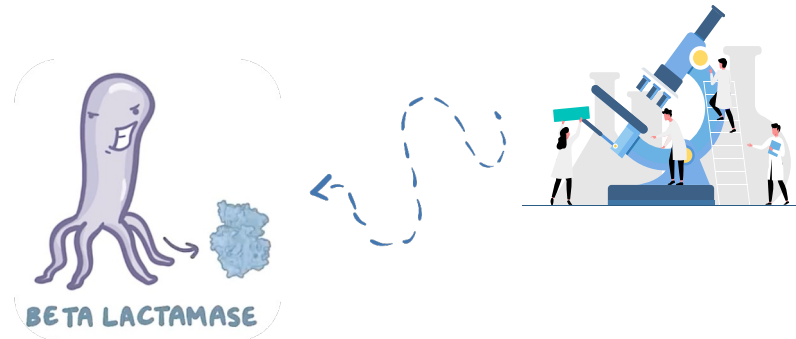


Resistencia a los antimicrobianos y presentación de datos acumulados sobre susceptibilidad

Dr. Carlos Espinoza V. – Médico Microbiólogo Clínico, UCh



Hoja de ruta

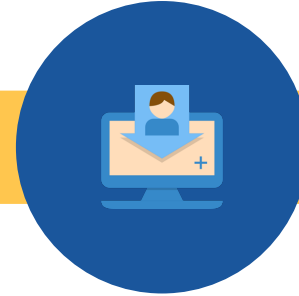
Resistencia a los
antimicrobianos



Estudio de
susceptibilidad y PROA



Datos locales



Resistencia a los antimicrobianos

Generalidades

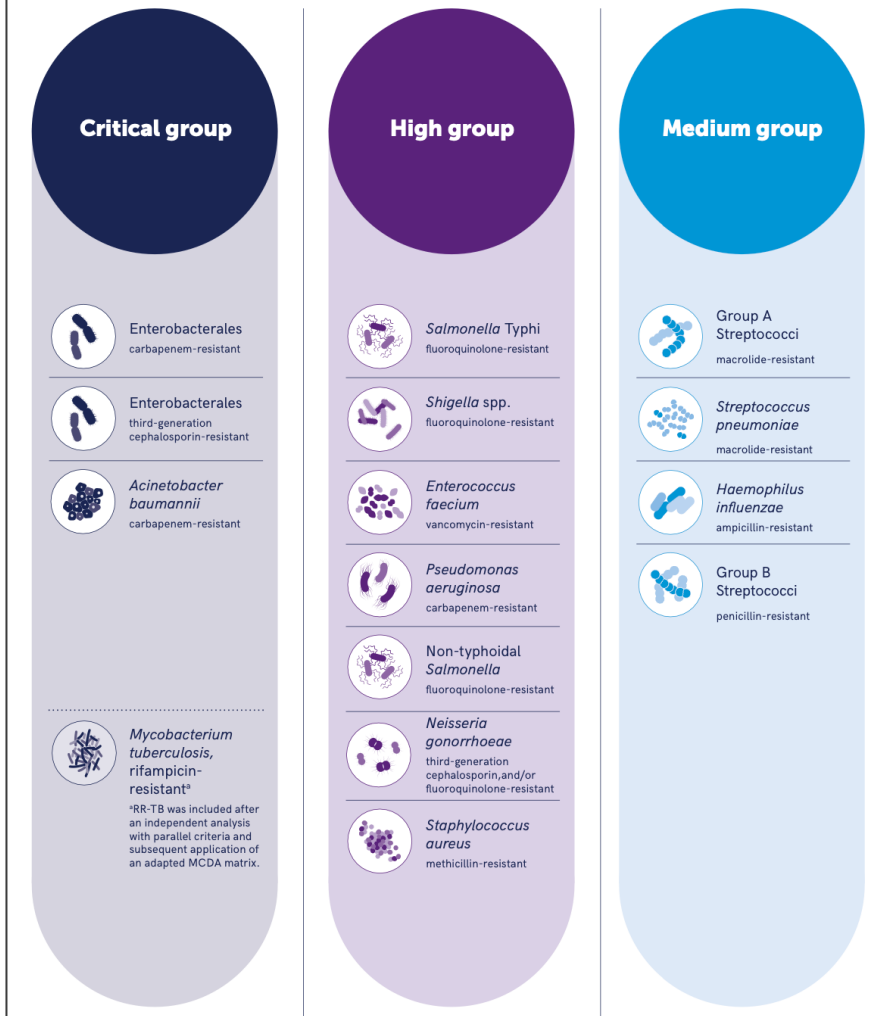
Introducción

- ✓ En la actualidad, la resistencia a los antimicrobianos (AMR) constituye una de las principales amenazas a la salud pública
- ✓ Estudios han estimado que la mortalidad anual asociada a la AMR para el año 2050 podría alcanzar los 10 millones de personas
- ✓ El uso indiscriminado de antimicrobianos ha favorecido la selección de cepas resistentes, y con ello la potencial diseminación de mecanismos de AMR, fundamentalmente mediante elementos genéticos móviles (MGE)
- ✓ Una **correcta interpretación de AST, junto a la detección precoz de marcadores de resistencia** son fundamentales para la toma de decisiones en el ámbito clínico y epidemiológico



Rol del laboratorio de microbiología

Fig 4. WHO Bacterial Priority Pathogens List, 2024

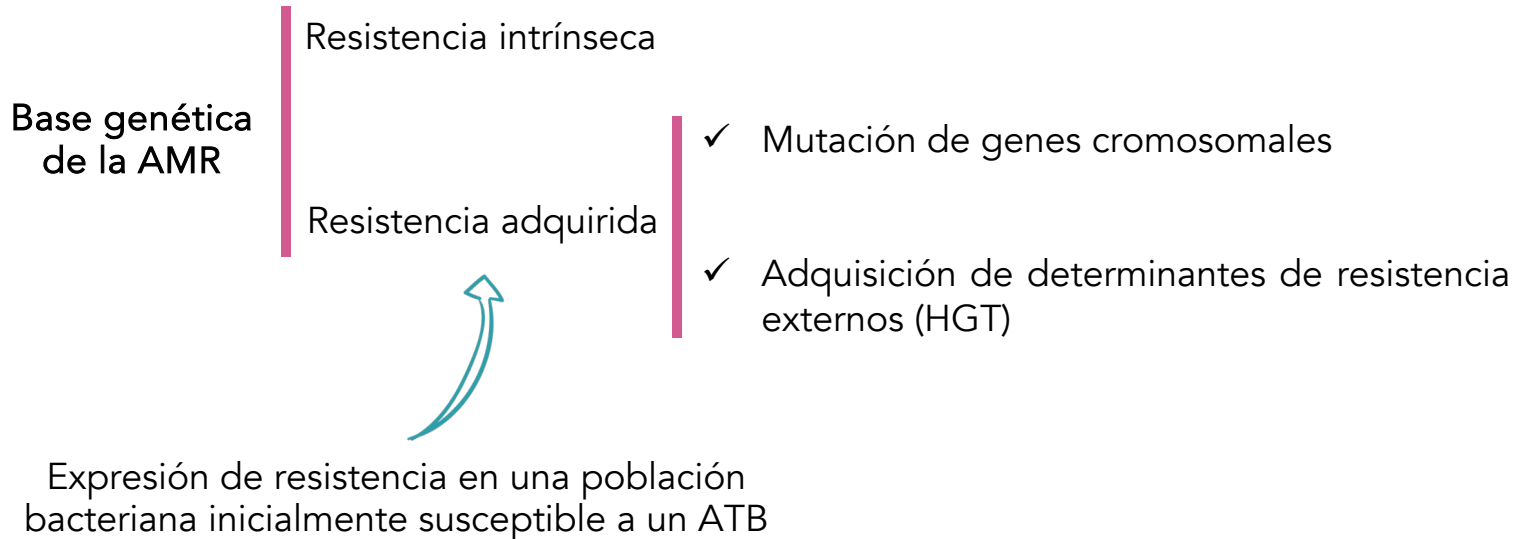


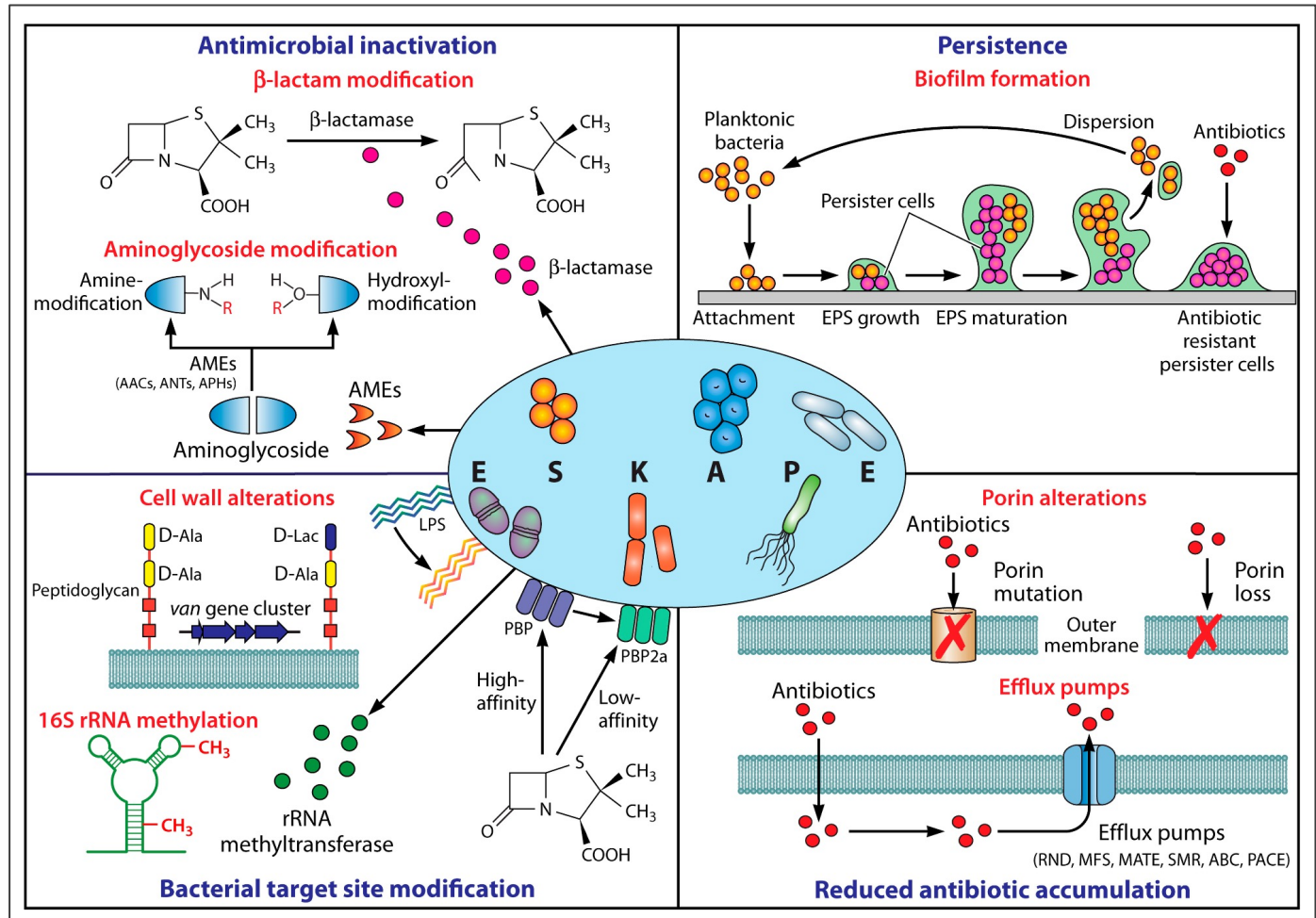
Criteria:

- ✓ Mortalidad
- ✓ Incidencia
- ✓ Impacto en salud pública
- ✓ Tendencia en la resistencia a antimicrobianos
- ✓ Transmisibilidad
- ✓ Prevenible en contexto de atención de salud y comunidad
- ✓ Moléculas candidatas activas

Bases genéticas de la resistencia a los antimicrobianos (AMR)

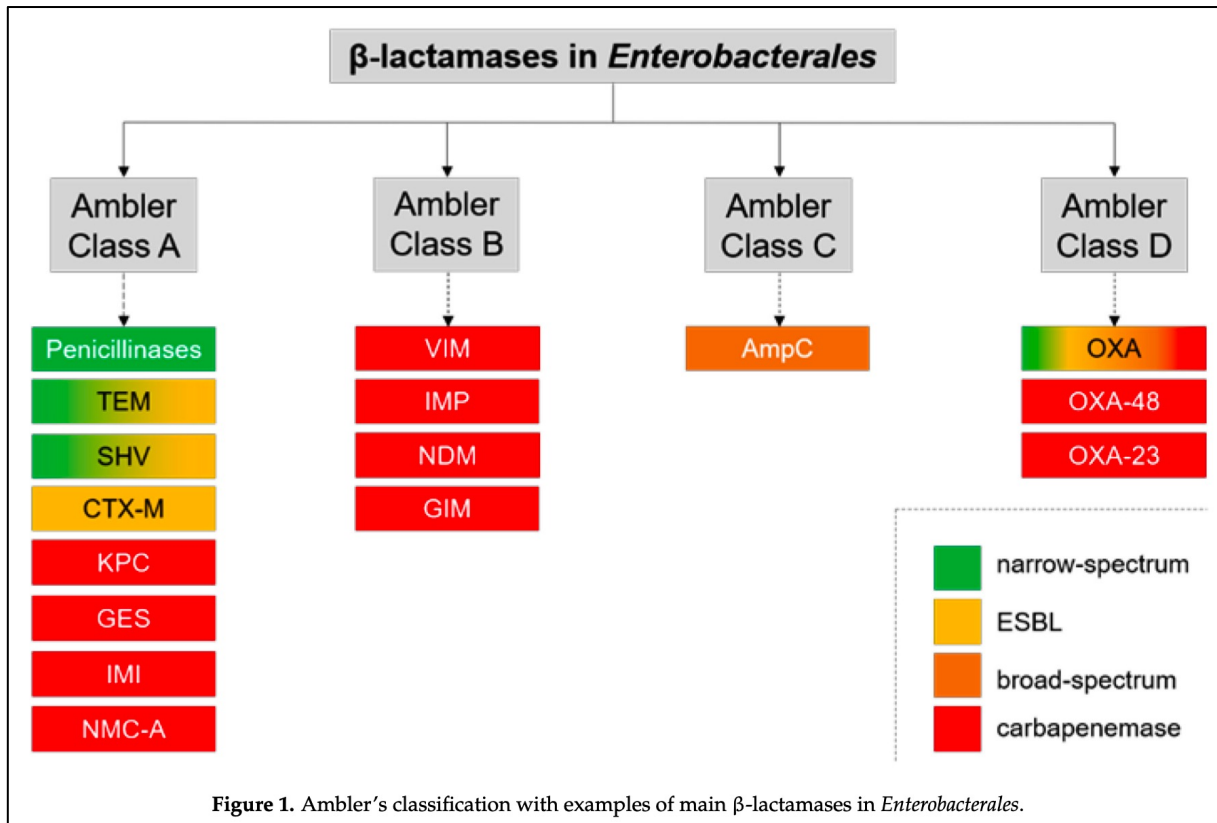
- ✓ La AMR es el resultado de la interacción de microorganismos con el ambiente
- ✓ La mayoría de los compuestos antimicrobianos son moléculas producidas naturalmente frente a las que bacterias co-residentes han desarrollado **mecanismos que favorecen su sobrevivencia.**





- ✓ *Enterococcus faecium*
- ✓ *Staphylococcus aureus*
- ✓ *Klebsiella pneumoniae*
- ✓ *Acinetobacter baumannii*
- ✓ *Pseudomonas aeruginosa*
- ✓ *Enterobacter* spp.

Clasificación de **b-lactamasas** en *Enterobacterales* (Clasificación de Ambler o estructural)



Diferencias

- ✓ Perfil de hidrólisis
- ✓ Distribución entre especies
- ✓ Epidemiología

Table 1. Classification of the most relevant carbapenemases in the clinic

Ambler-Bush Class	Carbapenemase	Most frequently identified in	Key characteristics
A	KPC	<i>K. pneumoniae</i> and other <i>Enterobacteriaceae</i>	<ul style="list-style-type: none">• Variable level of carbapenem hydrolysis.• Some are chromosomal (SME, NMC) others are mainly plasmidic (KPC).• Inhibition by boronic acid, avibactam and partial inhibition by clavulanic acid
	SME	<i>S. marcescens</i>	
	IMI, NMC, GES	<i>Enterobacteriaceae</i>	
B	Metallo-β-lactamases (VIM, IMP, GIM, SPM and NDM)	<i>Enterobacteriaceae</i> (<i>E. coli</i> , <i>Klebsiella</i> , <i>Enterobacter</i> , <i>Providencia</i> , <i>Citrobacter</i> , <i>Proteus mirabilis</i>)	<ul style="list-style-type: none">• Mainly plasmidic• High hydrolytic activity against carbapenems and cephalosporins• No activity against aztreonam by definition• Inhibition with EDTA and dipicolinic acid• No inhibition with boronic acid, clavulanic acid or avibactam
D	OXA-48-family	<i>Klebsiella pneumoniae</i> , <i>E.coli</i> and other <i>Enterobacteriaceae</i>	<ul style="list-style-type: none">• Low hydrolysis of oximino-cephalosporins and moderate hydrolysis of carbapenems• No inhibition with EDTA, dipicolinic and boronic acid. Partial inhibition with avibactam

Table adapted from Bush⁵²



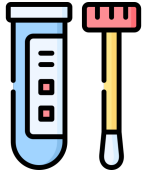
RESISTENCIA A CARBAPENÉMICOS **NO ES SINÓNIMO** DE PRODUCCIÓN DE CARBAPENEMASAS

Estudio de susceptibilidad y PROA

Rol del laboratorio de microbiología

Flujo de trabajo en el laboratorio

Fase pre-analítica



Fase analítica



Fase post-analítica



Flujo de trabajo en el laboratorio de microbiología



Evaluación clínica e indicación de examen



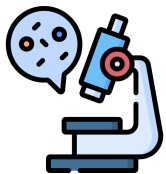
Recolección y transporte de muestra



Procesamiento y siembra



Análisis e identificación de microorganismo (cultivo)



Estudio de susceptibilidad a los antimicrobianos



Reporte selectivo o en cascada



Optimización terapia antimicrobiana



Methods of antimicrobial susceptibility testing



Phenotypic methods

Constrained by bacterial growth time

Dilution



48 h

Diffusion



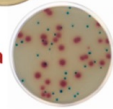
48 h

Gradient test



48 h

Chromogenic media



24 h

Automated devices



> 20 h

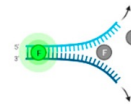
Molecular-based methods

PCR

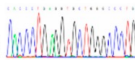


several h

qPCR



Cycle sequencing



24 - 48 h

NGS



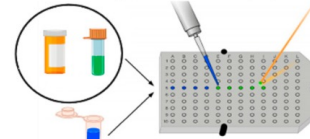
several days

** estimated time depend on a sample analysed (clinical specimen vs. isolated bacterial culture)*

Mass spectrometry

MALDI-TOF MS

Incubation (antibiotic + sample)



Matrix

several h

** estimated time depend on a sample analysed (clinical specimen vs. isolated bacterial culture)*

Detección de marcadores de resistencia

Estudio de Susceptibilidad a Antimicrobianos

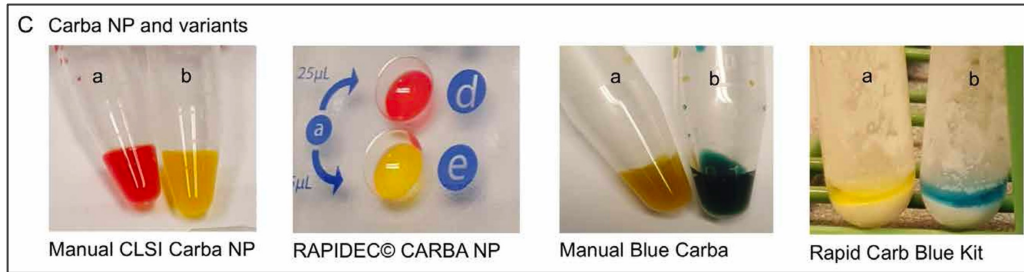
Métodos fenotípicos

Evalúan la respuesta bacteriana frente a la presencia de un agente antimicrobiano, por lo que dependen del crecimiento del microorganismo en un medio de cultivo. El tiempo de incubación suele ir desde las 18 a 24 horas.

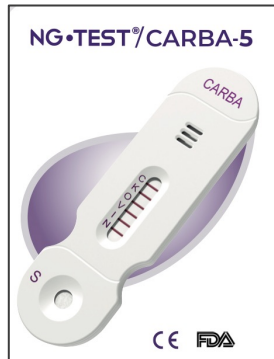


Susceptibilidad disminuida a carbapenémicos

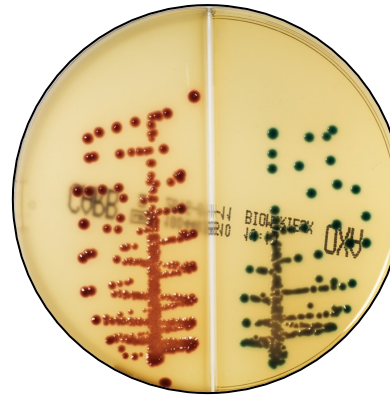
Carbapenemasas – métodos de detección y/o identificación



Colorimetría



Inmunocromatografía



Agar cromogénico (screening)



Métodos genotípicos

Flujo de trabajo en el laboratorio de microbiología



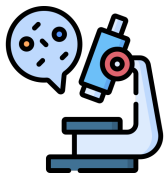
Evaluación clínica e indicación de examen



Recolección y transporte de muestra



Procesamiento y siembra



Análisis e identificación de microorganismo (cultivo)



Estudio de susceptibilidad a los antimicrobianos



Reporte
(selectivo o en cascada)



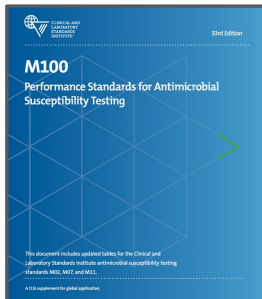
Optimización terapia antimicrobiana



Table 1A-1. Enterobacterales (excluding *Salmonella/Shigella*)^a

Tier 1: Antimicrobial agents that are appropriate for routine, primary testing and reporting	Tier 2: Antimicrobial agents that are appropriate for routine, primary testing but may be reported following cascade reporting rules established at each institution	Tier 3: Antimicrobial agents that are appropriate for routine, primary testing in institutions that serve patients at high risk for MDROs but should only be reported following cascade reporting rules established at each institution	Tier 4: Antimicrobial agents that may warrant testing and reporting by clinician request if antimicrobial agents in other tiers are not optimal because of various factors
Ampicillin			
Cefazolin	Cefuroxime		
Cefotaxime or ceftriaxone ^b	Cefepime ^c		
	Ertapenem	Cefiderocol	
	Imipenem	Ceftazidime-avibactam	
	Meropenem	Imipenem-relebactam Meropenem-vaborbactam	
Amoxicillin-clavulanate			
Ampicillin-sulbactam			
Piperacillin-tazobactam			
Gentamicin	Tobramycin	Plazomicin	
	Amikacin		
Ciprofloxacin			
Levofloxacin			
Trimethoprim-sulfamethoxazole			
	Cefotetan		
	Cefoxitin		
	Tetracycline ^d		
			Aztreonam
			Ceftaroline ^b
			Ceftazidime ^b
			Ceftolozane-tazobactam
Urine Only			
Cefazolin (surrogate for uncomplicated UTI) ^e			
Nitrofurantoin			
		Fosfomicin ^f (<i>Escherichia coli</i>)	

Abbreviations: MDRO, multidrug-resistant organism; UTI, urinary tract infection.



Estudio de Susceptibilidad Antimicrobiana (AST) en un aislado de muestra clínica



Optimización de terapia antimicrobiana



Generación y almacenamiento de datos sobre AST en el tiempo



Datos acumulados de AST



Elaboración de antibiograma

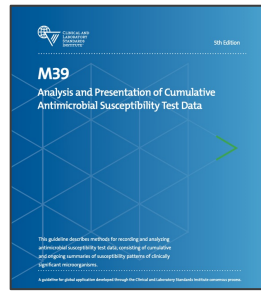
Definición actual



- Selección de tratamiento antimicrobiano empírico en paciente individual
- Desarrollo de guías locales/algoritmos de tratamiento ATB empírico (sitio de infección, servicio clínico, otros)

Susceptibilidad ATB

Tipos de reporte



Perfil de susceptibilidad antimicrobiana



Resultado obtenido al analizar la susceptibilidad antimicrobiana de un **aislado simple**

Antibiograma



- ✓ Reporte de un conjunto de perfiles de susceptibilidad (datos acumulados)
- ✓ Periodo de tiempo (anual)
- ✓ Porcentaje de microorganismos susceptibles

Recomendaciones básicas para la elaboración de un antibiograma

TABLE 1 Key recommendations for routine antibiogram development

Recommendation
Antibiogram reports should be analyzed and presented at least annually .
Only diagnostic (not surveillance) isolates should be included.
Only final, verified test results should be included.
Duplicates should be eliminated by including only the first isolate of a species, patient, and/or analysis period , regardless of specimen source or antimicrobial susceptibility profile.
Only species with testing data for ≥ 30 isolates should be included.
Only antimicrobial agents routinely tested against the population of isolates to be analyzed should be included, and the %S should be calculated from results reported as well as those that may be suppressed on patient reports for which selective or cascade reporting rules have been applied.
To decrease biases in susceptibility estimates, laboratorians should refrain from including results for supplemental antimicrobial agents selectively tested on resistant isolates only.
Laboratorians should report the %S but exclude the %I and %SDD in the %S statistic.

Supplemental Table 1. Antibiogram With Antimicrobial Agents Listed Alphabetically: Gram-Negative Isolates

Memorial Medical Center
1 January - 31 December 2020 Antibiogram^a
Percent Susceptible

Organism	Number of Strains	Amikacin	Ampicillin	Cefazolin (systemic ^b)	Cefazolin (urine ^c)	Cefepime	Ceftriaxone	Ceftazidime	Ciprofloxacin	Ertapenem	Gentamicin	Meropenem	Piperacillin-tazobactam	Trimethoprim-sulfamethoxazole	Tobramycin
<i>Acinetobacter baumannii</i>	32	60	R	R	R	33	34	42	41	R	57	60	46	48	59
<i>Citrobacter freundii</i>	49	100	R	R	R	81	72	67	90	98	96	99	83	67	97
<i>Enterobacter cloacae</i>	76	99	R	R	R	78	61	62	92	89	90	99	77	84	90
<i>Escherichia coli</i>	1433	99	35	68	87	92	93	90	72	99	91	99	94	73	92
<i>Klebsiella</i> (formerly <i>Enterobacter</i>) <i>aerogenes</i>	31	100	R	R	R	81	68	60	92	99	91	99	74	95	91
<i>Klebsiella pneumoniae</i>	543	99	R	72	89	93	91	87	84	99	94	95	86	81	94
<i>Morganella morganii</i>	44	100	R	R	R	94	85	81	89	98	100	99	96	75	100
<i>Proteus mirabilis</i>	88	100	87	80	92	99	99	92	79	100	90	100	70	73	93
<i>Pseudomonas aeruginosa</i>	397	97	R	R	R	88	R	86	75	R	80	80	85	R	83
<i>Salmonella</i> spp.	32	-	88	-	-	98	97	97	90	100	-	100	91	86	-
<i>Serratia marcescens</i>	50	100	R	R	R	95	87	80	95	99	94	99	94	91	89
<i>Shigella</i> spp.	33	-	64	-	-	98	98	96	90	100	-	100	91	69	-
<i>Stenotrophomonas maltophilia</i>	72	R	R	R	R	-	R	63	6	R	R	R	-	98	R

Abbreviation: R, intrinsic resistance.

Symbol: -, drug not tested or drug not indicated.

^a The percent susceptible for each organism/antimicrobial agent combination was generated by including the first isolate of that organism encountered in a given patient.

^b Cefazolin (systemic) refers to application of susceptibility breakpoint minimal inhibitory concentration (MIC) ≤ 2 $\mu\text{g}/\text{mL}$ and applies to the treatment of patients with infections other than uncomplicated urinary tract infections (UTIs).

^c Cefazolin (urine) refers to application of urinary susceptibility breakpoint MIC ≤ 16 $\mu\text{g}/\text{mL}$ (using a cefazolin dosage regimen of 1 g intravenously [IV] every 12 hours) and can be used to predict susceptibility for oral cefaclor, cefdinir, cefepodoxime, cefprozil, cefuroxime, cephalixin, and loracarbef when used for therapy of uncomplicated UTIs due to *E. coli*, *K. pneumoniae*, and *P. mirabilis*. Cefazolin as a surrogate may overcall resistance to cefdinir, cefepodoxime, and cefuroxime. If cefazolin tests resistant, these drugs should be tested individually if needed for therapy.

Table E4. Antibiogram for Gram-Positive Blood Isolates From Inpatients

Organism	Number of Strains	%S										
		Ampicillin	Clindamycin	Daptomycin	Erythromycin	Linezolid	Oxacillin	Penicillin	Trimethoprim-sulfamethoxazole	Vancomycin	Gentamicin Synergy	Streptomycin Synergy
<i>S. aureus</i>	107	5	71	99	60	99	57	5	97	100	-	-
<i>Enterococcus faecalis</i> ^a	54	100	R	99	16	100	-	100	R	96	54	62
<i>Enterococcus faecium</i> ^b	128	8	R	98 ^c	4	97	-	8	R	23	61	60

Abbreviations: %S, percent susceptible; R, intrinsic resistance.

Symbol: -, drug not tested or drug not indicated.

^a 19% high-level resistance to both gentamicin synergy and streptomycin synergy.

^b 25% high-level resistance to both gentamicin synergy and streptomycin synergy.

^c Percent susceptible-dose dependent.

Tipos de reporte de datos acumulados de susceptibilidad antimicrobiana

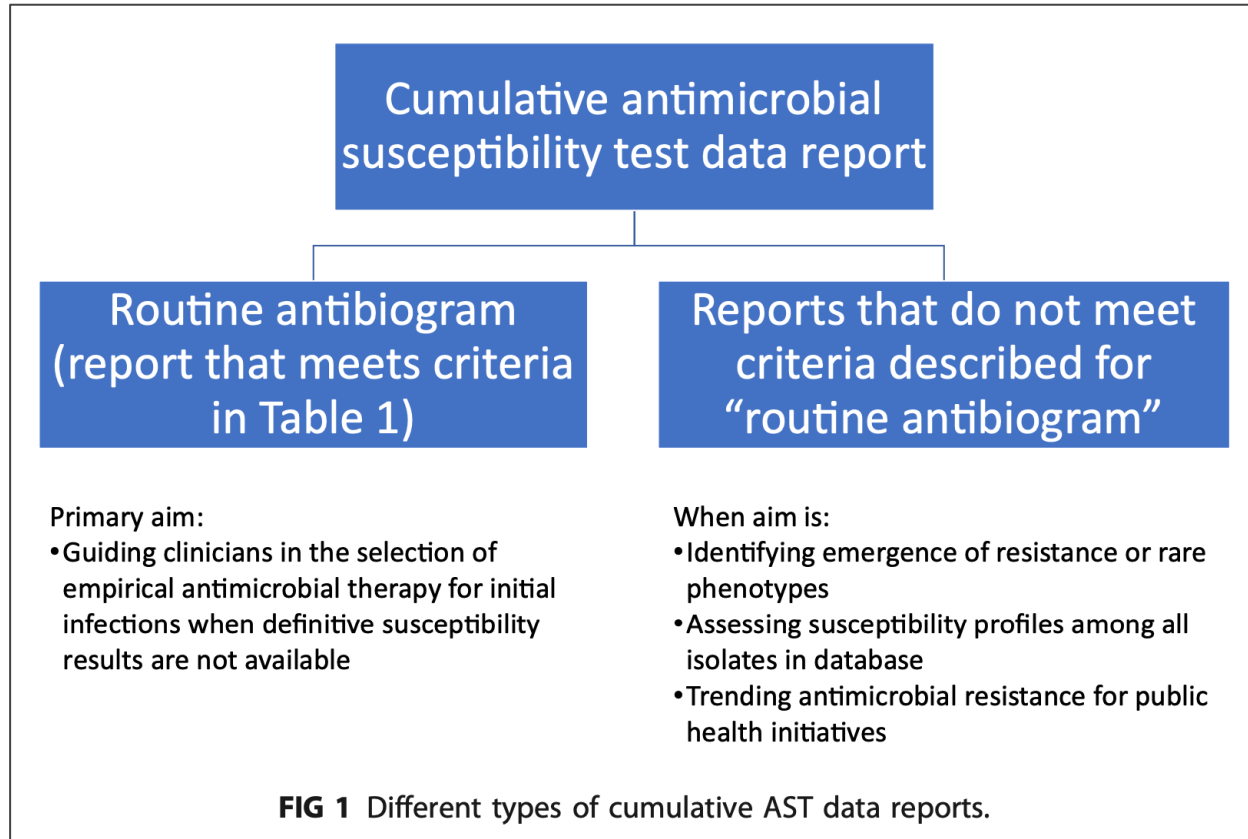


Table 26. Enhancing Antibiogram Data With Results From Molecular Detection of Resistance Markers for *K. pneumoniae* From Positive Blood Cultures

Organism	Number of Strains	%S									
		Amikacin	Aztreonam	Ampicillin	Cefepime	Ceftriaxone	Ciprofloxacin	Ertapenem	Gentamicin	Meropenem	Piperacillin-tazobactam
<i>K. pneumoniae</i> , all blood isolates	207	93	72	R	77	72	78	97	81	99	85
<i>K. pneumoniae</i> , negative for <i>bla</i> _{CTX-M} and carbapenemase genes	151	98	95	R	99	94	94	99	94	99	95
<i>K. pneumoniae</i> , positive for <i>bla</i> _{CTX-M}	35	96	0	R	33	0	36	96	46	100	50
<i>K. pneumoniae</i> , positive for <i>bla</i> _{KPC}	11 ^a	78	0	R	25	0	17	0	17	0	0
<i>K. pneumoniae</i> , positive for <i>bla</i> _{NDM}	10 ^{a,b}	0	70	R	0	0	10	0	0	0	0

Abbreviations: %S, percent susceptible; R, intrinsic resistance.

^a Calculated from fewer than the standard recommendation of 30 isolates.

^b Data collected over three years.



Table 24. Common Antimicrobial Resistance Genes and Predicted Phenotype Based on Presence and/or Absence of the Gene

Resistance Gene	Organisms	Phenotype Predicted and Accuracy of Prediction ^a			
		Presence	Approximate Accuracy	Absence	Approximate Accuracy
<i>mecA</i>	<i>S. aureus</i>	MRSA	98% to 100%	MSSA	98% to 100%
<i>vanA/vanB</i>	<i>E. faecalis</i> or <i>E. faecium</i>	VRE	95% to 100%	VSE	95% to 100%
<i>bla</i> _{CTX-M}	Enterobacteriales <i>P. aeruginosa</i> <i>A. baumannii</i> <i>S. maltophilia</i>	ESBL producing gram-negative organism: resistance to penicillins, narrow- and expanded-spectrum cephalosporins	95% to 100%	N/A. The lack of detection does not predict susceptibility because many other mechanisms can lead to resistance.	50% to 95%
<i>bla</i> _{KPC} , <i>bla</i> _{NDM} , <i>bla</i> _{OXA-48} , <i>bla</i> _{VIM} , <i>bla</i> _{IMP}	Enterobacteriales <i>P. aeruginosa</i> <i>A. baumannii</i>	Carbapenemase-producing gram-negative organism: resistance to penicillins, narrow- and expanded-spectrum cephalosporins, and carbapenems	95% to 100%	N/A. The lack of detection does not predict susceptibility because many other mechanisms can lead to resistance.	10% to 98%

Abbreviations: ESBL, extended-spectrum β-lactamase; MRSA, methicillin (oxacillin)-resistant *S. aureus*; MSSA, methicillin (oxacillin)-susceptible *S. aureus*; N/A, not applicable; VRE, vancomycin-resistant enterococci; VSE, vancomycin-susceptible enterococci.

^a The accuracy of prediction will vary based on the local epidemiology, and the values provided are estimates based on the presence or absence of the gene.

Susceptibilidad acumulada a los ATB

Datos locales, año 2023

Pacientes adultos

Hemocultivos

		Antimicrobianos										
Bacterias Gram positiva	N° aislados	Cloxacilina	Ampicilina	Vancomicina	Cotrimoxazol	Eritromicina	Clindamicina	Tetraciclina	Daptomicina	Linezolid	Gentamicina (HLAR)	Rifampicina
		<i>Staphylococcus epidermidis</i>	21	38		100	56	19	56	94	100	100
<i>Staphylococcus aureus</i>	14	54		100	100	62	62	92	100	100		100
<i>Enterococcus faecium</i>	12		0	0					SDD	100	25	

		Antimicrobianos											Betalactamasas				
Bacterias Gram negativa	N° aislados	Amikacina	Ampicilina/Sulbactam	Ceftazidima	Piperacilina/Tazobactam	Cefepime	Ciprofloxacino	Ertapenem	Meropenem	Imipenem	Ceftazidima/Avibactam	Ceftolozano/Tazobactam	Aztreonam	BLEE	KPC (n)	NDM (n)	VIM (n)
		<i>Escherichia coli</i>	36	100	42		92	75	44	100	100	100	100	97	69	25%	0
<i>Klebsiella pneumoniae</i>	27	70	26		33	37	37	54	59	59	85	48	30	41%	5	4	0
<i>Pseudomonas aeruginosa</i>	10	90		80	60	80	80		60	50	90	90	*		0	0	1
															5	4	1

Pacientes adultos

Urocultivos

		Antimicrobianos									
Bacterias Gram positiva	N° aislados	Ampicilina	Ciprofloxacino	Vancomicina	Daptomicina	Linezolid	Gentamicina (HLAR)	Penicilina	Nitrofurantoina	Clindamicina	Eritromicina
<i>Enterococcus faecalis</i>	49	94	84	100	100	100	82		98		
<i>Enterococcus faecium</i>	6	0	ND	ND	SDD	100	17				
<i>Streptococcus agalactiae</i>	16							100		80	67

		Antimicrobianos													Betalactamasas			
Bacterias Gram negativa	N° aislados	Amikacina	Ampicilina/Sulbactam	Ceftazidima	Cefazolina	Cefepime	Ciprofloxacino	Ertapenem	Meropenem	Ceftriaxona	Ceftazidima/Avibactam*	Fosfomicina	Cotrimoxazol	Nitrofurantoina	Betalactamasas			
															BLEE	KPC (N)	NDM (N)	VIM (N)
<i>Escherichia coli</i>	467	98	54		23	87	56	99	100	86	100	99	66	96	13%	1		
<i>Klebsiella pneumoniae</i>	61	92	44		5	48	51	73	84	51	83		60	18	44%	4	1	
<i>Pseudomonas aeruginosa</i>	24	96		79		74	79		74		0							
<i>Proteus mirabilis</i>	22	95	82		23	91	73	100	100	91	0		76					
															5	1	0	

Pacientes adultos

Secreciones

		Antimicrobianos										
Bacterias Gram positiva	N° aislados	Cloxacilina	Ampicilina	Vancomicina	Cotrimoxazol	Eritromicina	Clindamicina	Tetraciclina	Daptomicina	Linezolid	Gentamicina (HLAR)	Rifampicina
<i>Staphylococcus aureus</i>	39	77		100	97	44	59	95	100	100		100
<i>Enterococcus faecium</i>	10		0	10					SDD	100	20	
<i>Enterococcus faecalis</i>	5		100	100					100	100	71	

		Antimicrobianos											Betalactamasas				
Bacterias Gram negativa	N° aislados	Amikacina	Ampicilina/Sulbactam	Ceftazidima	Piperacilina/Tazobactam	Cefepime	Ciprofloxacino	Ertapenem	Meropenem	Imipenem	Ceftazidima/Avibactam	Ceftolozano/Tazobactam	Aztreonam				
														BLEE	KPC (N)	NDM (N)	VIM (N)
<i>Pseudomonas aeruginosa</i>	33	84		62	47	62	66		53	56	72	84			1		4
<i>Klebsiella pneumoniae</i>	25	88	44		52	56	56	65	76	72	96	60	52	24%	4	1	
<i>Escherichia coli</i>	10	100	25		83	25	17	100	100	100	100	100	25	75%			
<i>Enterobacter cloacae</i> complex	12	100			72	91	91	72	91	91	91	83	77		1	1	
														6	2	4	

Pacientes pediátricos

Hemocultivos

		Antimicrobianos									
Bacterias Gram positiva	N° aislados	Cloxacilina	Vancomicina	Cotrimoxazol	Eritromicina	Clindamicina	Tetraciclina	Daptomicina	Linezolid	Rifampicina	Rifampicina
<i>Staphylococcus aureus</i>	16	81	100	100	69	75	100	100	100	100	100
<i>Staphylococcus epidermidis</i>	20	12	100	69	38	56	94	100	100	100	100

		Antimicrobianos											Betalactamasas
Bacterias Gram negativa	N° aislados	Amikacina	Ceftazidima	Piperacilina/Tazobactam	Cefepime	Ciprofloxacino	Ertapenem	Meropenem	Imipenem	Ceftazidima/Avibactam	Ceftolozano/Tazobactam	Aztreonam	BLEE
<i>Escherichia coli</i>	13	100	85	85	85	85	100	100	100	92	92	80	15%
<i>Klebsiella pneumoniae</i>	4	100	80	60	80	80	100	100	100	100	100	85	20%
<i>Pseudomonas aeruginosa</i>	2	100	100	100	100	100		100	100	100	100		

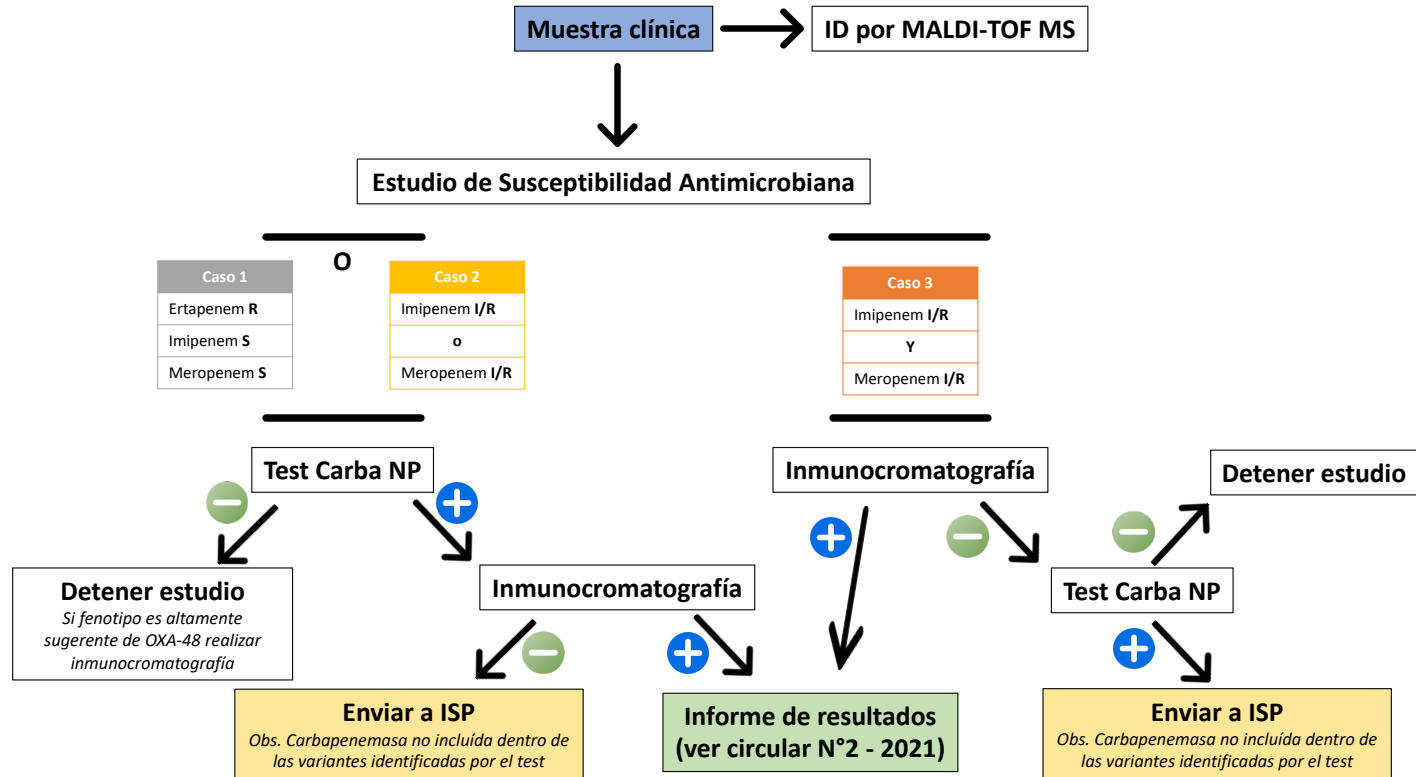
Pacientes pediátricos

Urocultivos

		Antimicrobianos										
Bacterias Gram positivas	N° aislados	Cloxacilina	Ampicilina	Vancomicina	Cotrimoxazol	Ciprofloxacino	Clindamicina	Nitrofurantoina	Daptomicina	Linezolid	Rifampicina	Gentamicina (HLAR)
<i>Enterococcus faecalis</i>	16		100	100		94		100	100	100		88
<i>Staphylococcus saprophyticus</i>	4	ND		100	100	100	75	100	100	100	100	

		Antimicrobianos												Betalactamasas	
Bacterias Gram negativas	N° aislados	Amikacina	Ampicilina/sulbactam	Ceftazidima	Cefazolina	Ceftriaxona	Cefepime	Ertapenem	Meropenem	Ciprofloxacino	Nitrofurantoina	Gentamicina	Cotrimoxazol	BLEE	Carbapenemasas
		<i>Escherichia coli</i>	325	100	47		26	93	93	100	100	70	95	84	62
<i>Proteus mirabilis</i>	42	100	90		29	98	98	98	100	90		95	76		
<i>Klebsiella pneumoniae</i>	12	100	67		25	92	92	92	92	92		100	100		NDM (1) y OXA-48 (1)
<i>Pseudomonas aeruginosa</i>	6	100		83			83		83	83		100			

Algoritmo de estudio de bacilos Gram negativo con susceptibilidad disminuida a carbapenémicos



Resistencia a los antimicrobianos y presentación de datos acumulados sobre susceptibilidad

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