EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Intrinsic Resistance and Unusual Phenotypes version 3.3 October 2021

EUCAST Expert Rules version 2.0 was published on 29 October 2011 and has since been updated several times. Current and previous versions are available at (http://www.eucast.org/expert_rules_and_intrinsic_resistance/). All major versions were subjected to public consultations

Contents

	Antimicrobial agent / microorganisms or rule	Modifications from previous version 3.2
Table 1	*Hafnia alvei*	Cefoxitin, cefuroxime and ampicillin-sulbactam no longer listed as R since they may appear susceptible. (R to amoxicillin-clavulanate is maintained as it is above 90%). Stock et al. Diagnostic Microbiol Infect Dis 2005: 51:151-63 Günthard & Pennekamp. Clin Infect Dis 1996; 22:1040-5
	Aeromonas hydrophila, *A. caviae, A. jandaei*	Removed R for amoxicillin-clavulanic acid and cefoxitin, since both may appear susceptible. Overman and Janda. J Clin Microbiol 1999; 37: 706-8. Vila et al J Antimicrob Chemother 2002; 49:701-2
	Aeromonas veronii	Added R to ticarcillin (references as above)
	Aeromonas jandaei	Removed R to narrow-spectrum cephalosporins, since strains may appear susceptible (Overman and Janda. J Clin Microbiol 1999; 37: 706-8).
Table 2	*Achromobacter xylosoxidans*	Added R to aztreonam Pérez Barragán et al. Rev Esp Quimioter 2018; 31: 268-73. Nakamoto et al. Yonago Acta Medica 2017; 60:67–70
	Elizabethkingia meningoseptica	Removed R to piperacillin Lin et al. J Clin Med 2018, 7(12):538. Cheng et al. Clin Microbiol Infect 2019; 25:340-5.
	Elizabethkingia anophelis	New species added because outbreaks have been described. Resistances are same as for *E. meningoseptica* although *E. anophelis* tends is more often susceptible to piperacillin. References as above.
	Chryseobacterium spp.	Species added, natural resistances according to: Lin et al. Antimicrob Agents Chemother 2019; 63:e02256-18. Chang et al. J Microbiol Immunol Infect 2015; 48: 559-64.

	Antimicrobial agent / microorganisms or rule	Modifications from version 2.0
All		Definitions of “Intrinsic Resistances”, “Unusual Phenotypes” and “Expert Rules”
		Tables, rules and footnotes have been renumbered when needed. Taxonomy have been also updated
Table 1	Heading	Updated, including *Enterobacterales* taxonomy and *Aeromonas*
	Hafnia alvei	R included for colistin
	Enterobacter aerogenes	Update to *Klebsiella aerogenes*
	Leclercia ascorbata	New inclusion, R included for fosfomycin
	Plesiomonas shigelloides	New inclusion, R included for different beta-lactams
	Providencia rettgeri	R removed for cefuroxime and tigecycline (now included in the expert rules)
	Providencia stuartii	R removed for cefuroxime and tigecycline (now included in the expert rules)
	Aeromonas hydrophila, Aeromonas veronii, Aeromonas dhakensis, Aeromonas caviae, and Aeromonas jandaei	New inclusion, R included for different beta-lactams
Table 2	Heading	Updated
Table 3	Heading	Updated
Table 4	*Clostridium ramosum, Clostridium innocuum*	Moved to a new table (table 5) which includes anaerobes
Table 6	*Salmonella* Typhi	Deletion of fluoroquinolones resistance
	Haemophilus influenzae	New footnote for fluroquinolones
	Neisseria gonorrhoeae	Deletion of azithromycin resistance
Table 7	Heading	“Exceptional” has been replaced by “unusual”
	Staphylococcus aureus, Coagulase-negative staphylococci, *Streptococcus pneumoniae*, Group A B, C and G β-haemolytic streptococci, and enterococcus spp.	Eravacycline and omadacycline added
Table 8	Heading	“Exceptional” has been replaced by “unusual”
	Bacteroides spp.	Deletion of carbapenem resistance
	Clostridioides difficile	Fidaxomicin added

Definitions of “Intrinsic Resistances and Unusual Phenotypes” and “Expert Rules”

Intrinsic Resistances and Unusual Phenotypes

The purpose of the Intrinsic Resistances and Unusual Phenotypes tables is to serve as a tool for the validation of species identification and/or susceptibility test results. The absence of intrinsic resistance or the presence of an unusual phenotype indicates that the laboratory should check the species identification, the susceptibility test results or both.

Microorganisms are only listed as “intrinsically resistant” to an agent (or group of agents) when a vast majority of wild type isolates exhibit MIC values that are so high that the agent should not be considered for either therapy or clinical susceptibility testing. If on the other hand, a significant proportion of the organisms have MIC values below the R breakpoint of species generally susceptible to the agent, it is not listed as intrinsically resistant. A typical example for the latter situation is *Enterobacter cloacae* complex and cefuroxime. About 40% of isolates of this complex have an MIC below the “R” clinical breakpoint for *Enterobacterales*, which means that a “Susceptible-increased exposure” result is not uncommon and therefore does not require review of their identification or the susceptibility test results. Instead, it is recommended that cefuroxime should not be used for therapy of a severe infection caused by *E. cloacae* complex and an expert rule is applied. The definition and application of “intrinsic resistance” is not absolute and a change in the designation of a species may occur over time as new data is available. http://www.eucast.org/expert_rules_and_intrinsic_resistance/

Expert Rules

Expert rules represent advice for antimicrobial therapy, most often indicating when to avoid the use of antimicrobials that are likely to result in treatment failure. In addition, Expert Rules give recommendations about how to handle situations that are currently controversial or unresolved.

“Expert rules” are general advice on the susceptibility or resistance of a species (or species group) against one or several agents, which can be drawn from the level of resistance or susceptibility to one or several agents or from the identification of a resistance mechanism. Most often the rules indicate when to avoid the use of antimicrobials that are likely to result in treatment failure. In addition, “Expert Rules” provide advice on how to handle situations that are currently controversial or unresolved.

Note:

Throughout the tables that follow “R” = intrinsically resistant, as defined above.

Table 1 Intrinsic resistance in *Enterobacterales* and *Aeromonas* spp. *Enterobacterales* and *Aeromonas* spp. are also intrinsically resistant to benzylpenicillin, glycopeptides, lipoglycopeptides, fusidic acid, macrolides (with some exceptions[1]), lincosamides, streptogramins, rifampicin, and oxazolidinones

Rule	Organisms	Ampicillin/Amoxicillin	Amoxicilin-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 ascorbata*											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
1.16	*Providencia stuartii*	R	R	R		R			R		R		R
1.17	*Raoultella* spp.	R			R								

1.18	*Serratia marcescens*	R	R	R		R	R	R	R[5]		R		R
1.19	*Yersinia enterocolitica*	R	R	R	R	R	R						
1.20	*Yersinia pseudotuberculosis*										R		
1.21	*Aeromonas hydrophila*	R		R									
1.22	*Aeromonas veronii*	R		R	R								
1.23	*Aeromonas dhakensis*	R		R			R						
1.24	*Aeromonas caviae*	R		R									
1.25	*Aeromonas jandaei*												

[1] Azithromycin is effective *in vivo* for the treatment of typhoid/paratyphoid fever and erythromycin may be used to treat travellers' diarrhoea.

[2] Clinical breakpoints for cefoxitin have not been defined. *Enterobacterales* species intrinsically resistant to this antibiotic produce a chromosomal inducible AmpC β-lactamase (AmpC) that is responsible for higher cefoxitin MIC values when compared with those from *Enterobacterales* species lacking production of this beta-lactamase.

[3] Also includes *Citrobacter sedlakii, Citrobacter farmeri* and *Citrobacter rodentium.*

[4] Also includes *Citrobacter braakii*, *Citrobacter murliniae*, *Citrobacter werkmanii* and *Citrobacter youngae.*

[5] *Serratia marcescens* is intrinsically resistant to tetracycline and doxycycline but not to minocycline or tigecycline.

Table 2 Intrinsic resistance in non-fermentative gram-negative bacteria. Non-fermentative gram-negative bacteria are also generally intrinsically resistant to benzylpenicillin, first- and second-generation cephalosporins, glycopeptides, lipoglycopeptides, fusidic acid, macrolides, lincosamides, streptogramins, rifampicin and oxazolidinones

Rule	Organisms	AmpiciAmpicillin/Amoxicillin	Amoxicillin-clavulanic acid	Ampicillin-sulbactam	Ticarcillin	Ticarcillin-clavulanic acid	Piperacillin	Piperacillin-tazobactam	Ceftriaxone, ceftriaxone	Ceftazidime	Cefepime	Aztreonam	Ertapenem	Imipenem	Meropenem	Ciprofloxacin	Chloramphenicol	Aminoglycosides	Trimethoprim	Fosfomycin	Tetracyclines	Tigecycline	Polymyxin B/Colistin
2.1	*Acinetobacter baumannii*, *A. pittii*, *A. nosocomialis*	R	R	Note[1]					R			R	R						R	R	R[2]	Note[2]	
2.2	*Achromobacter xylosoxidans*	R							R			R	R										
2.3	*Burkholderia cepacia* complex[3]	R	R	R	R	R	R	R	R			R	R			R	R	R[4]	R	R			R
2.4	*Elizabethkingia meningoseptica*	R	R	R	R	R			R	R	R	R	R	R	R								R
2.5	*Elizabethkingia anophelis*	R	R	R	R	R			R	R	R	R	R	R	R								
2.6	Ochrobactrum anthropi	R	R	R	R	R	R	R	R	R	R	R	R										
2.7	*Pseudomonas aeruginosa*	R	R	R					R				R				R	Note[5]	R		R	R	
2.8	*Stenotrophomonas maltophilia*	R	R	R	R		R	R	R			R	R	R	R			R[4]	R[6]	R	R[7]		
2.9	*Chryseobacterium* spp.	R	R	R	R	R			R	R		R	R	R	R			R					R

[1] *Acinetobacter baumannii* may appear to be susceptible to ampicillin-sulbactam due to activity of sulbactam with this species.

[2] *Acinetobacter* is intrinsically resistant to tetracycline and doxycycline but not to minocycline and tigecycline.

[3] *Burkholderia cepacia* complex includes different species. Some strains may appear susceptible to some beta-lactams *in vitro* but they are clinically resistant.

[4] *Burkholderia cepacia* and *Stenotrophomonas maltophilia* are intrinsically resistant to all aminoglycosides. Intrinsic resistance is attributed to poor permeability and putative efflux. In addition, most *Stenotrophomonas maltophilia* produce the AAC(6')Iz enzyme.

[5] *Pseudomonas aeruginosa* is intrinsically resistant to kanamycin and neomycin due to low level APH(3')-IIb activity.

[6] *Stenotrophomonas maltophilia* is typically susceptible to trimethoprim-sulfamethoxazole, but resistant to trimethoprim alone.

[7] *Stenotrophomonas maltophilia* is intrinsically resistant to tetracycline but not to doxycycline, minocycline and tigecycline.

Table 3 **Intrinsic resistance in gram-negative bacteria other than *Enterobacterales* and non-fermentative gram-negative bacteria. Gram-negative bacteria other than *Enterobacterales* and non-fermentative gram-negative bacteria listed are also intrinsically resistant to glycopeptides, lipoglycopeptides, lincosamides, and oxazolidinones.**

Rule	Organisms	Fusidic acid	Streptogramins	Trimethoprim	Nalidixic acid
3.1	*Haemophilus influenzae*	R	R		
3.2	*Moraxella catarrhalis*			R	
3.3	*Neisseria* spp.			R	
3.4	*Campylobacter fetus*	R	R	R	R
3.5	*Campylobacter jejuni, Campylobacter coli*	R	R	R	

Table 4 Intrinsic resistance in gram-positive bacteria. Gram-positive bacteria are also intrinsically resistant to aztreonam, temocillin, polymyxin B/colistin and nalidixic acid

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			

[1] Low-level resistance (LLR) to aminoglycosides. Combinations of aminoglycosides with cell wall inhibitors (penicillins and glycopeptides) are synergistic and bactericidal against isolates that are susceptible to cell wall inhibitors and do not display high-level resistance to aminoglycosides

[2] In addition to LLR to aminoglycosides, *Enterococcus faecium* produces a chromosomal AAC(6')-I enzyme that is responsible for the loss of synergism between aminoglycosides (except gentamicin, amikacin and streptomycin) and penicillins or glycopeptides

Table 5, Intrinsic resistance in anaerobes. Anaerobes are also intrinsically resistant to aztreonam, aminoglycosides, polymyxin B/colistin and nalidixic acid

Rule	Organisms	Vancomycin
5.1	*Clostridium ramosum*, *Clostridium innocuum*	R

Table 6 Unusual resistance phenotypes of gram-negative bacteria

Rule	Organisms	Unusual phenotypes
6.1	Any *Enterobacterales* (except *Morganellaceae* and *Serratia marcescens*)	Resistant to colistin[1,2]
6.2	*Salmonella* Typhi	Resistant to carbapenems
6.3	*Pseudomonas aeruginosa* and *Acinetobacter* spp.	Resistant to colistin[1]
6.4	*Haemophilus influenzae*	Resistant to any third-generation cephalosporin, carbapenems, fluoroquinolones[3]
6.5	*Moraxella catarrhalis*	Resistant to any third-generation cephalosporin or fluoroquinolones
6.6	*Neisseria meningitidis*	Resistant to any third generation cephalosporins or fluoroquinolones
6.7	*Neisseria gonorrhoeae*	Resistant to spectinomycin

[1] Except in countries where colistin resistance is not rare.
[2] Colistin MICs for some *Salmonella* serotypes are slightly above the breakpoint (S ≤2; R >2 mg/L).
[3]Except in countries where fluoroquinolone resistance is not rare.

Table 7 Unusual resistance phenotypes of gram-positive bacteria

Rule	Organisms	Unusual phenotypes
7.1	*Staphylococcus aureus*	Resistant to vancomycin, teicoplanin, telavancin, dalbavancin, oritavancin, daptomycin, linezolid, tedizolid, quinupristin-dalfopristin, tigecycline, eravacycline or omadacycline
7.2	Coagulase-negative staphylococci	Resistant to vancomycin, telavancin, dalbavancin, oritavancin, daptomycin, linezolid[1], tedizolid[1], quinupristin-dalfopristin[1], tigecycline, eravacycline or omadacycline
7.3	*Corynebacterium* spp.	Resistant to vancomycin, teicoplanin, telavancin, dalbavancin, oritavancin, daptomycin, linezolid, tedizolid, quinupristin-dalfopristin or tigecycline
7.4	*Streptococcus pneumoniae*	Resistant to carbapenems, vancomycin, teicoplanin, telavancin, dalbavancin, oritavancin, daptomycin, linezolid, tedizolid, quinupristin-dalfopristin, tigecycline, eravacycline, omadacycline or rifampicin.
7.5	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
7.6	*Enterococcus* spp.	Resistant to daptomycin, linezolid, tigecycline, eravacycline or omadacycline Resistant to teicoplanin but not vancomycin
7.7	*Enterococcus faecalis*	Resistant to ampicillin
7.8	*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*

[1] Except in countries where linezolid, tedizolid or quinupristin-dalfopristin resistant coagulase-negative staphylococci are not rare.

Table 8 Unusual resistance phenotypes of anaerobes

Rule	Organisms	Unusual phenotypes
8.1	*Bacteroides* spp.	Resistant to metronidazole
8.2	*Clostridioides difficile*	Resistant to metronidazole, vancomycin or fidaxomicin