

Standardisation of Cystic Fibrosis Microbiology Testing In Scotland

6 July 2023

NOTE

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined based on all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

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1. Background

Within Scotland there are five Specialist Cystic fibrosis (CF) Centres based in Glasgow, Edinburgh, Aberdeen, Dundee and Inverness. Scottish CF microbiology is therefore largely carried out in the five laboratories associated with these centres, although testing is also carried out in laboratories associated with smaller CF units.

Infection of the airways remains the primary cause of morbidity and mortality in persons with CF, resulting in this patient group having a life-long association with the microbiology laboratory. To deliver optimum care to those with CF, the long term picture of an individual's lung microbiology is important and it is recognised that this may be delivered by different centres, units and microbiology laboratories as the individual grows up.

CF microbiology is recognised as complex and challenging and the basic service delivered has historically been highly variable within Scotland. In accordance with the aims of all national clinical and managed diagnostic networks, it is the aim of the SMVN to deliver a service that is consistent and equitable across Scotland and which is focused on the patient. The first CF laboratory guidelines were developed in 2015 after the Paediatric CF network specifically requested that the SMVN agree to deliver a consistent basic Microbiology service across Scotland to support standardised delivery of care.

1.1 Standardisation of Cystic Fibrosis Microbiology Testing in Scotland: 3rd edition.

The CF Trust Laboratory guidelines were first published in 2010 and it was only in late 2022 that they were updated. In the intervening period there has been a notable improvement in microbial identification with the advent of MALDI-TOF and on the therapeutic side the new modulators are making a huge impact on clinical progression. The CF Microbiology sub-group of the SMVN was reconvened in 2022 and includes not only laboratory staff but also CF physicians and public health representation.

2. General considerations and sample preparation

- 2.1 Safety considerations and specimen storage should be in line with accredited standards for processing respiratory specimens in a routine Clinical Microbiology laboratory.¹
- 2.2 Sample preparation^{1,2}
 - 2.2.1 The following respiratory samples should be accepted for microbiological testing: cough swab, cough plate, oropharyngeal culture, laryngeal or naso-pharyngeal aspirate, expectorated sputum, induced sputum following hypertonic saline, bronchoalveolar lavage and bronchoscopy brush specimens. It should be borne in mind that pathogen yields

vary depending on the sample –bronchoscopy and induced sputum samples are best, then sputum, with cough swabs yielding the least.

- 2.2.2 Specimens should not be rejected based on macroscopic appearance.
- 2.2.3 Gram staining is not recommended. If mycobacterial testing of a sputum sample is requested, a relevant fluorochrome staining method should be used in line with the TB Action Plan for Scotland.
- 2.2.4 Use of a mucolytic agent is recommended.

3. Direct molecular detection

Direct PCR methods have been shown to be quicker and more sensitive than conventional culture methods, however the clinical benefit has not so far been demonstrated. It is acknowledged that there is little availability of direct molecular testing in Scotland. This area will be reviewed in an ongoing basis and the guidelines updated as and when appropriate.

4. Sample culture

Recommended culture media and conditions for respiratory samples from individuals with CF may be found in Table 1

Table 1 Recommended culture media and conditions for respiratory samples from individuals with CF

Target organism	Medium	Incubation conditions			Examination of plates
		Temperature (°C)	Atmosphere	Time (hr)	
<i>S. aureus</i>	Selective agar (Mannitol salt agar / CHROMagar)	35 - 37	Air	40 - 48	Daily
<i>S. pneumoniae</i> , <i>M. catarrhalis</i>	Chocolate agar or blood agar (with optochin disc for <i>S. pneumoniae</i>)	35 – 37	Chocolate: Air Blood: 5-10% CO ₂	40 - 48	Daily
<i>H. influenzae</i>	Selective agar. Eg. Chocolate agar with bacitracin / cefsulodin	35 - 37	Anaerobic or CO ₂	40 - 48	Daily
<i>P. aeruginosa</i>	CLED, MacConkey or selective agar	35 - 37	Air	40 - 48 Growth should be visible within 24hr but confirmation of mucoid <i>P. aeruginosa</i> may require 48hr	Daily
<i>B. cepacia</i> spp.	<i>B. cepacia</i> selective agar	35 - 37	Air	5 days	Daily
<i>S. maltophilia</i> , Differentiate LF from NLF	CLED, MacConkey	35 - 37	Air	40 - 48	Daily
Fungi	Sabouraud medium (with antibiotics)	35 – 37	Air	7days The use of high-volume sputum samples (≥100µl) increases the detection rate of moulds; the use of undiluted sample may potentially increase the yield	Daily

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Mycobacteria	Culture should be performed using both an automated liquid culture system and a solid medium in line with TB Action Plan for Scotland. The use of selective rapidly growing mycobacteria (RGM) agar can be considered as an adjunct- direct inoculation (without decontamination) to recover <i>M. abscessus</i> when incubated at 30°C for 21–28 days.
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5. Organism identification

While some organisms such as *Staph aureus*, *Strep pneumoniae*, *Haemophilus sp*, *Moraxella sp*, Fungi, and Enterobacteriaceae can reliably be identified following standard procedures as used for non –CF specimen processing, the non-fermenting gram negatives pose a specific challenge for species level identification due to their varied phenotypes, rare isolation in other settings and the occurrence of numerous closely related species.

As the correct identification is vital for infection control policies, treatment and eradication attempts it is important to ensure accurate exclusion of *Burkholderia cepacia* complex (BCC) and *Pseudomonas aeruginosa* (PA), as well as confirmation to genus level ID of other non-fermenters which have an increasingly recognised role in chronic biofilm infections and exacerbations such as *Achromobacter*, *Stenotrophomonas* and *Inquilinus*.

While MALDI –TOF technology has transformed the rapidity, cost and accuracy of bacterial identification there are still some difficulties with non-fermenters and this varies depending on the platform being used and the genus.⁴⁻⁹ Note that laboratories without MALDI-TOF should forward any CF non-fermenting gram negatives to a laboratory with this facility.

5.1 *Pseudomonas aeruginosa*

While Bruker and VITEK MS have been demonstrated to correctly identify *P. aeruginosa* with scores >2.2, non *P. aeruginosa*, *Pseudomonas* species can be incorrectly identified as *P. aeruginosa* (eg *P. nitroreducens* on VITEK MS – GGC experience). Therefore for a first isolate it is important to confirm the ID with another method, and not report as a final ID unless the phenotype is classic green pigmented spreading colony and a high certainty score on a MALDI platform. The confirmation can come from typing or (if available) a species specific PCR.

5.2 *Burkholderia cepacia* complex

Despite use of adjunctive steps for Bruker analysis with ethanol and formalin, the Bruker has been found to be reliable for only *B. multivorans* species level identification. While Bruker and VITEK has found to give 26% and 67% correct species and 100% and 97% genus level ID, recA PCR remains an accurate method for confirming BCC currently. Some species will not ID by any of these methods to species level and new isolates may require WGS level identification.

Building up of the local database for the MALDI platform can over time increase accuracy of the ID for the rarer non fermenters.

5.3 Non-tuberculous mycobacteria

Rapid identification of NTM species is helpful for infection control purposes and the combination of NTM agar with MALDI ID can expedite the process by a number of weeks and is recommended following in house validation.¹⁰

5.4 Typing

The importance of typing is as a final confirmation of identification and infection control strategies for both PA and BCC, and is critical for treatment options such as ET-12 lineage of *B. cenocepacia* being a contraindication for lung transplant. First isolates should be sent for typing as well as on transition from paediatric to adult services and if local epidemiology indicates the possibility of new strains circulating -see Section 7 (Isolates to be sent to Reference laboratories).

Table 2 Identification methods and reporting

Target Organism	Level of ID	Method	Confirmation	Typing	Reporting
<i>B. cepacia</i> complex	Species level 1 st isolate	MALDI	First isolate Reference lab (or local recA PCR) or recurrence post 12 months not isolated Thereafter phenotypic ID based on antibiogram	First isolate, and clinical indication of possible new strain Ref lab WGS speciation. For isolates failing to give species with MLST/recA	Presence always reported First isolate interim report pending final confirmation ID
<i>S. maltophilia</i>	Genus level	MALDI		First isolate as required locally	Presence always reported
Enterobacterales	Species level	VITEK/MALDI			Report “Doubtful significance” Unless clinically indicated eg exacerbation with repeated heavy growth single organism
Fungi	Species level	Microscopy and culture appearances (Aspergillus)	First isolate Ref lab for non-Aspergillus	N/A unless specific situation warrants	Report if present
<i>H. influenzae</i>	Species level	VITEK/MALDI			Report if present
<i>M. catarrhalis</i>	Species level	VITEK/MALDI			Report if heavy growth

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<i>Pseudomonads. E.g. Chryseobacterium, Ochrobactum, Sphingimonas, Inquilinus, Achomobacter, Ralstonia, Pandoraea, Elizabethkingia</i>	Genus level	MALDI	First isolate Reference lab if clinically relevant (local recA PCR to exclude BCC if available)	If Local concerns warrant	Presence always reported Interim report pending confirmation
<i>P. aeruginosa</i>	Mucoid or non-mucoid species level	MALDI	First isolate Reference lab (or local species specific PCR)	First isolate and on clinical request	Presence always reported. Interim report unless classic phenotype and high certainty ID Final report with confirmatory typing or PCR
<i>S. aureus</i>	Species level	VITEK/MALDI		MRSA to ref lab	Always report presence
<i>S. pneumoniae</i>	Species level	VITEK			Always report presence
Yeasts	"Yeasts" level Exophiala to species level	MALDI			Report Exophiala when present Report as "yeasts present"
<i>Mycobacterium</i>	Species level	MALDI if locally validated (recommended)	TB ref lab for WGS ID confirmation	First isolate TB Ref lab typing and sub-speciation	Always Report presence

6. Antibiotic susceptibility testing (AST)

General AST

The SMVN has a long established sub group which has addressed standardisation of AST methods across Scotland. This includes standardisation of AST on CF pathogens. General recommendations are summarised as follows:

- 6.1 Where possible, AST should be carried out on the Vitek 2 system, using EUCAST breakpoints and if these are not available CLSI.
- 6.2 If the Vitek 2 is not capable of performing AST for specific organisms alternative methods as per Tables 4 to 7 should be used.

CF pathogens (general)

- 6.3 As for identification tests³, AST should be performed from non-selective agar
- 6.4 AST of *S. aureus* and *S. pneumoniae* should be carried out on the Vitek 2. It is noted that some *S. pneumoniae* isolated from CF samples do not perform well in the Vitek 2 and these should be tested using disc diffusion.
- 6.5 Currently, automated AST (eg on the Vitek 2) is not recommended for glucose non-fermenting Gram negative bacilli (including *P. aeruginosa*) isolated from the respiratory tract of individuals with CF. Table 4 to 7 provide details of all the methodology and interpretive breakpoint (BP) criteria applicable for each pathogen group (there is no suggestion that all combinations are tested). All EUCAST and CLSI information is accurate according to the latest guidelines (as at May 2023) but laboratories should keep up to date with new versions.
 - 6.5.1 **DISC DIFFUSION:** Report S/R/I (“susceptible, increased exposure”) only antibiotics for which approved methods / interpretive criteria exist.
 - 6.5.2 **MIC:** Report S/R/I (“susceptible, increased exposure”) for antibiotics for which approved methods / interpretive criteria exist.
- 6.6 For glucose non-fermenting Gram negative bacilli the antibiotics in Table 3 should be tested. A locally-agreed first line battery should be tested and if fully sensitive then testing of the second line battery of antibiotic is not required.

In case of a patient in whom there is recurrent isolation of a Gram negative bacillus there is not a requirement for antibiotic susceptibility testing on every occasion the organism is isolated if there is no clinical exacerbation. In this scenario susceptibilities should ideally be carried out every 3 months and at a minimum every 6 months. Another approach in this scenario which could be agreed with local CF physicians is to save isolates for at least 7 days and carry out susceptibility testing only if contacted by the clinical team.

- 6.7 Samples should be checked annually for non-tuberculous mycobacteria (NTM). Mycobacterial AST should be carried out at the TB Reference Laboratory.
- 6.8 For fungi, the CF Trust has recommendations for cases of repeated isolation of *Aspergillus* spp. In spite of long-term treatment with antifungals, there may be a need for referral to a Reference laboratory, such as UKHSA Mycology Reference laboratory, Bristol.

Table 3 CF Antibiotics overview

Antibiotic	<i>P. aeruginosa</i> / spp		<i>B. cepacia</i> complex		<i>S. maltophilia</i>		Other non-fermenting Gram negative bacilli	
	Disc diff	MIC	Disc diff	MIC	Disc diff	MIC	Disc diff	MIC
Ciprofloxacin	I / R	I / R						S / I / R
Levofloxacin	I / R	I / R		S / I / R	S / I / R	S / I / R		S / I / R
Doxycycline								S / I / R
Minocycline			S / I / R	S / I / R	S / I / R	S / I / R		S / I / R
Trimethoprim-sulphamethoxazole			S / I / R	S / R	I / R	I / R		S / R
Chloramphenicol				S / I / R		S / I / R		S / I / R
Ceftazidime	I / R	I / R	S / I / R	S / I / R		S / I / R		S / I / R
Aztreonam	I / R	I / R						S / I / R
Piperacillin-Tazobactam	I / R	I / R						S / I / R
Meropenem	S / I / R	S / I / R	S / I / R	S / I / R				S / I / R
Tobramycin	S / R	S / R						
Gentamicin	S / R	S / R						
Colistin		S / R						
Fosfomycin		*						
Ceftolozane / tazobactam	S / R	S / R						
Ceftazidime/avibactam	S / R	S / R						
Cefiderocol	S / R	S / R			S / R	S / I / R		
Amikacin	S / R	S / R						S / I / R

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Greyed out- If both Disc diff and MIC columns then antibiotic unsuitable for treatment of infections caused by this organism or group.
If only Disc diff then zone diameter breakpoints not available.

*Agar dilution is the reference method for fosfomycin, only ECOFF available- see below.

Table 4 *Pseudomonas aeruginosa*^A
***Pseudomonas* species^B**

Antimicrobial	Testing guideline	Testing method	Disc content	Zone diameter BPs (mm)		MIC BPs (mg/L)	
			(µg)	S ≥	R <	S ≤	R >
Ciprofloxacin	EUCAST	Disc	5	50	26	0.001	0.5
Levofloxacin	EUCAST	Disc	5	50	18	0.001	2
Ceftazidime	EUCAST	Disc	10	50	17	0.001	8
Aztreonam	EUCAST	Disc	30	50	18	0.001	16
Piperacillin-Tazobactam	EUCAST	Disc	30-6	50	18	0.001	16 ¹
Meropenem	EUCAST	Disc	10	20 ^A /24 ^B	14 ^A /18 ^B	2	8
Tobramycin	EUCAST	Disc	10	18 ²	18 ²	2 ²	2 ²
Gentamicin	CLSI	Disc	10	15	(≤)12	4	(≥)16
Colistin	EUCAST	Broth microdilution	N/A	-	-	4	4
Fosfomycin	EUCAST	Agar dilution	N/A	-	-	256 ³	256 ³
Ceftolozane / tam ^A	EUCAST	Disc	30-10	23	23	4 ¹	4 ¹
Ceftazidime/avibactam ^A	EUCAST	Disc	10-4	17	17	8 ⁴	8 ⁴
Cefiderocol ^A	EUCAST	Disc	30	22	22	2 ⁵	2 ⁵
Amikacin	EUCAST	Disc	30	15	15	16	16

¹ For susceptibility testing purposes, the concentration of Tazobactam is fixed at 4 mg/L

² For systemic infections, aminoglycosides should be used in combination with other active therapy

³ ECOFF is 256 mg/L

⁴ For susceptibility testing purposes, the concentration of avibactam is fixed at 4 mg/L

⁵ Broth micro dilution MIC determination must be performed in iron-depleted Mueller-Hinton broth and specific reading instructions must be followed –see EUCAST guidance documents

Table 5 Burkholderia cepacia complex

Antimicrobial	Testing guideline	Testing method	Disc content	Zone diameter BPs (mm)		MIC BPs (mg/L)	
			(µg)	S ≥	R ≤	S ≤	R ≥
Levofloxacin	CLSI	Gradient strip MIC	N/A	-	-	2	8
Minocycline	CLSI	Disc	30	19	14	4	16
Trimethoprim-sulphamethoxazole	CLSI	Disc	1.25 - 23.75	16	10	2-38	4 - 76
Chloramphenicol	CLSI	Gradient strip MIC	N/A	-	-	8	32
Ceftazidime	CLSI	Disc	30	21	17	8	32
Meropenem	CLSI	Disc	10	20	15	4	16

Table 6 *Stenotrophomonas maltophilia*

Antimicrobial	Testing guideline	Testing method	Disc content	Zone diameter BPs (mm)		MIC BPs (mg/L)	
			(µg)	S ≥	R ≤	S ≤	R ≥
Levofloxacin	CLSI	Disc	5	17	13	2	8
Minocycline	CLSI	Disc	30	19	14	4	16
Trimethoprim-sulphamethoxazole	EUCAST	Disc	1.25 - 23.75	50	16	0.001	4
Chloramphenicol	CLSI	Gradient strip MIC	N/A	-	-	8	32
Ceftazidime	CLSI	Gradient strip MIC	N/A	-	-	8	32
Cefiderocol	EUCAST/CLSI	Disc	30	20 ¹	<20	8 ²	32 ²

¹ Zone diameter of ≥20mm corresponds to MIC values below the PK-PD breakpoint of 2 mg/L (EUCAST)

² Broth microdilution MIC determination must be performed in iron-depleted Mueller-Hinton broth and specific reading instructions must be followed –see EUCAST guidance documents. Note the CLSI breakpoints differ from EUCAST

Table 7 Other non-fermenting Gram negative bacilli**Excludes** *P. aeruginosa*, *Acinetobacter* spp., *B. cepacia* complex and *S. maltophilia*.

Antimicrobial	Testing guideline	Testing method	MIC BPs (mg/L)	
			S ≤	R ≥
Ciprofloxacin	CLSI	Gradient MIC	1	4
Levofloxacin	CLSI	MIC	2	8
Doxycycline	CLSI	MIC	4	16
Minocycline	CLSI	MIC	4	16
Trimethoprim-sulphamethoxazole	CLSI	MIC	2 - 38	4 - 76
Chloramphenicol	CLSI	MIC	8	32
Ceftazidime	CLSI	MIC	8	32
Aztreonam	CLSI	MIC	8	32
Piperacillin-Tazobactam	CLSI	MIC	16 - 4	128 - 4
Meropenem	CLSI	MIC	4	16
Tobramycin	CLSI	MIC	4	16
Gentamicin	CLSI	MIC	4	16
Amikacin	CLSI	MIC	16	64

7. Isolates to be sent to Reference Laboratories

See also Table 2 for details of when isolates require to be sent to Reference laboratories.

- 7.1 *P. aeruginosa* are sent for typing (and confirmation of ID if needed) to the AMRHA Reference Laboratory, UKHSA, Colindale. Use referral form H2 for single isolates, H1 for multiple isolates.
- 7.2 *B. cepacia* complex should be sent to the AMRHA Reference Laboratory, UKHSA, Colindale for confirmation of ID and genotyping. Use referral form H2 for single isolates, H1 for multiple isolates.
- 7.3 Other non-fermenter Gram negatives are sent for identification to the AMRHA Reference Laboratory, UKHSA, Colindale. Use referral form H2 for single isolates, H1 for multiple isolates.
- 7.4 Apart from first isolates, those with a change in antibiogram, clinical deterioration, multi-resistance and/or thought to be associated with cross-transmission should be sent to the appropriate Reference Laboratory for typing. Clinicians should be alerted of any common genotypes between patients as this may indicate infection prevention and control issues which will require active management.
- 7.5 MRSA should be sent to the Scottish Microbiology Reference Laboratory (SMiRL).
- 7.6 Mycobacteria should be sent to the Scottish Mycobacteria Reference Laboratory.
- 7.7 Currently the Service level agreement between Public Health Scotland and UKHSA, covering the referral of isolates from Scottish laboratories includes;
 - a) Confirmation of identification of *B.cepacia* and molecular typing
 - b) Identification/typing/AST of CF pathogens where there is an incident/outbreak or management of difficult cases
- 7.8 If whole genome sequencing is required the Public Health Scotland Pathogen Genomics Oversight Group should be contacted

8. Cystic fibrosis antibiotic susceptibility testing service (CFASS)

CFASS is a specialist laboratory funded by NSD for adults with CF and is currently hosted by NHS Grampian, located in Medical Microbiology at Aberdeen Royal Infirmary and provides synergy testing. Paediatric isolates may be sent to the service but a charge will be incurred.

Isolates of non-fermenter Gram negative organisms may be sent if:

- 8.1 There are problems locally with identifying suitable treatment regimens due to e.g. the isolate being multidrug-resistant, the individual has allergies to or is intolerant of antimicrobials

- 8.2 When it is deemed clinically necessary e.g. the individual is not responding to the antimicrobial therapy or their clinical picture significantly worse than would be expected with available bacteriology.

9. Public Health Reporting

All isolates of *Mycobacterium tuberculosis* complex must be reported. The Public Health (Scotland) Act 2008 and subsequent amendments includes the full list of notifiable infections.

10. Exceptional resistance phenotype reporting

See Table 6 in Appendix 13 of the National Infection Prevention and Control Manual (NIPCM) for the list of resistant organisms (unusual phenotypes) reported to ARHAI Scotland.

11. References

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