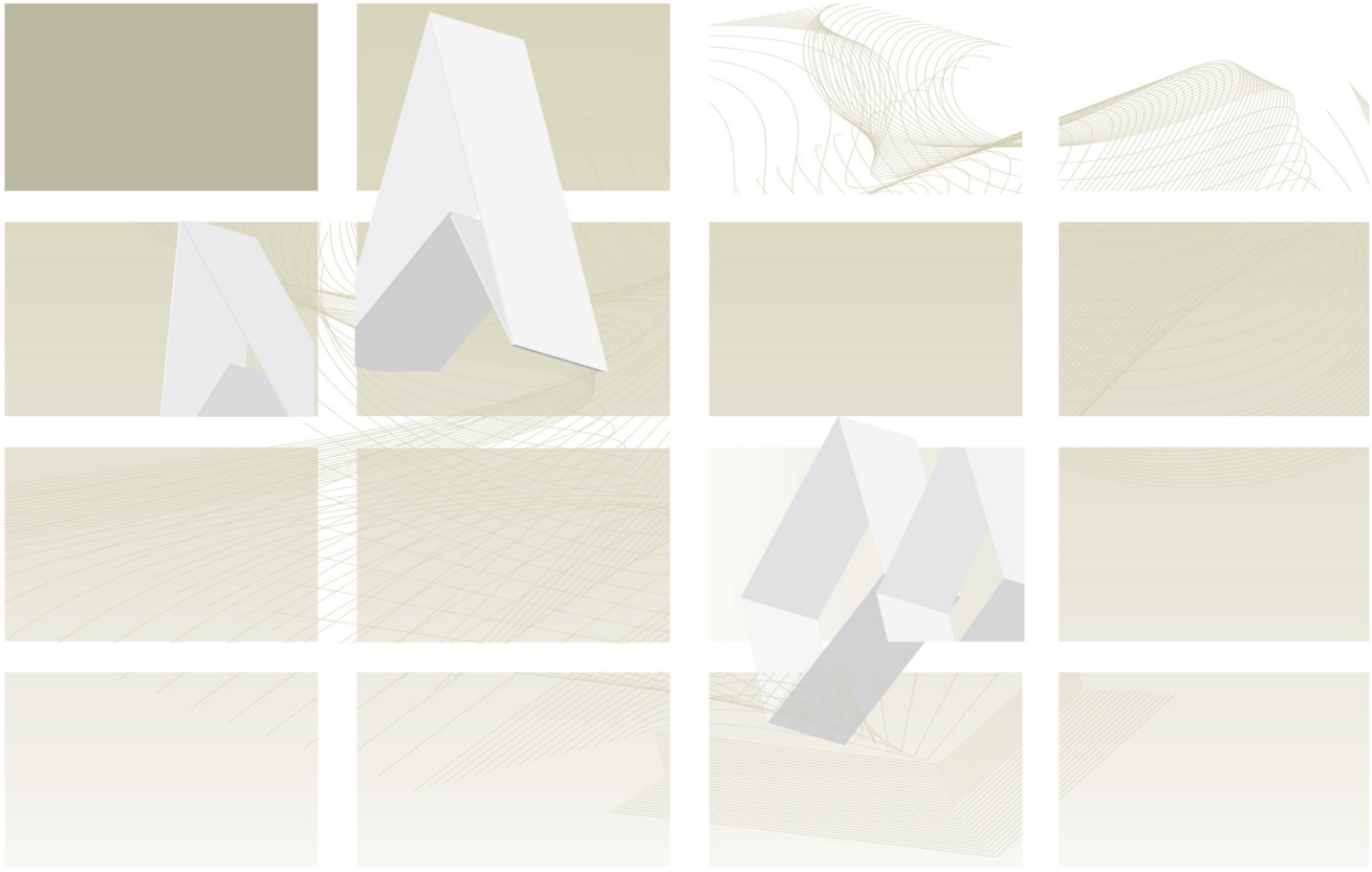
Public Health England

NHS

UK Standards for Microbiology Investigations

Review of users' comments received by Working group for microbiology standards in clinical bacteriology

B 60 Detection of bacteria with carbapenem-hydrolysing β-lactamases (carbapenemases)



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Recommendations are listed as ACCEPT/ PARTIAL ACCEPT/DEFER/ NONE or PENDING

Consultation: 03/06/2015 – 15/07/2015

Version of document consulted on: B 60dzg+

Proposal for changes

Comment number	1		
Date received	09/06/2015	**Lab name**	Royal Oldham Hospital
Section	Screening		
Comment			
We have found using ESBL media + an ertapenem 10ug disc a reasonable compromise for screening specimens. It is more inhibitory than CLED or MacConkey but more sensitive than chromogenic. It still gives very useful colour reactions for *E.coli* and other coliforms. We evaluated Colorex KPC and found it to be 100% sensitive for KPC positive strains of *Klebsiella* and *Enterobacter* but it had poor sensitivity for strains of KPC positive *E.coli* (4 out of 4 strains of KPC positive *E.coli* failed to grow).			
Evidence			
In-house validation (unpublished).			
National experts have recommended that all clinically significant coliform isolates cultured from all clinical samples should be tested against an indicator carbapenem as a matter of routine. This recommendation features in the current SMI protocol document: P 8 (Laboratory Detection and Reporting of Bacteria with Carbapenem-hydrolysing beta lactamases) which is being superseded by this new SMI. Routine screening is not recommended in this draft SMI. Do you think this would be desirable or practicable?			
Routine sensitivity testing of coliform isolates from systemic sites get tested against meropenem and ertapenem. To include ALL coliform isolates from urine would not be desirable or practicable. We would only test against carbapenems if the first line tests indicated resistance to 1st generation cephalosporin or 3 other antibiotics.			
There is no national guidance or recommendation on zone size cut-off for screening for carbapenem resistance on MacConkey/CLED agar plates with carbapenem indicator discs. If you have experience in the use of this methodology, what zone-size cut-off do you use for undertaking formal antimicrobial susceptibility testing?			
For screening purposes, we investigate any coliform with a zone diameter of <27mm on Colorex ESBL agar.			
Financial barriers			
No.			
Health benefits			
No.			
Recommended action	**NONE**		

	This comment was for information purpose only.

Comment number	2		
Date received	10/06/2015	**Lab name**	Freeman Hospital
Section	Various		
Comment			

a. General structure

i. I believe that the guideline could be structured / ordered in a more logical way to be more user-friendly. There also seems to be some unnecessary repetition in the guideline. For example, coliforms will need to be 'spotted' as potential CPE before a laboratory takes the decision to perform confirmatory tests. 'Spotting' potential CPE will usually be as a result of reading susceptibility tests. Table 4 (and the related text) deals with EUCAST cut-offs for detecting CPE, however this is currently placed towards the end of the document and after confirmation testing. My suggestion would be to move this information to page 10 / 11.

ii. With respect to interpretation of zone diameters, prominence is given to EUCAST recommendations – however there are many more users of the BSAC method in the UK. BSAC guidelines also specify a meropenem zone diameter cut-off of 32 mm (higher than the susceptibility breakpoint of 27 mm) to enable detection of CPE (See: http://bsac.org.uk/wp-content/uploads/2012/02/BSAC-Susceptibility-testing-version-141.xls). Perhaps you could consider adding this as a footnote to the EUCAST table to assist BSAC users.

b. Choice of screening carbapenem

On page 10 we have "Overview of the strategy for recognising potential carbapenemase producers"

The following criteria are given for the optimal choice of carbapenem:

"the ideal indicator carbapenem is one to which all carbapenemases confer resistance, even when production is scanty. No single carbapenem satisfies this criterion for all host species (Enterobacteriaceae and non-fermenters)"

And…

as a general principle, frontline diagnostic methods must have high sensitivity (ability to detect carbapenem resistance), even at the expense of specificity (ability to distinguish true carbapenemase producers)

I absolutely agree with these two statements and in my view they both logically point to the use of ertapenem for testing against Enterobacteriaceae. However it is then stated in Table 4 that "Ertapenem shows high sensitivity but low specificity in terms of detecting carbapenemase producers, and so is not recommended for routine use". At best, this is a direct contradiction to the two criteria given above.

In my view, the very high sensitivity afforded by ertapenem gives it a clear advantage. We use it in our laboratory and the specificity is highly acceptable in a

non-reference laboratory setting (less than 1 confirmatory test per week performed on non-CPE – if we exclude *Enterobacter* that are fully susceptible to meropenem). The other advantage of ertapenem is that the breakpoint for determining susceptibility is the same as that used to indicate possible CPE (25 mm) so any Enterobacteriaceae that are non-susceptible to ertapenem should be investigated. (the multiple zone diameter breakpoints for meropenem (R/I/S/possible CPE) does not simplify things for clinical laboratories.

It is inferred more than once in this document that meropenem is the best carbapenem to test. However, its lack of sensitivity is a concern. Since OXA-48 is not endemic in the UK, one presumes that UK users will use the cut-off of 25 mm for meropenem (EUCAST method). According to a recent study (J Antimicrob Chemother 2014; 69: 445-50), around 50% of OXA-48 producers are susceptible to meropenem and 20% will be undetected using the EUCAST cut-off of 25 mm.

Clearly ertapenem should not be tested against non-Enterobacteriaceae – and meropenem would need to be tested, however laboratories should already be using different disc sets for these different groups of bacteria. In my view, if ertapenem is not going to be specifically recommended as the best choice, the guideline should give a more balanced view of the merits of ertapenem versus meropenem rather than stating that ertapenem is “not recommended” (as in Table 4).

c. Choice of screening media

My only other major gripe with this guideline is section 4.5.1 (almost all of it). Prior to this section (page 13) it is stated that:

“Chromogenic agar media should be recommended for isolation as it is more sensitive and gives results more quickly than MacConkey agar with a disc, which is cheaper but not very sensitive and will require further confirmation”.

“In light of the limited available evidence we recommend that if stool samples or rectal swabs require screening for CPE, the method chosen should have demonstrated performance at least equivalent to plating on to a commercially-prepared agar specifically recommended for this purpose”.

These statements are both valid. However, it is then disappointing to see section 4.5.1 which validates the use of MacConkey or CLED plus a meropenem disc as a sole method for isolation of CPE from screening swabs.

As I indicated in my earlier comments (sent in September 2014) there is once again a danger that the guideline will be seen as inconsistent or even contradictory. Where is the study that demonstrates disc testing with meropenem on CLED / MacConkey to be “at least equivalent to plating on to a commercially-prepared agar”? The reference provided for this method (ref 89) is an old study (before chromogenic media for CPE were widely available) and ironically uses ertapenem as the test agent, rather than meropenem which is recommended here. It also deals exclusively with KPC producers (which in my experience are easier to detect than most others).

It may be that there is good evidence that meropenem disc testing on CLED / MacConkey is adequate for detection of the various types of CPE that laboratories might encounter – but I have not seen any. I have not performed a formal evaluation of disc testing direct from clinical samples as I regarded it as highly unscientific but it is very easy to demonstrate that the method has clear limitations as I did for my recent presentation. If the SMI remains unaltered in this

respect, it will be necessary for someone to perform and publish such an evaluation.

Laboratory scientists have it drummed into them that the inoculum is crucial for susceptibility testing (particularly true for ß-lactamase producers) and it is not easy to detect such organisms when technical factors are tightly controlled – what chance do we have when the inoculum is completely uncontrolled and mixtures of species abound? It is disappointing that the SMI is recommending a poor method with precious little evidence to support it. There is little doubt that many diagnostic laboratories (who may have little knowledge or specific interest in CPE) will look for the cheapest and easiest method allowed by this document and use it to justify compliance with national standards. They can point to section 4.5.1. and justify the choice of this method to ISO accreditation inspectors.

Finally, on this point….Section 4.7 states that "As the media used are not as recommended in BSAC/EUCAST/CLSI methodology, a cut-off value of within 20mm is recommended, taking due regard of inoculum density or mixed cultures". I do not understand this figure of 20 mm. Does this mean a zone diameter of 20 mm should be used as a cut-off? (at least 5 mm less stringent than that recommended for EUCAST testing??). If that is the case, there will be huge potential for missing CPE with OXA-48, NDM-1 etc….

d. Other issues with section 4.5.1

It is referred to here (and elsewhere in this SMI) the option of using a "chromogenic medium with carbapenem". This should be changed to something like "chromogenic medium for CPE". Although this is not widely known, the best chromogenic media designed specifically for isolation of CPE do not contain a carbapenem (which is the main reason they work so well).

The second half of Table 4.5.1 gives options for methods with increased sensitivity for detection of CPE. These methods are MacConkey with a meropenem disc (a bad method) plus TSB broth with a meropenem (or ertapenem) disc (possibly an even worse method). This broth method is that endorsed by the CDC before better methods were available and it states elsewhere in this SMI that "Enrichment broths supplemented with carbapenems have also been advocated, eg in guidelines from the Centers for Disease Control. However, the current limited evidence suggests an inferior performance to commercially available chromogenic agars with the added disadvantage that an extra day is required to obtain colonies for further testing" (page 12). Given this (correct) statement, it is inconsistent / contradictory to recommend the CDC method as a method for enhanced sensitivity in section 4.5.1. There is ample published evidence that the CDC broth method has poor sensitivity when compared with some commercially available selective agars and there is no evidence that I am aware of that suggests enhanced sensitivity.

Chromogenic agars are regarded by some as an expensive, inconvenient addition to the materials required by laboratories. However, I don't find this argument particularly persuasive. As a large tertiary teaching hospital, we have fully embedded the CPE tool kit into our procedures and training of nursing staff is well advanced. (we screen any patient who has been abroad or who has been hospitalized anywhere outside of the North East of England). Despite this, the number of screening swabs that we process is no more than 30 per week. If we used 1 chromogenic plate per specimen (eg chromID CARBA) the cost would be £57 per week – but if laboratories find this too expensive they could inoculate up

to 4 specimens per plate (as we do) and reduce costs considerably. (this is a compromise – but still a better option than using MacConkey plus carbapenem disc or the insensitive CDC broth method).

e. *Pseudomonas*

i. With respect to detection of carbapenemases in *P. aeruginosa*, I wondered whether it might be worth considering a footnote to suggest that isolates from patients with CF could be excluded. Although carbapenem resistance is very common in such isolates, acquired carbapenemases are rare. (eg see: http://www.ncbi.nlm.nih.gov/pubmed/25551306).

ii. 4.5.1 'Atmos' (typo)

f. Final comment

In September 2014, I highlighted some additional references for newer studies on chromogenic agars. These have now been cited as references 29-33 in the SMI. However, these studies have not been included in Table 6 – even though 3 of them fulfil the criteria for inclusion in this table. In case you want to use these, I have updated Table 6 (see separate file) with these and one newer study. The cut-off of 2014 (cited on page 12) is still applicable if online versions are included.

g. Table 4 and section 4.5.1.

i. Table 4.

The footnotes of this table suggest that ertapenem and imipenem are not recommended as screening agents for CPE in disc susceptibility testing - which leaves meropenem. It has been shown that testing meropenem (and using a cut-off of 25 mm) may lead to 20% of OXA-48 producers being 'missed'. [J Antimicrob Chemother 2014; 69: 445-50]. If a single carbapenem is to be used, ertapenem has the highest sensitivity and (in our laboratory at least) has acceptable specificity.

ii. Section 4.5.1.

I would be interested to know if the use of disc testing on CLED / MacConkey with a meropenem disc has been validated for detection of CPE. It seems surprising that this is recommended (in Appendix 1) as a valid method when the inoculum is completely uncontrolled and highly mixed cultures can be expected. Reference 89 is cited as evidence but this cited paper advocates ertapenem. In section 4.5.1., it is suggested here that a broth (supplemented with a carbapenem disc) may be used if a higher sensitivity of detection is required. There is very little evidence that such a method offers a higher sensitivity (and much evidence to the contrary eg J Clin Microbiol. 2012 Sep;50(9):3102-4).

National experts have recommended that all clinically significant coliform isolates cultured from all clinical samples should be tested against an indicator carbapenem as a matter of routine. This recommendation features in the current SMI protocol document: P 8 (Laboratory Detection and Reporting of Bacteria with Carbapenem-hydrolysing beta lactamases) which is being superseded by this new SMI. Routine screening is not recommended in this draft SMI. Do you think this would be desirable or practicable?

I would be fully supportive of a recommendation that all clinically significant

Enterobacteriaceae are tested against a carbapenem. **After much discussion, this is therefore not recommended by the Bacteriology Working Group.**	
There is no national guidance or recommendation on zone size cut-off for screening for carbapenem resistance on MacConkey/CLED agar plates with carbapenem indicator discs. If you have experience in the use of this methodology, what zone-size cut-off do you use for undertaking formal antimicrobial susceptibility testing?	
For formal antimicrobial susceptibility testing we use a zone diameter breakpoint of 25 mm for ertapenem (EUCAST methodology). This indicates non-susceptibility and triggers investigation of possible CPE. We briefly examined isolation methods using disc testing on CLED / MacConkey but quickly concluded it was likely to be unreliable as the inoculum level is absolutely critical.	
Financial barriers	
Some investment is required for purchase of chromogenic media in our laboratory but the cost of an outbreak would be far more significant.	
Health benefits	
There are very significant risks to patients if the SMI gives any encouragement to the use of inferior screening methods that have little evidence to support them.	
Recommended action	a. i. **ACCEPT** The document has been structured in an order most logical to the reader. ii. **ACCEPT** The EUCAST guidelines are the recommended standards used in almost all European countries including the UK where this standard has increasingly been taken on by many laboratories. Although there are BSAC users in the UK, they will be supported by BSAC to change to the EUCAST methodology. However, this has been added as a note under the table 2. b. **ACCEPT** The sentence has been rephrased to give a more balanced view of the merits of ertapenem versus meropenem. c. **ACCEPT** This has been updated in the document as the BWG members felt it will be helpful to add both chromogenic agar as well as MacConkey/CLED agar to give users a choice of plates to use in different scenarios. d. **ACCEPT**

	This has been updated in the document. e. i. **ACCEPT** This has been added as a footnote in section 4.5.1 and referenced. ii. **ACCEPT** The word has been amended in the document. f. **ACCEPT** This has been updated in appendix 2 of this document. g. i. **ACCEPT** This has been updated in the document. ii. **ACCEPT** The use of broths has been deleted and section 4.5.1 has been updated to reflect this.

Comment number	3		
Date received	25/06/2015	**Lab name**	BioConnections
Section	Confirmatory test - other methods		
Comment			
Colourimetric methods. Not all colourimetric methods are carba NP. The carba NP method is a simple modification of the acidometric penicillinase test and may be replaced by the blue carba test of Pires et al. This in turn may be replaced by further modifications. The use of the name Carba NP has been defended by its influential developers Nordmann & Poirel although it is not a registered name/trademark. I feel the term carba NP should not be used, acidometric is more appropriate.			
Evidence			
http://jcm.asm.org/content/51/12/4281.full			
Recommended action	a. **ACCEPT** Commercial versions of this test are available and the reference supplied above has been added to this sentence.		

Comment number	4		
Date received	10/07/2015	**Lab name**	IBMS

Section	Various
Comment	
a. Introduction Subsection: Acquired carbapenemases The link to www.lahey.org/studies seems to take you to the ESBL page not carbapenemases b. Specimen processing/procedure Subsection: 4.7 Antimicrobial susceptibility testing Paragraph 5: EUCAST has therefore recommended screening cut-off values (table 4)….. The IBMS would like to suggest that faropenem is included as an indicator disc (evidence is cited below). This disc is now commercially available.	
Evidence	
J Clin Microbiol. 2013 Jun;51(6):1881-6.	
Recommended action	a. **NONE** The link in the above comment does contain the carbapenemases but you will have to go to the subtitle below called “Others” highlighted in blue to be able to access the carbapenemases. However, the link has been updated to reflect the new website where the carbapenemases have been moved to. The new link is http://www.ncbi.nlm.nih.gov/pathogens/submit_beta_lactamase/. b. **NONE** The indicator disc, faropenem is covered in the screening section of the document under subheading Enterobacteriaceae as a carbapenem that could be used as it has been shown to have good sensitivity for detecting carbapenemase producers. However, EUCAST does not cover faropenem in its recommendations and therefore cannot be covered in section 4.7.

Comment number	5		
Date received	14/07/2015	**Lab name**	Microbiology Department Antrim Area Hospital
Section	Various		
Comment			

a. 4.7 Antimicrobial Susceptibility Testing Not sure what the first paragraph is referring to as the media used are not as recommended in BSAC/EUCAST/CLSI methodology, a cut-off value of within 20 mm is recommended. Is this for screening for CPE with MacConkey plate with carbapenem disc? b. Table 4.5.1 Culture Media, conditions and organisms Is MacConkey agar or CLED agar with Mero disc required to detect carbapenemase producing *Pseudomonas* and *Acinetobacter* or is chromogenic agar with carbapenem suitable as well?	
National experts have recommended that all clinically significant coliform isolates cultured from all clinical samples should be tested against an indicator carbapenem as a matter of routine. This recommendation features in the current SMI protocol document: P 8 (Laboratory Detection and Reporting of Bacteria with Carbapenem-hydrolysing beta lactamases) which is being superseded by this new SMI. Routine screening is not recommended in this draft SMI. Do you think this would be desirable or practicable?	
My feelings would be that it was desirable. However it is not practicable, would find it difficult to get a carbapenem onto our first line stampers without displacing a useful antibiotic. If we put it up on a separate plate, would add to workload of BMS's and we have limited incubator space. I wonder if a rule, ie test carbapenem against isolates resistant to Co-amoxiclav and/or Tazocin would be useful, it would prevent having to test a carbapenem against a pan-sensitive E. coli. Note: I would only test coliforms that are having antimicrobial susceptibilty done, not against every coliform isolated in the laboratory.	
There is no national guidance or recommendation on zone size cut-off for screening for carbapenem resistance on MacConkey/CLED agar plates with carbapenem indicator discs. If you have experience in the use of this methodology, what zone-size cut-off do you use for undertaking formal antimicrobial susceptibility testing?	
None.	
Financial barriers	
Yes.	
Recommended action	a. **ACCEPT** This has been removed and document updated accordingly. b. **ACCEPT** This has been updated to read that either MacConkey/CLED agar plates with carbapenem indicator disc or Chromogenic agar could be used. This depends on what media laboratories use and have validated.

Respondents indicating they were happy with the contents of the document

Overall number of comments: 1			
Date received	10/07/2015	**Lab name**	NHS Lanarkshire