

Expert rules in antimicrobial susceptibility testing

Roland Leclercq (Laboratoire de Microbiologie, CHU Côte de Nacre, Caen Cedex, 14033, France); Rafael Cantón (Servicio de Microbiología, Hospital Universitario Ramón y Cajal, Carretera de Colmenar Km 9,1, 28034-Madrid, Spain); Christian Giske (Department of Clinical Microbiology L2:02, Karolinska University Hospital, Solna, SE-17176 Stockholm, Sweden); Peter Heisig (Department of Pharmacy Biology & Microbiology, Institute of Pharmacy, University of Hamburg, Bundesstrasse 45, D-20146 Hamburg, Germany); David Livermore (Antibiotic Resistance Monitoring and Reference Laboratory, Health Protection Agency, 61 Colindale Avenue, London NW9 5EQ, UK); Patrice Nordmann (Service de Bactériologie-Virologie, Hôpital de Bicêtre, 78 rue du Général Leclerc, 94275 Le Kremlin-Bicêtre Cedex, France); Gian Maria Rossolini (Dip. di Biologia Molecolare, Sezione di Microbiologia, Policlinico Le Scotte, 53100 Siena, Italy); Trevor Winstanley (Department of Microbiology, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, UK)

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Introduction

A EUCAST Expert Rules Subcommittee (Chairman Roland Leclercq) was established early in 2006 with the remit to prepare tables of expert rules for antimicrobial susceptibility testing in order to assist microbiologists in the interpretation of antimicrobial susceptibility testing. Rules can also contribute to quality assurance by highlighting anomalous or unlikely results.

Rules should not conflict with EUCAST MIC breakpoints, but it is appreciated that some antimicrobial agents are not included in EUCAST breakpoints and many rules have developed over the years in conjunction with other breakpoint systems. Hence the first version is likely to be amended as EUCAST breakpoints are developed and in the light of experience with application of the rules. The contribution of all those who have commented on drafts during the preparation of this document is gratefully acknowledged.

The rules are presented in tables and are divided into intrinsic resistances, exceptional phenotypes and interpretive rules.

Intrinsic resistances (tables 1-4)

Intrinsic resistance is inherent (not acquired) resistance which is a characteristic of all or almost all representatives of the species. The antimicrobial activity of the drug is insufficient or antimicrobial resistance innate or so common as to render it clinically useless and antimicrobial susceptibility testing unnecessary. Hence “susceptible” results should be viewed with caution, as they most likely indicate an error in identification or susceptibility testing. Even if susceptibility is confirmed the drug should be used with caution. In some cases, intrinsic resistance to an antibiotic may be expressed at a low level, with MIC close to the susceptible breakpoint, although the antibiotic is not considered clinically active. The other situations where the antibiotic appears fully active in vitro but is inactive in vivo are generally not mentioned in the tables since they are rather matter of therapeutic recommendations.

Exceptional resistance phenotypes (tables 5-7)

Resistance of some bacterial species to particular antimicrobial agents has not yet been reported or is very rare. Exceptional resistance phenotypes should be checked as they may indicate an error in identification or susceptibility testing. If they are confirmed locally the isolate should be sent to a reference laboratory for independent confirmation. Exceptional resistance phenotypes may change with time as resistance may develop and increase over time. There may also be regional or national differences and a very rare resistance in one area may be more common in another.

Interpretive rules (tables 8-13)

On the basis of resistance to particular antimicrobial agents and the identification of an isolate it may be possible to infer resistance mechanisms and predict resistance to other agents. The applicability of such rules is limited by the range of agents tested, so individual laboratories will need to choose which agents to test for their local requirements. Also, it must be recognised that evidence of the clinical significance of interpretive rules varies and in these tables the evidence for rules has been graded as follows:

- A. There is clinical evidence that reporting the test result as susceptible leads to clinical failures.
- B. Evidence is weak and based only on a few case reports or on experimental models. It is presumed that reporting the test result as susceptible may lead to clinical failures.
- C. There is no clinical evidence, but microbiological data suggest that clinical use of the agent should be discouraged.

Table 1: Intrinsic resistance (R) in Enterobacteriaceae

Enterobacteriaceae are also intrinsically resistant to penicillin G, glycopeptides, fusidic acid, macrolides (with some exceptions¹), lincosamides, streptogramins, rifampicin, daptomycin and linezolid.

Rule no.	Organisms	Ampicillin	Amoxicillin-clavulanate	Ticarcillin	Piperacillin	Cefazolin	Cefoxitin	Cefamandole	Cefuroxime	Aminoglycosides	Tetracyclines/tigecycline	Polymyxin B/Colistin	Nitrofurantoin
1.1	<i>Citrobacter koseri</i>	R		R	R								
1.2	<i>Citrobacter freundii</i>	R	R			R	R						
1.3	<i>Enterobacter cloacae</i>	R	R			R	R						
1.4	<i>Enterobacter aerogenes</i>	R	R			R	R						
1.5	<i>Escherichia hermannii</i>	R		R	R								
1.6	<i>Hafnia alvei</i>	R	R			R	R						
1.7	<i>Klebsiella</i> spp.	R		R	R								
1.8	<i>Morganella morganii</i>	R	R			R			R		R	R	R
1.9	<i>Proteus mirabilis</i>										R	R	R
1.10	<i>Proteus vulgaris</i>	R				R		R	R		R	R	R
1.11	<i>Proteus penneri</i>	R				R		R	R		R	R	R
1.12	<i>Providencia rettgeri</i>	R	R			R				R ²		R	R
1.13	<i>Providencia stuartii</i>	R	R			R				R ²		R	R
1.14	<i>Serratia marcescens</i>	R	R			R		R	R	Note ³		R	
1.15	<i>Yersinia enterocolitica</i>	R	R	R	R	R	R	R					
1.16	<i>Yersinia pseudotuberculosis</i>											R	

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

² All *Providencia* spp. produce a chromosomal AAC(2'')-Ia enzyme. *Providencia* spp. should be considered resistant to all aminoglycosides except amikacin and streptomycin. Some isolates express the enzyme poorly and can appear susceptible to netilmicin *in vitro*, but should be reported as resistant as mutation can result in overproduction of this enzyme.

³ All *Serratia marcescens* produce a chromosomal AAC(6'')-Ic enzyme that may affect moderate the activity of all aminoglycosides except streptomycin and gentamicin.

Table 2: Intrinsic resistance (R) in non-fermentative Gram-negative bacteria

Non-fermentative Gram-negative bacteria are also intrinsically resistant to penicillin G, ceftazidime, ceftazidime, ceftazidime, ceftazidime, ceftazidime, glycopeptides, fusidic acid, macrolides, lincosamides, streptogramins, rifampicin, daptomycin and linezolid.

Rule no.	Organisms	Ampicillin	Amoxicillin-clavulanate	Ticarcillin	Ticarcillin-clavulanate	Piperacillin	Piperacillin-tazobactam	Cefazolin	Cefotaxime	Ceftriaxone	Ceftazidime	Ertapenem	Imipenem	Meropenem	Ciprofloxacin	Chloramphenicol	Aminoglycosides	Trimethoprim	Fosfomicin	Tetracyclines/ Tigecycline	Polymyxin B/Colistin	
2.1	<i>Acinetobacter baumannii</i> , <i>Acinetobacter calcoaceticus</i>	R ¹	R ¹					R	R	R		R						R	R			
2.2	<i>Achromobacter xylosoxydans</i>	R						R	R	R		R										
2.3	<i>Burkholderia cepacia</i> complex ²	R	R	R	R			R				R	R		R	R	R ³	R	R		R	
2.4	<i>Chryseobacterium meningosepticum</i>	R		R	R			R	R	R	R	R	R	R								R
2.5	<i>Ochrobactrum anthropi</i>	R	R	R	R	R	R	R	R	R	R	R										
2.6	<i>Pseudomonas aeruginosa</i>	R	R					R	R	R		R				R	Note ⁴	R ⁵		R		
2.7	<i>Stenotrophomonas maltophilia</i>	R	R	R		R	R	R	R	R	R ⁶	R	R	R			R ³	R ⁷	R			

¹ *A. baumannii* may be susceptible to ampicillin-sulbactam due to activity of sulbactam against this species.

² *Burkholderia cepacia* complex includes different species. Some strains may appear susceptible to some β -lactams in vitro.

³ *Burkholderia cepacia* and *Stenotrophomonas maltophilia* are intrinsically resistant to all aminoglycosides. Intrinsic resistance is attributed to poor permeability and putative efflux. In addition, most *S. maltophilia* produce AAC(6')Iz enzyme. On agar plates, resistance to aminoglycosides is more reliably detected after incubation at 30°C or ambient temperature than at 35-37°C.

⁴ *Pseudomonas aeruginosa* is intrinsically resistant to kanamycin and neomycin due to low level APH(3')-IIb activity.

⁵ *P. aeruginosa* typically is resistant to trimethoprim and moderately susceptible to sulphonamides. Although it may appear susceptible in vitro to co-trimoxazole, it should be considered resistant.

⁶ *S. maltophilia* may appear susceptible in vitro to ceftazidime but should be considered resistant.

⁷ *S. maltophilia* typically is susceptible to co-trimoxazole, but resistant to trimethoprim alone.

Table 3: Intrinsic resistance (R) in other Gram-negative bacteria

These bacteria are also intrinsically resistant to glycopeptides, lincosamides, daptomycin and linezolid.

Rule no.	Organisms	Macrolides	Fusidic acid	Streptogramins	Trimethoprim	Nalidixic acid
3.1	<i>Haemophilus influenzae</i>	R	R			
3.2	<i>Moraxella catarrhalis</i>				R	
3.3	<i>Neisseria</i> spp.				R	
3.4	<i>Campylobacter fetus</i>		R	R	R	R
3.5	<i>Campylobacter jejuni/coli</i>		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 no.	Organisms	Fusidic acid	Ceftazidime	Cephalosporins (except ceftazidime)	Aminoglycosides	Lincosamides	Qunupristin-dalfopristin	Vancomycin	Teicoplanin	Fosfomicin	Novobiocin	Nitrofurantoin	Trimethoprim-sulphamethoxazole
4.1	<i>Staphylococcus saprophyticus</i>		R							R	R		
4.2	<i>Staphylococcus cohnii</i> , <i>xylosus</i>		R								R		
4.3	<i>Staphylococcus capitis</i>		R							R			
4.4	Other coagulase-negative staphylococci and <i>Staphylococcus aureus</i>		R										
4.5	<i>Streptococcus</i> spp.	R			LLR								
4.6	<i>Enterococcus faecalis</i>	R	R	R	LLR	R	R						(R) ¹
4.7	<i>Enterococcus gallinarum</i> , <i>casseliflavus</i>	R	R	R	LLR	R	R	R					(R) ¹
4.8	<i>Enterococcus faecium</i>	R	R	R	LLR ²								(R) ¹
4.9	<i>Corynebacterium</i> spp.									R			
4.10	<i>Listeria monocytogenes</i>		R	R									
4.11	<i>Leuconostoc</i> , <i>pedicococcus</i>							R	R				
4.12	<i>Lactobacillus</i> spp. (some species)							R	R				

LLR: Resistance to low-levels of 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.

¹ Enterococci are usually susceptible *in vitro* to the combination trimethoprim-sulphamethoxazole, although they are resistant to sulphonamides alone. The use of trimethoprim sulphamethoxazole against enterococci remains controversial. It is probably best avoided in severe infections.

² In addition to low-level resistance to aminoglycosides, *E. faecium* produces a chromosomal AAC(6') enzyme that is responsible for the loss of synergism between aminoglycosides (except gentamicin, amikacin and streptomycin) and penicillins or glycopeptides.

Table 5: Exceptional phenotypes of Gram-negative bacteria.

Rule no.	Organisms	Exceptional phenotypes
5.1	Any Enterobacteriaceae	Resistant to ertapenem, meropenem, imipenem (except <i>Proteus</i> spp.).
5.2	<i>Pseudomonas aeruginosa</i> and <i>Acinetobacter</i> spp.	Resistant to colistin.
5.3	<i>Haemophilus influenzae</i>	Resistant to any third-generation cephalosporin, carbapenems, fluoroquinolones.
5.4	<i>Moraxella catarrhalis</i>	Resistant to ciprofloxacin, any third-generation cephalosporin.
5.5	<i>Neisseria meningitidis</i>	Resistant to penicillin (MIC >1 mg/L), third generation cephalosporins, ciprofloxacin.
5.6	<i>Neisseria gonorrhoeae</i>	Resistant to third-generation cephalosporins, spectinomycin.

Table 6: Exceptional phenotypes of Gram-positive bacteria.

Rule no.	Organisms	Exceptional phenotypes
6.1	<i>Staphylococcus aureus</i>	Resistant to vancomycin, linezolid, quinupristin/dalfopristin, daptomycin, tigecycline.
6.2	Coagulase-negative staphylococci	Resistant to vancomycin, linezolid, quinupristin/dalfopristin, daptomycin, tigecycline.
6.3	JK coryneform organisms	Resistant to vancomycin, teicoplanin, linezolid, quinupristin/dalfopristin, daptomycin, tigecycline.
6.4	<i>Streptococcus pneumoniae</i>	Resistant to imipenem, meropenem, vancomycin, teicoplanin, linezolid, quinupristin/dalfopristin, daptomycin, tigecycline, rifampicin.
6.5	Group A, B, C and G β -haemolytic streptococci	Resistant to penicillin, cephalosporins, vancomycin, teicoplanin, linezolid, quinupristin/dalfopristin, daptomycin, tigecycline.
6.6	<i>Enterococcus</i> spp.	Resistant to linezolid, daptomycin, tigecycline. Resistant to teicoplanin but not vancomycin.
6.7	<i>Enterococcus faecalis</i> , <i>Enterococcus gallinarum</i> , <i>Enterococcus casseliflavus</i> , <i>Enterococcus avium</i>	Susceptible to quinupristin-dalfopristin. Consider likelihood of mis-identification. If also resistant to ampicillin it is almost certainly <i>E. faecium</i> .
6.8	<i>Enterococcus faecium</i>	Resistant to quinupristin-dalfopristin. Consider likelihood of mis-identification, especially if also susceptible to ampicillin.

Table 7: Exceptional phenotypes of anaerobes.

Rule no.	Organisms	Exceptional phenotypes
7.1	<i>Bacteroides</i> spp.	Resistant to metronidazole, carbapenems.
7.2	<i>Clostridium difficile</i>	Resistant to metronidazole, vancomycin.

Table 8: Interpretive rules for β -lactam agents and Gram-positive cocci

Rule no.	Organisms	Agent	Rule	Exceptions	Scientific basis	Evidence grade	References
8.1	<i>Staphylococcus</i> spp.	Isoxazoly-penicillins	If resistant to isoxazoly-penicillins (as determined with oxacillin, ceftoxitin, or by detection of <i>mecA</i> -gene or of PBP2a) report as resistant to all β -lactams.	Developmental anti-MRSA cephalosporins, e.g. ceftobiprole and ceftaroline.	Production of PBP2a (encoded by <i>mecA</i>) leads to cross resistance to β -lactams except ceftobiprole and ceftaroline.	A	Chambers HF <i>et al.</i> , 1990 Page MG <i>et al.</i> , 2006
8.2	<i>Staphylococcus</i> spp.	Penicillins	If penicillinase is detected, report as resistant to all penicillins, regardless of MIC, except the isoxazoly-penicillins and combinations with β -lactamase inhibitors.	Testing of penicillinase production may be discouraged in certain countries due to high prevalence of penicillinase producers (>90%) and technical problems. In this case it may be considered appropriate to report all isolates resistant to benzylpenicillin, ampicillin and amoxicillin.	Production of penicillinase leads to resistance to all penicillins except the isoxazoly-analogues.	C	Nathwani D <i>et al.</i> Drugs. 1993
8.3	β -Haemolytic streptococci (Group A, B, C, G)	Benzylpenicillin	If susceptible to penicillin report susceptible to aminopenicillins, cephalosporins and carbapenems. If resistant to penicillin check identification and susceptibility.	Rare isolates of group B streptococci may have diminished susceptibility to penicillins.	Susceptibility to penicillins is currently the rule. No resistance to β -lactams reported so far except in Group B streptococci (MIC of benzylpenicillin up to 0.6 mg/L).	C	Karlowsky JA <i>et al.</i> , 2002 Casey JR <i>et al.</i> , Clin Infect Dis 2004
8.4	<i>Streptococcus pneumoniae</i>	β -lactams	If resistant by the oxacillin disk screening test, perform MIC for benzylpenicillin, ampicillin (or		Production of mosaic PBPs leads to various patterns of	B	Nagai K <i>et al.</i> 2002 File TM Jr. 2006

			amoxicillin) and cefotaxime (or ceftriaxone). Report as interpreted for each of the drugs. Results for cephalosporins and carbapenems cannot be inferred from benzylpenicillin.		β-lactam resistance.		
8.5	Viridans group streptococci	Benzylpenicillin	If resistant to benzylpenicillin perform MIC for benzylpenicillin, ampicillin (or amoxicillin) and cefotaxime (or ceftriaxone). Report as interpreted for each of the drugs as results cannot be inferred from benzylpenicillin.		Production of mosaic PBP _s leads to various patterns of β-lactam resistance.	C	Jones ME <i>et al.</i> , 2004. Kuriyama T <i>et al.</i> , 2002
8.6	<i>Enterococcus</i> spp.	Ampicillin	If resistant to ampicillin report as resistant to ureidopenicillins and carbapenems.		Alterations of PBP-5 lead to decreased affinity of β-lactams. Rare penicillinase-producing isolates have been reported in a few countries but not in Europe.	C	Weinstein MP <i>et al.</i> 2004. Ono S <i>et al.</i> 2005

Table 9: Interpretive rules for β -lactam agents and Enterobacteriaceae, *Pseudomonas* spp. and *Acinetobacter* spp.

Rule no.	Organisms	Agent	Rule	Exceptions	Scientific basis	Evidence Grade	References
9.1	Enterobacteriaceae (for <i>Klebsiella oxytoca</i> , and <i>Citrobacter koseri</i> see 9.3)	Oxyimino cephalosporins, aztreonam	If resistant or intermediate to any 3 rd or 4 th generation oxyimino-cephalosporin or aztreonam, test for ESBL. If positive, report any susceptible results for these cephalosporins (including fourth-generation agents) and for aztreonam as intermediate; and report any intermediate results as resistant. ESBL producers may appear susceptible to penicillin/ β -lactamase inhibitor combinations. The use of these combinations against ESBL producers remains controversial, and should be approached with caution. If ESBL-negative see rule 9.2.		A few ESBL producers may be tested susceptible in vitro for any of 3 rd or 4 th generation oxyimino-cephalosporin or aztreonam. Efficacy of cefotaxime, ceftazidime and ceftriaxone against ESBL-producing isolates with MICs lower than 2 mg/L remains to be fully documented.	C	Brun-Buisson et al., 1987. Jarlier V <i>et al.</i> , 1988. Livermore DM and Brown DF, 2001. Wong-Beringer A <i>et al.</i> , 2002. Paterson DL and Bonomo RA, 2005. Paterson DL, 2006. Paterson <i>et al.</i> 2004. Bhavnani et al. 2006
9.2	Enterobacteriaceae (for <i>Klebsiella oxytoca</i> , and <i>Citrobacter koseri</i> see 9.3)	Oxyimino cephalosporins	If resistant to cefotaxime, ceftazidime and ceftriaxone, but negative for ESBL and susceptible to cefepime and ceftipime, report as found.		These isolates are likely to be derepressed for AmpC, or to have plasmid-mediated AmpC. Cefepime and ceftipime remain therapeutic options for infections due to strains hyperproducing AmpC. Phenotypic verification of	A	Sanders WE <i>et al.</i> , 1996

					copious AmpC cephalosporinase production may be performed with synergy tests using either boronic acid or cloxacillin in combination with e.g. cefotaxime.		
9.3	<i>Klebsiella oxytoca</i> , <i>Citrobacter koseri</i>	Oxyimino cephalosporins, aztreonam	If resistant to aztreonam, cefuroxime, ceftriaxone and piperacillin/ tazobactam but susceptible to ceftazidime (cefotaxime and cefepime are variable in this context) test for ESBL. If positive for ceftazidime and inhibitor, proceed as for ESBL producer (see 9.1). If negative or very weak positive for ceftazidime and inhibitor, isolate is likely to be a hyperproducer of chromosomal β -lactamase and no editing of reports is needed.		Ceftazidime is not a substrate for the chromosomal β -lactamase of <i>K. oxytoca</i> (K1/KOXY) and <i>C. koseri</i> . and shows no inoculum effect. This mechanism does not arise with <i>K. pneumoniae</i> .	C	Potz NA <i>et al.</i> , 2004
9.4	<i>Enterobacter</i> spp, <i>Citrobacter freundii</i> , <i>Serratia</i> spp., <i>Morganella morganii</i>	Cefotaxime, ceftriaxone, ceftazidime	If susceptible in vitro, use in monotherapy of cefotaxime, ceftriaxone or ceftazidime should be discouraged owing to risk of selecting resistance. Reports should note this or results should be suppressed.	The use of a 3rd generation cephalosporin in combination with an aminoglycoside may also lead to failure by selection of resistant mutants. Combination with quinolones has, however, been found to be protective. The selection risk is absent or much diminished for cefepime and ceftipime.	Selection of AmpC derepressed cephalosporin resistant mutants during therapy.	A (<i>Enterobacter</i>) B (others)	Chow JW <i>et al.</i> , 1991. Schwaber MJ <i>et al.</i> , 2003

9.5	Enterobacteriaceae (mostly <i>Klebsiella</i> spp. and <i>E. coli</i>)	Piperacillin	If resistant to ticarcillin but susceptible to piperacillin, edit piperacillin to resistant.	Does not apply to inhibitor combinations involving these penicillins.	Ticarcillin hydrolyzing β -lactamases also attack piperacillin, but resistance may be less obvious if expression is low level.	C	Jarlier V <i>et al.</i> , 1986
9.6	Enterobacteriaceae, <i>Acinetobacter</i> spp., <i>Pseudomonas</i> spp.	Carbapenems	Test results regarding one carbapenem (imipenem, meropenem, ertapenem) cannot be extrapolated to the other carbapenems.	<i>Enterobacteriaceae</i> only: If resistant to either imipenem, meropenem, report as resistant to ertapenem without further testing.	There is variable stability to AmpC hydrolysis, dependence of porins and susceptibility to the efflux pumps.	C	
9.7	Enterobacteriaceae, <i>Acinetobacter</i> spp., <i>Pseudomonas</i> spp.	Carbapenems	If production of metallo- β -lactamase is confirmed, report the susceptible results as intermediate and the intermediate results as resistant for any β -lactam except aztreonam which should be reported as found.		Metallo- β -lactamases can hydrolyse all β -lactams except monobactams.	B	Walsh T <i>et al.</i> , 2005
9.8	Enterobacteriaceae	Carbapenems, oxyimino cephalosporins, aztreonam	If reduced susceptibility to carbapenems AND oxyimino cephalosporins AND aztreonam, resistance may reflect either KPC, IMI, GES β -lactamases or combinations of AmpC or ESBL plus impermeability. In either case, ertapenem tends to be the most affected carbapenem. Synergy between carbapenems and clavulanate		KPC carbapenemase or combinations of ESBL or AmpC and impermeability.	C	Livermore D and Woodford N., 2005. Bratu S <i>et al.</i> 2005. Woodford N <i>et al.</i> , 2007

			may arise with either KPC enzymes or with combinations of ESBL and impermeability.				
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Table 10: Interpretive rules for β -lactam agents and other Gram-negative bacteria

Rule no.	Organisms	Agent	Rule	Exceptions	Scientific basis	Evidence grade	References
10.1	<i>Haemophilus influenzae</i>	Ampicillin	Ampicillin is the class representative for amoxicillin.			C	
10.2	<i>Haemophilus influenzae</i>	Penicillins	If positive for production of penicillinase report as resistant to ampicillin or amoxicillin.		Resistance to ampicillin by production of β -lactamase may be misidentified by disk-diffusion technique. Production of penicillinase should be sought using a chromogenic test.	A	Thomas WJ <i>et al</i> , 1974 Medeiros AA and O'Brien TF, 1975
10.3	<i>Haemophilus influenzae</i>	Penicillins and cephalosporins	If β -lactamase negative but ampicillin-resistant (BLNAR) report as resistant to amoxicillin/ clavulanate, ampicillin/sulbactam, cefaclor, cefamandole, cefetamet, cefonicid, cefprozil, cefuroxime and loracarbef.		BLNAR isolates have reduced affinity of PBPs for β -lactams.	C	Ubukata K <i>et al</i> , 2001 Tristram S <i>et al</i> , 2007 Kim IS <i>et al</i> , 2007
10.4	<i>Haemophilus influenzae</i>	Penicillins and cephalosporins	If β -lactamase positive and resistant to amoxicillin/ clavulanate (BLPACR) report as resistant to ampicillin/ sulbactam, cefaclor, cefamandole, cefetamet, cefonicid, cefprozil, cefuroxime, loracarbef and piperacillin-tazobactam.		BLPACR isolates produce β -lactamase and have reduced affinity of PBPs for β -lactams.	C	Tristram S <i>et al</i> , 2007 Kim IS <i>et al</i> , 2007

10.5	<i>Moraxella catarrhalis</i>	Penicillins	Report resistant to benzylpenicillin, ampicillin and amoxicillin.	Rare strains do not produce penicillinase.	Resistance to ampicillin by production of β -lactamase (BRO-1/2 β -lactamase) may be misidentified by disk-diffusion technique. However, since >90% of <i>M.catarrhalis</i> strains produce β lactamase, testing of penicillinase production is discouraged and isolates should be reported resistant to benzylpenicillin, ampicillin and amoxicillin.	C	Farmer T <i>et al</i> , 1982
10.6	<i>Neisseria gonorrhoeae</i>	Penicillins	If positive for production of penicillinase, report resistant to benzylpenicillin, ampicillin or amoxicillin.		Penicillin-resistance can be caused by plasmid encoded β -lactamase production (TEM1). Chromosomal mutations affecting affinity to PBPs, impermeability or efflux also confer resistance to β -lactamase inhibitor combinations. Penicillin susceptibility in β -lactamase negative isolates is indicated	A	Dillon JA and Yeung KH, 1989 Olesky M <i>et al</i> 2002 and 2006 Ropp PA <i>et al</i> , 2004

					by the application of breakpoints. β -lactamase production can be examined with a chromogenic test.		
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Table 11: Interpretive rules for macrolides, lincosamides and streptogramins

Rule no.	Organisms	Agent	Rule	Exceptions	Scientific basis	Evidence grade	References
11.1	All	Erythromycin	Erythromycin is the class representative for 14- and 15-membered ring macrolides.		Resistance to erythromycin is generally due to the production of a ribosomal methylase encoded by <i>erm</i> genes conferring the macrolide-lincosamide-streptogramin B (MLS _B) phenotype or by production of an efflux pump. In both cases, there is cross-resistance between erythromycin and the other 14- and 15-membered ring macrolides.	C	Leclercq R, 2002
11.2	<i>Staphylococcus</i> spp.	Clindamycin, lincomycin	If resistant to erythromycin but susceptible to clindamycin or lincomycin, test for inducible MLS _B resistance. If negative, report susceptible to clindamycin and lincomycin. If positive, either report as resistant to clindamycin and lincomycin or report as susceptible with a warning: "Clinical failure during treatment with clindamycin or lincomycin may occur by		Staphylococci resistant to macrolides but susceptible to lincosamides (clindamycin and lincomycin) produce Erm ribosomal methylases conferring the inducible MLS _B phenotype or express efflux	B	Leclercq R, 2002 Lewis JS and Morgensen, 2005

			selection of constitutively resistant mutants". The use of clindamycin/ lincomycin is probably best avoided in severe infections.		pumps. In case of inducible MLS _B resistance, constitutively resistant mutants can be selected by lincosamides. In case of resistance by efflux, the risk for selection of mutants resistant to lincosamides is not greater than that for erythromycin-susceptible isolates. Both clinical failures and successes with clindamycin have been reported for staphylococci inducibly MLS _B resistant. By a disk diffusion test, the inducible MLS _B phenotype can be identified by the flattening of the clindamycin zone facing the erythromycin disk.		
11.3	<i>Streptococcus</i> spp.	Clindamycin, lincomycin	If resistant to erythromycin but susceptible to clindamycin or lincomycin, test for inducible MLS _B resistance. If negative, report susceptible to clindamycin and lincomycin. If positive, report resistant to		Streptococci may be resistant to macrolides by production of a ribosomal Erm methylase conferring the MLS _B phenotype	C	Leclercq R, 2002

			clindamycin and lincomycin.		or by production of an efflux pump encoded by the <i>mef(A)</i> class of genes. In case of inducible MLS _B resistance, clindamycin and lincomycin may remain active or not depending on the type and expression of <i>erm</i> gene. In case of resistance by efflux, the risk for selection of mutants resistant to lincosamides is not greater than that for erythromycin-susceptible isolates. By a disk-diffusion test, the inducible MLS _B phenotype can be identified by the flattening of the clindamycin zone facing the erythromycin disk.		
11.4	<i>Peptostreptococcus</i> spp., <i>Bacteroides</i> spp.	Clindamycin	If resistant to erythromycin but susceptible to clindamycin, report resistant to clindamycin.		Resistance to macrolides in <i>Peptostreptococcus</i> spp. and <i>Bacteroides</i> spp. is generally due to the production of a ribosomal Erm	C	Reig M <i>et al.</i> , 1992a Reig M <i>et al.</i> , 1992b

					methylase conferring the MLS _B phenotype. In the case of inducible MLS _B resistance, resistance to clindamycin is poorly expressed in vitro and this antibiotic should not be considered as active.		
11.5	<i>Staphylococcus</i> spp.	Quinupristin-dalfopristin	If resistant to clindamycin, report a warning that bactericidal activity of quinupristin-dalfopristin is reduced.		Resistance to clindamycin (associated with resistance to erythromycin) is a marker of the constitutive macrolide-lincosamide-streptogramin B (MLS _B) resistance phenotype. Cross resistance to the streptogramin B-type factor leads to diminished bactericidal activity of the combination of quinupristin and dalfopristin. Experimental models of staphylococcal endocarditis lead to conflicting results on the in vivo activity of	C	Batard E <i>et al.</i> , 2002 Fantin B <i>et al.</i> , 1997 Entenza JM <i>et al.</i> , 1995

					quinupristin-dalfopristin for the treatment of animals infected with constitutive MLS _B resistant isolates.		
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Table 12: Interpretive rules for aminoglycosides

Rule no.	Organisms	Agent	Rule	Exceptions	Scientific basis	Evidence grade	References
12.1	<i>Staphylococcus</i> spp.	Kanamycin	If resistant to kanamycin, synergism of kanamycin and amikacin with β -lactams or glycopeptides is lost. Report as resistant to kanamycin and amikacin.		Resistance to kanamycin is generally due to the production of APH(3')I-3, ANT(4') (4'')-I or bifunctional APH(2')-AAC(6) enzymes that determine loss of synergism of kanamycin and amikacin with β -lactams and glycopeptides irrespective of MIC values.	C	Courvalin P and Davies J., 1977 Le Goffic F <i>et al.</i> , 1976
12.2	<i>Staphylococcus</i> spp.	Tobramycin	If resistant to tobramycin synergism of kanamycin, tobramycin and amikacin with β -lactams or glycopeptides is lost. Report as resistant to kanamycin, tobramycin and amikacin.		Resistance to tobramycin is generally due to the production of ANT(4') (4'')I or bifunctional APH(2')-AAC(6) enzymes that determine loss of synergism of kanamycin, tobramycin and amikacin with β -lactams and glycopeptides irrespective of MIC values.	C	Le Goffic F <i>et al.</i> , 1976

12.3	<i>Staphylococcus</i> spp.	Gentamicin	If resistant to gentamicin, synergism of all aminoglycosides with β -lactams or glycopeptides is lost. Report as resistant to all aminoglycosides.	Streptomycin.	Resistance to gentamicin is generally due to the production of bifunctional APH(2')-AAC(6) enzyme that determines loss of synergism of all aminoglycosides (excepted streptomycin) with β -lactams and glycopeptides irrespective of MIC values.	B	Martel A <i>et al.</i> 1977 Asseray N <i>et al.</i> , 2002
12.4	<i>Enterococcus</i> spp., <i>Streptococcus</i> spp	Streptomycin	If high level-resistance to streptomycin is detected (>1024 mg/L) report as high-level resistant to streptomycin only.		High level resistance reflects production of ANT(6) or of other enzymes or of ribosomal mutation. No cross-resistance to other aminoglycosides can be observed. High level resistance to streptomycin suppresses synergy of streptomycin with β -lactams or glycopeptides.	A (<i>Enterococcus</i>) C (<i>Streptococcus</i>)	Chow JW, 2000
12.5	<i>Enterococcus</i> spp., <i>Streptococcus</i> spp	Kanamycin	If high level-resistance to kanamycin is detected (>512 mg/L) synergism of kanamycin and amikacin with β -lactams or glycopeptides is lost. Report as high-level resistant to		High-level resistance to kanamycin is generally due to the production of APH(3')I-3, or bifunctional APH(2')-	B (<i>Enterococcus</i>) C (<i>Streptococcus</i>)	Courvalin P and Davies J. , 1977 Thauvin C <i>et al.</i> , 1985

			kanamycin and amikacin.		AAC(6) enzymes that determine loss of synergism of kanamycin and amikacin with β -lactams and glycopeptides irrespective of MIC values.		
12.6	<i>Enterococcus</i> spp., <i>Streptococcus</i> spp.	Gentamicin	If high level-resistance to gentamicin is detected (>128 mg/L), synergism of all aminoglycosides with β -lactams or glycopeptides is lost. Report as high-level resistant to all aminoglycosides.	Streptomycin.	High-level resistance to gentamicin is generally due to the production of bifunctional APH(2')-AAC(6) enzyme that determines loss of synergism of all aminoglycosides (excepted streptomycin) with β -lactams and glycopeptides irrespective of MICs.	A (<i>Enterococcus</i>) C (<i>Streptococcus</i>)	Mederski-Samoraj <i>et al.</i> , 1983 Chow JW., 2000
12.7	All Enterobacteriaceae <i>Pseudomonas aeruginosa</i> , <i>Acinetobacter baumannii</i>	Tobramycin	If intermediate or resistant to tobramycin and susceptible to gentamicin and amikacin report amikacin as intermediate for Enterobacteriaceae or resistant for <i>Pseudomonas</i> and <i>Acinetobacter</i> .		Production of acquired AAC(6')I may not confer phenotypic resistance despite modification of amikacin.	C	Benveniste R, Davies J. 1971a Galimand <i>et al.</i> 1993 Martin <i>et al.</i> , 1988 Shaw KJ <i>et al.</i> 1991
12.8	All Enterobacteriaceae	Gentamicin	If intermediate to gentamicin and susceptible to other aminoglycosides report as resistant to gentamicin.		Expression of AAC(3)I enzyme may be low and isolates may have decreased	C	Witchitz JL. <i>et al.</i> , 1972 Shaw KJ, <i>et al.</i> , 1993

					susceptibility to gentamicin .		
12.9	All Enterobacteriaceae	Tobramycin	If intermediate to tobramycin, resistant to gentamicin and susceptible to amikacin report as resistant to tobramycin.		Expression of ANT(2 ^{''}) enzyme may be low and isolates may have decreased susceptibility to tobramycin.	C	Benveniste R and Davies J. 1971b Shaw KJ <i>et al.</i> , 1993
12.10	All Enterobacteriaceae	Netilmicin	If intermediate to netilmicin and intermediate or resistant to gentamicin and tobramycin report as resistant to netilmicin.		Expression of AAC(3 ^{''})II or AAC(3 ^{''})V may be low and isolates may appear with decreased susceptibility to netilmicin.	C	Le Goffic F <i>et al.</i> , 1974 Shaw KJ <i>et al.</i> , 1993
12.11	<i>Haemophilus influenzae</i>	Gentamicin	If gentamicin susceptible report susceptible to amikacin, tobramycin and netilmicin. It is not valid to cross-report for intermediate or resistant isolates.			C	

Table 13: Interpretive rules for quinolones

Rule no.	Organism	Agent	Rule	Exceptions	Scientific basis	Evidence grade	References
13.1	<i>Staphylococcus</i> spp.	Ofloxacin Ciprofloxacin	If resistant to ofloxacin or ciprofloxacin, but not to moxifloxacin or levofloxacin, report warning: acquisition of a first mutation may lead to resistance development during therapy with other quinolones.		Acquisition of at least one target mutation in <i>grlA</i> .	C	Jones ME <i>et al.</i> , 1999 Jacoby GA <i>et al.</i> , 2005
13.2	<i>Staphylococcus</i> spp.	Levofloxacin Moxifloxacin	If resistant to levofloxacin or moxifloxacin, report as resistant to all fluoroquinolones.		Acquisition of combined mutations in <i>grlA</i> and <i>gyrA</i> leads to complete or partial cross resistance to all fluoroquinolones.	C	Stein GE <i>et al.</i> , 2003; Jones ME <i>et al.</i> , 1999; Santos Sanches I <i>et al.</i> , 2000
13.3	Viridans group streptococci	Levofloxacin	If resistant to levofloxacin, report as resistant to all fluoroquinolones.		Acquisition of at least one target mutation in <i>gyrA</i> or <i>grlA</i> .	C	Razonable RR <i>et al.</i> , 2002
13.4	<i>Streptococcus pneumoniae</i>	Ofloxacin Ciprofloxacin	If resistant to ofloxacin or ciprofloxacin, but not to moxifloxacin or levofloxacin, report warning: acquisition of a first mutation may lead to resistance development under therapy with other quinolones.		Acquisition of at least one target mutation in e.g. <i>parC</i> (<i>parE</i>). First step mutations are better detected using norfloxacin.	C	Montanari MP <i>et al.</i> , 2004; Perez-Trallero E <i>et al.</i> , 2003; Urban C <i>et al.</i> , 2001; Varon E <i>et al.</i> , 2006
13.5	<i>Streptococcus pneumoniae</i>	Levofloxacin Moxifloxacin	If resistant to levofloxacin or moxifloxacin, report as resistant to all fluoroquinolones.		Acquisition of combined mutations in e.g. <i>parC</i> and <i>gyrA</i> leads to complete or partial	B	Davidson R <i>et al.</i> , 2002;

					cross resistance to all fluoroquinolones.		
13.6	Enterobacteriaceae	Ciprofloxacin	If resistant to ciprofloxacin, report as resistant to all fluoroquinolones.		Acquisition of at least two target mutations in <i>gyrA</i> plus <i>parC</i> or <i>gyrA</i> .	B	Komp Lindgren P <i>et al.</i> , 2003
13.7	<i>Salmonella</i> spp.	Nalidixic acid	If resistant to nalidixic acid, report as resistant to all fluoroquinolones.		Evidence for clinical failure of fluoroquinolones in case of resistance to nalidixic acid due to the acquisition of at least one target mutation in <i>gyrA</i>	A (<i>S. typhi</i>) B (other <i>Salmonella</i> spp.)	Helms M <i>et al.</i> , 2002 Kadhiravan T, <i>et al.</i> , 2005 Slinger R <i>et al.</i> , 2004
13.8	<i>Haemophilus influenzae</i>	Nalidixic acid	If resistant to nalidixic acid, determine MIC of the fluoroquinolone to be used in therapy (ofloxacin, ciprofloxacin, levofloxacin or moxifloxacin).		High level fluoroquinolone resistance by target mutation has been rarely described in <i>H. influenzae</i> .	C	Rodriguez-Martinez JM <i>et al.</i> , 2006
13.9	<i>Neisseria gonorrhoeae</i>	Ciprofloxacin	If resistant to ciprofloxacin or ofloxacin, report as resistant to all fluoroquinolones.			C	Knapp JS <i>et al.</i> , 1997

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Table 8: Interpretive rules for β -lactam agents and Gram-positive cocci

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Glossary

14- and 15-membered macrolides	Azithromycin, clarithromycin, dirithromycin and roxithromycin.
Aminoglycosides	Amikacin, gentamicin, kanamycin, netilmicin and tobramycin.
ESBL	Extended spectrum beta-lactamase.
Glycopeptides	Vancomycin and teicoplanin.
Intrinsic resistance	Intrinsic resistance is inherent (not acquired) resistance which is a characteristic of all or almost all representatives of the species. The antimicrobial activity of the drug is insufficient or antimicrobial resistance innate or so common as to render it clinically useless and antimicrobial susceptibility testing unnecessary.
Isoxazolyl penicillins	Cloxacillin, flucloxacillin, dicloxacillin, methicillin, oxacillin, nafcillin.
Lincosamides	Clindamycin, lincomycin.
Macrolides	Erythromycin, roxithromycin, clarithromycin, dirithromycin, azithromycin, spiramycin, josamycin.
MLS _B	Macrolide-lincosamide-streptogramin B phenotype.
MRSA	Methicillin resistant <i>Staphylococcus aureus</i> .
Oxyimino-cephalosporins	Cefepime, cefotaxime, cefpirome, cefpodoxime, ceftazidime or ceftriaxone.
Streptogramins	Pristinamycin, quinupristin-dalfopristin.
Ureidopenicillins	Azlocillin, mezlocillin, piperacillin.