ARHAI Scotland
Antimicrobial Resistance and Healthcare Associated Infection

NHS National Services Scotland

Reference laboratory referral guide for confirmation of unusual organism/antimicrobial resistance profiles

Version 2.0

June 2023

Version history

Version	Date	Summary of changes
V1.0	August 2019	First publication.
V2.0	June 2023	Changes to report format following transition from Health Protection Scotland to ARHAI Scotland. Change from "exceptional" to "unusual" phenotype and minor re-wording throughout for clarification. Organism specific changes to guide include: • Removal of pan-aminoglycoside resistance (local diagnostic laboratory confirmation only) for any *Enterobacterales* or *Acinetobacter* spp. • Removal of *Providencia* and *Proteus*, and addition of *Hafnia* spp. from colistin resistance referral criteria. • Addition of cefiderocol resistance and change of gradient MIC for temocillin from >128 to MIC ≥64 mg/L for referral of *Enterobacterales*. • Rewording of specimen type inclusion criteria, with addition of eye swabs for *Neisseria meningitidis*. • Addition of dalbavancin resistance and change to daptomycin MIC from >=8 mg/L to MIC >=4 mg/L for *Staphylococcus aureus* and coagulase-negative staphylococci. Clarification provided for reference laboratory service to use and that resistance to teicoplanin but not to vancomycin in coagulase-negative staphylococci should not be referred. • Removal of teicoplanin resistance for *Corynebacterium* spp. • Addition of levofloxacin resistance for *Streptococcus pneumoniae.*

Approvals

Version	Date Approved	Group/individual
V1.0	19/06/2019	Reference Laboratory Advisory Group
V2.0	07/06/2023	Reference Laboratory Operational Group

Reference laboratory referral guide for confirmation of unusual organism/antimicrobial resistance profiles

The following tables are linked to Appendix 13 (Table 6) of the Scottish National Infection Prevention & Control Manual. The tables identify unusual organism/antimicrobial resistance phenotypes requiring review by diagnostic microbiology laboratories in Scotland. Any unusual organism/antimicrobial combinations should be checked first to ensure microbiological accuracy in line with the latest EUCAST guidance. If confirmed, the isolates should be shared with the appropriate reference laboratory, as detailed below. Additionally, the local Infection prevention and control team (IPCT), health protection team (HPT) or antimicrobial management team (AMT) (as appropriate) need to be made aware of such results to ensure appropriate actions are put in place.

Table 1. Unusual resistance phenotypes of Gram-negative bacteria.

Organism(s)	Resistance phenotype detected by diagnostic laboratory	Should isolates be sent to a reference laboratory?	Test(s) to be provided by Reference lab service	Reference laboratory service to send isolates to
Any *Enterobacterales* (1)	Organisms above the ECOFF of 0.125mg/L should be considered as potential carbapenamase producers. If using VITEK for AST and meropenem MIC ≥ 0.5 mg/L, these isolates should be followed up by use of a gradient MIC test. If the MIC is confirmed as > 0.125 mg/L, then this should be sent to the reference laboratory. (EUCAST carbapenemase screening cut off is > 0.125 mg/L but VITEK calling range is ≤ 0.25 - ≥ 16 mg/L)	Yes	Inferred resistance mechanisms through expert review of reference laboratory antibiogram & screen for transmissible enzymes (if appropriate)	Scottish Microbiology Reference Laboratories (SMiRL), Glasgow
	Temocillin (MIC ≥ 32 mg/L) AND piperacillin/tazobactam resistance on VITEK. These isolates should be followed up by use of a gradient MIC test for temocillin and if the MIC is ≥64 mg/L, then this should be sent to the reference laboratory.			
	Resistance to ceftazidime-avibactam (2) or cefiderocol (2)			

Organism(s)	Resistance phenotype detected by diagnostic laboratory	Should isolates be sent to a reference laboratory?	Test(s) to be provided by Reference lab service	Reference laboratory service to send isolates to
Any *Enterobacterales* (except *Hafnia* spp., *Morganellaceae* & *Serratia marcescens*) (1)	Colistin resistance determined by commercial microbroth dilution method by local diagnostic laboratory (determination by use of VITEK, disc diffusion or gradient MIC test is not appropriate).	Yes - only isolates found to be resistant by commercial microbroth dilution testing by the local diagnostic laboratory	Screening for transmissible resistance (*MCR* genes by Whole Genome Sequencing (WGS)).	SMiRL, Glasgow
Any *Enterobacterales* (except *Proteus*, *Providencia* & *Morganella* spp.) (1)	High-level tigecycline resistance (MICs > 4 mg/L).	No - may be reviewed in the future	N/A	N/A
Acinetobacter spp. (1)	Colistin resistance (See *Enterobacterales* section).	See *Enterobacterales* section.	See *Enterobacterales* section.	SMiRL, Glasgow
	Resistance to meropenem or imipenem.	Yes	Inferred resistance mechanisms through expert review of reference laboratory antibiogram & screen for transmissible enzymes.	
Pseudomonas aeruginosa (1)	Ceftolozane-tazobactam (MIC ≥ 4 mg/L) resistance. (2)	Yes	Inferred resistance mechanisms through expert review of reference laboratory antibiogram & screen for transmissible enzymes.	SMiRL, Glasgow
	Meropenem/imipenem AND ceftazidime AND piperacillin/tazobactam resistance. If tested for ceftolozone/tazobactam and found to be sensitive does not require referral.	Yes		
	Colistin resistance (see *Enterobacterales* section).	Yes		
Other non-fermenters	Co-trimoxazole resistance.	Yes	Confirm resistance and provide alternative therapeutic options.	AMRHAI Reference Unit, Colindale, London

Organism(s)	Resistance phenotype detected by diagnostic laboratory	Should isolates be sent to a reference laboratory?	Test(s) to be provided by Reference lab service	Reference laboratory service to send isolates to
Salmonella and *Shigella* spp.	Every patient should have representative isolates submitted to the reference laboratory where follow up testing by WGS will be carried out.	Yes (susceptibility testing should be performed locally for clinical management)	Antimicrobial Susceptibility Testing (AST) as appropriate and WGS. Phenotypic AST will be conducted for all *Shigella* spp, *S.* Typhi, *S.* Paratyphi A, B and C and all invasive non-typhoidal salmonellae against ciprofloxacin and azithromycin using gradient MIC tests (future broth microdilution) and for ESBL and AmpC activity.	SMiRL, Glasgow
Haemophilus influenzae (Refer non-invasive isolates* Refer all invasive isolates regardless of susceptibility pattern)	* 3rd/4th/5th generation cephalosporin or carbapenem resistance.	Yes	AST and WGS as appropriate.	SMiRL, Glasgow
	Fluroquinolone resistance.	No - fluoroquinolone resistance should be locally confirmed by gradient MIC test	N/A	N/A
Moraxella catarrhalis	3rd /4th/5th generation cephalosporin, fluoroquinolone or carbapenem resistance	No - local confirmation only	N/A	N/A
Neisseria meningitidis	Isolates from invasive disease (sterile sites, eye swabs) as well as from throat swabs where meningococcal infection is clinically suspected/confirmed.	Yes	AST and WGS as appropriate.	SMiRL, Glasgow
Neisseria gonorrhoeae	All *N. gonorrhoeae* isolates should be submitted to the reference laboratory.	Yes	Confirmation and reference lab AST. Specifically to include resistance to spectinomycin, azithromycin and ceftriaxone in addition to other 3rd generation cephalosporins.	Scottish Bacterial Sexually Transmitted Infections Reference Laboratory (SBSTIRL), Edinburgh

Table 2. Unusual resistance phenotypes of Gram-positive bacteria.

Organism(s)	Resistance phenotype detected by diagnostic laboratory	Should isolates be sent to a reference laboratory?	Test(s) to be provided by Reference lab service	Reference laboratory service to send isolates to
Staphylococcus aureus [3]	Any resistance to ceftaroline [2], ceftobiprole [2], vancomycin, teicoplanin, telavancin [2], dalbavancin [2], daptomycin (MIC ≥4 mg/L) [4], linezolid, tedizolid [2], quinupristin-dalfopristin or tigecycline.	Yes	Confirmation of resistance. Molecular screening for linezolid or tedizolid resistance mechanisms where appropriate.	AMRHAI Reference Unit, Colindale, London
Coagulase-negative staphylococci	Any resistance to ceftaroline [2], ceftobiprole [2], vancomycin (but NOT teicoplanin alone), telavancin [2], dalbavancin [2], daptomycin (MIC ≥4mg/L) [4] linezolid, tedizolid [2], quinupristin-dalfopristin or tigecycline.	Yes - *S. epidermidis* isolates only. For other clinically significant CNS isolates; please discuss with the reference lab.	Confirmation of resistance. Molecular screening for linezolid or tedizolid resistance mechanisms where appropriate.	AMRHAI Reference Unit, Colindale, London
Corynebacterium spp.	Resistance to vancomycin or linezolid.	No - not for routine referral, local diagnostic lab confirmation only.	N/A	N/A
Streptococcus pneumoniae (Refer non-invasive isolates** Refer all invasive isolates regardless of susceptibility pattern).	**3rd generation cephalosporin resistant or intermediate isolates, or resistance to penicillin (MIC > 2 mg/L), vancomycin, teicoplanin, linezolid, levofloxacin or rifampicin.	Yes	AST, serotyping and genotyping.	SMiRL, Glasgow
	Fluoroquinolone resistance in respiratory isolates.	No - local confirmation only.	N/A	N/A
Group A streptococci (invasive/outbreak)	Refer all invasive or outbreak isolates regardless of susceptibility pattern. [5]	Yes	Molecular typing as appropriate.	SMiRL, Glasgow

Organism(s)	Resistance phenotype detected by diagnostic laboratory	Should isolates be sent to a reference laboratory?	Test(s) to be provided by Reference lab service	Reference laboratory service to send isolates to
Streptococci (Groups A, B, C and G, β-haemolytic)	Any resistance to penicillin, cephalosporin, vancomycin, teicoplanin, daptomycin, linezolid, tedizolid [2], dalbavancin [2], oritavancin [2] or tigecycline.	Yes	Confirmation of resistance. Molecular screening for linezolid or tedizolid resistance mechanisms where appropriate.	AMRHAI Reference Unit, Colindale, London
Enterococcus spp.	***E. faecalis:*** Ampicillin/amoxicillin or daptomycin (MIC > 2 mg/L) resistance.	Yes	Confirmation of resistance and further molecular confirmation as appropriate.	AMRHAI Reference Unit, Colindale, London
	E. faecium: Daptomycin (MIC > 4 mg/L) resistance.			
	All enterococci: Any resistance to tigecycline, linezolid or tedizolid [2]			

Table 3. Unusual resistance phenotypes of anaerobic bacteria.

Organism(s)	Resistance phenotype detected by diagnostic laboratory	Should isolates be sent to a reference laboratory?	Test(s) to be provided by Reference lab service	Reference laboratory service to send isolates to
Anaerobic bacteria [6]	Resistance to metronidazole (or resistance to other agents, as appropriate).	Yes	Confirmation of resistance.	UK Anaerobe Reference Unit (UKARU), Cardiff
Clostridioides difficile	Resistance to metronidazole or vancomycin.	Yes	Confirmation of resistance.	SMiRL, Glasgow

Table 4. Unusual resistance phenotypes of *Candida* species and *Aspergillus fumigatus*.

Organism(s)	Resistance phenotype detected by diagnostic laboratory	Should isolates be sent to a reference laboratory?	Test(s) to be provided by Reference laboratory service	Reference laboratory service to send isolates to
Candida species	Amphotericin B or echinocandin resistance.	Yes	Confirmation of resistance.	Mycology Reference Laboratory (MRL), Bristol
Candida albicans	Azole resistance in invasive isolates.	Yes	Confirmation of resistance.	Mycology Reference Laboratory (MRL), Bristol
Aspergillus fumigatus	Amphotericin B, echinocandin or azole resistance.	Yes	Confirmation of resistance.	Mycology Reference Laboratory (MRL), Bristol

Notes

(1) It is noted that some diagnostic laboratories will be introducing BMD testing for multi-drug resistant Gram negatives, which therefore would reduce the need for referral of those particular isolates to the Scottish Microbiology Reference Laboratories (SMiRL), Glasgow.

(2) Although not currently routinely tested by diagnostic laboratories, occasionally these may be tested in unusually resistant isolates/antibiotic allergic patients. EUCAST break-points may not be available.

(3) Please also submit any potential BORSA isolates, as identified by local methods, for Reference Laboratory confirmation.

(4) EUCAST state that staphylococci with an MIC > 1 mg/L are considered to be resistant to daptomycin. The SMiRL have advised that only isolates with an MIC ≥ 4 mg/L should be referred. This will be kept under review.

(5) The following Group A streptococcal isolates should be forwarded to the reference laboratory for typing;

a. All isolates from normally sterile body sites (such as blood, CSF, joint aspirate, pericardial/peritoneal/pleural fluids, bone, endometrium, deep tissue or abscess at operation or post mortem).
b. Isolates from normally non-sterile sites in combination with a severe clinical presentation, such as streptococcal toxic shock syndrome (STSS) or necrotising fasciitis.
c. On identification of a suspected or confirmed GAS outbreak (1) in acute health care or maternity setting (2) the reference laboratory should be informed and isolates sent for typing

(6) As a minimum, it is suggested that all strict anaerobes isolated from blood cultures or those from any other site associated with apparent antimicrobial treatment failure, should be tested for metronidazole susceptibility (and other agents, as appropriate) and where resistance is detected, isolates should be referred to the reference laboratory N.B some anaerobes are intrinsically resistant to metronidazole e.g. *Actinomyces* spp.