

La battaglia quotidiana contro le ICA

Prof. Matteo Bassetti

University of Genoa and Infectious Diseases Clinic, AOM Genoa



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AZIENDA OSPEDALIERA METROPOLITANA



Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

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Infezioni correlate all'assistenza (ICA)



Definizione OMS: infezioni che si verificano durante il processo di cura in ospedale o in altre strutture sanitarie, non presenti né in incubazione al momento del ricovero



Perchè sono rilevanti?

1. morbilità e mortalità
2. occupazione dei posti letto
3. durata della degenza ospedaliera
4. carico economico per le strutture sanitarie



Epidemiologia ICA



- Variazione significativa del loro peso a livello globale
- Prevalenza stimata più elevate nei paesi a basso e medio reddito [15.5% vs 4.5% USA (2002) vs 7.1% ECDC (2008)]

Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis

Benedetta Allegranzi, Sepideh Bagheri Nejad, Christophe Combescure, Wilco Graafmans, Homa Attar, Liam Donaldson, Didier Pittet



Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy





- 4,3 milioni/anno di pazienti negli ospedali dell'UE/SEE sono colpiti da ICA
- Almeno il **20%** delle ICA è considerata **prevenibile** attraverso programmi di **prevenzione e controllo delle infezioni (IPC)** sostenuti e multifattoriali





2024 VS 2023

- 9% CR-BSI
- 10% CA-UTI
- 2% delle VAP
- 4% SSI nella chirurgia del colon
- 7% BSI da MRSA a insorgenza ospedaliera
- 11% infezioni da C. difficile a insorgenza ospedaliera

- 8% delle SSI nelle isterectomie addominali



Fattori di rischio

FATTORI DELL'OSPITE

PRATICHE ASSISTENZIALI E
TERAPEUTICHE

ICA

PROCEDURE E DISPOSITIVI
INVASIVI

FATTORI AMBIENTALI



Fattori dell'ospite

- **Età avanzata:** >60 anni
- **Sesso maschile**
- **Comorbidità:** diabete mellito, BPCO, malnutrizione, neoplasie
- **Patologie neurologiche:** demenza, ictus, coma
- **Immunosoppressione:** cause iatrogene e non (HIV/AIDS, neutropenia)



Procedure e dispositivi invasivi

- **Cateteri venosi centrali:** rischio proporzionale ai giorni d'esposizione
- **Ventilazione meccanica**
- **Catetere urinario**
- **Interventi chirurgici:** tempo operatorio prolungato, reintervento, ferita contaminate/sporca



Pratiche assistenziali e terapeutiche

- **Ricovero in ICU:** durata di degenza
- **Degenza prolungata:** > 15 giorni
- **Terapia antibiotica**
- Emotrasfusioni, emodialisi, NPT



Fattori ambientali

- **Superfici contaminate:** ad alto contatto fungono da serbatoi
- **Persistenza ambientale:** alcuni patogeni sopravvivono per mesi (C. difficile, Acinetobacter, norovirus)
- **Formazione di biofilm:** superfici e dispositivi
- **Attrezzature contaminate**
- **Trasmissione crociata:** tramite le mani del personale contaminate da contatto diretto con pazienti/superfici



Sindromi cliniche

Table 4. Percentages of All Surveyed Patients with Specific Types of Health Care–Associated Infection, 2011 vs. 2015 Survey.*

| Type of Infection | 2011 Survey | | | 2015 Survey | | | P Value† |
|---|--------------------------------|-------------------|--|--------------------------------|-------------------|--|----------|
| | No. of Patients with Infection | No. of Infections | Percentage of Patients with Infection (95% CI) | No. of Patients with Infection | No. of Infections | Percentage of Patients with Infection (95% CI) | |
| Pneumonia | 110 | 110 | 0.98 (0.81–1.20) | 110 | 110 | 0.89 (0.74–1.10) | 0.52 |
| Ventilator-associated pneumonia | 43 | 43 | 0.38 (0.28–0.51) | 39 | 39 | 0.32 (0.23–0.43) | 0.41 |
| Other pneumonia | 67 | 67 | 0.59 (0.47–0.75) | 71 | 71 | 0.58 (0.46–0.73) | 0.87 |
| Gastrointestinal infection | 86 | 86 | 0.76 (0.62–0.94) | 91 | 91 | 0.74 (0.60–0.91) | 0.84 |
| <i>Clostridium difficile</i> infection‡ | 61 | 61 | 0.54 (0.42–0.69) | 66 | 66 | 0.54 (0.42–0.68) | 0.97 |
| Other gastrointestinal infection | 25 | 25 | 0.22 (0.15–0.33) | 25 | 25 | 0.20 (0.14–0.30) | 0.76 |
| Surgical-site infection | 109 | 110 | 0.97 (0.80–1.20) | 69 | 69 | 0.56 (0.44–0.71) | <0.001 |
| Deep incisional or organ-space infection | 77 | 77 | 0.68 (0.55–0.85) | 54 | 54 | 0.44 (0.34–0.57) | 0.01 |
| Superficial incisional infection | 33 | 33 | 0.29 (0.21–0.41) | 15 | 15 | 0.12 (0.07–0.20) | 0.004 |
| Bloodstream infection | 50 | 50 | 0.44 (0.34–0.58) | 51 | 52 | 0.41 (0.31–0.55) | 0.74 |
| Central catheter–associated bloodstream infection | 42 | 42 | 0.37 (0.27–0.50) | 37 | 38 | 0.30 (0.22–0.42) | 0.35 |
| Other primary bloodstream infection | 8 | 8 | 0.07 (0.03–0.14) | 14 | 14 | 0.11 (0.07–0.19) | 0.29 |
| Urinary tract infection | 65 | 65 | 0.58 (0.45–0.73) | 39 | 39 | 0.32 (0.23–0.43) | 0.003 |
| Catheter-associated urinary tract infection | 44 | 44 | 0.39 (0.29–0.52) | 24 | 24 | 0.20 (0.13–0.29) | 0.005 |
| Other urinary tract infection | 21 | 21 | 0.19 (0.12–0.29) | 15 | 15 | 0.12 (0.07–0.20) | 0.21 |
| Other infection§ | 78 | 83 | 0.69 (0.55–0.86) | 61 | 66 | 0.50 (0.39–0.64) | 0.05 |
| Any infection | 452 | 504 | 4.0 (3.7–4.4) | 394 | 427 | 3.2 (2.9–3.5) | <0.001 |

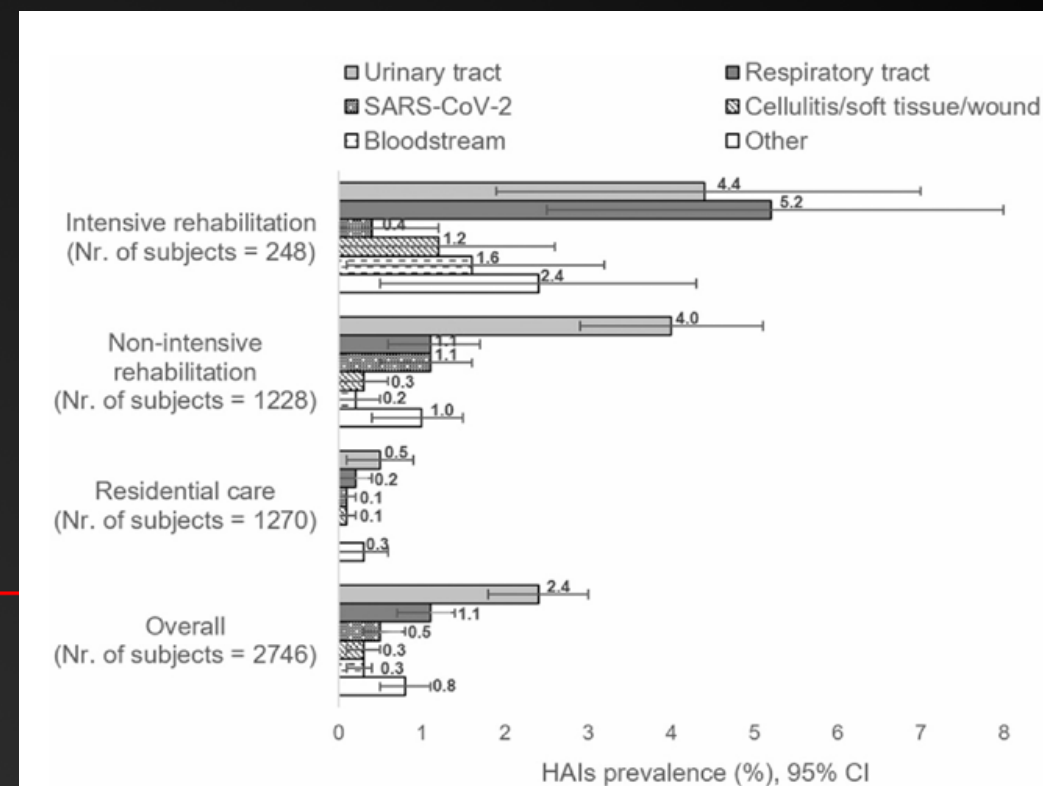
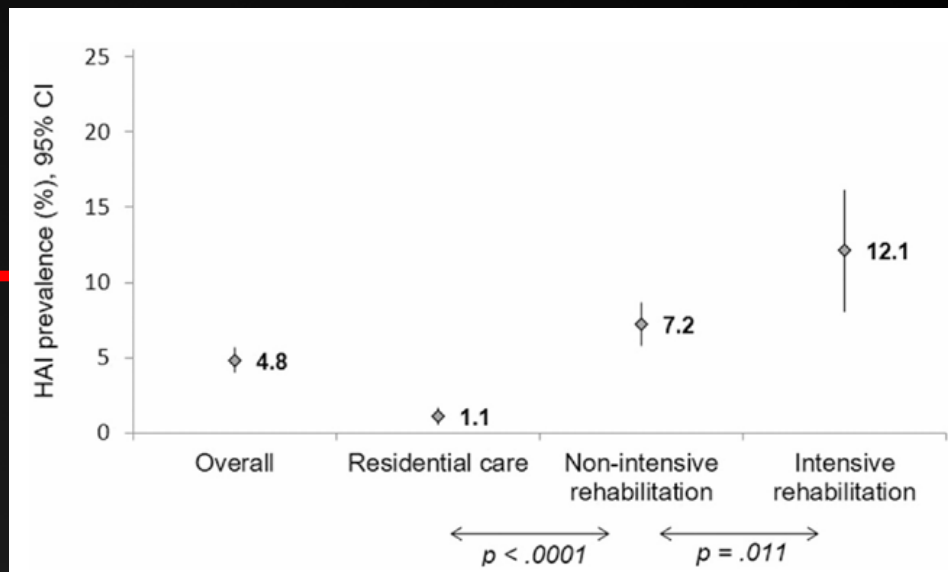
* A total of 11,282 patients were included in the 2011 survey, and 12,299 in the 2015 survey; these values are the denominators for the percentages of patients with infection. Patients could have more than one health care–associated infection.



Sindromi cliniche - Italia

Table 2
Frequencies of identified healthcare-associated infections according to care setting.

| Identified healthcare-associated infection, n (%) | Total (N = 147) |
|---|-----------------|
| Urinary tract (confirmed) | 38 (25.9) |
| Urinary tract (probable) | 28 (19.0) |
| Pneumonia | 15 (10.2) |
| Other lower respiratory tract | 14 (9.5) |
| SARS-CoV-2 (mild/moderate) | 11 (7.5) |
| Cellulitis/soft tissue/wound | 8 (5.4) |
| Bloodstream | 7 (4.8) |
| Clostridioides difficile | 5 (3.4) |
| SARS-CoV-2 (asymptomatic) | 4 (2.7) |
| Gastroenteritis | 4 (2.7) |
| Unexplained fever/conjunctivitis/herpes simplex or zoster | 5 (3.4) |
| Other | 8 (5.4) |



Patogeni responsabili di ICA

BATTERI

FUNGHI

VIRUS



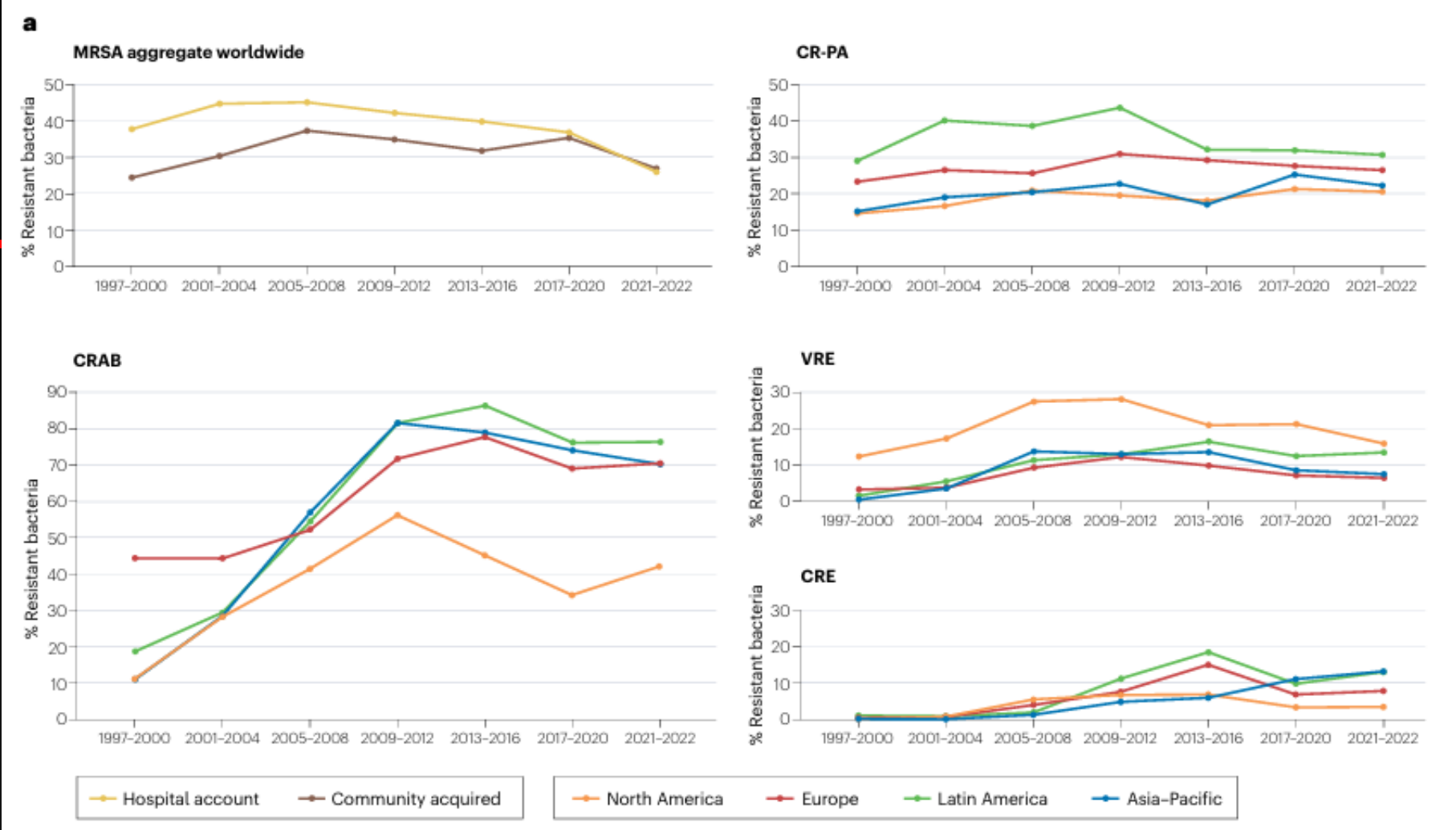
Batteri

- Enterococcus spp
- Staphylococcus aureus
- Klebsiella spp
- Acinetobacter baumannii
- Pseudomonas aeruginosa
- Enterobacterales
- Clostridioides difficile

Table 1 | Overview of ESKAPE pathogens

| Organism | Major clinical syndromes |
|---|---|
| Vancomycin-resistant <i>Enterococcus faecium</i> | Bloodstream infection, infective endocarditis, intra-abdominal infection, UTI |
| Methicillin-resistant <i>Staphylococcus aureus</i> | Bloodstream infection, infective endocarditis, ABSSSI, CAP, HAP/VAP, bone and joint infection |
| Carbapenem-resistant or ESBL-producing <i>Klebsiella pneumoniae</i> | Bloodstream infection, UTI, CAP, HAP/VAP, intra-abdominal infection |
| Carbapenem-resistant <i>Acinetobacter baumannii</i> | HAP/VAP, bloodstream infection, UTI |
| Carbapenem-resistant <i>Pseudomonas aeruginosa</i> | HAP/VAP, bloodstream infection, UTI |
| Carbapenem-resistant or ESBL-producing <i>Enterobacter cloacae</i> complex | Bloodstream infection, UTI, HAP/VAP, intra-abdominal infection |





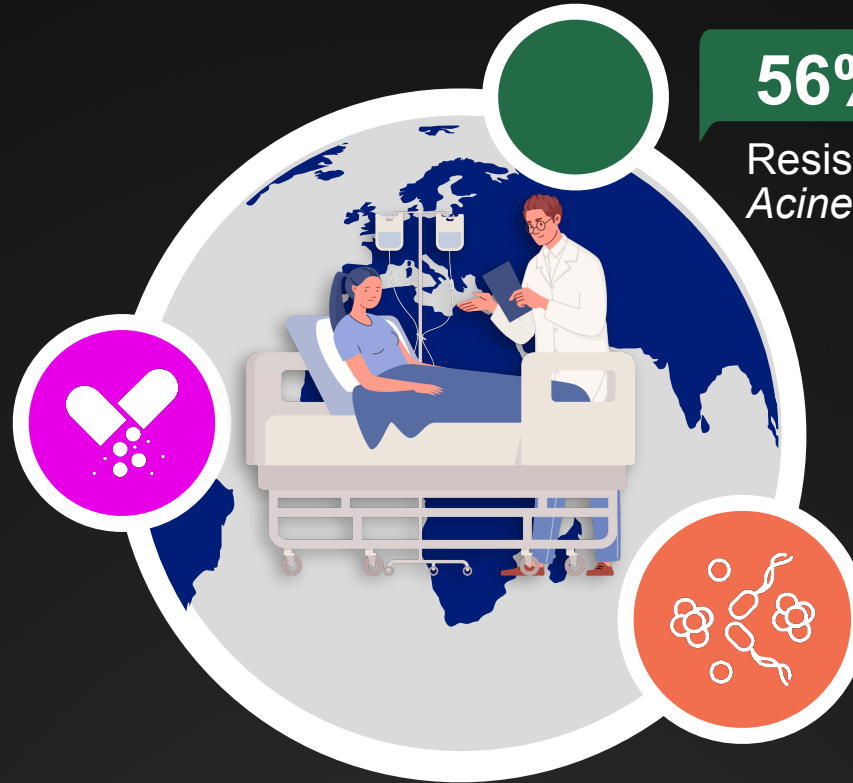
Incidenza globale degli organismi ESKAPE tra il 1997 e il 2022



AMR: A GLOBAL ISSUE...¹

46%

Global increase in consumption of prescribed antibiotics between 2000 and 2018¹

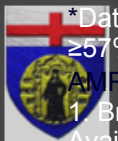


56%+*

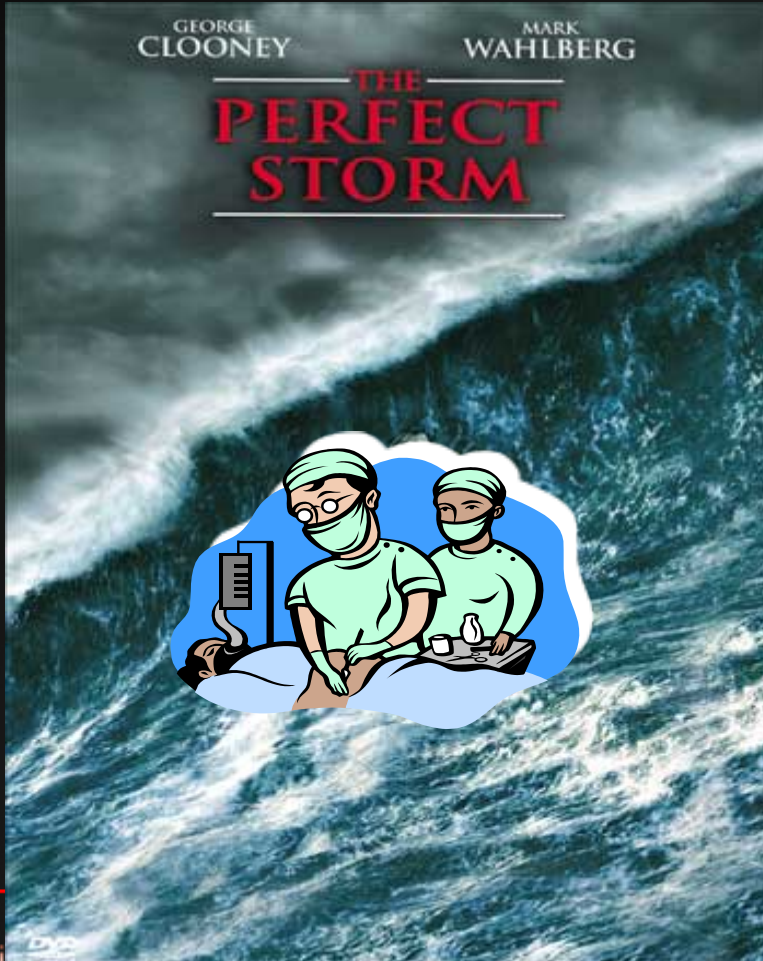
Resistance in key pathogens: *Acinetobacter spp.* and *Klebsiella spp.*²

4.95

million
Deaths globally in 2019 associated with bacterial AMR³

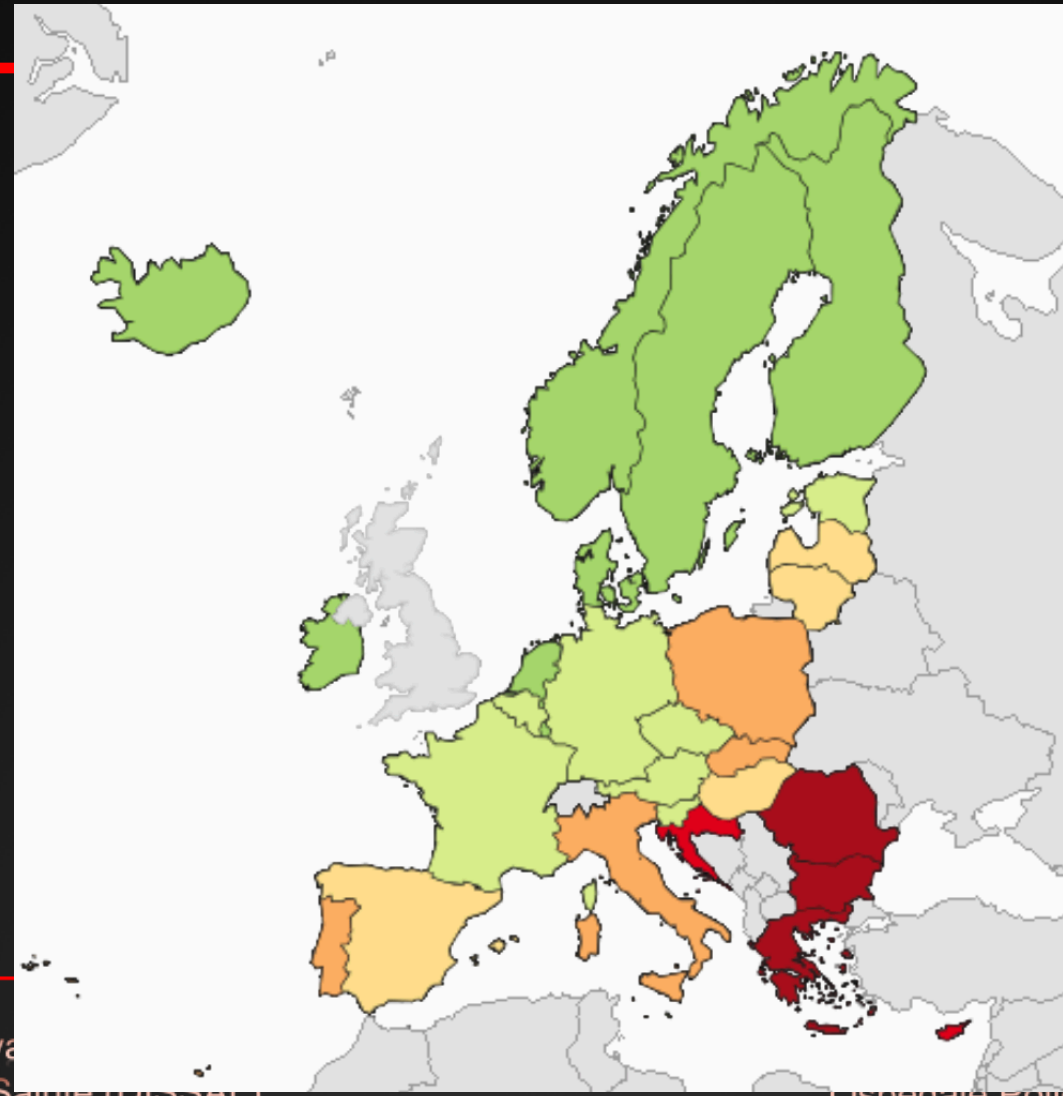
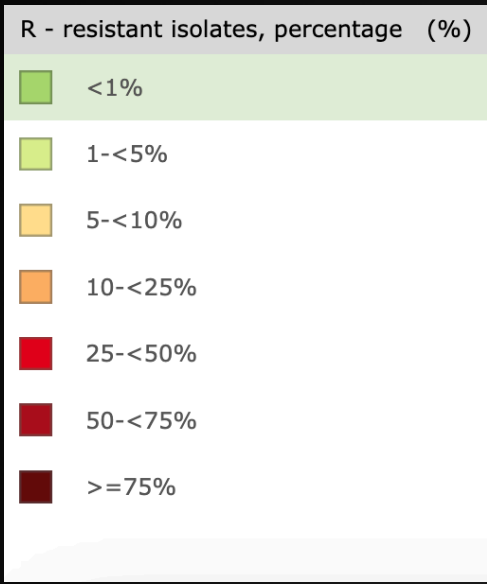


“Superbugs Perfect Storm”



- ❑ MRSA
- ❑ Vancomycin-resistant Enterococcus
- ❑ MDR *Acinetobacter baumannii*
- ❑ MDR *Pseudomonas aeruginosa*
- ❑ ESBL-producing Enterobacterales
- ❑ Carbapenem resistant Enterobacterales
- ❑ PR/MR *Streptococcus pneumoniae*
- ❑ MDR *Mycobacterium tuberculosis*
- ❑ MDR gonococci
- ❑ *Candida auris*
- ❑ *Aspergillus azole-resistant*

Klebsiella pneumoniae resistance to carbapenems



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Ospedale Policlinico San Martino IRCCS
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<https://atlas.ecdc.europa.eu/public/index.aspx>, 2024 data

Mortality Doubles With Infections Caused by CR - Pathogens

Infections caused by CR and MDR pathogens exacerbate an elevated risk of mortality^{1,2}

*Klebsiella pneumoniae*¹

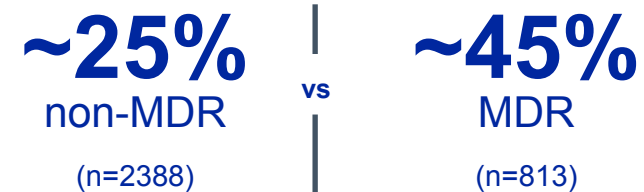
Pooled mortality



A systematic review and meta-analysis of 62 studies, involved 4701 patients, of whom 2462 had infection caused by CRKP.¹

*Pseudomonas aeruginosa*²

30-day mortality



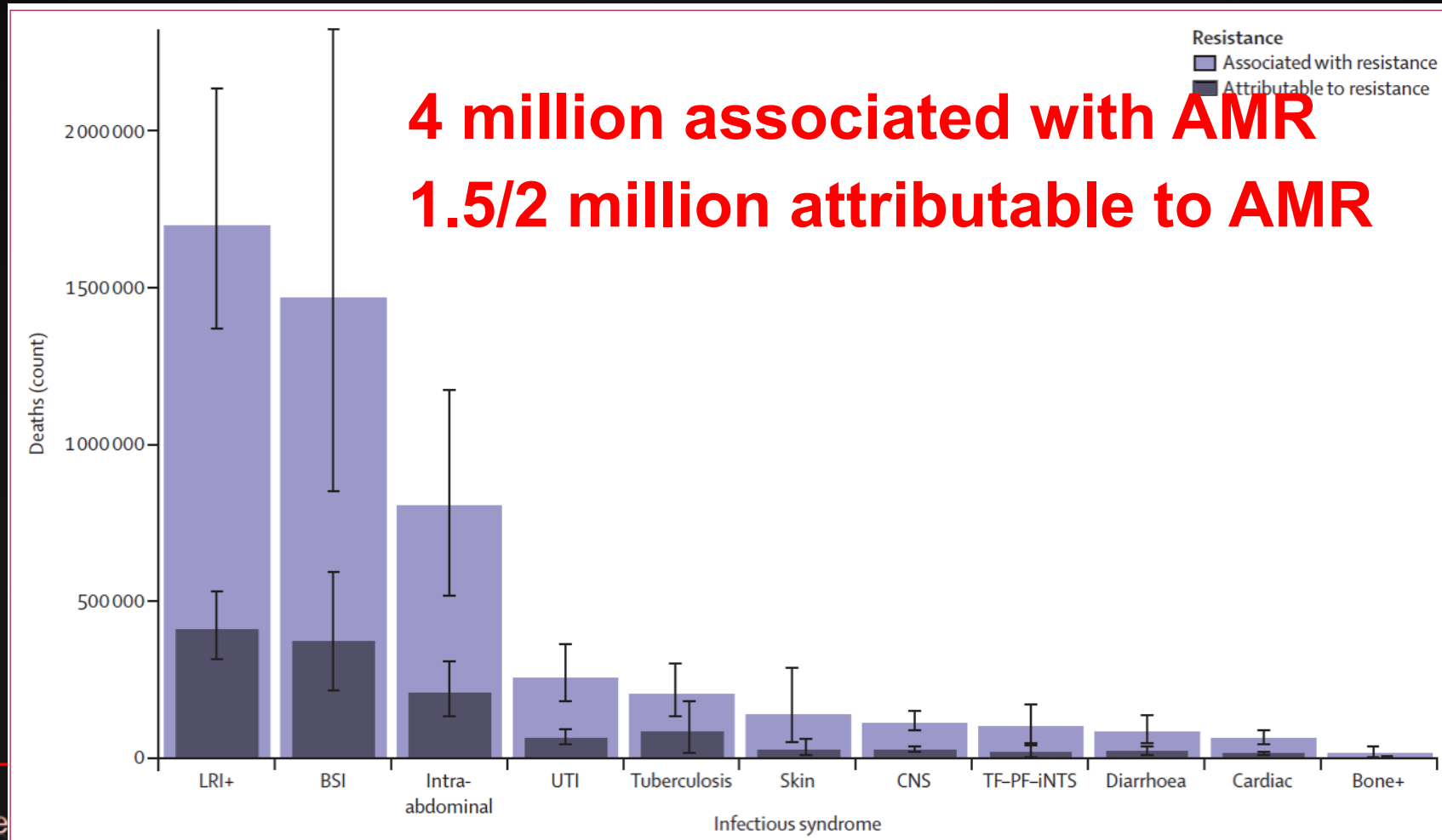
A meta-analysis of qualifying studies between 2006 and 2016 evaluated the risk of mortality in patients with infection caused by *P. aeruginosa*.

^aMDR was defined as resistance to at least 3 different classes of antimicrobials, including carbapenems, antipseudomonal cephalosporins, fluoroquinolones, aminoglycosides, and β -lactams with inhibitors.²
CR, carbapenem-resistant; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CSKP, carbapenem-susceptible *Klebsiella pneumoniae*; KPC, *Klebsiella pneumoniae* carbapenemase; MDR, multidrug-resistant; *P. aeruginosa*, *Pseudomonas aeruginosa*; VIM, Verona integron-encoded metallo- β -lactamase.

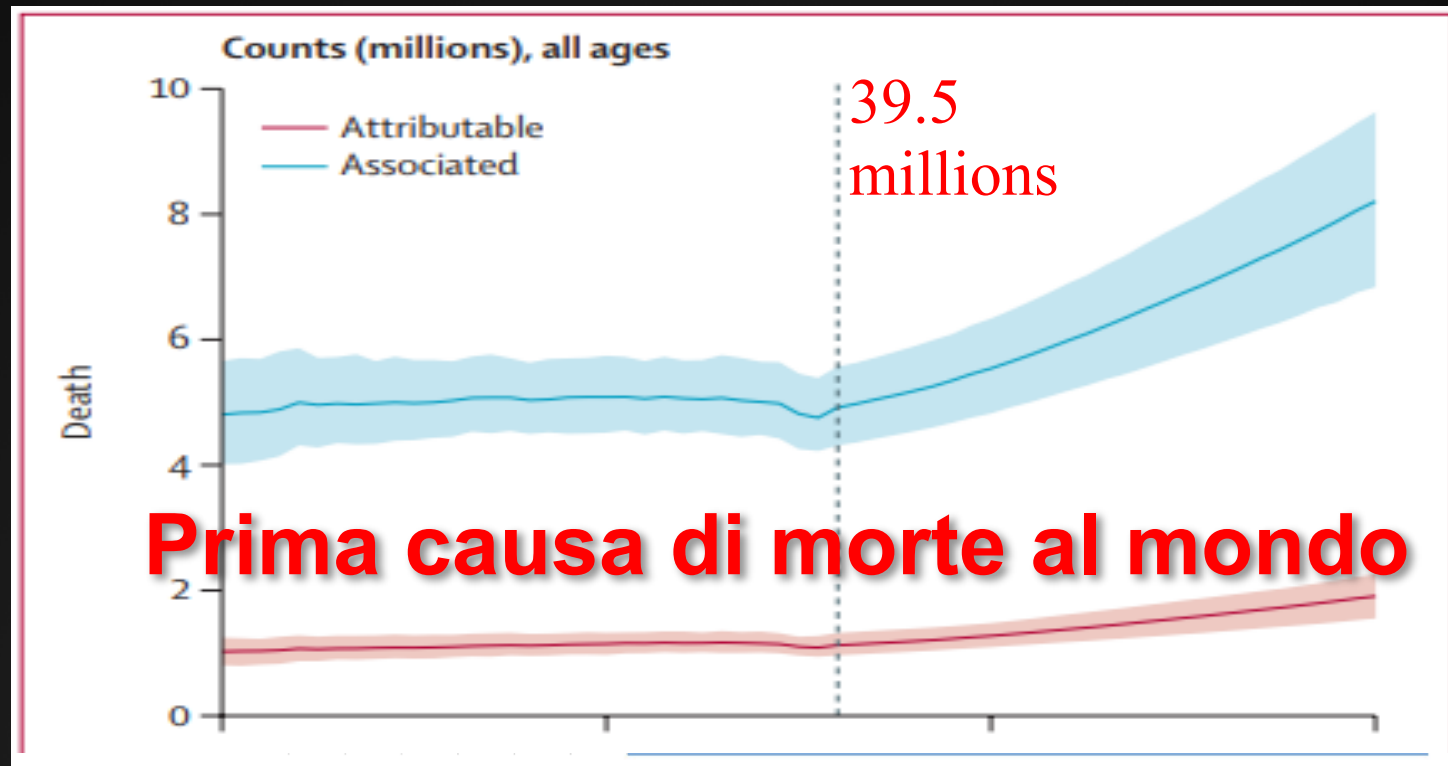
References: 1. Xu L et al. *Ann Clin Microbiol Antimicrob.* 2017;16:18. 2. Matos ECO et al. *Rev Soc Bras Med Trop.* 2018;51(4):415-420.



Global deaths (counts) attributable to and associated with bacterial antimicrobial resistance by infectious syndrome, 2019



AMR Without intervention.....by 2050



Bassetti M et al. *Intensive Care Med.* 2017 Jul 21. doi:10.1007/s00134-017-4878-x

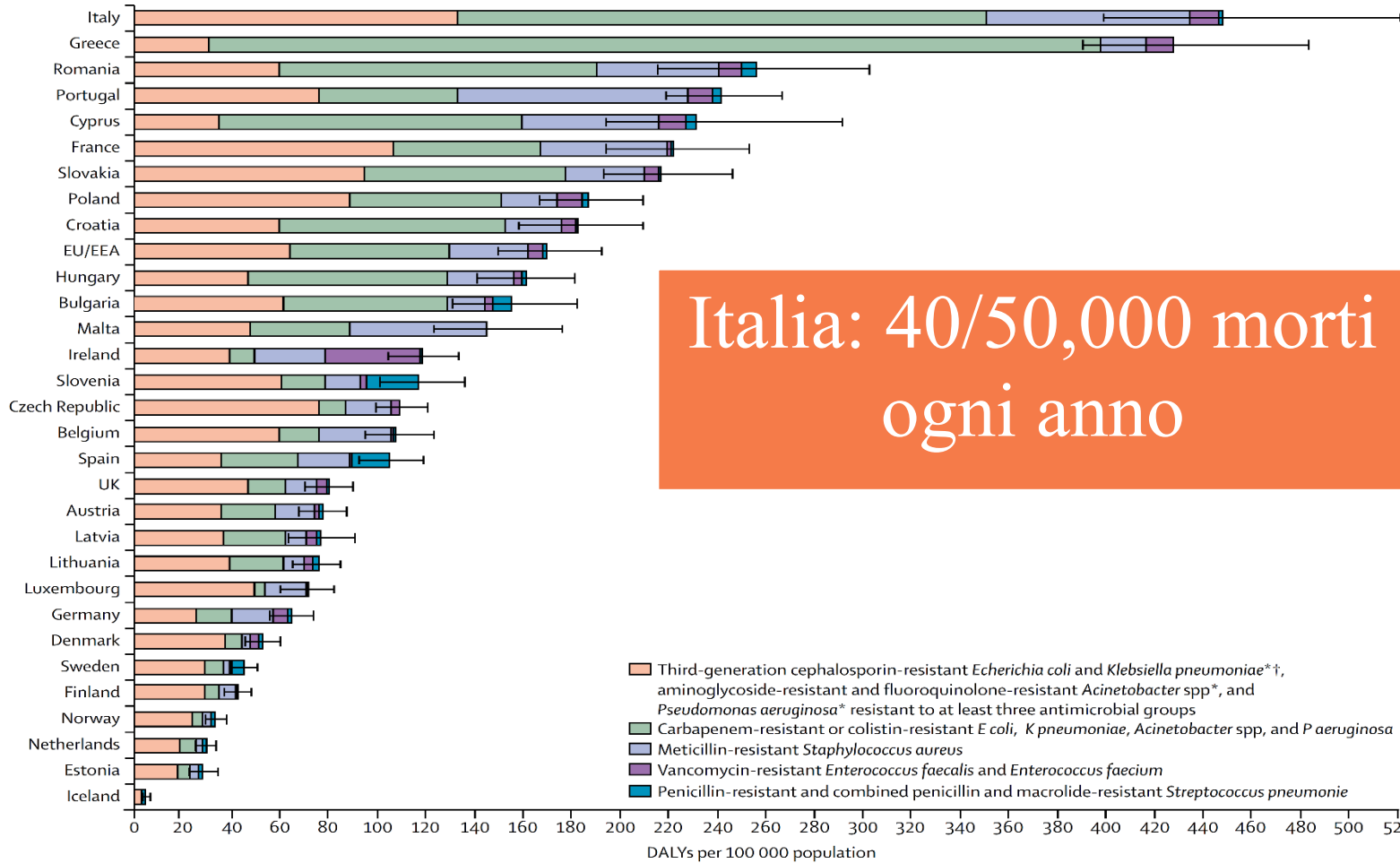
Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050. *Lancet*; Sept. 2024



Impact of antibiotic-resistant bacteria in the EU in hospital

Cases (median) Deaths (median)

| Cases (median) | Deaths (median) |
|----------------|-----------------|
| 201584 | 10762 |
| 18472 | 1626 |
| 25077 | 1470 |
| 24021 | 1158 |
| 1192 | 66 |
| 124806 | 5543 |
| 7622 | 379 |
| 41069 | 2218 |
| 4347 | 240 |
| 671689 | 33110 |
| 10271 | 543 |
| 5374 | 280 |
| 608 | 29 |
| 4893 | 219 |
| 2280 | 96 |
| 10438 | 486 |
| 12892 | 530 |
| 41345 | 1899 |
| 52971 | 2172 |
| 6634 | 276 |
| 847 | 44 |
| 1828 | 90 |
| 487 | 19 |
| 54509 | 2363 |
| 3351 | 124 |
| 4571 | 167 |
| 2524 | 90 |
| 1882 | 69 |
| 4982 | 206 |
| 365 | 15 |
| 27 | 1 |

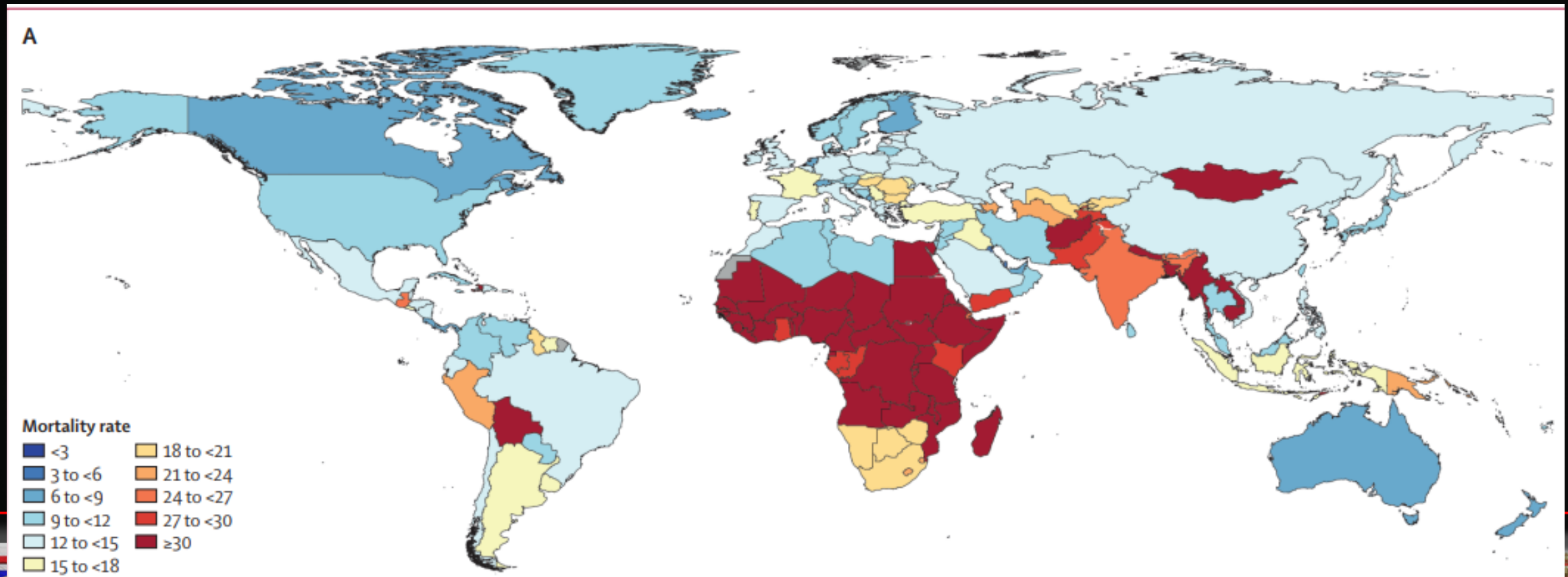


Italia: 40/50,000 morti ogni anno



Death rates per 100000 attributable to AMR, all ages, 1990, 2021, 2050

1990



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Global Health

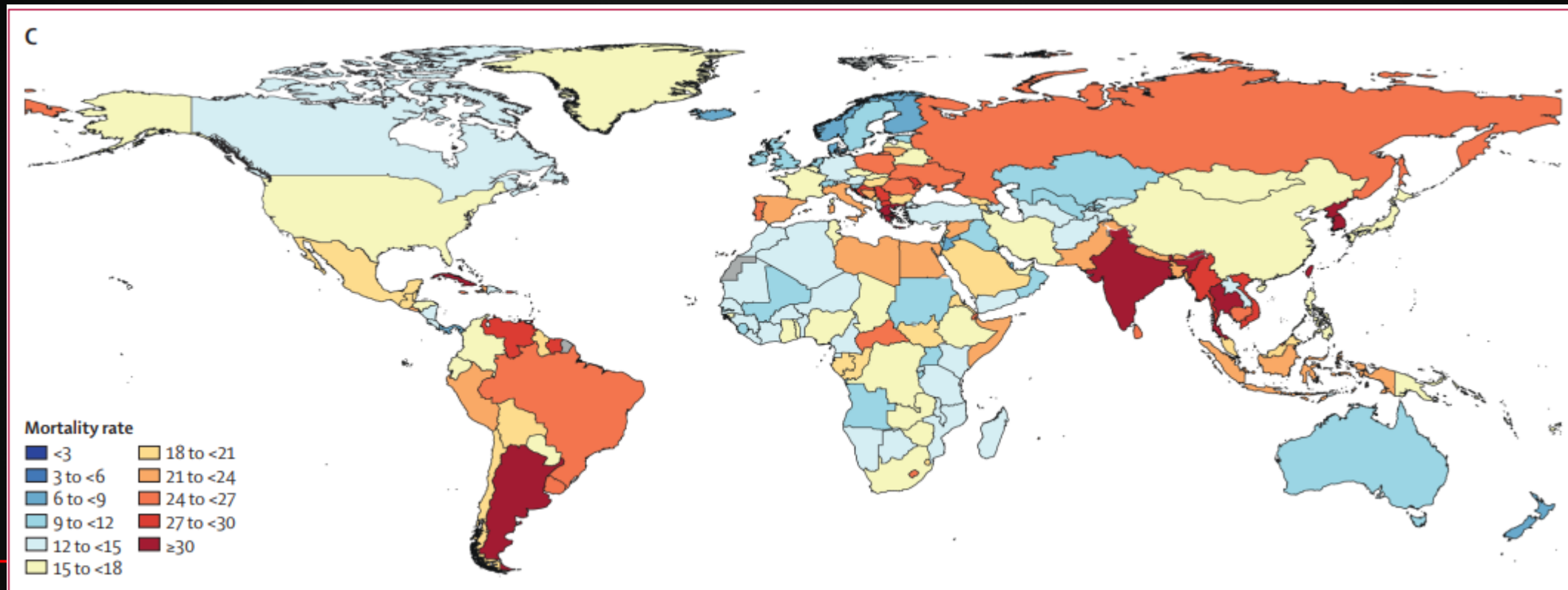
Ospedale Policlinico San Martino IRCCS

Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050. Lancet; Sept. 2024

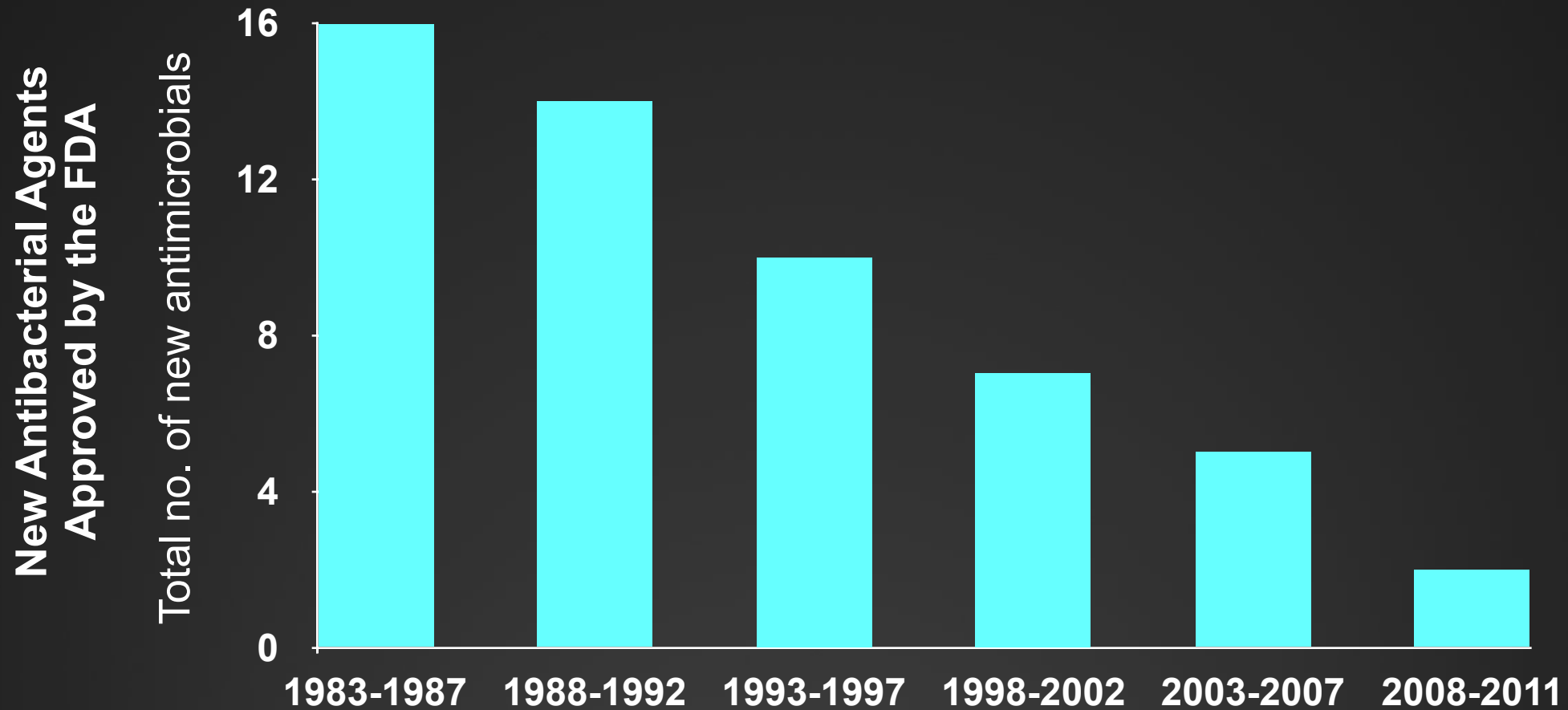


Death rates per 100000 attributable to AMR, all ages, 1990, 2021, 2050

2050



1980-2010. Antibiotic Options Decline...



Why the decrease?

- ❑ Reasons for decreased antibiotic development over the last twenty years:
 - Economic
 - ❑ Low price
 - ❑ Short-term treatment
 - ❑ Small markets for narrow spectrum antibiotics
 - Regulatory
 - ❑ Precedence of bigger studies
 - ❑ Shift to indication and non-inferiority
 - Science
 - ❑ Expertises lost in R&D and commercial groups





Bad bugs No drugs



IDSA

Infectious Diseases Society of America



**Bad Bugs
Need Drugs**

10x'20

Ten new **ANTIBIOTICS** by 2020



Università degli Studi di Genova
Dipartimento di Scienze Mediche
Genoa, Italy

Unità di Malattie Infettive
Istituto IRCCS Ospedale
Genoa, Italy



Approval of new classes has fallen behind

Number of antibiotic classes discovered or patented in the decade



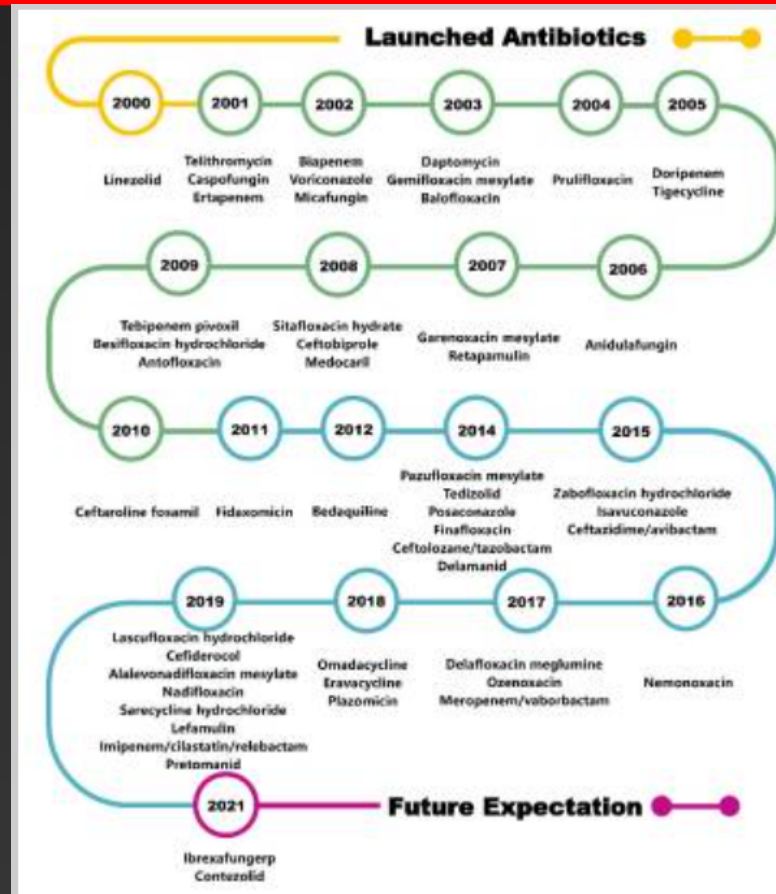
INNOVATION GAP
Every FDA-approved antibiotic in use today for the treatment of Gram-negative bacterial infections is based on a scientific discovery made prior to 1962.

* Cefiderocol was approved by FDA in 2019 and EMA in 2020. The FDA-approved label for cefiderocol classifies the drug as a cephalosporin, and therefore not a new class but certainly a new mechanism of action. Some experts consider cefiderocol to be a first-in-class sideromycin. The predecessors to cefiderocol were discovered at Shionogi in the early 1990s. CID 2019;69(7):S538-S543

* This chart excludes bedaquiline, which is the first drug in a new class to treat tuberculosis.

Source: Pew Charitable Trusts; Deak D, Powers JH, Outterson K, Kesselheim AS. Progress in the Fight Against Multidrug Resistant Bacteria?: A Review of FDA Approved Antibiotics 2010-2015. ANNALS OF INTERNAL MED. 2016 MAY 31. DOI: 10.7326/M16-0291.

Antibiotics approved in the past 25 years



Molecules. 2023 Feb 13;28(4):1762. doi: 10.3390/molecules28041762



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Ospedale Policlinico San Martino IRCCS
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The Situation twenty years later/today

- ❓ The late-stage clinical development pipeline remains unacceptably lean²
- Some important molecules for problematic pathogens such as MRSA
 - Some novel and highly microbiological active molecules for other ESKAPE pathogens
 - Few new drugs for infection due to MDR Gram-negative bacilli (e.g., *A baumannii* and *P. aeruginosa*)
 - **None (few) represent more than an incremental advance over currently available therapies**
 - **No drugs with new mechanism of action**



Inhibition spectrum of β -lactamases inhibitors

| Inhibitor | ESBL | AmpC | KPC | MBL | OXA-48-like | Intrinsic ATB activity |
|-----------------|------|------|-----|--------------------|-------------|------------------------|
| Clavulanic acid | ++ | - | + | - | - | - |
| Sulbactam | ++ | - | + | - | - | PBP2 |
| Tazobactam | ++ | - | + | - | - | - |
| Enmetazobactam | +++ | -/+ | ++ | - | - | - |
| Avibactam | +++ | ++ | +++ | - | + | - |
| Relebactam | +++ | ++ | +++ | - | +/- | - |
| Vaborbactam | +++ | ++ | +++ | - | +/- | - |
| Zidebactam | +++ | ++ | +++ | - | ? | PBP2 |
| Taniborbactam | +++ | ++ | +++ | ++ (except IMP) | ? | ? |

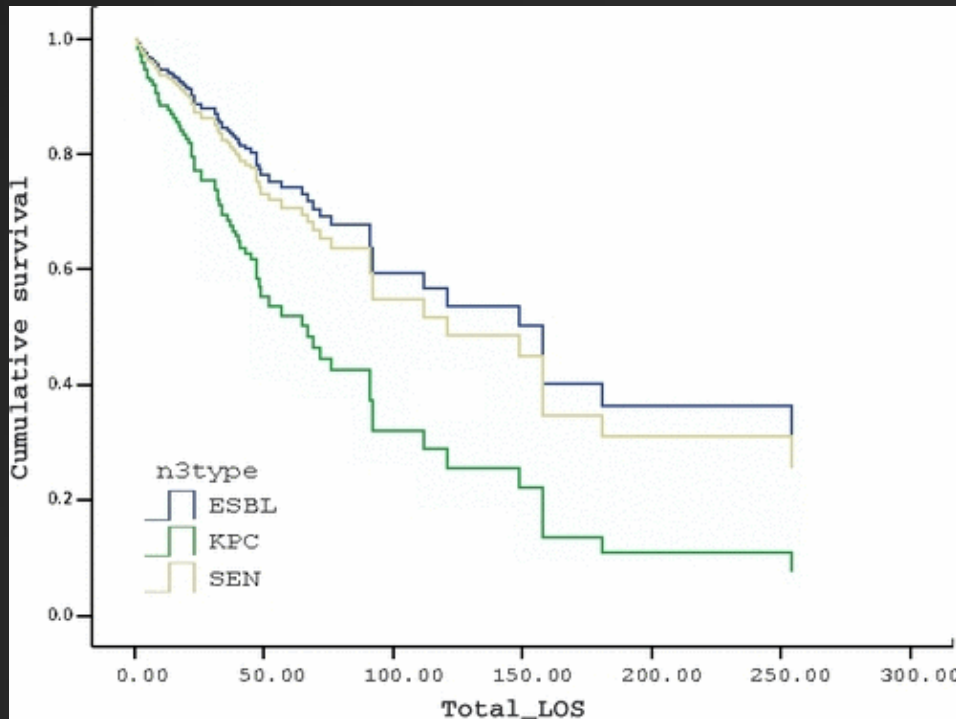
Activity of new agents against Gram-negative pathogens.

| | <i>Enterobacterales</i> | | | <i>Pseudomonas aeruginosa</i> | <i>Acinetobacter baumannii</i> | <i>Stenotrophomonas maltophilia</i> |
|------------------------|----------------------------------|----------------------------------|-------------------------------------|-------------------------------|--------------------------------|-------------------------------------|
| | Class A Carbapenemase (e.g. KPC) | Class B Carbapenemase (e.g. NDM) | Class D Carbapenemase (e.g. OXA-48) | | | |
| Ceftobiprole | Red | Red | Red | Grey | Red | Red |
| Ceftolozane-tazobactam | Red | Red | Red | Green | Red | Red |
| Ceftazidime-avibactam | Green | Red | Green | Green | Red | Red |
| Cefiderocol | Green | Green | Green | Green | Green | Green |
| Meropenem-vaborbactam | Green | Red | Red | Grey | Red | Red |
| Imipenem-relebactam | Green | Red | Red | Green | Red | Red |
| Aztreonam-avibactam | Green | Green | Green | Green | Red | Red |
| Plazomicin | Green | Grey | Green | Grey | Red | Red |
| Eravacycline | Green | Green | Green | Red | Green | Green |



Mortality












Comparison in mortality among patients with carbapenem-resistant (n=42), extended-spectrum β -lactamase producers (ESBL- n=68) and susceptible *K. pneumoniae* bloodstream infections (n=120),



- Infection-related mortality was 48% for carbapenem-resistant, 22% for ESBL producers and 17% for susceptible *K. pneumoniae*.



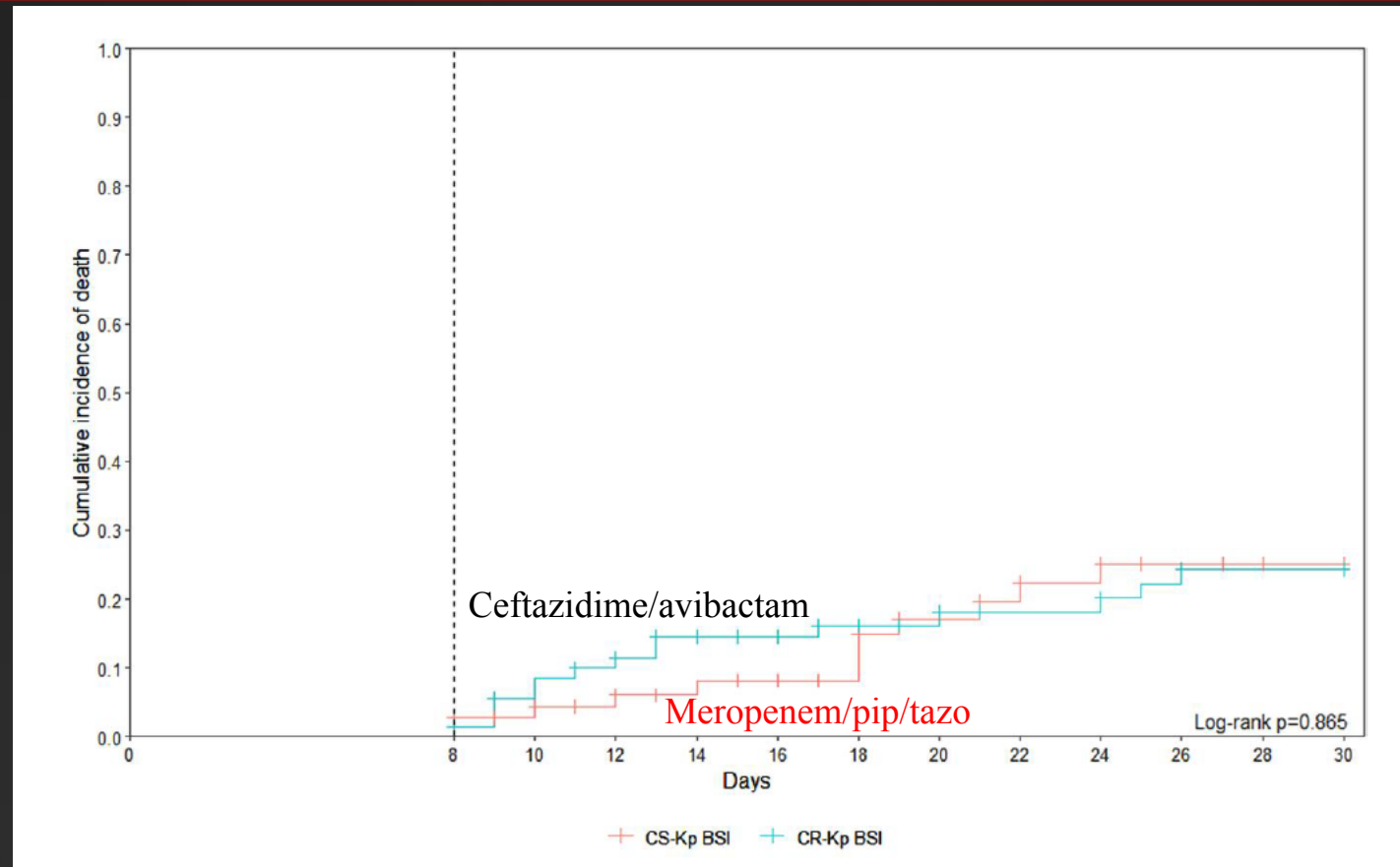
Mortality in KPC-producing *Klebsiella pneumoniae* bloodstream infections: a changing landscape

Daniele Roberto Giacobbe ^{1,2*}, Cristina Marelli ², Greta Cattardico^{1,2}, Chiara Fanelli^{2,3}, Alessio Signori⁴, Gabriele Di Meco², Vincenzo Di Pilato ⁵, Malgorzata Mikulska^{1,2}, Maria Mazzitelli ⁶, Anna Maria Cattelan^{6,7}, Carlo Pallotto⁸, Daniela Francisci⁸, Alessandra Calabresi⁹, Andrea Lombardi ^{10,11}, Andrea Gori^{11,12}, Valerio Del Bono¹³, Chiara Aldieri¹³, Angela Raffaella Losito¹⁴, Francesca Raffaelli¹⁴, Andrea Cortegiani^{15,16}, Marta Milazzo¹⁵, Filippo Del Puente¹⁷, Emanuele Pontali¹⁷, Francesco Giuseppe De Rosa ^{18,19}, Silvia Corcione ¹⁸, Alessandra Mularoni ²⁰, Giovanna Russelli²⁰, Mauro Giacomini ²¹, Flavia Badalucco Ciotta²², Chiara Oltolini²², Francesco Saverio Serino²³, Elena Momesso²⁴, Michele Spinicci^{25,26}, Lucia Graziani ²⁵, Carlo Torti^{27,28}, Enrico Maria Treçarichi^{27,28}, Marco Merli ²⁹, Federico D'Amico²⁹, Anna Marchese^{5,30}, Antonio Vena^{1,2} and Matteo Bassetti^{1,2}† on behalf of the CARBANEW study group

Giacobbe DR et al. J Antimicrob Chemother. 2023 Aug 22:dkad262. doi: 10.1093/jac/dkad262.



30 days mortality patients with CR-Kp BSI receiving appropriate therapy with ceftazidime/avibactam (cases) versus patients with CS-Kp BSI receiving appropriate therapy with agents other than ceftazidime/avibactam (controls).



Giacobbe DR et al. J Antimicrob Chemother. 2023 Aug 22:dkad262. doi: 10.1093/jac/dkad262.



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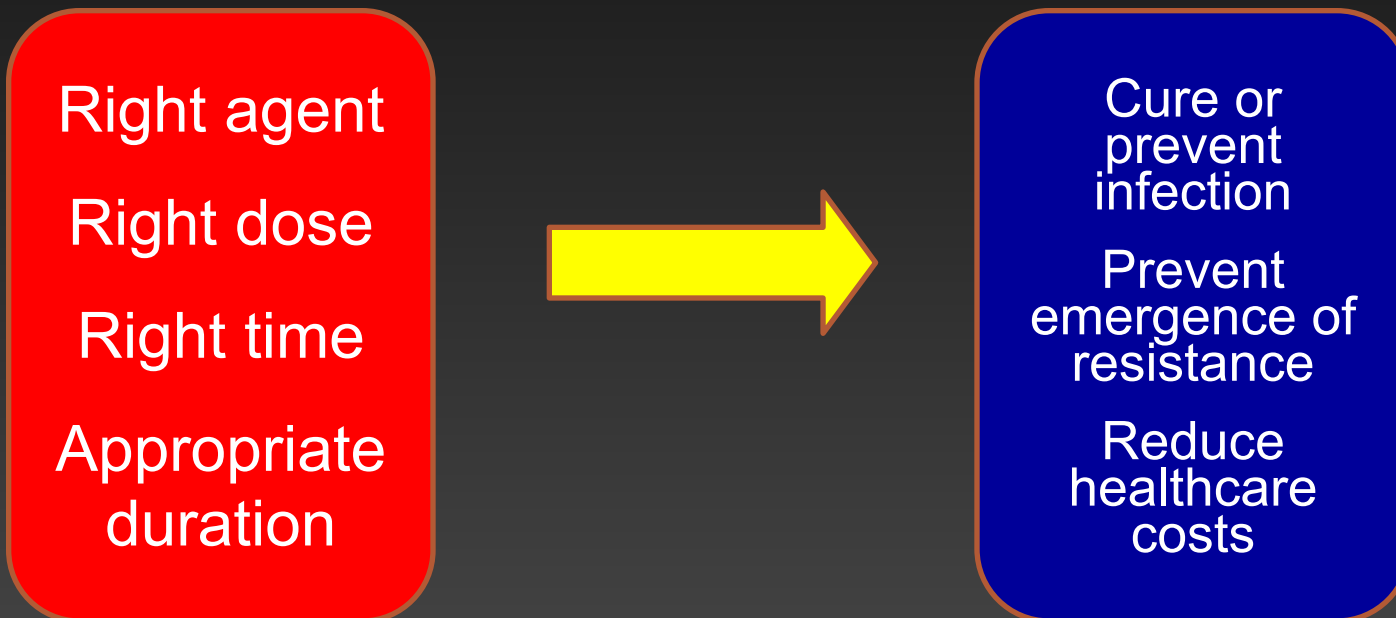
Antibiotic resistance is inevitable.

**The rate of spread of resistance
is not inevitable.**

What are the Goals of Antimicrobial Stewardship?

- Antimicrobial stewardship is a key strategy to overcome resistance by the careful and responsible management of antimicrobial use

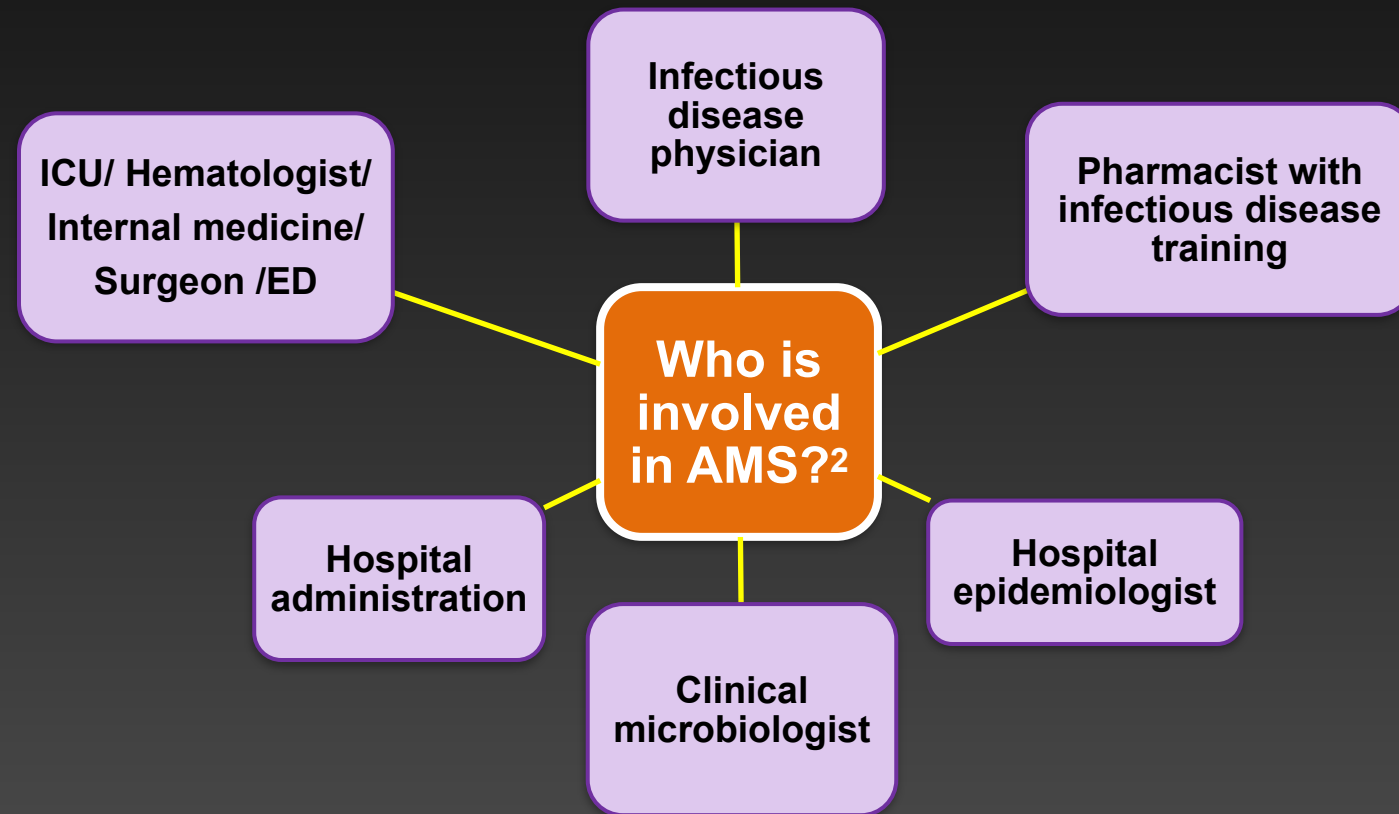
EFFECTIVE ANTIMICROBIAL STEWARDSHIP



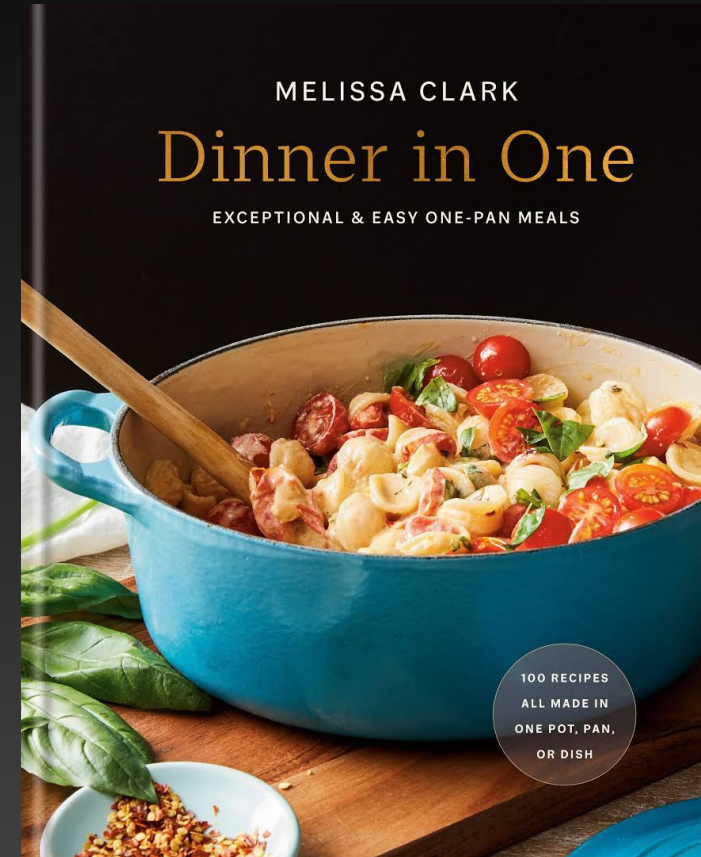
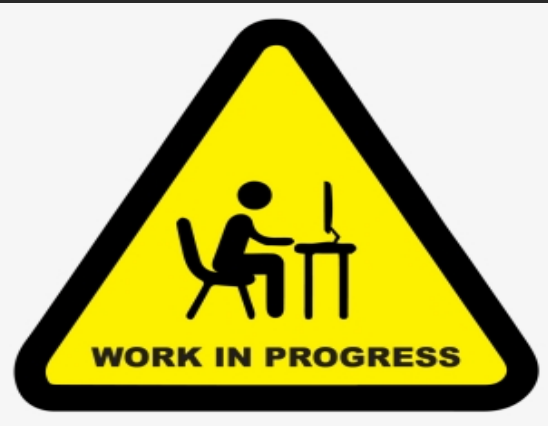
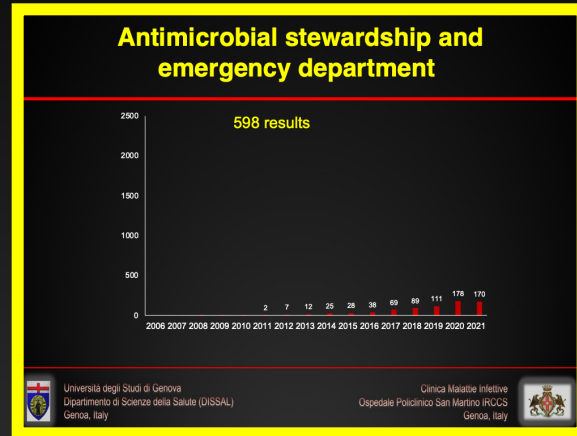
- 1. British Society for Antimicrobial Chemotherapy. A Practical Guide to Antimicrobial Stewardship in Hospitals.

Successful stewardship involves a multidisciplinary approach

Antimicrobial stewardship is an inter-professional effort¹, involving multidisciplinary collaboration from various core members²



Modello San Martino



Cooking book

1. Create a collaborative group
2. Identify the barriers for AMS implementation in the ED and possible tailored approach
3. Education, implementation and dissemination of guidelines.
4. Implement rapid (not always NEW) diagnostic test
5. Let's play with the informatics!
6. Daily Peer comparison
7. follow-up of discharged patients
8. Select indicators
9. Share your success
10. Never give-up!!!

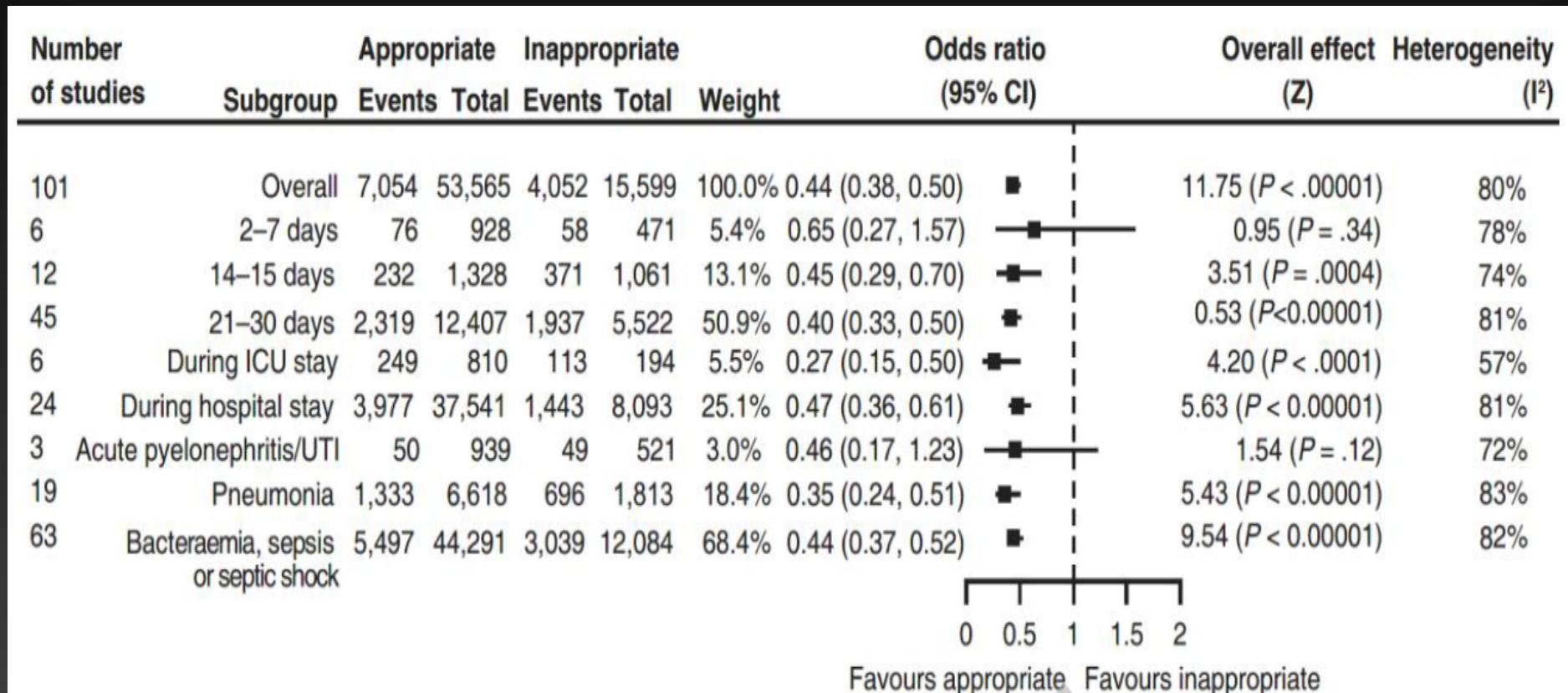
10 “golden rules” for antibiotic use in critically ill patients for treating MDR infections¹

- ❑ Early appropriate for septic patients
- ❑ Impact on bacterial resistance (collateral damages)
- ❑ Improve diagnosis/diagnostics (new techniques/rapid test)
- ❑ Risk stratification
- ❑ Combination (when needed)
- ❑ Role of established antibiotics
- ❑ Drug optimisation (PK/PD)
- ❑ De-escalation (rapid)
- ❑ Duration (shorter better than longer)
- ❑ Role of new antibiotics

MDR, multidrug resistant

1. Bassetti M, personal opinion

Summary of the effect of appropriate versus inappropriate therapy on mortality



CI, confidence interval; ICU, intensive care unit; UTI, urinary tract infection

Bassetti M, et al. *Int J Antimicrob Agents*. 2020:106184.

Inappropriate initial antibiotic therapy leads to excess mortality

Retrospective cohort study

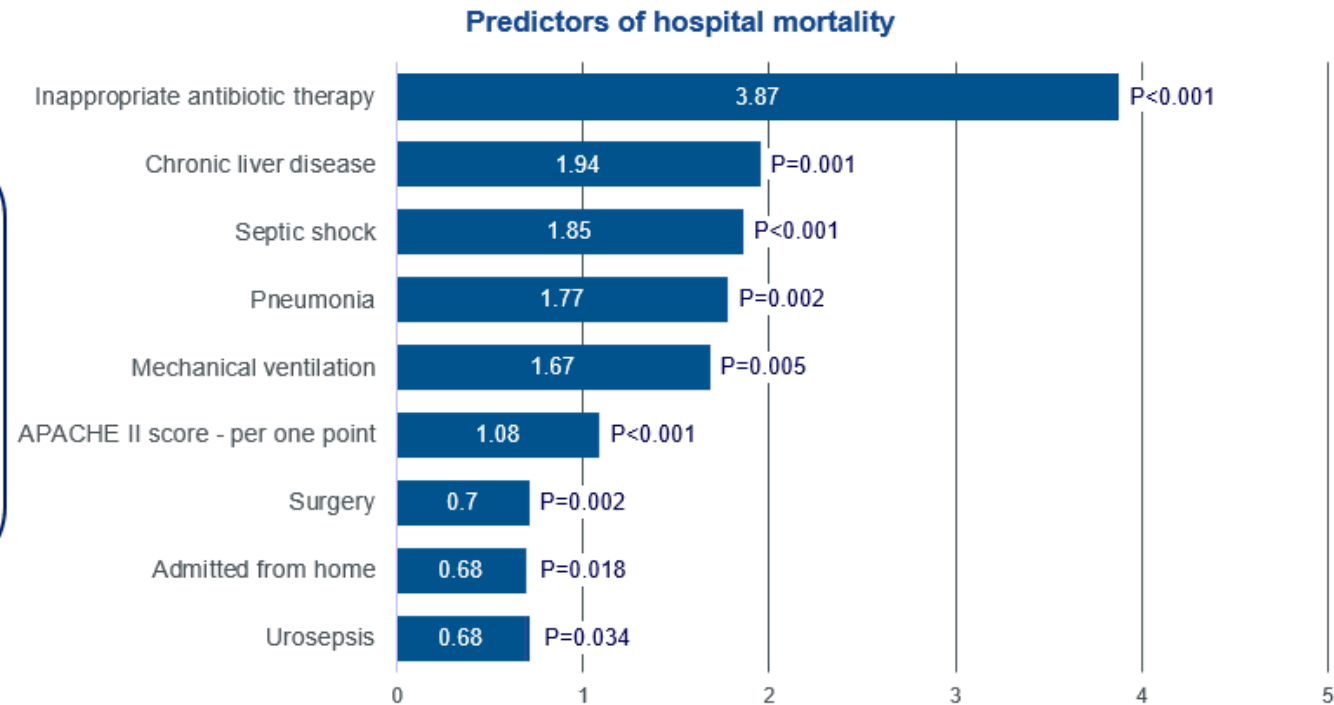
Patients with GNR bacteremia resulting in severe sepsis/septic shock

N=1064

E. coli: 26%,

K. pneumoniae: 20%,

P. aeruginosa: 16%



Inappropriate initial antibiotic therapy is a modifiable risk factor for mortality

RESEARCH

Open Access



Incidence of hospital-acquired infections due to carbapenem-resistant *Enterobacterales* and *Pseudomonas aeruginosa* in critically ill patients in Italy: a multicentre prospective cohort study

Gennaro De Pascale^{1,2†}, Andrea Cortegiani^{3,4†}, Matteo Rinaldi^{5,6}, Massimo Antonelli^{1,2}, Sergio Cattaneo⁷, Maurizio Cecconi^{8,9}, Raffaele Cuffaro¹⁰, Lidia Dalfino¹¹, Filomena Di Biase¹², Abele Donati^{13,14}, Francesca Romana Fasano¹⁵, Teresa Fasciana¹⁶, Giuseppe Foti^{17,18}, Antonella Frattari¹⁹, Roberto Fumagalli^{20,21}, Massimo Girardis²², Leonardo Gottin²³, Alessia Mattei²⁴, Marta Milazzo³, Giorgia Montrucchio^{25,26}, Daniela Paserio^{27,28}, Fabio Picciafuochi²⁹, Emanuela Sensi³⁰, Giuseppe Servillo³¹, Maria Alejandra Vidal Pereira¹⁵, Teresa Spanu^{32†}, Pierluigi Viale^{5,6†} and on behalf of the INCREASE-IT Study Group

59,2% inappropriate empirical therapy

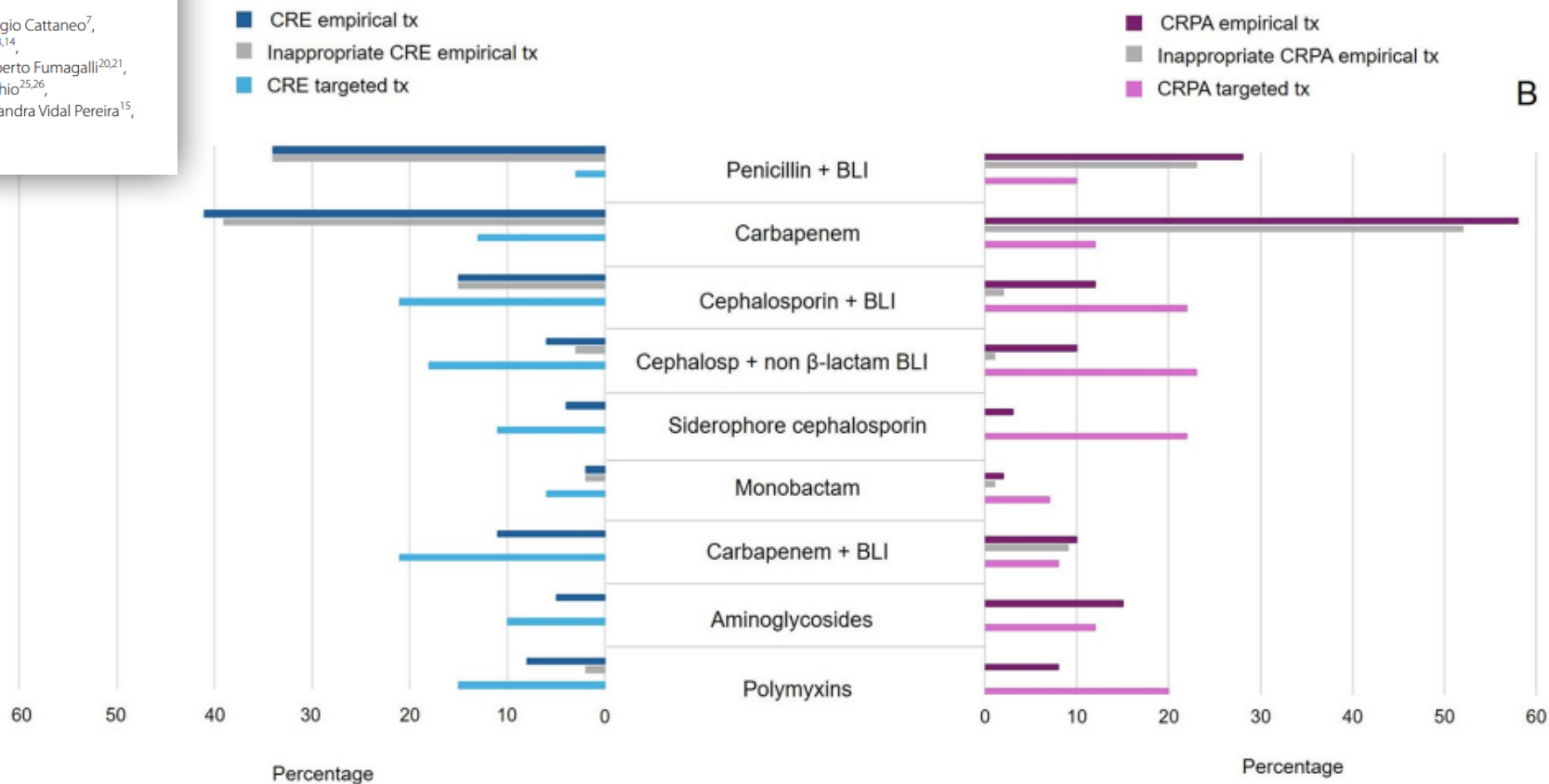


Fig. 2 Percentage of patients receiving classes of antibiotics against gram-negative bacteria as empirical, inappropriate empirical, and targeted therapy in A) CRE and B) CRPA groups

Antimicrobial Therapy: an authentic dilemma in sepsis

Appropriate initial antibiotic improves patient outcomes and healthcare and might reduce mortality

Unnecessary antibiotics adverse patient outcomes and increased resistance rate and cost

The important decision in antibiotic treatment turns out to be the choice between present and future patients

Stewardship

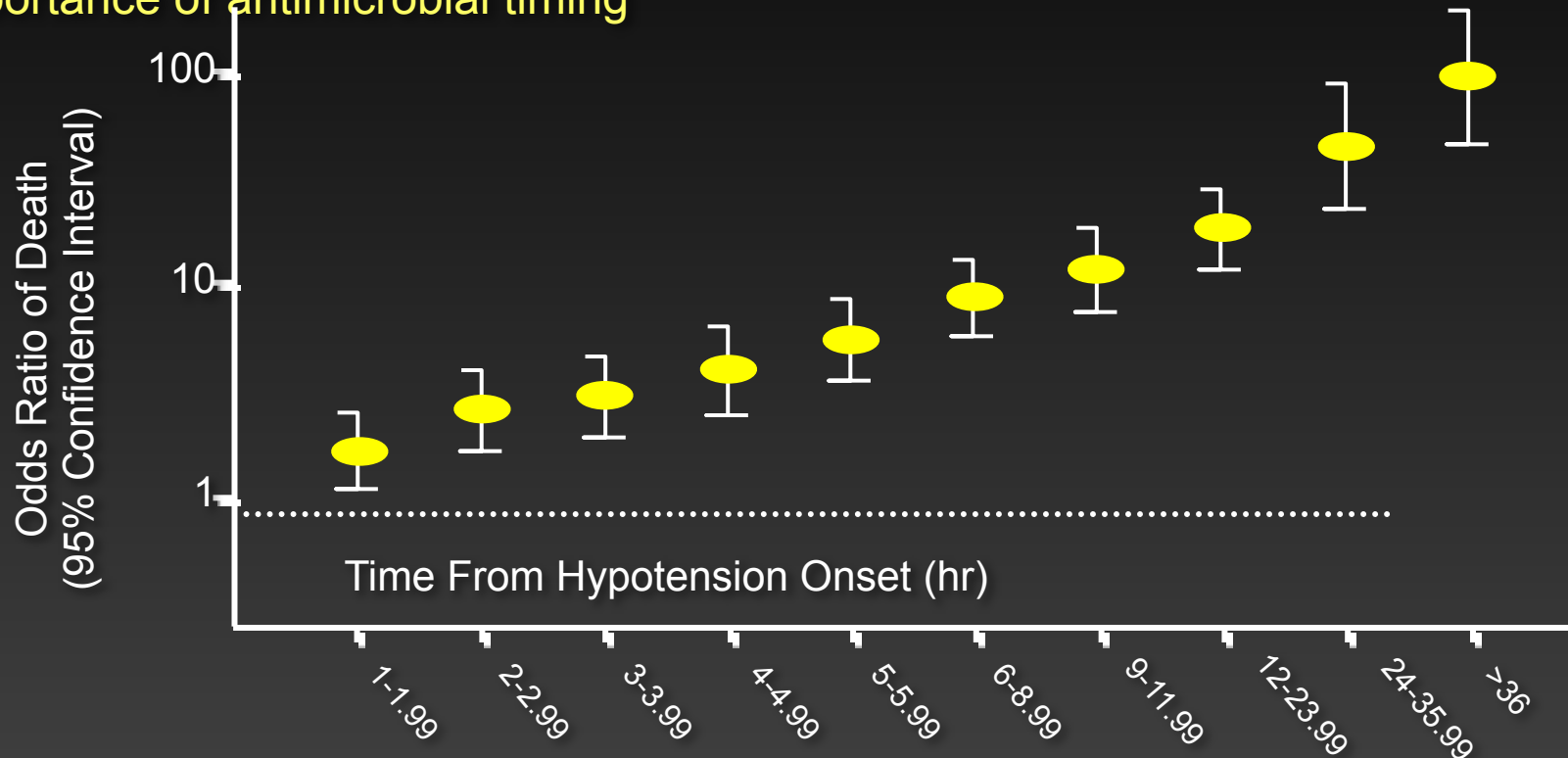
A Balancing Act

Think before you shoot!!



Every minute counts.....

An earlier study of septic shock (n = 2,731) explicitly demonstrated the importance of antimicrobial timing



- Every hour's delay until appropriate therapy resulted in a 12% increase in mortality
- Compared with starting appropriate therapy within 1 hour of the onset of hypotension, the OR for mortality increased from 1.67 in Hour 2 to 92.54 with delays >36 hours

Does Empirical Therapy Really Matter?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Time to Treatment and Mortality during Mandated Emergency Care for Sepsis

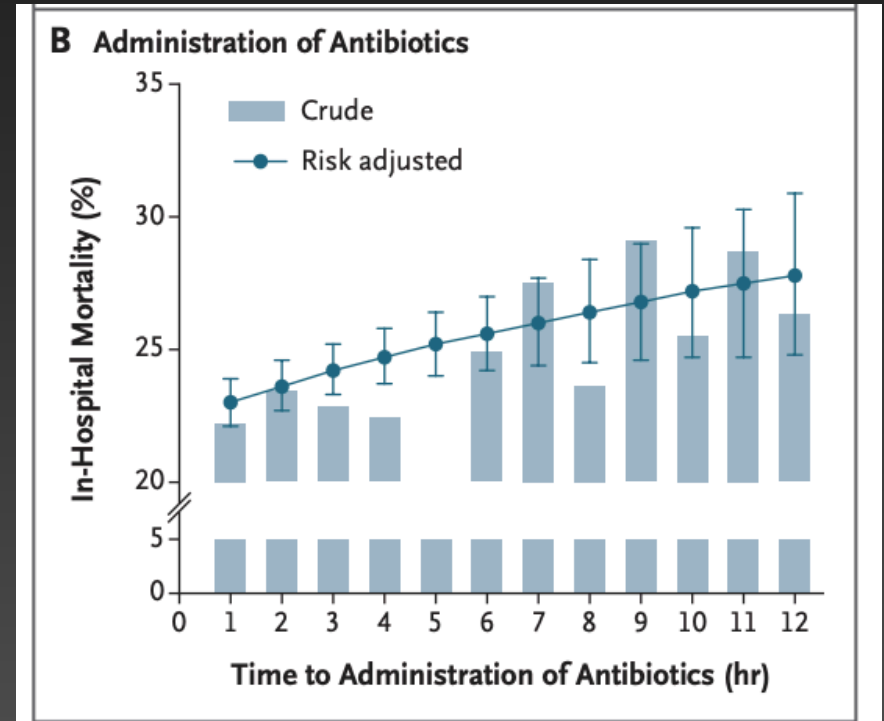
Sepsis protocol initiated within 6 hours after arrival in ED

Bundle: blood cultures, broad-spectrum antibiotic agents, and lactate measurement

49,331 patients at 149 hospitals, 82.5% had the 3-hour bundle completed within 3 hours

A longer time to the completion of the bundle was associated with higher risk-adjusted in-hospital mortality (OR, 1.04 per hour; 95% CI, 1.02 to 1.05; $P < 0.001$)

A longer time to the administration of antibiotics (OR, 1.04 per hour; 95% CI, 1.03 to 1.06; $P < 0.001$)



Disease severity evaluation

INFECTION



BEST PRACTICE

11 For adults with suspected sepsis or septic shock but unconfirmed infection, we **recommend** continuously re-evaluating and searching for alternative diagnoses and discontinuing empiric antimicrobials if an alternative cause of illness is demonstrated or strongly suspected.

12 For adults with possible septic shock or a high likelihood for sepsis, we **recommend** administering antimicrobials immediately, ideally within one hour of recognition.



LOW

Septic shock

Within 1 hour



VERY LOW

Sepsis without shock

2016 STATEMENT

We recommend that administration of intravenous antimicrobials should be initiated as soon as possible after recognition and within one hour for both a) septic shock and b) sepsis without shock."

SEPTIC SHOCK



BEST PRACTICE

13 For adults with possible sepsis without shock, we **recommend** rapid assessment of the likelihood of infectious versus non-infectious causes of acute illness.



VERY LOW

14 For adults with possible sepsis without shock, we **suggest** a time-limited course of rapid investigation and if concern for infection persists, the administration of antimicrobials within 3 hours from the time when sepsis was first recognized.

2016 STATEMENT

We recommend that administration of intravenous antimicrobials should be initiated as soon as possible after recognition and within one hour for both a) septic shock and b) sepsis without shock."

Deferred antibiotics



VERY LOW

15 For adults with a low likelihood of infection and without shock, we **suggest** deferring antimicrobials while continuing to closely monitor the patient.

2016 STATEMENT

We recommend that administration of intravenous antimicrobials should be initiated as soon as possible after recognition and within one hour for both a) septic shock and b) sepsis without shock."

SEPSIS WITHOUT SHOCK

Association Between Delayed Broad-Spectrum Gram-negative Antibiotics and Clinical Outcomes: How Much Does Getting It Right With Empiric Antibiotics Matter?

Jonathan D. Baghdadi,^{1,2} Katherine E. Goodman,^{1,2} Laurence S. Magder,¹ Kimberly C. Claeys,³ Mark E. Sutherland,⁴ and Anthony D. Harris^{1,2}

Retrospective observational cohort study in USA

GROUP 1) Early broad-spectrum therapy (EBT): Broad-spectrum GN empiric therapy

GROUP 2) Delayed broad-spectrum therapy (DBT): Early narrow spectrum GN empiric therapy → ESCALATED to broad-spectrum post-empiric therapy

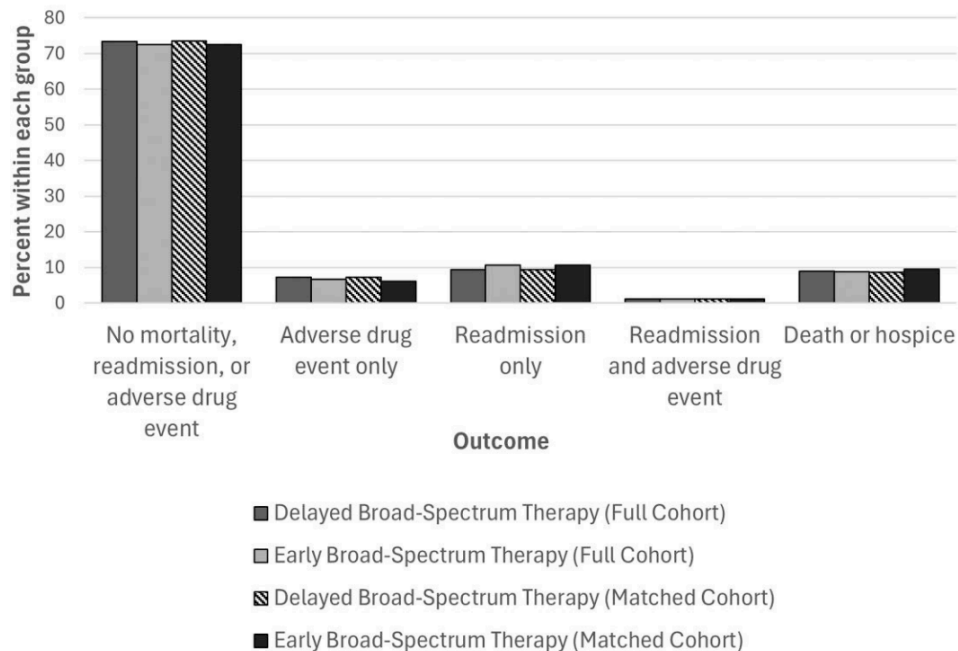
ESCALATION for ANY reason: isolation of a resistant pathogen from clinical culture, lack of clinical response to empiric therapy, drug toxicity, or clinician preference

| Limited Spectrum ^a | Narrow Spectrum | Broad Spectrum | Very Broad Spectrum |
|--|--|--|---|
| <ul style="list-style-type: none">• 2nd generation cephalosporins• Amoxicillin• Ampicillin• Metronidazole | <ul style="list-style-type: none">• 3rd generation cephalosporins• Amoxicillin/clavulanate• Ampicillin/sulbactam | <ul style="list-style-type: none">• 4th generation cephalosporins• Anti-pseudomonal penicillins• Aztreonam• Ertapenem• Ceftazidime• Fluoroquinolones• Aminoglycosides• Colistimethate | <ul style="list-style-type: none">• Anti-pseudomonal carbapenems• Tigecycline• Ceftazidime/avibactam• Ceftolozane/tazobactam• Imipenem/cilastatin/relebactam• Meropenem/vaborbactam• Cefiderocol• Eravacycline |

Impact of early broad spectrum EAT

EBT in 664 604 (**89.0%**) → mainly piperacillin/tazobactam (41.5% of 664 604)
DBT in 82 276 (**11.0%**) → mainly a third-generation cephalosporin (84.3% of 82 276)

Distribution of Outcomes by Empiric Treatment Group in Full and Matched Cohorts



Overall Cohort

- No difference in mortality (8.9% for **DBT**, 8.8% for **EBT**; $P = .59$)
- Readmission less frequent after **DBT** than **EBT** (10.6% vs 11.9%, $P < .0001$)
- AEs more frequent after **DBT** than **EBT** (8.4% vs 7.9%, $P < .0001$).

DOOR ANALYSIS of matched patients
(response=in-hospital mortality+30-day readmission+AEs)
clinical outcomes superior in DBT vs EBT
(win-ratio 1.06; $P < .0001$)

Impact of early broad spectrum EAT

ACCORDING
TYPE OF
INFECTION

Superior clinical outcomes after DBT compared with EBT
(UTI: win ratio 1.05, P = .0062; Pneumonia: win ratio 1.09, P < .0001).

| Critically Ill ^a | | | | | |
|-----------------------------|-----------------------------------|-------------------------|--------------------------|--|-----------------------------|
| DOOR | Outcome | All DBT (n = 16 532) | All EBT (n = 163 219) | Matched ^b DBT (n = 11 789) | Matched EBT (n = 11 789) |
| 1 | No mortality, readmission, or ADE | 9845 (59.6%) | 97 457 (59.7%) | 6956 (59.0%) | 6961 (59.1%) |
| 2 | ADE only | 1946 (11.8%) | 17 216 (10.6%) | 1408 (11.9%) | 1237 (10.5%) |
| 3 | Readmission only | 1414 (8.6%) | 15 507 (9.5%) | 1002 (8.5%) | 1131 (9.6%) |
| 4 | Readmission and ADE | 316 (1.9%) | 3036 (1.9%) | 230 (2.0%) | 204 (1.7%) |
| 5 | Death or hospice | 3011 (18.2%) | 30 003 (18.4%) | 2193 (18.6%) | 2256 (19.1%) |

Critically ill matched win ratio = 1.02 favoring DBST (P = .33)

| Non-critically Ill | | | | | |
|--------------------|-----------------------------------|-------------------------|--------------------------|-----------------------------|-----------------------------|
| DOOR | Outcome | All DBT (n = 65 744) | All EBT (n = 501 385) | Matched DBT (n = 53 199) | Matched EBT (n = 53 199) |
| 1 | No mortality, readmission, or ADE | 50 503 (76.8%) | 385 100 (76.8%) | 40 860 (76.7%) | 40 304 (75.8%) |
| 2 | ADE only | 4001 (6.1%) | 27 174 (5.4%) | 3266 (6.1%) | 2819 (5.3%) |
| 3 | Readmission only | 6341 (9.6%) | 55 397 (11.1%) | 5127 (9.6%) | 5901 (11.1%) |
| 4 | Readmission and ADE | 622 (6.5%) | 5201 (1.0%) | 511 (1.0%) | 488 (0.9%) |
| 5 | Death or hospice | 4277 (6.5%) | 28 513 (5.7%) | 3435 (6.5%) | 3687 (6.9%) |

Non-critically ill matched win ratio = 1.06 favoring DBST (P < .0001)

Critical illness in the first 2 days: 9.2% in DBT and 90.8% in EBT
Equivalent clinical outcomes
(win ratio 1.02 non-significantly favoring DBT, P = .33)



Non-critical illness:
superior clinical outcomes after DBT vs EBT
(win ratio 1.06, P < .0001)

For definitive therapy?

46/71 (64.8%) received adequate definitive monotherapy

25/71 (35.2%) received adequate definitive combination therapy

Table 2. Univariate Cox models for 30-day all-cause mortality in patients with septic shock due to *P. aeruginosa* BSI

| Variable | Alive (n=50) | Dead (n=48) | HR | 95% CI | P value |
|---|-----------------|----------------|------|-----------|---------|
| Definitive therapy, n (%) ^e | | | | | |
| Adequate monotherapy | 30 (60.0) | 16/21 (76.2) | Ref. | Ref. | Ref. |
| Adequate combination therapy | 20 (40.0) | 5/21 (23.8) | 0.48 | 0.17–1.31 | 0.152 |
| Need for CRRT after <i>P. aeruginosa</i> septic shock | 6 (12.0) | 7 (14.6) | 1.06 | 0.47–2.35 | 0.896 |

Univariate analysis: **similar risk of death** (HR 0.48; 95% CI 0.17–1.31; P = 0.152)
Multivariate Cox regression analysis: 30-day all-cause mortality did not significantly differ between ADCT and ADMT (aHR 0.73; 95% CI 0.25–2.14; P = 0.568)

Towards Personalized Empirical Therapy



Broad
EAT

Tailored
EAT

Clinical severity

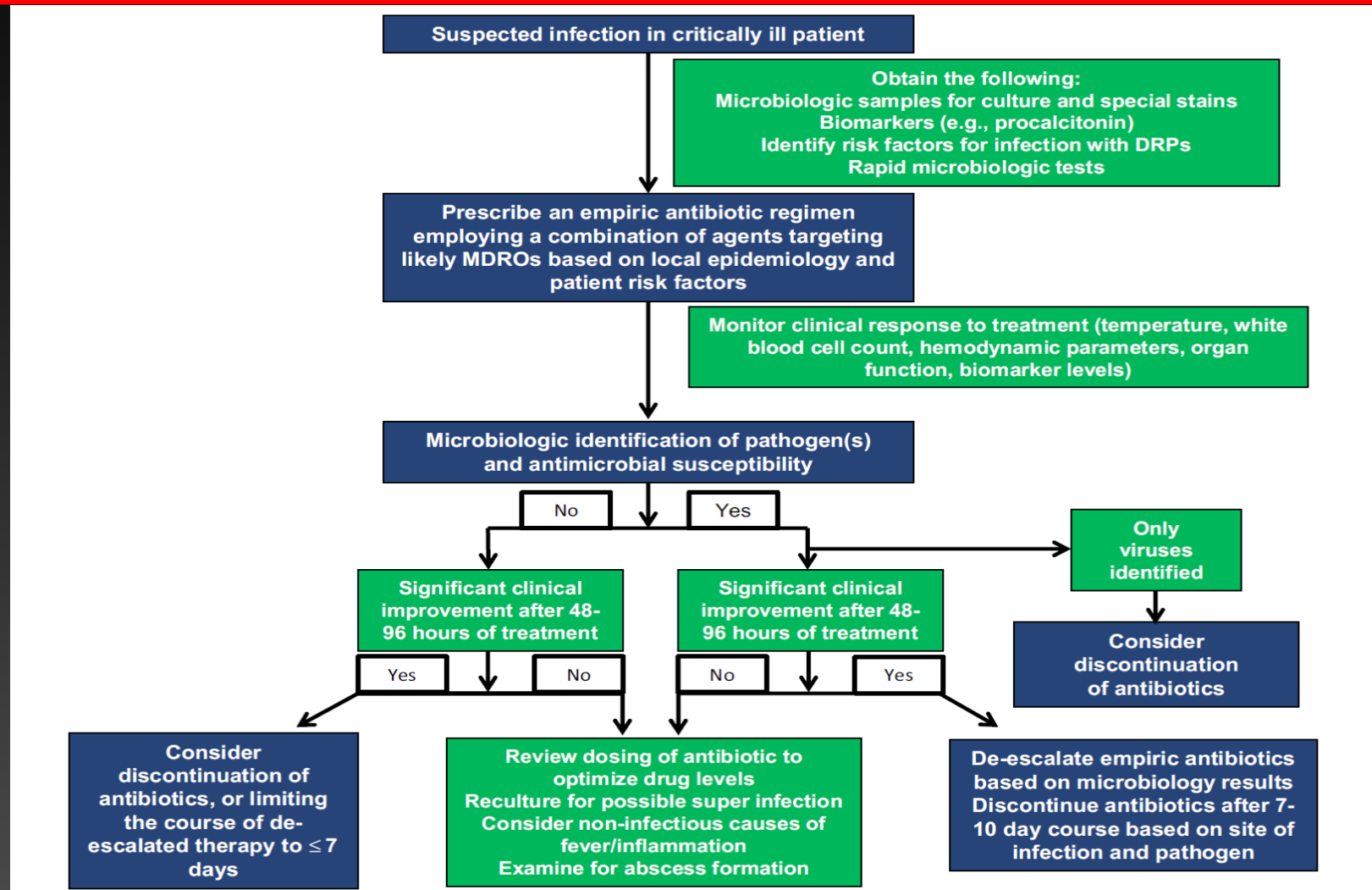
Local
epidemiology

Prior
colonization

Clinician's
anxiety

Rapid tests

Scheme of treatment in critically ill patients



Risk factors for resistant organisms¹

Table 2. Risk factors for antimicrobial-resistant Gram-negative bacteria.

| Risk factors for MDR pathogens | | | | |
|---|--|---|--|---|
| Baseline characteristics | Epidemiological background | Recent (<3 months) antibiotic therapy | Prior colonization | Indwelling devices |
| <ul style="list-style-type: none"> • Age >70 years • Diabetes mellitus • Charlson index ≥ 3 • Recurrent or obstructive UTIs • Use of corticosteroids • Immunosuppression • Trauma • Malignancy • Organ transplantation • COPD • Neutropenia • Recent surgery | <ul style="list-style-type: none"> • Prior hospital admission (in the last 12 months) • Prolonged hospitalization • Transfer from another health-care facility • Current or prior ICU admission • Local epidemiology, outbreak • Travel from high endemic area^a | <ul style="list-style-type: none"> • Recent aminopenicillins • Recent cephalosporins • Recent fluoroquinolones • Recent carbapenems • Recent aminoglycosides | <ul style="list-style-type: none"> • Gut colonization with ESBL • Gut colonization with CRE • Colonization with MRSA • Colonization with <i>Acinetobacter</i> • Endotracheal colonization with <i>P. aeruginosa</i> | <ul style="list-style-type: none"> • Urinary catheter • Gastrostomy or jejunostomy • Nasogastric tube • CVC • Mechanical ventilation • Hemodialysis |

Table adapted from Bassetti M, et al. 2017

^aCentral and western Asia for ESBL; USA, Italy, Greece, and Israel for K. pneumoniae carbapenemases; Greece for VIMs; Turkey for OXA-48; and the Indian subcontinent for New Delhi metallo-beta-lactamases.

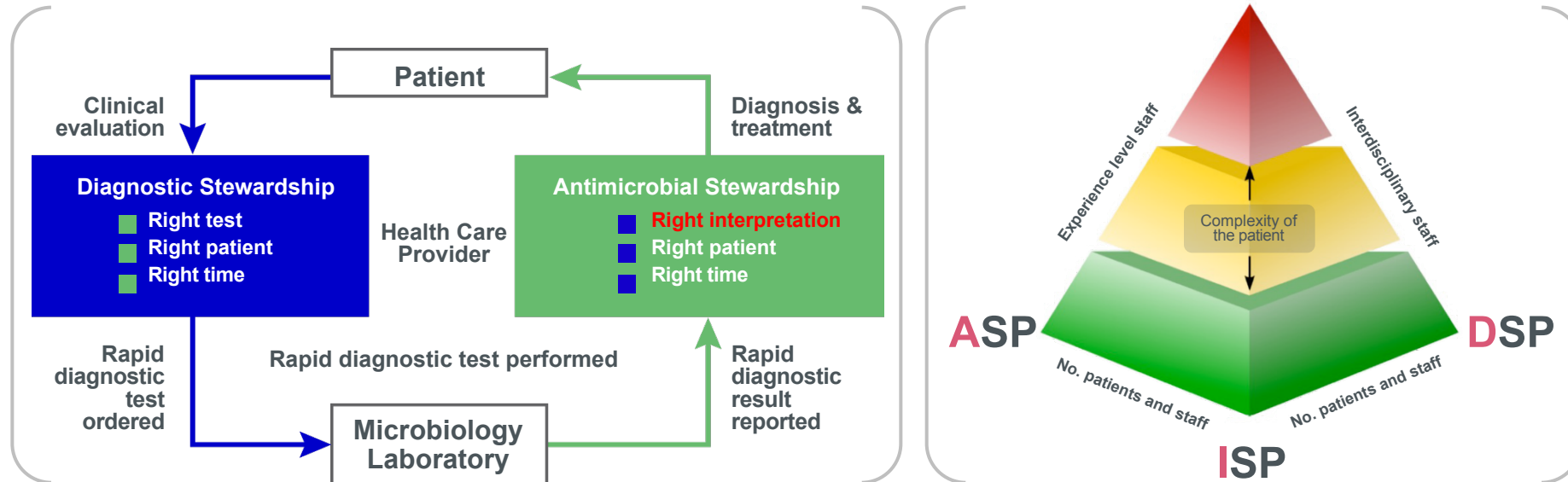
COPD, chronic pulmonary obstructive disease; CRE, carbapenem-resistant Enterobacteriaceae; CVC, central venous catheter;

ESBL, extended-spectrum β -lactamase; ICU, intensive care unit; MDR, multidrug-resistant; MRSA, methicillin-resistant *S. aureus*; Tx, treatment;

UTI, urinary tract infection.

1. Bassetti M, et al. Expert Rev Anti Infect Ther 2017;15(1):55–65.

Interactions Between Antimicrobial Stewardship, Diagnostic Stewardship and Infection Prevention



Adapted from Messacar et al. *J. Clin. Microbiol.* 2017;55:715-723



Critical importance of integrating rapid diagnostics not only with individual patient management but with infection prevention modalities such as ensuring minimal unnecessary time spent in isolation, best use of scant infection prevention resources.

ASP, antimicrobial stewardship program; DSP, diagnostic stewardship program; ISP, infection prevention stewardship program.
 1. Messacar K, et al. *J Clin Microbiol.* 2017;55(3):715-723. 2. Dik JH, et al. *J Clin Microbiol.* 2017;55(11):3306-3307.

Impact of mPCR + Antimicrobial Stewardship in RCTs



Higher de-escalation rate vs. conventional culture: 42% vs. 8%

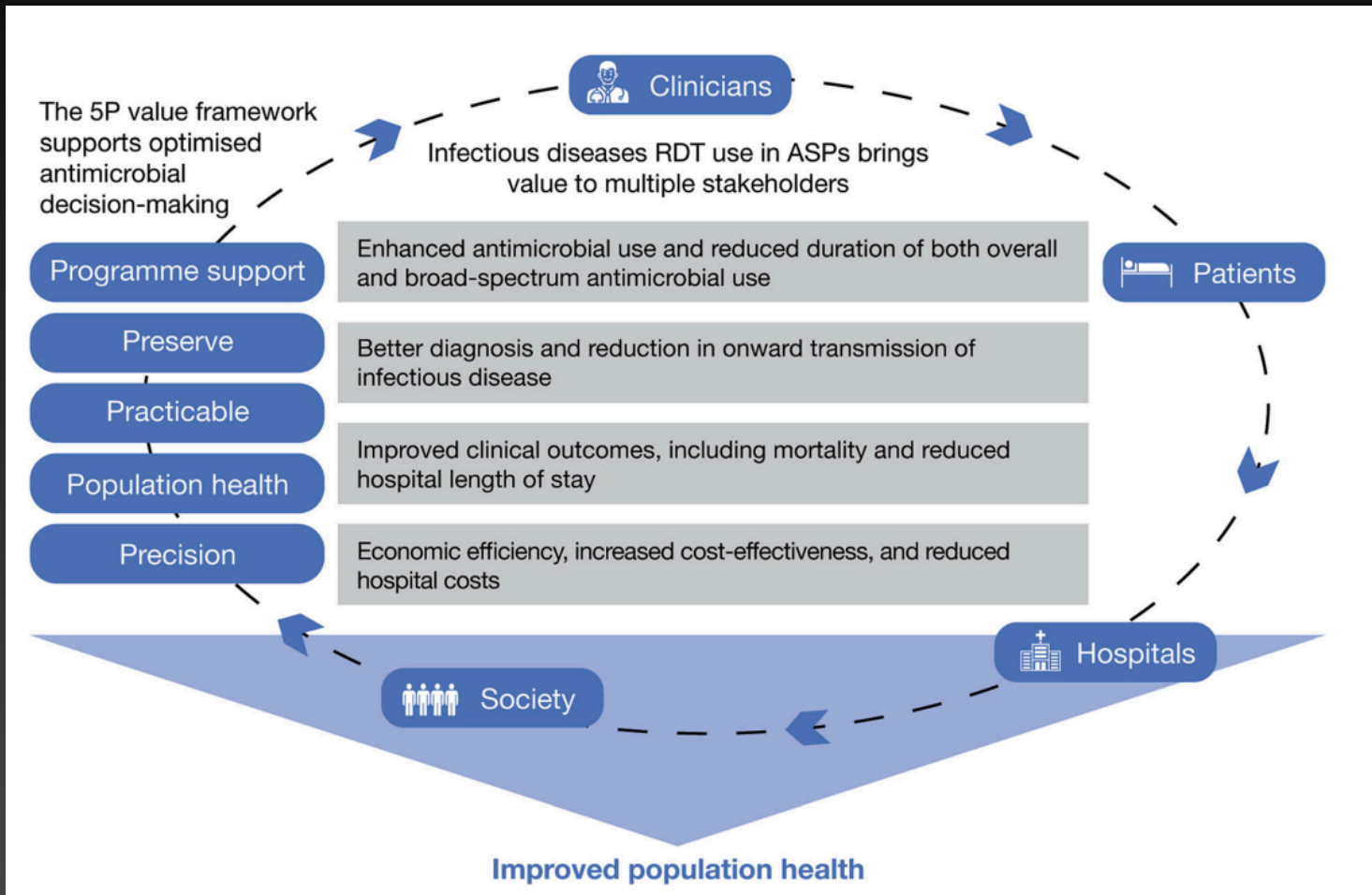


45% shorter inappropriate therapy duration (too long, broad, or inadequate)



No impact on clinical outcomes (cure rate, hospital stay, mortality, adverse events)

RDTs in AMS Strategies



Karri et al., *Clinical Infectious Diseases*, 2014;
 Moore et al. *Infectious diseases and therapy*, 2023.



AMS GOALS

- ACCELERATE PATHOGEN IDENTIFICATION
- OPTIMIZE ANTIMICROBIAL PRESCRIBING
- ACCELERATE DE-ESCALATION STRATEGIES
- CONTRIBUTE TO SURVEILLANCE AND EPIDEMIOLOGY
- PROMOTE COST-EFFECTIVE HEALTHCARE

DE-ESCALATION

Replacing broad-spectrum antimicrobials with agents of a narrower spectrum or a lower ecological impact

or

Stopping components of an antimicrobial combination

Stopping of an antimicrobial agent administered in combination therapy to provide double cover for certain pathogens

Stopping of an antimicrobial agent administered to cover pathogens that are not finally isolated in the clinical cultures

Empirical antimicrobials

PIVOTAL ANTIMICROBIAL

COMPANION ANTIMICROBIAL if necessary

De-escalation

Companion antimicrobial: stopped or becomes pivotal

Pivotal antimicrobial: Change in spectrum

DE-ESCALATION

❓ Scarcity of adequate evidence on its efficacy and safety

29. For adults with sepsis or septic shock, we suggest daily assessment for de-escalation of antimicrobials over using fixed durations of therapy without daily reassessment for de-escalation.

Weak, very low quality of evidence

Efficacy and safety of a structured de-escalation from antipseudomonal β -lactams in bloodstream infections due to Enterobacterales (SIMPLIFY): an open-label, multicentre, randomised trial



- RCT
- 21 Spanish Hospitals
- Oct 2016 - Jan 2020
- De-escalation within 48–72 h of susceptibility results (\approx 3–5 days after empirical therapy start)

López-Cortés, et al. Lancet 2024

| | De-escalation group (n=164) | Control group (n=167) |
|---|-----------------------------|-----------------------|
| Acquisition type | | |
| Community-acquired | 89 (54%) | 79 (47%) |
| Community-onset, health care-associated | 48 (29%) | 44 (26%) |
| Nosocomial | 27 (17%) | 44 (26%) |
| Severity of infection at presentation | | |
| Severe sepsis | 31 (19%) | 28 (17%) |
| Septic shock | 17 (10%) | 7 (4%) |
| Source of bacteraemia | | |
| Biliary tract | 62 (38%) | 67 (40%) |
| Urinary tract | 61 (37%) | 65 (39%) |
| Abdominal (other than biliary tract) | 16 (10%) | 14 (8%) |
| Vascular catheter | 7 (4%) | 12 (7%) |
| Skin and skin structure | 4 (2%) | 0 |
| Respiratory tract | 2 (1%) | 2 (1%) |
| Other | 2 (1%) | 1 (1%) |
| Unknown | 10 (6%) | 6 (4%) |
| Cause of bacteraemia | | |
| <i>Escherichia coli</i> | 103 (63%) | 112 (67%) |
| <i>Klebsiella pneumoniae</i> | 30 (18%) | 24 (14%) |
| <i>Klebsiella oxytoca</i> | 9 (6%) | 7 (4%) |
| <i>Enterobacter cloacae</i> | 3 (2%) | 11 (7%) |
| <i>Proteus mirabilis</i> | 6 (4%) | 7 (4%) |
| Other | 13 (8%) | 6 (4%) |

| | De-escalation group (n=164) | Control group (n=167) |
|--------------------------------|-----------------------------|-----------------------|
| Empirical drugs used | | |
| Imipenem or meropenem | 45 (27%) | 47 (28%) |
| Piperacillin-tazobactam | 104 (63%) | 107 (64%) |
| Cefepime or ceftazidime | 14 (9%) | 11 (7%) |
| Aztreonam | 1 (1%) | 2 (1%) |
| De-escalation intravenous drug | | |
| Ampicillin | 23 (14%) | NA |
| Trimethoprim-sulfamethoxazole | 6 (4%) | NA |
| Cefuroxime | 23 (14%) | NA |
| Cefotaxime or ceftriaxone | 52 (32%) | NA |
| Amoxicillin-clavulanic acid | 24 (15%) | NA |
| Ciprofloxacin | 18 (11%) | NA |
| Ertapenem | 18 (11%) | NA |
| Switched to oral drugs | | |
| Ciprofloxacin | 21 (20%) | 97 (78%) |
| Cefuroxime | 26 (25%) | 17 (14%) |
| Amoxicillin | 19 (18%) | 1 (1%) |
| Amoxicillin-clavulanic acid | 17 (17%) | 4 (3%) |
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| Ertapenem | 0 | 2 (2%) |

| | De-escalation group | Control group | Difference in percentage points (two-sided 95% CI) |
|---|---------------------|----------------|--|
| Primary analysis (modified intention-to-treat population) | | | |
| Clinical cure at test of cure | 148/164 (90%) | 148/167 (89%) | 1.6 (-5.0 to 8.2) |
| Reasons for not reaching clinical cure at test of cure | | | |
| Clinical failure | 7/164 (4%) | 12/167 (7%) | -2.9 (-7.9 to 2.1) |
| Missed assessment | 6/164 (4%) | 5/167 (3%) | 0.7 (-3.2 to 4.6) |
| Withdrawn due to adverse events | 3/164 (2%) | 2/167 (1%) | 0.6 (-2.0 to 3.2) |
| Secondary analysis | | | |
| Clinical cure at test of cure (clinically evaluable population) | 143/148* (97%) | 144/156† (92%) | 4.3 (-0.9 to 9.5) |
| Microbiological cure at test of cure (microbiologically evaluable population) | 124/128 (97%) | 125/132 (95%) | 2.2 (-2.7 to 7.1) |
| Clinical cure at day 60 | 142/153‡ (93%) | 144/160§ (90%) | 2.8 (-3.4 to 9.0) |
| Recurrence until day 60 | 9/153‡ (6%) | 18/160§ (11%) | -5.5 (-11.6 to 0.8) |
| Death at day 60 | 7/153‡ (5%) | 9/160§ (6%) | -1.0 (-5.9 to 3.9) |
| <i>Clostridioides difficile</i> infection until day 60 | 1/153‡ (1%) | 1/160§ (1%) | 0.10 (-1.7 to 1.9) |

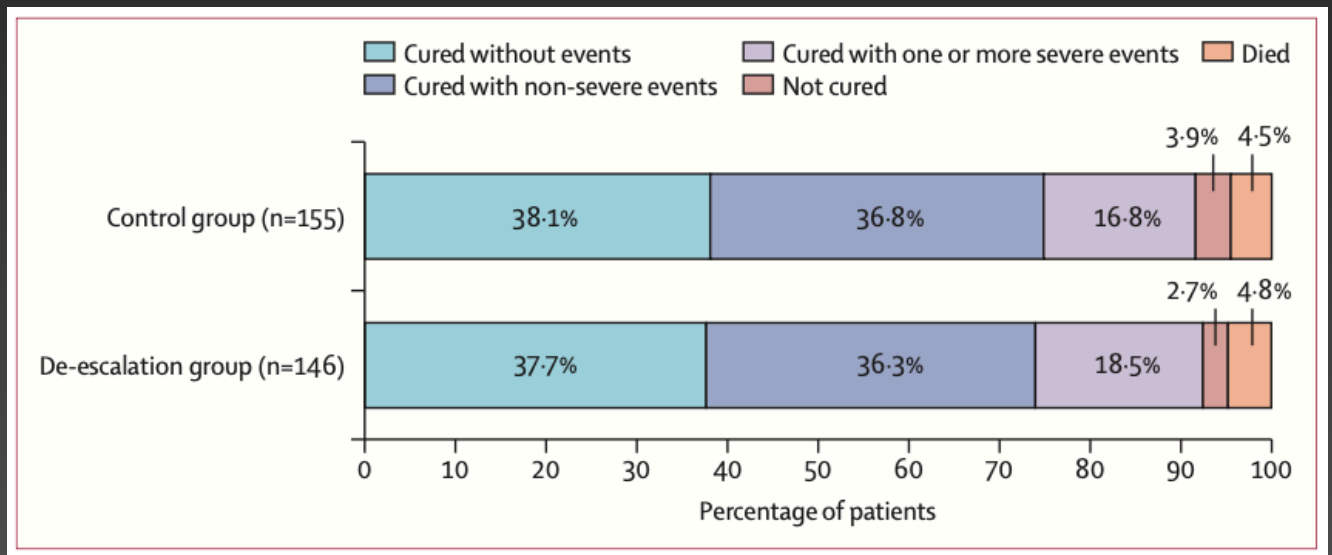
Data are n (%). *16 patients were excluded from the modified intention-to-treat population for not completing 5 days of treatment (n=13) or for missing the assessment at test of cure (n=3). †11 patients were excluded from the modified intention-to-treat population due to not completing 5 days of treatment (n=6), being withdrawn due to adverse events (n=2), or missing the assessment at test of cure (n=3). ‡11 patients excluded from the modified intention-to-treat population due to missed assessment at day 60. §Seven patients excluded from the modified intention-to-treat population due to missed assessment at day 60.

Table 2: Primary and secondary endpoint analyses

| | De-escalation group | Control group | Difference in percentage points (two-sided 95% CI) |
|--|---------------------|---------------|--|
| Age | | | |
| <80 years | 117/124 (94%) | 112/121 (93%) | 1.8 (4.4 to 8.0) |
| ≥80 years | 31/32 (97%) | 36/40 (90%) | 6.9 (-4.9 to 18.7) |
| Acquisition type | | | |
| Community | 82/85 (97%) | 70/75 (93%) | 3.1 (-3.6 to 9.9) |
| Non-community | 66/71 (93%) | 78/86 (91%) | 2.3 (-6.4 to 10.9) |
| Severe sepsis or septic shock | | | |
| Yes | 44/47 (94%) | 31/34 (91%) | 2.4 (-9.1 to 14.0) |
| No | 104/109 (95%) | 117/127 (92%) | 3.3 (-3.0 to 9.5) |
| Source | | | |
| Urinary | 59/60 (98%) | 55/63 (87%) | 11.0 (1.8 to 20.2) |
| Non-urinary | 89/96 (93%) | 93/98 (95%) | 2.2 (-9.0 to 4.6) |
| Biliary | 57/58 (98%) | 61/64 (95%) | 3.0 (-3.4 to 9.3) |
| Non-biliary | 89/96 (93%) | 86/96 (90%) | 3.1 (-4.9 to 11.2) |
| Urinary or biliary | 113/118 (96%) | 122/126 (97%) | 1.1 (-3.7 to 5.8) |
| Neither urinary or biliary | 36/39 (92%) | 33/33 (100%) | 7.7 (7.7 to 7.7) |
| Bacteraemia caused by <i>Escherichia coli</i> | | | |
| Yes | 95/100 (95%) | 98/106 (93%) | 2.5 (-4.1 to 9.2) |
| No | 53/56 (95%) | 50/55 (91%) | 3.7 (5.9 to 13.4) |

Data are shown for the modified intention-to-treat population. Eight patients in the de-escalation group and six in the control group were excluded for missing the assessment at test of cure.

Table 3: Subgroup analyses for clinical cure at test of cure



| | De-escalation group | Control group | Difference in percentage points (two-sided 95% CI) |
|---|---------------------|----------------|--|
| Primary analysis (modified intention-to-treat population) | | | |
| Clinical cure at test of cure | 148/164 (90%) | 148/167 (89%) | 1.6 (-5.0 to 8.2) |
| Reasons for not reaching clinical cure at test of cure | | | |
| Clinical failure | 7/164 (4%) | 12/167 (7%) | -2.9 (-7.9 to 2.1) |
| Missed assessment | 6/164 (4%) | 5/167 (3%) | 0.7 (-3.2 to 4.6) |
| Withdrawn due to adverse events | 3/164 (2%) | 2/167 (1%) | 0.6 (-2.0 to 3.2) |
| Secondary analysis | | | |
| Clinical cure at test of cure (clinically evaluable population) | 143/148* (97%) | 144/156† (92%) | 4.3 (-0.9 to 9.5) |
| Microbiological cure at test of cure (microbiologically evaluable population) | 124/128 (97%) | 125/132 (95%) | 2.2 (-2.7 to 7.1) |
| Clinical cure at day 60 | 142/153‡ (93%) | 144/160§ (90%) | 2.8 (-3.4 to 9.0) |
| Recurrence until day 60 | 9/153‡ (6%) | 18/160§ (11%) | -5.5 (-11.6 to 0.8) |
| Death at day 60 | 7/153‡ (5%) | 9/160§ (6%) | -1.0 (-5.9 to 3.9) |
| <i>Clostridioides difficile</i> infection until day 60 | 1/153‡ (1%) | 1/160§ (1%) | 0.10 (-1.7 to 1.9) |

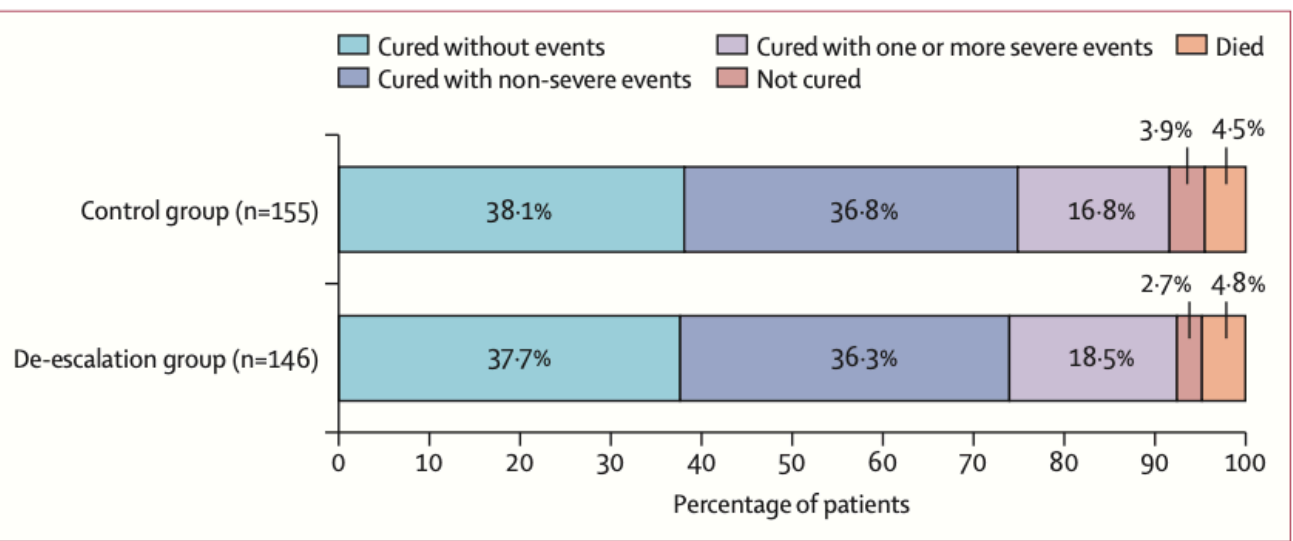
Data are n (%). *16 patients were excluded from the modified intention-to-treat population for not completing 5 days of treatment (n=13) or for missing the assessment at test of cure (n=3). †11 patients were excluded from the modified intention-to-treat population due to not completing 5 days of treatment (n=6), being withdrawn due to adverse events (n=2), or missing the assessment at test of cure (n=3). ‡11 patients excluded from the modified intention-to-treat population due to missed assessment at day 60. §Seven patients excluded from the modified intention-to-treat population due to missed assessment at day 60.

Table 2: Primary and secondary endpoint analyses

| | De-escalation group | Control group | Difference in percentage points (two-sided 95% CI) |
|--|---------------------|---------------|--|
| Age | | | |
| <80 years | 117/124 (94%) | 112/121 (93%) | 1.8 (4.4 to 8.0) |
| ≥80 years | 31/32 (97%) | 36/40 (90%) | 6.9 (-4.9 to 18.7) |
| Acquisition type | | | |
| Community | 82/85 (97%) | 70/75 (93%) | 3.1 (-3.6 to 9.9) |
| Non-community | 66/71 (93%) | 78/86 (91%) | 2.3 (-6.4 to 10.9) |
| Severe sepsis or septic shock | | | |
| Yes | 44/47 (94%) | 31/34 (91%) | 2.4 (-9.1 to 14.0) |
| No | 104/109 (95%) | 117/127 (92%) | 3.3 (-3.0 to 9.5) |
| Source | | | |
| Urinary | 59/60 (98%) | 55/63 (87%) | 11.0 (1.8 to 20.2) |
| Non-urinary | 89/96 (93%) | 93/98 (95%) | 2.2 (-9.0 to 4.6) |
| Biliary | 57/58 (98%) | 61/64 (95%) | 3.0 (-3.4 to 9.3) |
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| Urinary or biliary | 113/118 (96%) | 122/126 (97%) | 1.1 (-3.7 to 5.8) |
| Neither urinary or biliary | 36/39 (92%) | 33/33 (100%) | 7.7 (7.7 to 7.7) |
| Bacteraemia caused by <i>Escherichia coli</i> | | | |
| Yes | 95/100 (95%) | 98/106 (93%) | 2.5 (-4.1 to 9.2) |
| No | 53/56 (95%) | 50/55 (91%) | 3.7 (5.9 to 13.4) |

Data are shown for the modified intention-to-treat population. Eight patients in the de-escalation group and six in the control group were excluded for missing the assessment at test of cure.

Table 3: Subgroup analyses for clinical cure at test of cure



Structured de-escalation is non-inferior to continuing antipseudomonal β-lactams in patients with *Enterobacterales* BSI susceptible to narrower-spectrum agents

Principal components of strategies for stewardship and antimicrobial use in ICU

- Leadership commitment
 - Implementing antibiotic stewardship programs, infections control practices, communication between lab and clinical staff
 - Implement local resistance data for developing local antibiotic guidelines
- Multidisciplinary approach
 - A multidisciplinary team including infectious diseases specialists, microbiologists, pharmacist and nurses should be in charge of developing a specific antibiotic stewardship
 - Weekly round for MDR cases discussion
- **Implementation of modern antimicrobial use approach**
 - **Aggressive good quality microbiological sampling**
 - **Selection of empirical antimicrobials according to the clinical conditions, the presence of risk factors for resistant microorganisms and to the local epidemiology**
 - **Achievement of adequate pharmacokinetic / pharmacodynamic parameters of the antimicrobial agents used (extended/continuous infusion, TDM)**
 - **Systematic de-escalation**
 - **Short duration**

Bassetti M et al. Intensive Care Med 2015;41:776-795.

Conclusions

Empirical broad-spectrum therapy should be guided by the **severity of clinical presentation**

Toward **personalized antimicrobial selection**, based on **individual risk factors** such as **MDR colonization**

Once initiated, the goal should be **rapid de-escalation** to **targeted therapy**

Rapid diagnostic tests facilitate early effective therapy and rapid de-escalation

Empirical antifungal therapy and diagnostic-driven approaches have limited evidence in **critically ill patients**

HTIDE

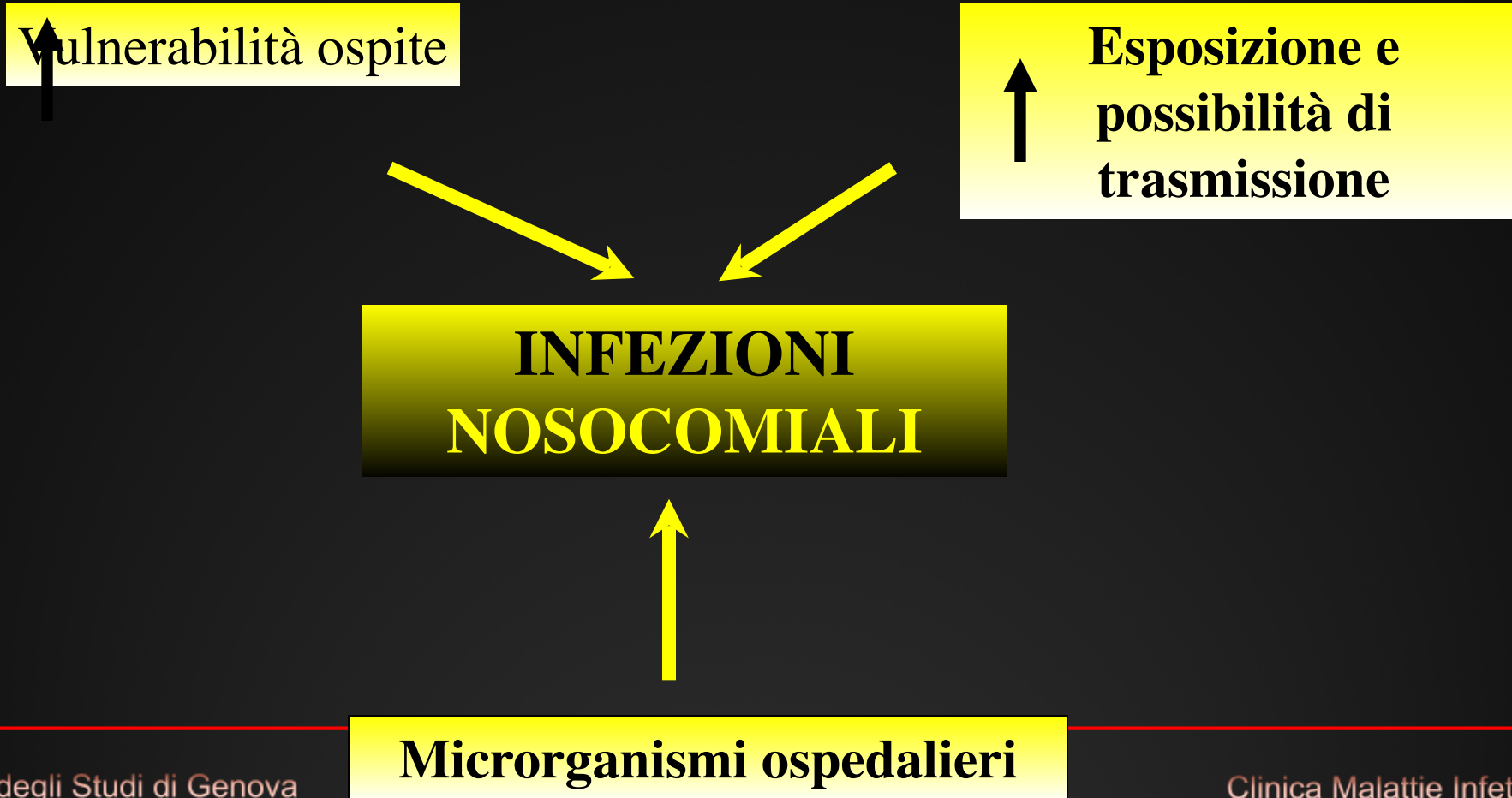
Hot Topics in Infectious Diseases

See you in Genoa on October 2026

Register at

www.htide.net

Perchè così tante infezioni ospedaliere?



Vulnerabilità dell'ospite

Persone sane non vanno in ospedale!!!!

- ❑ Diminuzione generale della salute
- ❑ Minor mobilità
- ❑ Rottura delle difese primarie
 - ferite
 - invasività strumenti
- ❑ Aumento uso antibiotici
- ❑ Aumentata immunodepressione
- ❑ Sovra-rappresentazione di categorie a rischio (Bambini, anziani, diabetici)



Trasmissione di infezione

Diretta

- da paziente a paziente
- da staff a paziente

Indiretta

Reservoir

Ospite intermedio

Staff come vettori
Strumentazione

Paziente



Reservoirs (source of organism)

- ☐ Exogenous
 - other patients
 - staff - carriers
 - normal flora
 - environment
- ☐ Endogenous - patients own normal flora

Effect of hospitalisation on normal flora

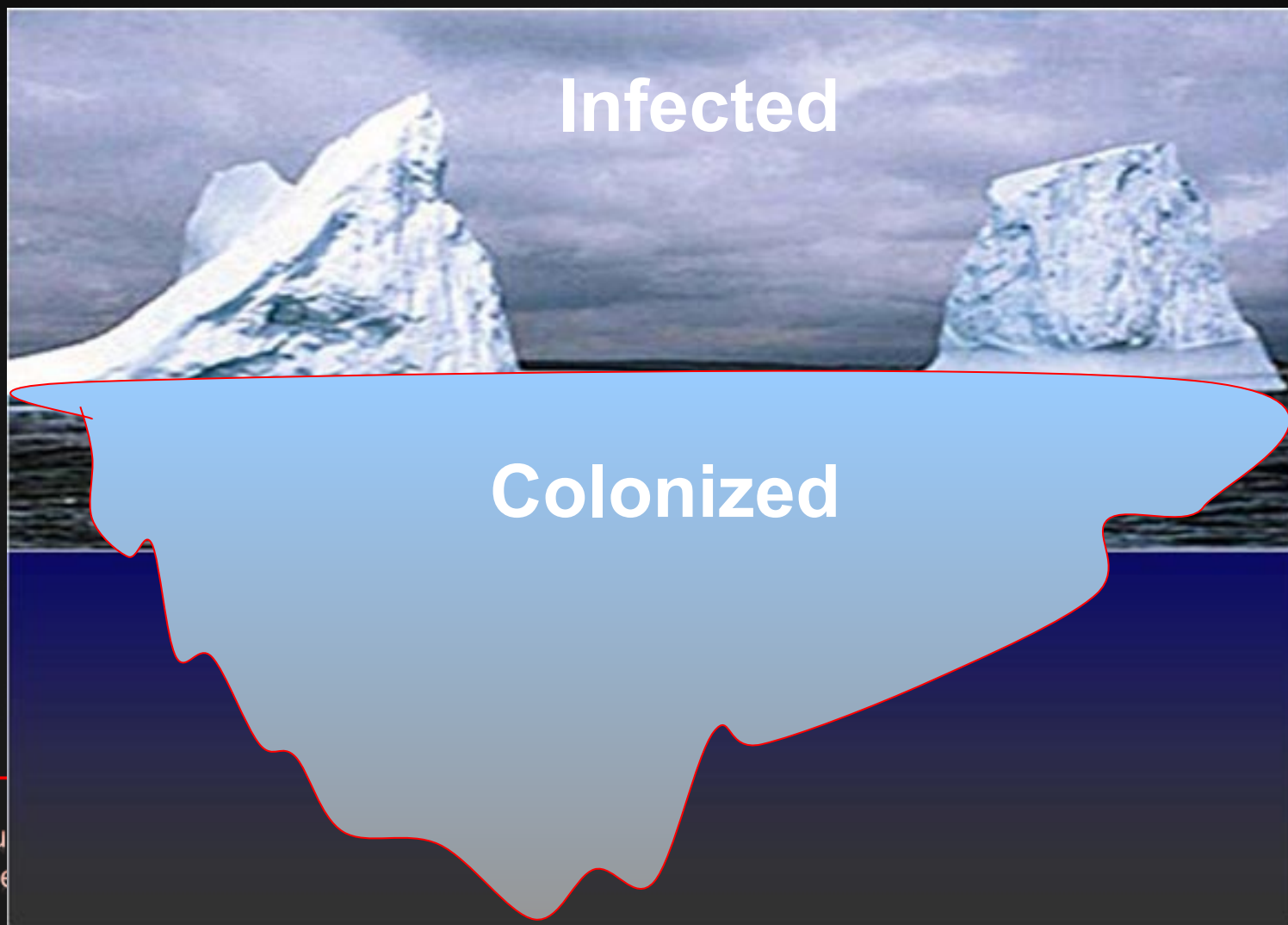
changes

increased contact

antibiotics



The Iceberg Effect



MDR bacteria are everywhere!

X represents VRE culture positive sites



Università degli Studi di Genova
Dipartimento di Scienze Mediche
Genoa, Italy

fettive
RCCS
a, Italy



Prevent Person to Person Transmission

- ❑ Health Care Facility:
 - Use standard infection control precautions
 - Follow airborne, droplet and contact precautions
 - When in doubt, consult infection control experts
- ❑ Community Setting
 - Stay home when you are sick
 - **Keep your hands clean**
 - Set an example



1st principle of infection prevention

□ *at least 35-50% of all healthcare-associated infections are associated with only 5 patient care practices:*

- Use and care of urinary catheters
- Use and care of vascular access lines
- Therapy and support of pulmonary functions
- Surveillance of surgical procedures
- **Hand hygiene and standard precautions**



**If healthcare-associated bugs would look like this -
compliance with hand hygiene would be 100%!!!**



Prevenzione



1. Igiene delle mani

2. Sanificazione degli ambienti

3. DPI: guanti, mascherine, calzari

4. Gestione ottimale dei dispositivi (CVC, CV): inserzione antisettica, manutenzione appropriata, rimozione tempestiva

5. Antimicrobial stewardship



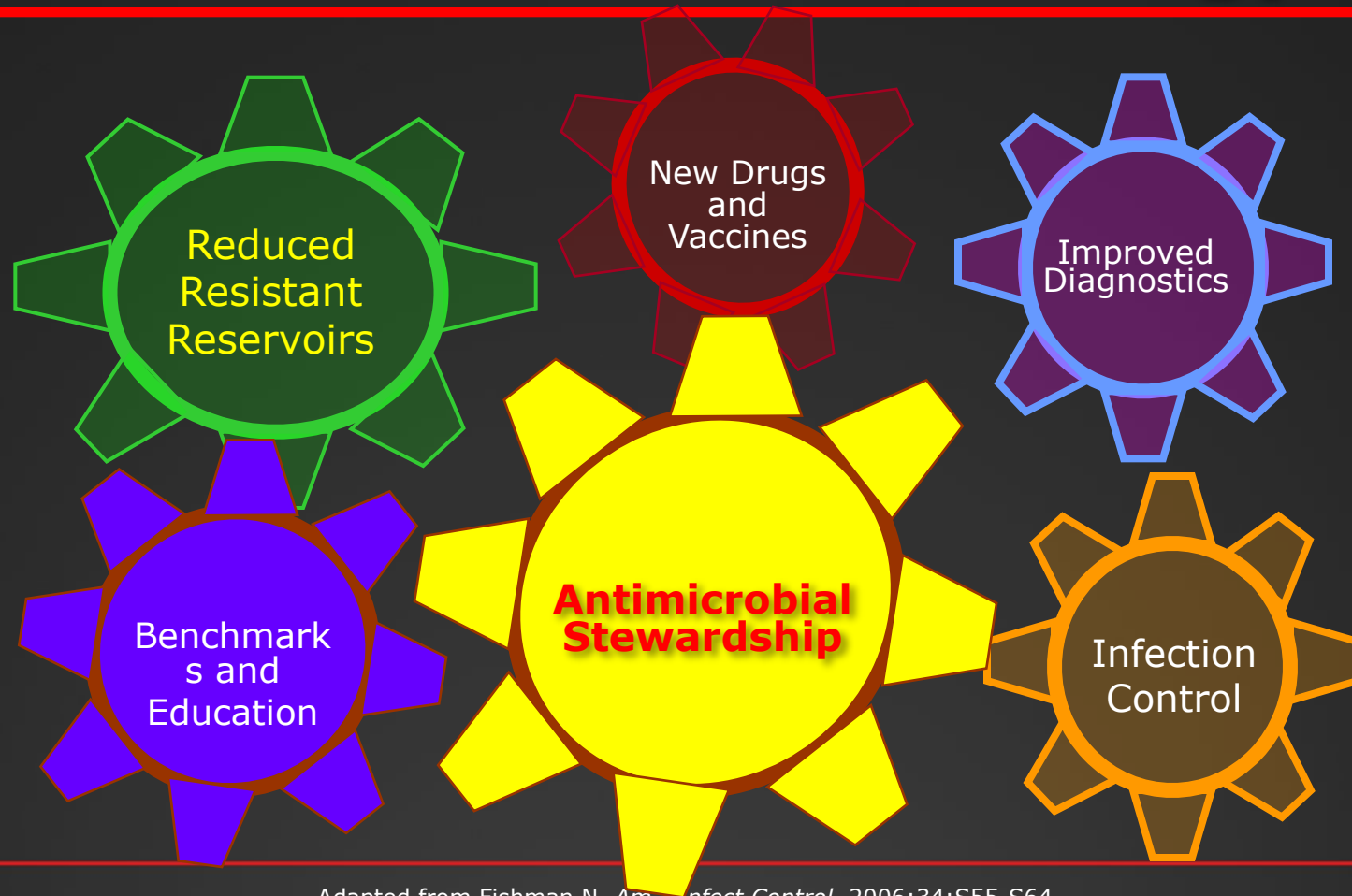
Cosa implementare

- 1. Educazione del personale sanitario:** igiene delle mani frequente, corretto utilizzo di DPI e dei dispositivi sanitari
- 2. Conoscenza dell'epidemiologia locale:** antimicrobial stewardship
- 3. Regolare ed efficace sanificazione degli ambienti:** prodotti che non inducano sviluppo di cross-resistenze con antibiotici (es metodi di sanificazione basati sull'utilizzo di probiotici, PCHS)



Antibiotic Stewardship:

A Multi-Factorial Strategy



Adapted from Fishman N. *Am J Infect Control*. 2006;34:S55-S64.



Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy



Evolution of the ID Clinician's Role



ID Clinician and Consultant



Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy



ID Consultant

Clinical Infectious Diseases

VIEWPOINTS



H.U.S.T.L.E: A Consult Fitness Guide for Infectious Diseases Providers

Gonzalo Bearman^{1,2} and Priya Nori^{2,3}

Being a good ID physician today means not only delivering high-quality clinical care, but also **strategically managing time, requests, and priorities to work efficiently and maximize impact**

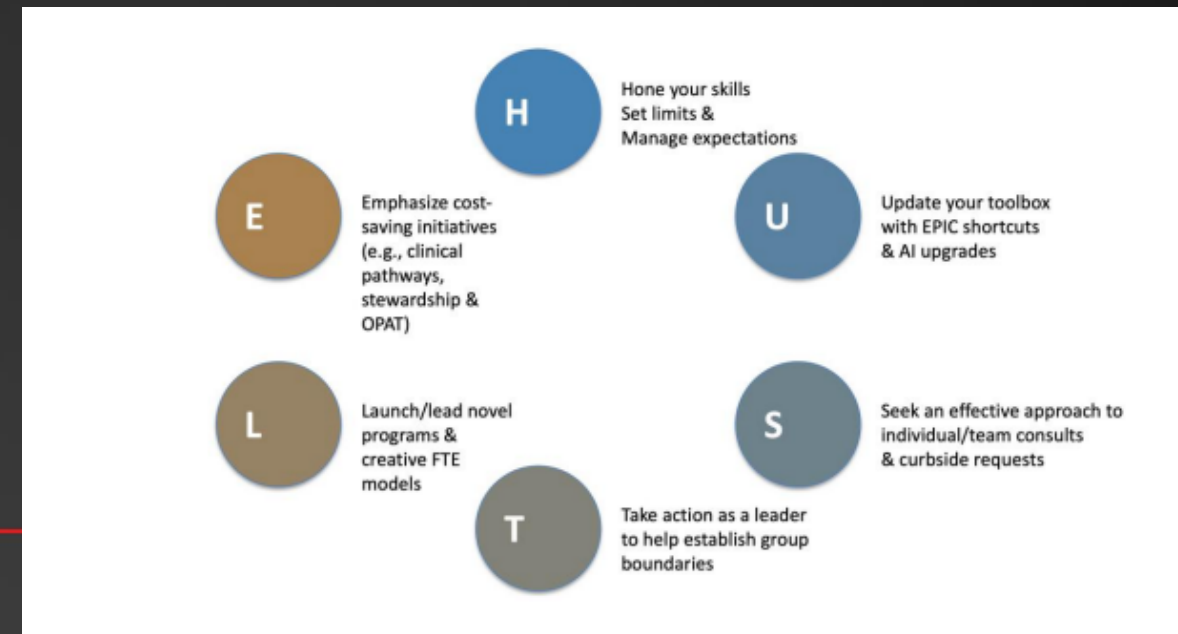
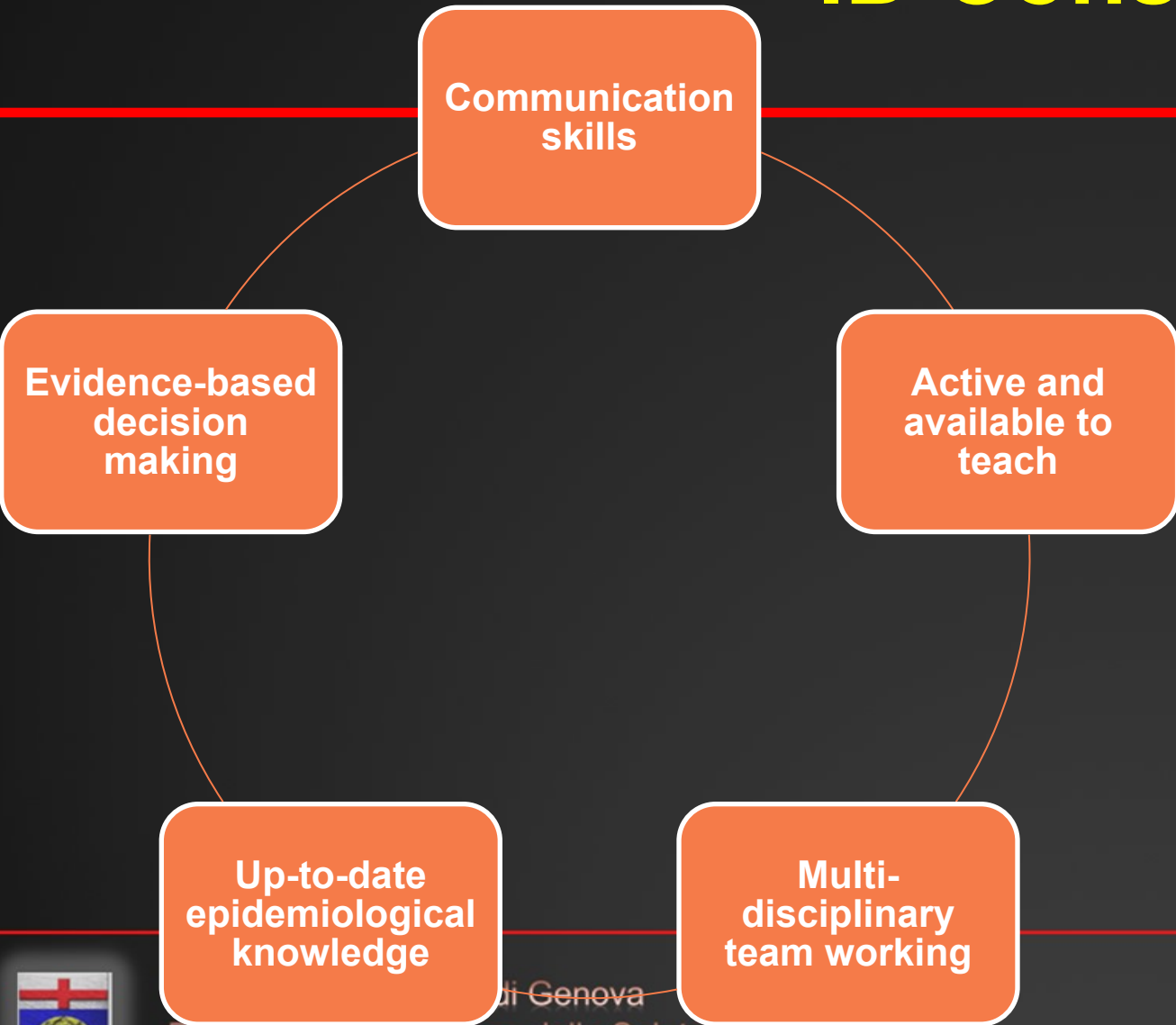


Figure 1. H.U.S.T.L.E: A consult fitness framework for infectious diseases providers.



ID Consultation Impact



Effect of infectious disease consultation on mortality and treatment of patients with candida bloodstream infections: a retrospective, cohort study

Carlos Mejia-Chew, Jane A O'Halloran, Margaret A Olsen, Dustin Stwalley, Ryan Kronen, Charlotte Lin, Ana S Salazar, Lindsey Larson, Kevin Hsueh, William G Powderly, Andrej Spec

✓ **Reduced mortality through improved management and appropriate antibiotic use**



Antimicrobial Agents and Chemotherapy

CLINICAL THERAPEUTICS
October 2016 Volume 60 Issue 10
<https://doi.org/10.1128/aac.00439-16>

Impact of Infectious Diseases Consultation on Clinical Outcomes of Patients with *Staphylococcus aureus* Bacteremia in a Community Health System

R. Brigg Turner^{a,b}, Elena Valcarlos^a, Regina Won^c, Eric Chang^c, Jacqueline Schwartz^b

✓ **Lower 90-day mortality**
✓ **Improved management:** appropriate AFT, source control, adherence to recommended diagnostic evaluations

Open Forum Infectious Diseases

MAJOR ARTICLE



OXFORD

Impact of Infectious Diseases Consultation on the Outcome of Patients With Enterococcal Bacteremia: A Systematic Literature Review and Meta-analysis

Joseph Tholany,^{1,6} Takaaki Kobayashi,¹ Alexandre R. Marra,^{1,2,3} Marin L. Schweizer,^{1,2} Riley J. Samuelson,⁴ and Hiroyuki Suzuki^{1,2}

✓ **Lower treatment failure**, including lower mortality and recurrence rates
✓ **Improved adherence to quality-of-care indicators**, even in resource-limited hospitals



Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Mejia-Chew et al. The Lancet. Infe dis 2019
Tholany, OFID 2022
Turner et al AAC. 2016

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy



CM vs ID specialty training

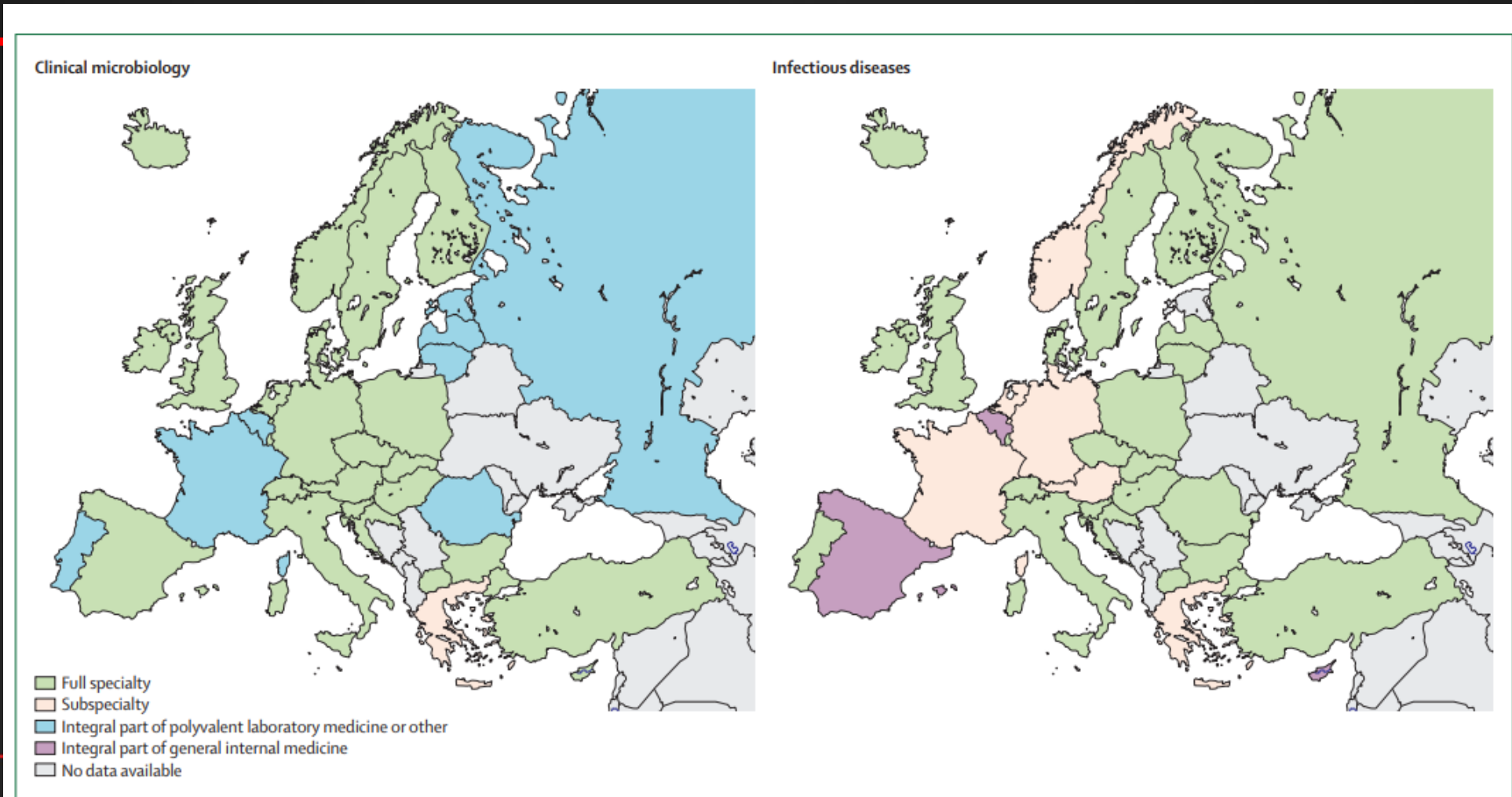
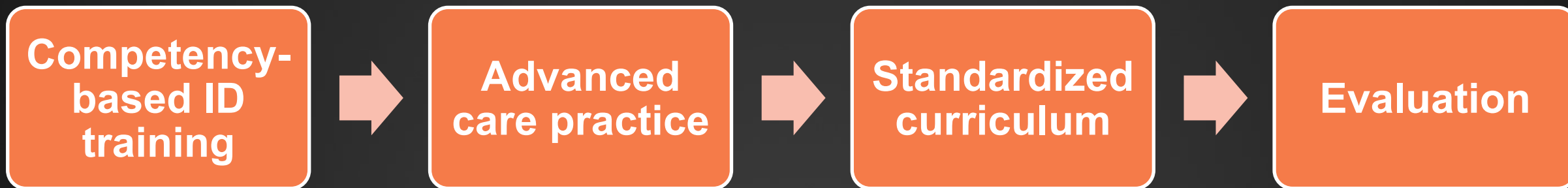


Figure: Recognition of clinical microbiology and infectious disease specialties by the European Union



We need STANDARDS!



Role of ID clinician, today

Combatting
AMR

Leading AMS
programs

Strengthening
infection prevention
and control

Managing
emerging IDs



Addressing
misinformation

Contributing to public
health policy and
preparedness

Integrating One
Health approach

Teaching to new
generations



Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Personal opinion

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

