

EUCAST Expert Rules v 3.3 on Enterobacterales

Rule No.	Organisms	Indicator Agent*	Agents affected*	Rule	Remarks	Grade	References
Beta-Lactams							
1	<i>E. coli</i> , <i>P. mirabilis</i>	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	<i>Klebsiella</i> spp. (except <i>K. aerogenes</i>), <i>Raoultella</i> spp.	piperacillin	piperacillin	Report all <i>Klebsiella</i> spp. (except <i>K. aerogenes</i>) and <i>Raoultella</i> spp. as piperacillin resistant, regardless of test result		A	Drusano, Schimpff, & Hewitt, 1984; Mouton, Beuscart, & Soussy, 1986; Pancoast, Prince, Francke, & Neu, 1981
3	<i>Enterobacter</i> spp., <i>K. aerogenes</i> , <i>Citrobacter freundii</i> [†] , <i>Hafnia alvei</i>	cefotaxime, ceftriaxone, ceftazidime	cefotaxime, ceftriaxone, ceftazidime, piperacillin±tazobactam	IF susceptible in vitro to cefotaxime, ceftriaxone, ceftazidime, or piperacillin±tazobactam THEN EITHER add a note that monotherapy with cefotaxime, ceftriaxone, ceftazidime or piperacillin±tazobactam 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 <i>Enterobacter</i> spp, <i>K. aerogenes</i> and <i>C. freundii</i> and low in <i>M. morganni</i> and <i>S. macescens</i> . For <i>Hafnia alvei</i> <i>in-vitro</i> mutation rates are similar to <i>Enterobacter</i> spp. or <i>C. freundii</i> . The use of a 3rd generation cephalosporin in combination with an aminoglycoside may also lead to failure by selection of resistant mutants. The 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 Maillard et al 2023

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4	<i>Serratia</i> spp., <i>Morganella morganii</i> , <i>Providencia</i> spp	cefotaxime, ceftriaxone, ceftazidime	cefotaxime, ceftriaxone and ceftazidime	IF susceptible to cefotaxime, ceftriaxone or ceftazidime, THEN note that monotherapy with cefotaxime, ceftriaxone or ceftazidime may infrequently select resistant mutants		A	Sanders & Sanders, 1988; Choi et al., 2008; Harris & Ferguson, 2012; Kohlmann, Bähr, & Gatermann, 2018
5	<i>Enterobacter</i> spp., <i>K. aerogenes</i> , <i>Citrobacter freundii</i> ^f , <i>Serratia</i> spp., <i>Morganella morganii</i> , <i>Hafnia alvei</i> , <i>Providencia</i> spp.	cefuroxime	cefuroxime other 2 nd generation cephalosporins	IF susceptible to cefuroxime, THEN report cefuroxime and/or any other 2 nd generation cephalosporin as resistant	Although the breakpoint table does not list cefuroxime breakpoints for species other than <i>E. coli</i> , <i>P. mirabilis</i> , <i>Klebsiella</i> spp. (except <i>K. aerogenes</i>) and <i>Raoultella</i> spp., isolates may appear susceptible in vitro but the MICs tend to be higher than with the mentioned species and therapy with cefuroxime is not recommended. In addition, de-repressed mutants may be selected as with a third-generation cephalosporin.	C	
6	<i>E. coli</i> , <i>Klebsiella</i> spp. (except <i>K. aerogenes</i>), <i>Raoultella</i> spp.	cefotaxime, ceftriaxone, ceftazidime, cefepime,	piperacillin-tazobactam, amoxicillin-clavulanic acid	IF resistant to any 3 rd generation (cefotaxime, ceftriaxone, ceftazidime) or 4 th generation (cefepime) cephalosporin AND susceptible to piperacillin-tazobactam or amoxicillin-clavulanic acid, THEN report as tested.	This phenotype is most often caused by ESBL production. ESBL producers sometimes test as susceptible to beta-lactam/ beta-lactamase-inhibitor combinations. The use of these combinations in infections caused by ESBL-producers has historically been a matter of controversy. A number of studies have shown that they may be safe provided appropriate dosing is used. One publication indicates that carbapenem therapy may be	A	Retamar, López-Cerero, Muniain, Pascual, & Rodríguez-Baño, 2013; Rodríguez-Baño, Cisneros, Gudiol, & Martínez, 2014; Ofer-Friedman et

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					superior to piperacillin-tazobactam, as measured by 30-day mortality and primarily in patients with terminal cancer		al., 2015; Tamma et al., 2015; Gutiérrez-Gutiérrez et al., 2016 Harris et al., 2018;
7	<i>E. coli</i> , <i>Klebsiella</i> spp. (except <i>K. aerogenes</i>), <i>Raoultella</i> 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 3 rd or 4 th 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 <i>Salmonella</i> 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 <i>gyrA</i> or <i>gyrA</i> plus <i>parC</i> . 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	<i>Serratia</i> spp. <i>Providencia</i> spp. <i>Proteus</i> spp. <i>Morganella morganii</i>	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	

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Aminoglycosides							
10	<i>Enterobacterales</i>	aminoglycosides	aminoglycosides	Breakpoints for aminoglycosides were reviewed by EUCAST in 2019 and the decision was to present them in brackets only, meaning that these drugs should always be used in combination with another active therapy. In addition, it was noted that many of the old expert rules for aminoglycosides were based on very few laboratory experiments only but not on clinical data. Therefore, expert rules for aminoglycosides were removed in the present edition.			

*unless indicated, all names refer to agents without inhibitors

[†]also includes: *Citrobacter braakii*, *Citrobacter murlinae*, *Citrobacter werkmanii* and *Citrobacter youngae*

References

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