EUCAST Expert Rules v 3.2 on 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. 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

Rule No.	Organisms	Indicator Agent*	Agents affected*	Rule	Remarks	Grade	References
4	*Serratia* spp., *Morganella morganii*, *Providencia* 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	*Enterobacter* spp., *K. aerogenes, Citrobacter freundii*, *Serratia* spp., *Morganella morganii, Hafnia alvei, Providencia* spp.	cefuroxime	cefuroxime other 2nd generation cephalosporins	IF susceptible to cefuroxime, THEN report cefuroxime and/or any other 2nd generation cephalosporin as resistant	Although the breakpoint table does not list cefuroxime breakpoints for species other than *E. coli*, *P. mirabilis, Klebsiella* spp. (except *K. aerogenes*) and *Raoultella* 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	*E. coli, Klebsiella* spp. (except *K. aerogenes*), *Raoultella* spp.	cefotaxime, ceftriaxone, ceftazidime, cefepime,	piperacillin-tazobactam, amoxicillin-clavulanic acid	IF resistant to any 3rd generation (cefotaxime, ceftriaxone, ceftazidime) or 4th 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

Rule No.	Organisms	Indicator Agent*	Agents affected*	Rule	Remarks	Grade	References
					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	*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	

Rule No.	Organisms	Indicator Agent*	Agents affected*	Rule	Remarks	Grade	References
Aminoglycosides							
10	*Enterobacterales*	aminoglycosides	aminoglycosides	Breakpoints for aminoglycosides are being revised during 2019 after which all rules pertaining to aminoglycosides will be revisited.			

*unless indicated, all names refer to agents without inhibitors

References

Bin C, Hui W, Renyuan Z., Yongzhong N, Xiuli, X, Yingchun, X, Minjun C. Outcome of cephalosporin treatment of bacteremia due to CTX-M-type extended-spectrum beta-lactamase-producing Escherichia coli. *Diagn Microbiol Infect Dis* 2006; 56(4), 351–7. doi.org/10.1016/j.diagmicrobio.2006.06.015

Cavaco L M, Frimodt-Møller N, Hasman H, Guardabassi L, Nielsen L, Aarestrup FM. Prevalence of quinolone resistance mechanisms and associations to minimum inhibitory concentrations in quinolone-resistant *Escherichia coli* isolated from humans and swine in Denmark. Microbial Drug Resist 2008; 14(2), 163–9 http://doiorg/101089/mdr20080821

Choi SH, Lee JE, Park SJ, Choi SH, Lee SO, Jeong JY, Kim MN, Woo JH, Kim YS. Emergence of antibiotic resistance during therapy for infections caused by Enterobacteriaceae producing AmpC beta-lactamase: implications for antibiotic use. Antimicrob Agents Chemother 2008; 52(3):995-1000.

Chopra T, Marchaim D, Veltman J, Johnson P, Zhao JJ, Tansek R, Hatahet D, Chaudhry K, Pogue JM, Rahbar H, Chen TY, Truong T, Rodriguez V, Ellsworth J, Bernabela L, Bhargava A, Yousuf A, Alangaden G, Kaye KS. Impact of cefepime therapy on mortality among patients with bloodstream infections caused by extended-spectrum-beta-lactamase-producing Kl*ebsiella pneumoniae* and *Escherichia coli*. Antimicrob Agents Chemother 2012; 56(7):3936-42. DOI: 10.1128/AAC.05419-11.

Drusano GL, Schimpff SC, Hewitt WL The acylampicillins: mezlocillin, piperacillin, and azlocillin. Rev of Infect Dis 1984; 6(1):13–32. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/6369480

Gutiérrez-Gutiérrez B, Pérez-Galera S, Salamanca E, de Cueto M, Calbo E, et al. A Multinational, Preregistered Cohort Study of β-Lactam/β-Lactamase Inhibitor Combinations for Treatment of Bloodstream Infections Due to Extended-Spectrum-β-Lactamase-Producing Enterobacteriaceae. Antimicrob Agents Chemother. 2016; 60(7):4159-69. DOI: 10.1128/AAC.00365-16.

Harris PN, Ferguson JK. Antibiotic therapy for inducible AmpC β-lactamase-producing Gram-negative bacilli: what are the alternatives to carbapenems, quinolones and aminoglycosides? Int J Antimicrob Agents. 2012; 40(4):297-305. DOI: 10.1016/j.ijantimicag.2012.06.004.

Harris PNA, Tambyah PA, Lye DC, Mo Y, Lee TH, Yilmaz M, et al.; MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN). Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With E coli or Klebsiella pneumoniae Bloodstream Infection and Ceftriaxone Resistance: A Randomized Clinical Trial. JAMA. 2018; 320(10):984-994. DOI: 10.1001/jama.2018.12163

Kohlmann R, Bähr T, Gatermann SG. Species-specific mutation rates for ampC derepression in Enterobacterales with chromosomally encoded inducible AmpC β-lactamase. J Antimicrob Chemother. 2018; 73(6):1530-1536. DOI: 10.1093/jac/dky084.

Lee NY, Lee CC, Huang WH, Tsui KC, Hsueh PR, Ko WC. Cefepime therapy for monomicrobial bacteremia caused by cefepime-susceptible extended-spectrum beta-lactamase-producing Enterobacteriaceae: MIC matters. Clin Infect Dis. 2013; 56(4):488-95. DOI: 10.1093/cid/cis916.

Lee NY, Lee CC, Li CW, Li MC, Chen PL, Chang CM, Ko WC. Cefepime Therapy for Monomicrobial *Enterobacter cloacae* Bacteremia: Unfavorable Outcomes in Patients Infected by Cefepime-Susceptible Dose-Dependent Isolates. Antimicrob Agents Chemother. 2015; 59(12):7558-63. DOI: 10.1128/AAC.01477-15.

Martínez-Martínez L, Eliecer Cano M, Manuel Rodríguez-Martínez J, Calvo J, Pascual A. Plasmid-mediated quinolone resistance. Expert Rev Anti Infect Ther. 2008; 6(5):685-711. DOI: 10.1586/14787210.6.5.685.

Mouton Y, Beuscart C, Soussy C. [Effectiveness and tolerance of piperacillin in 333 patients]. [Article in French]. Presse Med. 1986 Dec 20;15(46):2347-50.

Ofer-Friedman H, Shefler C, Sharma S, Tirosh A, Tal-Jasper R, Kandipalli D, et al.. Carbapenems Versus Piperacillin-Tazobactam for Bloodstream Infections of Nonurinary Source Caused by Extended-Spectrum Beta-Lactamase-Producing Enterobacteriaceae. Infect Control Hosp Epidemiol. 2015; 36(8):981-5. DOI: 10.1017/ice.2015.101.

Pancoast S, Prince AS, Francke EL, Neu HC. Clinical evaluation of piperacillin therapy for infection. Arch Intern Med. 1981; 141(11):1447-50.

Park SH, Choi SM, Chang YK, Lee DG, Cho SY, Lee HJ, et al. The efficacy of non-carbapenem antibiotics for the treatment of community-onset acute pyelonephritis due to extended-spectrum β-lactamase-producing *Escherichia coli*. J Antimicrob Chemother. 2014; 69(10):2848-56. DOI: 10.1093/jac/dku215.

Retamar P, López-Cerero L, Muniain MA, Pascual Á, Rodríguez-Baño J; ESBL-REIPI/GEIH Group. Impact of the MIC of piperacillin-tazobactam on the outcome of patients with bacteremia due to extended-spectrum-β-lactamase-producing Escherichia coli. Antimicrob Agents Chemother. 2013; 57(7):3402-4. DOI: 10.1128/AAC.00135-13.

Rodríguez-Baño J, Cisneros JM, Gudiol C, Martínez JA Treatment of infections caused by carbapenemase-producing Enterobacteriaceae. Enferm Infecc Microbiol Clin. 2014 Dec;32 Suppl 4:49-55. DOI: 10.1016/S0213-005X(14)70174-0.

Sanders WE Jr, Sanders CC. Inducible beta-lactamases: clinical and epidemiologic implications for use of newer cephalosporins. Rev Infect Dis. 1988 Jul-Aug;10(4):830-8.

Tamma PD, Han JH, Rock C, Harris AD, Lautenbach E, Hsu AJ, Avdic E, Cosgrove SE; Antibacterial Resistance Leadership Group. Carbapenem therapy is associated with improved survival compared with piperacillin-tazobactam for patients with extended-spectrum β-lactamase bacteremia. Clin Infect Dis. 2015; 60(9):1319-25. DOI: 10.1093/cid/civ003.

Thauvin-Eliopoulos C, Tripodi MF, Moellering RC Jr, Eliopoulos GM. Efficacies of piperacillin-tazobactam and cefepime in rats with experimental intra-abdominal abscesses due to an extended-spectrum beta-lactamase-producing strain of *Klebsiella pneumoniae*. Antimicrob Agents Chemother. 1997; 41(5):1053-7.