Policy

Testing for Carbapenemase-producing Enterobacteriales (CPE)

NSWHP_PD_020

1. Purpose

To outline the policy for the screening for, and the detection, confirmation and whole genome sequencing (WGS) of carbapenemase-producing Enterobacteriales (CPE).

2. Background

NSW Health has prioritised surveillance for and clinical response to the presence of CPE in NSW public hospitals and the community.

CPE organisms are notifiable in NSW with a requirement for detailed epidemiological study and transmission analysis using whole genome sequencing (WGS).

This policy is based on:

a) National Alert System for Critical Antimicrobial Resistances (CARAlert) Laboratory Handbook (Section 2.1) (ACSQHC, February 2016)

b) Recommendations for the control of carbapenemase-producing Enterobacteriaceae (CPE) A guide for acute care health facilities (Chapter 5), (ACSQHS, May 2017) and

c) European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations.

3. Scope

This policy is mandatory and applies to all staff involved in CPE testing and reporting.

4. Definitions

N/A

5. Policy Statement

5.1. Characteristics

There are at least six types of CPE described in Australia. The 2018 CARAlert report indicates the most commonly referred CPE gene types are:

- IMP (60%)
- NDM (23%)
- KPC (5%)
- OXA-48 like (12%).

5.2. Testing

Clinical samples taken for suspected infection should be processed in accordance with standard methods.

Screening for CPE colonisation is more problematic because not all CPEs are reliably detected by screening methods including those that employ meropenem or cefpodoxime minimum inhibitory concentration (MIC) breakpoints that infer susceptibility or resistance to screen for these organisms.

Screening for CPE must employ a meropenem concentration below the MIC breakpoint that infers susceptibility and not the concentration designated as the breakpoint. This is because:

a) CPEs are not always associated with high meropenem MICs and some, for example those carrying OXA-48-like enzymes, hydrolyse carbapenems inefficiently.

b) Isolates of this phenotype generally do not hydrolyse broad spectrum cephalosporins. Hence, ESBL-Chromogenic agar (incorporating cefpodoxime) will not detect OXA-48/181 type gene products reliably.

Screening for OXA-type CPEs should incorporate temocillin in addition to meropenem into the basal assay, and as above, employ a meropenem concentration below the MIC breakpoint for susceptibility.

5.3. Clinical Specimens for Screening for CPE Colonisation

Screening for colonisation may be performed on any of the following:

a) Rectal swabs with evidence of faecal matter

b) Endotracheal tube aspirates

c) Wound swabs

d) Other sites where there is suspicion of active infection.

If a single site is to be used, rectal swabs are the preferred sample for screening.

5.4. Screening for CPE

If meropenem is not routinely tested, for example disc testing of urine isolates, susceptibility testing for gentamicin and amikacin, and third generation cephalosporins should be considered, for example, urine disc testing.

Examples of antimicrobial susceptibility results that raise the question of CPE are in Table 1.

TABLE 1: Triggers to Consider Testing

Example Test System	Trigger
Automated systems	
Vitek-2; BD Phoenix (BD)	Meropenem MIC >/= 0.25 mg/L#
Disc methods	
CDS	5 µg meropenem disc, annular radius <6 mm
EUCAST	10 µg meropenem disc, zone diameter <28mm
In-house multi-resistant Gram negative agar with added discs	Mueller-Hinton agar with vancomycin plus ampicillin (4 mg/L) with four added discs*: MEM 10 µg (<28mm ~ CPE) TEM 30 µg (<11mm ~ OXA-type) CTX 5 µg (<21mm ~ ESBL, AmpC, CPE) FOX 30 µg (<19mm ~ AmpC, metalloenzymes)

*MEM, meropenem; TEM, temocillin; CTX, cefotaxime; FOX, cefoxitin; metalloenzymes, Ambler class B β-lactamases such as IMP, NDM, VIM enzymes (not KPC or OXA alone). #Not 1 mg/L which is the breakpoint MIC inferring susceptibility.

5.5. Confirmation of CPE

Where laboratories do not perform tests to confirm the presence of CPE, the Supervising Pathologist must refer isolates suspected to be CPE to a NSW Health Pathology Laboratory with the capacity to confirm isolates as CPE.

A variety of phenotypic methods are available but vary in their performance characteristics with occasional false negative results and significant intra- and inter- laboratory variation.

Confirmation by multiplex nucleic acid amplification tests (NAAT) are reliable and identify the gene encoding the CPE phenotype but may also miss a percentage of phenotypes that are not targeted.

Recommended approaches, depending on the screening method (MIC or disc diffusion testing), are:

5.6 Laboratory Algorithms for Screening for and Confirmation of CPE

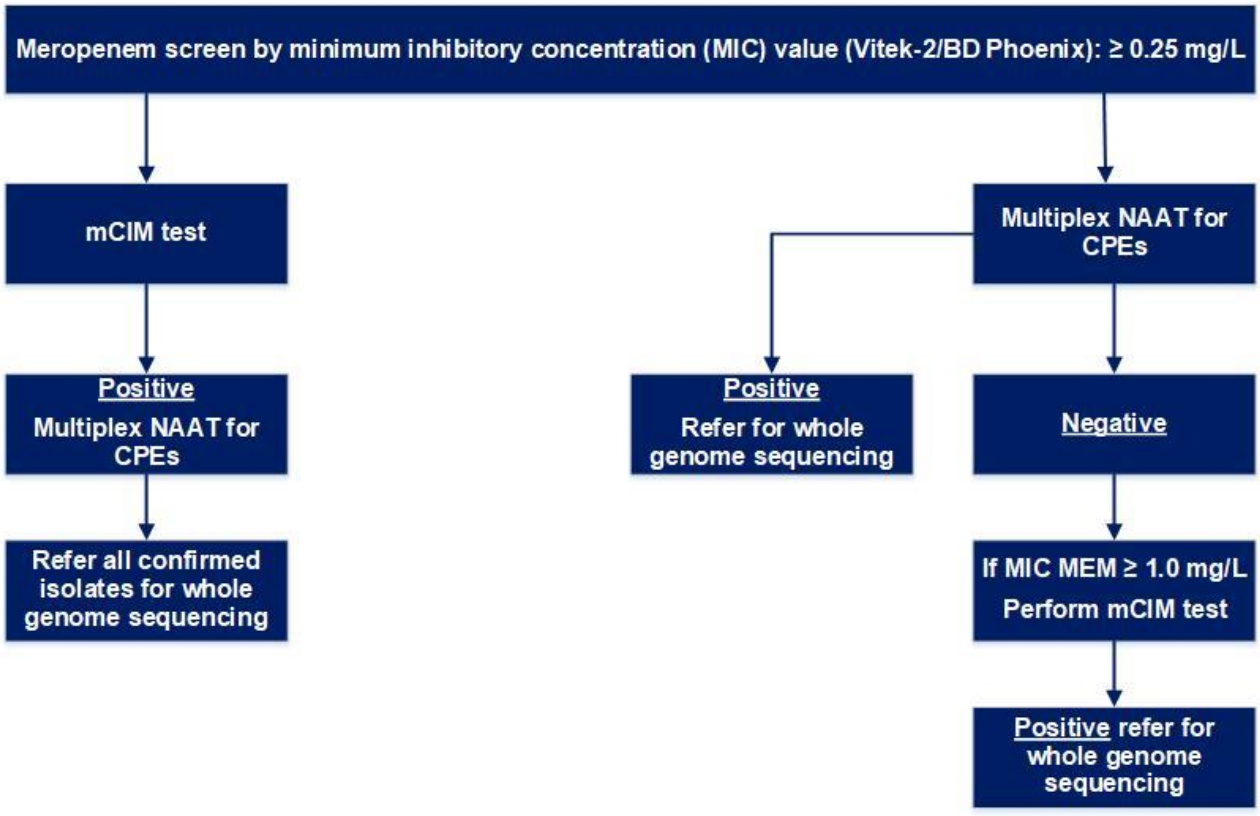
5.6.1 Screening for and Confirming the Presence of CPE: Screening by MIC Measurement

Figure 1 summarises where the MIC to meropenem is used as a screen (at 0.25 mg/L). Laboratories may choose to:

a) Use the CIM test or modified CIM test (mCIM) and then test CIM-positive isolates for the presence of carbapenemase-encoding genes by multiplex NAAT as a confirmatory test or

b) Proceed to multiplex NAAT directly. Should the NAAT yield a negative result but, for example, if the meropenem MIC is ≥1 mg/L, then the mCIM may be employed as a check.

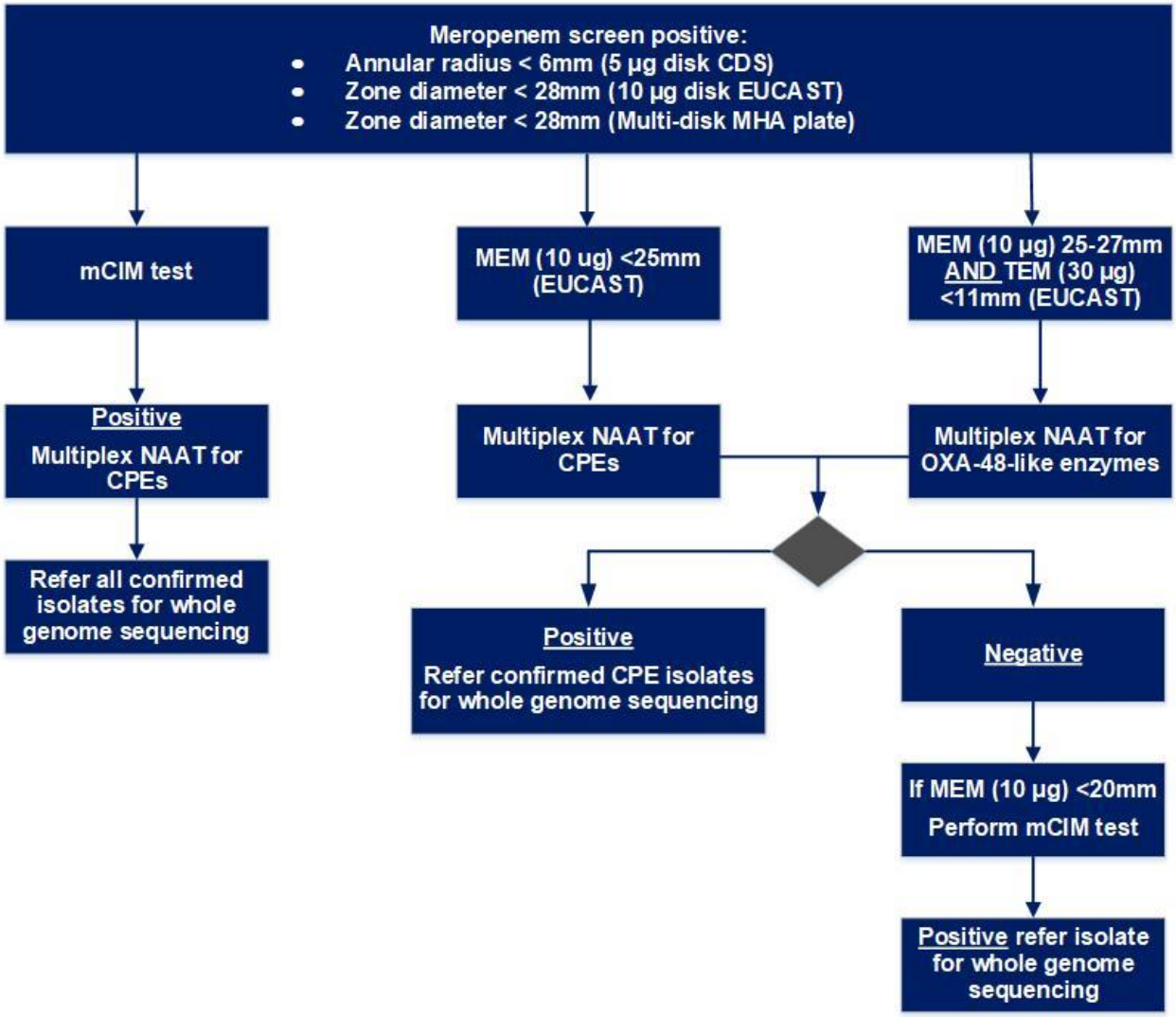
Figure 1



5.6.2 Screening for, and Confirming the Presence of, CPE: Screening by Disc Diffusion (Dotted Line Indicates Recommendation)

Figure 2 summarises the steps where disc methodology employing meropenem is used to screen for CPE. Disc diffusion employing temocillin has added value. Multiplex NAAT can then confirm the presence of a CPE with or without a prior mCIM test.

Figure 2



5.6.3 NAAT Platforms

NSW Health Pathology recommends a harmonised approach to confirmatory testing using NAAT.

A first-tier multiplex NAAT may be considered for IMP, VIM, NDM, KPC, OXA-48 like genes.

In general, turn-around-times for a confirmatory test should not exceed 72 hours.

Laboratories using various platforms for CPE NAAT should be aware of any limitations and employ the latest or most appropriate software for this purpose.

5.6.4 Expanded NAAT Testing

Expanded NAAT testing is recommended for:

a) Discrepant screening/confirmatory test results or where a result is inconclusive

b) Isolates with significantly raised MIC to meropenem, particularly E. coli, where the CIM test does not conclusively identify an alternate mechanism.

5.7 Reporting

The Supervising Pathologist(s) at a laboratory that does not perform tests to confirm the presence of CPE must refer isolates suspected to be CPE in a timely manner to a NSW Health Pathology Laboratory with the capacity to perform confirmation of CPE.

The Supervising Pathologist or Clinical Director who performs confirmatory tests for CPE must:

a) Report the presence of a confirmed CPE to the NSW Ministry of Health within 48 hours in a timely manner and

b) Refer CPE isolates also in a timely manner to the NSW Health Pathology Institute for Clinical Pathology and Medical Research (ICPMR) for WGS analysis.

The Supervising Pathologist(s) at ICPMR must report the results of WGS analysis to the NSW Ministry of Health using an agreed reporting method.

5.8 Evaluation

The Director of Public Health Pathology and Microbiology Clinical Stream, with the NSW Ministry of Health, will evaluate the utility of WGS of CPE after a 12-month period.

6. Roles and Responsibilities

6.1. Supervising Pathologist/Clinical Director

It is the responsibility of the Supervising Pathologist/Clinical Director to:

a) Report the presence of a confirmed CPE to the NSW Ministry of Health within 48 hours

b) Refer to the ICPMR all confirmed isolates of CPE isolates in a timely manner for WGS analysis with an agreed reporting method.

6.2. Director Public Health Pathology

It is the responsibility of the Director Public Health Pathology to:

a) Evaluate the CPE screening and utility of WGS of CPE in consultation with the Microbial Genomics Reference Laboratory, NSW Ministry of Health, Microbiology Clinical Stream and NSW Ministry of Health, after a 12-month period.

6.3. Lead, Microbiology Clinical Stream

It is the responsibility of the Lead, Microbiology Clinical Stream to:

a) Review this policy after a 12-month period, in consultation with the Director Public Health Pathology and the NSW Ministry of Health

b) Contribute to the evaluation of CPE screening and utility of WGS of CPE.

6.4. Scientific Staff

It is the responsibility of scientific staff to:

a) Comply with this policy

b) Consult with their Supervising Pathologists and refer isolates for confirmatory testing for CPE where CPE is suspected and refer isolates in a timely fashion to the ICPMR for WGS analysis.

7. Legal and Policy Framework

a) National Alert System for Critical Antimicrobial Resistances (CARAlert) Laboratory Handbook (Section 2.1) (ACSQHC, February 2016)

b) Recommendations for the control of carbapenemase-producing Enterobacteriaceae (CPE) A guide for acute care health facilities (Chapter 5), (ACSQHS, May 2017)

c) European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations

8. Notes

- Isolates that are resistant to gentamicin and amikacin may have a 16S methylase (associated with NDM and OXA type CPEs); high-level resistance is a good clue to this.
- Isolates that are resistant to amikacin and/or third generation cephalosporins (3GC) should be tested for reduced meropenem susceptibility: e.g. gentamicin resistant IMP isolates may be amikacin susceptible and amikacin-resistant KPC isolates may be gentamicin susceptible, and both may have meropenem MICs ≤ 0.5 mg/L.
- Isolate with OXA-type CPEs (for example OXA-48, 181) may be susceptible to 3GC and meropenem at standard clinical susceptibility breakpoints, and a temocillin disc or a low concentration meropenem disc (to detect an MIC of 0.25) should be considered.

9. Review

This policy will be reviewed by 31/09/2020.

10. Risk

Risk Statement	Referring suspected CPE isolates for confirmation and referring CPE isolates for WGS analysis will ensure timely detection of hospital and community outbreaks of CPE. Outbreaks of CPE may occur within the local setting or represent importations.
Risk Category	Clinical Care and Patient Safety

11. Further Information

For further information, please contact:

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12. Version History

The approval and amendment history for this document must be listed in the following table.

Version No	Effective Date	Approved By	Approval Date	Procedure Author	Risk Rating	Sections Modified
V1.0	02/10/19	Clinical Governance Quality and Risk Committee	02/10/19	Microbiology Clinical Stream Lead	Medium	New Policy.
V2.0	03/10/19	Policy Sponsor	03/10/19	Microbiology Clinical Stream Lead	Medium	Table 1 EUCAST annular radius changed to zone diameter; Figure 2 Annular radius changed to zone diameter; Disk changed to disc for consistency.