SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA
68° CONGRESSO NAZIONALE SIGG
Ritorno al futuro
FIRENZE, 13-16 DICEMBRE 2023
PALAZZO DEI CONGRESSI

Le polmoniti: Terapia delle infezioni multiresistenti

Stefano Romagnoli, *M.D. Ph.D*
AOU Careggi, University of Florence, IT

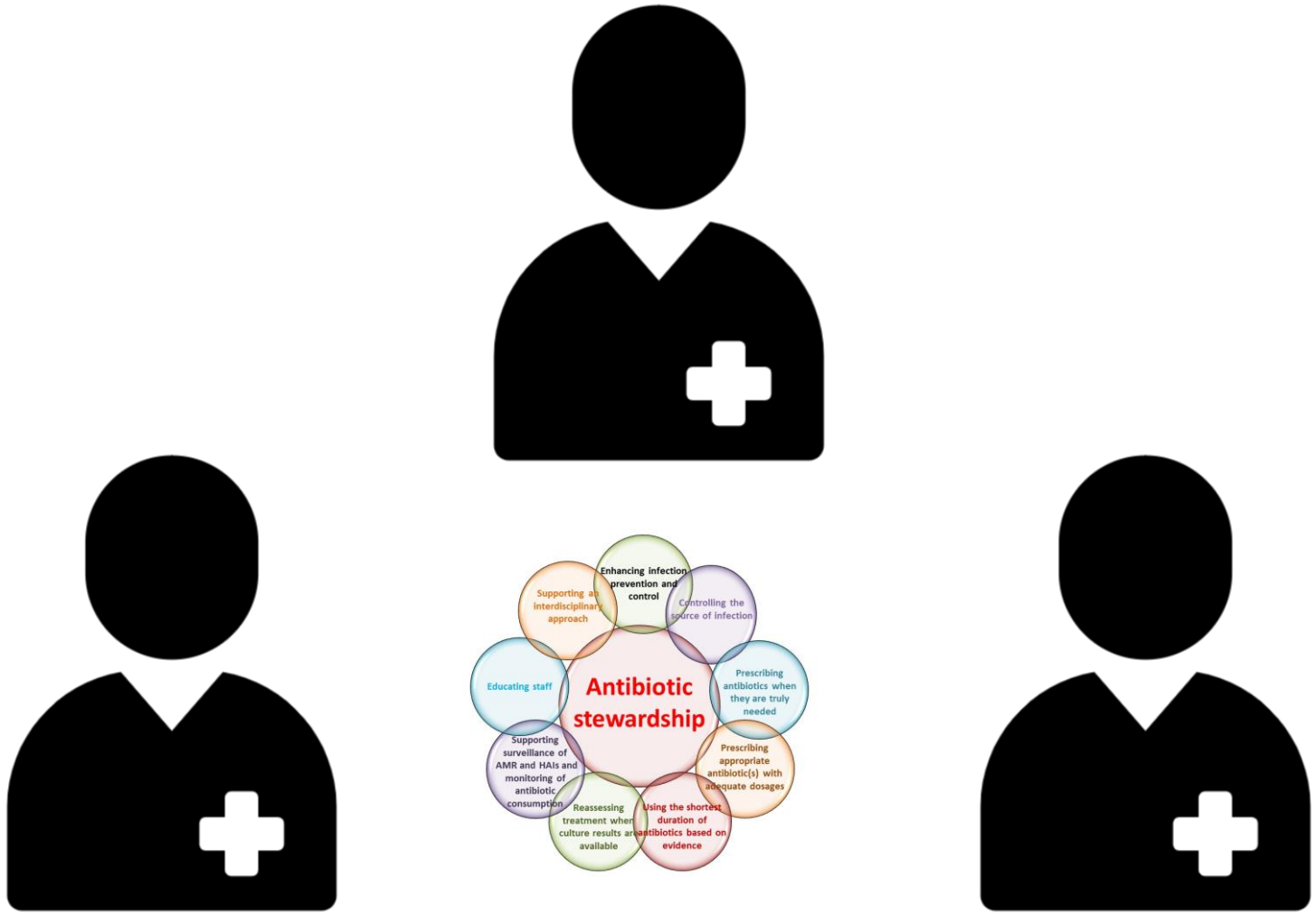
UNIVERSITÀ DEGLI STUDI FIRENZE
TLC TEACHING LEARNING CENTER
SCUOLA DI SPECIALIZZAZIONE IN ANESTESIA, RIANIMAZIONE TERAPIA INTENSIVA E DEL DOLORE
UNIVERSITÀ DI FIRENZE
aouc

Disclosure

- **Fee for lectures, travel/accommodation/congress registration support**: Baxter; BBraun; Biomérieux; Biotest; Edwards; Fisher & Paykel; Fresenius; Masimo; Medtronic; MSD; Pfizer, Piramal; Viatris, Vygon.
- **Research grants**: Baxter, Medtronic, Fisher & Paykel.
- **Advisory board**: Viatris.

Outline

- Teamwork against MDR infections → Antimicrobial stewardship
- Epidemiology: Gram Positive vs. Gram Negative Bacteria
- New antimicrobials
- Protocols and Conclusions


Antibiotic stewardship
Enhancing infection prevention and control
Controlling the source of infection
Prescribing antibiotics when they are truly needed
Prescribing appropriate antibiotic(s) with adequate dosages
Using the shortest duration of antibiotics based on evidence
Reassessing treatment when culture results are available
Supporting surveillance of AMR and HAIs and monitoring of antibiotic consumption
Educating staff
Supporting an interdisciplinary approach

Pseudomonas aeruginosa

07:49

Amikacina	S	<=4
Ceftazidime	R	16
Ciprofloxacina	I	0,25
Cefepime	R	>8
Imipenem	I	1
Levofloxacina	I	<=0,25
Meropenem	S	1
Tobramicina	S	<=1
Ceftazidime-Avibactam	R	>8/4
Piperacillina/tazobactam	I	16/4
Ceftolozane-tazobactam	R	>4/4
Meropenem/Vaborbactam	S	<=2/8

07:49

Ciao Bruno. Bronco-aspirato. Mi dai un tuo commento a questo antibiogramma per favore?

07:50

Ricoverata da 3 mesi

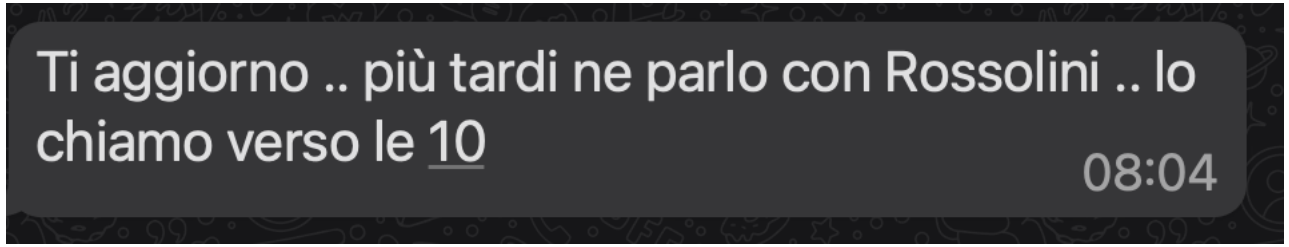
07:53

Dr. Bruno Viaggi.
Dir. UNIT Infezioni correlate all'assistenza del paziente critico
AOU Careggi

Strano ceppo .. se mi mandi nome sento se lo stanno sequenziando ..
07:58

Forse qualcosa su efflusso a ceftazidime associato ad AmpC mutata che potrebbe giustificare R a ceftolozano tazobactam
07:59

No carbapenemasi nota .. no VIM per intendere .. perché sensibile a Meropenem ..
08:00



Prof. Gian Maria Rossolini.
Professore Ordinario; SSD: MED/07 - Microbiologia e microbiologia clinica ;
Dir. MICROBIOLOGIA E VIROLOGIA
AOU Careggi

CLINICO

INFETTIVOLOGO

MICROBIOLOGO

Pneumonia

Assefa *Pneumonia (2022)14:4*
https://doi.org/10.1186/s41479-022-00096-z

REVIEW Open Access

Multi-drug resistant gram-negative bacterial pneumonia: etiology, risk factors, and drug resistance patterns

Muluneh Assefa*

Pneumonia can be classified into:

- Community-acquired pneumonia (CAP)
- Hospital-acquired (HAP) → after 48 h or more of hospital admission
- Ventilator-associated pneumonia (VAP)

CAP is the 6° leading cause of death in people aged **65** and above worldwide.

Assefa Pneumonia (2022) 14:4

Pneumonia

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Assefa Pneumonia (2022) 14:4

- **Age**
- Incomplete or inadequate vaccination
- Indoor environmental exposure
- Medical conditions (e.g., asthma, diabetes, heart disease, treatment-induced cytopenias in cancer, long-term **hospitalization**, **malnutrition**, **immunosuppression**)
- Smoking,
- Alcohol consumption,
- Poor dental hygiene,
- Contact with contaminated hospital equipment,
- Previous exposure to **antibiotics**,
- Presence of viral infections that compromise the respiratory tract that results in secondary bacterial colonization infection

Assefa. Pneumonia (2022) 14:4

- Wong JL, et al. Clin Chest Med. 2017;38(2):263–77.
- Henig O, et al. Infect Dis Clin.2017;31(4):689–713.
- Hanada S, et al. Front Immunol. 2018;9:2640.
- Marangu D, et al. Paediatr Respir Rev. 2019;32:3–9.

TIPICAL PNEUMONIA

- Streptococcus pneumoniae (MOST PREVALENT CAP),
- Staphylococcus aureus,
- Klebsiella pneumoniae,
- Haemophilus influenzae,
- Pseudomonas aeruginosa,
- Moraxella catarrhalis,
- Escherichia coli

ATIPICAL PNEUMONIA

- Legionella pneumophila,
- Chlamydia pneumoniae,
- Mycoplasma pneumoniae.

- Gram-Negative bacteria (i.e., K. pneumoniae, Acinetobacter baumannii, P. aeruginosa, and E. coli) are commonly related to HAP

TIPICAL PNEUMONIA

- Streptococcus pneumoniae (MOST PREVALENT CAP),
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- Legionella pneumophila,
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- Mycoplasma pneumoniae.

- **Gram-Negative bacteria (i.e., K. pneumoniae, Acinetobacter baumannii, P. aeruginosa, and E. coli) are commonly related to HAP**

- Antibiotic resistance is an emerging public health threat

Fig. 5 *K. pneumoniae*: percentage of invasive isolates resistant to carbapenems (imipenem/meropenem), by country/area, WHO European Region, 2020

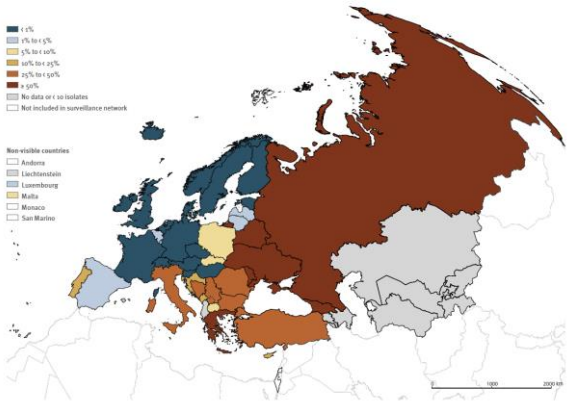


Fig. 6 *P. aeruginosa*: percentage of invasive isolates with resistance to carbapenems (imipenem/meropenem), by country/area, WHO European Region, 2020

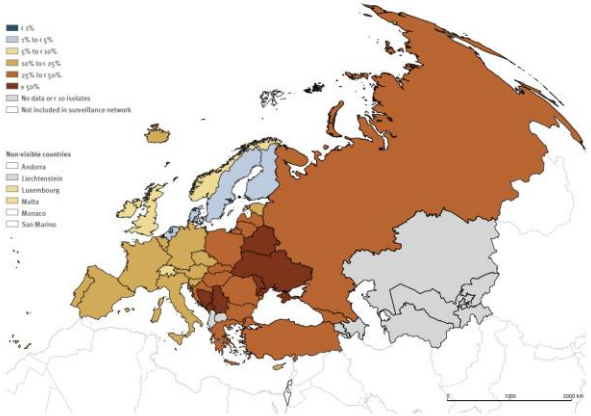
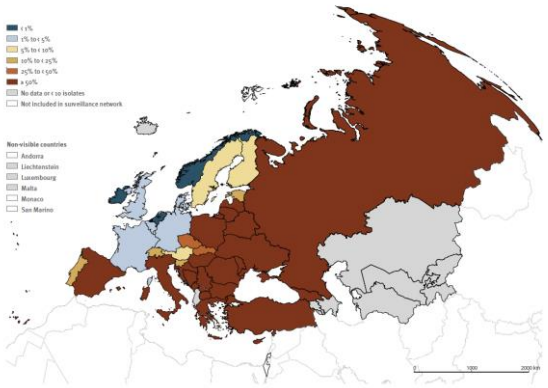
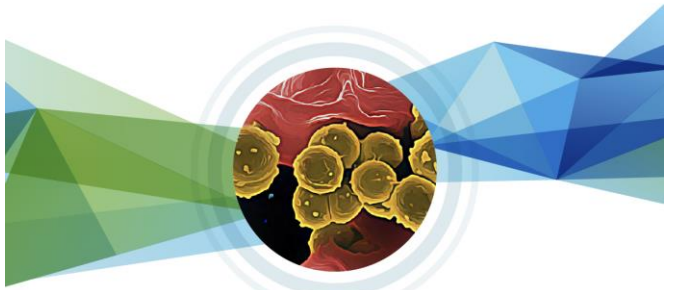


Fig. 7 *Acinetobacter* spp.: percentage of invasive isolates with resistance to carbapenems (imipenem/meropenem), by country/area, WHO European Region, 2020



- 33,000 attributable deaths per year in Europe and up to 1.2 million worldwide

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL
World Health Organization REGIONAL OFFICE FOR Europe



Antimicrobial resistance surveillance in Europe

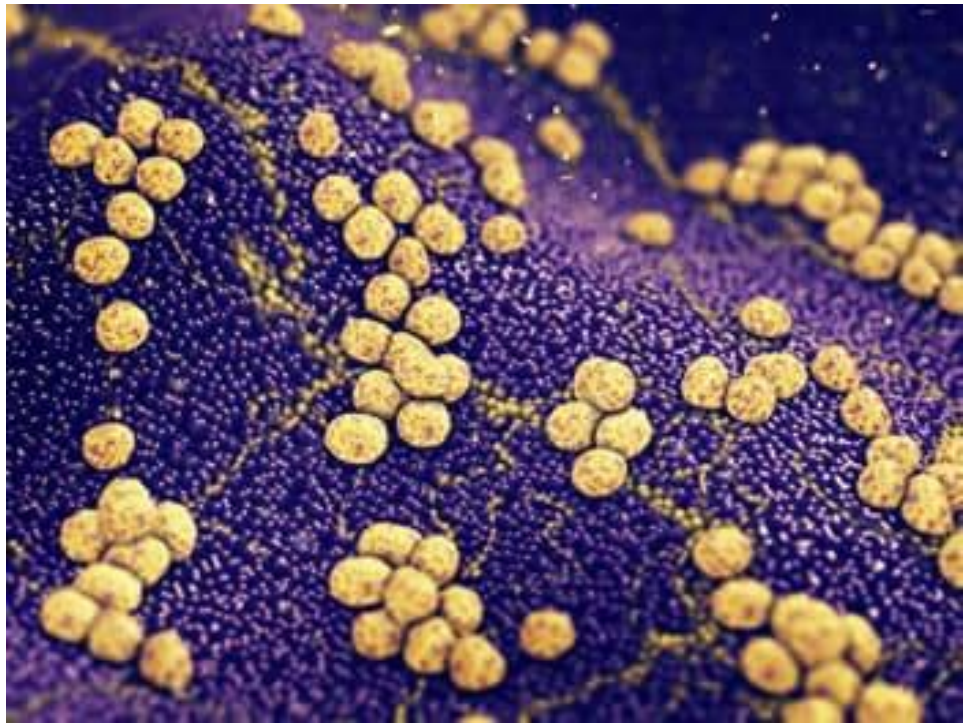
2022

2020 data

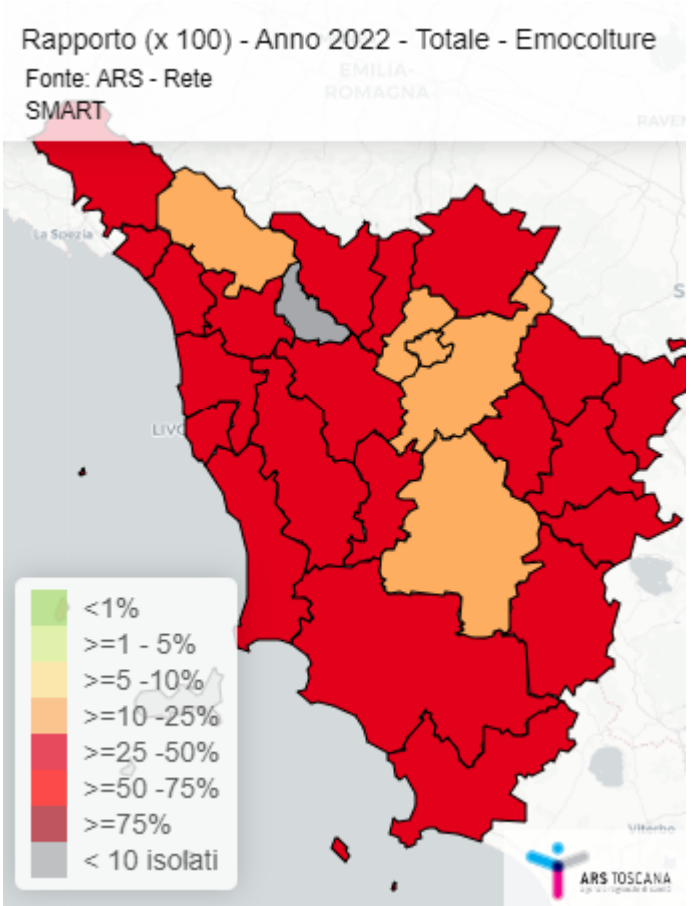
- https://op.europa.eu/en/publication-detail/-/publication/9387811c-e79f-11ec-a534-01aa75ed71a1/language-en

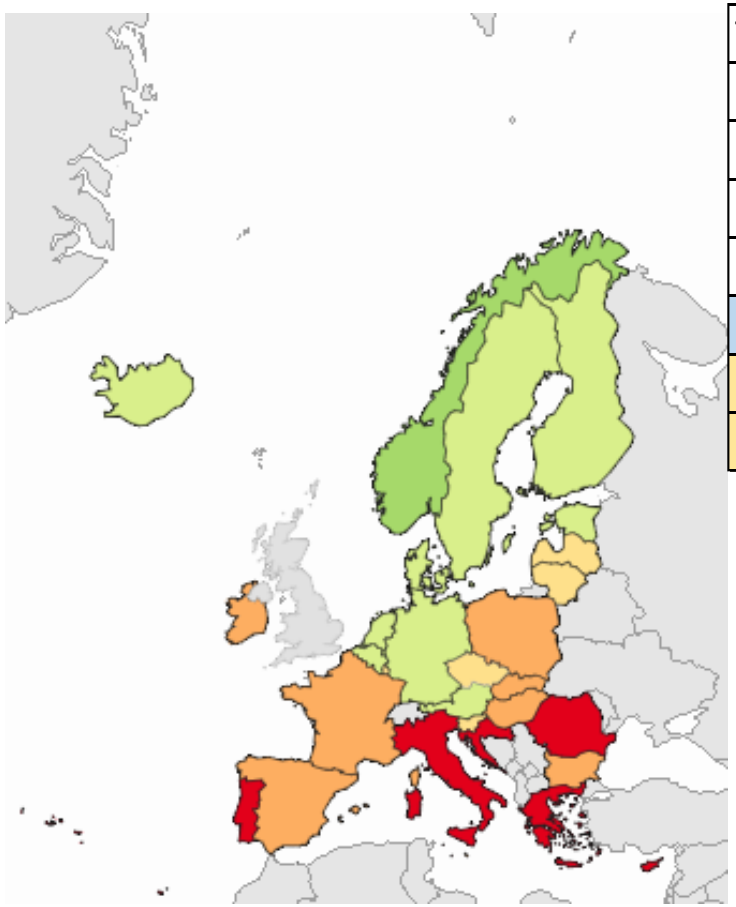
- Cassini A et al. Lancet Infect Dis. 2019;19:56–66.

- Tra i batteri **Gram positivi**, il trend di **diminuzione della meticillino-resistenza** in Staphylococcus aureus (MRSA) iniziato nel 2015 in Toscana continua anche per il 2022
- La percentuale attuale è 22,4% [contro il 30% dell'Italia].
- Meno dello **0,1%** degli isolati di S. aureus in Toscana risultano resistenti alla **vancomicina**.



Staphylococcus aureus meticillino-resistente (MRSA)

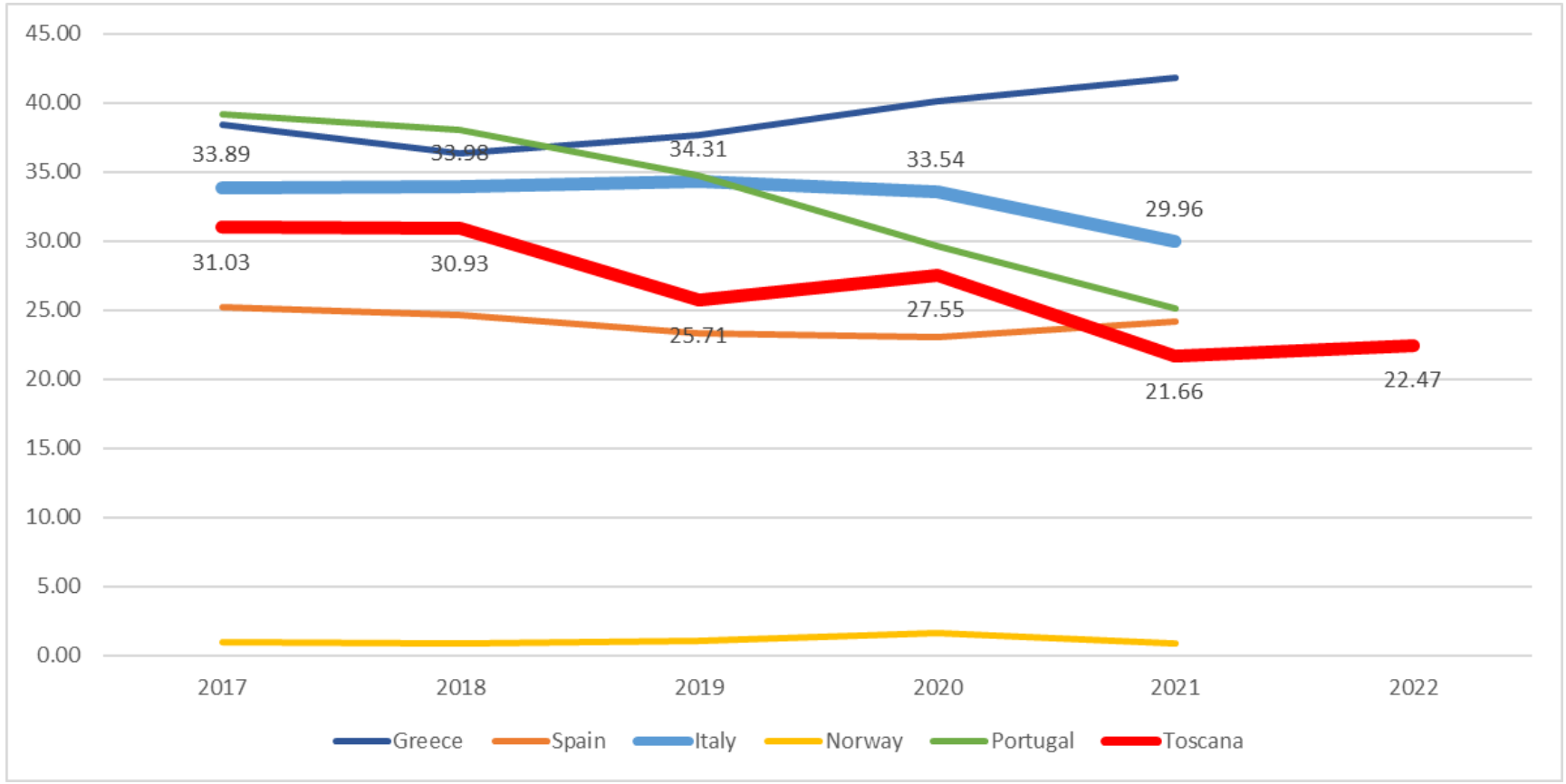




Time	RegionCode	RegionName	NumValue
2021	EL	Greece	41.85
2021	ES	Spain	24.22
2021	NO	Norway	0.92
2021	PT	Portugal	25.13
2021	IT	Italy	29.96
2021	TOSC	Toscana	21.66
2022	TOSC	Toscana	22.47

(1667 isolati di *S.aureus* da sangue non ripetuti, 2022)

Staphylococcus aureus meticillino-resistente (MRSA)

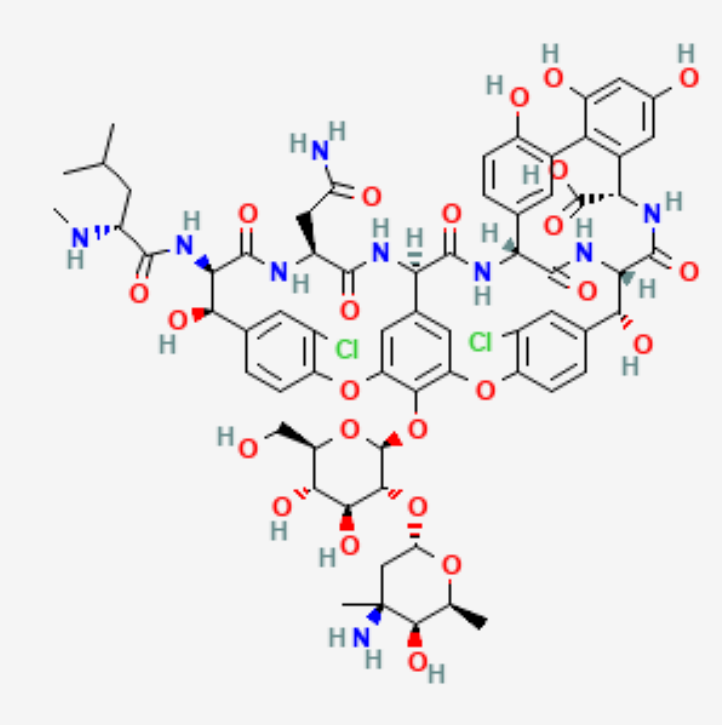


Cortesia del Prof. GM Rossolini

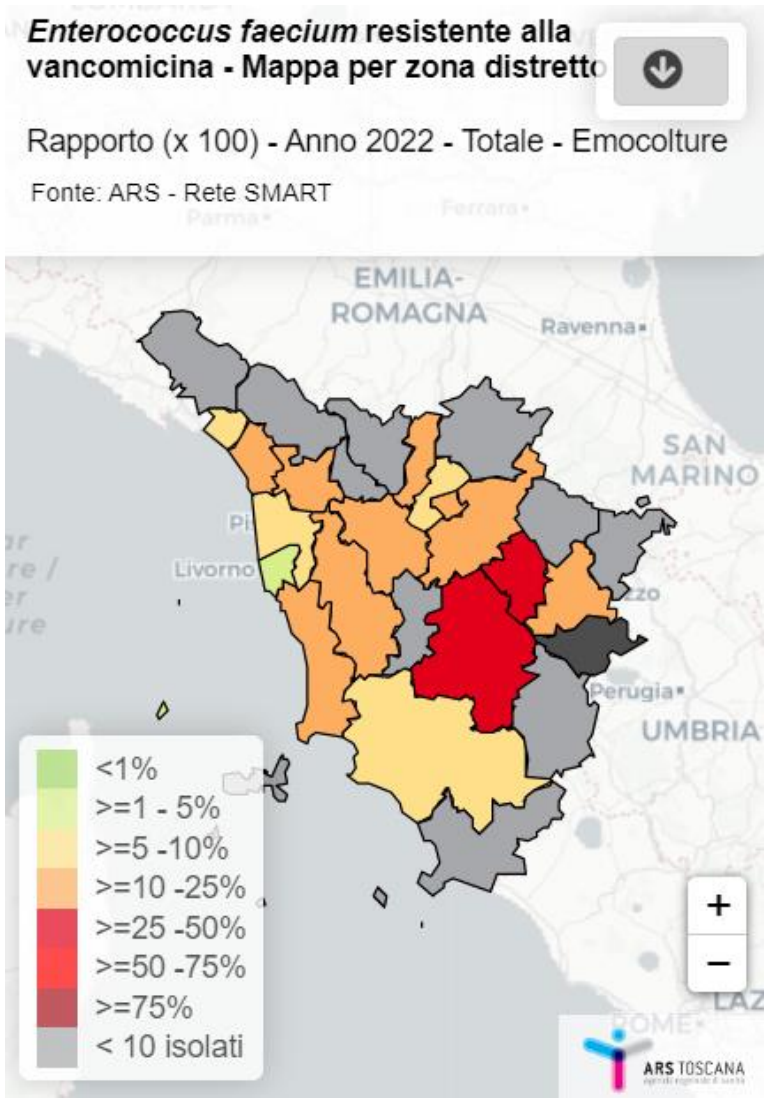
- Dal 2015 al 2021, in Italia le percentuali di isolati di **Streptococcus pneumoniae** resistenti alla penicillina (5%) e all'eritromicina (24%), sono rimaste stabili.

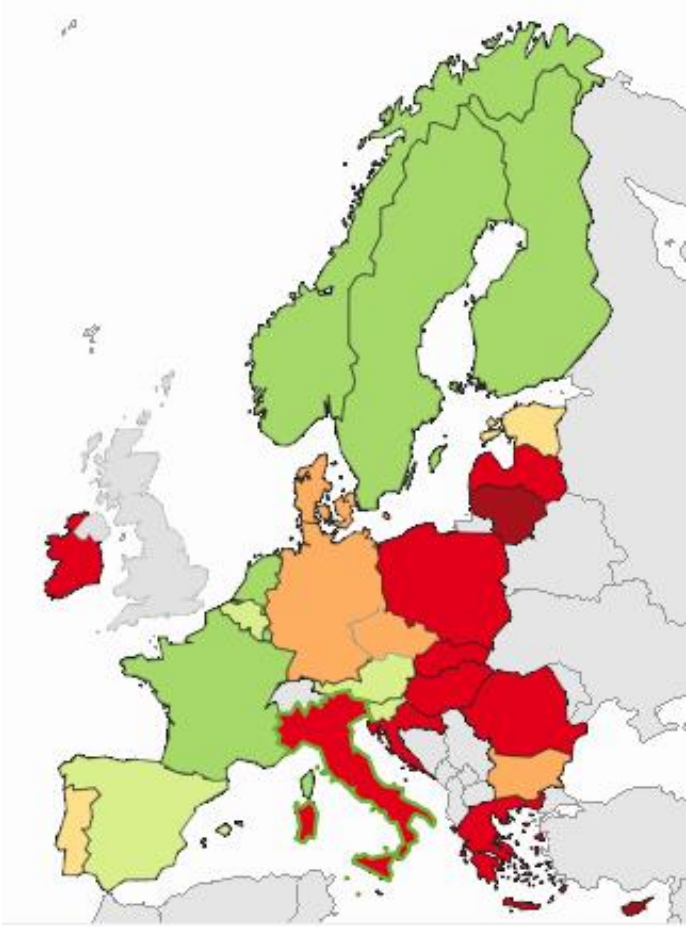
- In Toscana (2022) risulta **resistente alla penicillina nel 7%** dei casi, in diminuzione negli ultimi tre anni, e all'eritromicina nel **20%** (forte riduzione rispetto al 2021 – 37,5% e al 2020 – 30,3%).

- Per contro, la **resistenza alla vancomicina** in **Enterococcus faecium (VRE)** risulta in notevole **aumento** rispetto agli anni precedenti (**29,4%** nel 2022; 16% nel 2021) in Toscana.
- In **Italia** la percentuale di VRE era **28,2%** (2021), con un trend in aumento.



Enterococcus faecium resistente alla vancomicina (VRE)





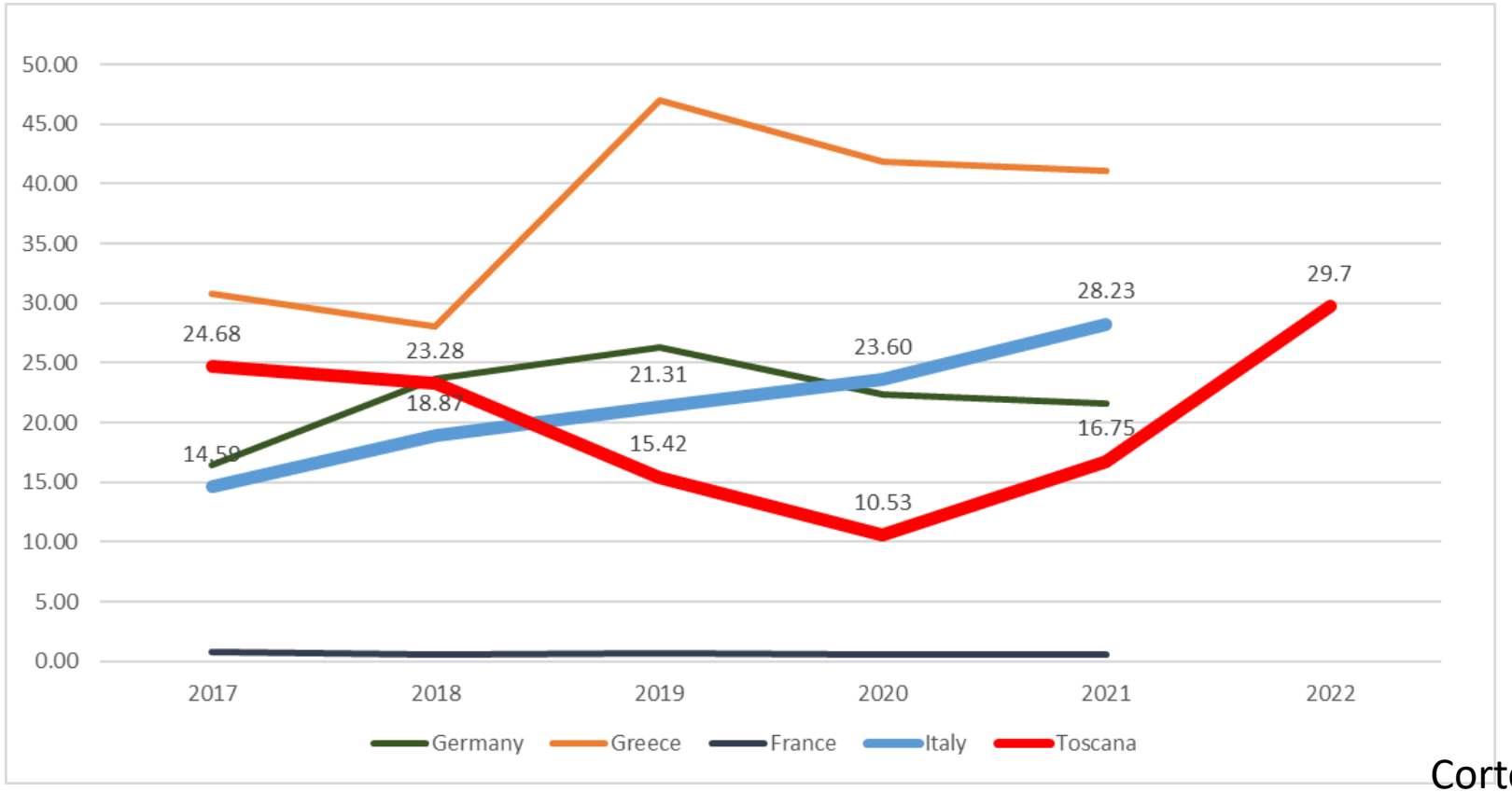
Time	Region(	RegionI	NumValue
2021	DE	Germany	21.63
2021	EL	Greece	41.05
2021	FR	France	0.53
2021	IT	Italy	28.23
2021	TOSC	Toscana	16.75
2022	TOSC	Toscana	29.7

(623 isolati di *E.faecium* da sangue non ripetuti, 2022)

Cortesia del Prof. GM Rossolini

Enterococcus faecium resistente alla vancomicina (VRE)

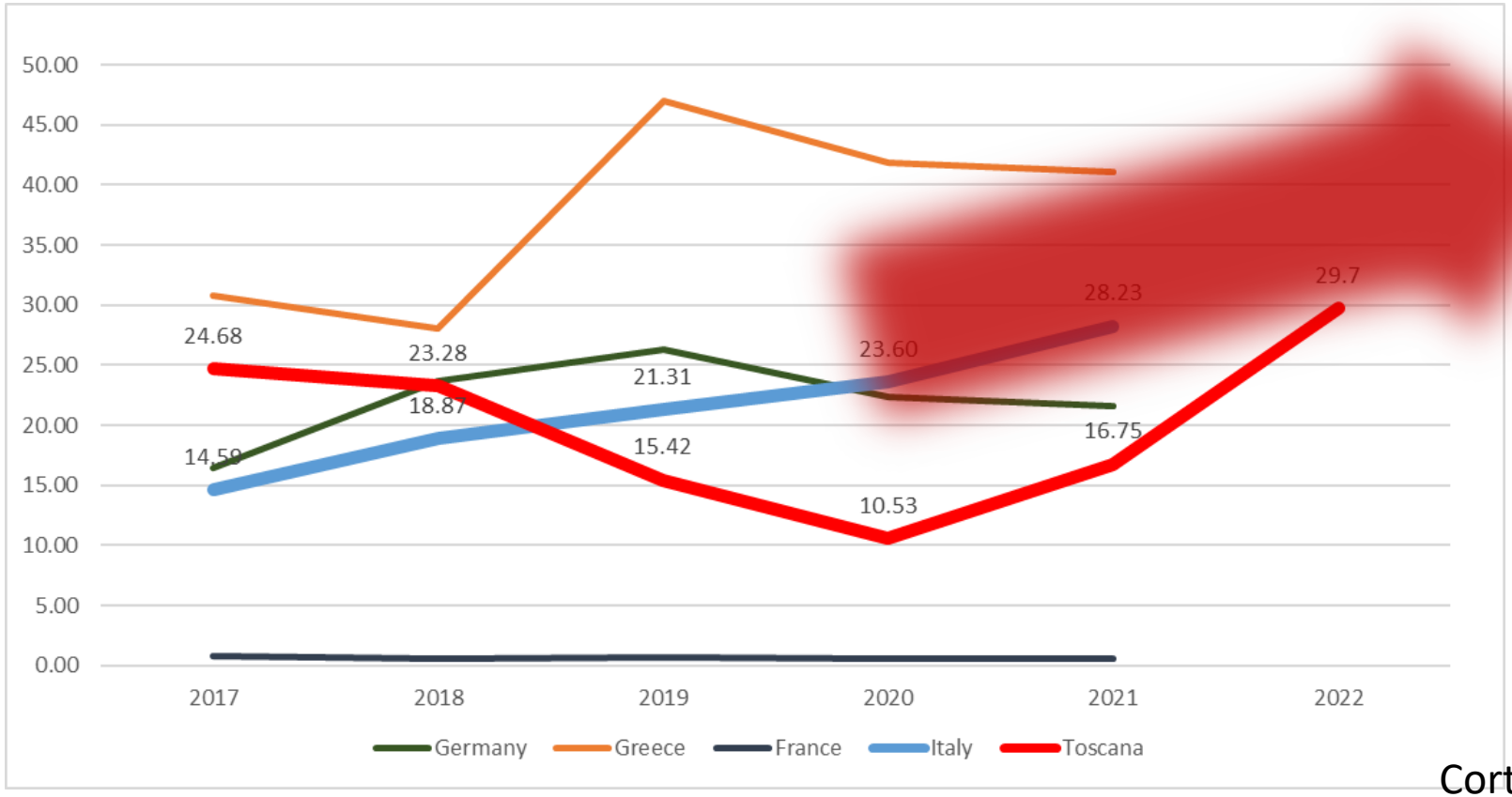
Aumento dal 2021 in Toscana



Cortesia del Prof. GM Rossolini

Enterococcus faecium resistente alla vancomicina (VRE)

Aumento dal 2021 in Toscana



Cortesia del Prof. GM Rossolini

- **Antibiotic resistance** is increasingly being recognized as a major worldwide health concern resulting from antibiotic overuse and improper administration

  - Chen G, et al. Can J Infect Dis Med Microbiol. 2020;2020:7268519.

- **Pneumonia caused by multidrug-resistant gram-negative bacteria** (MDR-GNB) is **growing** more common and has a detrimental impact on patient outcomes, indicating a shift in infection trends to GNB and their rapid dissemination, particularly in the **hospital** settings,

  - Gao B, et al. Front Pharmacol. 2019;10:262.
  - Cillóniz C, et al. Ann Update Intensive Care Emerg Med. 2019;2019:459–75.
  - Sader HS, et al. Intensive Care Med. 2020;46(4):766–70.
  - Kidd JM et. Expert Opin Pharmacother. 2018;19(4):397–408.

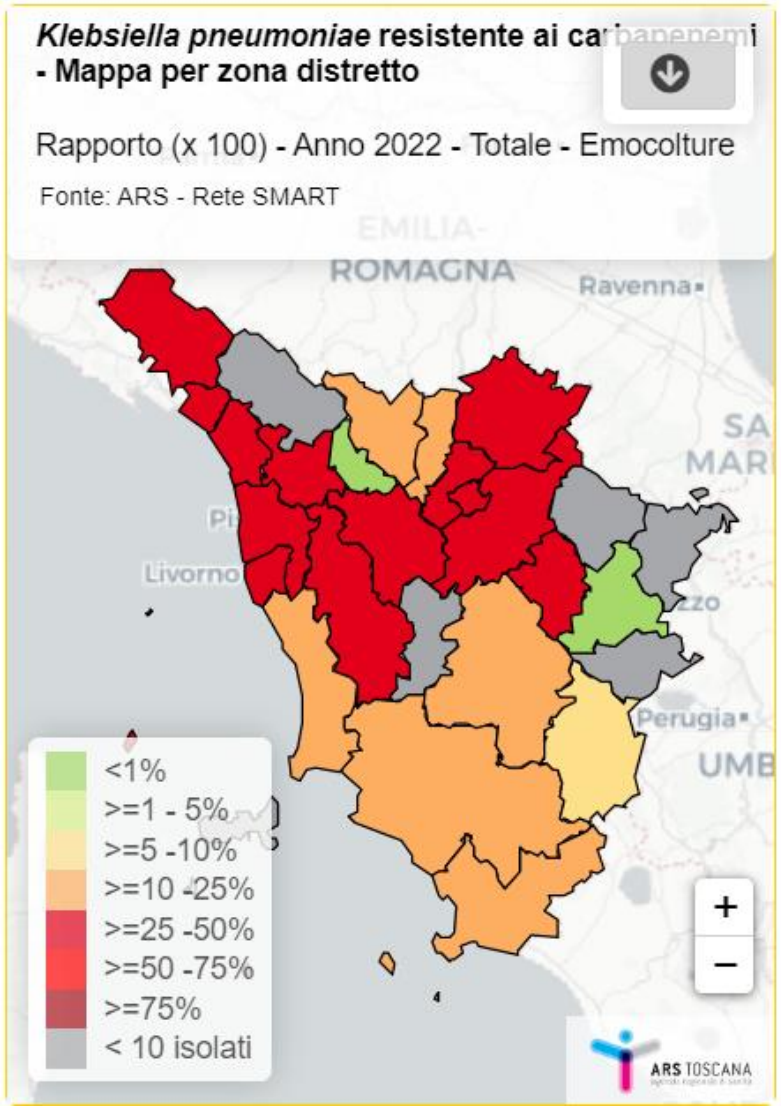
- The **frequency has increased in the elderly** because of physiological changes linked to the progressive **dysfunction of the respiratory tract and/or weakened immunity** supported by **72.6% GNB prevalence in elderly patients with CAP.**

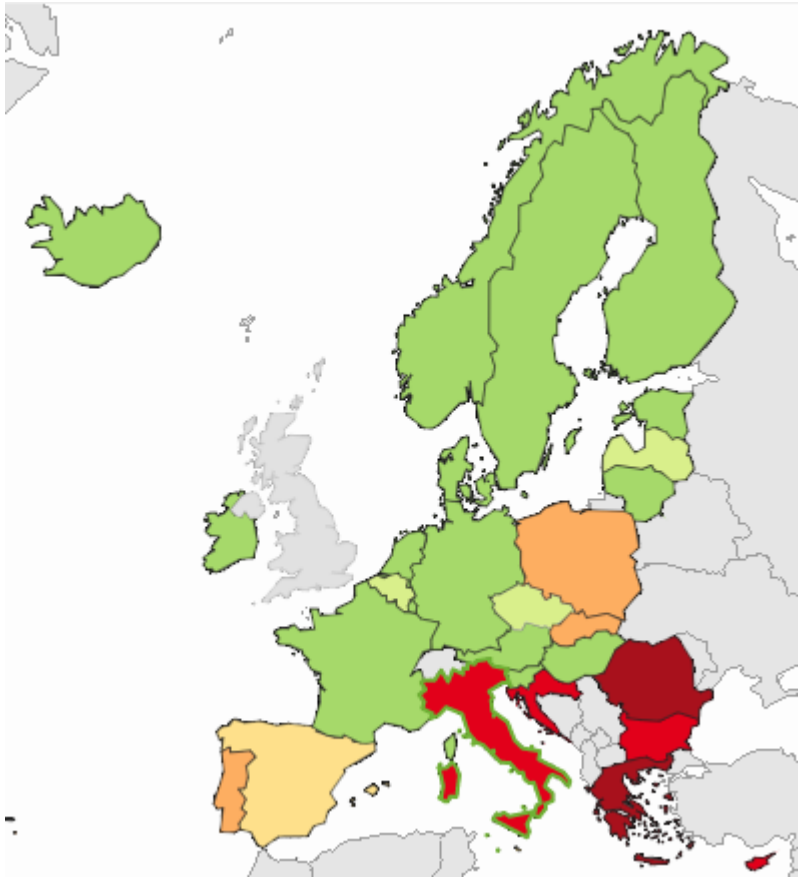
  - Luan Y, et al. J Int Med Res. 2018;46(11):4596–604.
  - Malézieux-Picard A, et a.. Aging Clin Exp Res. 2021;33(4):1091–100.

- **Pseudomonas aeruginosa** la resistenza ai **carbapenemi** → valore nazionale del 2021 (**16,4%** con trend in crescita).

- **Klebsiella pneumoniae** resistenti ai **carbapenemi**: IT: **26,7%** nel 2021 (trend in calo) con un andamento in diminuzione dal 2017 al 2022.
- La resistenza alle **cefalosporine di III generazione** (**61,2%** nel 2022) risulta stabile rispetto agli anni precedenti.

Klebsiella pneumoniae resistente ai carbapenemi

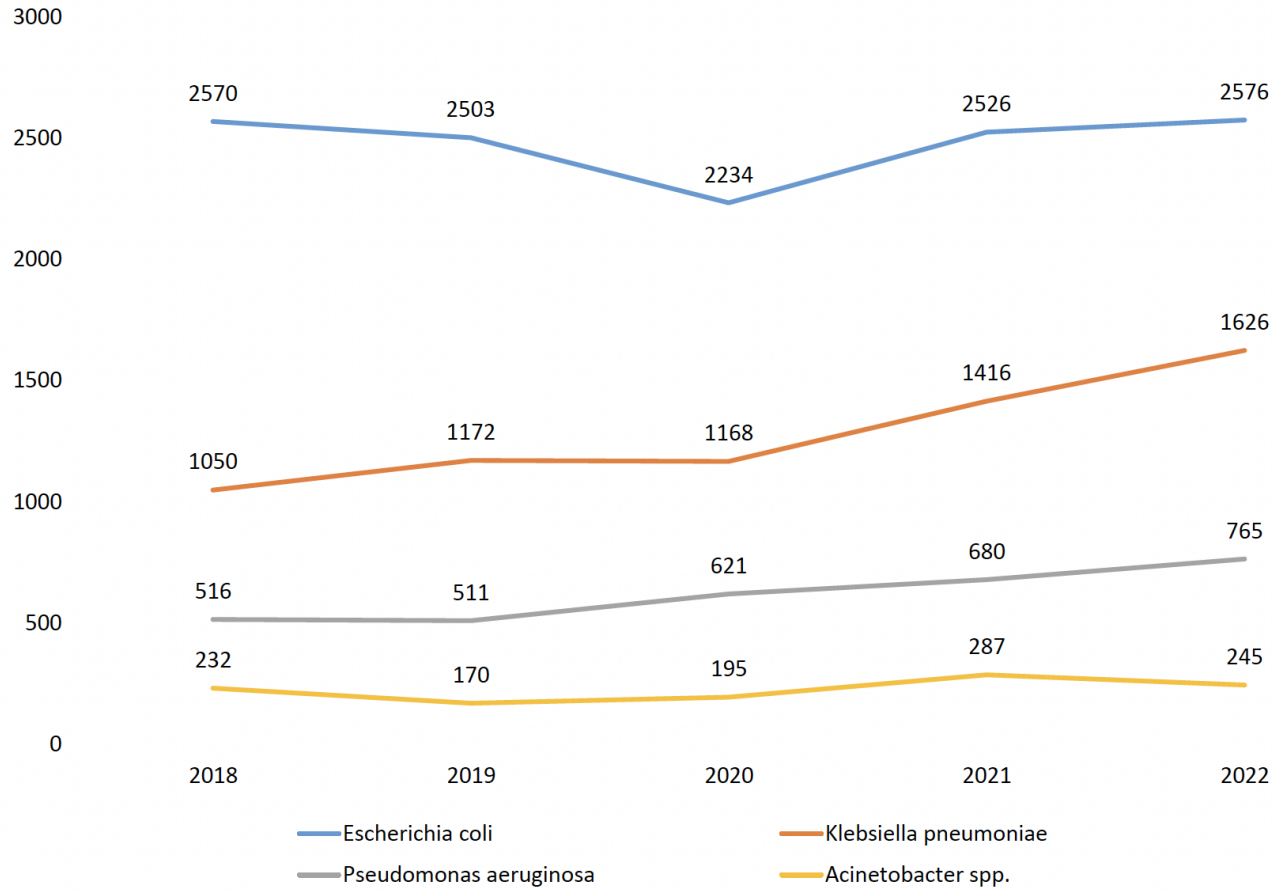




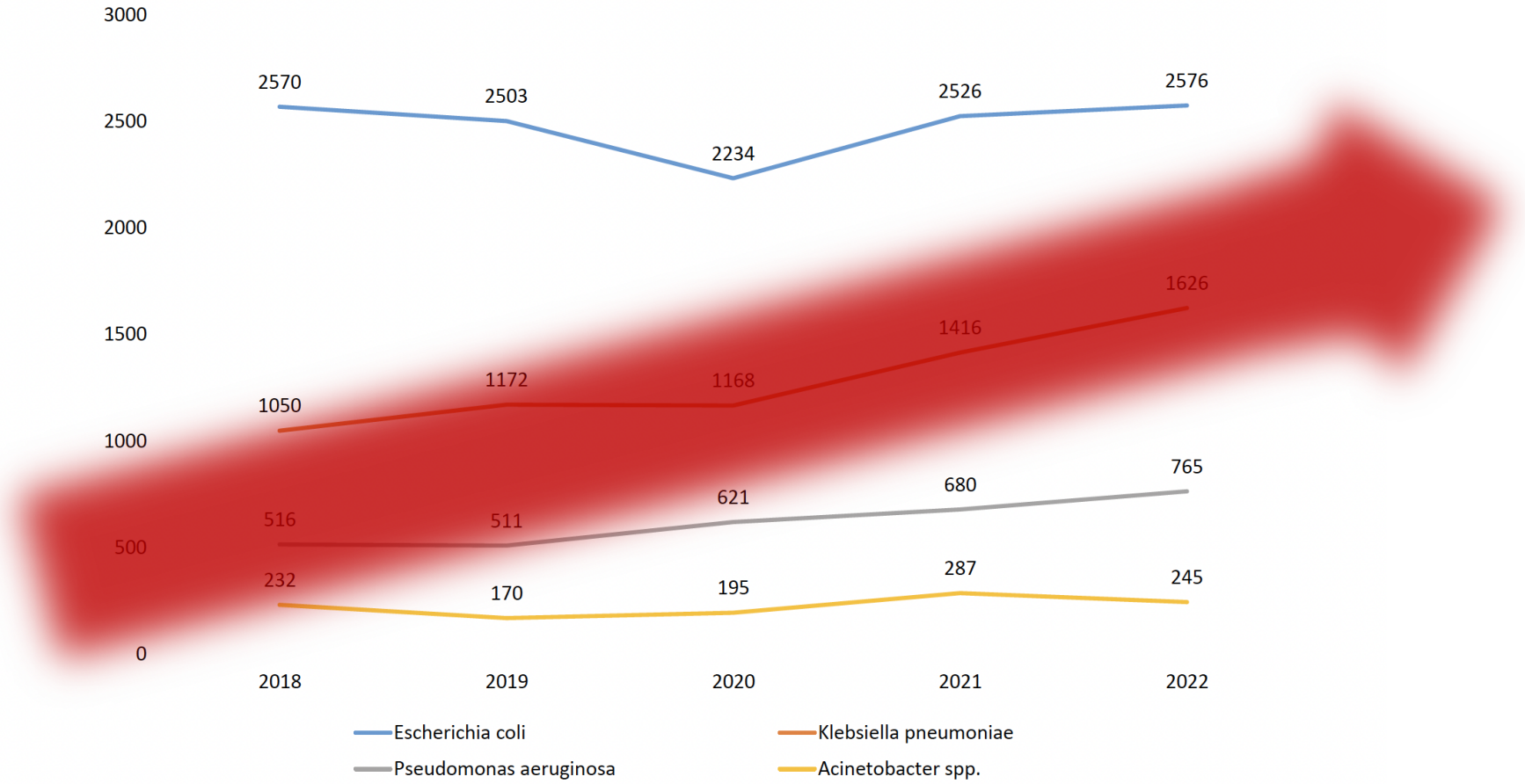
Time	Region(	RegionN	NumVa
2021	DE	Germany	0.80
2021	EL	Greece	73.70
2021	ES	Spain	5.92
2021	IT	Italy	26.74
2021	TOSC	Toscana	19.22
2022	TOSC	Toscana	17.99

(1625 isolati di *K.pneumoniae* da sangue non ripetuti, 2022)

Emocolture, andamento degli isolati di Gram negativi - Toscana 2018-2022 - Fonte: ARS - Smart



Emocolture, andamento degli isolati di Gram negativi - Toscana 2018-2022 - Fonte: ARS - Smart



- Gram-negative bacteria are responsible for most bacterial causes of HAP/VAP (50–80%)
  → common etiologic agents of **K. pneumoniae**, **P. aeruginosa**, and **E. coli**

- Cilloniza C, et al. Curr Opin Infect Dis. 2019;32:656–62.
- Dessie T, et al. Int J Microbiol. 2021;2021:6680343.
- Assefa M, et al. PLoS One. 2022;17(2):e0262956.
- Kishimbo P, et al. Pneumonia. 2020;12(1):1–9.
- Ibrahim A. et al. Sudan Med Lab J. 2018;6(1):78–94.

- **VAP** caused by **multidrug-resistant GNB** has emerged as a significant and intractable clinical problem.

- Gu W-J, et al. Int J Antimicrob Agents. 2014;44(6):477–85.

GNB prevalence between **76.13** to **95.3%** with highly MDR **P. aeruginosa**, and **A. baumannii** strains

- Gupta R, et al. J Glob Antimicrob Resist. 2017;9:47–50.
- Yehia FAA, et al. Zagazig. J Pharm Sci. 2017;26(1):39–47.
- Ahsan AA, et al. Bangladesh Crit Care J. 2016;4(2):69–73.
- Nguyen TT, et al. Pharmaceut Sci Asia. 2020;47(4):387–98.

Why has pneumonia etiology shifted to GNB?

- Cheap and freely available antibiotics from local drug stores

Ineffective killing of the causative agent, treatment failure, and the survival of resistant GNB, which increases the percentage of GNB resistant to drugs.

- Breijyeh Z, et al. Molecules. 2020;25(6):1340

- Poor infection control,
- Inadequate antimicrobial stewardship,
- GNB high burden in the hospital settings as a source of drug-resistant GNB spread to the community through hospital effluents,
- Difficult nature of acquiring resistance through transmissible genes,
- Increased comorbid conditions
- Increased elderly populations,
- Aggressive virulence determinants to cause severe disease

} are all reasons for the colonization of GNB

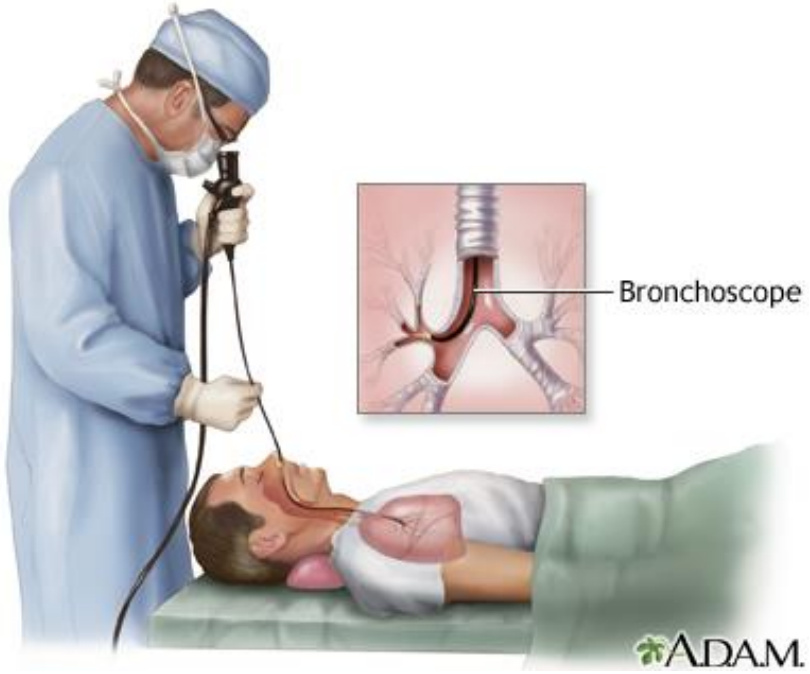
- Asfaw T. J Res Environ Sci Toxicol. 2018;7(2):47–52.
- Cerceo E, et al. Microb Drug Resist. 2016;22(5):412–31.

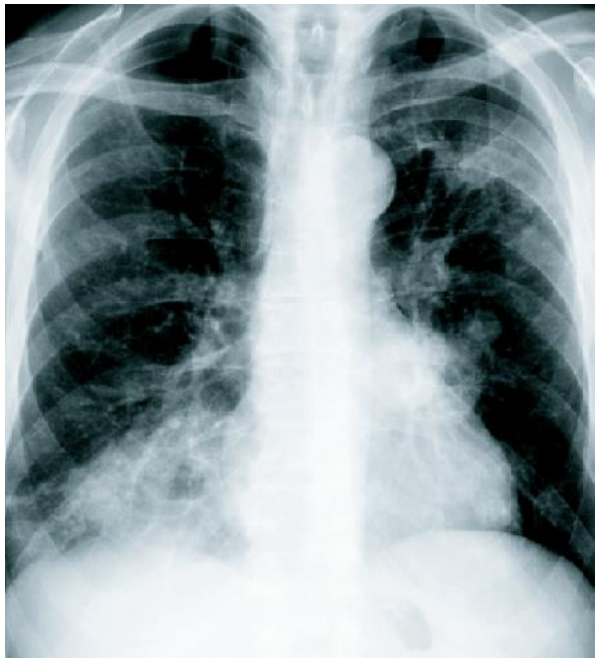
Significant risk factors

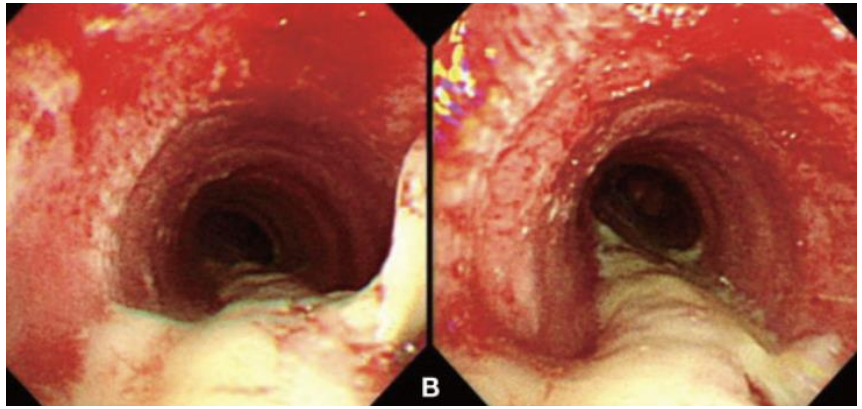
- Prolonged hospital stay,
- Prior MDR-GNB colonization or infection,
- High frequency of antibiotic resistance in the setting,
- ICU admission,
- Mechanical ventilation,
- Surgical intervention,
- **Elderly** population,
- Patients with prior antibiotic use,
- Underlying pulmonary diseases (such as chronic obstructive pulmonary disease and bronchiectasis),
- Diabetes mellitus,
- Immunosuppressive conditions (like HIV and malignancies),
- Prior hospitalization,
- Chronic alcoholism,
- Enteral malnutrition,
- Use of carbapenem drugs.

- Maruyama T, et al. Clin Infect Dis. 2019;68(7):1080–8.
- Watkins RR, et al. F1000Research. 2019;8.
- Rubio-Perez I, et al. Surg Infect (Larchmt). 2017;18(5):625–33.
- Shindo Y, et al. Am J Respir Crit Care Med. 2013;188(8):985–95.
- Prina E, et al. Ann Am Thorac Soc. 2015;12(2):153–60.
- Aliberti S, et al. Thorax. 2013;68(11):997–9.
- Eugenin EA. Et al Virulence. 2013;4(6):435–6.
- Inghammar M, et al. Trans R Soc Trop Med Hyg. 2018;112(2):57–63

- Optimal specimen **must** be obtained for laboratory identification of bacteria.
- The inability to obtain good quality sputum due to contamination with normal respiratory flora, the good safety profile of transthoracic **lung aspirates**, and the difficulty of obtaining sputum in children and the elderly all posed challenges.
  - Claassen Ccet al. NeoReviews. 2019;20(3):e145–e51.







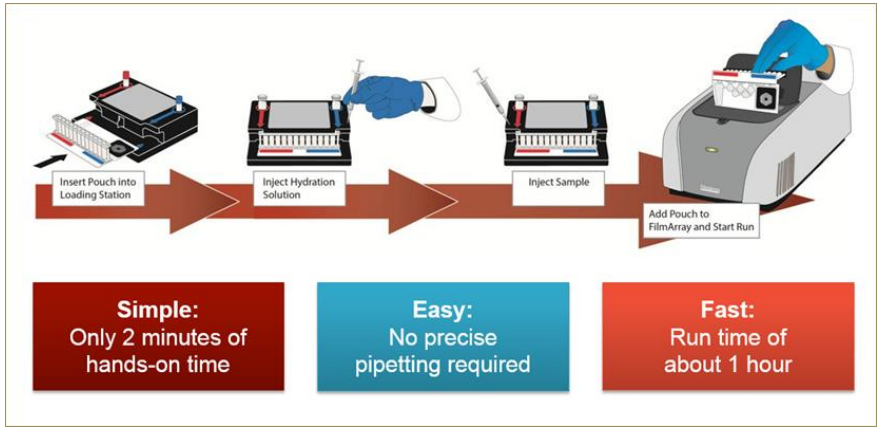
- Rapid **molecular** detection of the pathogen can **minimize** the empirical use of **broadspectrum antibiotics** in severe CAP, HAP, and VAP, but their **interpretation is difficult** due to . . . . (differences in the local treatment guidelines and resistance genes, the discrepancy between genotype and phenotype, the ongoing discovery of new resistance mechanisms, and, as a result, the potential presence of unknown mechanisms, which may lead to false-negative results using molecular techniques . . . . .)

  - Gadsby NJ, et al. Clin Infect Dis. 2016;62(7):817–23.

- The **Bio Fire Film Array Pneumonia Plus Panel** is an FDA-cleared sample-to-answer assay that enables the detection of **bacteria** and antimicrobial **resistance marker genes** from sputum and bronchoalveolar lavage fluid.

  - Murphy CN, et al. J Clin Microbiol. 2020;58(7):e00128–0.

BioFire® FilmArray®
Pneumonia *plus* Panel
Sample Type: Sputum (including ETA) and BAL (including mini-BAL)
CE-marked and US FDA-cleared



Lista esami Tutti

Esame	Campione			U.M.	V. Riferimento	10/12/2023 10:18	11/12/2023 05:49	11/12/2023 06:00	13/12/2023 12:50
SARS CoV-2 Antigene 3° gen	Tampone rino-faringeo Tempo T0							Negativo	
SARS-CoV-2 RNA	Tampone rino-faringeo Tempo T0								**Non Rilevato**
Tamp rettale x monitoraggio	Tampone rettale								
Esame colturale CRE							Negativo		
Urinocoltura	Urina								
Esame colturale						Positivo			
Carica Microbica						60.000 UFC/ml			
Flora residente faringea	Broncoaspirato					assente			
Colturale respiratori	Broncoaspirato								
Esame colturale aerobi						Positivo			
PCR multiplex Pannello Polmoniti	Broncoaspirato								
Acinetobacter calcoaceticus-baumannii complex						Non Rilevato			
Enterobacter cloacae complex						Non Rilevato			
Escherichia coli						Non Rilevato			
Haemophilus influenzae						Non Rilevato			
Klebsiella aerogenes						Non Rilevato			
Klebsiella oxytoca						Non Rilevato			
Klebsiella pneumoniae group						Non Rilevato			
Moraxella catarrhalis						Non Rilevato			
Proteus spp						Non Rilevato			
Pseudomonas aeruginosa						Rilevato			
Serratia marcescens						Non Rilevato			
Staphylococcus aureus						Rilevato			
Streptococcus agalactiae						Non Rilevato			
Streptococcus pneumoniae						Non Rilevato			
Streptococcus pyogenes						Non Rilevato			
CTX-M						Non Rilevato			
IMP						Non Rilevato			
KPC						Non Rilevato			
mecA/C e MREJ						Non Rilevato			

Serratia marcescens						Non Rilevato			
Staphylococcus aureus						Rilevato			
Streptococcus agalactiae						Non Rilevato			
Streptococcus pneumoniae						Non Rilevato			
Streptococcus pyogenes						Non Rilevato			
CTX-M						Non Rilevato			
IMP						Non Rilevato			
KPC						Non Rilevato			
mecA/C e MREJ						Non Rilevato			
NDM						Non Rilevato			
VIM						Non Rilevato			
Chlamydia pneumoniae						Non Rilevato			
Legionella pneumophila						Non Rilevato			
Mycoplasma pneumoniae						Non Rilevato			
Adenovirus						Non Rilevato			
Coronavirus						Non Rilevato			
Metapneumovirus						Non Rilevato			
Rhinovirus/Enterovirus						Non Rilevato			
Influenza A						Non Rilevato			
Influenza B						Non Rilevato			
MERS Coronavirus						Non Rilevato			
Parainfluenza Virus						Non Rilevato			
Respiratorio Sinciziale Virus						Non Rilevato			
1,3 Beta-D-Glucano	Siero						Dubbio		

Esame	Data	Nota
Coronavirus	10/12/2023 10:18	*Il test non ricerca Sars CoV-2*
	10/12/2023 10:18	*Il test non ricerca Sars CoV-2*
1,3 Beta-D-Glucano	11/12/2023 05:49	*Valori di riferimento per la popolazione adulta:* *<60 pg/mL Negativo* *60-79 pg/mL Dubbio* *>=80 pg/mL Positivo* *N.B. Il saggio non rileva alcune specie fungine (genere Cryptococcus, Zigomiceti, Blastomyces dermatitidis)*
	11/12/2023 05:49	73 pg/mL

New antibiotics for Gram-negative pneumonia

Patients at risk for Gram-negative bacilli CAP as well as the risk factors associated with the isolation of multidrug-resistant (MDR) strains.

Mechanisms for resistance to antibiotics

- Alteration of the drug target,
- Decreased membrane permeability
- Drug efflux pumps
- Hydrolysis mediated by the production of degrading enzymes is the **most common mechanism of resistance** in clinically important Gram-negative bacteria

- Bassetti M, et al. Curr Opin Infect Dis 2020; 33: 474–481.
- Vena A, et al. Curr Opin Infect Dis 2019; 32: 638–646.

TABLE 1 Risk factors associated with community-acquired pneumonia (CAP) caused by Gram-negative bacteria (including multidrug-resistant (MDR) strains)

	Risk factor for MDR strain
Demographics	
Older age [102]	No
Underweight [103]	Yes
Residence in a nursing home or extended care facility [102]	No
Underlying conditions	
Chronic lung disease, mainly COPD and bronchiectasis [104–106]	Yes
Immunodepression [102]	No
Chronic dialysis [102]	No
Cardiovascular disease [103, 105]	Yes
Cerebrovascular disease [105]	No
Diabetes [107]	No
Others	
Smoking [107]	No
Antimicrobial (both oral and intravenous) in the preceding 90 days [104, 106]	Yes
Home wound care [102]	No
Prior infection or colonisation with an MDR Gram-negative pathogen (*e.g. Pseudomonas aeruginosa*) [104, 107]	Yes
Prior hospitalisation [103]	Yes
Enteral tube feeding [105]	No
Clinical presentation	
Severe disease (*e.g.* CAP requiring ICU admission) [103, 106]	No
PSI score III, IV [104]	No

ICU: intensive care unit; PSI: pneumonia severity index.

- Bassetti M, et al.. Eur Respir Rev 2022; 31: 220119

Ceftobiprole

- Fifth-generation cephalosporin approved for the treatment of CAP and HAP, excluding VAP.

- Potent activity against several Gram-negative pathogens:
  - Haemophilus influenzae,
  - Moraxella catarrhalis,
  - P. aeruginosa
- But not against Enterobacterales:
  - Extended-spectrum β-lactamases (ESBL)-,
  - Carbapenemases-
  - Metallo-β-lactamases (MBL)-producing
- No activity against A. baumannii and Stenotrophomonas maltophilia.

	Ceftobiprole
Antimicrobial activity	*Moraxella catarrhalis*, *Haemophilus influenza*, non-ESBL-, non-AmpC- and noncarbapenemases-producing Enterobacterales; *Pseudomonas aeruginosa*
Approved dosage for the treatment of pneumonia	2 h *i.v.* infusion 500 mg every 8 h
Pros	Approved for CAP and HAP, but not for VAP

- Pronounced bactericidal activity against **Gram-positive bacteria**, such as Str. pneumoniae and methicillin-resistant Staphylococcus aureus (MRSA).

- Mendez R, et al. Rev Esp Quimioter 2022; 35: Suppl. 1, 25–27.

Ceftolozane-tazobactam (Zerbaxa®)

- Combination of a modified cephalosporin (ceftolozane) with a well-established β-lactamase inhibitor (tazobactam).
- Stable against multiple **resistance mechanisms** of Gram-negative bacteria, including overexpression of **AmpC**, **porin loss** or **drug efflux pumps.**
- The MOST active β-lactam against **P. aeruginosa**, including MDR or extremely drug resistant (XDR) isolates.
- Activity against ESBL-producing Enterobacterales
- It **lacks activity** against all **carbapenemases-producing strains** (e.g. **MBL** or serine carbapenemases), including P. aeruginosa and Enterobacterales.
- The combination also lacks efficacy against A. baumannii or S. maltophilia

	Ceftolozane-tazobactam
Antimicrobial activity	ESBL-producing Enterobacterales; MDR *P. aeruginosa*
Approved dosage for the treatment of pneumonia	2 g of ceftolozane and 1 g of tazobactam every 8 h by *i.v.* infusion over 1 h
Pros	Best β-lactam with activity against *P. aeruginosa* Carbapenem-sparing agent Lower mortality observed in patients with ventilated HAP

- Candel FJ, et al. Rev Esp Quimioter 2022; 35: Suppl. 1, 35–39.
- Tamma PD, et al. J Pediatric Infect Dis Soc 2019; 8: 251–260.

	Enterobacterales					
	Class A Carbapenemase (*e.g.* KPC)	**Class B Carbapenemase (*e.g.* NDM)**	**Class D Carbapenemase (*e.g.* OXA-48)**	***Pseudomonas aeruginosa***	***Acinetobacter baumannii***	***Stenotrophomonas maltophilia***
Ceftolozane-tazobactam						

The drug achieves good penetration in the lung parenchyma

- Bassetti M,, et al.. Eur Respir Rev 2022; 31: 220119

Ceftazidime-avibactam (Zavicefta®)

- Combination agent containing a semi-synthetic **third-generation cephalosporin** and a **novel non β-lactam/β-lactamases inhibitor**.

- **Avibactam protects** ceftazidime from the hydrolytic activity of a wide range of class **A** (e.g. ESBL and K. pneumoniae carbapenemases (KPC)), **C** (e.g.AmpC) and **D** β-lactamases (e.g. OXA-48 enzymes).

- It **lacks activity** against class B β-lactamases and has **low activity** against **A. baumannii** or anaerobic Gram-negative bacteria and **Gram-positive cocci**

	Ceftazidime-avibactam
Antimicrobial activity	ESBL-, KPC-, AmpC- and OXA-48-producing Enterobacterales; MDR *P. aeruginosa*
Approved dosage for the treatment of pneumonia	2 g of ceftazidime and 0.5 g of avibactam every 8 h by *i.v.* infusion over 2 h
Pros	Good clinical experience for treatment of KPC infection Carbapenem-sparing agent Good activity OXA-48-producing Enterobacterales Can be combined with aztreonam for the treatment of MBL-producing Enterobacterales

	Enterobacterales					
	Class A Carbapenemase (*e.g.* KPC)	**Class B Carbapenemase (*e.g.* NDM)**	**Class D Carbapenemase (*e.g.* OXA-48)**	***Pseudomonas aeruginosa***	***Acinetobacter baumannii***	***Stenotrophomonas maltophilia***
Ceftazidime-avibactam						

ceftazidime-avibactam currently represents the drug of choice for the treatment of HAP or VAP due to OXA-48- or KPC-producing Enterobacterales. It may also have a role in nosocomial pneumonia caused by ESBL-producing Enterobacterales or CR *P. aeruginosa*

Lung penetration … epithelial lung fluid and plasma concentrations of ceftazidime and avibactam increase in a **dose-dependent manner** for both molecules, with a plasma/ELF ratio of 40%.

- Dimelow R, et al. Drugs R D 2018; 18: 221–230.
- Bassetti M, et al.. Eur Respir Rev 2022; 31: 220119

Cefiderocol (Fectroja®)

- Cefiderocol is a **new modified cephalosporin** with a cathecol side chain that forms a chelated complex with ferric iron.
- This mechanism facilitates its penetration into bacterial cells, where cefiderocol inhibits cell-wall synthesis by binding to penicillin-binding proteins and inhibiting peptidoglycan synthesis

• Sato T, et al. Clin Infect Dis 2019; 69: Suppl. 7, S538–S543.

- Retains activity even in the presence of **β-lactamases such as Ambler class A, B, C and D β-lactamases**

	Cefiderocol
Antimicrobial activity	ESBL- and CRE (class A, B, and D enzymes)-producing Enterobacterales; MDR *P. aeruginosa*, *S. maltophilia* and *A. baumannii*
Approved dosage for the treatment of pneumonia	2 g every 8 h by *i.v.* infusion over 3 h
Pros	Wide spectrum of activity Unique drug with activity against MBL-producing Enterobacterales

	Enterobacterales					
	Class A Carbapenemase (*e.g.* KPC)	**Class B Carbapenemase (*e.g.* NDM)**	**Class D Carbapenemase (*e.g.* OXA-48)**	***Pseudomonas aeruginosa***	***Acinetobacter baumannii***	***Stenotrophomonas maltophilia***
[redacted]						
Cefiderecol						
[redacted]						

To conclude, we believe that cefiderocol currently represents an interesting therapeutic choice for the treatment of HAP and VAP due to MBL-producing Enterobacterales, MDR *P. aeruginosa* and other CR Gram-negative bacteria.

Cefiderecol showed a similar **lung** tissue concentration (ELF/plasma AUC ratio 0.239 for cefiderocol compared to 0.229 for ceftazidime)

- Katsube T, et al. J Antimicrob Chemother 2019; 74: 1971–1974.
- Bassetti M, et al.. Eur Respir Rev 2022; 31: 220119

Meropenem-vaborbactam (Vaborem®)

- Combination of:
  - 1) a well-established carbapenem, meropenem, with
  - 2) vaborbactam, a new non-β-lactam β-lactamase inhibitor derived from boric acid.

- Vaborbactam protects meropenem from the degradation by **class A and C** β lactamases.

  - Novelli A et al. Expert Rev Anti Infect Ther 2020; 18: 643–655.

- However, no activity was observed against class B and D β-lactamases.

	Meropenem-vaborbactam
Antimicrobial activity	ESBL-, KPC- and AmpC-producing *Enterobacterales*; non-MDR *P. aeruginosa*; non-MDR *A. baumannii*
Approved dosage for the treatment of pneumonia	2 g of meropenem and 2 g of vaborbactam every 8 h by *i.v.* infusion over 3 h
Pros	Potent activity against KPC Low-propensity for developing *in vivo* resistance

	Enterobacterales					
	Class A Carbapenemase (*e.g.* KPC)	**Class B Carbapenemase (*e.g.* NDM)**	**Class D Carbapenemase (*e.g.* OXA-48)**	***Pseudomonas aeruginosa***	***Acinetobacter baumannii***	***Stenotrophomonas maltophilia***
Meropenem-vaborbactam						

The **lung** penetration of meropenem vaborbactam was considerable, with AUC values of 63% and 53% in the ELF and total plasma, respectively.

- Wenzler E, et al. Antimicrob Agents Chemother 2015; 59:7232–7239.
- Bassetti M, et al.. Eur Respir Rev 2022; 31: 220119

Imipenem-relebactam

- Relebactam: β-lactamase inhibitor developed to restore the activity of imipenem against Gram-negative isolates producing class A and C β-lactamases, but not class B and class D

- Haidar G et al. Antimicrob Agents Chemother 2017; 61: e00642-17.
- Barnes MD, et al. Antimicrob Agents Chemother 2018; 62: e02406-17..

- The addition of relebactam to imipenem substantially restores the activity of imipenem against the majority of imipenem nonsusceptible **P. aeruginosa** and **KPC-producing Enterobacterales**, but not against A. baumannii or Stenotrophomonas maltophilia

	Imipenem-relebactam
Antimicrobial activity	ESBL- and KPC-producing *Enterobacterales*; MDR *P. aeruginosa*
Approved dosage for the treatment of pneumonia	500 mg of imipenem and 250 mg of relebactam by *i.v.* infusion every 6 h over 30 min
Pros	Potent activity against KPC Potent activity against MDR *P. aeruginosa*

	Enterobacterales					
	Class A Carbapenemase (*e.g.* KPC)	**Class B Carbapenemase (*e.g.* NDM)**	**Class D Carbapenemase (*e.g.* OXA-48)**	***Pseudomonas aeruginosa***	***Acinetobacter baumannii***	***Stenotrophomonas maltophilia***
Imipenem-relebactam						

imipenem-relebactam should be always considered for the treatment of suspected or confirmed HAP/VAP caused by KPC-producing Enterobacterales or by CR *P. aeruginosa* (nonmetallo-carbapenemases)

- Bassetti M, et al.. Eur Respir Rev 2022; 31: 220119

Aztreonam-avibactam

- Aztreonam is a β-lactam which has activity **against MBL**.
- Avibactam confers aztreonam stability against **most MDR Gram-negative bacteria**, including those coharbouring class A, C and D β-lactamases

- Shields RK et al. Clin Infect Dis 2020; 71: 1099–1101.
- Sader HS, et al. Antimicrob Agents Chemother 2018;62: e01856-17

- Drug efficacy and safety **are currently being evaluated** in an ongoing pivotal trial for the treatment of serious Gram-negative infections

- ClinicalTrials.gov. A study to determine the efficacy, safety and tolerability of aztreonam-vibactam (ATM-AVI)±metronidazole (MTZ) versus meropenem (MER)±colistin (COL) for the treatment of serious infections due to Gram negative bacteria (REVISIT). https://clinicaltrials.gov/ct2/show/NCT03329092 Date last updated: 28 October 2022.

	Enterobacterales					
	Class A Carbapenemase (*e.g.* KPC)	**Class B Carbapenemase (*e.g.* NDM)**	**Class D Carbapenemase (*e.g.* OXA-48)**	***Pseudomonas aeruginosa***	***Acinetobacter baumannii***	***Stenotrophomonas maltophilia***
[redacted]						
Aztreonam-avibactam						
[redacted]						

- Bassetti M, et al.. Eur Respir Rev 2022; 31: 220119

Eravacycline

- New tetracycline derivate that acts on the 30s ribosomal subunit to inhibit bacterial protein synthesis.

- It is available in both an intravenous formulation and an oral one.
- The activity of eravacycline ranges from **Gram-positive to Gram-negative bacteria**, showing a great spectrum of effectiveness, which includes difficult-to-treat bacteria such as **A. baumannii** isolates resistant to sulbactam.
- On the other hand, it shows no activity against P. aeruginosa

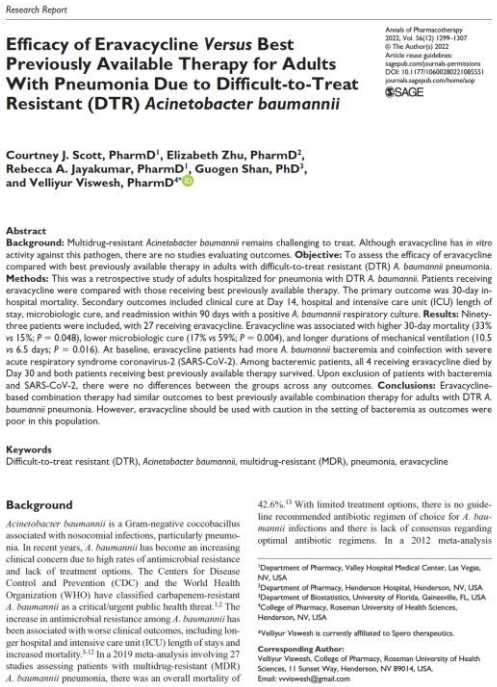
- Zhanel GG, et al. Drugs 2016; 76: 567–588.
- Seifert H, et al. Int J Antimicrob Agents 2018; 51: 62–64.

	Enterobacterales					
	Class A Carbapenemase (*e.g.* KPC)	**Class B Carbapenemase (*e.g.* NDM)**	**Class D Carbapenemase (*e.g.* OXA-48)**	***Pseudomonas aeruginosa***	***Acinetobacter baumannii***	***Stenotrophomonas maltophilia***
[redacted]						
Eravacycline						

- Bassetti M, et al.. Eur Respir Rev 2022; 31: 220119

Eravacycline

- Phase 1 study → volunteers → concentrations of eravacycline were found to be six times greater in the ELF compared to plasma and 50 times in the alveolar macrophages.
  - Connors KP,, et al.. Antimicrob Agents Chemother 2014; 58: 2113–2118.



Research Report

Efficacy of Eravacycline *Versus* Best Previously Available Therapy for Adults With Pneumonia Due to Difficult-to-Treat Resistant (DTR) *Acinetobacter baumannii*

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Courtney J. Scott, PharmD[1], Elizabeth Zhu, PharmD[2], Rebecca A. Jayakumar, PharmD[1], Guogen Shan, PhD[3], and Velliyur Viswesh, PharmD[4*]

Abstract

Background: Multidrug-resistant *Acinetobacter baumannii* remains challenging to treat. Although eravacycline has *in vitro* activity against this pathogen, there are no studies evaluating outcomes. **Objective:** To assess the efficacy of eravacycline compared with best previously available therapy in adults with difficult-to-treat resistant (DTR) *A. baumannii* pneumonia. **Methods:** This was a retrospective study of adults hospitalized for pneumonia with DTR *A. baumannii*. Patients receiving eravacycline were compared with those receiving best previously available therapy. The primary outcome was 30-day in-hospital mortality. Secondary outcomes included clinical cure at Day 14, hospital and intensive care unit (ICU) length of stay, microbiologic cure, and readmission within 90 days with a positive *A. baumannii* respiratory culture. **Results:** Ninety-three patients were included, with 27 receiving eravacycline. Eravacycline was associated with higher 30-day mortality (33% *vs* 15%; $P = 0.048$), lower microbiologic cure (17% *vs* 59%; $P = 0.004$), and longer durations of mechanical ventilation (10.5 *vs* 6.5 days; $P = 0.016$). At baseline, eravacycline patients had more *A. baumannii* bacteremia and coinfection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Among bacteremic patients, all 4 receiving eravacycline died by Day 30 and both patients receiving best previously available therapy survived. Upon exclusion of patients with bacteremia and SARS-CoV-2, there were no differences between the groups across any outcomes. **Conclusions:** Eravacycline-based combination therapy had similar outcomes to best previously available combination therapy for adults with DTR *A. baumannii* pneumonia. However, eravacycline should be used with caution in the setting of bacteremia as outcomes were poor in this population.

Keywords

Difficult-to-treat resistant (DTR), *Acinetobacter baumannii*, multidrug-resistant (MDR), pneumonia, eravacycline

Background

Acinetobacter baumannii is a Gram-negative coccobacillus associated with nosocomial infections, particularly pneumonia. In recent years, *A. baumannii* has become an increasing clinical concern due to high rates of antimicrobial resistance and lack of treatment options. The Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) have classified carbapenem-resistant *A. baumannii* as a critical/urgent public health threat.[1,2] The increase in antimicrobial resistance among *A. baumannii* has been associated with worse clinical outcomes, including longer hospital and intensive care unit (ICU) length of stays and increased mortality.[3-12] In a 2019 meta-analysis involving 27 studies assessing patients with multidrug-resistant (MDR) *A. baumannii* pneumonia, there was an overall mortality of 42.6%.[13] With limited treatment options, there is no guideline recommended antibiotic regimen of choice for *A. baumannii* infections and there is lack of consensus regarding optimal antibiotic regimens. In a 2012 meta-analysis

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Email: vviswesh@gmail.com

- **Retrospective study** → A. baumannii pneumonia → eravacycline was associated with higher 30-day mortality (33% versus 15%; p=0.048), lower microbiologic cure (17% versus 59%; p=0.004) and longer durations of mechanical ventilation (10.5 versus 6.5 days; p=0.016).

- According to these results,further data are needed before administering eravacycline for the treatment of pneumonia
  - Scott CJ et al.. Ann Pharmacother 2022; 56: 1299–1307.

Conclusion and recommendations

- Worldwide, the prevalence of **GNB** among pneumonia patients is **GROWING**.

- The predominant MDR-GNB in recently published studies causing pneumonia were **A. baumannii**, **K. pneumoniae**, and **P. aeruginosa**, with A. baumannii isolated particularly in VAP patients.

- The prevalence of MDR-GNB is higher in the **elderly population**, prior MDR-GNB infection, prolonged hospital stays, ICU admission, mechanical ventilation, surgical intervention, prior antibiotic use, comorbidity, chronic alcoholism, and enteral malnutrition.

- **Novel PCR-based techniques** should be implemented for the early detection of drug-resistant genes to overcome the transmission of highly resistant genes between bacteria.
- Since there are increased MDR and PDR gram-negative strains, it makes the **treatment more complicated**, which may lead to high morbidity, economic losses, and mortality.
- To this end, newer, effective combination therapies with minimal clinical side effects, antibiotics against drug-resistant genes, antibiofilm agents, should be developed.

Conclusion and recommendations

- **All these new antibiotics** show good in vitro and in vivo activity against these pathogens, with a low risk of developing in vivo resistance at the currently recommended dosage.

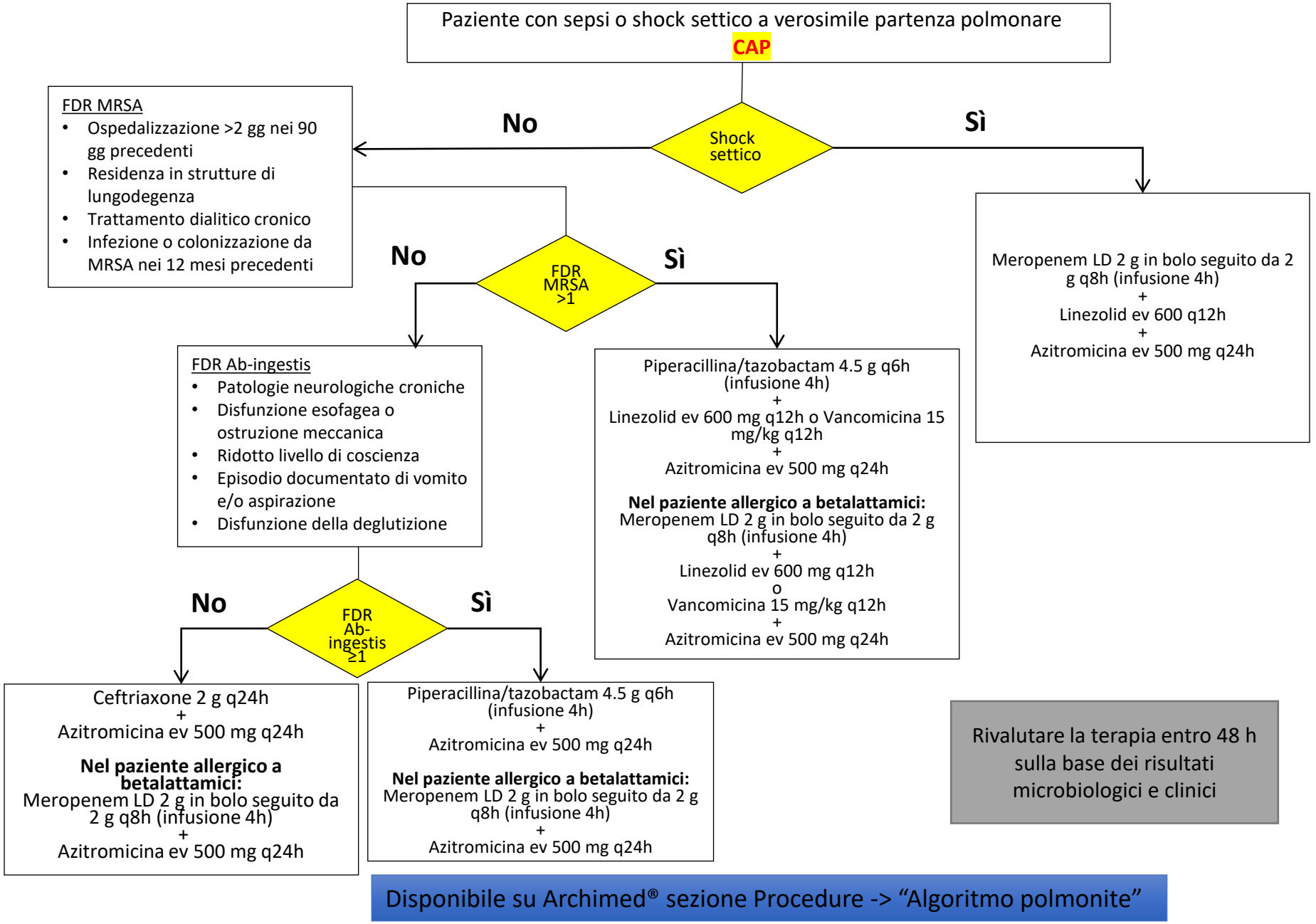
- The available data demonstrate their efficacy and **safety** in patients with MDR infections, with a **low potential for toxicity** in comparison with old regimens including colistin or aminoglycosides, which have been the standard of care until very few years ago.

- A good antimicrobial stewardship and a clever usage of these agents will make it possible to keep the resistance levels as low as they are now, thus ensuring their longevity in our armamentarium.

- The use of new antibiotics (ceftazidime–avibactam, ceftolozane–tazobactam, cefiderocol) should be **restricted to documented infection or suspected infection in colonized patients**, when no other option exists; their use increasing the risk of emergence of resistance

- Ruedas-López A, et al. Antimicrob Agents Chemother. 2022;66: e0206721.
- Sadek M, et al. Eur J Clin Microbiol Infect Dis. 2022;

Terapia empirica del paziente con sepsi o shock settico a verosimile partenza polmonare



Rivalutare la terapia entro 48 h sulla base dei risultati microbiologici e clinici

Disponibile su Archimed® sezione Procedure -> “Algoritmo polmonite”

Terapia empirica del paziente con sepsi o shock settico a verosimile partenza polmonare

Paziente con sepsi o shock settico a verosimile partenza polmonare

HAP

FDR Ab-ingestis

- Patologie neurologiche croniche
- Disfunzione esofagea o ostruzione meccanica
- Ridotto livello di coscienza
- Episodio documentato di vomito e/o aspirazione
- Disfunzione della deglutizione

No

Ceftolozane/tazobactam 3 g q8h (infusione almeno 2h)
+
Linezolid ev 600 mg q12h (1a scelta)
o
Vancomicina 15 mg/kg q12h
+
Azitromicina* ev 500 mg q24h

Nel paziente allergico a betalattamici:
Meropenem LD 2 g in bolo seguito da 2 g q8h (infusione 4h)
+
Linezolid ev 600 mg q12h
o
Vancomicina 15 mg/kg q12h
+
Azitromicina* ev 500 mg q24h

Sì

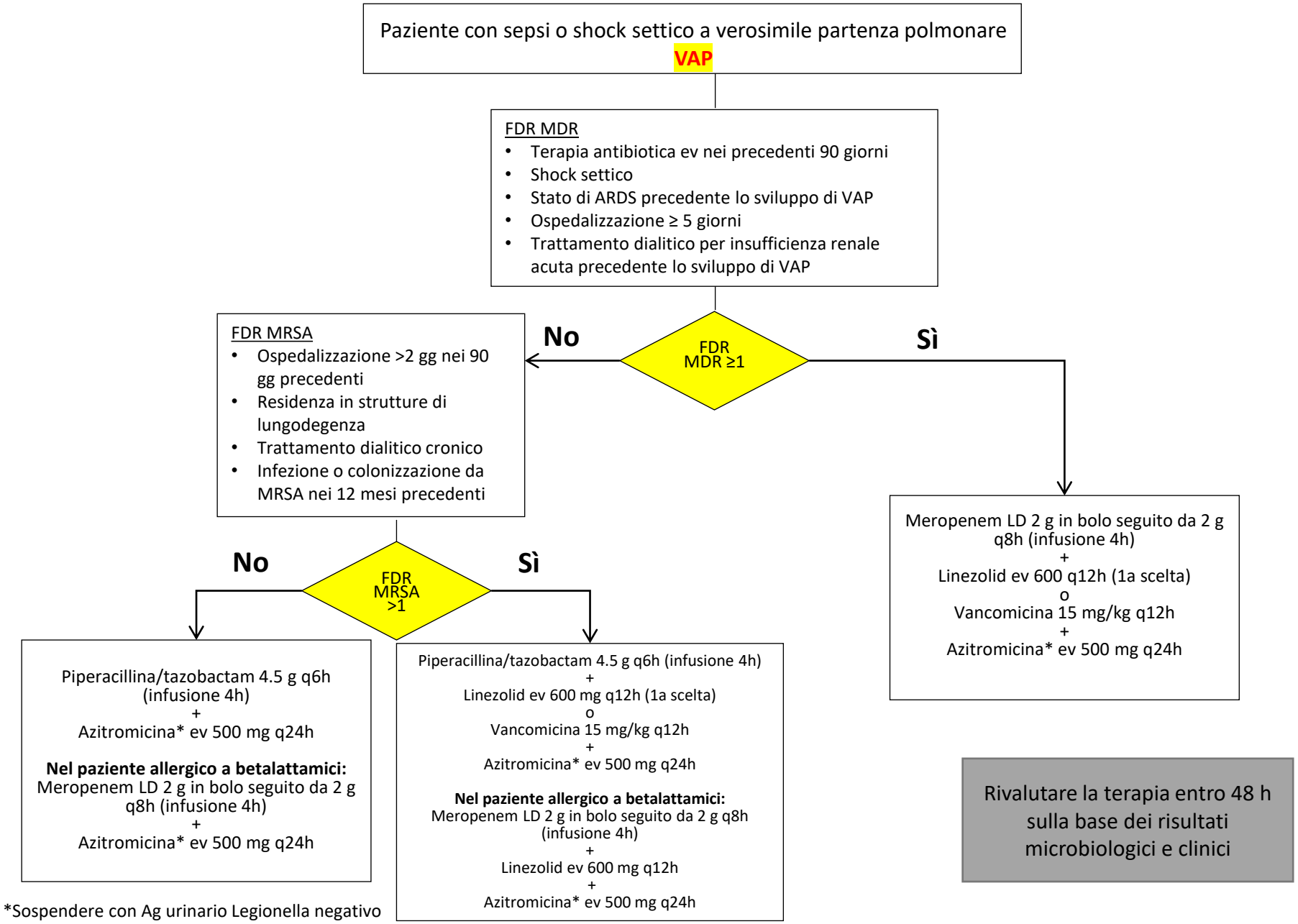
Ceftolozane/tazobactam 3 g q8h (infusione almeno 2h)
+
Linezolid ev 600 mg q12h (1a scelta)
o
Vancomicina 15 mg/kg q12h
+
Metronidazolo ev 500 mg q6h
+
Azitromicina* ev 500 mg q24h

Nel paziente allergico a betalattamici:
Meropenem LD 2 g in bolo seguito da 2 g q8h (infusione 4h)
+
Linezolid ev 600 mg q12h
o
Vancomicina 15 mg/kg q12h
+
Azitromicina* ev 500 mg q24h

Rivalutare la terapia entro 48 h sulla base dei risultati microbiologici e clinici

*Sospendere con Ag urinario Legionella negativo

Terapia empirica del paziente con sepsi o shock settico a verosimile partenza polmonare



*Sospendere con Ag urinario Legionella negativo