

**L'infettivologo come riferimento tra
laboratorio, specialista di
reparto, farmacologo e farmacista**

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**L' inquadramento del paziente infettivo:
non tutti i pazienti sono inquadrabili nello stesso modo**

...stewardship...

- Antimicrobial stewardship includes not only limiting inappropriate use but also optimizing antimicrobial selection, dosing, route, and duration of therapy to maximize clinical cure or prevention of infection while limiting the unintended consequences, such as the emergence of resistance, adverse drug events, and cost.

Il mondo reale: la stewardship negli Ospedali pubblici di oggi

- 6 terapie intensive
- 7 medicine
- 2 chirurgie
- Ematologia
- Oncologia
- Centro Ustioni
- Unità Spinale
- Neurochirurgia
- Neurologia
- Epatologia
- Ortopedia
- Traumatologia
- 4 Cardiologie
- Cardiochirurgia
- Chirurgia toracica
- Urologia
- Nefrologia
- Riabilitazione

E inoltre:

Pronto Soccorso

Microbiologia

Farmacia

Farmacologo clinico (se c'è)

Direzione Sanitaria/CIO



MA...



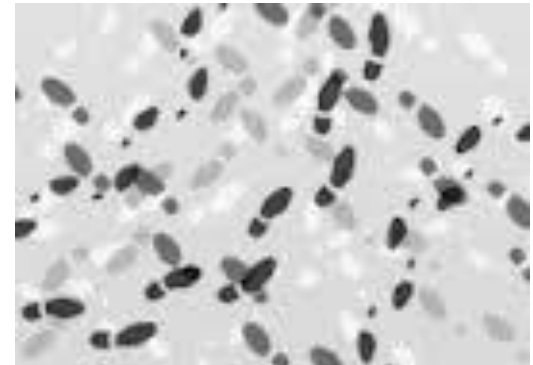
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“...programs should be comprehensive, multidisciplinary, supported by hospital and medical staff leadership, and should employ evidence-based strategies that best fit local needs and resources...” (Ohl CA, Antimicrobial stewardship for inpatient facilities, J Hosp Med 2011 Jan;6 Suppl 1:S4-15)

Interventi

- Consulenze per “risolvere problemi”
- Ottimizzare prescrizioni: farmaci, dosi, durate, semplificazioni.
- Creare un indirizzo terapeutico per le più comuni situazioni, ma anche
- **“MODULARE LE ECCEZIONI”**

“stewardship passiva e stewardship attiva”



Esempi difficili in T.I.



- Candida score “borderline”
- Isolati addominali di germi resistenti
- Gestione di cateteri centrali e port in Ematologia
- Terapie antifungine empiriche e pre-emptive nei pazienti a rischio
- Scelte nei pazienti molto critici, emofiltrati, ustionati, obesi, multitrattati
- Malattie rare

In generale tutto ciò che è difficilmente protocollabile è meglio sia comunque discusso e in qualche modo “centralizzato” su un referente

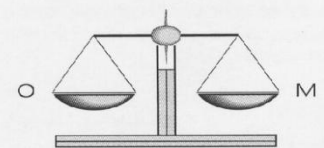
Incubi a cavallo del millennio

- **MRSA, VANCO CREEP OF MRSA**
- **VRE**
- **ESBL *ENTEROBACTERIACEAE***
- **CARBAPENEM- and MDR- RESISTANCE OF *P. Aeruginosa***
- **KPC *ENTEROBACTERIACEAE***
- **MDR ACINETOBACTER**

ESKAPE: Enterococcus faecium (E), S. aureus (S), Klebsiella pneumoniae (K), Acinetobacter baumannii (A), P. aeruginosa (P), and Enterobacter spp. (E)

ESCAPE, C. difficile (C) replaces K. pneumoniae (K), and E now stands for Enterobacteriaceae, which encompasses K. pneumoniae and Enterobacter spp., as well as other critically important pathogens that can express increasing levels of antibiotic resistance (e.g., E. coli) (Paterson, CID 2009).

Batteri, miceti, protozoi e virus:
tutti si approfittano dell'ospite
indifeso



suscettibilità
dell'ospite



potenziale
di patogenicità

Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship

Timothy H. Dellit,¹ Robert C. Owens,² John E. McGowan, Jr.,³ Dale N. Gerding,⁴ Robert A. Weinstein,⁵ John P. Burke,⁶ W. Charles Huskins,⁷ David L. Paterson,⁸ Neil O. Fishman,⁹ Christopher F. Carpenter,¹⁰ P. J. Brennan,⁹ Marianne Billeter,¹¹ and Thomas M. Hooton¹²

Table 2. Causal associations between antimicrobial use and the emergence of antimicrobial resistance.

Changes in antimicrobial use are paralleled by changes in the prevalence of resistance.

Antimicrobial resistance is more prevalent in health care-associated bacterial infections, compared with those from community-acquired infections.

Patients with health care-associated infections caused by resistant strains are more likely than control patients to have received prior antimicrobials.

Areas within hospitals that have the highest rates of antimicrobial resistance also have the highest rates of antimicrobial use.

Increasing duration of patient exposure to antimicrobials increases the likelihood of colonization with resistant organisms.

Interventions to improve antibiotic prescribing practices for hospital inpatients (Review)

Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A, Ramsay CR, Wiffen PJ, Wilcox M

The Cochrane Library, april 30 2013

the challenge to reduce inappropriate antibiotic prescribing, the implication being that antibiotic resistance is largely a consequence of the selective pressures of antibiotic usage and that reducing these pressures by the judicious administration of antibiotics will facilitate a return of susceptible bacteria or, at least, will prevent or slow the pace of the emergence of resistant strains.

sepsis kills more people annually than myocardial infarction or breast, colon and lung cancer combined ([Robson 2008](#)), and delay in effective antibiotic treatment is associated with increased mortality ([Daniels 2010](#); [Kumar 2006](#)).

The term 'antibiotic stewardship' is used to capture the twin aims of ensuring effective treatment of patients with infection and minimizing collateral damage from antimicrobial use

Carbapenem-Resistant *Enterobacteriaceae*: Epidemiology and Prevention

Neil Gupta,^{1,2} Brandi M. Limbago,² Jean B. Patel,² and Alexander J. Kallen²

¹Epidemic Intelligence Service and ²Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia



KPC

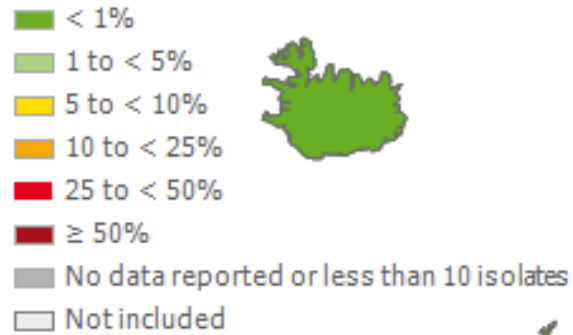


NDM

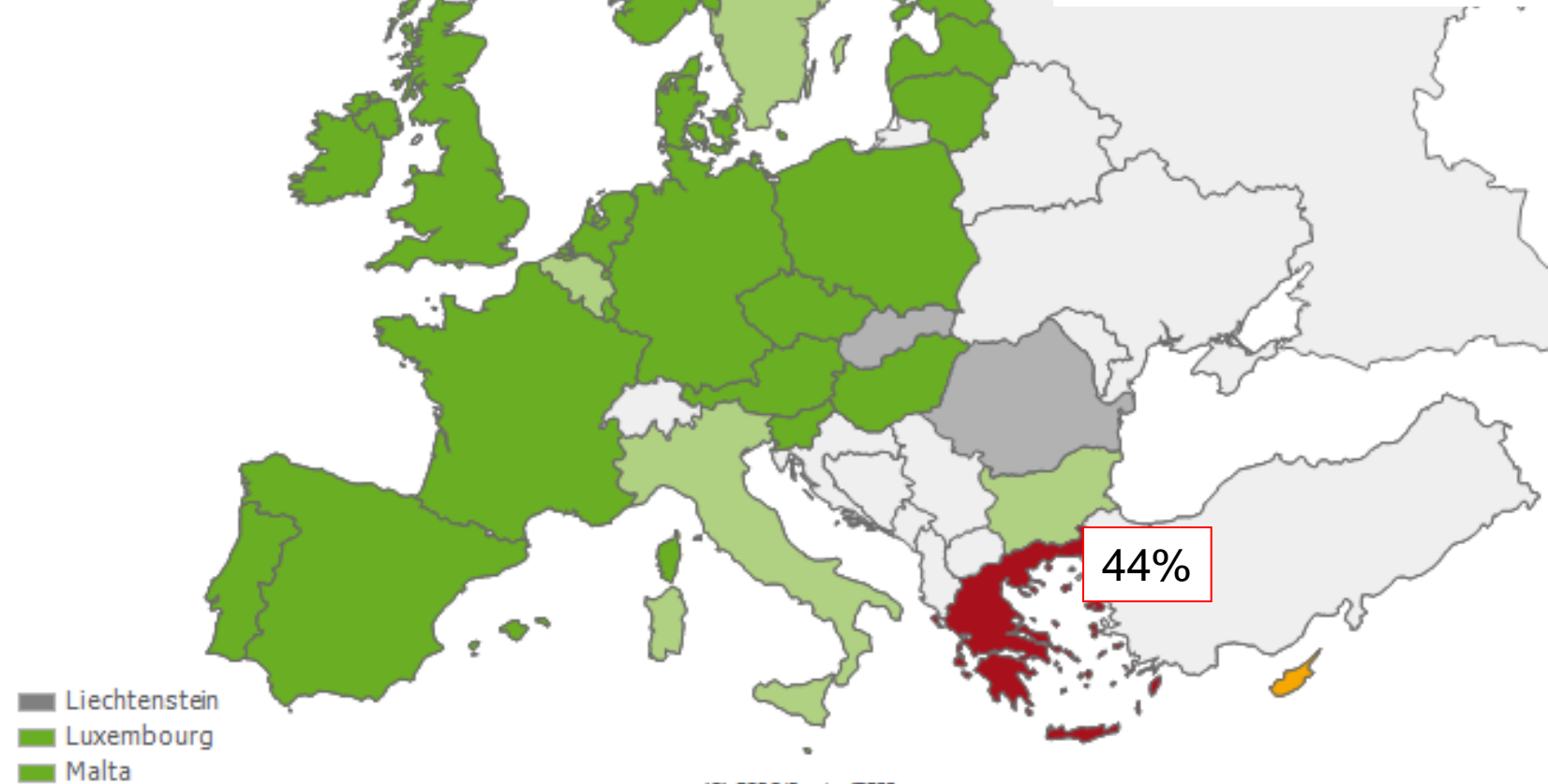
...globalizing...



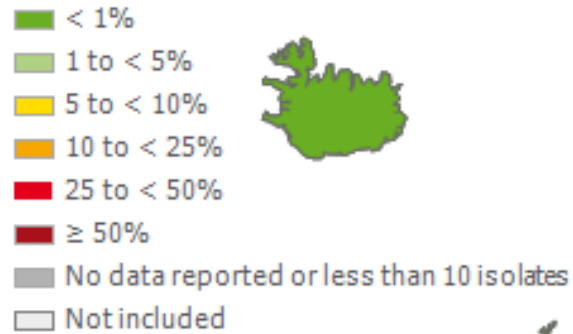
Percentage resistance



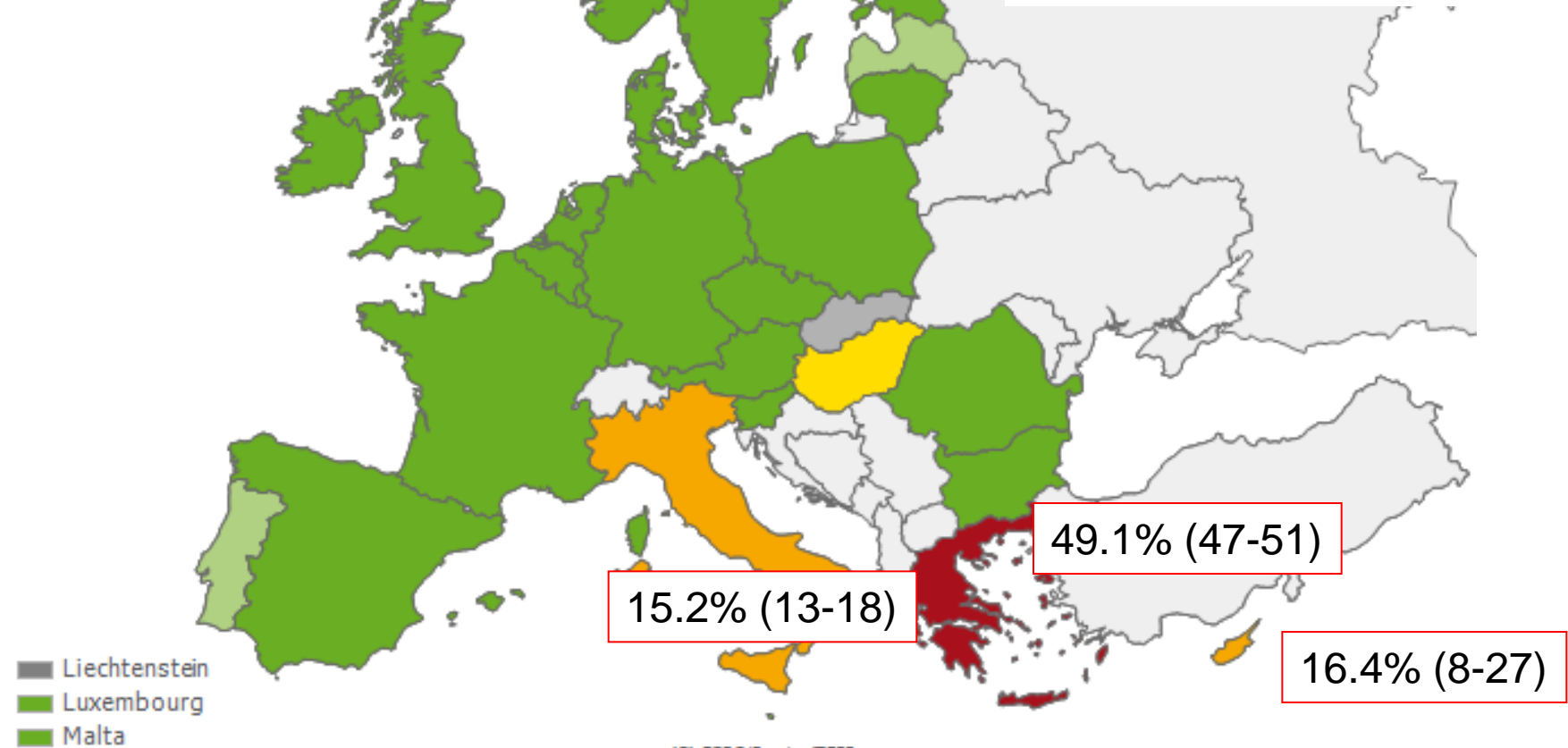
Proportion of Carbapenem Resistant (R+I) *Klebsiella pneumoniae* Isolates in Participating Countries in 2009



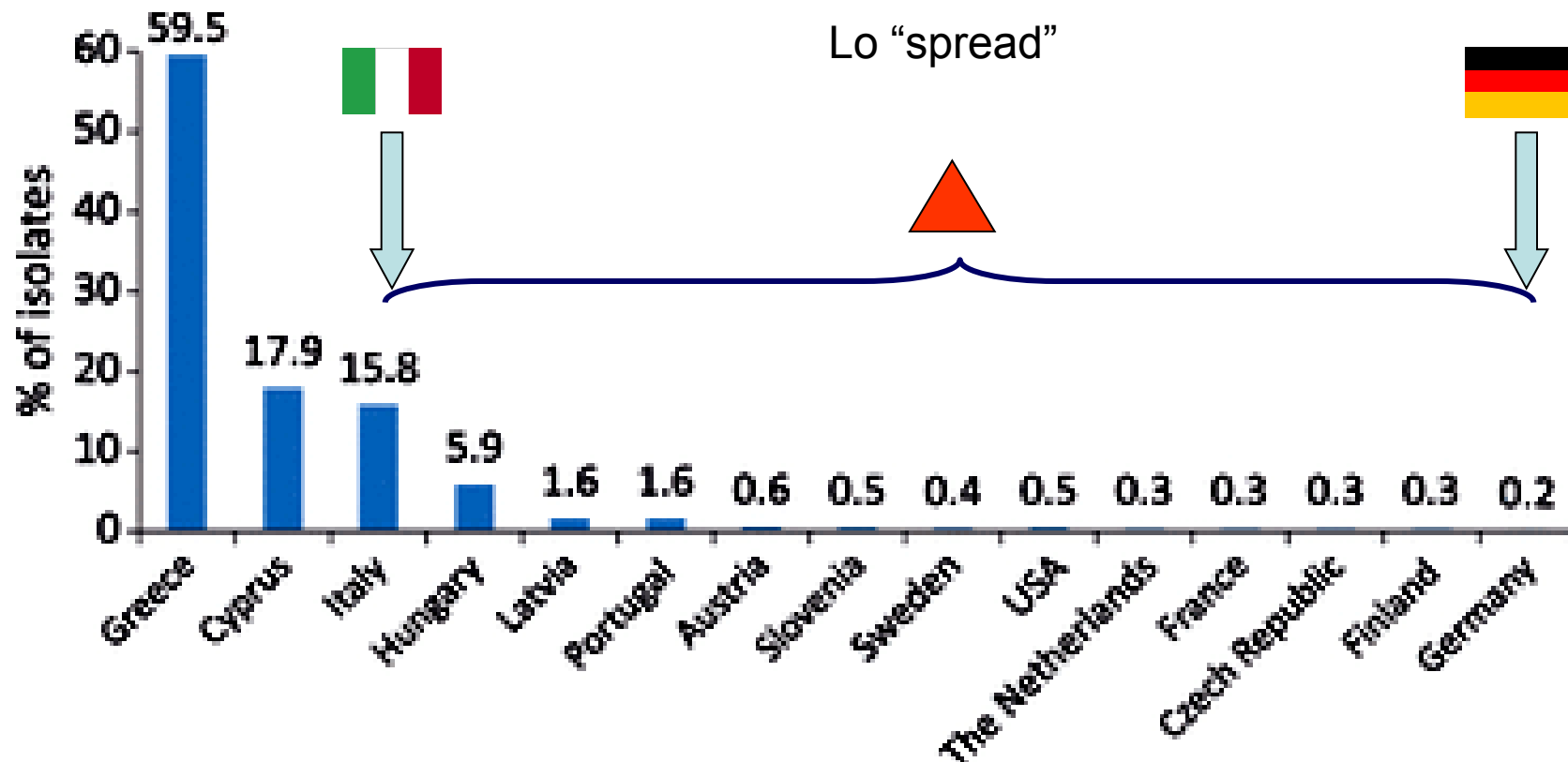
Percentage resistance



Proportion of Carbapenem Resistant (R+I) *Klebsiella pneumoniae* Isolates in Participating Countries in 2010



Carbapenemase-producing *Enterobacteriaceae* in Europe



KPC-producing *K. pneumoniae* – the Italian epidemics



late 2008

The first reported cases of KPC-Kp

ST258

Giani *et al* – JCM 2009



early 2011

ST258, ST512 (CC258)

Fontana *et al* – BMC Res Notes 2010

Marchese *et al* – J Chemother 2010

Ambretti *et al* – New Microb 2010

Gaibani *et al* – Eurosurv 2011

Mezzatesta *et al* – CMI 2011

Agodi *et al* – JCM 2011

Richter *et al* – JCM 2011

Di Carlo *et al* – BMC Gastroent 2011



late 2012

ST512

ST258

ST101

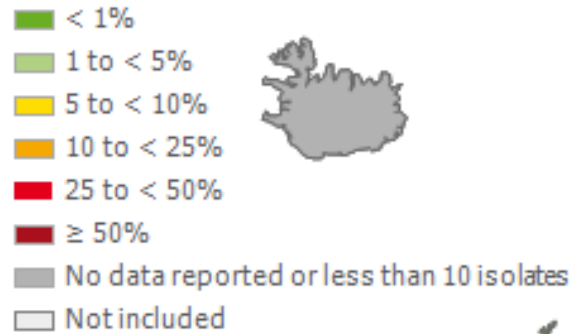
ST15

ST147-like

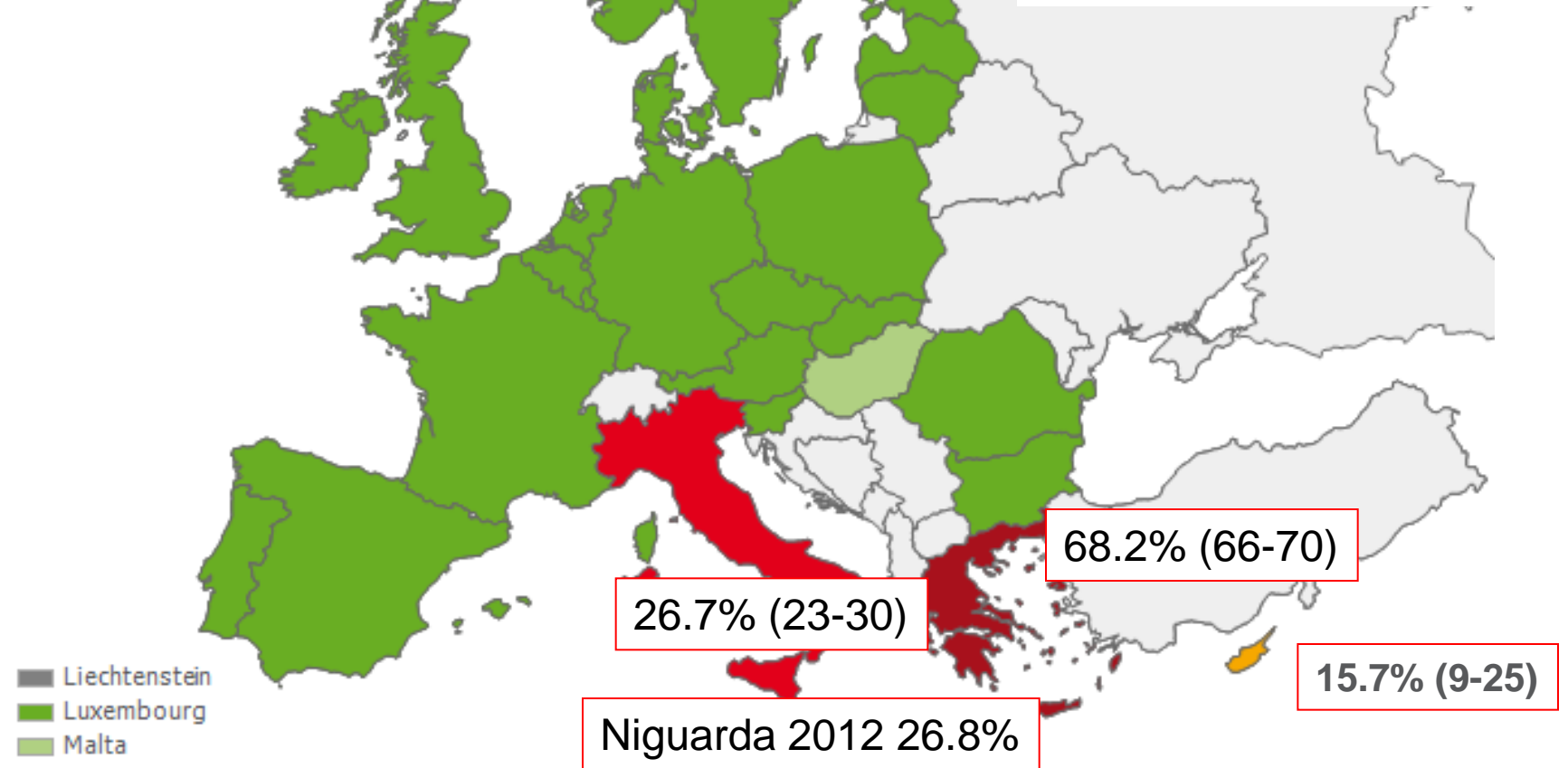
AMCLI – CoSA CRE network

Frasson *et al* – JCM 2012

Percentage resistance



Proportion of Carbapenem Resistant (R+I) *Klebsiella pneumoniae* Isolates in Participating Countries in 2011



Interventi di contenimento per le enterobatteriacee carbapenemasi-produttrici

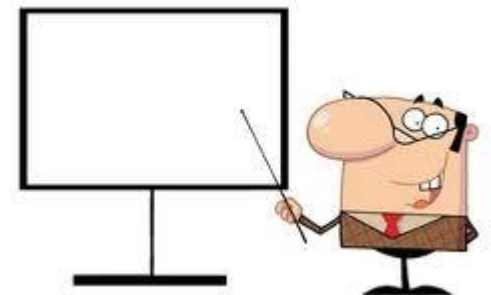


Stewardship interventions

- Increase effective prescribing
- Decrease excessive prescribing
- Review and make change
- Decrease targeted antibiotics
- Decrease colonisation and infection CD
- Decrease colonisation and infection MDR
- Decrease costs and improve savings
- Improve clinical outcome
- Decrease mortality

Persuasive interventions:

- Dissemination of educational materials in printed form or via educational meetings;
- Reminders;
- Audit and feedback;
- Educational outreach (academic detailing or review and recommend change).



Restrictive interventions (a change to the antibiotic formulary or policy implemented through an organizational change that restricts the freedom of prescribers to select some antibiotics).



1. **Compulsory order form** - prescribers had to complete a form with clinical details to justify use of the restricted antibiotics;
2. **Expert approval** - the prescription for a restricted antibiotic had to be approved by an Infection specialist or by the Head of Department;
3. **Restriction by removal** - a restrictive policy was imposed in target wards, units or operating theatres, for example by removing restricted antibiotics from drug cupboards;
4. **Review and make change** - the difference between this intervention and review and recommend change (educational outreach) is that the reviewer changed the prescription rather than giving health professionals either a verbal or written recommendation that they should change the prescription.

In addition some studies included **automatic stop orders.**



- The results show that interventions to reduce excessive antibiotic prescribing to hospital inpatients **can reduce antimicrobial resistance or hospital-acquired infections**, and interventions to increase effective prescribing **can improve clinical outcome**. This update provides more evidence about unintended clinical consequences of interventions and about the effect of interventions to reduce exposure of patients to antibiotics. The meta-analysis supports the **use of restrictive interventions when the need is urgent, but suggests that persuasive and restrictive interventions are equally effective after six months.**



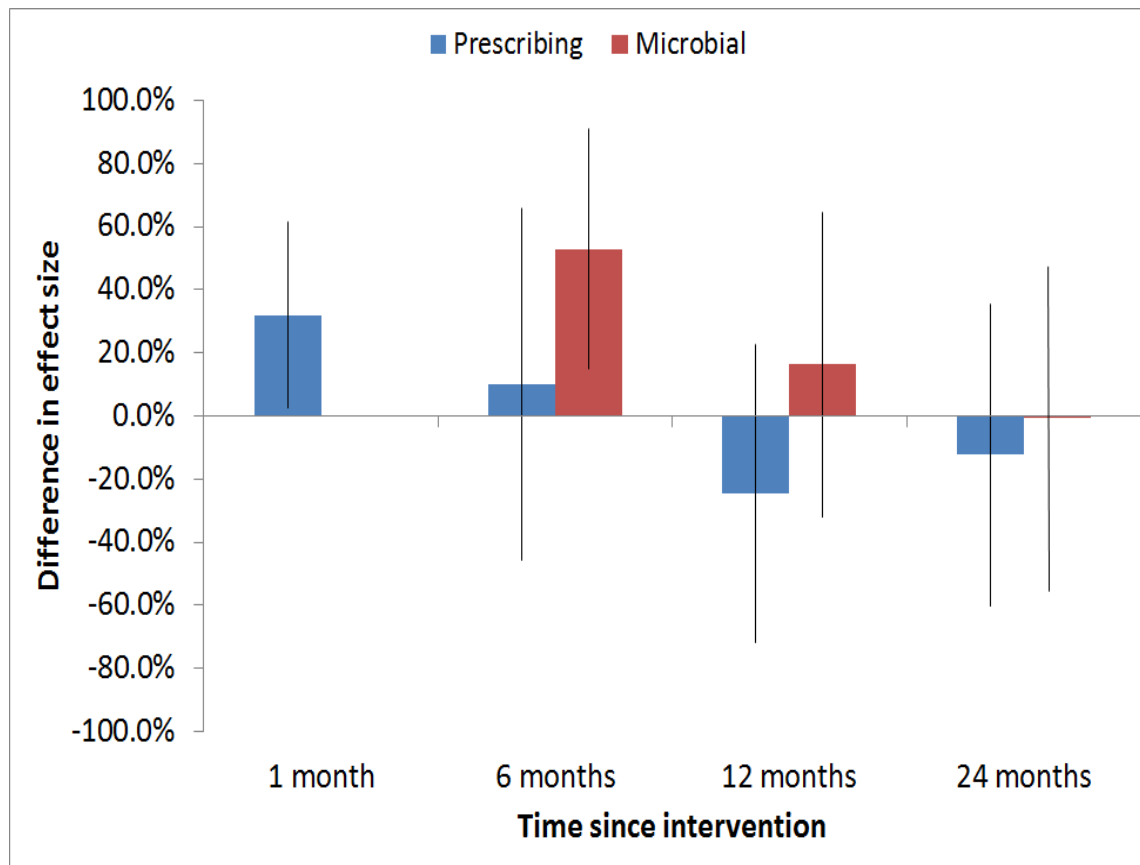


Figure 3. Meta-regression of the difference in effect size between restrictive and persuasive interventions at 1, 6, 12 and 24 months after the intervention. The difference is Restrictive minus Persuasive so positive values for the difference indicate greater effect size for Restrictive interventions and negative values indicate greater effect size for Persuasive interventions. The bars show 95% CI for the mean difference

Misure amministrative

- Restrizioni somministrative
- Preautorizzazioni
- Fogli somministrativi
- Educazione
- CIO: implementazione
- Istruzione di audit

**MODULO
RICHIESTA
COLISTINA**

Esempio: SCHEDA
DI PRESCRIZIONE



U.O.

Data della richiesta / /

CODICE

PAZIENTE

Data inizio terapia / /

Richiesta per: ↑ Inizio Terapia

Durata prevista terapia.....giorni

↑ Prosecuzione Terapia

Durata prevista terapia.....giorni

DOSE RICHIESTA: _____ mg x _____ die ↑ per aerosol ↑ per ev

Status del paziente: ↑ Shock Settico ↑ Sepsi Grave ↑ Sepsi (vedi definizioni allegate)

Motivazione della Richiesta :

↑ Terapia empirica per sospetta infezione : ↑ Sepsi grave ↑ Shock settico

Sede: ↑ Sangue (Cuore e vasi) ↑ SNC ↑ Apparato respiratorio ↑ Addome ↑ Cute e annessi ↑ altro

Precedente isolamento di germe Gram – multi resistente: No ↑ Si ↑ (allegare antibiogramma): data _____ materiale ↑

Tampone cutaneo ↑ Tampone orofaringeo ↑ Urina ↑ Basse vie respiratorie ↑ Tampone rettale/feci

Ricerche batteriologiche in corso: ↑ Nessuna

↑ Coltura → ↑ Sangue ↑ Liquor ↑ Pus ↑ Urina ↑ Basse vie respiratorie

↑ altro

↑ Terapia mirata per isolamento di (battere/i)

.....) da ↑ Sangue ↑ Liquor ↑ Pus ↑ Basse vie respiratorie in data / /

(allegare antibiogramma)

↑ Insuccesso precedente terapia con

dal / / al / / Note.....

Richiesto Parere dell'Infettivologo Dr.

↑ NO

↑ SI

↑ In attesa

Spazio riservato alla FARMACIA

Farmaco consegnato Quantità Data ... / ... /

Il Farmacista

Sul retro Allegato 1 ed Allegato 2 del documento

*Timbro
Firma del Medico*

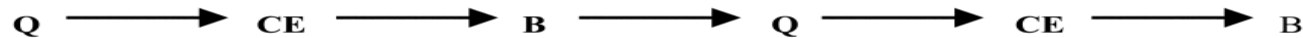
Misure mediche

- “Cycling”
- Ottimizzazione delle dosi
- De-escalation e conversione a terapie per OS
- Limitazione di antibiotici
- Limitazione delle terapie di combinazione
- Implementazione di linee-guida e orientamenti terapeutici

Is Antibiotic Cycling the Answer to Preventing the Emergence of Bacterial Resistance in the Intensive Care Unit?

Probably not

1. Antibiotic cycling or antibiotic rotation: A fixed temporal pattern for the predominant use of an antibiotic class or classes, followed by their repeated removal and reintroduction over time.



2. Scheduled antibiotic changes: A predetermined and scheduled change in the predominant antimicrobial agent employed. Changes in the antibiotic classes employed are often based on changing patterns of antimicrobial sensitivities and are not simply time based.



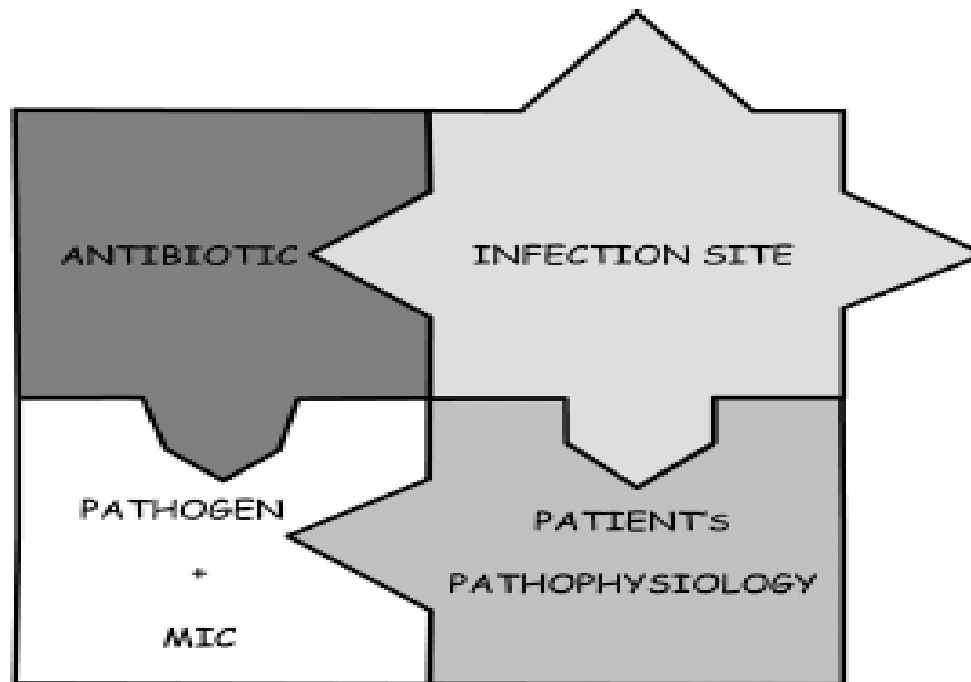
3. Antibiotic mixing: A strategy whereby all or most available antimicrobial classes are employed to minimize undue pressure for the emergence of resistance from having a single or limited number of antibiotic classes available.



Review

Bench-to-bedside review: Appropriate antibiotic therapy in severe sepsis and septic shock - does the dose matter?

Federico Pea¹ and Pierluigi Viale²



The antimicrobial therapy puzzle. MIC, minimum inhibitory concentration. Reproduced with permission from Pea and Viale [5].

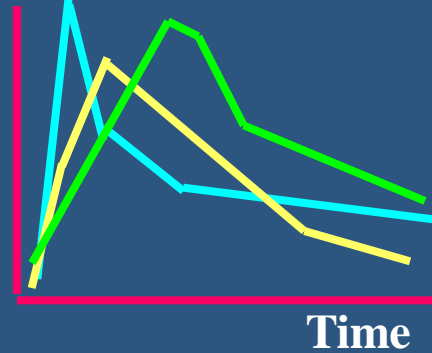
Sources of variability in pharmacology

Pharmacological variability depending on :

PATIENT

- Aged
- Children
- Male or female
- Female:
 - Menstrual cycle
 - Pregnancy
 - Suckling

Concentration



Time

DRUG: galenic

- Immediate release
- Sustained release

DRUG:

- Route of administration
- Oral: fasting
 - Cutaneous: patches

DRUG:

- Conditions of administration
- Single dose
 - Repeated doses
 - Constant rate infusion

PATHOLOGY

- Renal failure
- Hepatic failure
- Cardiac failure
- Immunodépression
- Dénutrition
- Obesity

TERAPIA ANTIBIOTICA EMPIRICA NELLA SEPSI GRAVE SHOCK SETTICO

Criteri di base

- **Entro la prima ora**
- **Ampio spettro**
- **Dose di carico indipendente dalla creatinina clearance**
- **De-escalation e rivalutazione dose e spettro terapia a 24, 48 e 72 h* con emocolture , gram su campioni biologici, creatinina clearance, Ag urinari → consulenza infettivologica, TDM**
- **Considerare diffusione nel sito d'infezione**
- **Considerare sempre focolai eradicabili**
- **Consultare specialista (ematologo, oncologo, infettivologo) se casi complessi o paz. immunodepressi**

Terapia antibiotica empirica nella sepsi grave- shock settico

Tabella riassuntiva

Sito d'infezione	Caratteristiche epidemiologicje	Terapia
Sede ignota	ESBL-	Piperacillina Tazobactam + Vancomicina
	ESBL+	Meropenem + Vancomicina
Polmonite	Comunitaria	Rocefin+ Levofloxacina/Azitromicina
	Nosocomiale o Alto Rischio	Meropenem + Levofloxacina ± Vancomicina
IAI	Di comunità rischio ESBL-	Piperacillina Tazobactam
	Di comunità rischio ESBL +	Meropenem
	Nosocomiale	Meropenem + Vancomicina + Echinocandina*
SSTI	Non Fournier	Daptomicina* + Meropenem + Rifampicina
	Fournier	Daptomicina + Meropenem + Echinocandina
Urosepsi	ESBL-	Piperacillina/tazobactam
	ESBL+	Meropenem

* Da richiedere con consulenza infettivologica

What is the optimal duration of antibiotic therapy?

John Paul

antibiotics may be associated with adverse reactions, and prolonged exposure to antibiotics, may encourage the development or acquisition of antibiotic resistant organisms. Also, antibiotic treatment is expensive and problems may occur with compliance.

Comparative outcome studies provide a solution but require large numbers to provide the statistical power for significance. Pooling of multiple studies may be affected by inconsistencies in study design but may still yield clues...

When optimising therapy for an infection, a lot of variables have to be juggled, including choice of antibiotic, the patient's immune status, the infecting agent, and the nature of the septic focus...

Antimicrobial stewardship: a matter of process or outcome?

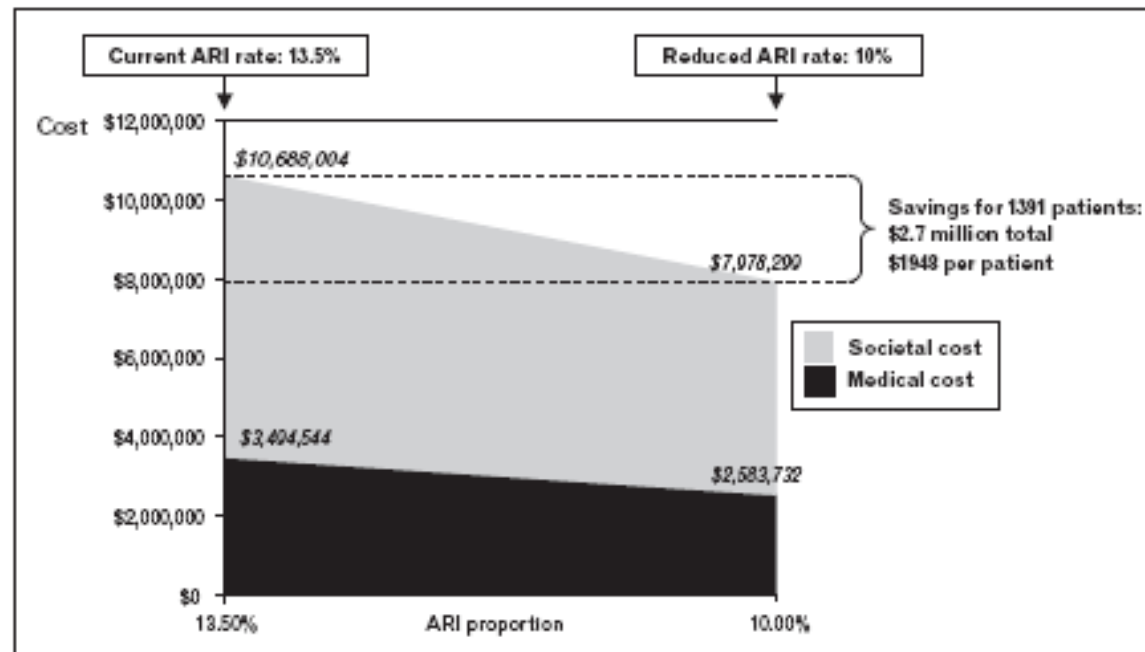
Khadem TM, Dodds Ashley E, Wrobel MJ, Brown

- **Process measures** have been validated and can evaluate quality of care; however, they do not adequately describe the clinical impact of these programs at the patient level. **Outcome measures** also have limitations; they are not a direct measure of quality of care. Therefore, **both process and outcome measures need to be defined and assessed when evaluating an ASP to confirm that goals of the intervention are attained and clinical objectives are met.**
- Most available well-designed studies judging the effectiveness of ASPs use process measures alone. Adding improvements in clinical outcomes to process measures would theoretically attract the attention of a broader audience and provide additional support to expand current ASPs and develop novel ASPs

Antimicrobial stewardship: bridging the gap between quality care and cost

Debra A. Goff

Figure 1 Projected cost savings if antimicrobial-resistant infection rates were reduced from 13.5 to 10%



“estimated cost of MDR in USA, 2005: 5billions\$

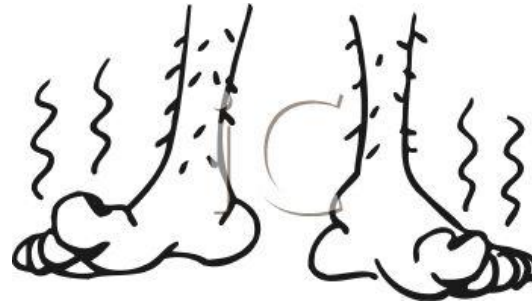
Qualities for a stewardship: le malattie infettive e il futuro...



brillantezza



riflessione



dinamismo



Un esperto di antibiotici



aggressività



persuasione



E un ottimismo quasi infantile



Grazie dell' attenzione