MINISTERIO DE SANIDAD

agencia española de medicamentos y productos sanitarios

Plan Nacional Resistencia Antibióticos

CoESAnt

seimc

I Jornada del Comité Español del Antibiograma (COESANT)

Madrid 24 de noviembre de 2022

Lectura interpretada de antibiograma en 2022

Ferran Navarro
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Fenotipo esperado

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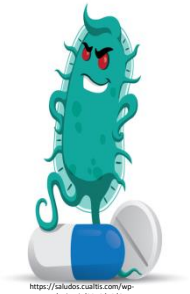
Reglas de expertos



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Mecanismos de resistencia

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

search term

- Organization
- Consultations
- EUCAST News
- New definitions of S, I and R
- Clinical breakpoints and dosing
- Rapid AST in blood cultures
- Expert rules and expected phenotypes
- Resistance mechanisms
- Guidance documents
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QUICK NAVIGATION

The European Committee on Antimicrobial Susceptibility Testing - EUCAST

April 21, 2022

EUCAST is a standing committee jointly organized by ESCMID, ECDC and European national breakpoint committees. EUCAST was formed in 1997. It has been chaired by Ian Phillips (1997 - 2001), Gunnar Kahlmeter (2001 - 2012), Rafael Canton 2012 - 2016) and Christian Giske (2016 -). Its scientific secretary is Derek Brown (1997 - 2016) and John Turnidge (2016 -). Its webmaster is Gunnar Kahlmeter (2001 -). From 2016, Rafael Canton is the Clinical Data Co-ordinator and from 2012, Gunnar Kahlmeter is the Technical Data Co-ordinator and Head of the EUCAST Development Laboratory.

Martin Steinbakk, former EUCAST Steering Committee member, sadly died Monday 11 April, 2022. Martin chaired the Norwegain breakpoint committee (NWGA) for many years and was in 2001 one of the original members of the EUCAST Steering Committee. He represented the Norwegian committee for more than 10 years and we learnt to appreciate his experience in susceptibility testing, his quiet humour and his sonorous voice. We worked with Martin for a long time and and now our thoughts are with his wife, children, grandchildren and friends.

The EUCAST **Development Laboratory for antibacterial agents** is located in Sweden and

EUCAST News

29 Jul 2022
Corynebacterium consultation - amendments and corrections pos

24 Jul 2022
SOPs 3, 4, 7, 8 and 9 updated.

21 Jul 2022
Tigecycline rationale and guidanc documents

20 Jul 2022
General consultation on propose revision of chloramphenicol breakpoints

20 Jul 2022
Fosfomycin - revised MIC distributions and ECOFFs

http://www.eucast.org/

Fenotipo esperado

~~Intrínseco~~

Esperado

El propósito de las tablas de fenotipos esperados es para:

- Servir como una herramienta para la validación de la identificación de especies
- Ayudar en la validación de los resultados de las pruebas de sensibilidad
- Evitar pruebas de sensibilidad innecesarias.

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... Expected phenotypes

Expected resistant and susceptible phenotypes

Expected resistant phenotypes v 1.1 (25 March, 2022)

For many years EUCAST and other committees have struggled with the term "intrinsic

and a very high proportion (99%) of isolates should be devoid of acquired resistance to the agent (*Streptococcus pyogenes* vs. benzylpenicillin is one example).

In both cases, susceptibility testing is best avoided. A result which goes against the expected phenotype should be viewed with suspicion.

- Aislamientos generalmente resistente (>90 % muestran un mecanismo de resistencia característico o valores de CIM por encima del punto de corte PK/PD)
- Un resultado sensible debe confirmarse. En general deben evitar estas pruebas

EUCAST Expected Resistant Phenotypes v 1.1 March 2022

Enterobacterias

Rule	Organisms	Ampicillin/Amoxicillin	Amoxicillin-clavulanic acid	Ampicillin-sulbactam	Ticarcillin	Cefazolin, Cephalothin Cefalexin, Cefadroxil	Cefoxitin[2]	Cefuroxime	Tetracyclines	Tigecycline	Polymyxin B, Colistin	Fosfomycin	Nitrofurantoin
1.1	*Citrobacter koseri, Citrobacter amalonaticus*[3]	R			R								
1.2	*Citrobacter freundii*[4]	R	R	R		R	R						
1.3	*Enterobacter cloacae* complex	R	R	R		R	R						
1.4	*Escherichia hermannii*	R			R								
1.5	*Hafnia alvei*	R	R								R		
1.6	*Klebsiella aerogenes*	R	R	R		R	R						
1.7	*Klebsiella pneumoniae* complex	R			R								
1.8	*Klebsiella oxytoca*	R			R								
1.9	*Leclercia adecarboxylata*											R	
1.10	*Morganella morganii*	R	R	R		R			R		R		R
1.11	*Plesiomonas shigelloides*	R	R	R									
1.12	*Proteus mirabilis*								R	R	R		R
1.13	*Proteus penneri*	R				R		R	R	R	R		R
1.14	*Proteus vulgaris*	R				R		R	R	R	R		R
1.15	*Providencia rettgeri*	R	R	R		R			R		R		R

AmpC / Cefamicinasa

EUCAST Expected Resistant Phenotypes v 1.1 March 2022

Grampositivos

Rule	Organisms	Fusidic acid	Ceftazidime	Cephalosporins (except ceftazidime)	Aminoglycosides	Macrolides	Clindamycin	Quinupristin-dalfopristin	Vancomycin	Teicoplanin	Fosfomycin	Novobiocin	Sulfonamides
4.1	*Staphylococcus saprophyticus*	R	R								R	R	
4.2	*Staphylococcus cohnii*		R									R	
4.3	*Staphylococcus xylosus*		R									R	
4.4	*Staphylococcus capitis*		R								R		
4.5	Other coagulase-negative staphylococci and *S. aureus*		R										
4.6	*Streptococcus* spp.	R	R		R[1]								
4.7	*Enterococcus faecalis*	R	R	R	R[1]	R	R	R					R
4.8	*Enterococcus gallinarum, Enterococcus casseliflavus*	R	R	R	R[1]	R	R	R	R				R
4.9	*Enterococcus faecium*	R	R	R	R[1,2]	R							R
4.10	*Corynebacterium* spp.										R		
4.11	*Listeria monocytogenes*		R	R									
4.12	*Leuconostoc* spp., *Pediococcus* spp.								R	R			
4.13	*Lactobacillus* spp. (*L. casei, L. casei* var. *rhamnosus*)								R	R			
5.1	*Clostridium ramosum, Clostridium innocuum*								R				

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... Expected phenotypes

Expected resistant and susceptible phenotypes

Expected susceptible phenotypes v 1.1 (25 March, 2022)

For many years EUCAST and other committees have struggled with the term "intrinsic resistance".
There is no agreed definition and since breakpoints are always "exposure dependent" it is hard to agree on a definition which will survive changes in dosing, modes of administration

In both cases, susceptibility testing is best avoided. A result which goes against the expected phenotype should be viewed with suspicion.

- Son generalmente sensibles (> 99% no se han informado mecanismos de resistencia de importancia clínica y/o porque los valores de MIC están consistentemente por debajo del punto de corte PK/PD)
- Un resultado resistente debe verse con sospecha.

EUCAST Expected Susceptible Phenotypes v 1.1 March 2022

Rule	Organisms	Unusual phenotypes
1.1	Any *Enterobacterales* (except *Morganellaceae* and *Serratia marcescens*)	Resistant to colistin[1,2]
1.2	*Salmonella* Typhi	Resistant to carbapenems
1.3	*Pseudomonas aeruginosa* and *Acinetobacter* spp	Resistant to colistin[1]
1.4	*Haemophilus influenzae*	Resistant to any third-generation cephalosporin, carbapenems, fluoroquinolones[3]
1.5	*Moraxella catarrhalis*	Resistant to any third-generation cephalosporin or fluoroquinolones
1.6	*Neisseria meningitidis*	Resistant to any third generation cephalosporins or fluoroquinolones
1.7	*Neisseria gonorrhoeae*	Resistant to spectinomycin

EUCAST Expected Susceptible Phenotypes v 1.1 March 2022

Rule	Organisms	Unusual phenotypes
2.1	*Staphylococcus aureus*	Resistant to vancomycin, teicoplanin, telavancin, dalbavancin, oritavancin, daptomycin, linezolid, tedizolid, quinupristin-dalfopristin, tigecycline, eravacycline or omadacycline
2.2	Coagulase-negative staphylococci	Resistant to vancomycin, telavancin, dalbavancin, oritavancin, daptomycin, linezolid[1], tedizolid[1], quinupristin-dalfopristin[1], tigecycline, eravacycline or omadacycline
2.3	*Corynebacterium* spp.	Resistant to vancomycin, teicoplanin, telavancin, dalbavancin, oritavancin, daptomycin, linezolid, tedizolid, quinupristin-dalfopristin or tigecycline
2.4	*Streptococcus pneumoniae*	Resistant to carbapenems, vancomycin, teicoplanin, telavancin, dalbavancin, oritavancin, daptomycin, linezolid, tedizolid, quinupristin-dalfopristin, tigecycline, eravacycline, omadacycline or rifampicin.
2.5	Group A, B, C and G β-haemolytic streptococci	Resistant to penicillin, cephalosporins, vancomycin, teicoplanin, telavancin, dalbavancin, oritavancin, daptomycin, linezolid, tedizolid, quinupristin-dalfopristin, tigecycline, eravacycline or omadacycline
2.6	*Enterococcus* spp.	Resistant to daptomycin, linezolid, tigecycline, eravacycline or omadacycline Resistant to teicoplanin but not vancomycin
2.7	*Enterococcus faecalis*	Resistant to ampicillin
2.8	*Enterococcus faecalis, Enterococcus gallinarum, Enterococcus casseliflavus, Enterococcus avium*	Susceptible to quinupristin-dalfopristin, consider misidentification. If also resistant to ampicillin it is almost certainly *E. faecium*

3.1	*Bacteroides* spp.	Resistant to metronidazole
3.2	*Clostridioides difficile*	Resistant to metronidazole, vancomycin or fidaxomicin

Reglas de expertos

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Expert rules and expected phenotypes

Expert rules and expected phenotypes

Expert rules and expected phenotypes

EUCAST expert rules (see below) are a tabulated collection of expert knowledge on interpretive rules, expected resistant phenotypes and expected susceptible phenotypes which should be applied to antimicrobial susceptibility testing in order to reduce testing, reduce errors and make appropriate recommendations for reporting particular resistances.

Rules are graded according to A, B and C:

A. There is good clinical evidence for the rule, i.e., applying the rule likely improves patient care. Grade A required clinical studies supporting the rule.
B. Evidence is weak or based on only a few case reports or on experimental data. Animal studies were accepted as experimental data.
C. There is no clinical evidence, but *in vitro* microbiological data suggest that the rule should be applied.

For question and comments on EUCAST expert rules and expected phenotypes, use the **EUCAST subject related contact form.**

Expected phenotypes (follow link)

Expert rules

All documents revised 2019. Following the revision and a period of public consultation, the revised rules are now published as separate documents, each corresponding to a tab in the breakpoint table. Species listed without a link to a document lack expert rules. Documents may be updated separately why dates may eventually differ between documents.

Enterobacterales (June, 2019; typographical corrections October, 2021)

Salmonella spp.

Pseudomonas aeruginosa

Stenotrophomonas maltophilia

- Extrapolar a ATB no evaluados
- En función de S/I/R dar alertas
- En función de S/I/R Interpretar

EUCAST Expert Rules v 3.2 Enterobacterales

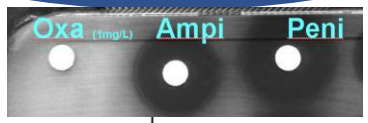
Rule No	Organisms	Indicator Agent*	Agents affected*	Rule	Remarks	Grade	References
Beta-Lactams							
1	*E. coli, P. mirabilis*	ampicillin	piperacillin	IF resistant to ampicillin, THEN report resistant to piperacillin regardless of test result IF susceptible to ampicillin, THEN report as susceptible to piperacillin		A	Drusano, Schimpff, & Hewitt, 1984
2	*Klebsiella* spp. (except *K. aerogenes*), *Raoultella* spp.	piperacillin	piperacillin	Report all *Klebsiella* spp. (except *K. aerogenes*) and *Raoultella* spp. as piperacillin resistant, regardless of test result		A	Drusano, Schimpff, & Hewitt, 1984; Mouton, Beuscart, & Soussy, 1986; Pancoast, Prince, Francke, & Neu, 1981
3	*Enterobacter* spp., *K. aerogenes, Citrobacter freundii* complex, *Hafnia alvei*	cefotaxime, ceftriaxone, ceftazidime	cefotaxime, ceftriaxone, ceftazidime	IF susceptible in vitro to cefotaxime, ceftriaxone or ceftazidime, THEN EITHER add a note that monotherapy with cefotaxime, ceftriaxone or ceftazidime as well as combination therapy of these agents with an aminoglycoside should be discouraged owing to risk of selecting resistance, OR suppress the susceptibility testing results for these agents	Selection of AmpC de-repressed cephalosporin resistant mutants may occur during therapy. The risk is relatively high in *Enterobacter*, *K. aerogenes* and *Citrobacter* and low in *Morganella* and *Serratia*. For *Hafnia alvei in-vitro* mutation rates are similar to *Enterobacter* or *Citrobacter*. The use of a 3rd generation cephalosporin in combination with an aminoglycoside may also lead to failure by selection of resistant mutants. he combination with a quinolone, however, has found to be protective, although the clinical utility of this combination is not known. The selection risk is absent or much diminished for cefepime	A	Sanders & Sanders, 1988; Choi et al., 2008; Harris & Ferguson, 2012; Kohlmann, Bähr, & Gatermann, 2018

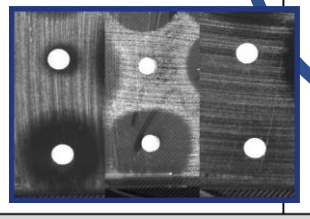
EUCAST Expert Rules v 3.2 Enterobacterales

7	*E. coli, Klebsiella* spp. (except *K. aerogenes*), *Raoultella* spp.	cefotaxime, ceftriaxone, ceftazidime, cefepime,	cefotaxime, ceftriaxone, ceftazidime, cefepime	IF resistant to any 3rd generation (cefotaxime, ceftriaxone, ceftazidime) or 4th generation (cefepime) cephalosporin and susceptible to another 3rd or 4th generation cephalosporin THEN report each as tested and enclose a warning on uncertain therapeutic outcome for infections other than urinary tract infections.	This phenotype is most often caused by ESBL production. Available evidence indicates that the cephalosporin phenotype predicts treatment outcome, although there is still a paucity of clinical data outside the urinary tract.	A	Thauvin-Eliopoulos, Tripodi, Moellering, & Eliopoulos, 1997; Bin et al., 2006; Chopra et al., 2012; Lee et al., 2013; Lee et al., 2015
Fluoroquinolones							
8	Enterobacterales except *Salmonella* spp.	ciprofloxacin	all fluoroquinolones	IF resistant to ciprofloxacin, THEN report as resistant to all fluoroquinolones IF susceptible to ciprofloxacin, THEN report other fluoroquinolones as tested	Acquisition of at least two target mutations in either *gyr*A or *gyr*A plus *parC*. The AAC(6')-Ib-cr enzyme partially inactivates ciprofloxacin but not levofloxacin; however, with current breakpoints this difference cannot be detected	B	Cavaco et al., 2008; Martínez-Martínez, Eliecer Cano, Manuel Rodríguez-Martínez, Calvo, & Pascual, 2008
Tetracyclines							
9	*Serratia spp.* *Providencia spp.* *Morganella morganii*	tigecycline	tigecycline	Tigecycline has poor activity against these species and should be reported as resistant irrespective of susceptibility testing result	Data on efficacy of tigecycline towards these organisms is scarce	C	
Aminoglycosides							
10	*Enterobacterales*	aminoglycosides	aminoglycosides	Breakpoints for aminoglycosides are being revised during 2019 after which all rules pertaining to aminoglycosides will be revisited.			

EUCAST Expert Rules v 3.2 — Pneumococcus

Rule No.	Organism(s)	Indicator Agent	Agents Affected	Rule	Remarks	Grade	References
Beta-lactams							
1	*Streptococcus pneumoniae*	oxacillin (disk diffusion) screening test	phenoxymethylpenicillin, benzylpenicillin, aminopenicillins, cephalosporins, carbapenems	IF susceptible in the oxacillin screening test, THEN report beta-lactam agents with breakpoints for *S. pneumoniae* susceptible. IF resistant in the oxacillin screening test, THEN refer to the flowchart in the Breakpoint Tables.		A	Dixon et al., 1977; Swenson et al., 1986; Jetté and Sinave, 1999;
Macrolides, lincosamides and streptogramins							
2	*Streptococcus pneumoniae*	erythromycin, clindamycin	clindamycin	IF resistant to erythromycin AND susceptible to clindamycin THEN test for inducible MLS_B resistance; IF negative THEN report clindamycin susceptible; IF positive THEN report clindamycin resistant	Streptococci resistant to macrolides but susceptible to clindamycin produce Erm ribosomal methylases conferring the inducible MLS_B phenotype or express efflux pumps. In case of inducible MLS_B resistance, constitutively resistant mutants can be selected by clindamycin.	A	Lewis et al., 2014
Fluoroquinolones							
3	*Streptococcus pneumoniae*	Norfloxacin screening test	levofloxacin moxifloxacin	IF susceptible in the norfloxacin screening test, THEN report levofloxacin and moxifloxacin susceptible IF resistant in the norfloxacin screening test, THEN report levofloxacin and moxifloxacin resistant OR report individual agents as tested.	Acquisition of at least one target mutation in e.g. *parC (parE)*. First step mutations can be more reliably detected in tests with norfloxacin.	C	Varon, Houssaye, Grondin, & Gutmann, 2006; Kays et al., 2007; de Cueto et al., 2008





EUCAST Expert Rules v 3.2 Staphylococcus

Rule No.	Organisms	Indicator Agent	Agents affected	Rule	Remarks	Grade	References
Beta-lactams							
1	*Staphylococcus aureus*	cefoxitin screening for MRSA by MIC determination or disk diffusion.	All beta-lactams except those specifically licensed to treat infections caused by methicillin-resistant staphylococci expressing low affinity PBP2a	IF resistant in the cefoxitin screening test (MRSA), THEN report resistant to all beta-lactams, except those specifically licensed to treat infections caused by methicillin-resistant staphylococci expressing low affinity PBP2a; such agents must be tested individually. IF susceptible in the cefoxitin screening test (MSSA), THEN report as susceptible to all beta-lactams with recognised anti-staphylococcal activity. *EUCAST does not encourage the use of oxacillin for the screening for mecA/mecC mediated beta-lactam resistance in* S. aureus.	Production of PBP2a leads to cross- resistance to beta-lactams. Ceftobiprole and ceftaroline are less affected by these changes than other beta-lactams and many MRSA isolates test susceptible. The specificity of oxacillin screening is poorer than for cefoxitin and other resistance mechanisms (hyperproduction of beta-lactamase) will influence the test result. The majority of "oxacillin positive" *S. aureus* will be *mecA*-positive, but some *mecC*-positive isolates will go undetected. Furthermore, some oxacillin-screen positive isolates (MIC-values of 4-8 mg/L) will have other beta-lactam resistance mechanisms than those mediated by *mec* genes (typically called BORSA, Borderline Oxacillin-Resistant *S. aureus*). EUCAST does not encourage screening for BORSA	A	Chambers, Hackbarth, Drake, Rusnak, & Sande, 1984; Skov, Larsen, Kearns, Holmes, Teale, Edwards, Hill. 2014

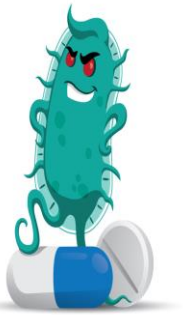
EUCAST Expert Rules v 3.2

Staphylococcus

Rule No.	Organisms	Indicator Agent	Agents affected	Rule	Remarks	Grade	References
2	*Staphylococcus aureus* and *S. lugdunensis*	benzylpenicillin (and beta-lactamase detection)	penicillins apart from isoxazolyl-penicillins and combinations with beta-lactamase inhibitors	IF resistant to benzylpenicillin OR IF beta-lactamase is detected, THEN report as resistant to all penicillins, regardless of MIC, except the isoxazolyl-penicillins and combinations with beta-lactamase inhibitors	Testing for beta-lactamase production with nitrocefin is discouraged. The appearance of the zone edge is more reliable, provided that the EUCAST-recommended benzylpenicillin 1U disk is used	C	Papanicolas et al., 2014 Hombach et al., 2017
Macrolides, lincosamides and streptogramins							
3	*Staphylococcus* spp.	erythromycin, clindamycin	clindamycin	IF resistant to erythromycin AND susceptible to clindamycin, THEN test for inducible MLS_B resistance IF negative for inducibility, THEN report clindamycin susceptible IF positive for inducibility, THEN report clindamycin resistant. IF susceptible to erythromycin and clindamycin, THEN report as susceptible to all macrolides and lincosamides	Staphylococci resistant to macrolides but susceptible to clindamycin produce Erm-type ribosomal methylases conferring the inducible MLS_B phenotype, or express efflux pumps. In the case of inducible MLS_B resistance, constitutively resistant mutants can be selected by clindamycin. Adding a note may be considered, stating that clindamycin may still be used in less severe skin and soft tissue infections	A	LaPlante, Leonard, Andes, Craig, & Rybak, 2008

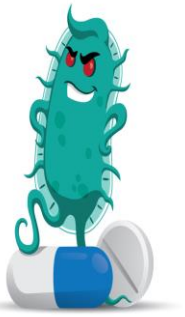
Ciprofloxacino

Organism(s)	Indicator Agent	Agents Affected	Rule
Fluoroquinolones			
Enterobacterales except *Salmonella* spp.	ciprofloxacin	all fluoroquinolones	IF resistant to ciprofloxacin, THEN report as resistant to all fluoroquinolones IF susceptible to ciprofloxacin, THEN report other fluoroquinolones as tested
Salmonella spp.	ciprofloxacin (MIC), pefloxacin (disk diffusion) screening test	fluoroquinolones	IF ciprofloxacin MIC >0.06 mg/L OR resistant to pefloxacin THEN report resistant to ciprofloxacin and include a caution against the use of other fluoroquinolones IF ciprofloxacin MIC ≤ 0.06 mg/L OR susceptible to pefloxacin by the screening test, THEN report as susceptible to ciprofloxacin (and other fluoroquinolones with proven efficacy in invasive *Salmonella* infections)



Ácido Nalidíxico

Organism(s)	Indicator Agent	Agents Affected	Rule
Fluoroquinolones			
Moraxella catarrhalis	nalidixic acid screening test	all fluoroquinolones	IF susceptible in the nalidixic acid screening test THEN report susceptible to all indicated fluoroquinolones IF resistant in the nalidixic acid screening test THEN report indicated fluoroquinolones resistant OR determine the susceptibility of the agent to be used in therapy AND if susceptible add a note that resistance may develop during therapy.
Haemophilus influenzae	nalidixic acid screening test	all fluoroquinolones	IF susceptible in the nalidixic acid screening test THEN report susceptible to all indicated fluoroquinolones; IF resistant in the nalidixic acid screening test, THEN report resistant to ciprofloxacin, levofloxacin and moxifloxacin, OR determine the susceptibility of the agent to be used in therapy AND if susceptible add a cautionary remark that resistance may develop during therapy.



Norfloxacino

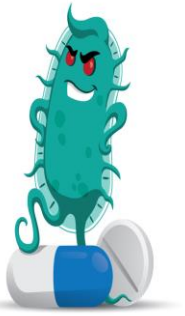
Organism(s)	Indicator Agent	Agents Affected	Rule
Fluoroquinolones			
Enterococcus spp.	norfloxacin screening test	ciprofloxacin levofloxacin	IF susceptible in the norfloxacin screening test THEN report susceptible to ciprofloxacin and levofloxacin IF resistant in the norfloxacin screening test THEN test ciprofloxacin and levofloxacin individually and report as tested NOTE: this rule applies to isolates from uncomplicated UTI only
Streptococcus pneumoniae	Norfloxacin screening test	levofloxacin moxifloxacin	IF susceptible in the norfloxacin screening test, THEN report levofloxacin and moxifloxacin susceptible IF resistant in the norfloxacin screening test, THEN report levofloxacin and moxifloxacin resistant OR report individual agents as tested.
Streptococcus spp. A, B, C, G	norfloxacin screening test	levofloxacin, moxifloxacin	IF susceptible in the norfloxacin screening test THEN report susceptible to levofloxacin and moxifloxacin IF resistant in the norfloxacin screening test THEN report levofloxacin and moxifloxacin resistant OR test the individual agents and report as tested

Norfloxacino
Levofloxacino

Organism(s)	Indicator Agent	Agents Affected	Rule
Fluoroquinolones			
Streptococcus pneumoniae	Norfloxacin screening test	levofloxacin moxifloxacin	IF susceptible in the norfloxacin screening test, THEN report levofloxacin and moxifloxacin susceptible IF resistant in the norfloxacin screening test, THEN report levofloxacin and moxifloxacin resistant OR report individual agents as tested.
			IF resistant to norfloxacin and susceptible to levofloxacin and/or moxifloxacin, THEN add a warning that resistance may develop during therapy with the agent.
Streptococcus pneumoniae	Levofloxacin, moxifloxacin	All fluoroquinolones	IF resistant to levofloxacin or moxifloxacin, THEN report as resistant to all fluoroquinolones
Staphylococcus spp.	norfloxacin screening test	all fluoroquinolones	IF susceptible in norfloxacin screening test, THEN report as susceptible to ciprofloxacin, levofloxacin, moxifloxacin and ofloxacin IF resistant in norfloxacin screening test, THEN report individual agents as tested, and IF susceptible to either of ciprofloxacin, levofloxacin or moxifloxacin, THEN report agent as tested with a warning of risk for development of resistance during therapy with quinolones.
Staphylococcus spp.	Levofloxacin, moxifloxacin	all fluoroquinolones	IF resistant to levofloxacin or moxifloxacin, THEN report as resistant to all fluoroquinolones.

Mecanismos de resistencia

https://saludos.cualtis.com/wp-content/uploads/2019/10/GettyImages-871920402.jpeg



Procedimientos en Microbiología Clínica

Recomendaciones de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica

Editores: Emilia Cercenado y Rafael Cantón

38.

Detección fenotípica de mecanismos de resistencia en gramnegativos

2 0 1 1

Coordinador: Ferran Navarro

Autores: Jorge Calvo
Rafael Cantón
Felipe Fernández Cuenca
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Ferran Navarro

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39.

Detección fenotípica de mecanismos de resistencia en grampositivos

2 0 1 1

Coordinadora: María Isabel Morosini

Autores: Carmen Ardanuy
Emilia Cercenado
María Isabel Morosini
Carmen Torres

Resistance mechanisms

- Organization
- EUCAST News
- Definitions of S, I and R
- Clinical breakpoints and dosing
- Rapid AST in blood cultures
- Expert rules and intrinsic resistance
- **Resistance mechanisms**
- Guidance documents
- Consultations
- MIC and zone distributions and ECOFFs
- AST of bacteria

EUCAST guideline for the detection of resistance mechanisms and specific resistances of clinical and/or epidemiological importance

The first version of the EUCAST guideline for the detection of resistance mechanisms and specific resistances of clinical and/or public health importance was first published in December 2013. Following general consultation a revised version was published in 2017.

The EUCAST guideline on detection of resistance mechanisms v 2.0 (2017-07-11)

Previous version:

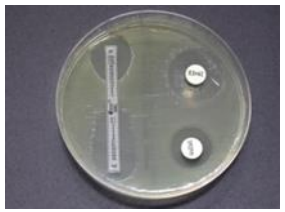
The EUCAST guideline on detection of resistance mechanisms v 1.0 (2013-12-11)

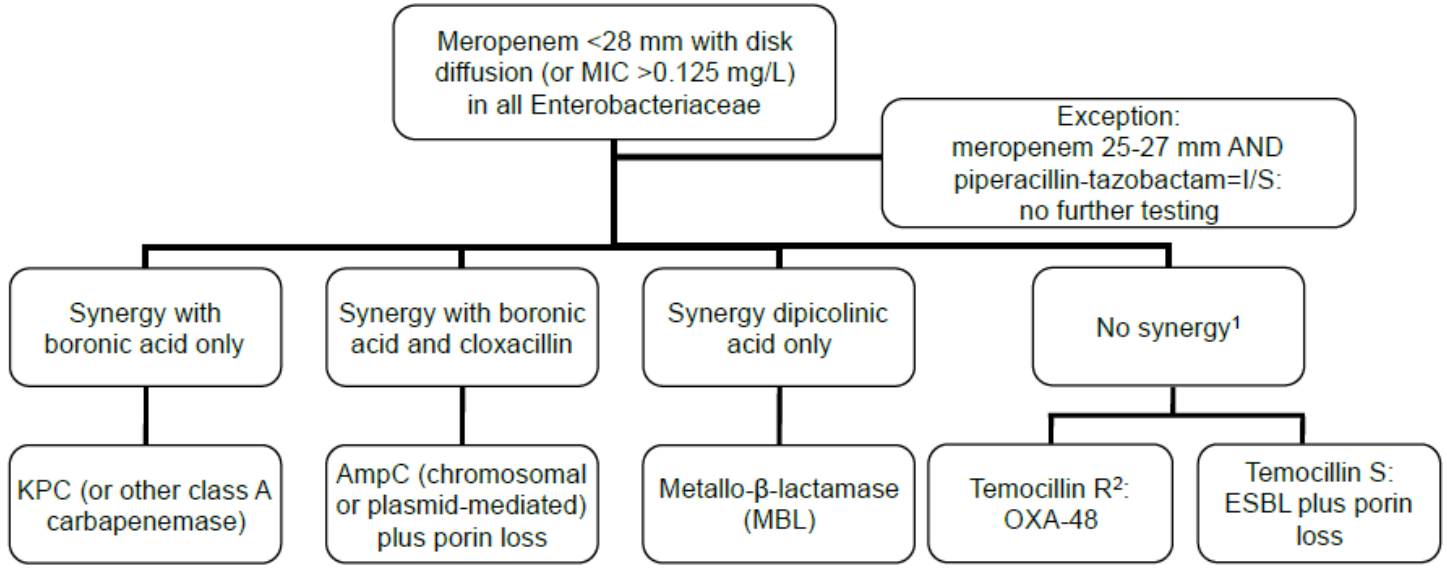
http://www.eucast.org/

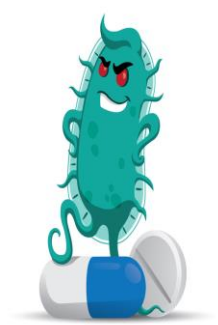
Carbapenemase-producing Enterobacteriaceae

Importance of detection of resistance mechanism	
Required for clinical antimicrobial susceptibility categorization	No
Infection control purposes	Yes
Public health purposes	Yes

Carbapenem	MIC (mg/L)		Disk diffusion zone diameter (mm) with 10 µg disks	
	S/I breakpoint	Screening cut-off	S/I breakpoint	Screening cut-off
Meropenem[1]	≤2	>0.125	≥22	<28[2]
Ertapenem[3]	≤0.5	>0.125	≥25	<25







Extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae

Importance of detection of resistance mechanism	
Required for clinical antimicrobial susceptibility categorization	No
Infection control purposes	Yes
Public health purposes	Yes

Method	Antibiotic	Conduct ESBL-testing if
Broth or agar dilution[1]	Cefotaxime/ceftriaxone AND Ceftazidime	MIC >1 mg/L for either agent
	Cefpodoxime	MIC >1 mg/L
Disk diffusion[1]	Cefotaxime (5 µg) or Ceftriaxone (30 µg) AND Ceftazidime (10 µg)	Inhibition zone <21 mm Inhibition zone <23 mm Inhibition zone <22 mm
	Cefpdoxime (10 µg)	Inhibition zone <21 mm

Extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae

ESBL SCREENING:
I/R to one or both of cefotaxime and ceftazidime
(or cefpodoxime R)

No → No ESBL

Yes → Species dependent ESBL confirmation

Group 1:
E.coli, Klebsiella spp., *P. mirabilis, Salmonella* spp., *Shigella* spp.

ESBL CONFIRMATION[1]
with ceftazidime and cefotaxime+/- clavulanic acid

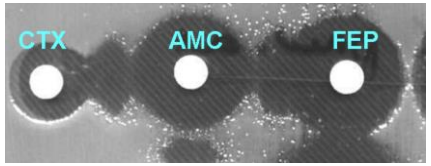
- Negative: No ESBL
- Indeterminate
- Positive: ESBL

Group 2:
Enterobacteriaceae with inducible chromosomal AmpC:
Enterobacter spp., *Citrobacter freundii, Morganella morganii, Providencia stuartii, Serratia* spp., *Hafnia alvei.*

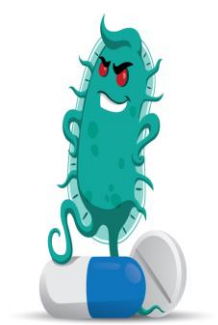
ESBL CONFIRMATION
with cefepime +/- clavulanic acid

- Negative: no ESBL
- Indeterminate[2]
- Positive: ESBL

Extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae



Method	Antimicrobial agent (disk content)	ESBL confirmation is positive if
ESBL gradient test	Cefotaxime +/- clavulanic acid	MIC ratio ≥8 or deformed ellipse present
	Ceftazidime +/- clavulanic acid	MIC ratio ≥8 or deformed ellipse present
Combination disk diffusion test (CDT)	Cefotaxime (30 µg) +/- clavulanic acid (10 µg)	≥5 mm increase in inhibition zone
	Ceftazidime (30 µg) +/- clavulanic acid (10 µg)	≥5 mm increase in inhibition zone
Broth microdilution	Cefotaxime +/- clavulanic acid (4 mg/L)	MIC ratio ≥8
	Ceftazidime +/- clavulanic acid (4 mg/L)	MIC ratio ≥8
	Cefepime +/- clavulanic acid (4 mg/L)	MIC ratio ≥8
Double disk synergy test (DDST)	Cefotaxime, ceftazidime and cefepime	Expansion of indicator cephalosporin inhibition zone towards amoxicillin-clavulanic acid disk



Extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae

Method	Antibiotic	Confirmation is positive if
ESBL gradient test Etest®® ESBL	Cefepime +/- clavulanic acid	MIC ratio ≥8 or deformed ellipse present
Combination disk diffusion test	Cefepime (30 µg) +/- clavulanic acid (10 µg)	≥5 mm increase in inhibition zone
Broth microdilution	Cefepime +/- clavulanic acid (fixed concentration 4 mg/L)	MIC ratio ≥8
Double disk synergy test (DDST)	Cefotaxime, ceftazidime, Cefepime	Expansion of indicator cephalosporin inhibition zone towards amoxicillin-clavulanic acid disk

Acquired AmpC β-lactamase-producing Enterobacteriaceae

Importance of detection of resistance mechanism	
Required for clinical antimicrobial susceptibility categorization	No
Infection control purposes	Yes
Public health purposes	Yes

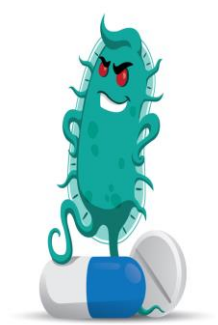
	Enterobacterias					*Pseudomonas* Resistente a carbapenémicos	*Acinetobacter* Resistente a carbapenémicos
	ESBL	AmpC	KPC	OXA-48	NDM/VIM/IMP		
Ceftolozano-tazobactam	+	+/-	-	+/-	-	+/-	-
Ceftazidima-avibactam	+	+	+	+	-	+/-	-
Meropenem-vaborbactam	+	+	+	-	-	-	-
Imipenem-relebactam	+	+	+	-	-	+	-
Aztreonam-avibactam	+	+	+	+	+	+/-	-
Eravacyclina	+	+	+	+	+	-	+
Plazomicin	+	+	+	+	-	+/-	-
Cefiderocol	+	+	+	+	+	+	+
Tigeciclina	+	+	+	+	+	-	+

Modificado de Tamma PD, Hsu AJ. J. Pediat Infect Dis Society. 2019 Jul;8(3):251-

Polymyxin resistance in Gram-negative bacilli

Importance of detection of resistance	
Required for clinical antimicrobial susceptibility categorization	Yes
Infection control purposes	Yes
Public health purposes	Yes

are therefore expected. However, the current focus is on detecting polymyxin resistance regardless of mechanism. Laboratories are advised to always use broth microdilution for susceptibility testing of colistin, and to always use colistin sulfate (9). Specifically, disk diffusion and gradient tests should not be used, as they are associated with high-risk of both very major and major AST errors (10). Recently, a colorimetric method was also introduced, but it has so far not

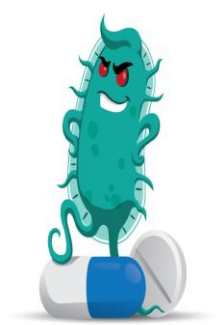


Carbapenemase producing *P. aeruginosa* and *Acinetobacter*

Importance of detection of resistance mechanism	
Required for clinical antimicrobial susceptibility categorization	No
Infection control purposes	Yes
Public health purposes	Yes

In general, genotypic approaches should be performed for characterization of putatively carbapenemase-producing *P. aeruginosa* and *Acinetobacter,* but particularly for *P. aeruginosa* some of the above mentioned phenotypic approaches could likely be of value for initial testing.

It should be noted that carbapenemase testing would be most clinically relevant in *P. aeruginosa*, since this species may be carbapenem resistant through multiple chromosomal mechanisms (active efflux, porin alteration or deficiencies). Contrarily, carbapenem resistance in *Acinetobacter* is almost constantly due to production of OXA carbapenemases.

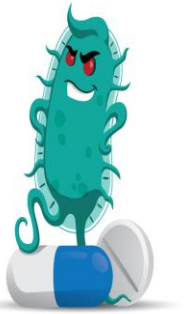


Methicillin resistant *Staphylococcus aureus* (MRSA)

Importance of detection of resistance	
Required for clinical antimicrobial susceptibility categorization	Yes
Infection control purposes	Yes
Public health purposes	Yes

7.4 Recommended methods for detection of methicillin resistance in *S. aureus*

Methicillin/oxacillin resistance can be detected phenotypically by MIC determination and by disk diffusion. Agglutination can be used to detect PBP2a, but will not reliably detect PBP2c. Genotypic detection with PCR is reliable.



Vancomycin-resistant *Staphylococcus aureus*

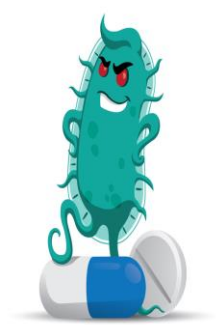
Importance of detection of resistance	
Required for clinical antimicrobial susceptibility categorization	Yes
Infection control purposes	Yes
Public health purposes	Yes

VRSA: Vancomycin resistant *S. aureus*:
S. aureus isolates with high-level resistance to vancomycin (MIC >8 mg/L).

VISA: Vancomycin intermediate *S. aureus*
S. aureus isolates with low-level resistance to vancomycin (MIC 4 - 8 mg/L).

hVISA: Heterogeneous vancomycin intermediate *S. aureus*.
S. aureus isolates susceptible to vancomycin (MICs ≤2mg/L) but with minority populations (1 in 10^6 cells) with vancomycin MIC >2 mg/L, as judged by population analysis profile investigation.

It should be noted that although these terms still remain, all of the above-mentioned categories should be regarded clinically resistant.



Vancomycin resistant *Enterococcus faecium* and *Enterococcus faecalis*

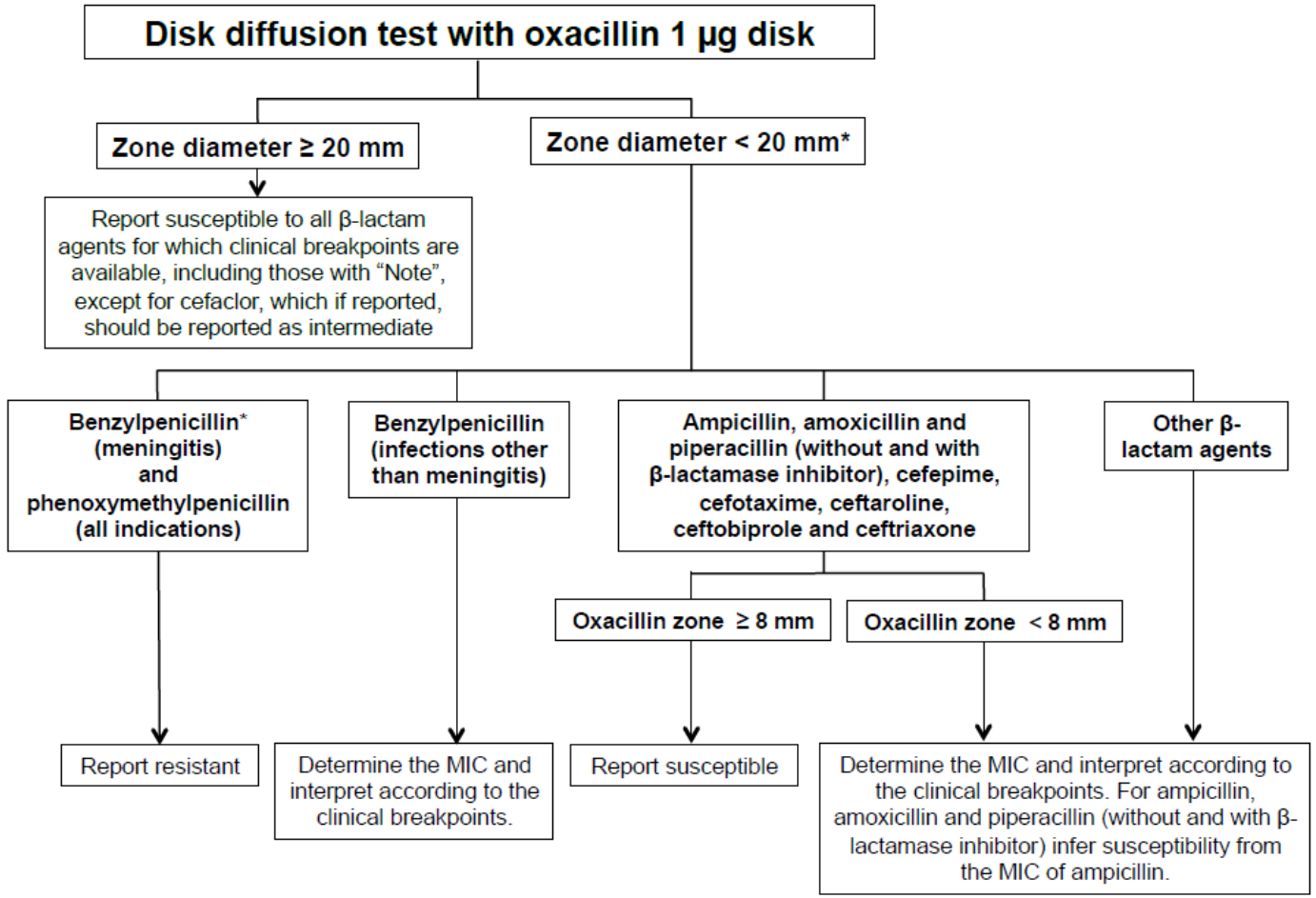
Importance of detection of resistance	
Required for clinical antimicrobial susceptibility categorization	Yes
Infection control purposes	Yes
Public health purposes	Yes

Glycopeptide	MIC (mg/L)	
	VanA	VanB
Vancomycin	64-1024	4-1024
Teicoplanin	8-512	0.06-1

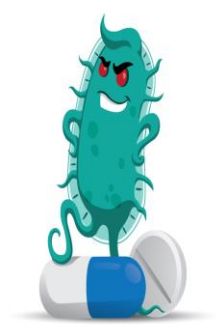
Vancomycin resistance can be detected by MIC determination, disk diffusion and the breakpoint agar method. For all three methods, it is essential that plates are incubated for a full 24 h in order to detect isolates with inducible resistance.

Penicillin non-susceptible (non-wild type) *Streptococcus pneumoniae*

Importance of detection of resistance	
Required for clinical antimicrobial susceptibility categorization	Yes
Infection control purposes	No
Public health purposes	Yes



Indications	MIC breakpoint (mg/L)		Notes
	S ≤	R >	
Benzylpenicillin (non-meningitis)	0.06	2	**In pneumonia**, when a dose of 1.2 g x 4 is used, isolates with **MIC ≤0.5 mg/L** should be regarded as susceptible to benzylpenicillin. **In pneumonia**, when a dose of 2.4 g x 4 or 1.2 g x 6 is used, isolates with **MIC ≤1 mg/L** should be regarded as susceptible to
			benzylpenicillin. **In pneumonia**, when a dose of 2.4 g x 6 is used, isolates with **MIC ≤2 mg/L** should be regarded as susceptible.
Benzylpenicillin (meningitis)	0.06	0.06	



Reflexiones finales

- Nuevos antimicrobianos y nuevos inhibidores de betalactamasas útiles para interpretar el mecanismo de resistencia.

- ¿Con las técnicas rápidas de estudios fenotípicos de sensibilidad a los antimicrobianos se pierde información del mecanismo de resistencia? ¿Necesidad de estudios complementarios?

- Nuevas herramientas como detecciones de antígeno de determinadas betalactamasas o PBP2a, las técnicas cromogénicas/colorimétricas para detectar actividad enzimática, las basadas en espectrometría de masas (MALDI), y las detecciones de ácidos nucleicos pueden ser de gran ayuda como técnica rápida y como complemento a las técnicas rápidas fenotípicas.