La stewardship antimicrobica in ospedale ed in comunità

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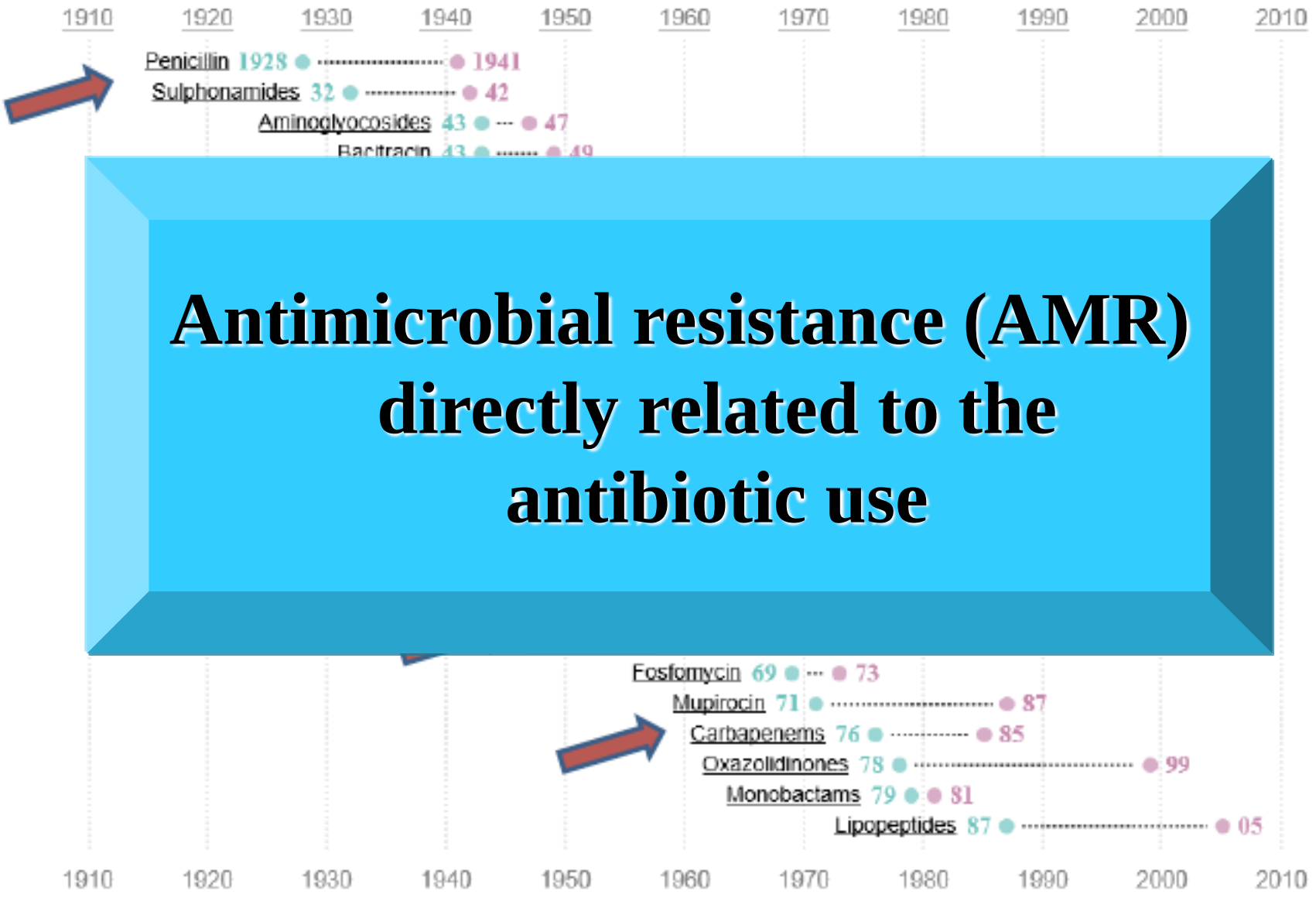
Disclosures 2022-2023

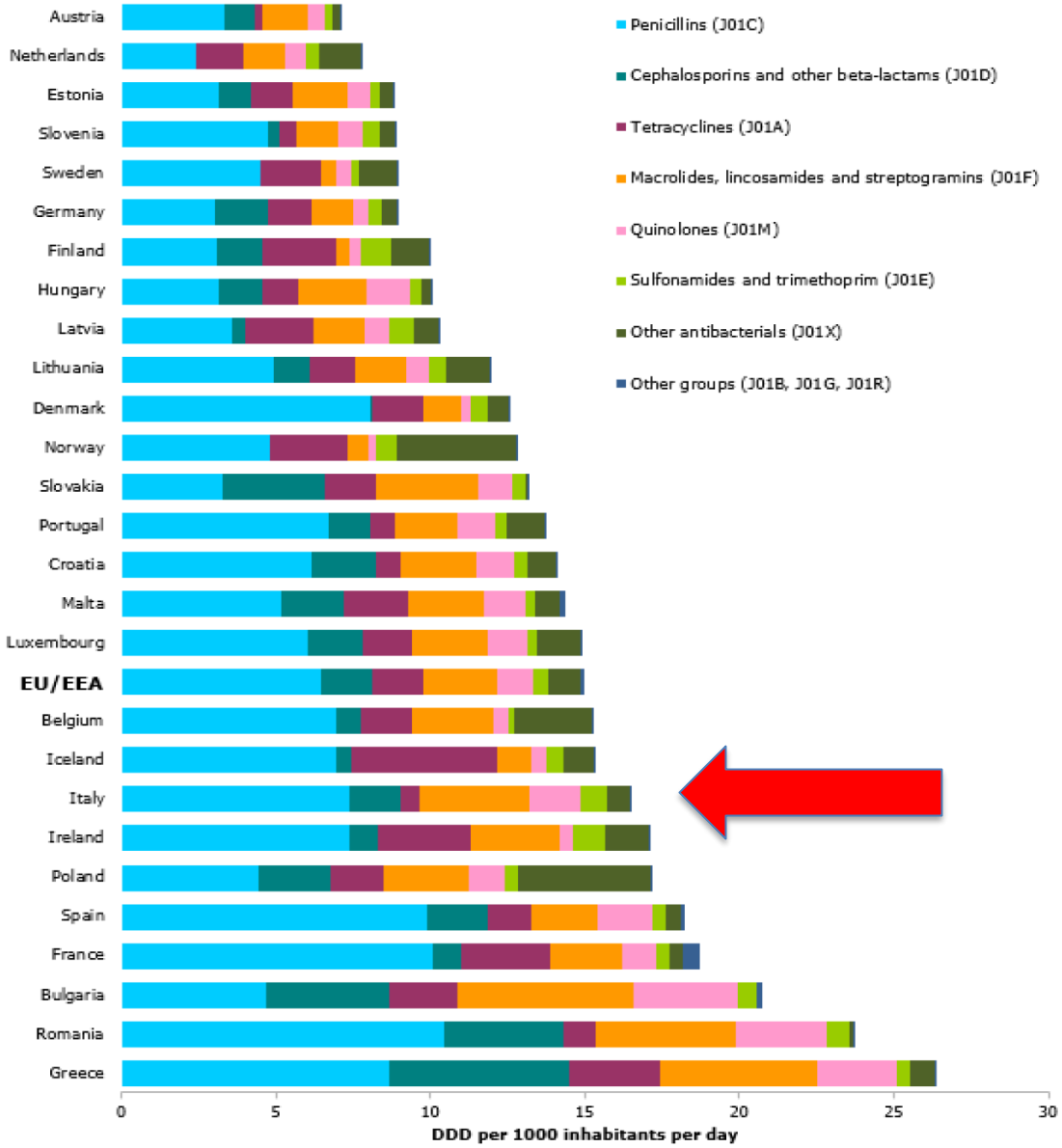
- **Advisory Board**: AstraZeneca, Roche
- **Speaker/chairman**: AstraZeneca
- **Events Sponsorshi**p: Angelini, AstraZeneca, Advanz Pharma, Gilead, Pfizer, MSD, Shionogi, Menarini, ViiV, Janssen, BioMerieux, Thermofisher

A history of resistance



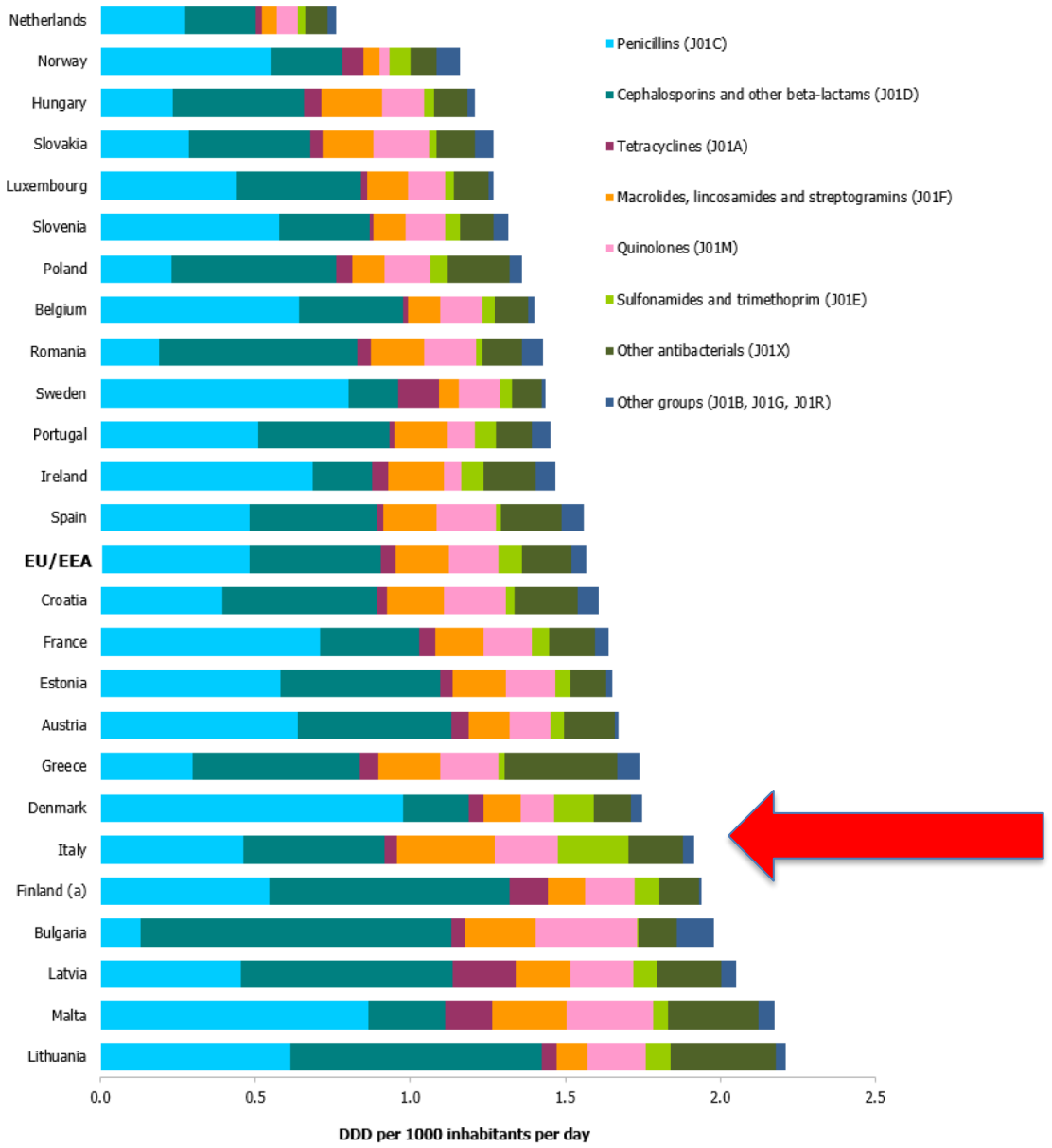
Antimicrobial resistance (AMR) directly related to the antibiotic use

Figure 2. Community consumption of antibacterials for systemic use (ATC group J01) at ATC group level 3, by country, EU/EEA, 2020 (expressed as DDD per 1 000 inhabitants per day)



EU/EEA refers to the corresponding population-weighted mean consumption based on the reported community data for 2020 (27 countries).

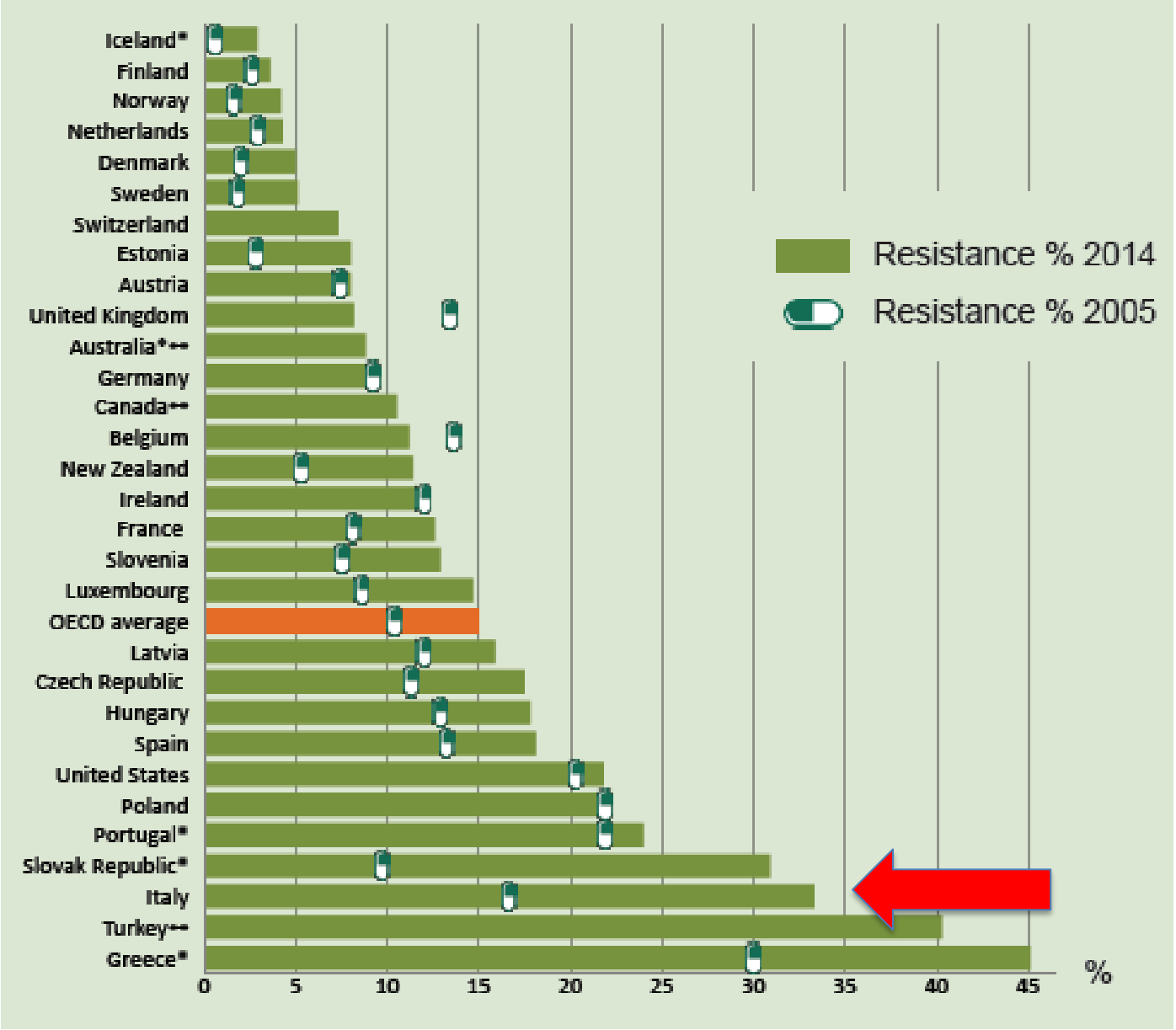
Figure 4. Hospital sector consumption of antibacterials for systemic use (ATC group J01), by country and ATC group, EU/EEA, 2020 (expressed as DDD per 1 000 inhabitants per day)



(a) Finland: data include consumption in remote primary healthcare centres and nursing homes.

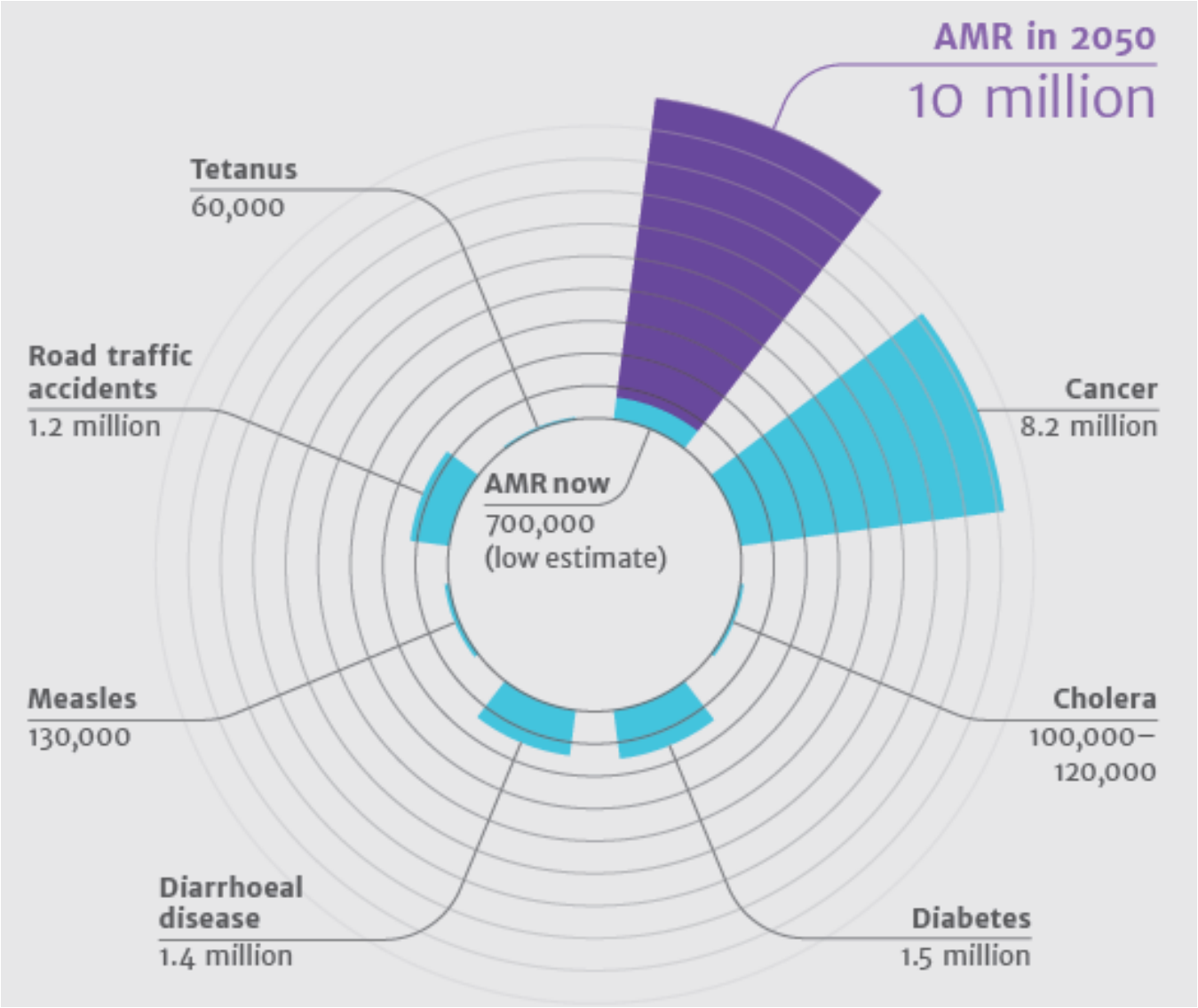
EU/EEA refers to the corresponding population-weighted mean consumption based on countries that provided hospital sector data for 2020 (25 countries).

AMR, Europe



OECD 2016

Stima della mortalità correlata alla AMR



Review on Antimicrobial Resistance. 2014

Consumo di antibiotici in Italia e ASP

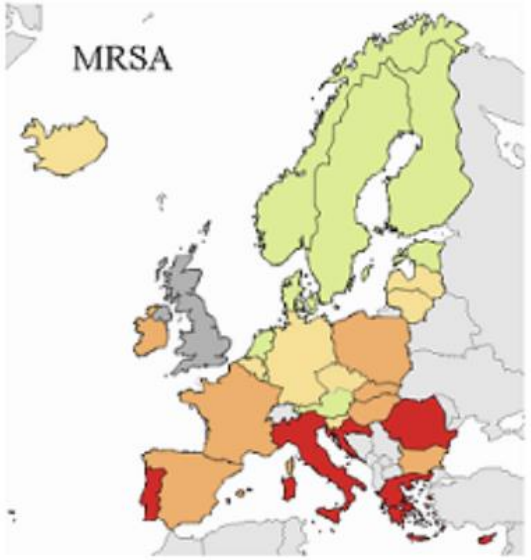
- **Il 90% del consumo di antibiotici è territoriale**
- **La genesi di germi MDR è prevalentemente ospedaliera**
- **La riduzione dell'uso degli antibiotici riduce l'emergenza di germi MDR**
- **La diagnostic stewardship ne riduce l'uso inutile e contiene la durata delle terapie**
- **L'infection control riduce le infezioni e la trasmissione di germi MDR**
- **Programmi di stewardship antimicrobica con infection control e diagnostic stewardship sono centrali in ospedale**
- **Nel territorio campagne di contenimento dei consumi sono possibili ed utili**

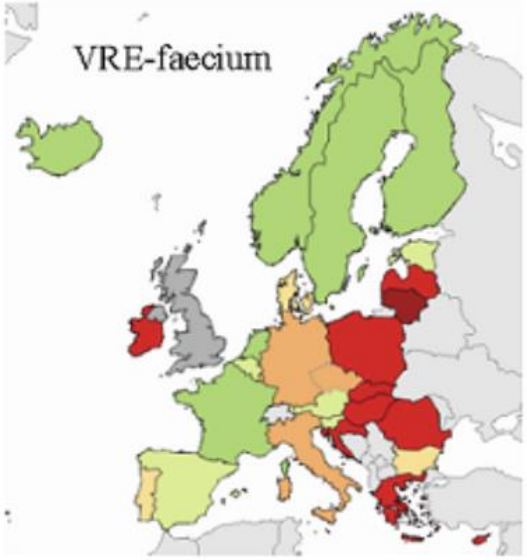
Emocolture: ARS-Rete SMART, Toscana

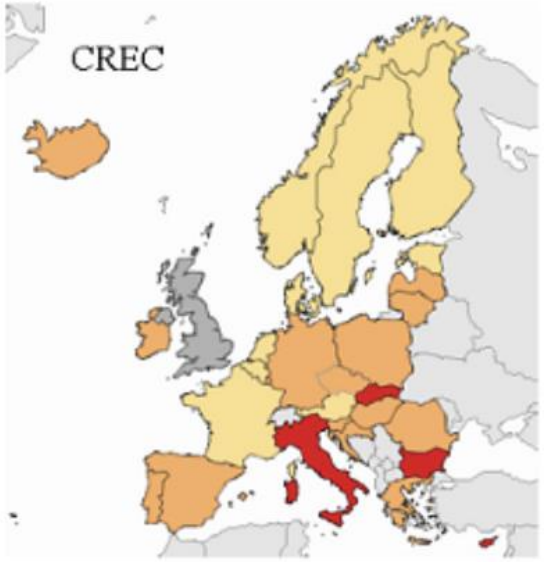
Tabella 1.3
Emocolture, numerosità delle specie sorvegliate, Toscana 2018 - 2021 – Fonte ARS-SMART

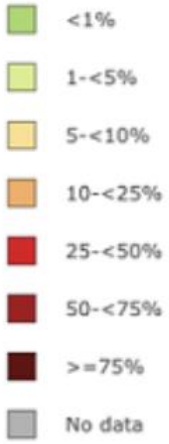
SPECIE n		2021		2020		2019		2018	
		%	n	%	n	%	n	%	
Gram +	*Staphylococcus aureus*	1572	18,3%	1295	17%	1312	18%	1315	17%
	Enterococcus faecalis	917	10,7%	805	11%	696	9%	740	10%
	Enterococcus faecium	560	6,5%	457	6%	389	5%	370	5%
	Streptococcus pneumoniae	72	0,8%	82	1%	192	3%	177	2%
Gram -	*Escherichia coli*	2450	28,5%	2234	30%	2503	33%	2570	34%
	Klebsiella pneumoniae	1389	16,1%	1168	16%	1172	16%	1050	14%
	Pseudomonas aeruginosa	663	7,7%	621	8%	511	7%	516	7%
	Acinetobacter spp.	281	3,3%	195	3%	170	2%	232	3%
Miceti	*Candida spp.*	700	8,1%	642	8,6%	541	7%	654	9%
Totale		**8604**	**100%**	**7499**	**100%**	**7486**	**100%**	**7624**	**100%**

Percentuale di isolati resistenti nelle 4 combinazioni patogeno/antiobiotico principali sotto osservazione (2020)









MRSA: *S. aureus* resistente alla meticillina

VRE-faecium: *E. faecium* resistente alla vancomicina

CREC: *E. coli* resistente alle cefalosporine di terza generazione

CRKP: *K. pneumoniae* resistente ai carbapenemi

Fonte dati e immagini: ECDC Surveillance Atlas of Infectous Disease
https://www.ecdc.europa.eu/en/antimicrobial-resistance/surveillance-and-disease-data/data-ecdc

CAUSES OF ANTIBIOTIC RESISTANCE

Over-prescribing of antibiotics

Patients not taking antibiotics as prescribed

Unnecessary antibiotics used in agriculture

Poor infection control in hospitals and clinics

Poor hygiene and sanitation practices

Lack of rapid laboratory tests

#AntibioticResistance
www.who.int/drugresistance

Le direttrici principali e le criticità * della resistenza antimicrobica (AMR)

Determinanti/criticità *	Obiettivo	Strumenti
Pressione selettiva antibiotici	Ridurre uso improprio	Antimicrobial & Diagnostic Stewardship
Diffusione crociata microrg. resistenti	Contenimento	Infection Control
Carenza nuovi farmaci *	Rilancio ricerca IF	Nuove regole, fast-track, incentivi economici
Carenza strategie terapeutiche validate*	Acquisire evidenze scientifiche	Fondi per la ricerca indipendente

Contenere la pressione selettiva degli antibiotici

Contrastare l'uso empirico:

- Raccomandazioni per la profilassi in chirurgia
- Protocolli condivisi di terapia ABT per gruppi di pazienti/patologie basati sulla epidemiologia locale
- Diagnosi microbiologica rapida ed accurata
- **Programmi di Stewardship Antimicrobica (ASP)**

What is Antimicrobial Stewardship?

- Institution-wide comprehensive antimicrobial management program intended to **improve patient outcomes from infection while minimizing negative consequences such as healthcare associated infections, and limiting the development of bacterial resistance**
- A multidisciplinary approach
- Focuses on: through the **optimal diagnosis, drug selection**, **dosage, de-escalation** and **duration** (the so called 5 “Ds” of antimicrobial stewardship)

Dellit TH. Clin Infect Dis 2007 Jan 15; 44(2):159

Antimicrobial Stewardship

AS: the governance of antimicrobial therapy

Tamma PD, Cosgrove SE. Infect Dis Clin N Amer 2011; 25: 245-60

Antimicrobial Stewardship Program Goals

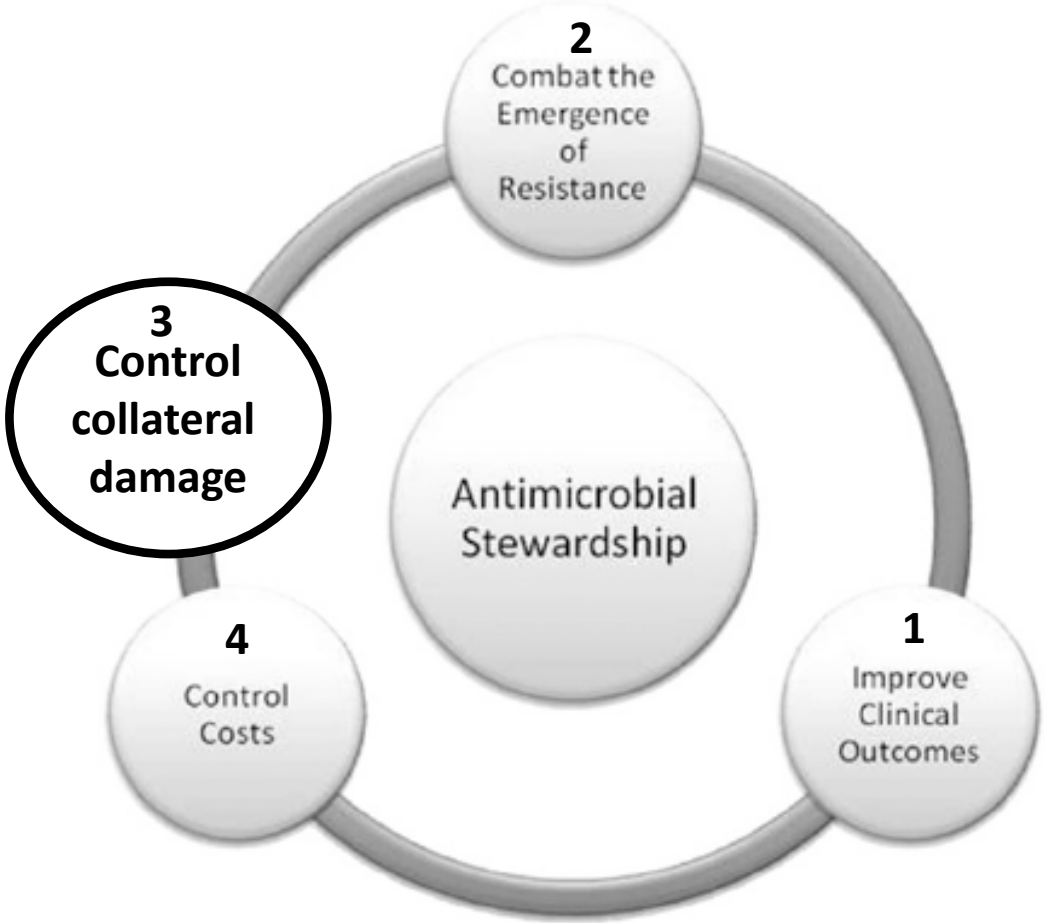


Figure 1. Goals that antimicrobial stewardship strives to achieve.

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

ASP rationale

- **The need to balance two conflicting goals:**

1. **the provision of therapy that is adequate to treat documented or presumed infection, and**
2. **the minimization of antimicrobial use to avoid adverse drug events (e.g., *Clostridium difficile* infection and allergy) and the emergence of antimicrobial resistance, and to reduce costs.**

List of interventions considered as part of antimicrobial stewardship

Table 1. List of interventions considered as part of antimicrobial stewardship[9,11,12]

Intervention*	Description/comment	Healthcare setting
Formulary restriction	Antibiotics may be prescribed only: • For certain approved clinical indications • By certain physicians (i.e., infectious diseases specialists)	Inpatient/outpatient
Drug preauthorization	Permission (from ASP team member or infectious diseases specialist) required for release of certain antibiotics. Often implemented together with formulary restriction.	Inpatient/outpatient
Prospective audit and feedback	Case review by trained ASP team member and feedback of recommendations if reviewed antibiotics are deemed to be inappropriately prescribed. Labor-intensive.	Inpatient
Prescriber education	More effective as a supplementary strategy to other interventions.	Inpatient/outpatient
Patient education	Usually focus groups or mass media campaigns.	Outpatient
Clinical guidelines	Treatment protocols for various infections – may be institution-specific	Inpatient/outpatient
Clinical decision support systems	Information technology systems for improving antibiotic prescription. Requires existing electronic records and electronic prescribing system to be effective.	Inpatient/outpatient
Point of care diagnostic tests	Mostly undergoing research evaluation. Diagnosis of non-bacterial etiologies may help reduce antibiotic prescription.	Inpatient/outpatient
Microbiology laboratory susceptibility reporting	Selective reporting of susceptibility profiles for positive cultures may dramatically alter prescribing patterns of physicians.	Inpatient/outpatient
Antimicrobial cycling	Substitution of selected antibiotics over pre-defined periods. Little clear evidence for efficacy.[12]	Inpatient

Strategies To Improve Antimicrobial Prescribing

Restrictive strategy uses interventions that either prevent or provide a 'barrier' to prescribing or administering an antibiotic

Persuasive strategy uses interventions that attempt to persuade healthcare professionals to prescribe appropriately by addressing underlying knowledge deficiencies and/or attitudes and/or behavior's

ASP: Process & Outcome Measures

Process Measures	Outcome Measures
Excess days of therapy (ie, unnecessary days of therapy avoided based on accepted targets and benchmarks)[a]	Hospital length of stay
Duration of therapy	30-day mortality
Proportion of patients compliant with facility-based guideline or treatment algorithm[a]	Unplanned hospital readmission within 30 d
Proportion of patients with revision of antibiotics based on microbiology data	Proportion of patients diagnosed with hospital-acquired *Clostridium difficile* infection or other adverse event(s) related to antibiotic treatment[a]
Proportion of patients converted to oral therapy	Proportion of patients with clinical failure (eg, need to broaden therapy, recurrence of infection)

Ruolo del Laboratorio di Microbiologia

- Nuove tecnologie: «fast microbiology»
- Riduzione tempi di identificazione ed ABG
- **ABG genotipico vs. fenotipico**
- Report per paziente vs. report per campione
- Sorveglianza epidemiologica (ARS-SMART, Toscana)
- Alert system

Molecular genotyping

Molecular ATBG	Species	Report
KPC + **NDM –** **VIM –** **OXA –** **CTX-M -**	**Enterobacteriaceae**	***Presence of the KPC carbapenemases gene: high probability of resistance to ALL BETALACTAM ANTIBIOTICS except: CEFTAZIDIME/AVIBACTAM***
KPC – **NDM +** **VIM –** **OXA –** **CTX-M -**	**Enterobacteriaceae**	***Presence of the NDM carbapenemases gene: high probability of resistance to ALL BETALACTAM ANTIBIOTICS except for AZTREONAM (to be combined with avibactam)***

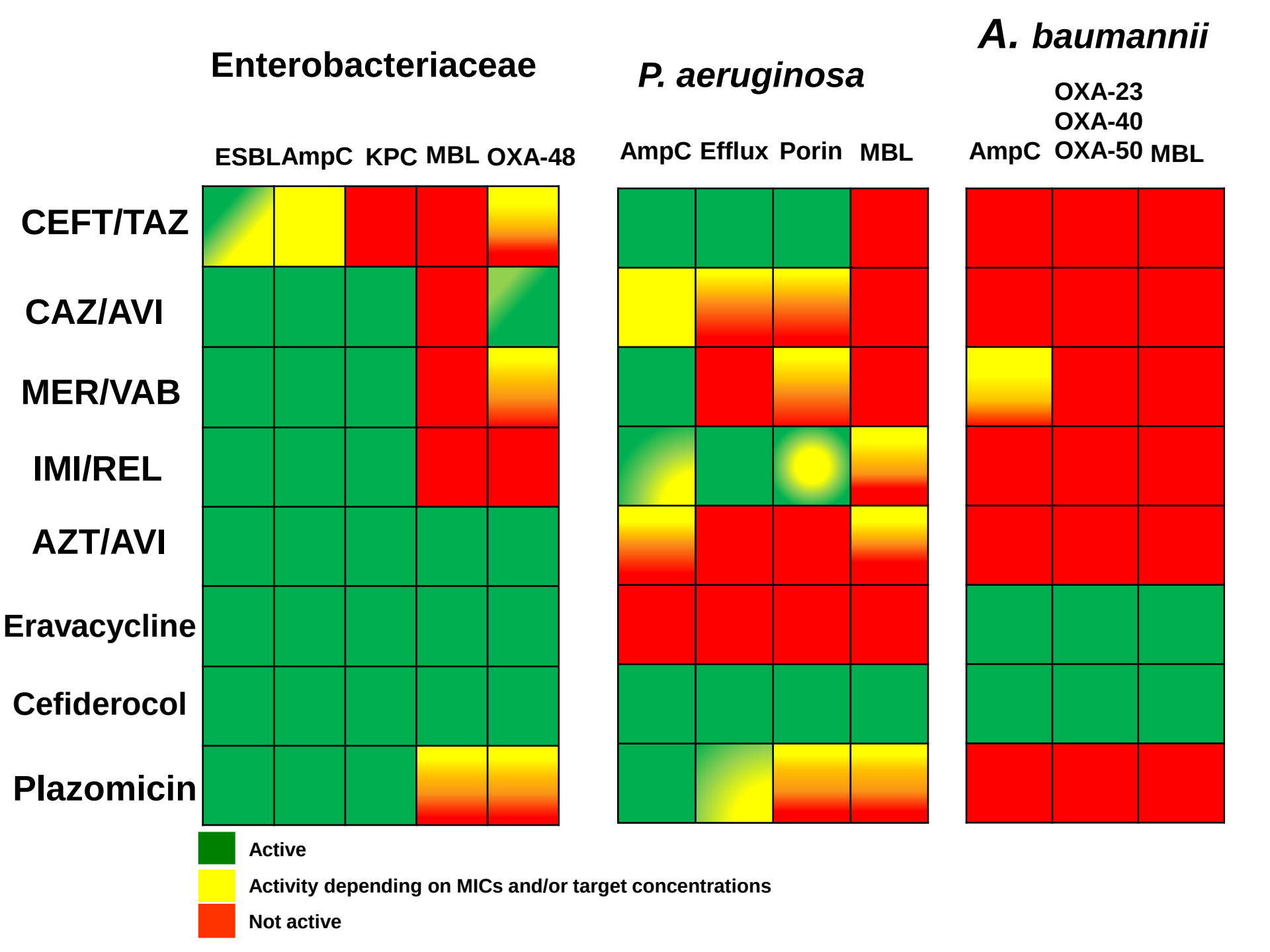
Antibiotic choice for MDR Enterobacteriaceae and non-fermenting GNB depending on genotype

	Enterobacteriaceae					*P. aeruginosa* (except for MBL)	*A. baumannii*
	ESBL	AmpC	KPC	OXA-48	IMP/VMP /NDM		
Piperacillin–tazobactam							
Imipenem/meropenem							
Cefepime							
Ceftazidime							
Aztreonam							
Colistin							
Tigecycline							
Aminoglycosides							

Active

Activity depending on MICs and/or target concentrations

Not active


Enterobacteriaceae
P. aeruginosa
A. baumannii
ESBL
AmpC
KPC
MBL
OXA-48
AmpC
Efflux
Porin
MBL
AmpC
OXA-23
OXA-40
OXA-50
MBL
CEFT/TAZ
CAZ/AVI
MER/VAB
IMI/REL
AZT/AVI
Eravacycline
Cefiderocol
Plazomicin
Active
Activity depending on MICs and/or target concentrations
Not active

Antibiotic choice for MDR Enterobacteriaceae and non-fermenting GNB depending on genotype

Table 1. Microbiological targets.

	ESBL	KPC	MBL	AmpC	OXA-48	*P. aeruginosa* (MDR/XDR)	*Acinetobacter* (MDR/XDR)	*S. maltophilia*
Aztreonam/avibactam								
Cefepime/enmetazobactam								
Cefepime/taniborbactam								
Cefepime/zidebactam								
Cefiderocol								
Ceftaroline/avibactam								
Ceftolozane/tazobactam								
Ceftazidime/avibactam								
Imipenem/relebactam								
Meropenem/nacubactam								
Meropenem/vaborbactam								

Green = antimicrobial activity, red = no antimicrobial activity, yellow = partial antimicrobial activity, grey = not available. ESBL = extended-spectrum β-lactamase, Ambler Class A β-lactamases; KPC = *Klebsiella pneumoniae* carbapenemase, Ambler Class A β-lactamases; MBL = metallo-β-lactamases, Ambler Class B β-lactamases; AmpC = cephalosporinase, Ambler Class C β-lactamases; OXA-48 = oxicillinase-48, Ambler Class D β-lactamases; MDR = multidrug resistant; XDR = extended drug resistant.

Pharmaceuticals **2022**, *15*, 463

Gene-oriented antibiotic therapy for Enterobacterales

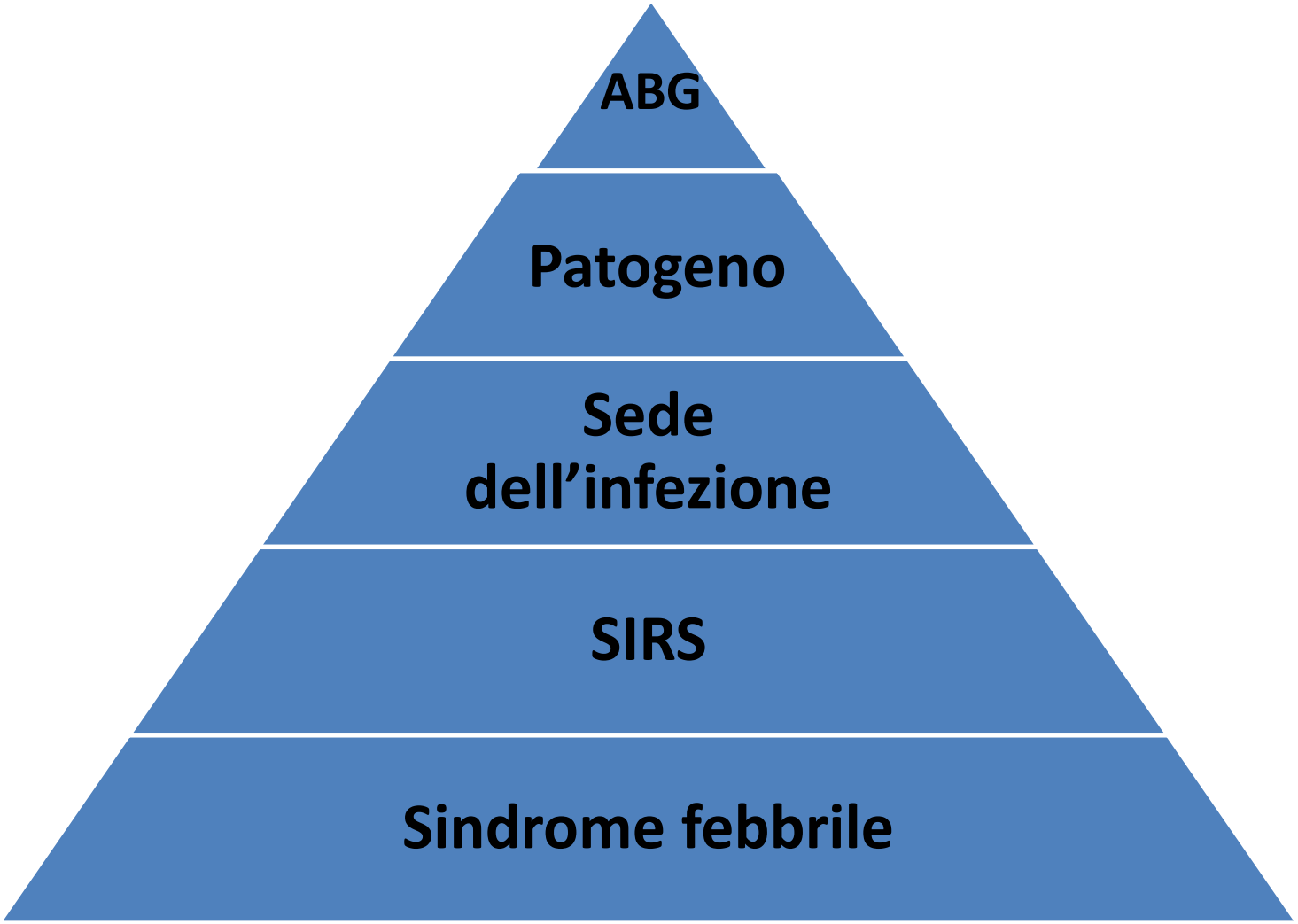
Molecular ATBG

CTX –	CTX +	CTX –	CTX –	CTX –
OXA 48 –	OXA 48 –	**OXA 48 +**	OXA 48 –	OXA 48 –
KPC –	KPC –	KPC –	**KPC +**	KPC –
NDM –	NDM –	NDM –	NDM –	**NDM +**
VIM –	VIM –	VIM –	VIM –	VIM –
IP -	IP -	IP -	IP -	IP -
Pipera/tazo	**Meropenem** or **Ceftolozane/ tazobactam 3 g TID (*E. coli*)** or **Ceftazidime/ avibactam (*K. pneumoniae*)**	**CAZAVI or Cefiderocol** or Meropenem +/- Tigecicyine +/- Fosfomycin	**CAZAVI or Vaborem (+ fosfo)** or Colistin +/- Tigecyline +/- Fosfomycin	**CAZAVI or Vaborem/ avibactam** or **Cefiderocol** or Colistin + Fosfomycin +/- Tigecycline

Appropriatezza della terapia antimicrobica

1. **Livello di evidenza diagnostica**
2. **Modalità prescrittiva della terapia antibiotica**
3. **Scelta dell'antibiotico** (LG, raccomandazioni locali, Sanford Guide, altro)
4. **Dosaggio** (età, peso, funzione renale, etc.)
5. **Via di somministrazione** (parenterale, orale)
6. **Modalità di somministrazione** (bolo, infusione estesa, infusione continua)
7. **Durata della terapia** (predefinita, variabile)
8. **Outcome del paziente** (sopravvivenza, cura, recidiva)

1. Livello di evidenza diagnostica



2. Modalità di scelta ATBT

- Tera
- Tera
- Tera
- Profi
- Altro

Larga prevalenza di terapie empiriche, per febbre……

30% quota stimata di ATBT inappropriata

3. Scelta dell'antibiotico

- Profilo di **efficacia e tollerabilità**
- Congrua con le indicazioni di Linee-guida validate ed aggiornate (SNLG)
- Ispirata a "raccomandazioni locali", divisate dal gruppo per l'ASP, su base epidemiologica
- Scelta del professionista (Sanford Guide, altro)
- Scelta della molecola a minor costo nell'ambito della stessa classe o delle stesse indicazioni
- **Scelta della molecola che offra la durata più breve del ciclo terapeutico**

Antibiotics: Acces-Watch-Reserve (AWARE)

[1] WHO Priority Pathogens List

Antibiotic	Class	ATC code	Category	Listed on EML 2021
Aztreonam	Monobactams	J01DF01	Reserve	No
Carumonam	Monobactams	J01DF02	Reserve	No
Cefiderocol	Other-cephalosporins	J01DI04	Reserve	Yes
Ceftaroline-fosamil	Fifth-generation cephalosporins	J01DI02	Reserve	No
Ceftazidime/avibactam	Third-generation-cephalosporins	J01DD52	Reserve	Yes
Ceftobiprole-medocaril	Fifth-generation cephalosporins	J01DI01	Reserve	No
Ceftolozane/tazobactam	Fifth-generation cephalosporins	J01DI54	Reserve	No
Colistin_IV	Polymyxins	J01XB01	Reserve	Yes
Colistin_oral	Polymyxins	A07AA10	Reserve	No
Dalbavancin	Glycopeptides	J01XA04	Reserve	No
Dalfopristin/quinupristin	Streptogramins	J01FG02	Reserve	No
Daptomycin	Lipopeptides	J01XX09	Reserve	No
Eravacycline	Tetracyclines	J01AA13	Reserve	No
Faropenem	Penems	J01DI03	Reserve	No
Fosfomycin_IV	Phosphonics	J01XX01	Reserve	Yes
Iclaprim	Trimethoprim-derivatives	J01EA03	Reserve	No
Imipenem/cilastatin/relebactam	Carbapenems	J01DH56	Reserve	No
Lefamulin	Pleuromutilin	J01XX12	Reserve	No
Linezolid	Oxazolidinones	J01XX08	Reserve	Yes
Meropenem/vaborbactam	Carbapenems	J01DH52	Reserve	Yes
Minocycline_IV	Tetracyclines	J01AA08	Reserve	No
Omadacycline	Tetracyclines	J01AA15	Reserve	No
Oritavancin	Glycopeptides	J01XA05	Reserve	No
Plazomicin	Aminoglycosides	J01GB14	Reserve	Yes
Polymyxin-B_IV	Polymyxins	J01XB02	Reserve	Yes
Polymyxin-B_oral	Polymyxins	A07AA05	Reserve	No
Tedizolid	Oxazolidinones	J01XX11	Reserve	No
Telavancin	Glycopeptides	J01XA03	Reserve	No
Tigecycline	Glycylcyclines	J01AA12	Reserve	No

4. Dosaggio

- **Dose congrua** per età, peso, funzione renale, insufficienza epatica, sede dell'infezione
- **Età**: dosaggio pediatrico
- **Peso**: dosi "fisse" o mg/Kg
- **Funzione renale**: dose singola ed intervallo delle somministrazioni variabili
- **CAPD, CRRT**
- **Insufficienza epatica**
- **Sede dell'infezione**: meningite, ascesso etc.

4. Via di somministrazione

- Orale
- Parenterale IV, CVC o altra linea IV
- Parenterale-orale sequenziale
- **Orale in alternativa alla parenterale**
- Areosolica (device)
- Congrua con caratteristiche del paziente e della sede d'infezione
- Considera la compliance ed i rischi del CVC

5. Modalità di somministrazione

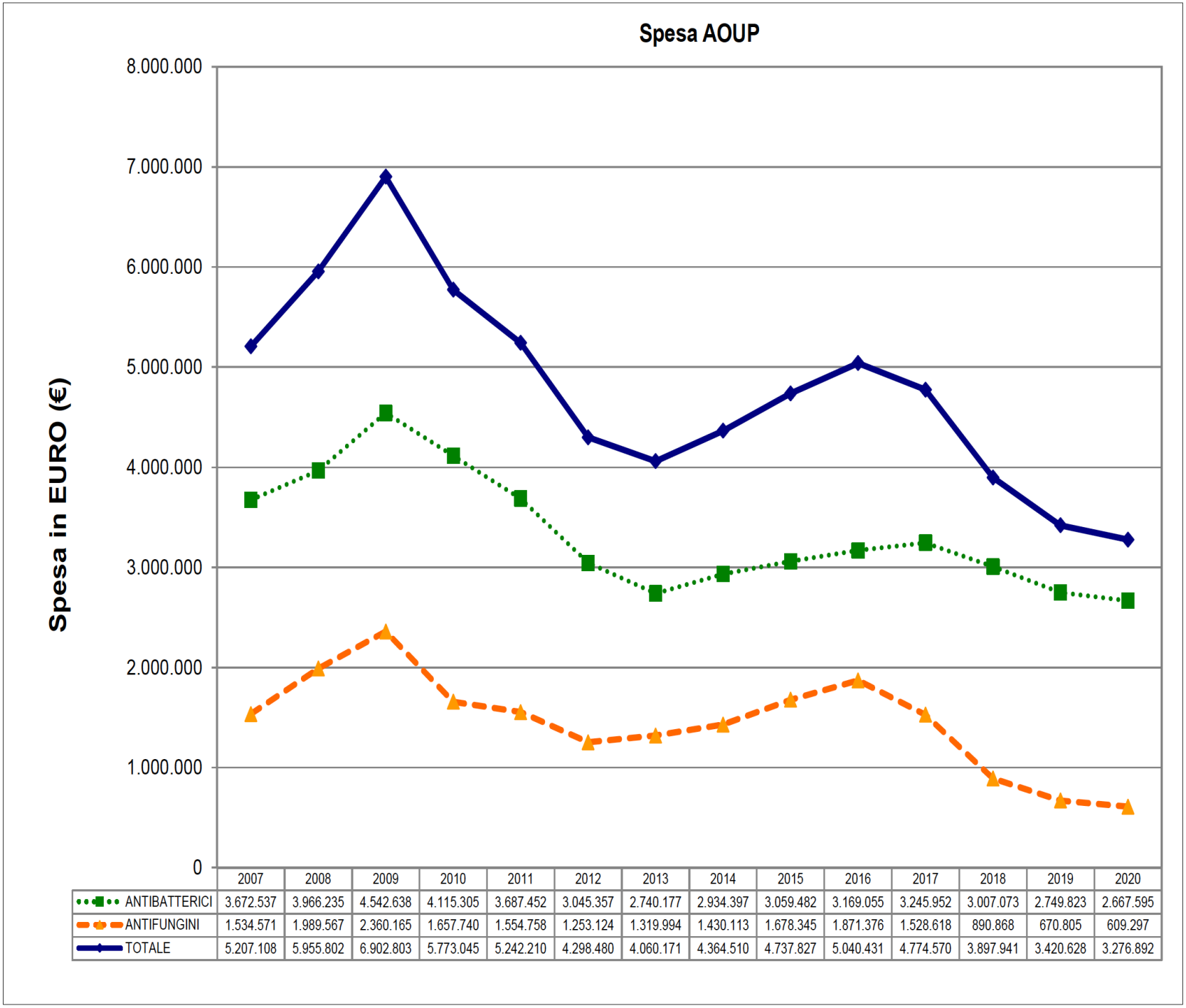
- Congruo con le caratteristiche PK/PD del farmaco (tempo-dipendente, concentrazione-dipendente, misto)
- Dose da carico
- Bolo
- Infusione estesa
- Infusione continua (ICU)

6. Durata della ATBT

- Uno dei campi più inesplorati dalla ricerca clinica
- LG indicano durate estese e “fisse” (ad es.: per endocarditi, infezioni osteo-articolari, etc)
- Prevale giudizio clinico sul singolo paziente (defervescenza per 3-5 giorni, miglioramento clinico)
- **Terapie di più breve durata: meno impatto sulla flora intestinale (microbioma) e degenza più breve**
- Iniziali evidenze cliniche
- Metanalisi

Primary ASP metrics

- **Antimicrobial use & cost**
- **Impact on microbiological resistance**
- **Clinical outcomes (cure, mortality)**
- **Adverse events of antibiotic therapy (*C.difficile*.)**
- **Duration of antibiotic therapy**
- **Lenght of hospital stay (LOS)**



	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
ANTIBATTERICI	3.672.537	3.966.235	4.542.638	4.115.305	3.687.452	3.045.357	2.740.177	2.934.397	3.059.482	3.169.055	3.245.952	3.007.073	2.749.823	2.667.595
ANTIFUNGINI	1.534.571	1.989.567	2.360.165	1.657.740	1.554.758	1.253.124	1.319.994	1.430.113	1.678.345	1.871.376	1.528.618	890.868	670.805	609.297
TOTALE	5.207.108	5.955.802	6.902.803	5.773.045	5.242.210	4.298.480	4.060.171	4.364.510	4.737.827	5.040.431	4.774.570	3.897.941	3.420.628	3.276.892

Length of hospital stay (LOS)

- Outcome measure
- Easy to obtain metric
- Suffers from many of the same problems as mortality (secular trends in developed countries where an emphasis has been placed on early discharges)
- **Attempts to discontinue or transition to oral antimicrobial therapy from parenteral therapy has, perhaps, the strongest relationship to length of stay**

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

Table 2. Distribution of the Four Components of the Primary Composite Outcome.*

Component	Intravenous Treatment (N = 199)	Oral Treatment (N = 201)	Difference	Hazard Ratio (95% CI)
	number (percent)		*percentage points (95% CI)*	
All-cause mortality	13 (6.5)	7 (3.5)	3.0 (–1.4 to 7.7)	0.53 (0.21 to 1.32)
Unplanned cardiac surgery	6 (3.0)	6 (3.0)	0 (–3.3 to 3.4)	0.99 (0.32 to 3.07)
Embolic event	3 (1.5)	3 (1.5)	0 (–2.4 to 2.4)	0.97 (0.20 to 4.82)
Relapse of the positive blood culture†	5 (2.5)	5 (2.5)	0 (–3.1 to 3.1)	0.97 (0.28 to 3.33)

CONCLUSIONS

In patients with endocarditis on the left side of the heart who were in stable condition, changing to oral antibiotic treatment was noninferior to continued intravenous antibiotic treatment. (Funded by the Danish Heart Foundation and others; POET ClinicalTrials.gov number, NCT01375257.)

Iversen K, Ihlemann N, Gill SU, et al. Partial oral versus intravenous antibiotic treatment of endocarditis. N Engl J Med 2019; 380: 415-24. POET trial

The POET trial: length of hospital stay

- After randomization, pts were treated according to the assigned regimen **for a median of 19 days (interquartile range, 14 to 25) in the IV treated group and 17 days (interquartile range, 14 to 25) in the orally treated group.**
- **In the orally treated group, 160 patients (80%) were partially or completely treated as outpatients.**
- **After randomization, the median length of stay in the hospital (not a prespecified outcome) was 19 days (interquartile range, 14 to 25) in the IV treated group and 3 days (interquartile range, 1 to 10) in the orally treated group (P<0.001).**

Iversen K, Ihlemann N, Gill SU, et al. Partial oral versus intravenous antibiotic treatment of endocarditis. N Engl J Med 2019; 380: 415-24. POET trial

Endocarditis

Oral vs. IV Abx for Endocarditis

Author	Yr	N	Regimen (Oral vs. IV)	Success
Stamboulian	'91	30	Amox 1 gm qid vs. CTX—*Strep*	100% (15/15) v 100% (15/15)
Heldman	'96	93	Cipro + Rif vs. std IV—*Staph*	95% (18/19) v 88% (22/25)
Iversen/ Bungaard[†]	'19	400	Std oral vs. std IV—GPC	74% (146/199) v 62% (125/201)
*Tissot-Dupont**	*'19*	*341*	*TMP-SMX+clinda vs. std IV--Staph*	*81% (138/171) v 70% (119/170)*
Totals (N=3 RCTs)	523			77% (179/233) v 70% (162/241)
(+ 1 quasi expt)*	*(864)*			*78% (317/404) v 68% (281/411)*

*Quasi-experimental, pre-post study. Italicized totals include the quasi-experimental data.
[†]Iversen reported early follow up, Bungaard 3 year follow up from the same study.
Refs at https://www.bradspellberg.com/oral-antibiotics

Oral versus Intravenous Antibiotics for Bone and Joint Infection

Among the 1054 participants, treatment failure occurred in 74 of 506 participants (14.6%) in the intravenous group and 67 of 509 participants (13.2%) in the oral group.
The intention-to-treat analysis showed a difference in the risk of definitive treatment failure (oral group vs. intravenous group) of −1.4 percentage points (90% confidence interval [CI], −4.9 to 2.2; 95% CI, −5.6 to 2.9), indicating noninferiority.
Complete-case, per-protocol, and sensitivity analyses supported this result.

CONCLUSIONS

Oral antibiotic therapy was noninferior to intravenous antibiotic therapy when used during the first 6 weeks for complex orthopedic infection, as assessed by treatment failure at 1 year

Ho-Kwong Li et al. N Engl J Med 2019; 380:425-436

The OVIVA trial: length of hospital stay

- We found that appropriately selected oral antibiotic therapy was noninferior to intravenous therapy when used during the first 6 weeks in the management of bone and joint infection, as assessed by treatment failure within 1 year.
- **Oral antibiotic therapy was associated with a shorter length of hospital stay and with fewer complications than intravenous therapy.**

N Engl J Med 2019;380:425-36

Oral Is the New IV. Challenging Decades of Blood and Bone Infection Dogma: A Systematic Review

Noah Wald-Dickler, MD,[a,b,c] Paul D. Holtom, MD,[a,b] Matthew C. Phillips, MD,[a] Robert M. Centor, MD,[d,e] Rachael. A. Lee, MD,[d,e] Rachel Baden, MD,[a] Brad Spellberg, MD[a]

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Oral vs. IV Abx for Osteomyelitis

Author	Yr	N	Regimen (Oral vs. IV)	Success
Greenberg	'87	30	Ciprofloxacin vs. std IV	50% (7/14) v 65% (11/16)
Gentry	'90	59	Ciprofloxacin vs. βL+aminoglyc	77% (24/31) v 79% (22/28)
Mader	'90	26	Ciproflox vs. βL/clinda+aminoglyc	79% (11/14) v 83% (10/12)
Gentry	'91	33	Ofloxacin vs. cephalosporin	74% (14/19) v 86% (12/14)
Gomis	'99	32	Ofloxacin vs. imipenem	69% (11/16) v 50% (8/16)
Schrenzel	'04	39	Fleroxacin+rifampin v βL/vanco	82% (18/22) v 65% (11/17)
Euba	'09	48	TMP-SMX+rifampin vs. cloxacillin	81% (17/21) v 77% (21/27)
Li	'19	1054	Std oral vs. std IV	87% (457/527) v 85% (450/527)
Manning	'22	60	PJI/DAIR: IV/Oral vs. IV only	71% (22/31) v 76% (22/29)
Total (N=9 RCTs)		1,381		84% (581/695) v 83% (567/686)

Success = absence of osteo at long term follow up (most studies >1 year); std = standard of care, protocol specified; all RCTs comparing oral to IV-only are in adults, however there are also 9 other adult and 8 pediatric RCTs or quasi-experimental studies comparing mostly oral vs. mostly oral, with high cure rates; refs at https://www.bradspellberg.com/oral-antibiotics

Partial Oral Therapy for Osteomyelitis and Endocarditis — Is It Time?

Helen W. Boucher, M.D.

- Surveillance and stewardship through the use of narrow-spectrum therapy, **shorter durations of therapy, and oral rather than parenteral therapy,** as well as the development of new medicines and diagnostics and improvements in infection prevention through a “One Health” approach — with connections among human patients, animals, and the environment taken into account — **are key strategies for combating antimicrobial resistance**

N ENGL J MED 380;5 NEJM.ORG JANUARY 31, 2019

Bacteremia

Oral vs. IV Abx for Bacteremia

Author	Yr	N	Regimen (Oral vs. IV)	Success
Amodio-Groton	'96	50	Ciprofloxacin oral vs. IV—GNB	83% (20/24) v 77% (20/26)
San Pedro	'02	51	Linezolid vs. ceph—*S. pneumo*	93% (27/29) v 68% (15/22)
Deville	'03	36	Linezolid vs. vanco—GPC (peds)	80% (20/25) v 64% (7/11)
Jantausch	'03	103	Linezolid vs. vanco—GPC (peds)	72% (54/75) v 64% (18/28)
Kaplan	'03	80	Linezolid vs. vanco—GPC (peds)	82% (47/57) v 74% (17/23)
Schrenzel	'04	67	FQ + rif vs. βL/vanco—*Staph*	87% (34/39) v 89% (25/28)
Wilcox	'04	56	Linezolid vs. teicoplanin—GPC	89% (23/26) v 57% (17/30)
Wilcox	'09	166	Linezolid vs. vancomycin—GPC	75% (70/93) v 81% (59/73)
Monmaturopaj*	'12	17	Cefditoren vs. ceftriaxone—GNB	100% (6/6) v 91% (10/11)
Park	'14	59	Ciprofloxacin vs. std IV—GNB	93% (27/29) v 93% (28/30)
Total (N=10 RCTs)		685		81% (328/403) v 77% (216/282)

*N = 82 pts with pyelonephritis of whom 17 were bacteremic with *E. coli*, patients were randomized to continue ceftriaxone or switch to oral ceftditoren at day 3. Refs at https://www.bradspellberg.com/oral-antibiotics

Intra-abdominal infections

Oral vs. IV Abx for Intra-Abdominal

Author	Yr	N	Regimen (Oral vs. IV)	Success
			Liver Abscesses	
Chen	'02	31	Fleroxacin vs. cefazolin/gent	70% (14/20) v 82% (18/22)
Molton	'20	152	Ciprofloxacin vs. ceftriaxone	96% (71/74) v 93% (72/78)
Total (N=2)		183		90% (85/94) v 90% (90/100)
			cIAI*	
Solomkin	'96	671	Cipro/metro vs. Cipro/metro or Imipen	84% (183/219) v 82% (371/452)
Cohn	'00	250	Cipro/metro vs. pip-tazo	74% (99/134) v 63% (73/116)
Wacha	'06	475	Cipro/metro vs. CTX/metro	91% (213/235) v 88% (211/240)
Fraser	'10	102	Augmentin vs. CTX/metro (peds)**	60% (30/50) v 63% (33/52)
Arnold	'18	82	Augmentin vs. Ertapenem (peds)**	71% (27/38) v 73% (32/44)
Total (N=5)		1580		82% (552/676) v 80% (720/904)

*Patients stepped down to the oral option when tolerating POs
**Both peds studies of perforated appendicitis
Refs at https://www.bradspellberg.com/oral-antibiotics

Early discontinuation of antibiotics for febrile neutropenia versus continuation until neutropenia resolution (Protocol)

Stern A, Carrara E, Yahav D, Leibovici L, Paul M

MAIN RESULTS:

- 8 RCTs, a total of 662 febrile neutropenia episodes with FUO
- No significant difference between the short-antibiotic therapy arm and the long-antibiotic therapy arm for all-cause mortality.
- **Total antibiotic days were fewer in the intervention arm by three to seven days compared to the long antibiotic therapy**.
- No significant differences in the rates of clinical failure
- No difference in the incidence of bacteraemia occurring after randomisation
- No significant difference in the incidence of invasive fungal infection and development of antibiotic resistance

Cochrane Database of Systematic Reviews 2016, Issue 5. Art. No.: CD012184.
DOI: 10.1002/14651858.CD012184

Comparing the Outcomes of Adults With Enterobacteriaceae Bacteremia Receiving Short-Course Versus Prolonged-Course Antibiotic Therapy in a Multicenter, Propensity Score–Matched Cohort

Darunee Chotiprasitsakul,[1] Jennifer H. Han,[2] Sara E. Cosgrove,[3] Anthony D. Harris,[4] Ebbing Lautenbach,[2] Anna T. Conley,[5] Pam Tolomeo,[2] Jacqueleen Wise,[2] and Pranita D. Tamma[6]; for the Antibacterial Resistance Leadership Group

Table 2. Enterobacteriaceae Isolated in the Bloodstream of Hospitalized Adult Patients Between 2008 and 2014

		Duration of Therapy in Matched Cohort	
Enterobacteriaceae	Entire Cohort (N = 1769)	6–10 d (n = 385)	11–16 d (n = 385)
Escherichia coli	841 (47.5)	177 (46.0)	184 (47.8)
Klebsiella species	557 (31.5)	137 (35.6)	114 (29.6)
Enterobacter species	200 (11.3)	36 (9.4)	54 (14.0)
Serratia species	58 (3.3)	13 (3.4)	9 (2.3)
Proteus species	81 (4.6)	13 (3.4)	14 (3.6)
Citrobacter species	32 (1.8)	9 (2.3)	10 (2.6)

Data are presented as No. (%).

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Table 3. Thirty-Day All-Cause Mortality for Hospitalized Adult Patients With Enterobacteriaceae Bacteremia in a Propensity Score–Matched Cohort

Variable	Unadjusted HR (95% CI)	*P* Value	Adjusted HR[a] (95% CI)	*P* Value
Short-course therapy (6–10 d)	1.12 (.70–1.80)	.64	1.00 (.62–1.63)	.97
Urinary source	0.36 (.19–.67)	.001	0.49 (.26–.94)	.03
Pneumonia	3.06 (1.73–5.42)	<.001	1.60 (.85–3.02)	.15
Pitt bacteremia score	1.31 (1.21–1.42)	<.001	1.29 (1.17–1.43)	<.001
ICU on day 1 of bacteremia	2.38 (1.48–3.81)	<.001	0.99 (.56–1.76)	.98
End-stage liver disease	3.58 (2.05–6.06)	<.001	4.12 (2.30–7.39)	<.001
Immunocompromised status	1.03 (.63–1.70)	.89	1.40 (.83–2.36)	.21

Abbreviations: CI, confidence interval; HR, hazard ratio; ICU, intensive care unit.

[a]Adjusted for immunocompromised status and variables with $P < .10$ in univariable analysis.

Results. There were 385 well-balanced matched pairs. The median duration of therapy in the short-course group and prolonged-course group was 8 days (interquartile range [IQR], 7–9 days) and 15 days (IQR, 13–15 days), respectively. No difference in mortality between the treatment groups was observed (adjusted hazard ratio [aHR], 1.00; 95% confidence interval [CI], .62–1.63). The odds of recurrent bloodstream infections and CDI were also similar. There was a trend toward a protective effect of short-course antibiotic therapy on the emergence of MDRGN bacteria (odds ratio, 0.59; 95% CI, .32–1.09; $P = .09$).

Conclusions. Short courses of antibiotic therapy yield similar clinical outcomes as prolonged courses of antibiotic therapy for Enterobacteriaceae bacteremia, and may protect against subsequent MDRGN bacteria.

Shorter Is Better

Diagnosis	Short (d)	Long (d)	Result	#RCT
CAP	3-5	5-14	Equal	14
Atypical CAP	1	3	Equal	1
Possible PNA in ICU	3	14-21	Equal	1*
VAP	8	15	Equal	2
cUTI/Pyelonephritis	5 or 7	10 or 14	Equal	9**
Intra-abdominal Infection	4	10	Equal	2
GNB Bacteremia	7	14	Equal	3†
Cellulitis/Wound/Abscess	5-6	10	Equal	4‡
Osteomyelitis	42	84	Equal	2
Osteo with Removed Implant	28	42	Equal	1
Debrided Diabetic Osteo	10-21	42-90	Equal	2φ
Septic Arthritis	14	28	Equal	1
AECB & Sinusitis	≤5	≥7	Equal	>25
Neutropenic Fever	AFx72 h	+ANC>500	Equal	1
Post Op Prophylaxis	0-1	1-5	Equal	56Ψ
P. vivax Malaria	7	14	Equal	1

Total: 16 Conditions **>120 RCTs**

*Infiltrate on CXR but low CPIS score (≤6), both ventilated and non ventilated, likely CAP, HAP, and VAP combined; **2 RCT included males, the smaller one found lower 10-18 d f/up cure in males with 7 days of therapy but no difference at longer follow-up, larger exclusive male study found no diff in cure; †GNB bacteremia also in UTI/cIAI RCTs; ‡3 RCTs equal, 1 (low dose oral flucox) ↑relapses 2° endpoint; φall patients debrided, in 1 study total bone resection (clean margins); ΨIncludes meta-analysis of 52 RCTs; refs at https://www.bradspellberg.com/shorter-is-better

Shorter Is Better Exceptions

Diagnosis	Short (d)	Long (d)	Result	#RCT
Prosthetic Joint Infection	6 wk	12 wk	Inferior	1*
Early Pros. Joint Infect.	8 wk	12-26 wk	Equal	1*
Otitis Media < 2 yr old	5	10	Inferior	1
Otitis Media >2 yr old	<10	10	Equal	49**
Strep Throat: Nml PCN	3-5	7-10	Inferior	5†
Strep Throat: Other Abx	3-5	7-10	Equal	>20†
Strep Throat: QID PCN	5	10	Equal	1
Chronic Pulm Aspergillus	6 mo	12 mo	Inferior	1

Total: 4 Diseases >25 RCTs

* 6 vs. 12 week inferior for all-comers in largest trial, driven primarily but not entirely by DAIR cohort, but other RCT from Shorter Is Better table demonstrated 4-6 weeks may be non inferior, and small RCT of PJI within 1 month of implant showed non-inferiority of 8 vs. 12-26 wks;
**meta-analysis of 49 trials; 3% increased short term failure, but by 1 month of follow up, no difference;
†meta-analysis of >25 trials.
refs at https://www.bradspellberg.com/shorter-is-better

7. Outcome

- Indicatore di esito (il piu' importante)
- Cura
- Miglioramento
- Modifiche ATBT
- LOS
- Sopravvivenza
- Mortalità (generale, attribuibile)

Clinical outcomes

- A biased belief that “better” antimicrobial use must be better for the patient
- Clinical outcomes are useful balancing measures, **to help ensure that patients are not harmed through efforts to better rationalize antimicrobial prescribing.**

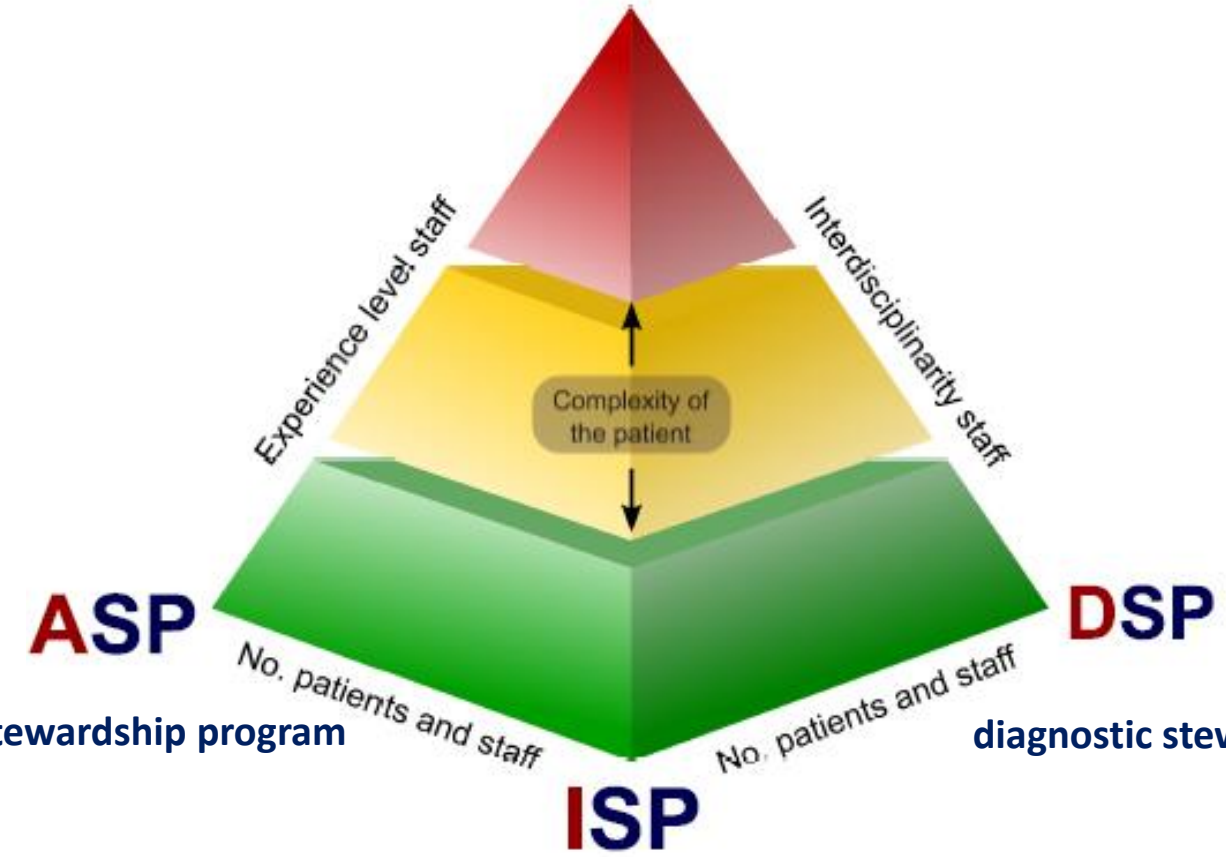
Cure

- There are various ways to measure cure of an infectious disease.
- There is **clinical cure** (whereby the patient is believed to be clinically well after effective treatment of their infection)
- **Microbiological cure** (whereby microbiological cultures or other tests demonstrate that the pathogen is no longer present in a manner capable of causing disease)
- Other forms (e.g., **radiographic cure**).
- These are potentially useful metrics, but are very difficult for programs to reliably measure on a consistent basis.

Mortality

- Most objective clinical outcome for ASPs is mortality.
- Problems with using mortality as an outcome, **especially when ASP evaluate their interventions as before–after studies, rather than randomized controlled interventions**
- *Secular trends in healthcare mortality may result in lower "after" mortality (because of concurrent quality improvement initiatives) or higher "after" mortality (because of a trend to limit hospitalization to sicker and/or older patients).*
- Accordingly, mortality results should be interpreted with caution

Multistakeholder platform of antimicrobial stewardship model



antimicrobial stewardship program

diagnostic stewardship program

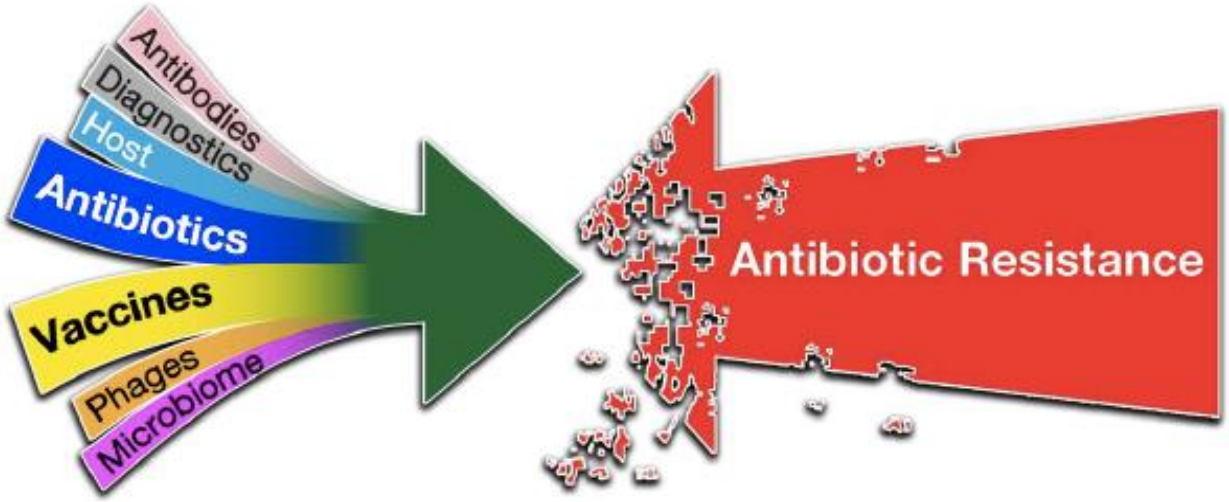
infection prevention stewardship program

Dik JH, J Clin Microbiol. 2017;55:3306-3307

Conclusions

- **ASP require metrics & resources**
- **Build your own local ASP**
- **Clinical governance is warranted**
- **Key role for *infection control & fast microbiology***
- **Decrease LOS: short IV course, shift to oral ATBT**
- **Improve the patient access to the new antibiotics**

AMR control require joining forces



Infection control