

**PICNet**

PROVINCIAL INFECTION CONTROL  
NETWORK OF BRITISH COLUMBIA

A program of the Provincial Health Services Authority

## Toolkit for the Management of Carbapenemase Producing Organisms (CPO)



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## Glossary of Acronyms

BC	British Columbia
BCAMM	BC Association of Medical Microbiologists
BCPHRML	BC Public Health Reference Microbiology Laboratory
CPE	carbapenemase producing <i>Enterobacteriaceae</i>
CPO	Carbapenemase-producing organism
ICU	Intensive Care Unit
IPAC	Infection Prevention and Control
KPC	<i>Klebsiella pneumoniae</i> carbapenemase
MHO	Medical Health Officer
OPMT	Outbreak Prevention and Management Team
PICNet	Provincial Infection Control Network of British Columbia

# Management of Carbapenemase Producing Organisms

## Introduction

Carbapenemase producing gram-negative bacilli are becoming increasingly common due both to selective antibiotic pressure as well the transfer of patients who have been hospitalized or had a medical procedure in countries with endemic organisms that harbor carbapenemase producing genes. Examples of these include *Klebsiella pneumoniae* carbapenemase (KPC), found mostly in *K. pneumoniae* but also in other *Enterobacteriaceae*; and the metallo-beta-lactamases found in *P. aeruginosa* and *Acinetobacter spp.*, and rarely in other *Enterobacteriaceae*. The New Delhi metallo-beta-lactamase (NDM-1 enzyme) is an example of this latter form of resistance that was identified originally in *E. coli* and *K. pneumoniae*, but which has recently been detected in other *Enterobacteriaceae*. In British Columbia, isolates containing these carbapenemase genes, located on transferable plasmids, are being increasingly identified in patients, and transmission between patients has occurred within our healthcare institutions.

The following protocol has been written specifically for these newer forms of carbapenemase resistance in healthcare settings. *It is not meant to address carbapenem resistance due to loss of membrane permeability commonly seen in P. aeruginosa. Nor is it meant to address carbapenem resistance noted in strains with inherent resistance such as Stenotrophomonas maltophilia or Burkholderia cepacia.*

**The most common mechanism of transmission for these organisms is contact, both direct and indirect. The following protocol has been written with the intent of managing patients with carbapenemase producing organism (CPO) (as described above) to prevent transmission in the acute care setting.**

## Screening

The following acute care in-patients should be screened for CPOs:

- Anyone who has had an overnight stay in a hospital or undergone a medical/surgical procedure outside Canada within the past 12 months
- Anyone who has had haemodialysis outside Canada within the past 12 months
- Anyone who was transferred from a facility with known, active CPO transmission
- Anyone who had close contact with a known CPO patient within the past 12 months (Close contact is defined as: household member, roommate in hospital or shared nursing staff and physicians. In high risk units, such as transplant units, ICU etc., close contact may constitute all patients on the entire unit.)

**Place patient on Contact Precautions upon admission while waiting screening culture results. If respiratory infection is suspected, use Droplet and Contact Precautions. Assignment to a single room is preferable. This is in addition to other routine appropriate admission screens (e.g. for methicillin-resistant *S. aureus*).**

## Specimen types

Screening or Contact tracing

- Rectal swab with fecal staining (preferred)
- Perianal swab or stool is acceptable if rectal swab is not available

Repeat screening on patients who are deemed very high risk but who screened negative upon admission may be considered after consultation with medical microbiologists or infection control practitioners (ICPs) in the facility

Check with your local laboratory to confirm the correct way they would like requisitions labelled for screening swabs. This may include wording such as: "Carbapenemase Producing Organism Search".

Isolates suspected of harboring a CPO gene should be sent to the BC Public Health Reference Microbiology Laboratory (BCPHRML) for confirmation. Please use the following requisition: [https://www.picnet.ca/wp-content/uploads/PHSA\\_Labs-CPO-Testing-Form-2017.pdf](https://www.picnet.ca/wp-content/uploads/PHSA_Labs-CPO-Testing-Form-2017.pdf)

## Laboratory Testing

Screening samples are submitted to the local microbiology laboratory for detection of *Enterobacteriaceae* that might be harbouring the resistant genes (NDM, KPC, OXA-48, VIM and IMP) on their plasmids. There are a number of methods currently available for screening and confirmation of suspicious isolates. For clinical specimens both *Enterobacteriaceae* and other gram negative bacilli (e.g. *Acinetobacter spp*, *Pseudomonas spp*, etc.) that express phenotypic resistance to carbapenem antibiotics are further evaluated for the presence of one of the CPO genes.

These methods and their supporting literature prepared by the BC Association of Medical Microbiologists (BCAMM) are detailed in Appendix 2.

## Prevention of Transmission

1. As always, diligent hand hygiene is the most effective way to prevent transmission between other patients and/or staff. Alcohol-based hand rub (ABHR) is effective against these organisms.
2. Any non-ventilated patient confirmed to be CPO positive should remain on **Contact Precautions** until discharge.
3. **Use Droplet and Contact Precautions on ventilated** patients pending the results of the sputum culture.
4. Use **Droplet and Contact Precautions** if a CPO is found in the patient's sputum, whether or not they are ventilated, until discharge.

5. Limit equipment that goes into the patient room (particularly respiratory equipment). Ideally, equipment will be dedicated to that patient until discharge. Meticulously clean and disinfect all equipment and devices (e.g. stethoscopes) before use with another patient.
6. Frequently touched surfaces in patient rooms should be cleaned twice daily (see table in Appendix 1).
7. Transfers and/or bed moves should be avoided unless clinically necessary.
8. Communication with the receiving unit/facility of a suspected or known positive CPO status of any transferred patient should occur **prior** to his/her transfer.

## Education

1. Request infection prevention and control (IPAC) aid in providing education sessions to all staff/volunteers/family members who provide direct care. Issues to be reviewed will include:
  - Proper use of personal protective equipment (PPE)
  - Meticulous hand hygiene
  - The potential for environmental contamination
  - Understanding the difference between colonization and infection.

## Surveillance:

1. Nursing should collaborate with IPAC and the Medical Microbiology Laboratory to direct ward/unit screening of patients for detection of possible transmission based on risk assessment (e.g. patient population, environment, unit, previous transmission history).
2. As CPO is an emerging pathogen, an enhanced surveillance protocol is underway. For patients confirmed to be positive for a CPO, IPAC will collaborate with ward/unit staff and the Medical Microbiology Laboratory to collect data required for surveillance purposes. Please see the protocol at the following link: <https://www.picnet.ca/wp-content/uploads/CPO-Surveillance-Protocol-2017.pdf>

## Notification:

1. If a unit or facility is under investigation for CPO transmission, the HA should inform PICNet and PHL. Use the form in Appendix E of the surveillance protocol (link above). PICNet will then inform other HAs of the investigation.
2. In case of an outbreak of CPO in an acute care facility, IPAC will consult with MHO regarding outbreak investigation and control. If the outbreak occurs in a community setting, such as residential care facilities and outpatient clinics, IPAC will assist the MHO in case management and infection control. The HA should communicate with or inform other HAs, PICNet, PHL, as well as the public as per established outbreak management processes.

## **Discontinuing Precautions**

Consult with IPAC. If a patient is confirmed as being colonized or infected with a CPO, Contact Precautions should continue for the duration of the hospitalization during which the CPO was isolated. Individuals with confirmed CPO should have their patient record flagged in a way that provides an automatic alert should they be re-admitted. Patients readmitted within 12 months of that hospitalization should be rescreened for CPO and placed on Contact Precautions until results of screening cultures are known.

# Internal Alerts and Outbreaks of CPO

## Internal Alert

Definition: When the number of CPO cases in a unit or facility is above the pre-determined threshold (trigger point) or there is suspected transmission. The purpose of an internal alert is to identify an opportunity to intervene with enhanced control measures to prevent further spread of these emerging organisms.

- Triggering an internal alert does not require confirmed laboratory results and may include patients that were known or found to be positive for a CPO on admission.
- Suspected transmission within a unit may also trigger an internal alert.
- When a “trigger point” has been reached, staff within the facility should be alerted to the situation and the need for enhanced control measures.
- Facility administration should work with the unit staff and IPAC to put additional control measures and additional resources in place.
- An internal alert is for the operational purposes of that facility, and a public announcement is not required. It is strongly recommended that notification be given to the IPAC of other facilities that commonly receive patients from, or send patients to, the affected facility.

## Outbreak Definition

CPO cases are classified as an outbreak when the number of new, time-related, nosocomial CPO cases in a unit or facility is above the expected threshold for that unit or facility, and where there is evidence of ongoing transmission despite appropriate interventions.

- The criteria for defining an outbreak should be pre-determined for each individual facility, in consultation with the medical health officer (MHO) or their designate.
- Molecular confirmation of CPO genes in patient’s isolates is required to determine ongoing transmission.

## Outbreak Management

Healthcare facility IPAC teams and the Medical Health Officer (MHO), or designate, work collaboratively in the prevention, early detection, and management of outbreaks. IPAC teams, public health, and the medical microbiology laboratory should collaborate with the BCPHMRL to facilitate rapid testing of isolates to determine CPO gene types (see surveillance protocol at <http://s.picnet.ca/cpoprotocol>).

The decision to limit new admissions or close a portion of a unit, an entire unit, or an entire facility may be required. Under the Public Health Act, consultation is required with the MHO or designate for the management of outbreaks by IPAC, and the facility Administrator.

## **Role of the Hospital in CPO Outbreak Management**

Each facility, in consultation with the MHO or designate, should have a pre-determined set of criteria that define an outbreak. If these criteria are met, the MHO or designate must be consulted under the Public Health Act. The facility must then mobilize the Outbreak Prevention and Management Team (OPMT). The OPMT is primarily responsible for operationalizing outbreak management processes.

- Review current IPAC evidence based practice in outbreak management to identify gaps and issues and ensure control measures are implemented.
- Collaborate with the BCPHMRL to facilitate rapid testing of isolates to determine CPO gene types.
- Communicate outbreak situation to receiving hospitals of all transferred patients.
- Advocate for enhanced resources required to implement control measures.
- Summarize suggested improvements and lessons learned to share with local/regional Infection Prevention and Control committees.

## **Role of Public Health in Acute Care Facility CPO Outbreak Management**

The MHO has legislated authority under the Public Health Act to give direction regarding health hazards and infectious diseases in BC. They may choose to designate this authority. These bullets need an introductory sentence.

- Assist in the investigation, confirmation, declaration and management of the outbreak
- Provide support and consultation to IPAC staff at the hospital, if needed
- Provide representation on the outbreak prevention and management team (OPMT)
- Provide guidance and assistance on surveillance and IPAC policies and procedures required to control the outbreak
- Consult with the hospital to declare the outbreak over
- Facilitate provincial assistance when local resources for outbreak control are exhausted

## Appendix 1: Enhanced Cleaning Checklist for Inpatient Rooms (to be Done Twice Daily)

Area	Yes	No	Comments/Reason not done
Door knobs			
Bedrails			
Light switches			
Bathroom faucets (including handles)			
Any grab bars mounted on walls			
Toilet (including flush handle)			
Remote controls			
Telephone			
Over-bed table			
Bed-side table/stand (including drawer handles)			
Call light controls			
Medical Equipment (IV pump, monitor leads)			

**NB:** *This is intended for inpatient rooms only and not for areas where patients spend a short amount of time such as: diagnostics, ambulatory care, operating room etc. For these areas use a transmission risk assessment to determine the level of additional cleaning required. Consult Infection Control if in doubt.*

## Appendix 2: BCAMM Laboratory methods for Screening Samples for detection of Carbapenemase Producing Enterobacteriaceae (CPE)



**BRITISH COLUMBIA ASSOCIATION OF  
MEDICAL MICROBIOLOGISTS**

### **BACKGROUND:**

Carbapenems are broad-spectrum antibiotics that are often considered “antibiotics of last resort”. However their efficacies are increasingly becoming compromised because of the worldwide emergence of resistant isolates. This resistance is mainly caused by production of carbapenemases, enzymes that are encoded for by genes that are frequently located on plasmids which facilitates their transmission.

The morbidity and mortality associated with infections due to carbapenemase producing organisms (CPO) is a cause of major global concern. While both *Enterobacteriaceae* and non-*Enterobacteriaceae* gram negative organisms can harbor carbapenemase genes, in Canada, carbapenemase producing *Enterobacteriaceae* (CPE) have been implicated in several hospital outbreaks. All carbapenem resistant isolates from clinical specimens should be investigated for the presence of carbapenemase genes.

In addition, active screening for carbapenemase producing *Enterobacteriaceae* (CPE) is now considered as one of the most important measures to halt the transmission of CPE within healthcare facilities. Laboratory detection of CPE can be challenging, since some of these isolates may only have borderline reductions in susceptibility to carbapenems.

The following patients would be eligible for CPE screening:

- Individuals who have had an overnight stay in a hospital or undergone a medical/surgical procedure outside of Canada within the past 12 months
- Individuals who received haemodialysis outside of Canada within the past 12 months
- Individuals who are transferred from a healthcare unit or facility with a high prevalence of CPO.
- Individuals who had close contact with a known CPO patient within the past 12 months, e.g. stayed in the same room or ward in the facility, shared nursing staff, lived in the same household, etc.

The following specimens are appropriate for patient screening:

- Rectal swab with fecal staining (preferred)
- Perianal swab or stool is acceptable if rectal swab is not available

N.B. Repeat testing may be needed for patients in whom initial testing is negative but the clinical suspicion for CPE carriage is high. Some of these patients are found to be heavily colonized only after the initiation of antibiotics

#### **PURPOSE:**

The purpose of this document is to review the available microbiological methods for the detection of CPE in screening specimens and to compare the performance characteristics of each method by reviewing the published literature.

Currently available methods for detection of carbapenemase producing *Enterobacteriaceae* in screening specimens include:

#### Culture-based Methods:

In these methods a selective culture media is chosen for preliminary surveillance. Colonies that grow on these selective agars are investigated further by phenotypic/genotypic methods. The following media are available as **primary screening plates**.

#### **A. Non-Chromogenic media:**

##### 1- CDC method:

This method is a modification of the procedure originally described by Landman et al <sup>1</sup>. It is described in detail in the CDC CRE toolkit, 2012.

Briefly, 10-µg ertapenem or meropenem or imipenem disc is placed aseptically in 5 ml trypticase soy broth (TSB)<sup>2</sup>. The broth is inoculated with the rectal culture swab and incubated overnight at 35 ± 2°C, ambient air. This is followed by subculture on MacConkey agar plate, followed by confirmatory phenotypic or genotypic methods.

##### 2- MacConkey agar with 1µg/ml imipenem <sup>3</sup>

##### 3- MacConkey agar + carbapenem disks<sup>4</sup>

##### 4- SUPERCARBA media <sup>5</sup>:

Drigalski/MacConkey for selection of Gram negative rods Medium supplemented with a carbapenem for the inhibition of ESBL and carbapenem susceptible isolates, cloxacillin for inhibition of AmpC overproducers and Zinc Sulphate.

The performance specifications of Non-Chromogenic media is provided in Table I.A

**Table I.A: Performance specifications of non-chromogenic media for isolation of CPE**

	Sensitivity	Specificity	Cost of plate	Shelf-Life	Reference
<b>CDC method</b>	65.6%	49.6%	\$1.29	Up to expiration date under appropriate storage conditions	2
<b>MacConkey + 1µg/ml imipenem</b>	84.9%	94.3%	NA	NA	3
<b>MacConkey agar + carbapenem disks</b>	75.8%-87%	89.6%-100%	\$0.64	Up to expiration date	3,4
<b>SUPERCARBA media</b>	96.5%	70.6%	US \$0.75	10-14 d	5

**B. Chromogenic media:**

These products are commercially available and are marketed as:

1. CHROM agar KPC (Chromagar)
  - Lack of detection of carbapenemase activity if weak hydrolysis of carbapenems (ex: OXA-48)
  - Sensitivity 43%, specificity 67.8%)<sup>6</sup>Costs about 4 US\$
2. Brilliance CRE(Oxoid)Sensitivity 76.3%, Specificity 57.1%<sup>6</sup>
  - Costs about 4US\$
3. ChromID ESBL(bioMérieux):
  - Efficient for detection of producer of IMP/VIM and KPC-type carbapenemases based on the hydrolysis property of those enzymes toward expanded-spectrum cephalosprins.
  - Reported failure of detection of OXA-48 producing Enterobacteriaceae that do not co-express an Extended spectrum beta lactamase enzyme (ESBL) 7
4. Chrom ID Carba (bioMérieux)<sup>8</sup>
5. ChromID® OXA-48 (bioMérieux)<sup>9</sup>
  - Selective chromogenic medium for the surveillance of OXA-48 type Carbapenemase-Producing Enterobacteriaceae (CPE).

**Table I.B: Performance specifications of chromogenic media for isolation of CPE**

	Sensitivity	Specificity	Cost of plate	Shelf-Life	Reference
<b>CHROM agar KPC (Chromagar)</b>	43%	67.8%	US \$ 4	2 years (manufacturer's data)	6
<b>Brilliance CRE(Oxoid)</b>	76.3%	57.1%	US \$ 4	12 months (manufacturer's data)	6
<b>ChromID ESBL(bioMérieux):</b>	NA	NA	NA	NA	7
<b>Chrom ID Carba (bioMérieux)</b>	100%	93%	NA	NA	8
<b>ChromID® OXA-48 (bioMérieux)</b>	91%	100%	NA	NA	9

**Confirmation of carbapenemase production of isolates:**

*A. Phenotypic Methods:*

1- Modified Hodge Test (MHT):

A CLSI-recommended confirmatory test for carbapenemase production, suffers from lack of specificity, a long turnaround time, and poor sensitivity for metallo- $\beta$ -lactamase detection<sup>10</sup>

2- Antibiotic Susceptibility testing using CLSI updated breakpoints for carbapenems

3- ROSCO Discs (ROSCO Diagnostica Denmark):

This test is based on the inhibition of the different classes of carbapenemases by different chemicals. The test includes: meropenem disk, and meropenem disks supplemented with 1000  $\mu$ g of dipicolinic acid (DPA), 600  $\mu$ g of aminophenylboronic acid (APBA), or 750  $\mu$ g of cloxacillin<sup>10</sup>. Recently, the manufacturer substituted the aminophenylboronic acid with phenyl boronic acid (400  $\mu$ g/tablet) and also added Temocillin disc to improve the detection of OXA-48-like carbapenemases (OXA-48-like enzymes producing isolates show no zone of inhibition with Temocillin disc).

4- Mastdiscs ID inhibitor combination disks (MDI) <sup>10</sup>

5- CarbaNP test:

A colorimetric method based on visual detection of a colour change (from red to yellow) upon hydrolysis of imipenem.

Kit should be prepared freshly in house by combining imipenem powder with diluted phenol red pH 7.8 + Zinc Sulphate 0.1mM. This mixture is added to lysed bacterial cells (using a lysis buffer) or whole bacterial cells

Mean time for positivity for KPC, VIM, IMP, NDM producing isolates was 20-60 minutes. Mean time for positivity for OXA-48 producing isolates was 30-40 minutes<sup>11</sup>.

6- MALDI -TOF Imipenem Hydrolysis assay:

MALDI TOF MS has been utilized in the detection of carbapenemase production in Enterobacteriaceae and *Acinetobacter baumannii*. The assay is based on disappearance of the imipenem spectrum and appearance of an imipenem hydrolysis product at a particular m/z (Da) upon incubation of imipenem with a carbapenemase producing organism for 2-4 hours.

**Table I.C: Performance specifications of some phenotypic confirmatory tests for CPE**

	Sensitivity	Specificity	TAT (Turnaround Time)	Cost per test	Reference
<b>ROSCO Disks</b>	80%	93%	18-24 h	\$6.6	10,11
<b>Mastdiscs</b>	78%	93%	18-24 h	NA	10,11
<b>CarbaNP</b>	98%	100%	60 min	\$1	11
<b>MALDI Imipenem Hydrolysis Assay</b>	95.2%	100%	60 min	\$1	12

B. *Genotypic methods:*

Multiplex PCR assays for the detection of genes encoding for carbapenemase production (KPC, NDM, VIM, IMP and OXA-48 genes) can be used as a confirmatory method . In house PCR assays have shown excellent sensitivity and specificity. This is the only method that can accurately identify the CPO gene responsible for phenotypic resistance to carbapenem antibiotics.

**I. Molecular based Methods for direct detection of CPE/CPO in surveillance specimens:**

Two multiplex PCR assays are currently commercially available for detection of Carbapenemase genes.

1- GeneXpert® Carba-R:

The GeneXpert® Carba-R Assay, performed on the GeneXpert® Instrument Systems, is a qualitative in vitro test designed for rapid detection and differentiation of the blaKPC, blaNDM, blaOXA-48 and bla IMP-1 gene sequences associated with carbapenem-non-susceptibility in gram-negative bacteria. It is designed to be used directly on rectal swabs collected using the Cepheid Collection kit.

The sample extraction, as well as the amplification and detection reactions, all occur in one cartridge. Time to result is approximately 48 minutes as per the product package insert. It is a random access system. In a recent publication by Tenover et al <sup>13</sup>, the analytical sensitivity of the assay was 99%-99.4% and the analytical specificity was 93.4%- 100%.from rectal surveillance swabs.

2- BD MAX™ CRE Assay:

The BD MAX™ CRE Assay is designed to detect three antimicrobial resistance genes (KPC, OXA-48 and NDM) found predominantly in carbapenem-resistant Enterobacteriaceae (CRE). The assay is performed on the BD MAX™ System instrument which automates sample extraction, amplification and detection using real-time PCR. This kit is designed for use with rectal swabs.

3- A multiplex In-house PCR assay has been developed and may be performed on enriched rectal swabs for the detection of genes encoding for carbapenemase production (KPC, NDM, and OXA-48 genes).

(Dr. Hoang unpublished data)

**Table II: Performance specifications of commercially available genotypic tests for detection of CPE**

	<b>GeneXpert® Carba-R on GeneXpert® System</b>	<b>BD MAX™ CRE Assay on BD MAX™ System</b>	<b>In-house PCR</b>
<b>Capital Equipment</b>	16/8 modules \$91,600 16/12 modules \$110,000	120,000\$(in case another instrument is bought)	Real-time PCR equipment (e.g. Lightcycler 7500)
<b>Equipment service</b>	1 <sup>st</sup> year free; after warranty period: 12% of capital purchase option	NA	NA
<b>Kit: Average Cost/Test</b>	\$67.50 per test	\$18	NA
<b>Supplies: Average Cost/Test</b>	0.74 (Swabs: \$37; box of 50)	NA	NA
<b>Hands on time/sample(sample prep, reading/reporting)</b>	10 min.	15 min	
<b>Total Average cost/Test</b>	\$74	\$26	\$10
<b>Turn around Time</b>	< 1 h	>2 h	<2h *

N.B. NA=Data not available for author; \* TAT does not include enrichment time

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## Appendix A: Quality Control Recommendations

**Quality Control (QC)** recommendations are available for the Modified Hodge test and the Disk diffusion assay in the Clinical and Laboratory Standards Institute (CLSI) M100-S24, January 2014. The following table summarizes the QCT recommendation by CLSI. In addition, a summary of some of the available ATCC strains harbouring the CPO genes of interest are also detailed below. The CLSI QC recommendation is to test positive and negative QC organisms each day of testing.

Test Method	QC Recommendations	Description or Reaction expected
<b>Modified Hodge Test*</b>	<i>K. pneumoniae</i> ATCC® BAA-1705 <i>K. pneumoniae</i> ATCC® BAA-1706	-Positive -Negative
<b>Disk diffusion*</b>	<i>E.coli</i> ATCC® BAA-25922 <i>E.coli</i> ATCC® BAA-25922 (or equivalent)	-Positive -Negative

CPO Gene of Interest	ATCC Strains	
<b>NDM</b>	<b>NDM-1 Panel (ATCC® MP-18)</b> - <i>E. cloacae</i> ATCC® BAA-2468 - <i>E. coli</i> ATCC® BAA-2469 - <i>K. pneumoniae</i> ATCC® BAA-2470 - <i>E. coli</i> ATCC® BAA-2471 - <i>K. pneumoniae</i> ATCC® BAA-2472 - <i>K. pneumoniae</i> ATCC® BAA-2473 Many other ATCC strains are also catalogued	6 clinical strains expressing NDM. Covers resistance to 36 representative antibiotics in a large variety of classes
<b>KPC</b>	<i>K. pneumoniae</i> ATCC® BAA-1705 <i>K. pneumoniae</i> ATCC® BAA-1706 Many other ATCC strains are also catalogued	-Positive -Negative
<b>OXA-48</b>	Not available	
<b>VIM</b>	Not available	
<b>IMP</b>	Not available	

\* CLSI M100-S24. January 2014

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