SITA
Società Italiana di Terapia Antinfettiva
Antibatterica Antivirale Antifungina

13° CONGRESSO NAZIONALE
PADOVA | 23-24 novembre 2023

Innovazione ed impatto dell'AMS e novità dal PNCAR 2023-2025

Pierluigi Viale

Dipartimento Inter-Aziendale per la Gestione Integrata del Rischio Infettivo

Città Metropolitana di Bologna

Il PNCAR

Il Piano Nazionale Contro le Antibiotico-Resistenze 2017-2021

Obiettivi

- Identificare principali esiti di salute che si vogliono raggiungere attraverso la sua realizzazione
- Individuare azioni principali da realizzare a livello nazionale e regionale/locale per il contrasto dell'AMR:
  - sorveglianza, prevenzione e controllo delle infezioni da microrganismi resistenti e dell'AMR;
  - uso appropriato e sorveglianza del consumo degli antimicrobici;
  - potenziamento dei servizi diagnostici di microbiologia;
  - formazione degli operatori sanitari;
  - informazione/educazione della popolazione;
  - ricerca e sviluppo
- obiettivi a medio (2017-2018) e a lungo termine (2017-2020) e gli indicatori per le azioni considerate prioritarie;
- Piani operativi e documenti tecnici, locali, regionali e nazionali per le specifiche attività e responsabilità operative.

Il PNCAR

Il Piano Nazionale Contro le Antibiotico-Resistenze 2017-2021

Obiettivi strategici

1. Rafforzare l'approccio One Health
2. Rafforzare la prevenzione e la sorveglianza delle infezioni correlate all'assistenza (ICA) in ambito ospedaliero e territoriale;
3. Promuovere l'uso appropriato degli antibiotici e ridurre la frequenza delle infezioni causate da batteri resistenti in ambito umano e animale;
4. Promuovere l'innovazione e la ricerca nell'ambito della prevenzione, diagnosi e terapia delle infezioni resistenti agli antibiotici;
5. Rafforzare la cooperazione nazionale e la partecipazione dell'Italia alle iniziative internazionali nel contrasto all'AMR;
6. Migliorare la consapevolezza della popolazione e promuovere la formazione degli operatori sanitari e ambientali sul contrasto all'AMR

Il PNCAR

Il Piano Nazionale Contro le Antibiotico-Resistenze 2017-2021

Confronto PNCAR 17-21 vs 22-25

- Ampliato negli obbiettivi
- Ampliati gli ambiti di intervento
  - Inclusione della componente ambientale
  - Smaltimento degli antibiotici e dei contaminanti
  - Informazione, comunicazione e trasparenza
  - Aspetti etici
  - Cooperazione nazionale e internazionale
- Riviste le tempistiche di raggiungimento degli obbiettivi
  - «da breve a lungo termine» verso «semestrali»
- Ridistribuiti gli obbiettivi e le azioni
  - Maggior peso al livello nazionale
  - Recepimento a livello regionale

Il PNCAR

Il Piano Nazionale Contro le Antibiotico-Resistenze 2017-2021

Capitoli del Piano

1. *Governance*
2. Sorveglianza dell'Antibiotico-Resistenza (ABR)
3. Sorveglianza dell'utilizzo di antibiotici
4. Sorveglianza delle infezioni correlate all'assistenza (ICA)
5. Sorveglianza e monitoraggio ambientale
6. Prevenzione delle infezioni correlate all'assistenza
7. Prevenzione delle malattie infettive e zoonosi
8. Buon uso degli antibiotici in ambito umano
9. Buon uso degli antibiotici in ambito veterinario
10. Buon uso degli antibiotici e corretta gestione e raccolta differenziata
11. *Formazione*
12. *Informazione, comunicazione e trasparenza*
13. *Ricerca, innovazione e bioetica*
14. *Cooperazione nazionale e internazionale*

Il PNCAR

Il Piano Nazionale Contro le Antibiotico-Resistenze 2017-2021

La sorveglianza del consumo degli antibiotici

Obbiettivi:

1. **Modello integrato di sorveglianza dell'uso degli antibiotici in ambito umano e veterinario (modello One Health) a livello nazionale**
2. **Monitoraggio dell'impatto delle azioni del PNCAR sulla riduzione del consumo inappropriato di antibiotici**

Azioni	Attori	Periodo stimato di completamento	Indicatori/Indicatori SPiNCAR (ove disponibili riportare il codice numerico)
2.1 Monitoraggio dell'**impatto** delle azioni sulla **riduzione** del consumo inappropriato di **antibiotici** in ambito **territoriale**.	AIFA, MdS, Regioni/PA, Azienda Sanitaria	Per tutta la durata del Piano	NAZIONALE **Riduzione ≥10% del consumo (DDD/1000 ab die) di antibiotici sistemici** in ambito territoriale nel 2025 rispetto al 2022. Riduzione ≥20% del rapporto tra il consumo (DDD/1000 ab die) di molecole ad ampio spettro e di molecole a spettro ristretto nel 2025 rispetto al 2022.
2.2 Monitoraggio dell'**impatto** delle azioni sulla **riduzione** del consumo inappropriato di **antibiotici** nella popolazione **pediatrica**.	AIFA, MdS, Regioni/PA, Azienda Sanitaria	Per tutta la durata del Piano	NAZIONALE Incremento ≥30% ratio prescrizioni amoxicillina/amoxicillina+acido clavulanico. **Riduzione ≥10% del consumo (DDD/1000 ab die) di antibiotici sistemici in ambito territoriale nel 2025 rispetto al 2022**. Riduzione ≥20% del rapporto tra il consumo (DDD/1000 ab die) di molecole ad ampio spettro e di molecole a spettro ristretto nel 2025 rispetto al 2022
2.3 Monitoraggio dell'**impatto** delle azioni sulla **riduzione** del consumo inappropriato di **antibiotici** in ambito **ospedaliero**.	AIFA, MdS, Regioni/PPAA, Azienda Sanitaria ASL	Per tutta la durata del Piano	NAZIONALE **Riduzione >5% del consumo (DDD/100 giornate di degenza) di antibiotici sistemici in ambito ospedaliero nel 2025 rispetto al 2022.** Riduzione del consumo (DDD/100 giornate di degenza) di carbapenemi ≥10% in ambito ospedaliero nel 2025 rispetto al 2022. Riduzione del consumo (DDD/100 giornate di degenza) di fluorochinoloni ≥10% in ambito ospedaliero nel 2025 rispetto al 2022Incremento ≥30% ratio prescrizioni amoxicillina/amoxicillina+acido clavulanico.
2.4 Monitoraggio dell'**impatto** delle azioni sulla **riduzione** del consumo inappropriato di **antibiotici** in ambito **veterinario**.	MdS, Regioni/PPAA, Azienda Sanitaria, AIFA	Entro il primo semestre 2025	NAZIONALE **Riduzione ≥30% del consumo totale di antibiotici totali (mg/PCU) nel 2025 rispetto al 2020**. Riduzione ≥ 20% del consumo di antibiotici autorizzati in formulazioni farmaceutiche per via orale (premiscele, polveri e soluzioni orali) nel 2025 rispetto al 2020. Mantenimento a livelli sotto la soglia dell'1 mg/PCU dei consumi (mg/PCU) delle polimixine. Mantenimento a livelli sotto la soglia europea dei consumi (mg/PCU) delle classi di antibiotici considerati critici per l'uomo. Riduzione ≥ 10% del numero totale delle prescrizioni veterinarie di antimicrobici HPCIAs per animali da compagnia/deroga.
		Entro il primo semestre 2023	NAZIONALE Valutare il consumo di antimicrobici nelle diverse specie animali e categorie utilizzando le DDD totali, critici, formulazioni orali.
		Entro il primo semestre 2024	NAZIONALE Definire una % di riduzione del consumo distinto per specie/categoria animale.

Antibiotic resistance patterns among uropathogens in female outpatients affected by uncomplicated cystitis: Focus on fosfomycin.

Cai T et al, Int J Antimicrob Ag 2023 Nov; 62:106974

Urinary samples were collected from three high-volume laboratories from Jan 2015 to Dec 2020. The pattern of resistance to fosfomycin was analysed by using the Vitek II automated system. A total of 7289 urinary samples were collected and 8321 strains were analysed during the study period.

Isolated strain prevalente

Escherichia coli	6585
Klebsiella spp.	1241
Enterococcus faecalis	236
Enterococcus faecium	43
Pseudomonas spp.	156
Enterobacter spp.	54
ESBL producing	2338 (35.5%)

Fosfo R Escherichia coli	12.2%
Fosfo R Klebsiella spp.	16.2%

ESBL Escherichia coli	27.1%
ESBL Klebsiella spp.	44.3%

antibiotics

MDPI

Article

An Improvement in the Antimicrobial Resistance Patterns of Urinary Isolates in the Out-of-Hospital Setting Following Decreased Community Use of Antibiotics during the COVID-19 Pandemic

Sara Tedeschi [1,2,*], Elena Sora [3,4], Andrea Berlingeri [5], Denis Savini [3], Elena Rosselli Del Turco [2,4], Pierluigi Viale [1,2] and Fabio Tumietto [4,*]

[1] Department of Medical and Surgical Sciences, University of Bologna, 40138 Bologna, Italy
[2] Infectious Diseases Unit, Department for Integrated Infectious Risk Management, IRCCS Azienda Ospedaliero Universitaria di Bologna, 40138 Bologna, Italy
[3] Pharmacy Department, Bologna Local Health Unit, 40138 Bologna, Italy
[4] Antimicrobial Stewardship Unit, Bologna Local Health Unit, 40138 Bologna, Italy
[5] Microbiology Unit, IRCCS Azienda Ospedaliero Universitaria di Bologna, 40138 Bologna, Italy
* Correspondence: sara.tedeschi5@unibo.it (S.T.); fabio.tumietto@unibo.it (F.T.); Tel.: +39-0512144307 (S.T.); +39-0512144307 (F.T.)

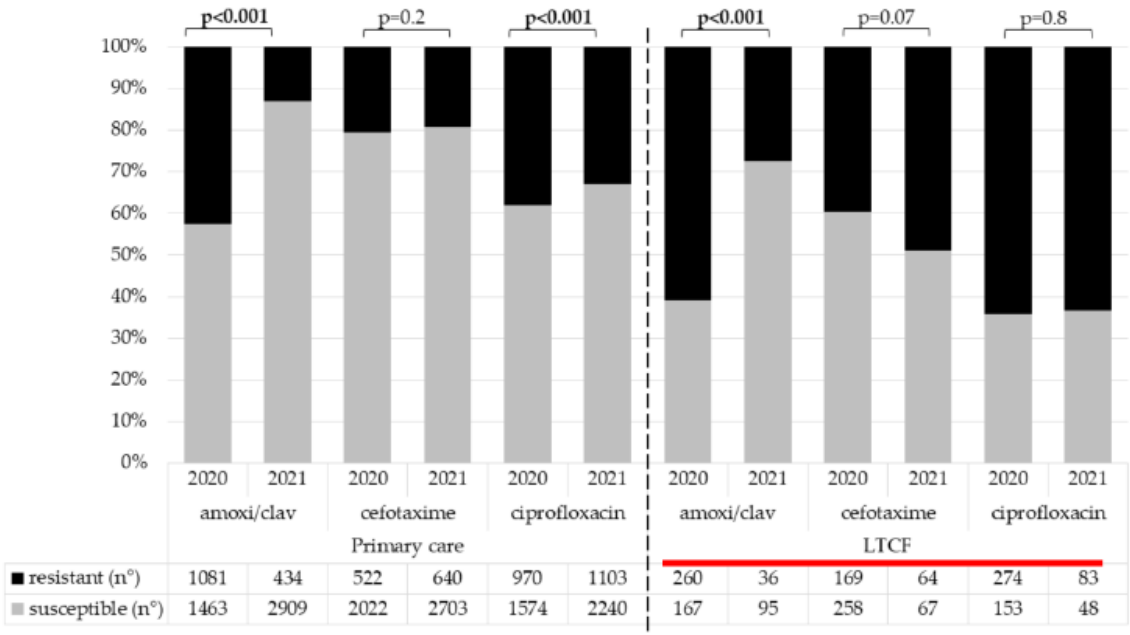
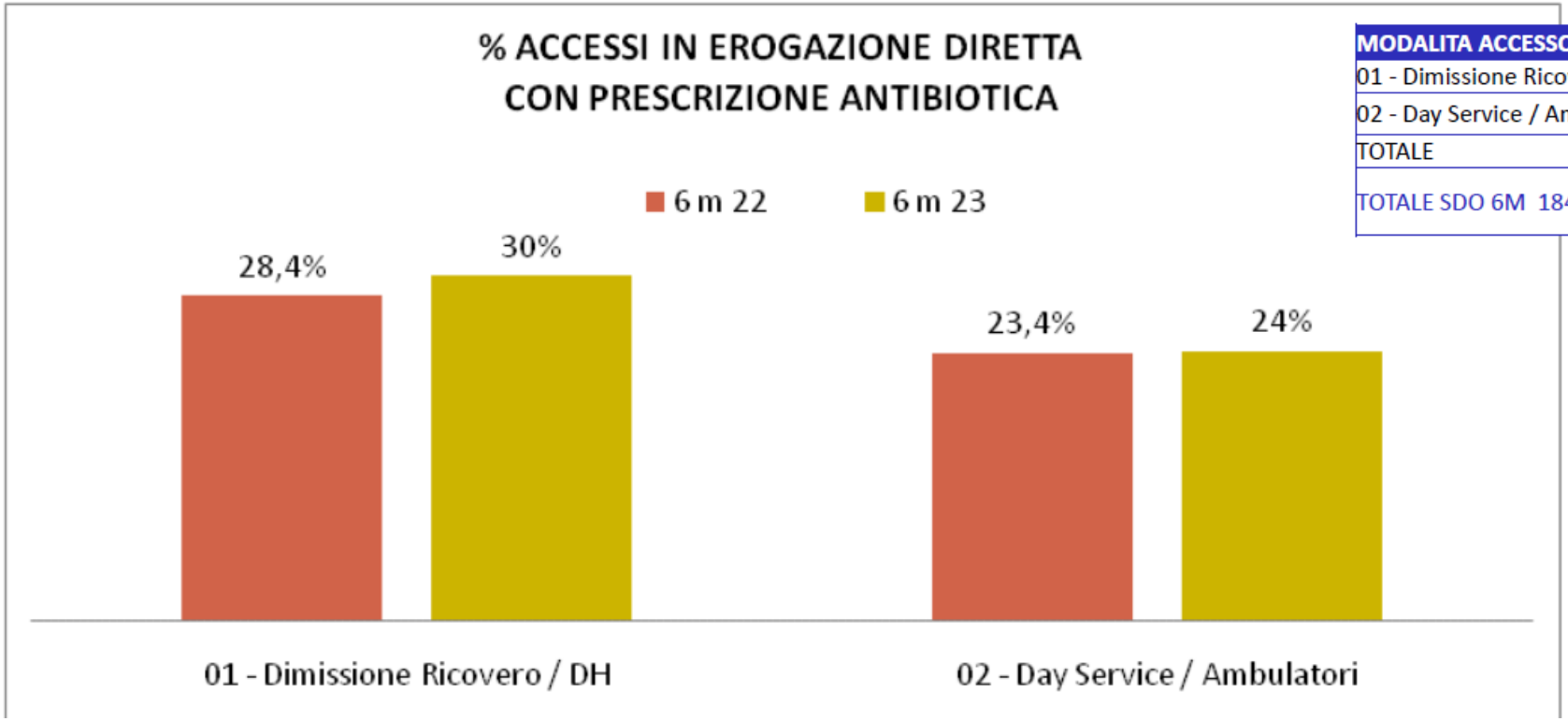


Figure 1. Comparison of antimicrobial susceptibility of *Enterobacterales* cultured from urine samples collected in the out-of-hospital setting during the first semester of 2020 and 2021.

***Antibiotics* 2023, *12*, 126.**

MONITORAGGIO CONSUMO ANTIMICROBICI NELLE TRANSIZIONI DI CURA
(Prescrizione dimissione_vis. Specialsitica)

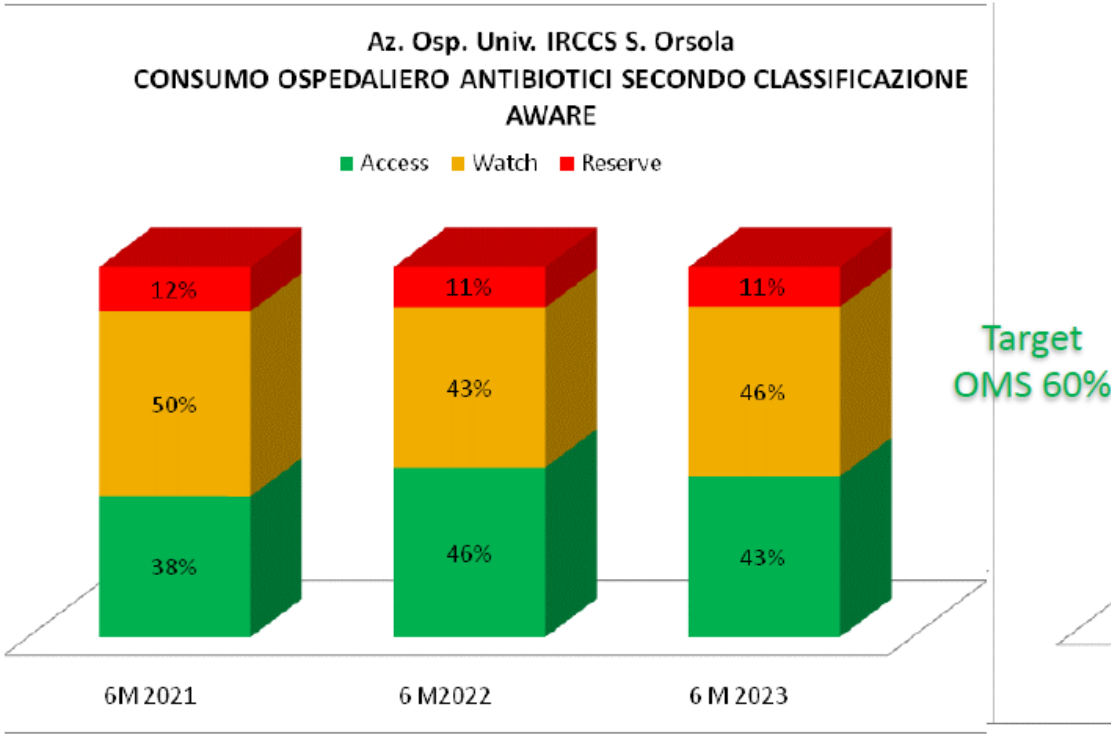
Az. Ospedaliero Universitaria IRCCS S. ORSOLA



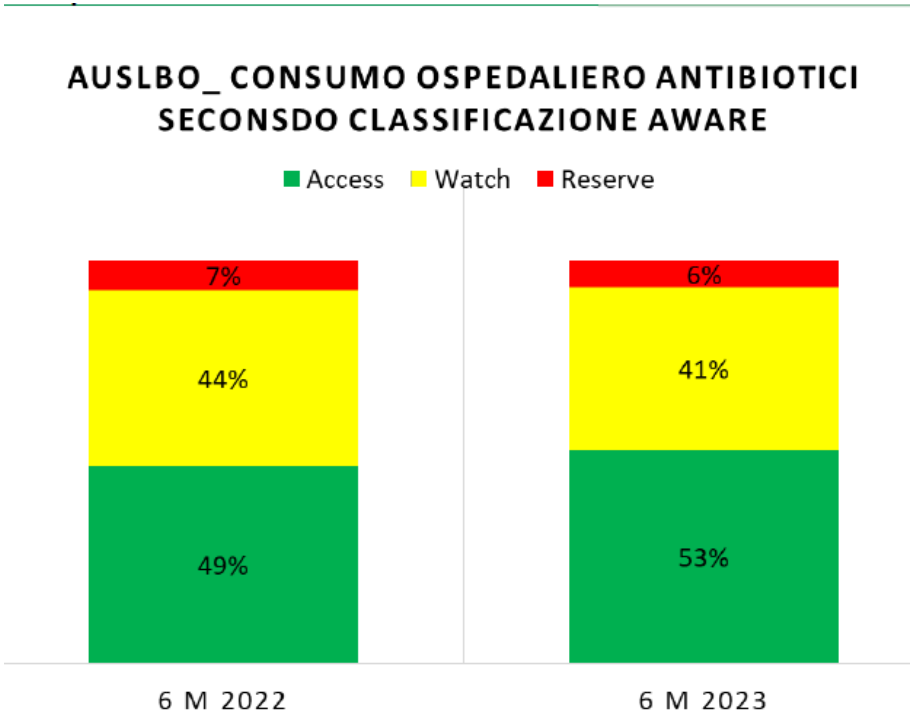
MODALITA ACCESSO IN ED	ED con antibiotico
01 - Dimissione Ricovero / DH	2.773
02 - Day Service / Ambulatori	2.960
TOTALE	**5.733**
TOTALE SDO 6M 184.0695	

Az. Osp. Univ. IRCCS S. Orsola

Consumo/spesa ospedaliero degli antibiotici sistemici per classificazione AWaRe dell'OMS



Target OMS 60%



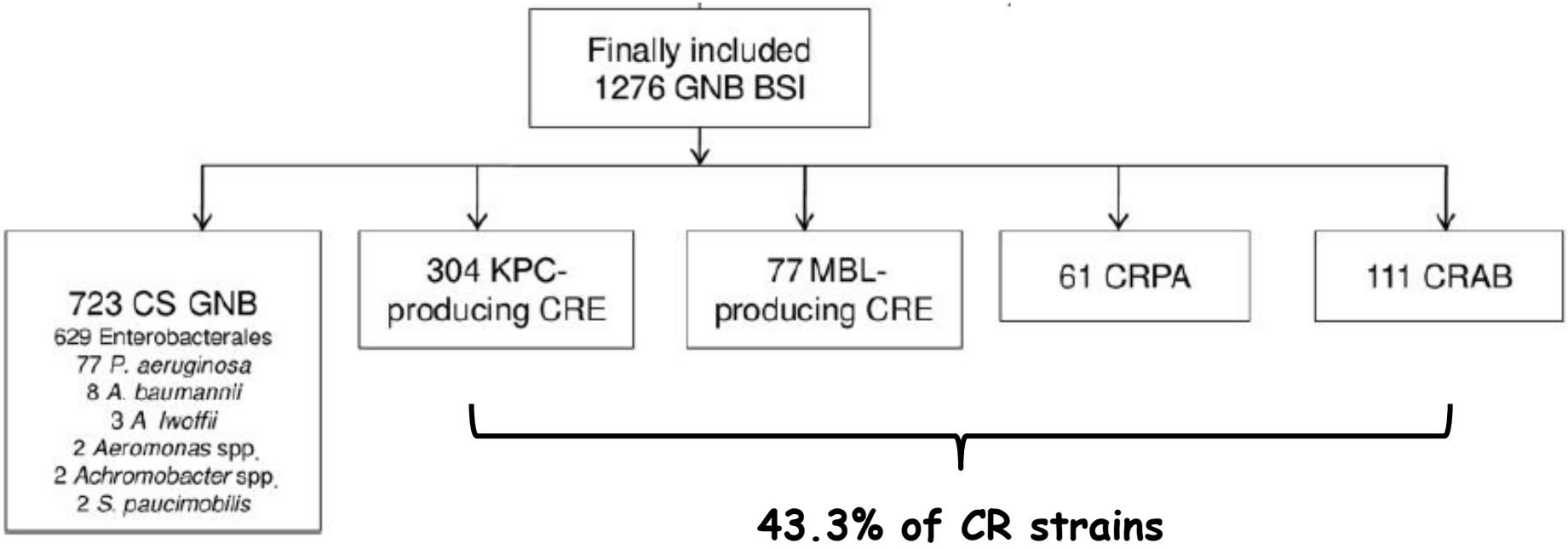
Az. USL Bologna

Consumo/spesa ospedaliero degli antibiotici sistemici per classificazione AWaRe dell'OMS

Mortality Attributable to Bloodstream Infections Caused by Different Carbapenem-Resistant Gram-Negative Bacilli: Results From a Nationwide Study in Italy (ALARICO Network).

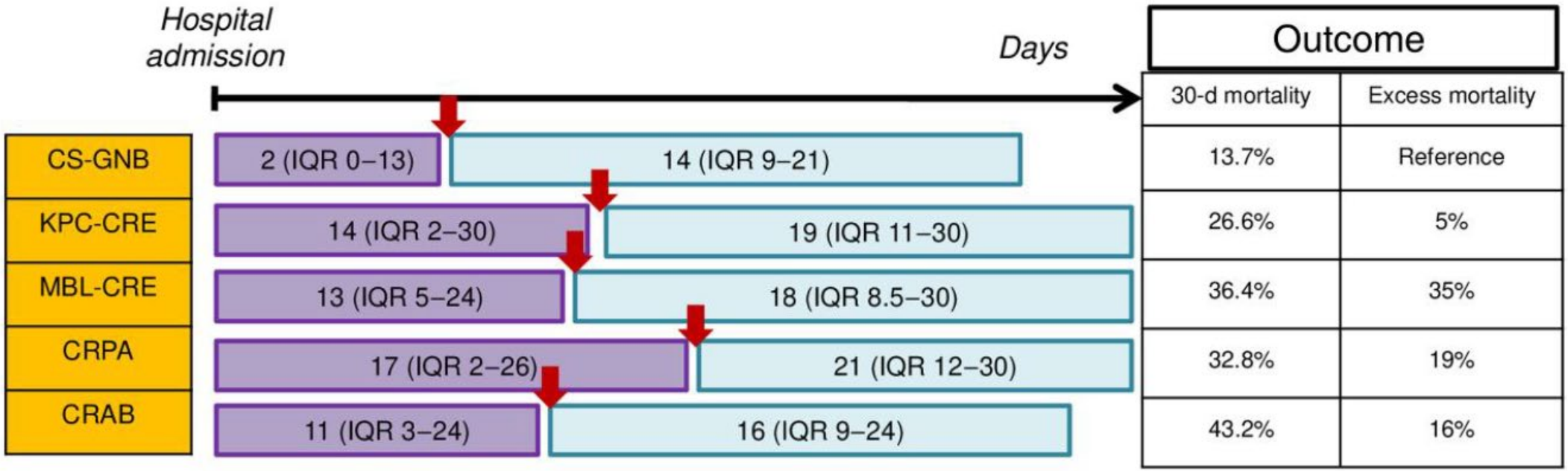
Falcone M et al Clin Infect Dis 2023; 76(12):2059–69

Prospective multicentric study including patients with GNB-BSI from 19 Italian hospitals (Jun 2018–Jan 2020). Patients were followed to 30 days. Primary outcomes were 30-day mortality and attributable mortality. A total of 1276 pts with monomicrobial GNB BSI were included.



Mortality Attributable to Bloodstream Infections Caused by Different Carbapenem-Resistant Gram-Negative Bacilli: Results From a Nationwide Study in Italy (ALARICO Network). *Falcone M et al Clin Infect Dis 2023; 76(12):2059–69*

Timeline of patient events in relation to the hospital admission, exposures, and outcomes



Outcome	
30-d mortality	Excess mortality
13.7%	Reference
26.6%	5%
36.4%	35%
32.8%	19%
43.2%	16%

Bloodstream infections due to Gram-negative bacteria in patients with hematologic malignancies: updated epidemiology and risk factors for MDR strains in an Italian perspective survey. *Trecarichi EM, et al. Int J Antimicrob Agents. 2023. Jun;61(6):106806.*

A total of 834 GNB were recovered in 811 BSI episodes from Jan 2016 to Dec 2018

The overall 30-day mortality rate was 16.3% (132/811).

Mortality rate was significantly higher in patients who had a BSI caused by an MDR GNB than in those who had a non-MDR GNB BSI: 34.4% vs. 7.9%; $P < 0.001$),

Bloodstream infections due to Gram-negative bacteria in patients with hematologic malignancies: updated epidemiology and risk factors for MDR strains in an Italian perspective survey.

Trecarichi EM, et al. Int J Antimicrob Agents. 2023. Jun;61(6):106806.

A total of 834 GNB were recovered in 811 BSI episodes from Jan 2016 to Dec 2018

Multivariable analysis of RF for BSI caused by MDR GNB, adjusted for hospital effect.

Variables	OR (95% C)	P -values
MDR bacteria in surveillance rectal swabs	3.38 (2.20-5.19)	< 0.001
Fluoroquinolone prophylaxis	2.38 (1.53-3.70)	< 0.001
Previous aminoglycosides therapy	2.29 (1.12-4.65)	0.02
Previous carbapenems therapy	2.33 (1.24-4.39)	0.008
Time at risk (days)	1.02 (1.01-1.03)	0.02

THE MOST WORRISOME QUESTIONS AT PRESENT

could AMR pandemic hamper

progresses of modern medicine ?

SEARCHING ONE (*OR MORE*) SOLUTION (*S*)

Improve build quality of our hospitals

Re-locate several Health Care activities

Increase public Health Care resources

Re-discovering the Infection Control culture

Blindly believe in antimicrobial stewardship activities

ANTIMICROBIAL STEWARDSHIP MISSION

TO PREVENT MDR selection and to TREAT correctly

Culture, Method, Experience, Honesty, Organization, Multidisciplinarity

1. Start and choice antimicrobials using a risk assessment based approach
2. Not be impulsive in starting antimicrobial therapy

3. Properly use microbiology lab resources (for diagnosis, epidemiology, infection control)
4. Avoid redundant prescriptions and useless combinations
5. but be aware about PK/PD issues
6. Early rethink how antibiotics are prescribed
7. Shorten therapy duration and Shorten Length of Hospital stay

8. Share the right place in therapy of new drugs and … work together!

Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis

Antimicrobial Resistance Collaborators, Lancet 2022; 399: 629–55

On the basis of predictive statistical models, there were an estimated 4·95 million (3·62–6·57) deaths associated with bacterial AMR in 2) deaths attributable to bacterial AMR.

IS IT WRONG ?

The six leading pathogens for deaths associated with resistance (*Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*) were responsible for 929,000 (660,000–1,270000) deaths attributable to AMR and 3·57 million (2·62–4·78) deaths associated with AMR in 2019.

Activity of New Agents Against Carbapenem-resistant Gram-negative Pathogens

	Entero KPC	Entero NDM	Entero OXA48	P.aeruginosa	A.baumannii	S.maltophila
CAZ-AVI	+++	-	+++	++	-	-
CEF-TAZO	-	-	-	+++	-	-
MERO-VAB	+++	-	-	-	-	-
IMI-RELE	+++	-	-	++	-	-
CEFIDEROCOL	++	++	++	+++	++	+++
FOSFOMYCIN	+	++	++	+	-	-
ERAVACYCLIN	+++	++	+++	-	++	++
PLAZOMYCIN	+++	+	+++	+	-	-

New drugs 2019-23

•CLINICAL URGE	VERY HIGH
•IN VITRO ACTIVITY	APPEALING
•CLINICAL EVIDENCE	TO BE IMPROVED
•UNANSWERED QUESTIONS	MANY
•RESISTANCE SELECTION RISK	HIGH
•COSTS	TO BE CONSIDERED

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

September 2022 Volume 66 Issue 9

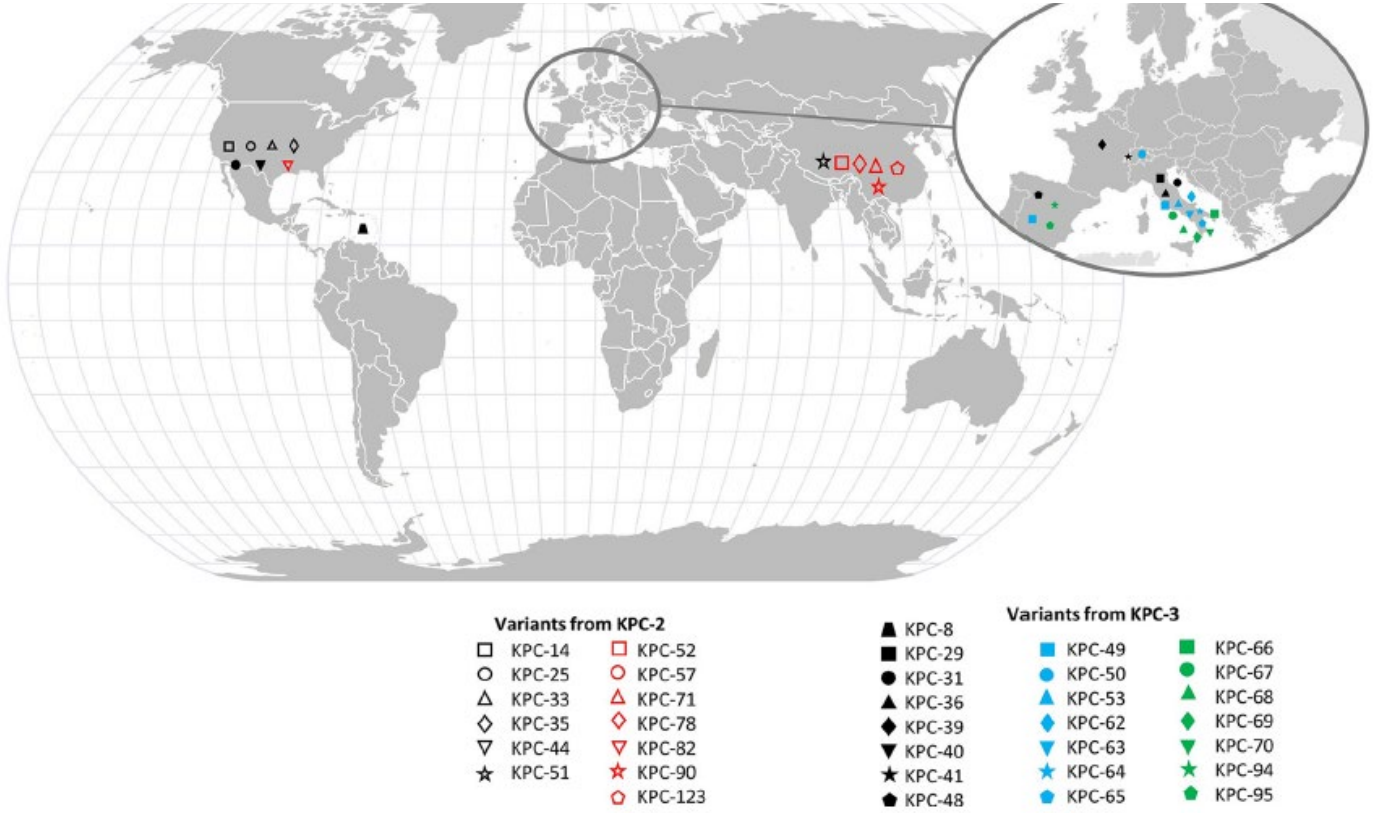
MINIREVIEW

Check for updates

Klebsiella pneumoniae Carbapenemase Variants Resistant to Ceftazidime-Avibactam: an Evolutionary Overview

Claire Amaris Hobson,[a] Gautier Pierrat,[a] Olivier Tenaillon,[a] Stéphane Bonacorsi,[a,b] Béatrice Bercot,[a,c] Ella Jaouen,[a] Hervé Jacquier,[a,c] André Birgy[a,b]

Geographical distribution of CAZAVI-resistant KPC-2 and KPC-3 alleles.



ANTIBIOTIC THERAPY in the MDRO era SHOULD BE INDIVIDUALIZED

Patient's features:
age, renal function, neutropenia, underlying conditions...

Bacteria:
susceptibility (MIC), resistance mechanisms?

Source of infection

Inflammatory response (severe sepsis/shock)

Drug availability

PK/PD behavior

Drug(s), dose

ESCMID guidelines for the treatment of infections caused by MDR Gram negative bacilli

Paul M et al, Clin Microbiol Infect 2022;28:521

ESCMID guidelines for the treatment of infections caused by MDR Gram-negative bacilli

Paul M et al, Clin Microbiol Infect 2022;28:521

Recommendations on the choice of antibiotic treatment for 3GCephRE

For patients with BSI and severe infection due to 3GCephRE → carbapenem (imipenem or meropenem) as targeted therapy

For patients with low-risk, non-severe infections due to 3GCephRE, → piperacillin-tazobactam, amoxicillin/clavulanic acid or quinolones

Tigecycline for infections caused by 3GCephRE → not recommended

new BLBLI → to avoid their use

ESCMID guidelines for the treatment of infections caused by MDR Gram-negative bacilli

Paul M et al, Clin Microbiol Infect 2022;28:521

Recommendations on the choice of antibiotic treatment for CRE

Severe infections due to CRE → meropenem-vaborbactam or ceftazidime-avibactam if active in vitro

Severe infections due to CRE carrying metallo-b-lactamases and/or resistant to all other antibiotics, including ceftazidime-avibactam and meropenem-vaborbactam, → cefiderocol (conditionally)

There is no evidence to recommend for or against the use of imipenem-relebactam and fosfomycin monotherapies for CRE at the time of writing.

For patients with non-severe infections due to CRE → an old antibiotic

ESCMID guidelines for the treatment of infections caused by MDR Gram-negative bacilli

Paul M et al, Clin Microbiol Infect 2022;28:521

Recommendations on the choice of antibiotic treatment for CRE

CRE infections susceptible to and treated with ceftazidime-avibactam, meropenem-vaborbactam or cefiderocol → combination therapy not recommended

Severe infections due to CRE carrying metallo-b-lactamases and/or resistant to new antibiotic monotherapies → aztreonam and ceftazidime-avibactam combination therapy.

Severe infections caused by CRE susceptible in vitro only to polymyxins, aminoglycosides, tigecycline or Fosfomycin → treatment with more than one drug active in vitro. No recommendation for or against specific combinations can be provided

ESCMID guidelines for the treatment of infections caused by MDR Gram-negative bacilli

Paul M et al, Clin Microbiol Infect 2022;28:521

Recommendations on the choice of antibiotic treatment for Carbapenem-R *P. aeruginosa* (CRPA)

severe infections due to difficult to treat CRPA, → ceftolozane-tazobactam if active in vitro.

non-severe or low-risk CRPA infections, under the consideration of antibiotic stewardship → old antibiotics.

No recommendation for or against the use of combination therapy with the new BLBLI (ceftazidime-avibactam and ceftolozane-tazobactam) or cefiderocol for CRPA infections.

ESCMID guidelines for the treatment of infections caused by MDR Gram-negative bacilli

Paul M et al, Clin Microbiol Infect 2022;28:521

Carbapenem-resistant Acinetobacter baumannii (CRAB)

For patients with CRAB susceptible to sulbactam and HAP/VAP, we suggest ampicillin-sulbactam.

For patients with CRAB resistant to sulbactam, a polymyxin or high-dose tigecycline can be used if active in vitro. Lacking evidence, we cannot recommend on the preferred antibiotic.

We conditionally recommend against cefiderocol for the therapy of infections caused by CRAB.

For patients with severe and high-risk CRAB infections, we suggest combination therapy including two in vitro active antibiotics among the available antibiotics (polymyxin, aminoglycoside, tigecycline, sulbactam combinations).

For patients with CRAB infections with a meropenem MIC 8 mg/L, we consider carbapenem combination therapy, using high-dose extended-infusion carbapenem dosing, as good clinical practice.

What about … ?

- *Site of infection related choice*
- *Source control value*
- *Well defined severity criteria*
- *Microbiology role in driving the treatment*
- *PK/PD behavior of antibiotics*
- *Antibiotics daily doses and modality of administration*
- *Host Immunocompetence*
- *Treatment duration and de-escalation criteria*
- *Need for an empirical use*

Diagnosis and management of infections caused by multidrug-resistant bacteria: guideline endorsed by the Italian Society of Infection and Tropical Diseases (SIMIT), the Italian Society of Anti-Infective Therapy (SITA), the Italian Group for Antimicrobial Stewardship (GISA), the Italian Association of Clinical Microbiologists (AMCLI) and the Italian Society of Microbiology (SIM).

Tiseo G et al. Int J Antimicrob Agents 2022;60:106611

pros

- *Well defined microbiology role in driving the treatment*
- *Attention to the PK/PD behavior of antibiotics and TDM value*
- *Role of epidemiological data*

IDSA Practice Guidelines

IDSA Clinical Practice Guidelines are developed by a panel of experts who perform a systematic review of the available evidence and use the GRADE process to develop evidence-based recommendations to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances.

IDSA Clinical Guidance documents are developed based on a comprehensive (but not necessarily systematic) review of the available evidence, coupled with experience of clinical and research experts on the topic. They do not include a formal grading of the evidence. Over time, IDSA Guidance documents may be transitioned to a clinical practice guideline.

IDSA acknowledged that the ability to address rapidly evolving topics such as AMR was limited by prolonged timelines needed to generate new or updated clinical practice guidelines, which are based on systematic literature reviews and rigorous GRADE methodology.

As an alternative to practice guidelines, IDSA endorsed developing more narrowly focused guidance documents for the treatment of difficult-to-manage infections. Guidance documents are prepared by a small team of experts, who answer questions about treatment based on a comprehensive (but not necessarily systematic) review of the literature, clinical experience, and expert opinion. Documents do not include formal grading of evidence, and they are made available and updated at least annually online.

Clinical Infectious Diseases

IDSA GUIDELINES

Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*)

Pranita D. Tamma,[1] Samuel L. Aitken,[2] Robert A. Bonomo,[3] Amy J. Mathers,[4] David van Duin,[5] and Cornelius J. Clancy[6]

Clinical Infectious Diseases® 2022;75(2):187–212

Clinical Infectious Diseases

IDSA GUIDELINE

Infectious Diseases Society of America Guidance on the Treatment of AmpC β-Lactamase–Producing Enterobacterales, Carbapenem-Resistant *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* Infections

Pranita D. Tamma,[1] Samuel L. Aitken,[2] Robert A. Bonomo,[3] Amy J. Mathers,[4] David van Duin,[5] and Cornelius J. Clancy[6]

Clinical Infectious Diseases® 2022;74(12):2089–114

APPROACH TO INTRA ABDOMINAL COMPLICATED INFECTIOS DECISION MAKING

1ST STEP (EMPIRIC) - Variable to be considered

Primary surgical source	…
Clinical Severity	septic shock/ sepsis / no sepsis
Site Of Acquisition	Community/ Hospital
Source Control	Qualified / Incomplete / Delayed /not requested
Biomarkers (PCT – CRP)	Normal/Pathological
Severe Immunodepression	Y/N
Native Country	…
Gut colonization	Y/N/NA
Ongoing outbreak	Y/N
History of antibiotic exposure	Y/N
History of previous infections	Y/N

2ND STEP (TARGETED) - Variable to be considered

MICROBIOLOGY

MICROBIOLOGICAL BIOMARKERS (BDG)