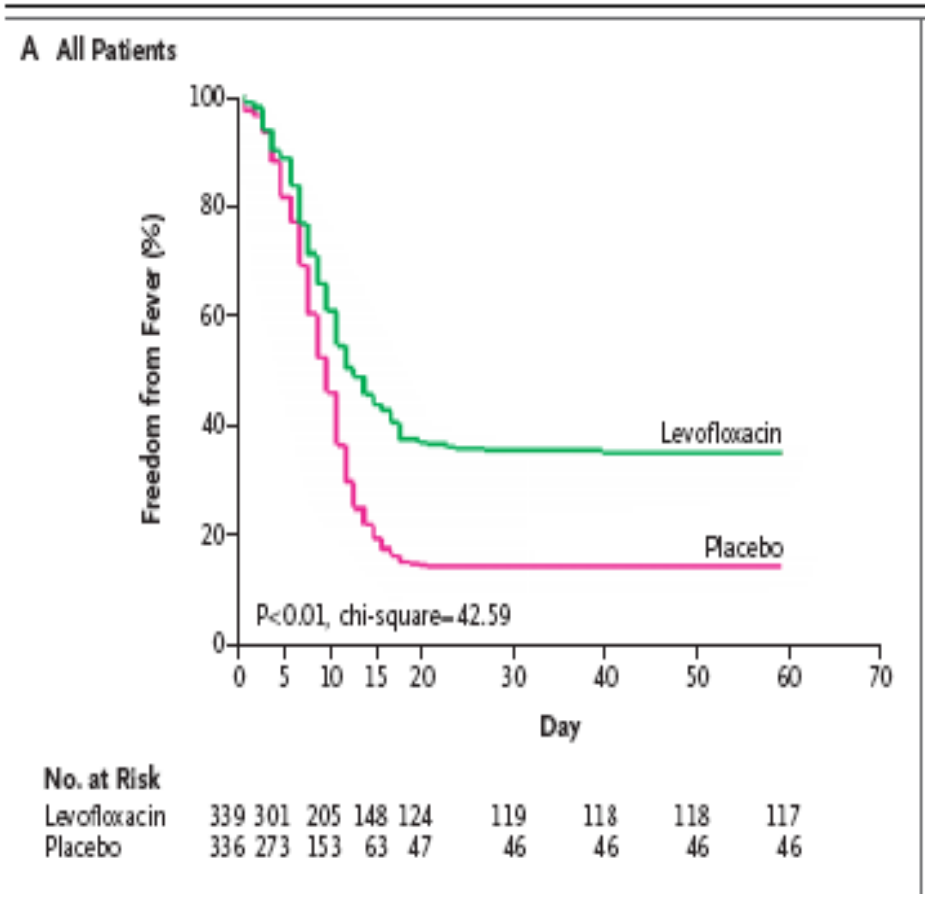
- Immuno-profilassi attiva -> vaccini
- Immuno-profilassi passiva -> immunoglobuline

Prevenzione Primaria / Secondaria

- **Profilassi antibiotica**

Prevenzione Primaria / Secondaria / Terziaria


Diagnosi
•probabile
•documentata
Probabilità che l'evento si verifichi
Fattori di rischio +
colonizzazione
Fattori di rischio
Profilassi
Pre-emptive therapy
Terapia



Bucaneve G et al. NEJM 2005; 353:977-87

Modalities of CMV Prevention

- **Prophylactic Therapy**

  Prophylaxis - Prevention of Disease
  Greek - Guard before, take

- **Preemptive Therapy**

  Preemption - Obtaining Something in Advance
  Identifying Patients with Subclinical CMV and treat them in Advance, before they develop CMV disease.

Chemio-profilassi del rischio infettivo - DEFINIZIONI

Somministrazione di un antimicrobico **PRIMA** che si verifichi la POTENZIALE INTERAZIONE tra MICRO e MACRORGANISMO.

Somministrazione di un antimicrobico **IMMEDIATAMENTE DOPO** la ACCERTATA o PROBABILE INTERAZIONE tra MICRO e MACRORGANISMO.

Somministrazione di un antimicrobico **IMMEDIATAMENTE DOPO** l' ACCERTAMENTO di MALATTIA ad ETIOLOGIA MICROBICA

E' quindi SEMPRE una pratica EMPIRICA, basata sulla PROBABILITA' che un certo evento si verifichi.

Chemio-profilassi del rischio infettivo - DEFINIZIONE

Prevenzione primaria (prevenzione dell'evento)

L'insieme delle misure tendenti ad evitare l'evento interazione micro-macroganismo e l' infezione

PROFILASSI PRE-ESPOSIZIONE al MICRORGANISMO

Prevenzione secondaria (prevenzione della progressione verso la malattia)

L'insieme delle misure tendenti ad ostacolare la progressione e/o le complicanze dell'infezione

PROFILASSI POST-ESPOSIZIONE al MICRORGANISMO

Prevenzione terziaria

l'insieme delle misure tendenti a ridurre il rischio complicanze permanenti e/o gravi, compreso il trattamento delle infezioni ad andamento cronico

TERAPIA PRECOCE della MALATTIA

PROFILASSI POST-RISOLUZIONE di MALATTIA ACUTA

Chemio-profilassi del rischio infettivo - PUNTI CARDINE

1. CORRETTO MOMENTO di SOMMINISTRAZIONE

2. CORRETTO TEMPO TOTALE di PROFILASSI

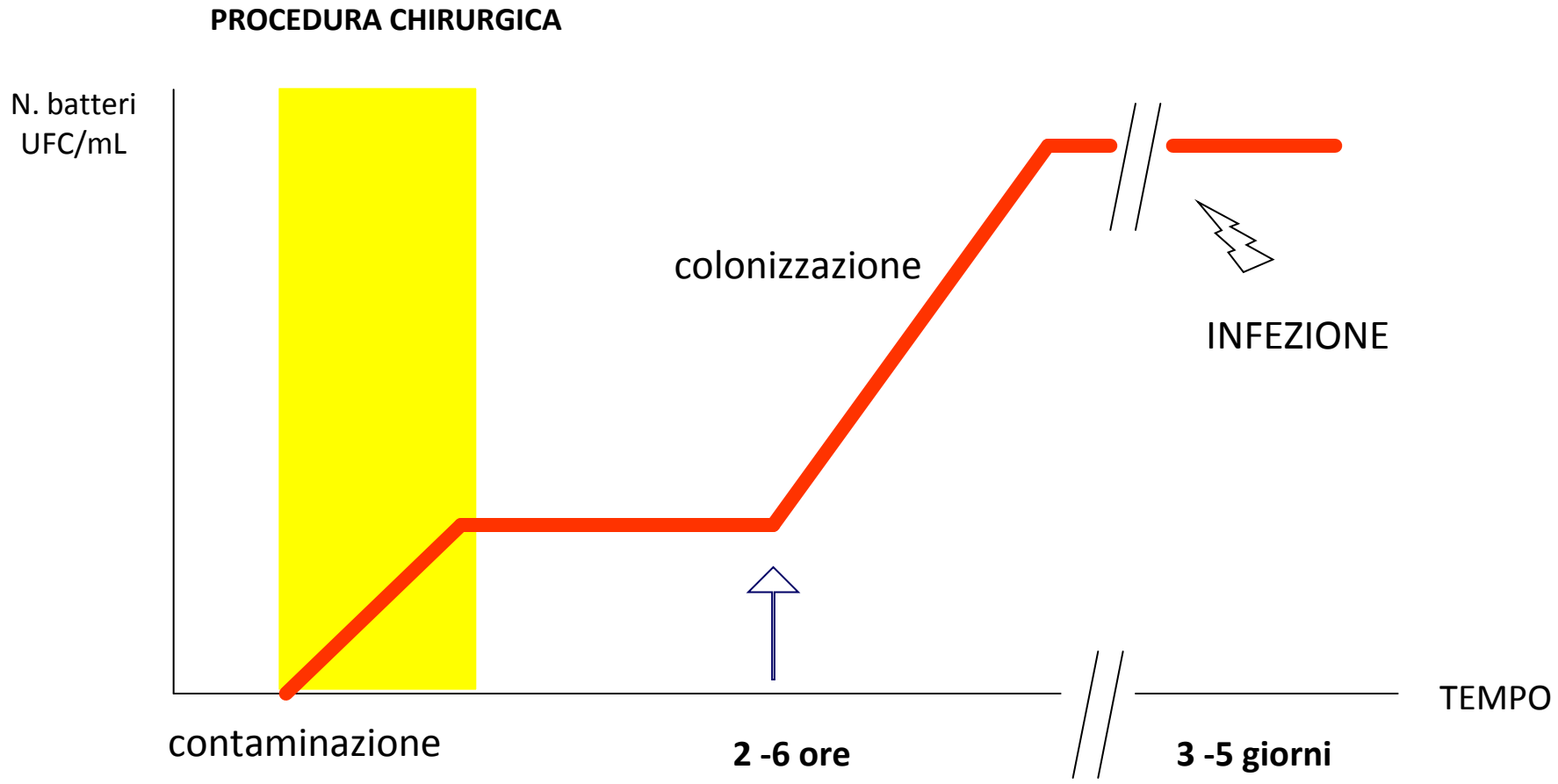
3. CORRETTA SCELTA della MOLECOLA *per EFFICACIA*

per TOLLERABILITA'

4. CONTROLLO dell'ADERENZA del SOGGETTO

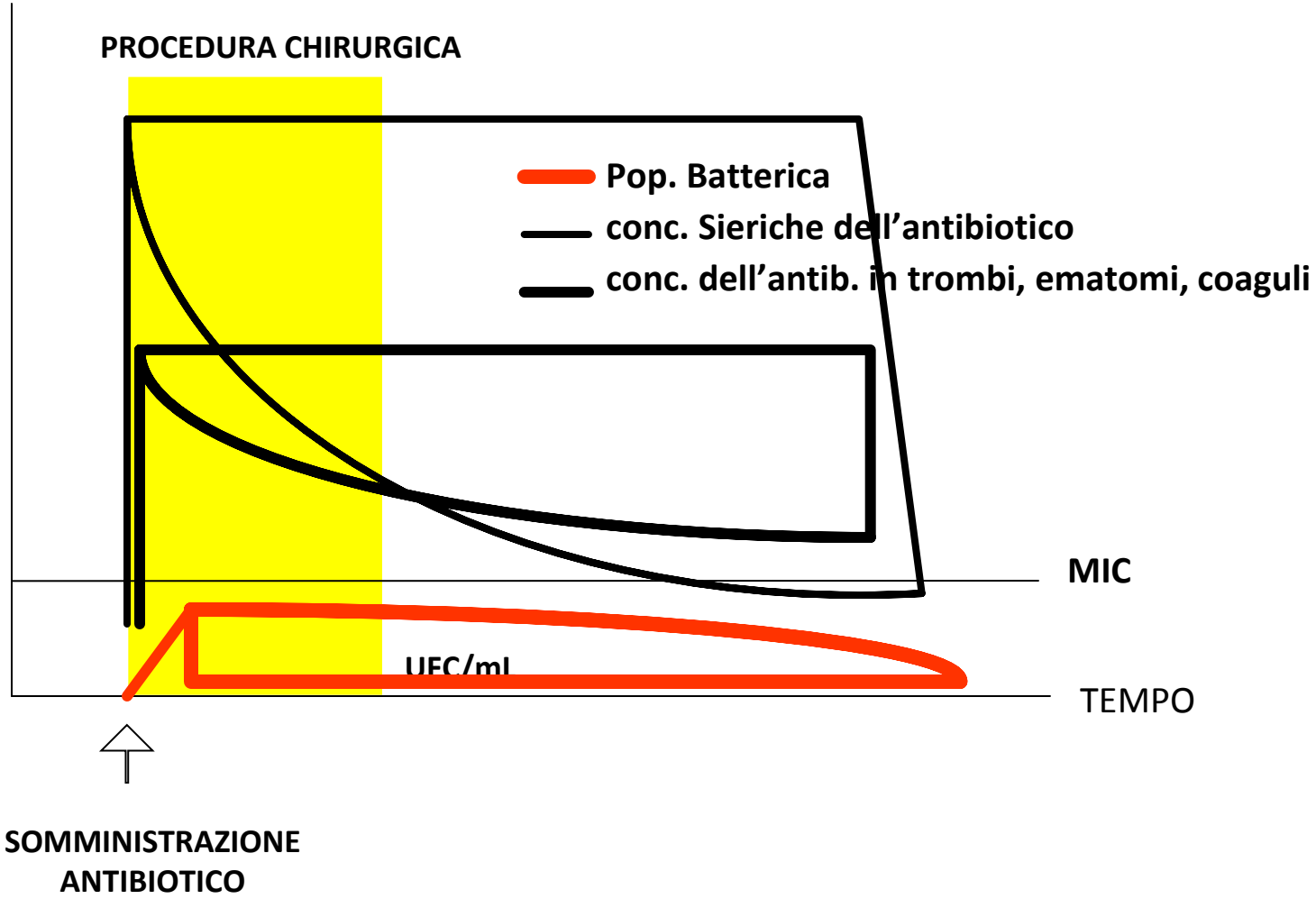
CINETICA di CRESCITA BATTERICA

dopo CONTAMINAZIONE INTRA-OPERATORIA



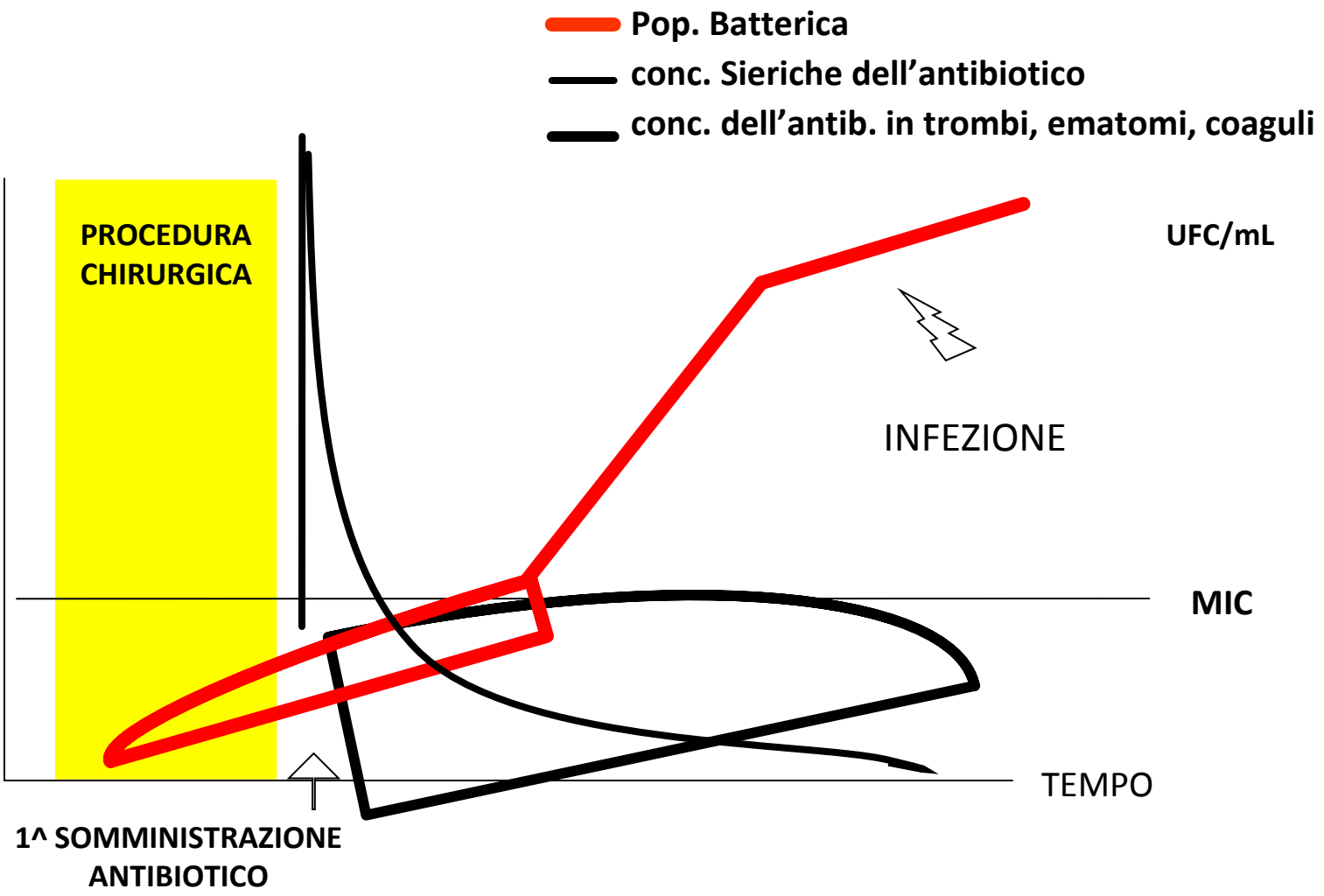
BASI TEORICHE della PROFILASSI CHIRURGICA

MOMENTO di INIZIO CORRETTO



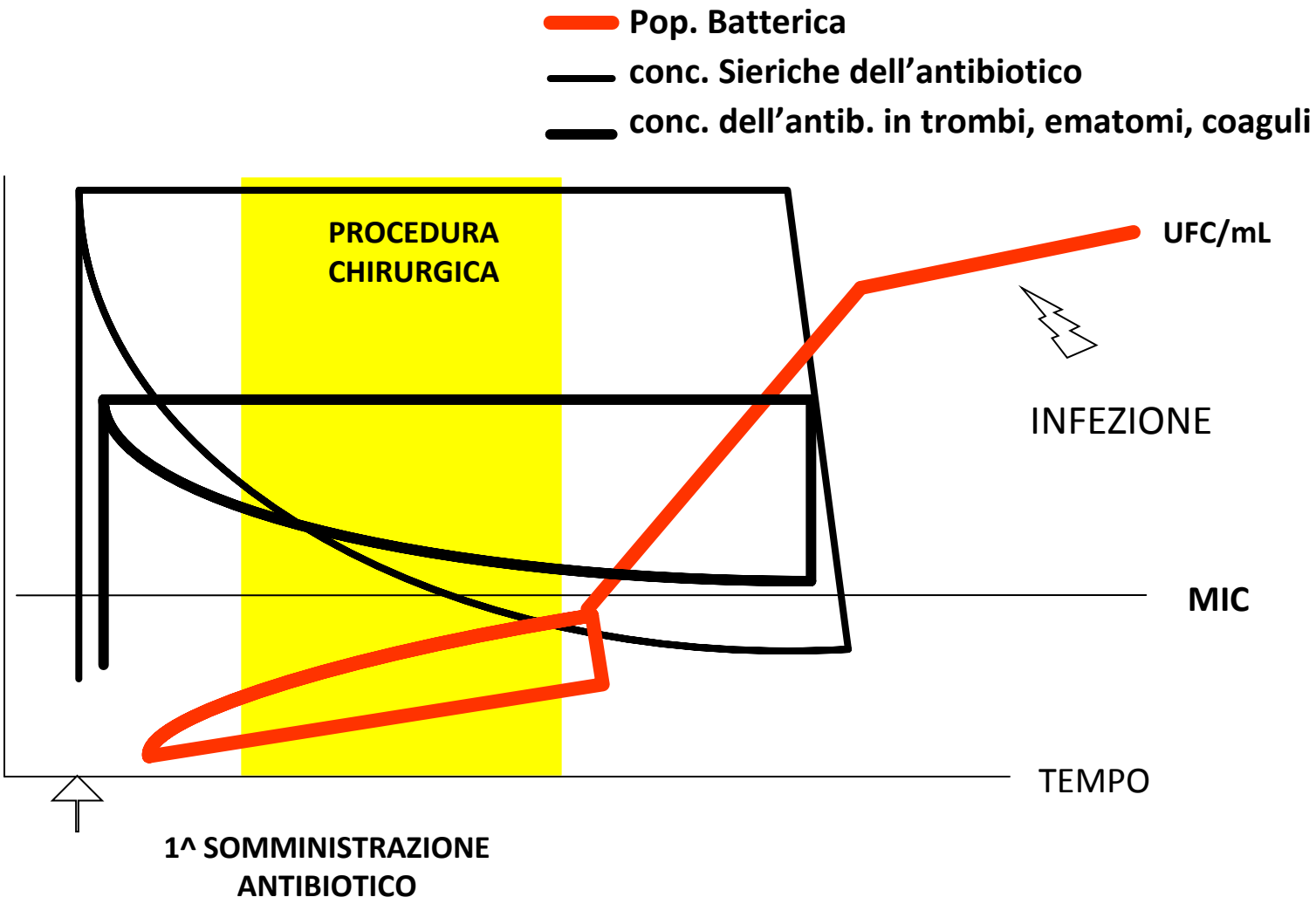
BASI TEORICHE della PROFILASSI CHIRURGICA

MOMENTO di INIZIO SCORRETTO - tardivo



BASI TEORICHE della PROFILASSI CHIRURGICA

MOMENTO di INIZIO SCORRETTO - troppo precoce



BASI TEORICHE della PROFILASSI CHIRURGICA

RIPETIZIONE della DOSE

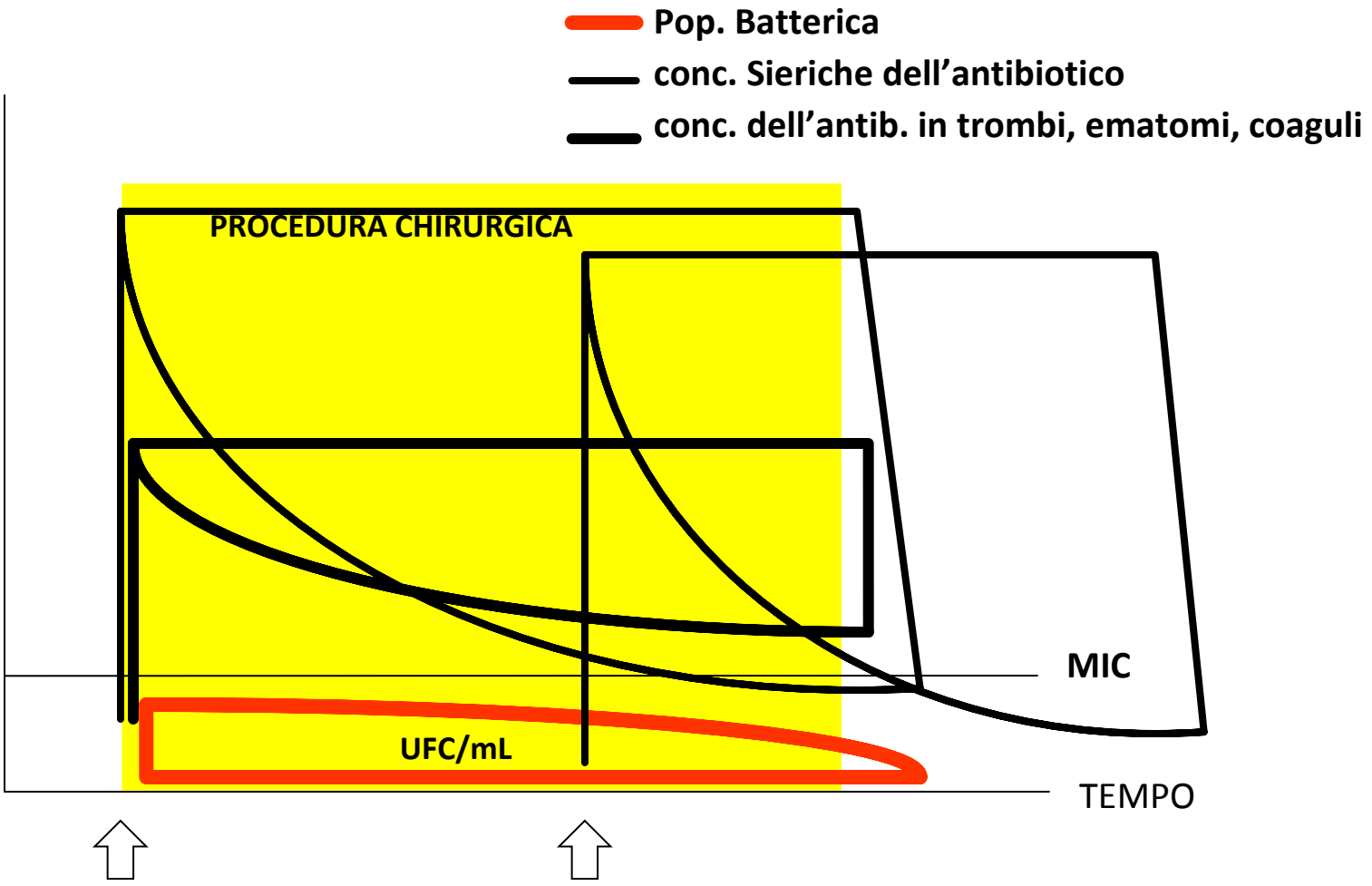


TABELLA 35

Profilassi antinfettiva nei trapiantati

Fattori di rischio	Agenti	Farmaci
Virus latenti	CMV, EBV, HSV, VZV	acyclovir, ganciclovir
Parassiti latenti	*Pneumocystis, Nocardia, Listeria, Toxoplasma gondii*	TMT/SMX, oppure dapsone e pirimetamina
TBC latente o storia di esposizione	storia di esposizione, *Tubercolosis*	isoniazide

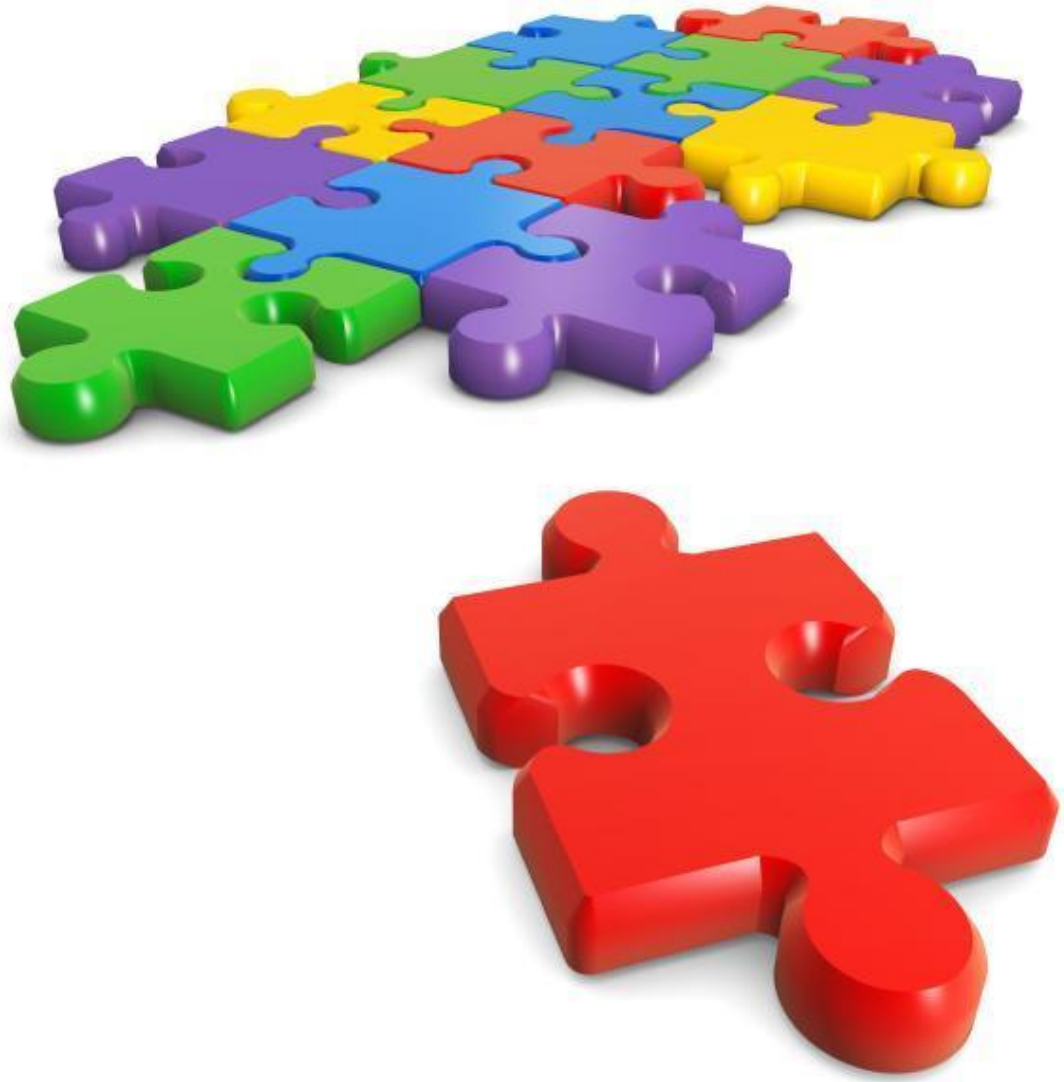
Pieces of the puzzle necessary for an appropriate antimicrobial therapy

antibiotic

MIC driven therapy

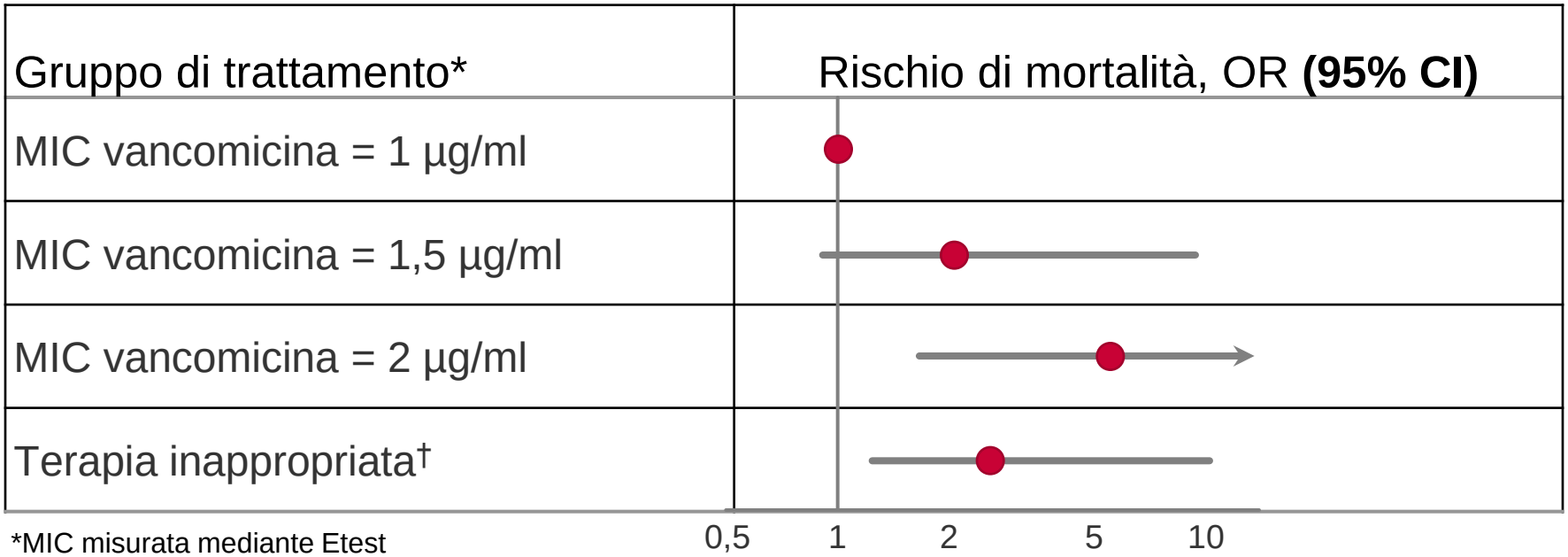
Physiopathology of the patient

PK/PD



MIC driven therapy

La MIC della vancomicina è un fattore predittivo significativo di mortalità nelle infezioni da MRSA

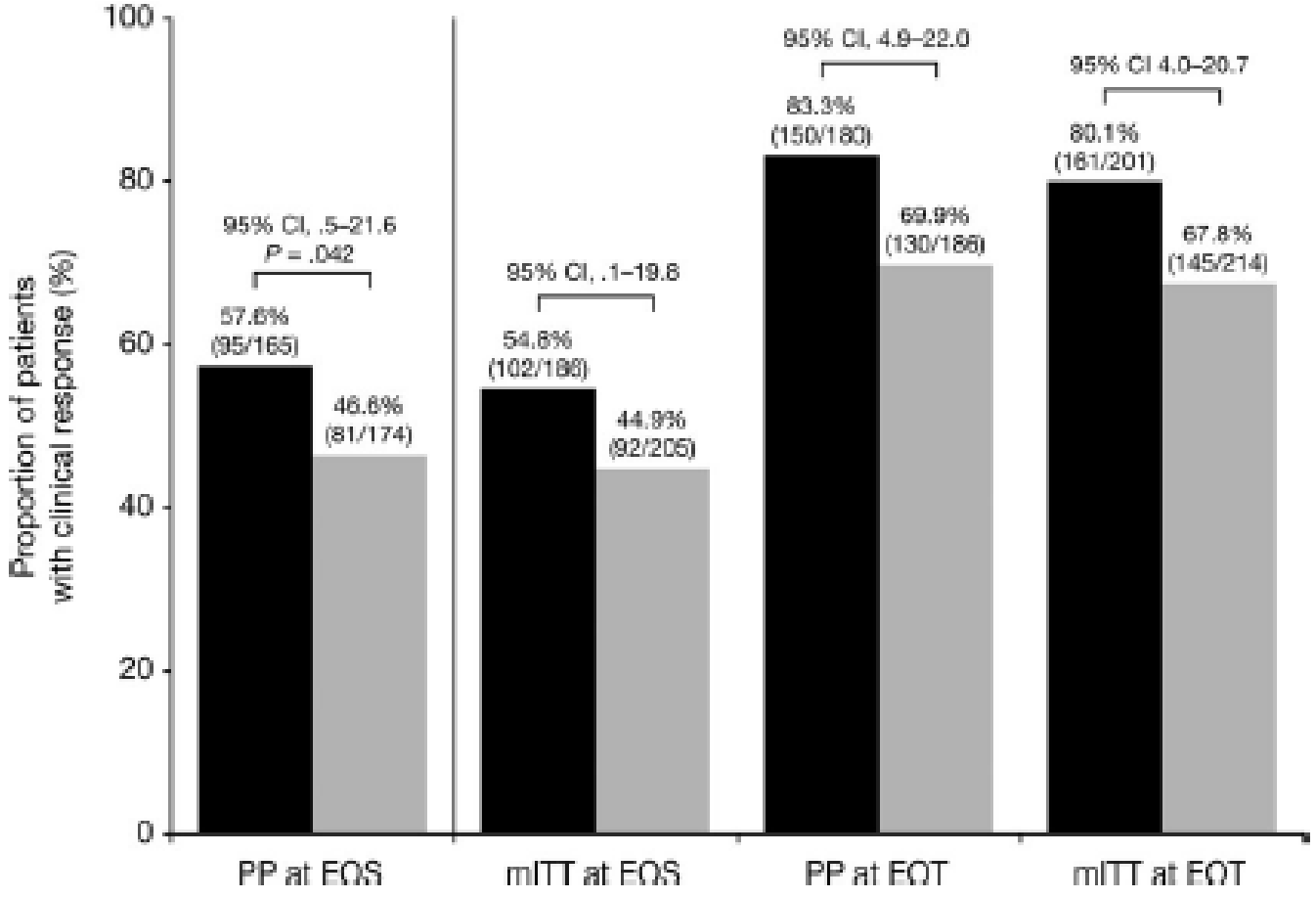


*MIC misurata mediante Etest

†Terapia inappropriata definita come terapia empirica a cui il ceppo di MRSA è risultato resistente

Soriano A, et al. Clin Infect Dis 2008; 46:193-200

Linezolid in Methicillin-Resistant *Staphylococcus aureus* Nosocomial Pneumonia: A Randomized, Controlled Study



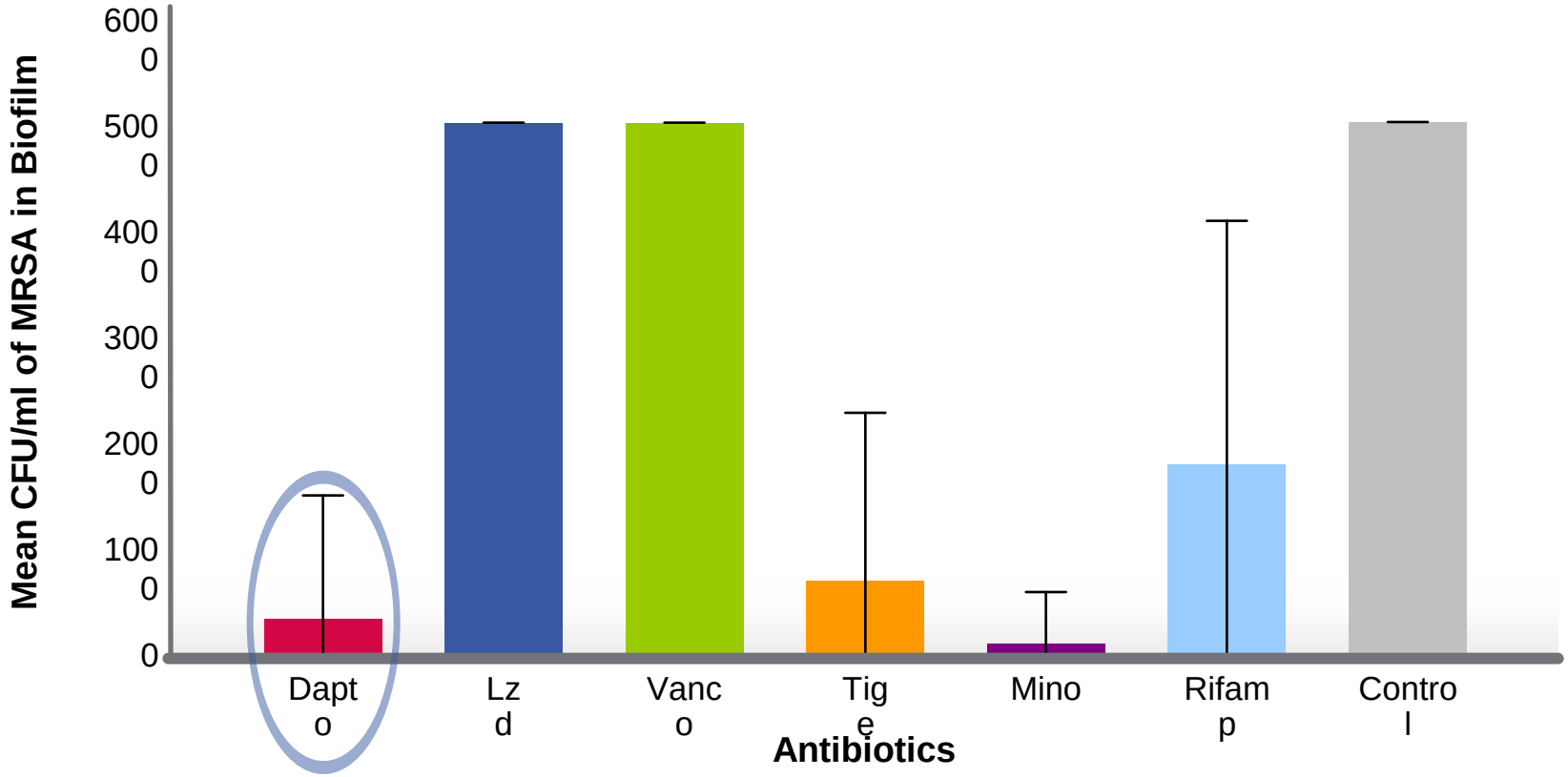
Wunderink RG et al. Clin Infect Dis 2012; 54:621-9

Attività battericida rapida di daptomicina nella peritonite da *Staphylococcus aureus* meticillino-resistente e meticillino-sensibile nel topo, valutata con batteri luminescenti

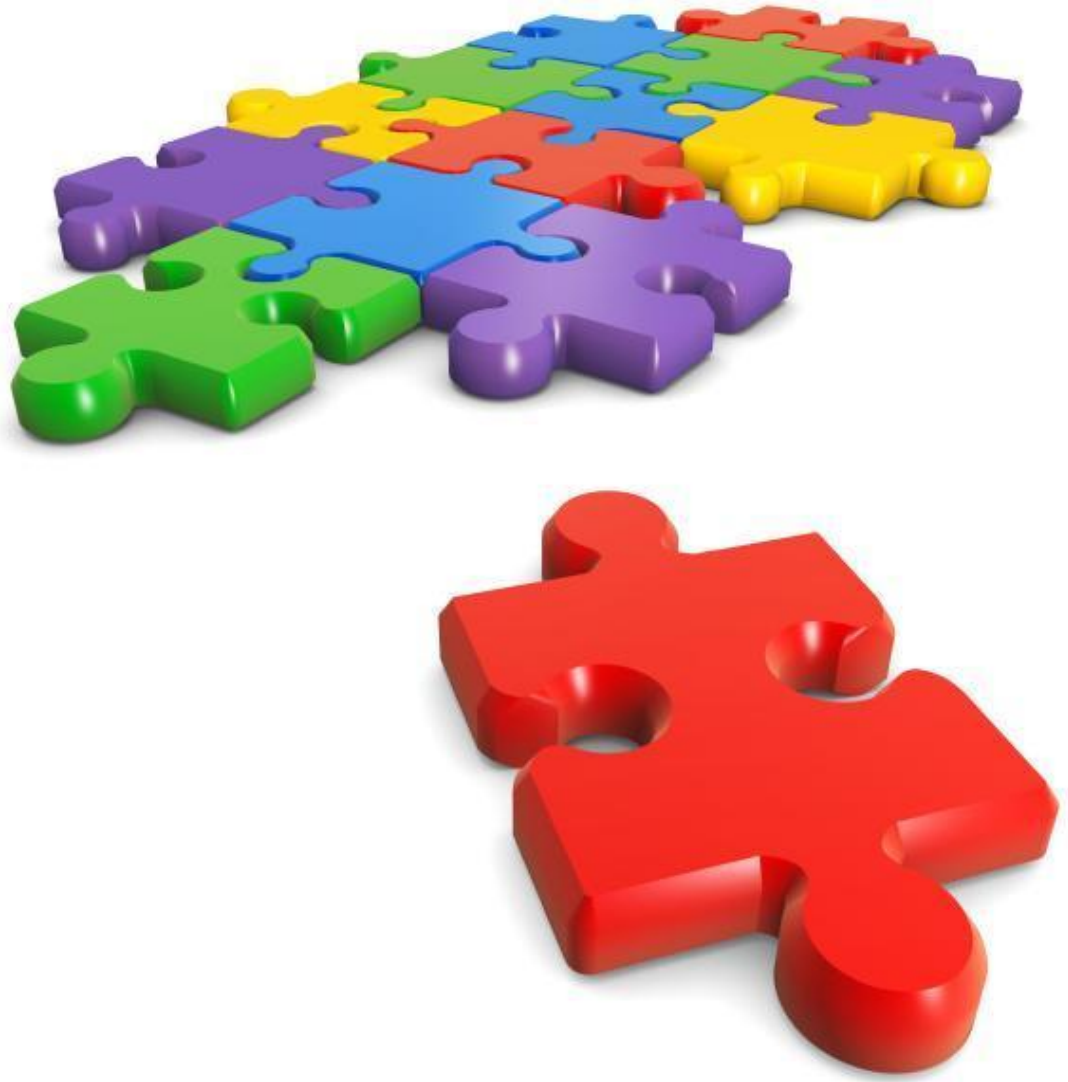
MRSA in topi neutropenici

Martin Li, et al. *AAC*, May 2007; 51:1787-1794

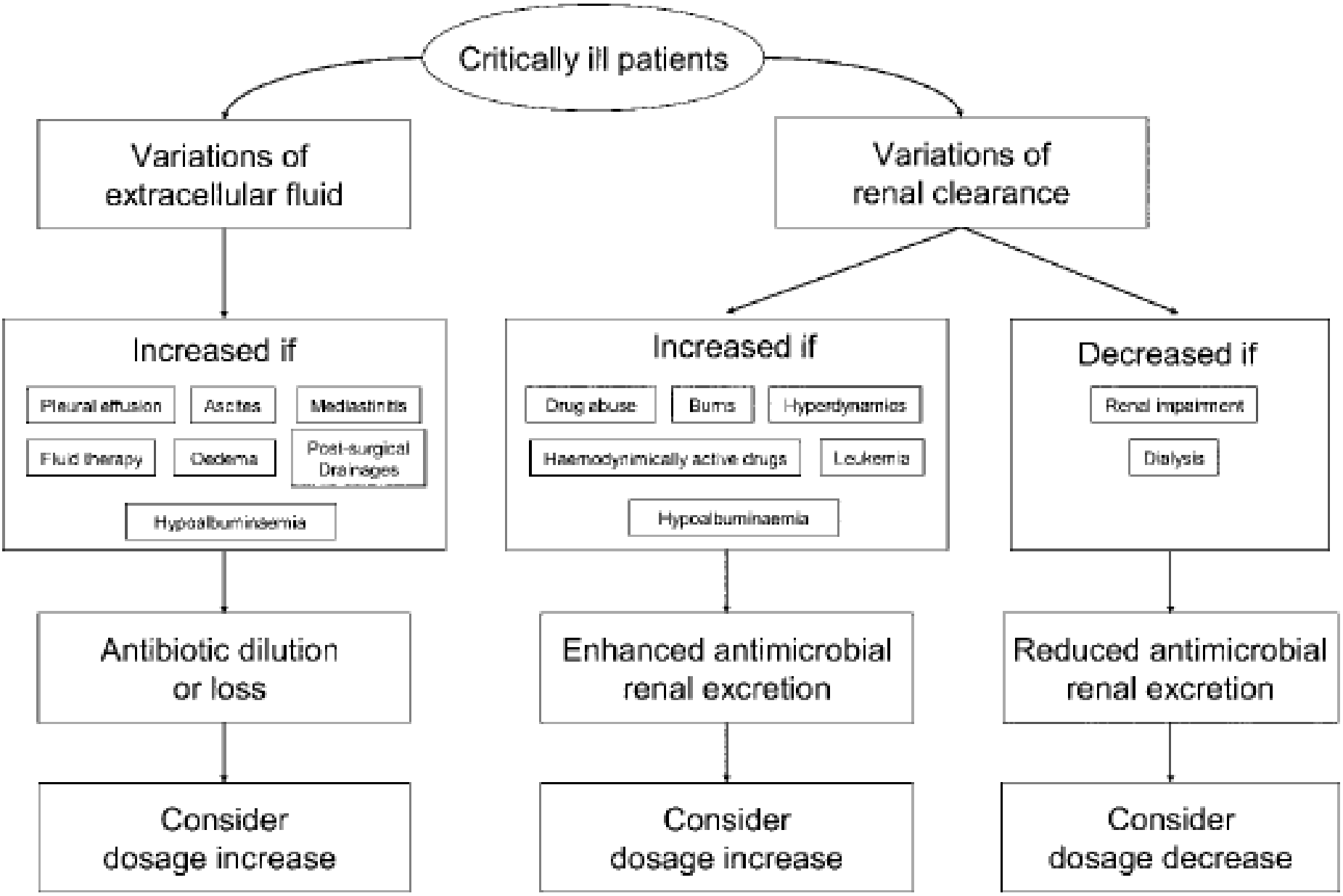
Attività contro MRSA in biofilm dopo 24 ore di esposizione(Biofilm: agglomerato di cellule batteriche immerse in una matrice extra-cellulare polisaccaridica)



Raad I, et al. AAC May 2007; 1656-1660



Patient's pathophysiology



Pea F et al.. Clin Infect Dis 2006; 42: 1764-71

The Effects of Hypoalbuminaemia on Optimizing Antibacterial Dosing in Critically Ill Patients

- **Low serum albumin levels are very common in critically ill patients, with reported incidences as high as 40–50%.**

- **This condition appears to be associated with alterations in the degree of protein binding of many highly protein-bound antibacterials, which lead to altered pharmacokinetics and pharmacodynamics, although this topic is infrequently considered in daily clinical practice.**

- **Hypoalbuminemia → increase of the unbound fraction of the drug**
  increase of the apparent total volume of distribution (Vd)
  increase of (CL) of a drug
  decrease of antibiotic exposure

Ulldemolins M et al. Clin Pharmacokinet 2011; 50 : 99-110

Pieces of the puzzle necessary for an appropriate antimicrobial therapy

Antibiotic

Limits due to the lack of new (and efficient) antimicrobials

Cooper MA, Shlaes D. Nature 2011;472:32.

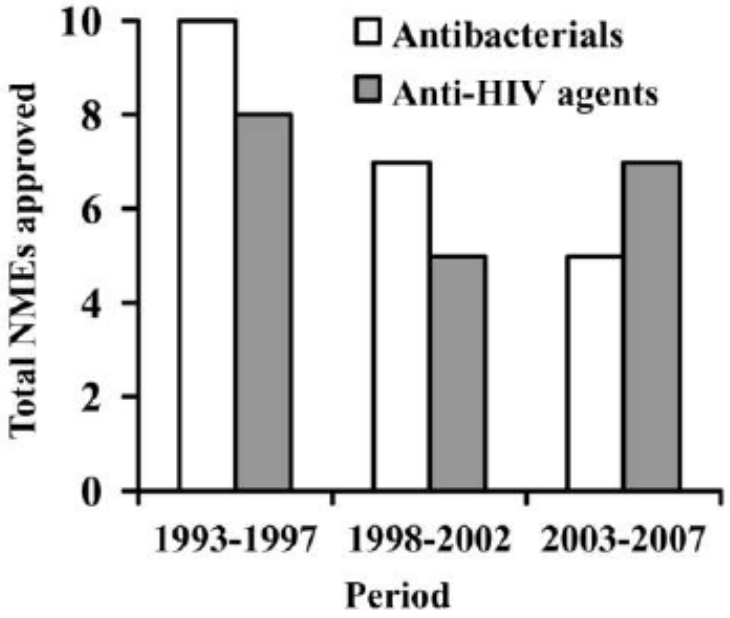


Figure 2. Antibacterial and anti-HIV new molecular entities (NMEs) approved by the US Food and Drug Administration, per 5-year period.

Spellberg B et al, Clin Infect Dis 2008; 46:155-64

Table 2. Advantages and disadvantages of combination antimicrobial treatment.

Effects of the combination	Advantages	Disadvantages
Synergistic effect	*In vitro* studies, lessons from HIV, TB and endocarditis	Difficult to demonstrate in clinical studies for Gram-negative infections
Prevention of emergence of resistant bacteria	Improved bactericidal activity (synergism) suppresses growth of partially resistant subpopulations	Exposure of patient and environment to more than one class of antimicrobial might increase the risk of carriage and transmission of multidrug-resistant bacteria
Likelihood of covering the responsible pathogen	Broadened spectrum of coverage	Scant clinical data Other variables, including timely and adequate empirical initial antimicrobial therapy, play a role in improving patient cure and outcome

Petrosillo N et al. Expert Review Anti Infect Ther 2010;8:289-32

Colonization and infection by colistin-resistant Gram-negative bacteria in a cohort of critically ill patients

Kontopidou F et al. Clin Microbiol Infect 2011; 17: E9–E11

Limits of treatment for MDR Gram negative agents:

How can we overcome it?

Carbapenemase-producing *Klebsiella pneumoniae:* (when) might we still consider treating with carbapenems?

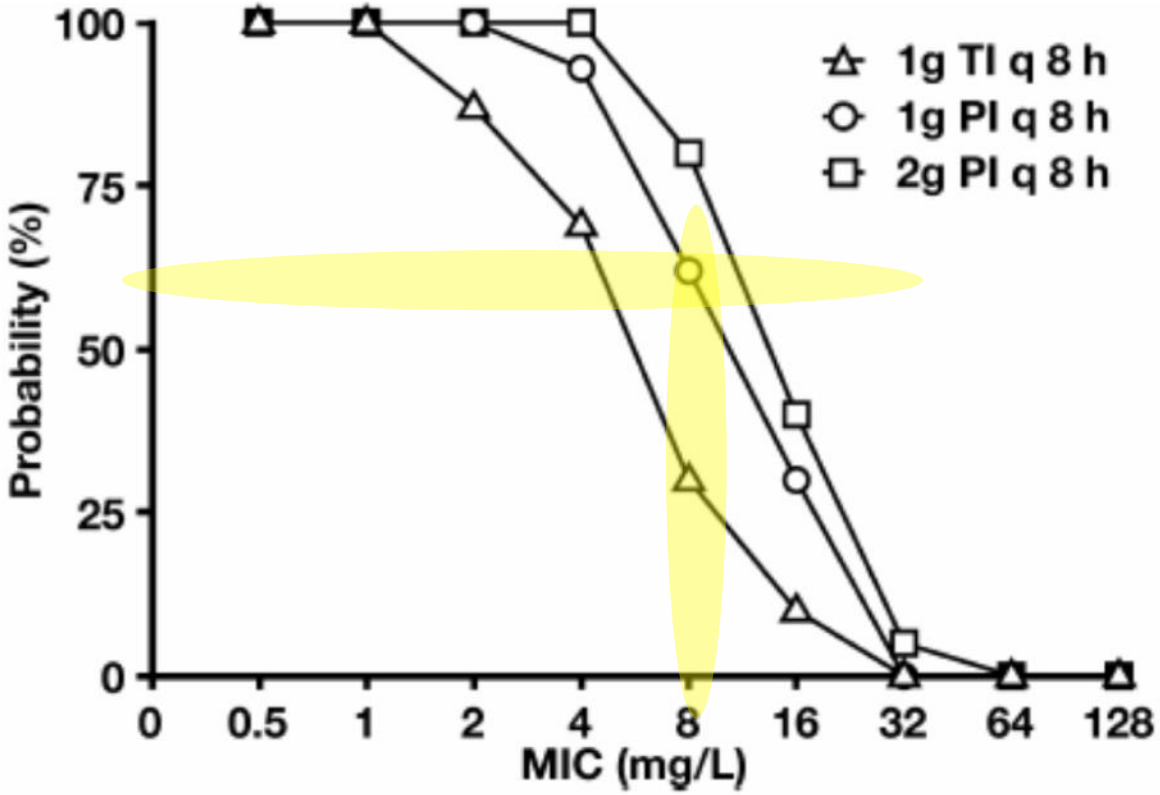
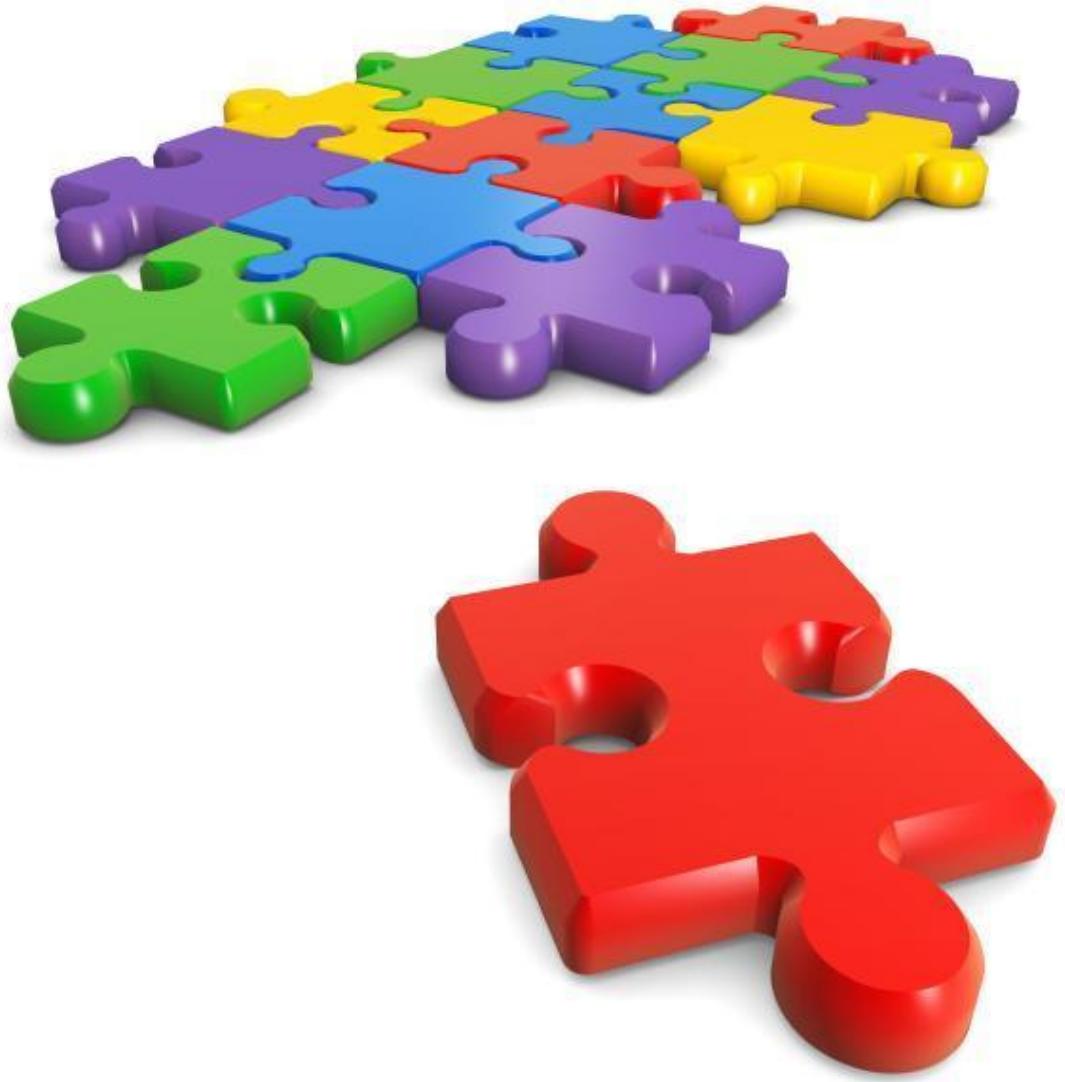


FIG. 2. Simulated target attainment probabilities for 50% time above the MIC (50% *T* > MIC) of three different regiments of meropenem. TI, traditional 30-min infusion; PI, prolonged 3-h infusion. Adapted from [36].

Daikos GL et al. Clin Microbiol Infect 2011; 17: 1135–1141



Infection site

Steady-State Pharmacokinetics and BAL Concentration of Colistin in Critically Ill Patients After IV Colistin Methanesulfonate Administration

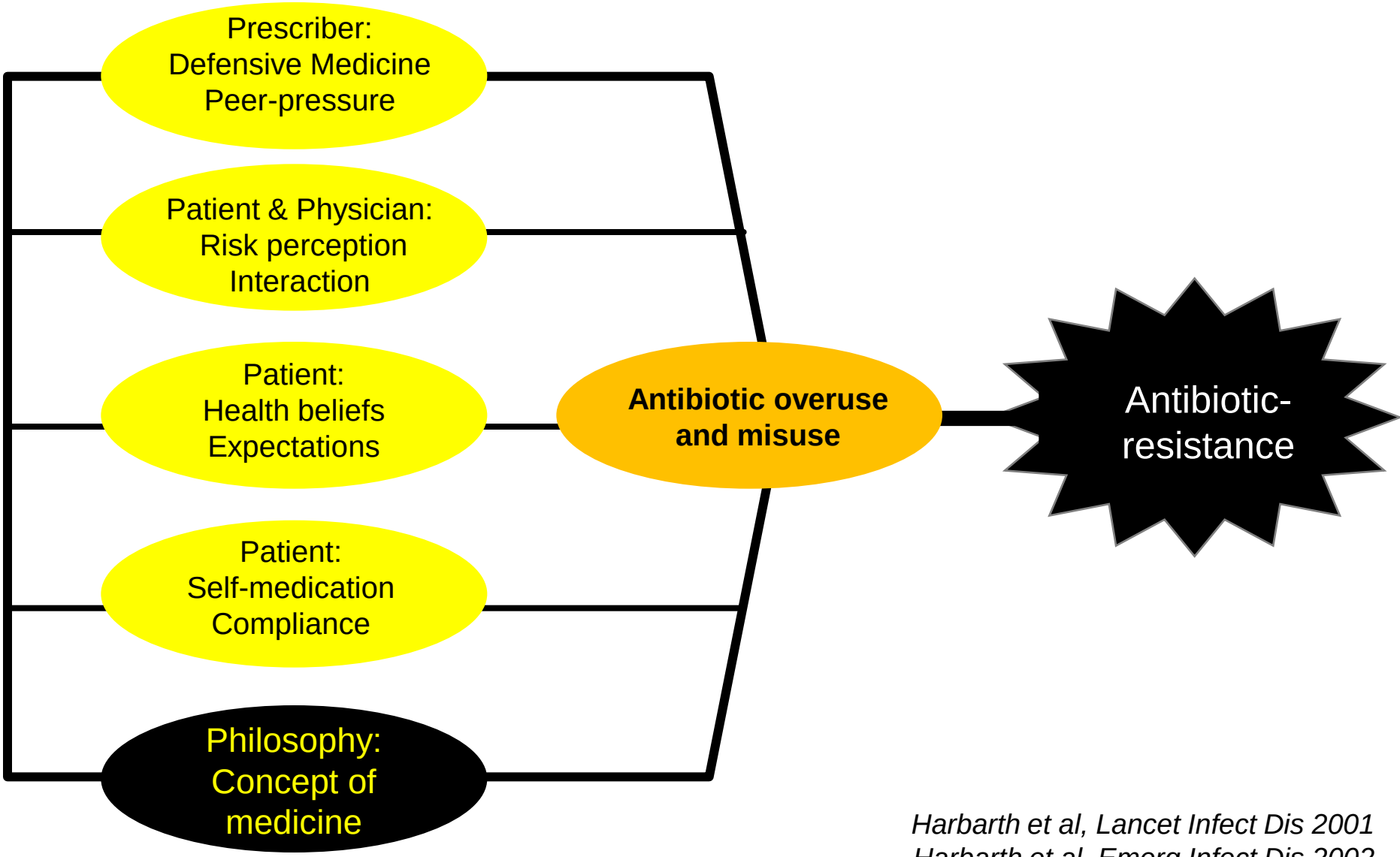
Roberto Imberti, Maria Cusato, Paola Villani, Livio Carnevale, Giorgio A. Iotti, Martin Langer and Mario Regazzi

CHEST 2010; 138(6):1333–1339

Concentration of Colistin in BAL

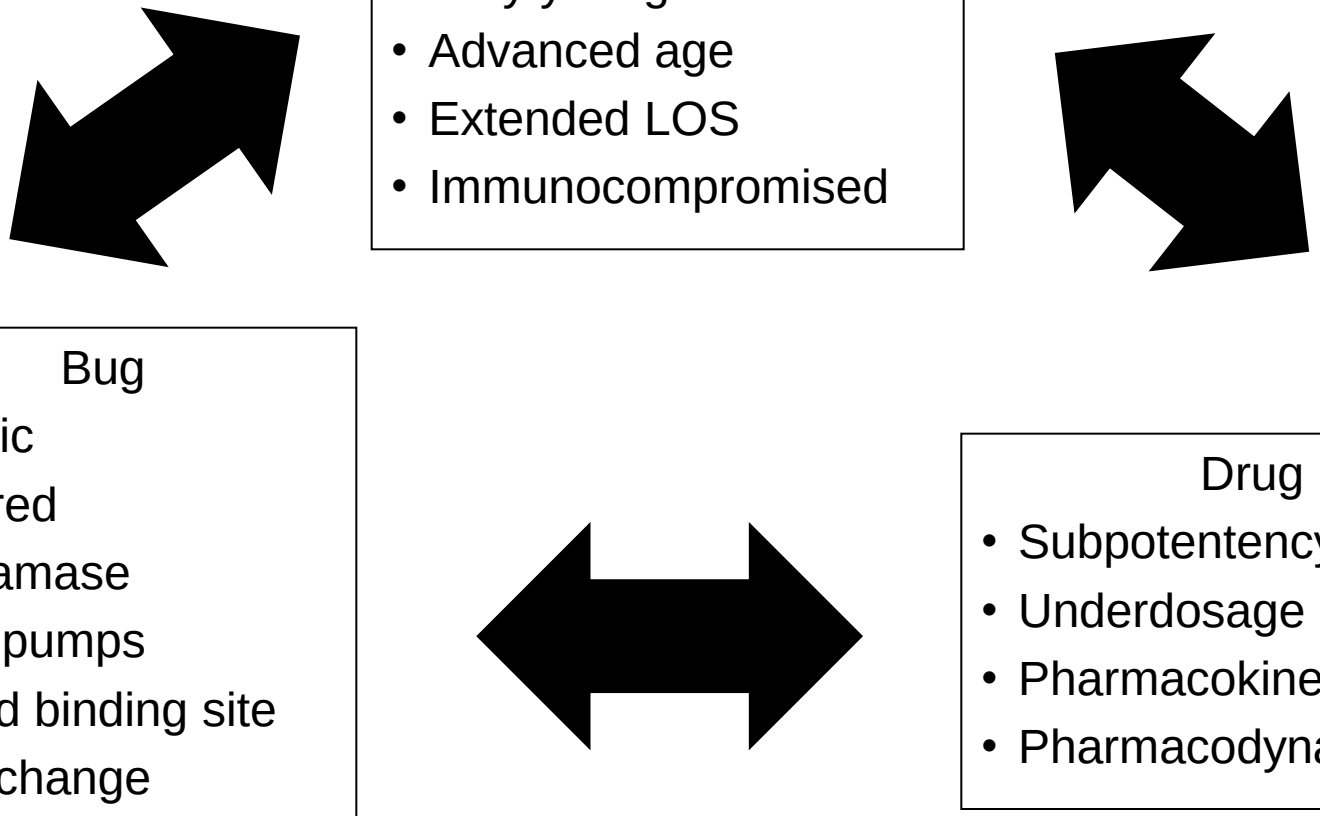
Two hours after the start of CMS infusion, colistin was undetectable in BAL but was present at a relevant concentration in the BAL of a patient who received CMS by aerosol, used as internal control (0.48 m g/mL).

Socio-cultural determinants influencing antibiotic use & resistance



Harbarth et al, Lancet Infect Dis 2001
Harbarth et al, Emerg Infect Dis 2002

Drivers of Resistance



Antimicrobial Prescribing Facts: Rule of “1/3”

~ 1/3 of all hospitalised inpatients at any given time receive antibiotics

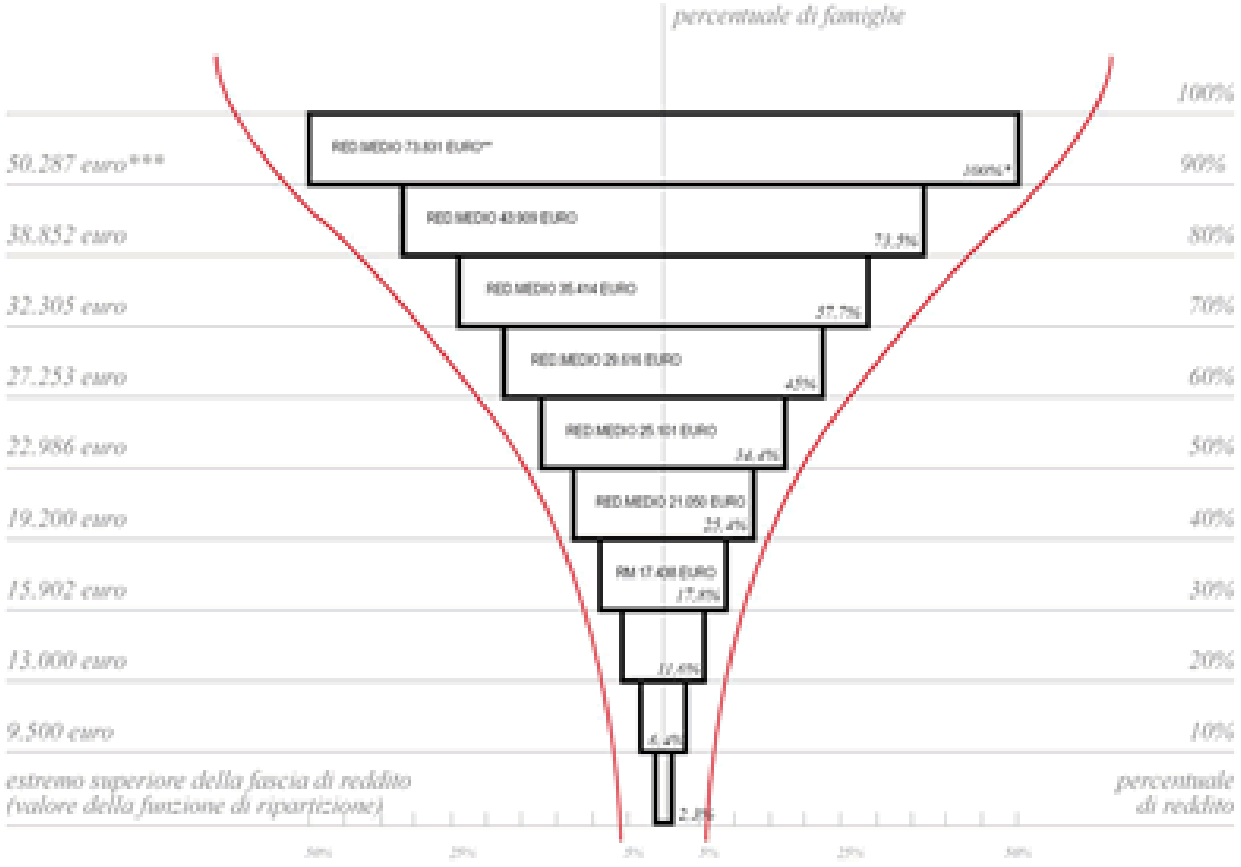
~ up to 1/3 to ½ are inappropriate

~ up to 30% of all surgical prophylaxis in inappropriate

~ 30% of hospital pharmacy budgets.

Stewardship programmes can save up to 10-30% of pharmacy budgets.

Vilfredo Pareto ed il principio 80/20: il poco, determina il tutto...



Priority Topics for Study

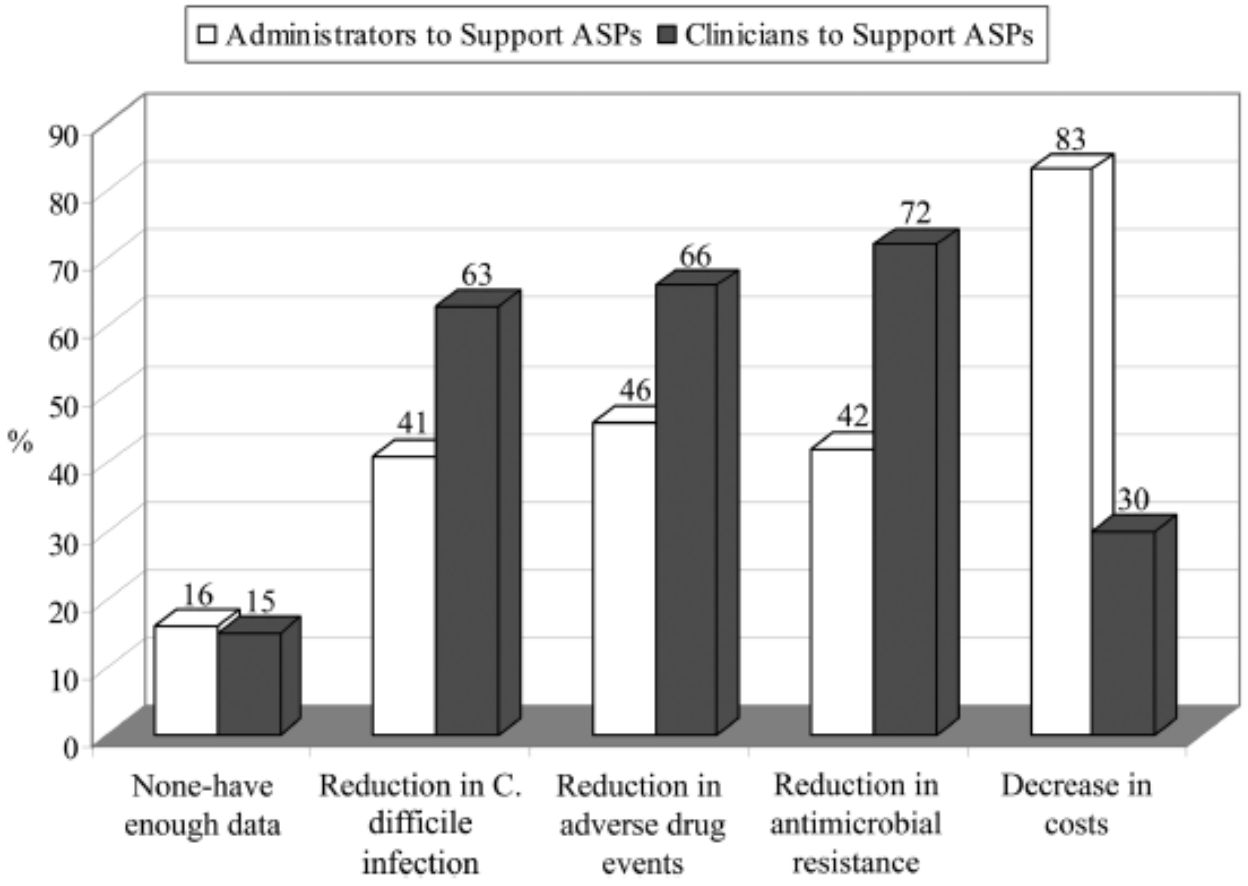


FIGURE 1. Outcomes data that would be most useful in convincing clinicians and administrators to support antimicrobial stewardship programs.

Johannsson B et al. Infect Control Hosp Epidemiol 2011; 32: 367-374

Antimicrobial Stewardship Programs

ASPs are designed

- to optimize antimicrobial therapy for patients,
- to improve patients' outcomes,
- ensure cost-effective therapy and
- reduce adverse effects associated with antimicrobial use, including antimicrobial resistance

(Note: does not refer to reduction of use as the main goal)

MacDougall C et al. *Clin Microbiol Rev 2005; 18; 638–656*
Lesprit P et al. *Curr Opin Infect Dis 2008:21; 344–349*

Box 1. Elements to minimize the spread of and to adequately manage patients with multidrug-resistant organisms in intensive care.

Prevention of spread

- Reducing the antibiotic pressure
- Antimicrobial stewardship programs
- Infection control

Clinical management

- Timeliness, appropriateness and adequacy of the initial antibiotic regimen
- De-escalation therapy
- MIC-driven therapy
- Maximizing antimicrobial exposure at the infection site
- Better understanding of pharmacokinetic–pharmacodynamic relationships and the pattern of bactericidal activity

Petrosillo N. et al. *Expert Rev Anti Infect Ther 2010;* 8: 289–302.

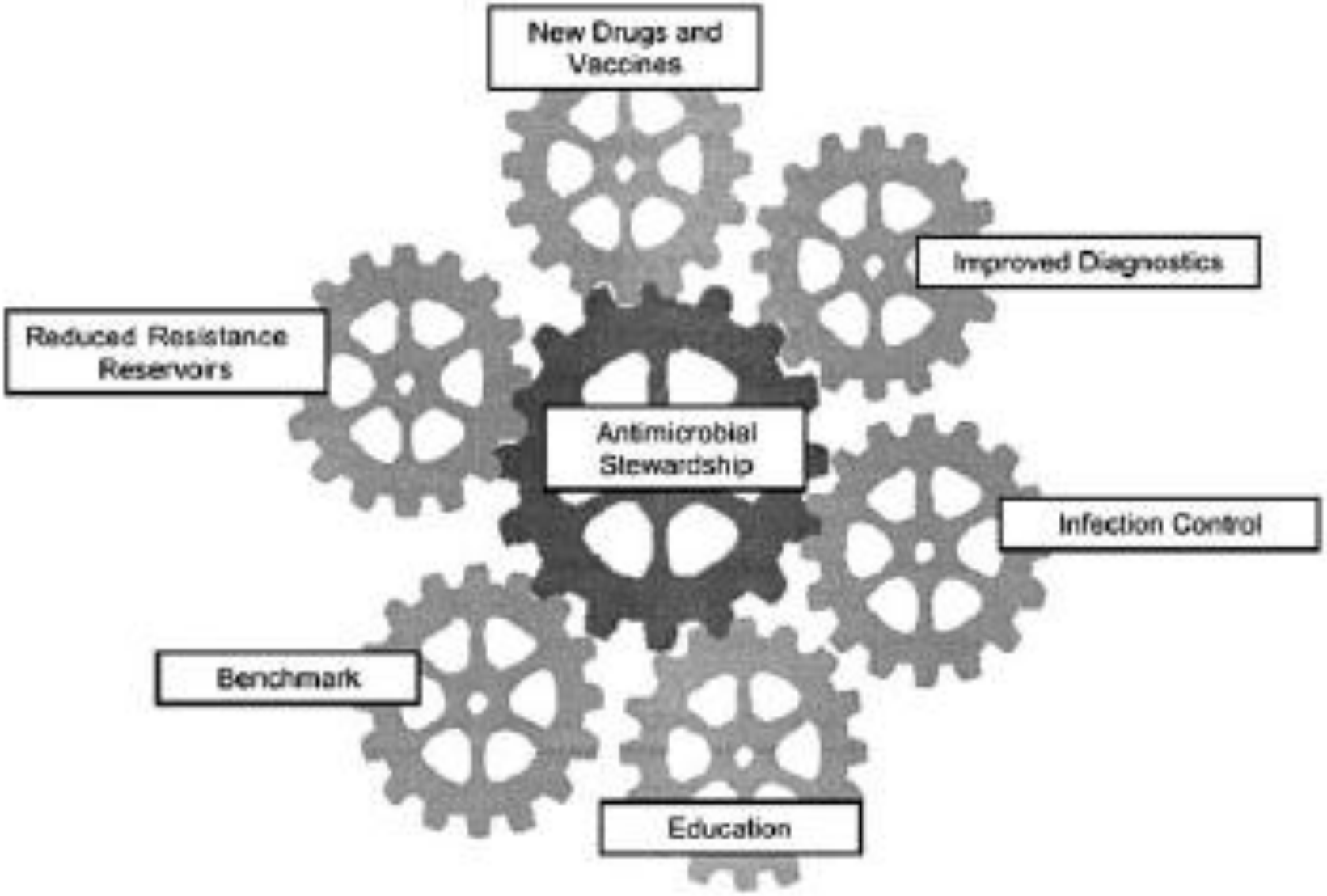


Fig 2. Efforts to control antimicrobial resistance.