Interpretative reading: recognizing the unusual and inferring resistance mechanisms from resistance phenotypes

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If isolates are identified to species level and if a sufficient range of antibiotics is tested, then underlying resistance mechanisms can often be inferred from the antibiogram data. This allows: (i) anomalous combinations of phenotype and organism to be reconsidered before reporting; (ii) prediction of further antibiotics that deserve testing; and (iii) the suppression of susceptibilities that are anomalous in the light of the inferred mechanism. This 'interpretative reading' is widely undertaken in France but is largely precluded in the UK by limited species identification, especially for ‘coliforms’, and the use of narrow ranges of antibiotics, with only around six agents being tested per isolate. Nevertheless, UK laboratories should be aware of: (i) grossly anomalous combinations of species and phenotype, demanding reference laboratory confirmation; (ii) useful indicator drugs, where the observed resistance implies a mechanism conferring other resistances that may be less obvious in direct tests; and (iii) antibiotics that are prone to select resistant mutants of particular species during therapy. Details of these combinations of organism and resistance are presented. Relationships between antibiogram and mechanism are also presented to allow full interpretative reading for those testing wide panels of drugs against isolates that have been identified to species level.

Introduction

Susceptibility test results for bacteria normally conventionally are recorded and categorized individually, as 'susceptible to this drug'; 'resistant to this drug', etc. This strategy under-utilizes the data, since it ignores the fact that resistances to related antibiotics often depend on single mechanisms.[1,2] 'Interpretative reading' aims to analyse the overall susceptibility pattern, not just the results for individual antibiotics, and so to predict the underlying mechanisms. Based on this interpretation, susceptibilities that appear doubtful in the light of the inferred mechanism can be identified and reviewed, and further drugs that merit testing can be identified.[1,2]

To exploit its full potential, interpretative reading requires that isolates are identified accurately to species level and tested with large batteries of different antibiotics. This is done in France, where panels of 16 antibiotics are routinely tested against most isolates, and in some commercial systems, such as the VITEK 2, which tests panels of up to 20 antibiotics.[1-4] Interpretative reading with such comprehensive data is discussed in the second part of this paper, where the resistance patterns associated with different mechanisms are outlined, along with their implications for antibiotic choice. Most UK laboratories presently test too few drugs for interpretative reading to this standard and although modern chromogenic media are increasingly used to aid the identification of Enterobacteriaceae, some laboratories still report non-bacteraemia isolates as 'coliforms'. Such practices preclude reliable interpretative reading. Nevertheless, however limited the data, susceptibility tests can and should be read with due attention to: (i) recognizing unusual results; (ii) recognizing drugs best avoided owing to their risk of selecting resistance in the particular pathogen; and (iii) using 'indicator' drugs.

Recognizing unusual resistances

New resistances of public health concern should be recognized. A list is given in Table I. Laboratories finding the organism/resistance combinations listed should re-check their result, as the most probable explanation is always an error in identification or susceptibility testing. If the results are reproducible, the isolate(s) should be sent to a reference or academic laboratory for independent confirmation. In England and Wales, the Health Protection Agency provides this service. In most instances, the organisms should be sent to the Antibiotic Resistance Monitoring and Reference Laboratory, CPHL, 61 Colindale Avenue, London NW9 5HT. Exceptions are that salmonellas and shigellas should be sent to the Laboratory of Enteric Pathogens, also at CPHL; meningococci to the Meningococcal Reference Unit, Public Health Laboratory, Withington Hospital, Manchester M20 2LR; anaerobes to the Anaerobe Reference Unit, Public Health Laboratory, University Hospital of Wales, Cardiff CF4 4XW; and *Haemophilus* spp. to the Haemophilus Reference Unit, John Radcliffe Hospital, Oxford 0X3 9DU. If there is concern about the spread of an unusually resistant strain among patients, identification, typing and infection control advice can be provided by appropriate Health Protection Agency units: for nosocomial pathogens this is the Laboratory of Healthcare-Associated Infection, CPHL. Appropriate academic units include those with a particular research interest in the resistance type, or, for hospital infection advice, the Hospital Infection Research Laboratory, City Hospital, Birmingham.

In some cases, a report of 'susceptible' is anomalous, and laboratories should be aware of the natural (inherent) resistance phenotypes of common pathogens. A list is provided in Table II. If any of these combinations of species and susceptibility is found, it is reasonable to be skeptical. Once again, the most probable cause of the result is an error, and ideally both the species identification and antibiogram data should be re-checked. If this is not considered worthwhile (e.g. because the isolate is susceptible to multiple other antibiotics), the unlikely results should not be used as a basis for prescribing.

Antibiotics likely to select resistance

If a resistance emerges by high frequency mutation, there is a significant risk that it will be selected in the individual patient during therapy. Table III provides a list of high-risk combinations of organism and antibiotic. The risk is modulated by the site of infection, being increased in those where it is difficult to obtain high drug levels, but reduced at sites where the drug concentrates. In general, the antibiotic/organism combinations listed in Table III should be avoided unless there is no alternative agent or unless, as with *Pseudomonas aeruginosa* or *Burkholderia cepacia*, there is a risk of selecting resistance with virtually any antibiotic active against the species.

Indicator drugs

An indicator drug is one used to detect the presence of a mechanism that gives resistance not only to the indicator itself, but also to related agents. It is chosen as the member of the drug family to which the mechanism gives the most obvious resistance. Indicator drugs are already used in several critical cases. Thus, (i) methicillin, oxacillin or (perhaps best of all!) cefoxitin are used to screen staphylococci which, if found resistant, are inferred to have mecA and be resistant to all ß-lactams;[5,6] (ii) oxacillin is used to screen for penicillin resistance in pneumococci;[7] and (iii) either both ceftazidime and cefotaxime, or cefpodoxime alone, can be used to screen klebsiellae and *Escherichia coli* for extended-spectrum β-lactamases (ESBLs).[8] As Table IV illustrates, there is scope for wider use of indicators.

Full interpretative reading: predicting mechanisms from resistance patterns

The strategies outlined above are only part of interpretative reading in its fuller and more sophisticated form.[1,2,4] If isolates are fully identified and are tested with extended arrays of antibiotics, it is often possible to predict the underlying mechanisms from the resistance profile. This can be done manually, based on operator knowledge of phenotypes and mechanisms or, more conveniently, using the 'expert rules' that increasingly feature on automated zone and MIC readers such as the VITEK 2 and Phoenix..[3,4] Interpretative reading at this level allows: (i) estimation of the spread of resistance mechanisms; (ii) identification of susceptibility or identification results that appear anomalous in the light of the inferred mechanisms; and (iii) identification of little-used antibiotics that merit testing against problem isolates.[1,2,9] To illustrate these points, a Klebsiella isolate might appear to be resistant to ceftazidime but susceptible to cefotaxime and ceftriaxone. Conventionally these results would be reported without change.[10] However, interpretative reading would infer ESBL production and, since cefotaxime and ceftriaxone are substrates for ESBLs, would alter the reports for these drugs to resistant.[9] Cephamycins, carbapenems and β-lactamase inhibitor combinations would be highlighted as further drugs to test.[9] If, on the other hand, therapy is being sought, for an infection caused by an *Enterobacter cloacae* interpreted to hyper-produce its AmpC enzyme, it may be worth testing cefpirome and temocillin as second-line drugs, but there would be little point in testing cefotetan or piperacillin/tazobactam.

For those wishing to undertake interpretative reading manually, or to program a computer, zone reader or laboratory information management system themselves, Tables V-XI illustrate prevalent resistance phenotypes, the underlying mechanisms inferred and any editing of the antibiogram that should be considered. Confirmatory tests are indicated as appropriate. Note that editing a result from susceptible to resistant is sometimes advocated; editing from resistant to susceptible is never recommended, although it may be appropriate to re-check an unlikely resistance. These tables and the accompanying text are organized by antibiotic class and, within each class, by bacterial species. Rarer phenotypes are omitted unless they are a significant potential public health concern, in which case '!!!' appears in the 'interpretation' and 'frequency' columns, and the finder is advised to refer the isolate to an appropriate Health Protection Agency or academic laboratory for confirmation (see also Table I).

β-Lactams

β-Lactams are the ideal drugs for interpretative reading since there is a wide range of resistance mechanisms, including >300 types of β-lactamase, and since different resistance mechanisms give substantially different resistance phenotypes.[9,11] Important phenotypes and interpretations are illustrated in Table V for Enterobacteriaceae, in Table VI for non-fermenters, Table VII for fastidious Gram-negative cocci and cocco-bacilli, and Table VIII for Gram-positive cocci. Use of Table V, in particular, demands accurate species identification of Enterobacteriaceae and it is not possible to devise an all-purpose panel for 'coliforms'. No laboratory will routinely test all the β-lactam analogues listed in Table V, so the diagnostic value of particular analogues should be underscored.

Comparisons of results for inhibitor-protected and –unprotected penicillins are especially useful. The available inhibitors (clavulanate, sulbactam and tazobactam) affect Class A enzymes such as TEM and SHV, but not most AmpC types (inhibition of *Morganella morganii* AmpC enzyme by tazobactam is a notable exception to this latter generalization).[12]

Ceftazidime resistance is the best indicator for TEM- and SHV-derived ESBLs in *E. coli* and *Klebsiella* spp,[8,9,13] whereas cefotaxime resistance is a better indicator for the CTX-M enzymes.[14,18] Since CTX-M enzymes are of fast-growing importance in the UK and elsewhere, the laboratory should test both cefotaxime and ceftazidime (no longer just ceftazidime) first-line against Enterobacteriaceae, and should suspect the presence of ESBLs in isolates that are resistant to either or both of these, *but which are still susceptible to cefoxitin or cefotetan*. Alternatively, the laboratory can include cefpodoxime, which is a good substrate for all ESBLs. ESBL production can then be confirmed with one of the tests listed by Livermore & Brown.[8]

Resistance that encompasses cefoxitin and cefotetan as well as to third-generation cephalosporins in Enterobacteriaceae most often indicates AmpC production.[9,19] Derepression of chromosomal AmpC in *Enterobacter* spp., *Citrobacter freundii, Morganella morganii and Serratia* spp. arises readily by mutation, giving this phenotype. AmpC hyperproduction can also arise by mutation in *E. coli*, though it is much rarer. Plasmid-mediated AmpC enzymes are increasingly encountered in *E. coli* and *Klebsiella* spp. and are mostly constitutive.[20] Inducible AmpC, as in the classical phenotypes of *Enterobacter* and *Citrobacter freundii* gives resistance to cefoxitin without obvious cross-resistance to oxyimino cephalosporins (or cefotetan); a confirmatory test is cefoxitin mediated antagonism of oxyimino-cephalosporins.[9,13]

Resistance *only* to cefoxitin and cefuroxime in *E. coli* and *Klebsiella* spp. is mostly due to impermeability and porin loss; and is especially likely if the isolate retains moderate susceptibility/low level resistance to ampicillin.

Klebsiella oxytoca isolates that hyperproduce their chromosomal Kl β-lactamase often are mistaken for ESBL producers, but are distinguished by being highly resistant to aztreonam and

cefuroxime but not ceftazidime or cefotaxime.[9,21] They consistently are resistant to inhibitor combinations, even though extracted KI enzyme is susceptible to inhibition.[9,12]

Most resistance to β-lactams in Enterobacteriaceae is mediated by acquired or chromosomal β-lactamases (Table V) but efflux and impermeability are more important in *P. aeruginosa* and in fastidious Gram-negative bacteria (Table VI and VII). These non-ß-lactamase-mediated mechanisms mostly give low-level broad-spectrum resistances, often affecting quinolones as well as ß-lactams.[22] Imipenem, but not meropenem, escapes the commonest form of efflux-mediated resistance in *P. aeruginosa* (up-regulation of MexAB-OprM) but is more strongly compromised than meropenem by mutational loss of the OprD (=D2) porin, which provides carbapenem-specific channels through the outer membrane.[23] In cases where *P. aeruginosa* isolates are highly resistant both to carbapenems (MIC >32 mg/L or growth up to the disc) and to other ß-lactams it may be worth doing a metallo-ß-lactamase test, seeking synergy between imipenem and EDTA.[8] These tests are, however, complicated by the facts that not all gene-positive isolates are obviously resistant to carbapenems and that synergy between imipenem and EDTA can arise, at least in *P. aeruginosa*, for reasons other than inhibition of metallo-ß-lactamases.[8] Resistance to carbapenems in Enterobacteriaceae (except for low-level resistance to imipenem in Proteeae) is unusual, and deserves reference laboratory examination, as does carbapenem resistance in

Acinetobacter spp.

The role of *mecA* in giving resistance to all β-lactams in methicillin-resistant staphylococci is discussed elsewhere[5] and no comment is needed here, except to stress that isolates found resistant to indicator agents (Table IV) should be reported as resistant to all ß-lactams. In pneumococci, β-lactam resistance accrues stepwise and affects all members of the antibiotic class.[24] Oxacillin resistance can be taken as an indicator of the underlying penicillin-binding protein changes.[25] Cefotaxime, ceftriaxone and meropenem generally remain more active than penicillin against strains with the mechanism (Table VIII), but the position is reversed for a few isolates at least for the cephalosporins.[26] Rare pneumococci are resistant to oxacillin, but not penicillin.[24]

Glycopeptides

At present, transferable glycopeptide resistance is exclusive to enterococci, the exceptions being two recent reports of VanA-positive S. aureus.[27] The common forms of this resistance are ht VanA and VanB types; VanD and VanE are rare, whereas VanC is intrinsic to clinically-infrequent enterococci, specifically *Enterococcus casseliflavus* and *E. gallinarum. E. faecalis* and *E. faecium* strains with the classical VanA phenotype show resistance to vancomycin and resistance, or markedly reduced susceptibility, to teicoplanin; those with classical VanB are resistant to vancomycin but remain susceptible to teicoplanin.[28] Teicoplanin remains acceptable therapy against strains inferred, on this basis, to have VanB. VanC confers low-level resistance to Vancomycin, but not Teicoplanin.[24] From the limited data available for the two recorded isolates, VanA behaves variably similarly in *S. aureus* to enterococci, affecting both vancomycin and teicoplanin, though not always giving frank resistance to the latter agent. Intermediate glycopeptide resistance which does not involve Van determinants -remains very rare in *S. aureus*, although teicoplanin resistance is frequent in coagulase-negative staphylococci. MIC tests are required to detect these mechanisms, disc tests being inadequate.

Aminoglycosides

In contrast to the β-lactamases, aminoglycoside-modifying enzymes modify their substrate compounds at different positions, variously acetylating, nucleotidylating or phosphorylating amino or hydroxyl groups. There are different forms of some modifying enzymes, often with markedly different substrate specificities. This variation is particularly evident in the AAC(3) and AAC(6') families.[29,30] Counterwise, unrelated enzymes, affecting different sites, can confer same resistance phenotypes. Despite these difficulties the enzymes produced by isolates can often be predicted from the antibiogram data, as illustrated in Table IX and X.

Because few organisms have chromosomally encoded aminoglycoside-modifying enzymes, it is not necessary to split bacteria into as many groups as for β-lactamases and, with a few exceptions, Enterobacteriaceae can be treated as a single group (Table IX). However, *Klebsiella* spp. are shown separately, because resistance is more frequent than in most other genera.[31] *Serratia* is also shown separately because of its chromosomally encoded AAC(6') enzyme.[32] This usually is expressed weakly and the organism remains susceptible to aminoglycosides, but mutational hyper-production gives a characteristically resistant phenotype.[33] *Providencia stuartii* possesses a chromosomal AAC(2') enzyme, which usually is expressed weakly but nevertheless confers low-level resistance to its substrates.[34] This enzyme is virtually unknown outside *Providencia* spp.

Many of the plasmid-encoded enzymes seen in Enterobacteriaceae also occur in *P. aeruginosa* (Table IX), but AAC(3)II is very rare whereas AAC(3)III and AAC(6')II are more frequent.[35] Broad-spectrum resistance, normally low level, is frequent in pseudomonads and is presumed to reflect poor up-take,[35,36] although efflux may also be a factor in some organisms.[37] *P. aeruginosa* is inherently resistant to kanamycin and neomycin, (kanamycin MICs around 64 mg/L) owing to low-level APH(3') activity.[36]

Resistance to amikacin (and isepamicin) in *Acinetobacter* spp. is often associated with APH(3')VI.[38] This enzyme cannot modify gentamicin, netilmicin or tobramycin, so producers may be susceptible to some or all of these agents; many nevertheless are resistant owing to co-production of other modifying enzymes. Gram-positive organisms have different aminoglycoside-modifying enzymes to Gram-negative ones (Table X). Bi-functional APH(2')/AAC(6') is by far the most important and frequent[35,39] conferring resistance to all aminoglycoside analogues except streptomycin. Enterococci characteristically have low-level resistance to all aminoglycosides, but detection of high-level resistance (MICs $\geq$ 256 mg/L though more often >1024 mg/L), mostly mediated by AAC(6')/APH(2') is significant, since it contra-indicates synergy with cell wall active agents.

Streptomycin is omitted from Table IX since it is seldom tested or used, and because there is no cross-resistance with other aminoglycosides, except when resistance is caused by impermeability.[36,40] Streptomycin resistance in Enterobacteriaceae mostly depends on ANT(3')I or APH(3').[41] High-level resistance in enterococci mostly reflects ANT(6)[39] which, like other streptomycin-modifying enzymes, does not give cross-resistance to other aminoglycosides.

Production of multiple enzymes is more frequent with aminoglycoside-modifying enzymes than with β-lactamases.[35,40] The simultaneous production of APH(3') plus a gentamicin-modifying enzyme can often be inferred from the resistance pattern; however, it is difficult to more than guess at the identity of combinations of enzymes that modify gentamicin or tobramycin, e.g. AAC(3)II + AAC(6'), without resorting to use of experimental compounds such as the 2' and 6'-N-ethyl derivatives of netilmicin. Experimental drugs such as these are a powerful tool in the prediction of aminoglycoside modifying enzyme types,[40,42] but are beyond the scope of this review.

Most laboratory susceptibility test results with aminoglycosides can be accepted without editing.

Quinolones

Quinolones differ in their activity against bacterial species, doubtless reflecting differences in their ability to permeate, evade efflux and bind to different topoisomerases. Resistance, however, is a class effect, and isolates resistant to one analogue invariably show reduced susceptibility or resistance to other members of the family. In these circumstances there is little scope for interpretative reading, but a few general principles can be proposed.

Firstly, based on recent literature,[43,44] the most active analogues against different groups are:
Enterobacteriaceae: ciprofloxacin
Non-fermenters: ciprofloxacin
Pneumococci: moxifloxacin, gemifloxacin
Enterococci: no available analogue has convincing activity
Staphylococci: high risk of mutational resistance to all analogues

Secondly, the differentials in activity between ciprofloxacin, ofloxacin, norfloxacin, levofloxacin and moxifloxacin against Enterobacteriaceae are small (four-fold MIC variation).[43,44] If an isolate is resistant to one of these drugs, susceptibility to the others is likely to be marginal at best and, in these circumstances, quinolones should only be used if there are no alternatives in other therapeutic classes. If an isolate appears highly susceptible to one fluoroquinolone but highly resistant to others, a testing problem is likely.

Thirdly, non-fermenters and Gram-positive cocci have lower inherent susceptibility to quinolones than Enterobacteriaceae. Isolates (even of classical phenotypes) may be susceptible to some analogues but marginally resistant to others. The most active analogues should be recommended for therapy, since it is hardest for resistance to develop.

Lastly, the value of using nalidixic acid as an indicator for reduced susceptibility or resistance to fluoroquinolones in fastidious Gram-negative bacteria (Table IV) should be re-emphasized, especially in the light of growing ciprofloxacin resistance in gonococci.

MLS drugs (macrolides, lincosamides and streptogramins)

Table XI gives interpretative guidelines for these agents. The most important source of resistance is the macrolide, lincosamides, streptogramin B (MLS_B) system encoded by the *erm* genes, which may be constitutive or inducible in expression.[45,46] Expression is regulated further by the sequences upstream of *erm*, which vary among the host elements prevalent in different species.

In the case of staphylococci, 14- and 15-membered macrolides, (e.g. erythromycin, clarithromycin and azithromycin) are inducers of erm whereas clindamycin and 16-membered macrolides do not induce. MLS_B-inducible strains consequently express resistance to erythromycin but not clindamycin, whereas MLS_B-constitutive ($MLS_{B/c}$) organisms express resistance to both drugs. For MLS_B-inducible isolates, erythromycin antagonizes clindamycin, a phenomenon easily demonstrated in double disc tests. Distinguishing $MLS_{B/c}$ resistance in staphylococci is important since the dosage frequency for quinupristin/dalfopristin is changed from twice to thrice daily in skin and soft tissue infections when this mechanism is inferred.[47]

Whether to report MLS_B-inducible staphylococci (erythromycin-resistant, clindamycin-susceptible) as clindamycin-resistant remains debatable. Some authors support this approach, since MLS_B-inducible strains segregate clindamycin resistant $MLS_{B/c}$ mutants, which may be selected in therapy.[48,49]

Nevertheless, one of the most-cited examples[50] of resistance emerging during clindamycin treatment concerns a staphylococcal strain that was susceptible to erythromycin and so was unlikely to have harboured an *erm* gene. Lincosamide inactivation is an occasional source of resistance to clindamycin (not macrolides) in coagulase-negative staphylococci, but is very rare in *Staphylococcus aureus*.[46] MLS resistance occurs in streptococci as well as staphylococci and, once again, can be inducible or constitutive. However, clindamycin as well as erythromycin often acts as an inducer. Thus, cross-resistance to both erythromycin and clindamycin indicates MLS_B but does not prove constitutive expression. Resistance to erythromycin but not clindamycin may indicate an MLS_B -inducible phenotype, but may also be contingent on efflux mediated by the products of *mef* genes. In the case of enterococci, a critical point is that *E. faecalis* is resistant to quinupristin/dalfopristin whereas almost all *E. faecium* isolates are susceptible—a mirror image of the pattern for ampicillin. Microbiologists should be sceptical of any isolate that is resistant or susceptible to both of these drugs or susceptible to both; such organisms deserve reference investigation.

Tetracyclines
No interpretative reading table for tetracyclines is provided, since multiple analogues are rarely tested. Nevertheless, not all the analogues are equally affected by the prevalent efflux [*tet*(A)-*tet*(F), *tet*(K) and *tet*(L)] or ribosomal protection [*tet*(M) and *tet*(O)] mechanisms, and a system of interpretative reading could be devised. In Gram-negative bacteria, *tet*(B) and *tet*(E) confer high-level resistance to all tetracycline derivatives whereas *te*t(A), *tet*(C), *tet*{D), *tet*(K) and *tet*(L) provide little or no protection against doxycycline and minocycline.[51] In the case of gram-positive bacteria minocycline retains activity against strains with *tet*(K), but is compromised agasint those with *tet*(M).[52] The glycylcycline derivative, tigecycline[52] evades both efflux and ribosomal modes of resistance in both Gram-negative and Gram-positive bacteria.

Other antibiotics
Those antibiotics not discussed above are either the sole analogues within a class (e.g. chloramphenicol, fosfomycin; nitrofurantoin, trimethoprim) or belong to classes with little differentiation in microbiological activity (sulphonamides), meaning that there is little or no scope for interpretative reading. Nevertheless, interpretation is possible to the extent of recognizing inherently unlikely combinations of organisms and antibiotic susceptibility or resistance (Tables I and II); moreover the microbiologist should be alert to the likelihood of resistance emerging to many of these agents (Table III).

The limits of interpretative reading
Interpretative reading can never be so complete a strategy as identifying resistance mechanisms by genetic and biochemical investigation, and its limits should be recognized. First, bacteria with multiple resistance determinants affecting the same class(es) of antibiotics are increasingly frequent. Shaw et al.[40] found multiple determinants in over 70% of 4088 amino-glycoside-resistant enterobacteria examined, and Essack *et al*[53] found 84 TEM and SHV ß-lactamase genes among a collection of 25 *K. pneumoniae* isolates, only 20 of which were ESBL producers. The resistance patterns of isolates with multiple mechanisms may be confusing or misleading. For example, there is little to reliably distinguish the resistance pattern of a Klebsiella with an AmpC enzyme from that of a strain with both an ESBL and a permeability lesion. Secondly, interpretative reading cannot identify new resistance mechanisms if these give a resistance profile identical to that given by a known mechanism.[1,3] Thirdly, some species and genera, notably *Acinetobacter* spp. and *Burdholdera* spp. frequently have complex multi-resistance profiles that are difficult to relate reliably to genetically-defined mechanism. Nevertheless, despite these caveats, there can be little doubt that interpretative reading, with attention to identifying the unusual and unlikely, editing out of dubious sensitivities and potential for surveillance resistance mechanisms is a useful advance over the standard practice of accepting all resistance data at face value.

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Table I. Unusual resistances needing reference laboratory confirmation (see text for addresses)

Organism	Resistances requiring confirmation
Staphylococcus aureus	**Any of**: vancomycin, teicoplanin, linezolid, quinupristin/dalfopristin
Coagulase-negative staphylococci	**Any of**: vancomycin, linezolid
Jeikeium coryneforms	**Any of**: vancomycin, teicoplanin, linezolid
Streptococcus pneumoniae	**Any of**: meropenem, vancomycin, teicoplanin, linezolid.
Group A, B, C, G ß-haemolytic streptococci	**Any of**: penicillin, vancomycin, teicoplanin, linezolid.
Enterococci	Both ampicillin and quinupristin/dalfopristin. Linezolid. Teicoplanin but not vancomycin.
Enterobacteriaceae	Meropenem
Haemophilus influenzae	Any third-generation cephalosporin, or carbapenem
Moraxella catarrhalis	Ciprofloxacin
Neiseria meningitides	Any of: penicillin (high-level), ciprofloxacin
Neisseria gonorrhoeae	Any third-generation cephalosporin
Acinetobacter; P. aeruginosa	Colistin
Anaerobes in general	Metronidazole
Bacteroides	Any of: metronidazole, co-amoxiclav, carbapenems
Clostridium difficile	Any of: metronidazole, vancomycin

Note to all tables: β-lactam groups
First generation cephalosporins: cephalexin, cephalothin, cephazolin and cephradine.
Second generation cephalosporins: cefamandole, cefaclor and cefuroxime.
Third generation cephalosporins: cefotaxime, cefpodoxime, ceftazidime and ceftriaxone.
Fourth generation cephalosporins: cefepime and cefpirome.
Oxyimino cephalosporins: cefepime, cefotaxime, cefpirome, cefpodoxime, ceftazidime, ceftriaxone and cefuroxime.
Cephamycins: cefoxitin, cefotetan.
Aminopenicillins: amoxycillin, ampicillin, mezlocillin and piperacillin.
Carboxypenicillins: carbenicillin and ticarcillin.

Table II. Natural resistances typical of common pathogens

Organisms	Natural resistances to
All Enterobacteriaceae	Penicillin G, glycopeptides, fusidic acid, macrolides, clindamycin, linezolid, streptogramins (e.g. quinupristin/dalfopristin), mupirocin
Acinetobacter baumannii	Ampicillin, amoxycillin, first-generation cephalosporins
Pseudomonas aeruginosa	Ampicillin, amoxycillin, co-amoxiclav, first-generation cephalosporins, second-generation cephalosporins, cefotaxime, ceftriaxone, nalidixic acid, nitrofurantoin, trimethoprim
Burkholderia cepacia	Ampicillin, amoxycillin, first-generation cephalosporins, colistin, aminoglycosides
Stenotrophomonas maltophilia	All ß-lactams except ticarcillin/clavulanate, aminoglycosides
Flavobacterium (Chryseobacterium/Myroides)	Ampicillin, amoxycillin, first-generation cephalosporins
Salmonella spp.	Cefuroxime and aminoglycosides (active *in vitro*, not active *in vivo*)
Klebsiella spp., *Citrobacter diversus*	Ampicillin, amoxycillin, carbenicillin, ticarcillin
Enterobacter spp., *C. freundii*	Ampicillin, amoxycillin, co-amoxiclav, first-generation cephalosporins, cefoxitin
M. morganii	Ampicillin, amoxycillin, co-amoxiclav, first-generation cephalosporins, cefuroxime, colistin, nitrofurantoin, tetracyclines
Providencia spp.	Ampicillin, amoxycillin, co-amoxiclav, first-generation cephalosporins, cefuroxime, gentamicin, netilmicin, tobramycin, colistin, nitrofurantoin, tetracyclines
Proteus mirabilis	Colistin, nitrofurantoin, tetracyclines
Proteus vulgaris	Ampicillin, amoxycillin, cefuroxime, colistin, nitrofurantoin, tetracyclines
Serratia spp.	Ampicillin, amoxycillin, co-amoxiclav, first-generation cephalosporins, cefuroxime, colistin
Yersinia enterocolitica	Ampicillin, amoxycillin, carbenicillin, ticarcillin, first-generation cephalosporins
Campylobacter jejuni, Campylobacter coli	Trimethoprim
H. influenzae	Penicillin G, erythromycin, clindamycin
M. catarrhalis	Trimethoprim
All Gram-positive bacteria	Aztreonam, temocillin, colistin, nalidixic acid
Streptococci	Fusidic acid, aminoglycosides[a]
S. pneumoniae	Trimethoprim, aminoglycosides
Methicillin-resistant *S. aureus*	All ß-lactams
Enterococci	Carbenicillin, ticarcillin, all cephalosporins, aminoglycosides,[a] mupirocin
Listeria	Third-generation cephalosporins, fluoroquinolones

See note relating to all tables at foot of Table I.
[a]Low-level resistance: aminoglycosides are useful for synergy with penicillins against typical streptococci and enterococci.

Table III: Antibiotic/organism combinations where mutational resistance is likely to develop

Organism	Antibiotic
Staphylococci	Fusidic acid, rifampicin, fluoroquinolones
Erythromcyin-resistant staphylococci	Clindamycin
S. pneumoniae	Ciprofloxacin
P. aeruginosa	All anti-pseudomonal antibiotics, except colistin and, possibly, meropenem
B. cepacia	All relevant antibiotics
Enterobacter, Citrobacer, Serratia, Morganella	All third-generation cephalosporins
Coliforms iwth ESBLs	Cephamycins (via impermeability)
All coliforms	Fosfomycin, nalidixic acid (not fluoroquinolones)
Serratia marcescens	Netilmicin, tobramycin, amikacin, kanamycin

See note relating to all tables at foot of Table I.
This table excludes rarely used antibiotic/organism combinations; it also only considers the risk of resistance arising in the original pathogen, not the likelihood of overgrowth by other species (e.g. enterococci and *C. difficile*), which may also be a significant clinical hazard.

Table IV. Useful indicator antibiotics

Organism	Resistance to	Inference /action
Staphylococci	oxacillin or methicillin, cefoxitin	Resistant to all ß-lactams.
Staphylococci	erythromycin	Inducible clindamycin resistance likely; avoid clindamycin, or use with caution.
Staphylococci	erythromycin and clindamycin (lincomycin may be better indicator than clindamycin)	Constitutive $MLS_{B/c}$ resistance. Quinupristin/ dalfopristin likely to be bacteriostatic, not bactericidal; dosage should be increased to thrice daily even in skin and soft tissue infection
Pneumococci	oxacillin (zone ≤18 mm)	Probably penicillin resistant. Perform E-test for any penicillin or cephalosporin to be used
E. faecalis	ampicillin	Probably *E. faecium*, but may be less frequent species or (just possibly) may have acquired resistance: check speciation or refer
H. influenzae	cefaclor	Likely non-ß-lactamase-type resistance (better indicator than ampicillin)
Neisseria spp. *H. influenzae* *Campylobacter* spp.	nalidixic acid	Indicates reduced susceptibility or resistance to fluoroquinolones
Klebsiella / E. coli	Ceftazidime or cefpodoxime	Likely ESBL producer8[6] Avoid all cephalosporins except cephamycins
Any Enterobacteriaceae	any second-generation cephalosporin	Likely to have potent ß-lactamase; avoid first-generation cephalosporins
Any Enterobacteriaceae	any third -generation cephalosporin	Likely to have potent ß-lactamase; avoid first- and second- generation cephalosporins except, possibly, cephamycins
Any Enterobacteriaceae	resistant to any ureidopenicillins	Likely to have penicillinase, avoid all amino-, ureido- and carboxy-penicillins
Any Enterobacteriaceae	resistant to any ß-lactamase inhibitor combinations	Assume resistance to the corresponding unprotected penicillin

See note relating to all tables at foot of Table I.

Table V. Phenotypes: interpretation of mechanisms and editing of antibiograms: B-lactams versus Enterobacteriaceae

AMP	AMX/ CLAV	TIC	TIC/ CLAV	PIP, CFP	PIP/ TAZ	CEF	FOX	CXM	CAZ	CTX, CRO	CPR, FEP	ATM	IMP, MEM	Interpretation	Frequency	Edit/action
E. Coli, P. mirabilis, Salmonella, Shigella spp.																
S	S	S	S	S	S	S	S	S	S	S	S	S	S[a]	classical	common	
R	S	R	S	r	S	r	S	S	S	S	S	S	S	penicillinase-low	common	Edit pip to R; edit 1st gen cephs to R except in UTI where e.g. Cephalexin retains acceptable activity
R	r/R	R	r/R	R	r/R	R	S	S	S	S	S	S	S	penicillinase-high	common	Edit 1st gen cephs to R except in UTI
R	R	r	R	R	R	R	R	R	R	r/R	S	r/R	S	AmpC high-plasmid or chromosomal	rare	Consider TEMO as alternative to carbapenems
R	any[b]	R	any[b]	R	any[b]	R	S	R	R	R	R	R	S	ESBL-broad	rare	ESBL test; if +ve, edit 2/3/4 gen cephs to R[c]
R	any[b]	R	any[b]	R	any[b]	R	S	r	R	r	r	r	S	ESBL-ceftazidimase	rare	ESBL test; if +ve, edit 2/3/4 gen cephs to R[c]
R	any	R	any	R	any	R	S	r	r	R	r	r		ESBL-CTX-M	increasing	ESBL test; if +ve, edit 2/3/4 gen cephs to R[c]
R	R	R	R	R	r/R	S	S	S	S	S	S	S	S	IRT[d]	???	
r	r	r	r	r	r	r	R	R	S	S	S	S	S	impermeability	rare	
any	any	any	any	any	any	any	any	any	any	any	any	any	R[1]	!!!	!!!	Refer

AMP	AMX/ CLAV	TIC	TIC/ CLAV	PIP, CFP	PIP/ TAZ	CEF	FOX	CXM	CAZ	CTX, CRO	CPR, FEP	ATM	IMP, MEM	Interpretation	Frequency	Edit/action
Klebsiella spp.																
R	S	R	S	r	S	S	S	S	S	S	S	S	S	Classical-low SHV-1 or K1	common	Edit all penicillins (except TEMO) to R.
R	r/R	R	any[b]	R	r/R	R	S	S	S	S	S	S	S	Penicillinase-high	common	
R	any[b]	R	any[b]	R	any[b]	R	S	R	R	R	R	R	S	ESBL-broad	scattered	ESBL test; if +ve, edit 2/3/4 gen cephs to R[c]
R	any[b]	R	any[b]	R	any[b]	R	S	r	R	r	r	r	S	ESBL-ceftazidimase	scattered	ESBL test; if +ve, edit 2/3/4 gen cephs to R[c]
R	any	R	any	R	any	R	S	r	r	R	r	r		ESBL-CTX-M	increasing	ESBL test; if +ve, edit 2/3/4 gen cephs to R[c]
R	R	R	R	R	r/R	S	S	S	S	S	S	S	S	IRT[d]	???	
R	R	R	R	R	R	R	S	R	S	S	S	R	S	K1, high, K. oxytoca only	scattered	Edit CTX to R; ??? CAZ
R	R	R	R	R	R	R	R	R	R	R	S	r/R	S	Plasmid AmpC	Rare	
R	r	R	r	r	r	r	R	R	S	S	S	S	S	impermeability	Rare	
any	any	any	any	any	any	any	any	any	any	any	any	any	any	!!!	!!!	Refer
Enterobacter, C. freundii																
R	R	S	S/r	S	S	R	R	S/r	S	S	S	S	S	classical, AmpC inducible	common	Advise against use of 2/3 gen cephs[e]
R	R	R	any[b]	R	S/r	R	R	S	S	S	S	S	S	Penicillinase	common	Advise against use of 2/3 gen cephs[e]

AMP	AMX/ CLAV	TIC	TIC/ CLAV	PIP, CFP	PIP/ TAZ	CEF	FOX	CXM	CAZ	CTX, CRO	CPR, FEP	ATM	IMP, MEM	Interpretation	Frequency	Edit/action
Enterobacter, *C. freundii* cont.																
R	R	R	any[b]	R	S/r	R	R	R	R	R	R	R	S	ESBL-broad	increasing	Edit 2/3/4 gen cephs to R[f]
R	R	R	any[b]	R	S/r	R	R	r	R	r	R	r	S	ESBL-ceftazidimase	increasing	Edit 2/3/4 gen cephs to R[f]
R	any	R	any	R	any	R	S	r	r	R	r	r		ESBL-CTX-M	rare	ESBL test; if +ve edit 2/3/4 gen cephs to R[c]
R	R	R	R	R	R	R	R	R	R	R	S	R	S	AmpC derepressed	common	Consider TEMO as therapy alternative
any	any	any	any	any	any	any	any	any	any	any	any	any	R	!!!	!!!	Refer
***M. morganii/Providencia* spp.**																
R	R	S	S/r	S	S	R	r	R	S	S	S	S	S	classical, AmpC inducible	common	Advise against use of 2/3 gen cephs[e]
R	R	R	S	R	S/r	R	r	R	S	S	S	S	S	penicillinase	common	Advise against use of 2/3 gen cephs[e]
R	R	R	R	R	S	R	r	R	R	R	S	R	S	AmpC derepressed	scattered	Consider TEMO as therapy alternative
any	any	any	any	any	any	any	any	any	any	any	any	any	R	!!!	!!!	Refer
Proteus vulgaris																
R	S	R	S	S	S	R	S	R	S	S	S	S	S	classical, inducible class A	common	
R	S	R	S	R	S	R	S	R	S	S	S	S	S	Penicillinase	common	

AMP	AMX/ CLAV	TIC	TIC/ CLAV	PIP, CFP	PIP/ TAZ	CEF	FOX	CXM	CAZ	CTX, CRO	CPR, FEP	ATM	IMP, MEM	Interpretation	Frequency	Edit/action
***Proteus vulgaris* cont.**																
R	S	R	S	R	S	R	S	R	S	R	S	S	S	Chromosomal derepressed	Rare	
any	any	any	any	any	any	any	any	any	any	any	any	any	R	!!!	!!!	Refer
Citrobacter diversus																
R	S	R	S	r	S	R	S	S	S	S	S	S	S	classical, inducible class A	common	Edit all penicillins (except TEMO) to R.
R	R/R	R	any[b]	R	r/R	R	S	S	S	S	S	S	S	penicillinase-high	common	
any	any	any	any	any	any	any	any	any	any	any	any	any	any	!!!	!!!	Refer
***Serratia* spp.**																
R	R	S	S	S	S	R	r	R	S	S	S	S	S	classical, AmpC inducible	common	Advise against use of 2/3 gen cephs[e]
R	R	R	any[b]	R	any	R	r	R	S	S	S	S	S	penicillinase	common	Advise against use of 2/3 gen cephs[e]
R	R	R		R	r/R	R	r	R	S	R	S	R	S	AmpC derepressed	rare	Consider TEMO as therapy alternative
any	any	any	any	any	any	any	any	any	any	any	any	any	R	!!!	!!!	Refer

See note relating to all tables at foot of Table I.

General notes for Tables V-XI:

Classical means the historic phenotype of the species, without acquired resistance; **Common** means seen in >10% of isolates; **scattered** means seen in 5-10% of isolates; **uncommon** means seen in 1-5% of isolates; and **rare** means seen in <1%; **increasing** is used in cases where a resistance is still rare, but is proliferating rapidly. Local frequencies may be very different, especially during outbreaks and in specialist units. **Refer** and **!!!** mean send to an appropriate reference or academic laboratory for confirmation (see text); **???** means uncertain as insufficient data.

Abbreviations: AMK, amikacin; AMX, amoxicillin; AMP, ampicillin; AMX/CLAV, co-amoxiclav; ATM, aztrenam; CAZ, ceftaxzidime; Ceph, cephalosporins; FEP, cefepime; CLI, clindamycin; CEF, cephalothin; CF, cystic fibrosis; CFP, cefoperazone, CPR, cefpirome; CRO, ceftriaxone; CTX, cefotaxime; CXM, cefuroxime; ERY, erythromycin; FOX, cefoxitin; GEN, gentamicin; IMP, imipenem; KAN, kanamycin; MEM, meropenem; NEO, neomycin; NET, netilmicin; OXA, oxacillin/cloxacillin; PCG, penicillin G; PIP, Piperacillin; TZP, Piperacillin/tazobactam; Q-D, quinupristin/dalfopristin; TEMO, temocillin; TIC, ticarcillin;' TIC/CLAV, ticarcillin/clavulanate; TOB, Tobramycin; 1st gen ceph, first generation cephalosporins; 2/3/4 gen ceph, second/third/fourth generation cephalosporins; R, resistant; r, reduced zones but likely to remain susceptible at BSAC breakpoints; B, borderline (MICs for typical strains of the species without acquired resistance, fall around the zone/MIC breakpoints); S, susceptible.

[a]Discount low-level imipenem resistance in *P.mirabilis*

[b]Varies with amount of ß-lactamase produced.

[c]See Livermore and Brown[8] for ESBL tests for these species.

[d]IRT; inhibitor-resistant TEM mutant.

[e]If second or third generation cephalosporins are used, there is substantial risk of selection of derepressed, mutants during therapy. See Table III.

[f]ESBL tests[8] are difficult with AmpC-inducible species since clavulanate-induced AmpC enzymes (which evade the action of clavulanate) are prone to attack the indicator cephalosporin, but cefepime/clavulanate may be useful, as cefepime is less likely to be affected by induced AmpC than are third-generation cephalosporins. The pattern of cefotetan-susceptible, ceftazidime-resistant would imply ESBL production, but this principle has not been evaluated critically.[8]

Table VI. Phenotypes, interpretation of mechanism and editing of antibiograms; ß-lactams versus non-fermenters

TIC	TIC/CLAV	PIP,CFP	PIP/TAZ	CAZ	CPR,FEP	ATM	IMP	MEM	Interpretation	Frequency	Edit/Action
P. aeruginosa											
S	S/r	S	S	S	S	S	S	S	classical	common	Beware mutational resistance; see Table III
R	any	R	any	S	S	S	S	S	penicillinase	rare	
r	R	r	r	r	r	R	S	S	AmpC part derepressed	common	
r/R	r/R	R	R	R	S/r	R	S	S	AmpC fully derepressed	rare	
R	R	r/R	r/R	r/R	R	r/R	S	r	Increased efflux[a]	common	
S	S/r	S	S	S	S	S	R	r	loss of OprD porin	scattered	
R	R	r/R	r/R	R	R	R	R	R	Acquisition of multiple mutations[a] or, rarely, metallo-ß-lactamases	Mutational form common e.g. in CF	Seek metallo-ß-lactamases by imipenem/EDTA synergy if highly R
***Acinetobacter* spp**.		Relationships between antibiogram and mechanisms poorly defined. Carbapenems have the most consistent activity against the genus, but carbapenemases or the OXA and VIM/IMP classes are a growing concern. Isolates with carbapenem resistance should be referred for specialist investigation. ESBL tests do not work, as many isolates are susceptible to clavulanate alone.									
S. maltophilia		May appear susceptible to penicillins and cephalosporins on Iso-Sensitest agar, but is generally resistant on Mueller-Hinton agar. Among ß-lactams, ticarcillin/clavulanate has best provenance, although co-trimoxazole (not trimethoprim alone) is the usual drug of choice.									

See note to all tables at foot of Table 1 and general notes and abbreviations for Tables V-XI at the foot of Table V.

[a]Isolates typically also have r/R to quinolones

Table VII. Phenotypes; interpretation of mechanism and editing of antibiograms; ß-lactams versus fastidious Gram-negative bacteria and *M. catarrhalis*

PCG	AMP, AMX	AMX/CLAV	CCL	CTX, CRO,CFIX	MEM	IMP	Interpretation	Frequency	Edit/action
H. influenaze									
R	S	S	S	S	S	S	Classical	Common	
R	R	S	S	S	S	S	ß-lactamase +ve	Common	Confirm with ß-lactamase test[a]
R	r/r	r/R	R	r	S	S/R[8]	Intrinsic resistance-altered PBPs; impermeability or efflux	Rare	
any	any	any	any	any	R	any	!!!	!!!	Refer
any	any	any	any	R	any	any	!!!	!!!	Refer
N. gonorrhoeae									
S	S	S	-	S	-	-	Classical	common	
R	R	S	-	S	-	-	ß-lactamase +ve	common	Confirm with ß-lactamase test[a]
r/R	r/R	r/R	-	S	-	-	Impermeability or efflux	common	
any	any	any	any	R	-	any	!!!	!!!	Refer
N. meningitides									
S	S	S	-	S	-	-	Classical	Common	
r	R	R	-	S	-	-	Impermeability or efflux	Common	
Substantial R to any ß-lactam							!!!	!!!	Refer
M. catarrhalis									
R	S	S	S	S	S	S	Classical	Common	Confirm ß-lactamase negative by direct test; if +ve, report as ampicillin/resistant-resistant
R	R	S	S	S	S	S	BRO-1/2 ß-lactamase +ve	common	

See note to all tables at foot of Table I and general notes and abbreviations for Tables V-XI at the foot of Table V.

[a]See Livermore & Brown[8] for ß-lactamase tests

[b]*H. influenzae* with intrinsic resistance to penicillins and cephalosporins are either fully susceptible to imipenem, or show a high level of resistance, implying that the group encompasses at least two different genotypes.

Table VIII. Phenotypes; interpretation of mechanism and editing of antibiograms: ß-lactams versus Gram-positive cocci

PCG	AMP, AMX	AMX/CLAV	OXA	Any ceph	IMP, MEM	Interpretation	Frequency	Edit/Action
Staphylococci								
S	S	S	S	S	S	Classical, now uncommon	Scattered	
R	R	S	S	S	S	ß-lactamase +ve	Common	Edit all penicillins except oxacillin and methicillin to R
any	any	any	any	any	any	Methicillin/oxacillin resistant	Common	Edit all ß-lactams to R
S. pyogenes								
S	S	S	S	S	S	Classical	Common	
R	any	any	any	any	any	!!!	!!!	Refer
S. pneumoniae								
S	S	S	S	S	S	Classical		
any	any	any	R	any	any	PenR pneumococcus	Common	Determine MICs of drugs intended for use. Cefotaxime and ceftriaxone, also meropenem, often remain active, with oral cephalosporins mostly less active than amoxicillin
E. faecalis								
r	S	S	R	R	S	Classical	Common	
R	R	S	R	R	S	ß-lactamase +ve	!!!	Refer
R	R	R	R	R	R	Probably E. faecium	Error	Check speciation
E. faecium								
R	S	S	R	R	S	Classical, now rare	Scattered	
R	R	R	R	R	R	Uses PBP-5 to cross-link peptidoglycan	common	

See note to all tables at foot of Table I and general notes and abbreviations for Tables V-XI at the foot of Table V.

Table IX. Phenotypes; interpretation of mechanism and editing of antibiograms: aminoglycosides versus Gram-negative bacteria

GEN	NET	TOB	AMK	KAN	NEO	Interpretation	Frequency	Edit/action and comments
***E. coli* and other Enterobacteriaceae not shown separately**								
S	S	S	S	S	S	classical	common	
R	S	S	S	S	S	AAC(3)I	Rare	Also R to fortimicin
R	R	R	S	R	S	AAC(3)II	rare	Greater R to GEN than to TOB or NET
R	R	R	S	r	R	AAC(3)IV	rare	Also R to apramycin (used in veterinary practice). Mostly in *E. coli*
S/r	R	R	R	R	R	AAC(6')	rare	One component of GEN remains active but *in vivo* use best avoided.
R	S	R	S	R	S	ANT(2')	rare	Equal R to GEN and TOB
S	S	S	S	R	R	APH(3')	common	Usually more R to KAN than NEO. Was common, now rarely tested.
r/R	r/R	r/R	r/R	r/R	r/R	'impermeability'	rare	Low-level R to all aminoglycosides
***Klebsiella* spp.**								
S	S	S	S	S	S	classical	common	
R	S	S	S	S	S	AAC(3)I	rare	Also R to fortimicin
R	R	R	S	r	S	AAC(3)II	scattered/rare	Greater R to GEN than to TOB or NET
S/r	R	R	R	R	R	AAC(6')	rare	One component of GEN remains active, but *in vivo* use of GEN vs suspect isolates.
R	S	R	S	R	S	ANT(2')	scattered/rare	Equal R to GEN and TOB
S	S	S	S	R	R	APH(3')	common?	Usually more R to KAN than NEO. Was common, now rarely tested.
r/R	r/R	r/R	r/R	r/R	r/R	'impermeability'	rare	Low-level R to all aminoglycosides
***Serratia* spp.**								
S	S	S	S	S	S	classical	common	Chromosomal AAC(6') expressed weakly: risk of selection of over-producers in therapy with AMK, TOB, NET.
R	S	S	S	S	S	AAC(3)I	rare	Also R to fortimicin
R	R	R	S	r	S	AAC(3)III	rare	Greater R to GEN than TOB or NET
S/r	R	R	R	R	R	AAC(6')	common	Mutation causes over-production of chromosomal AAC(6')
R	S	R	S	R	S	ANT(2')	rare	Equal R to GEN and TOB
S	S	S	S	R	R	APH(3')	rare	Usually more R to KAN than NEO
r/R	r/R	r/R	r/R	r/R	r/R	'impermeability'	rare	Low-level R to all aminoglycosides
Providencia stuartii								
R	R	R	S	S	R	AAC(2')	classical	Chromosomal AAC(2'); poorly expressed
R	R	R	S	S	R	AAC(2')	common	Mutation causes overproduction of AAC(2')
P. aeruginosa								
S	S	S	S	R	R	classical	common	
R	S	S	S	R	R	AAC(3)I	rare	Also R to fortimicin
R	S	R	S	R	R	AAC(3)III	rare	
S/r	R	R	R	R	R	AAC(6')	rare	One component of GEN remain active, but *in vivo* use best avoided
R	R	R	S	R	R	AAC(6')II	rare	R pattern not obviously predictable from enzyme activity

GEN	NET	TOB	AMK	KAN	NEO	Interpretation	Frequency	Edit/action and comments
***P. aeruginosa* cont.**								
R	S	R	S	R	R	ANT(2')	rare	Equal levels of R to GEN and TOB
S	S	S	S	R	R	APH(3')	common	Usually more R to KAN than to NEO
r/R	r/R	r/R	r/R	r/R	r/R	'impermeability'	scattered	Low-level R to all aminoglycosides

See note to all tables at foot of Table I and general notes and abbreviations for Tables V-XI at the foot of Table V.

Mechanism varies in level among isolates and may also involve efflux; Tobramycin retains best activity against most representatives.

Table X. Phenotypes; interpretation of mechanism and editing of antibiograms: aminoglycosides versus Gram-positive bacteria

GEN	NET	TOB	AMK	KAN	NEO	Interpretation	Frequency	Edit/action and comments
Staphylococci								
S	S	S	S	S	S	classical	common	
S	S	R	R	R	S	ANT(4')(4")I	rare	Unlike 'Gram-negative' ANT(4'), also modifies dibekacin at 4".
R	R	R	r	R	R	APH(2") AAC(6')	rare scattered	Greater R to TOB
S	S	S	S	R	R	APH(3')	common	Usually more R to KAN than NEO
S	S	S	R	R	R	APH(3')III	rare	Rare
r/R	r/R	R/R	r/R	r/R	r/R	'impermeability'	rare	Low-level to all aminoglycosides
E. faecalis								
R	R	R	R	R	R	Classical	common	Intrinsic low-level resistance
R	R	HLR	HLR	HLR	R	ANT(4')(4")I	rare	
HLR	R	HLR	R	HLR	R	APH(2")/AAC(6')	common	Greater R to GEN than TOB
R	R	R	R	HLR	HLR	APH(3')	common	Usually more R to Kan than NEO
R	R	R	HLR	HLR	HLR	APH(3')III	rare	Rare
E. faecium								
R	R	R	R	R	R	AAC(6')I	classical	Chromosomal AAC(6'), intrinsic to *E. faecium*
R	R	HLR	HLR	HLR	R	ANT(4')(4')	rare	
HLR	R	HLR	R	HLR	R	APH(2")/AAC(6')	common	Greater R to GEN than TOB
R	R	R	R	HLR	HLR	APH(3')	common	Usually greater R to KAN than NEO
R	R	R	HLR	HLR	HLR	APH(3')III	rare	

See note to all tables at foot of Table I and general notes and abbreviations for Tables V-XI at the foot of Table V.
HLR = high-level resistance in enterococci.

Table XI. Phenotypes; interpretation of mechanism and editing of antibiograms: MLS drugs versus Gram-positive bacteria

ERY[a]	CLI	Q-D	Interpretation	Frequency	Edit/action
Staphylococci					
S	S	S	classical	common	
R	S	S	May be MLS_B inducible may have macrolide efflux	common	Check if erythromycin antagonizes clindamycin; if antagonism seen, isolate have MLS_b and clindamycin should be used with caution (if at all)
R	R	S	MLS_B constitutive	common	Note specification of product characteristics recommendation that Q-D should be given thrice daily even in skin and soft tissue infection
any	any	R	!!!	refer	
Streptococci, including *S. pneumoniae*					
S	S	R	classical	common	
R	R	S	MLS_B constitutive/inducible	common	NB – inducible resistance usually affects clindamycin as well as erythromycin in streptococci
R	S	S	Efflux; MLS_B inducible	common	
any	Any	R	!!!	refer	
E. faecalis					
S	S	R	classical	common	
R	S	R	May be MLS_B inducible may have macrolide efflux	common	Check if erythromycin antagonizes clindamycin, e.g. with a double disc test. If antagonism is seen, the isolate have MLS_B and clindamycin should be used with caution (if at all)
R	R	R	MLS_B constitutive	common	
any	any	S	Probably mis-speciation		If also AMP resistant, almost certainly *E. faecium,* not *E. faecalis.* Refer if confirmed as *E. faecalis.*
E. faecium					
S	S	S	classical	common	
R	S	S	May be MLS_B inducible may have macrolide efflux	common	Check if erythromycin antagonizes clindamycin; if antagonism seen, isolate have MLS_b and clindamycin should be used with caution (if at all)
R	R	S	MLS_B constitutive	common	
any	any	R	Probable mis-speciation; possible quinupristin efflux or modification		If also AMP susceptible, almost certainly *E. faecalis,* not *E. faecium.* Refer if confirmed as *E. faecium.*

See note to all tables at foot of Table I and general notes and abbreviations for Tables V-XI at the foot of Table V.

[a]Other macrolides, e.g. clarithromycin and azithromycin behave similarly to erythromycin