

Specimen Collection, Handling, Transport and Processing



Part 1:

Specimen Collection

Handling and Transport

Specimen Quality is Important

The results of tests, as they affect patient diagnosis and treatment, are directly related to the quality of the specimen collected and delivered to the laboratory.

<http://www.aphl.org/aphlprograms/infectious/tuberculosis/Pages/tbtool.aspx>

Working with Healthcare Providers

- Laboratories must develop a good working relationship with health care providers collecting patient specimens
- Laboratories should have a reference manual for providers that includes:
 - Specimen type and volume requirements
 - Specimen collection, labeling, storage and transport instructions
 - Specimen rejection criteria
- Laboratories should provide specific feedback to individual healthcare providers regarding problems with the quality of specimens received and provide recommendations for improvement

Specimen Types

I. Respiratory

- Sputum
(expectorated,
induced)
- Bronchoalveolar
lavage (BAL)
- Bronchial
wash/brush
- Transtracheal
aspirate

II. Non-respiratory

- Tissue
- Body fluids
- Blood
- Stool
- Gastric lavage
- Urine

Refer to the CLSI M48-A document, Laboratory Detection and Identification of Mycobacteria

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RESPIRATORY (PULMONARY) SPECIMENS



Sputum

- Recently discharged material from the bronchial tree, with minimal amounts of oral or nasal material
- Expecterated Sputum: Generated from a DEEP productive cough
- Induced Sputum: produced with hypertonic saline if patient is unable to produce sputum on their own
- Indications for sputum collection
 - To establish an initial diagnosis of TB
 - To monitor the infectiousness of the patient
 - To determine the effectiveness of treatment

Sputum Quality

- Specimens are thick and contain mucoid or mucopurulent material.
- Ideally, 3–5 ml in volume, although smaller quantities are acceptable if the quality is satisfactory.
- Poor quality specimens are thin and watery. Saliva and nasal secretions are unacceptable.
- Laboratory requisition form should indicate when a specimen is induced to avoid the specimen being labeled as “unacceptable” quality.



Clinical and Laboratory Standards Institute. Laboratory detection and identification of mycobacteria; approved guideline. CLSI Document M48-A. Wayne, PA: CLSI; 2008.

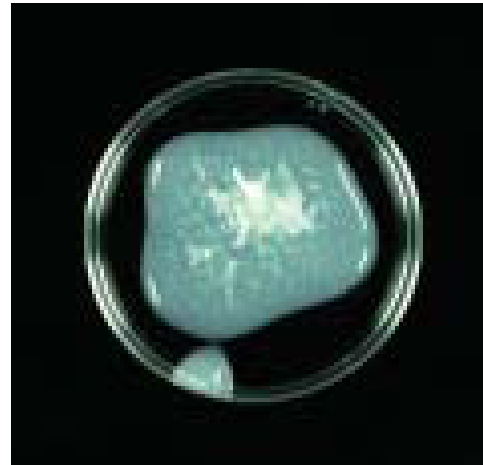
http://www.stoptb.org/wg/gli/assets/documents/29_specimen_condition_transport.doc

Sputum Quality

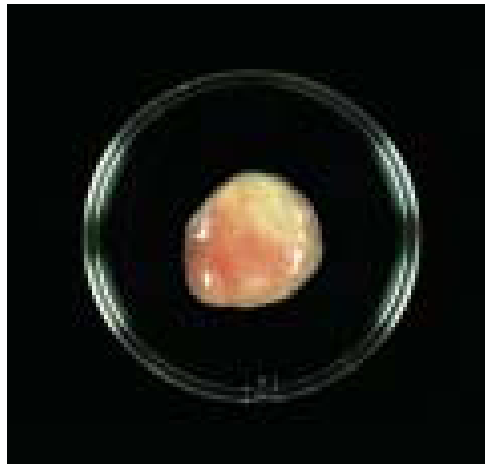
Thick,
Mucopurulent



Watery
(acceptable if
induced)



Hemoptysis
(Bloody
Sputum)



Salivary



Indications for Sputum Collection

- Initial diagnosis of TB:
 - Collect a series of three sputum specimens, 8-24 hours apart, at least one of which is an early morning specimen
 - Optimally, sputum should be collected before the initiation of drug therapy
- For release from home isolation:
 - If patient is smear positive and on treatment: Collect sputum until 3 specimens are negative.
- Monitoring of therapy: Obtain sputum specimens for culture at least monthly until cultures convert to negative

Specimen Collection: All aerosol producing procedures pose a risk of exposure

Whether collecting specimen via sputum collection or bronchoscopy, if a patient is suspected or confirmed of have tuberculosis, airborne precaution must be used.

Specimen Collection

- Suspect or confirmed TB patients should be in a negative pressure room
- Specimen collection is an aerosol generating procedure, anyone in the room during specimen collection must wear a particulate respirator type N-95 and be part of the respirator protection plan
- All mycobacteria specimens are collected into a sealed leak proof container

Storage and Transport of Sputum Specimens

- Collection sites should refrigerate samples that cannot be transported immediately to reduce growth of contaminating organisms
- Specimens should be delivered to the laboratory as soon as possible, within 24 hours of collection is optimal (avoid batching)
- Laboratories may include a cold pack with specimen transport materials

Pulmonary Specimens Other Than Sputum: Collection Guidance

Specimen Types	Collection	Volume Requirements	Transport
Bronchoalveolar lavage (BAL)	Collect washing or aspirate in sputum trap	Minimum volume is 3 ml	50-ml conical tube or other sterile container
Bronch brush or washing	Place the brush in a sterile, leak-proof container with up to 5 ml of sterile saline		Transport as soon as possible at room temperature
Endotracheal aspirate			If transport is delayed more than 1 hour, refrigerate specimen.
Transtracheal aspirate			

- The doubling time for other common respiratory flora is 15 to 20 minutes
- The doubling time for *M. tuberculosis* is 12 to 24 hours

Specimen Collection, Handling, Transport and Processing

**NON-RESPIRATORY
(EXTRAPULMONARY) SPECIMENS**

Extrapulmonary Specimens

- The laboratory should expect to receive a variety of extrapulmonary specimens which may be divided into two groups
 - specimens from non-sterile body sites
 - specimens from normally sterile body sites
- Should be collected in a sterile leak-proof container
- Should be transported as soon as possible
- Swabs are generally not acceptable

Extrapulmonary Specimen Collection Guidance

Specimen from Non-Sterile Body Sites	Recommended Collection Time	Volume Requirements	Collection Frequency	Transport	Recommended for Isolation of MTBC?
Gastric Aspirate	Early morning before patient eats and while still in bed	5–10 ml is optimal; maximum volume is 15 ml	One specimen per day on three consecutive days	Room temperature; if delayed >1 hour, neutralize with 100 mg sodium carbonate	Yes
Urine	First morning specimen (void midstream)	10–15 ml minimum; prefer up to 40 ml	One specimen per day on three consecutive days	If delayed >1 hour, refrigerate	Yes
Stool	No recommendation	Minimum volume is 1 gram	No recommendation	Refrigerate if delayed >1 hour, do not freeze	Mainly for diagnosis of disseminated MAC disease in patients with AIDS

Extrapulmonary Specimen Collection Guidance

Specimen from Normally Sterile Body Sites	Volume Requirements	Transport	Recommended for Isolation of MTBC?
Cerebral Spinal Fluid	10 ml is optimal; minimum volume is 2-3 ml	As soon as possible at room temperature; do not refrigerate	Usually paucibacillary; culture may have limited sensitivity
Other Body Fluids (pleural, peritoneal, pericardial, synovial)	10-15 ml is optimal; minimum volume is 10 ml	If delayed, refrigerate	Yes
Tissues or Lymph Nodes	As much as possible; add 2-3 ml sterile saline	As soon as possible at room temperature (no formalin, preservatives, or fixatives)	Yes
Blood	10ml preferred, minimum 5 ml. Collect in SPS or heparin tube, no EDTA	At room temperature, do not refrigerate or freeze	Mainly for diagnosis of disseminated MAC disease in patients with AIDS

Specimen Collection, Handling, Transport and Processing

SUBOPTIMAL AND UNACCEPTABLE SPECIMENS

Suboptimal and Unacceptable Specimens

- Processing of suboptimal or poor quality specimens is a burden on both financial and personnel resources
- Results generated from processing inappropriate specimens may not be reliable
- Each laboratory must develop its own specimen rejection criteria and make these criteria readily accessible to providers
- Clinicians should be notified when a specimen is rejected and the reason for rejection should be provided
- Specimens collected by invasive procedures should not be rejected

Possible Rejection Criteria (1)

- Labeling of specimen does not match identifiers on requisition form
- Insufficient volume
- Dried swabs
 - Swabs in general are not optimal
 - Provide limited material
 - Hydrophobicity of mycobacterial cell envelope inhibits transfer to media
- Pooled sputum or urine
- Sputum left at room temperature for 24 hours

Possible Rejection Criteria (2)

- Broken specimen containers or leaking specimens
- Excessive delay between specimen collection and receipt in the laboratory
- Blood specimens collected in EDTA might be rejected for culture as these inhibit growth of MTB
- Tissue or abscess material in formalin
- Gastric lavage fluid if pH not adjusted within 1 hour of collection

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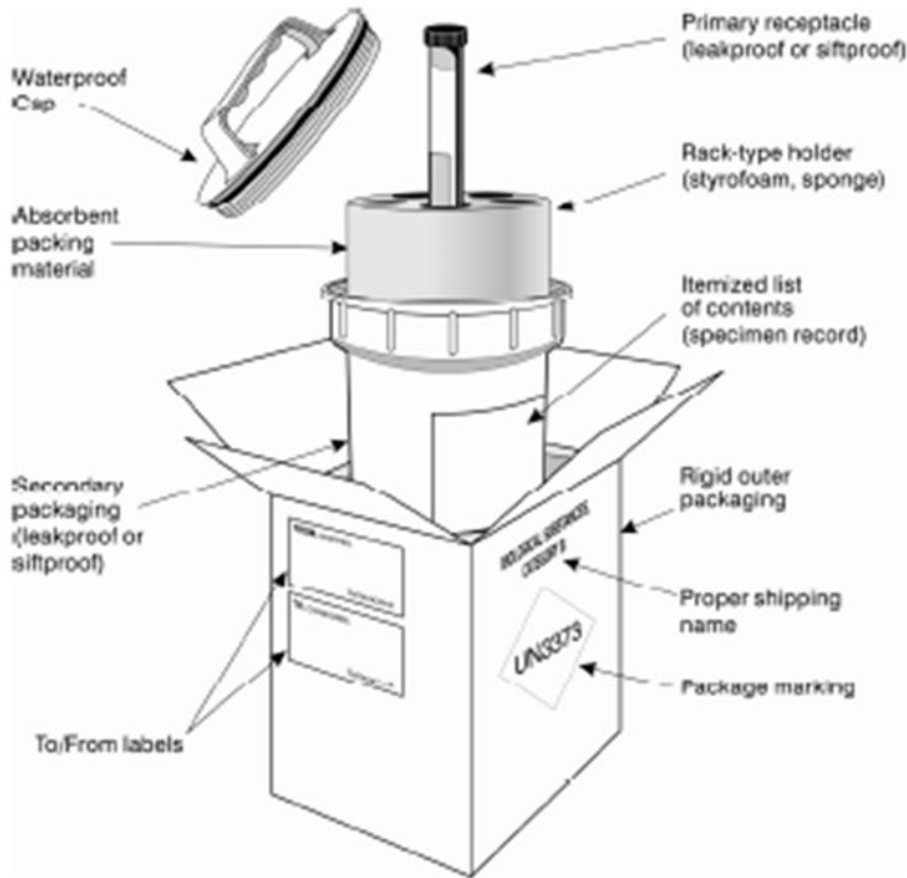
SPECIMEN TRANSPORT: REFERRAL OF SPECIMENS WITHIN A LABORATORY NETWORK

Transport of Biological Substances (Category B)

Basic triple packaging system

- (i) a leak-proof primary receptacle(s);
- (ii) a leak-proof secondary packaging containing sufficient additional absorbent material shall be used to absorb all fluid in case of breakage
- For cold transportation conditions, ice or dry ice shall be placed outside the secondary receptacle. Wet ice shall be placed in a leak-proof container.
- (iii) an outer packaging of adequate strength for its capacity, mass and intended use.

Transport of Biological Substances (Category B)



Biological Substance,
Category B

Sputum Collection Kit



An example from the Wisconsin State Laboratory of Hygiene

- Insulated mailer with address label
- UN3373 marking and proper shipping name “Biological Substance, Category B”
- Sterile plastic conical tube with label
- Sealable biohazard specimen transport
- Cool pack
- Absorbent pad
- Instruction sheet

Transport of Biological Substances

- Transport of patient specimens is regulated by both the Department of Transportation (DOT) and by International Air Transport Association (IATA) rules.
- Laboratories must have personnel trained in and familiar with these regulations
- For details regarding these regulations, please see the information provided in the next slide.

Packing and Shipping Guidance

- ASM website-Guidance: [Packing and Shipping Infectious Substances](#)
- DOT guidance: [Transporting Infectious Substances Safely](#)
- More DOT Guidance: [Infectious substances guide](#)
- IATA website: [FAQs | Infectious Substances](#)
- FedEx Guidance: [Clinical Samples, Biological Substances Category B\(UN 3373\) and Environmental Test Samples](#)
- UPS Guidance: [Packing Hazardous Materials](#)

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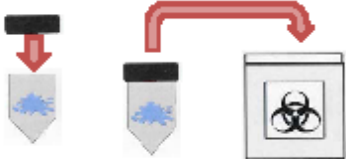




ADDITIONAL INFORMATION

Instructions for Sputum Collection

- Healthcare providers should educate patients on proper specimen production and collection
- Patients should also be informed of the possible infectious nature of his or her secretions
- Specimens should be collected in appropriate tubes that are sterile, clear, plastic, and leak-proof (50 ml screw capped centrifuge tubes that can withstand 3000 x g are preferred)
- Proper labeling protocols should be put in place by the laboratories
- Work with TB program to provide instructions for submitters

Examples for Instructions for Sputum Collection

Sputum Specimen Collection for Tuberculosis Testing

 <p>Sputum comes from the lungs after a deep cough.</p>	 <p>When you first wake up in the morning, cough up the sputum before eating, drinking or smoking</p>	 <p>Sputum kit includes:</p> <ol style="list-style-type: none"> 1. Plastic collection tube 2. Biohazard bag with pad 3. Ice Pack - Freeze 4. Lab slip with clear bag 5. Foam box 6. Pre-addressed postage-paid outer mailer <p>The public health nurse will give you the collection kit which contains the items listed above. Freeze the ice pack.</p>
 <p>Lab Form</p> <p>The nurse will help you fill out the lab form and put the return address on the mailer. Write the collection date on the lab slip and collection tube.</p>	 <p>Cough the sputum directly into the tube. DO NOT get the sputum on the outside of the tube. If necessary, wash the outside of the tube.</p>	 <p>Replace the cap on the plastic tube. Fasten the cap SECURELY. Place the tube INTO the biohazard bag containing an absorbent pad. SEAL and refrigerate the specimen bag.</p>
 <p>Place the frozen ice pack and biohazard bag(s) containing the sputum tube into the foam insert box.</p>	 <p>Put the slip(s) into the clear plastic bag. Place the foam box into the pre-addressed postage-paid outer cardboard box. Place the lab forms into the cardboard box outside of the foam insert.</p>	 <p>Put the box into the US Post Service.</p> <p>PA Department of Health Bureau of Laboratories 110 Pickering Way Exton, PA 19341-1310</p> 

Part 2: Specimen Processing



Principles of Specimen Processing

Respiratory specimens (and other specimens from non-sterile sites) require digestion, decontamination, and concentration:

- **Digestion:** Mucolytic agent used to liquefy sputum specimens to release AFB and expose normal flora for decontamination
- **Decontamination:** Toxic agent used to kill rapidly growing normal flora that would otherwise overgrow slow growing mycobacteria
- **Centrifugation:** Used to sediment bacteria following digestion/decontamination

Effect of Processing Procedure

- Reagents used for digestion and decontamination, to some extent, are toxic to mycobacteria
- Procedures must be precisely followed
 - Time in contact with digestion/decontamination reagents is critical
 - Centrifugation procedures also affect mycobacteria recovery rates and must be carefully followed
- Culture positivity rates and contamination rates should be monitored to evaluate performance of processing methods

Safety

- Many of the steps within the specimen processing procedure are aerosol-generating
- The following activities should be performed in a biological safety cabinet:
 - ✓ Digestion and decontamination
 - ✓ Preparation of concentrated smear
 - ✓ Inoculation of culture media
- Do not disrupt airflow of the cabinet
- Avoid excess clutter inside the BSC

*For more information on the biosafety practices in the Mycobacteriology laboratory, **please review the module on biosafety** within this series*

Aseptic Techniques: Getting Started

- Disinfect BSC, centrifuge, and tabletop with tuberculocidal disinfectant (repeat after specimen and culture workup complete)
- Perform all work on absorbent pad soaked with disinfectant to absorb any droplets that may inadvertently occur
- When possible, leave an empty space in the rack between each specimen tube
- Work in sets equivalent to one centrifuge load (e.g., 8 specimens at a time)

Aseptic Techniques: Processing

- Use a fresh individual, disposable, sterile pipette at every step to avoid transfer of bacilli
- To avoid droplet aerosol cross-contamination, open and remove caps from tubes one at a time
- Add diluent to centrifuge tubes from individual tubes without the lip of the tube touching or creating an aerosol (do not use common containers or carboys)
- Use aerosol-proof sealed centrifuge cups
- Discard supernatant from decontaminated specimens into splash-proof container with disinfectant. Autoclave the discard container daily

Digestion & Decontamination Methods

Several methods are available for digestion and decontamination of clinical specimens:

- *N-acetyl-L-cysteine*-sodium hydroxide (NALC-NaOH)
 - Commercially available: Alpha-Tec NAC-PAC™, BD MycoPrep™
- Oxalic acid
- Cetylpyridinium chloride (CPC)-sodium chloride
- NaOH method (Petroff's method)
- Zephiran-trisodium phosphate (Z-TSP)

NALC-NaOH Method: Principle

- Most common and preferred method
- Rapid and relatively effective in reducing the number of contaminants
- Addition of the mucolytic agent 2% NALC allows effective decontamination with 1% NaOH (less harsh on mycobacteria) (final concentrations)
- Sodium citrate also included in digestion mixture to bind heavy metal ions in specimen that could inactivate *N-acetyl-L-cysteine*

NALC-NaOH Method: Reagents

- NaOH and sodium citrate can be prepared and combined in advance
- NALC should be prepared and added fresh daily
- Once NALC added, solution should be used within 24 hours

Volume of digestant needed	4% NaOH	2.9% sodium citrate dehydrate	Add NALC (fresh)
50 ml	25 ml	25 ml	0.25 g
100 ml	50 ml	50 ml	0.50 g
500 ml	250 ml	250 ml	2.50 g

NALC-NaOH Method: Procedure for Sputum

1. Add equal volume of NALC-NaOH solution to 5-10 ml of sputum in 50 ml plastic screw cap centrifuge tube
2. Cap tube tightly. Invert the tube so that the NALC-NaOH solution contacts all inside surfaces of the tube and cap and then mix the contents for approximately 5-20 seconds with a Vortex mixer.
3. Allow mixture to stand for **15 minutes** at room temperature with occasional gentle shaking by hand.
4. Add sterile distilled water or sterile pH 6.8 phosphate buffer to the 50 ml mark on tube. Securely cap tube and mix by inversion
5. Centrifuge the tubes for 15 min at 3,000 x g using aerosol-proof sealed centrifuge cups

NALC-NaOH Method: Procedure for Sputum

- After centrifugation, open centrifuge cups in BSC, slowly pour off supernatant into splash-proof discard container containing disinfectant
 - Take care to not disturb or pour off sediment (pellet)
 - Take care to avoid aerosol production and to prevent contamination of the lip of the tube
- Wipe the lip of the tube with gauze soaked with disinfectant
- Resuspend sediment in 1-2 ml of saline solution or phosphate buffer
- Mix gently and proceed to culture inoculation and smear preparation

NaOH Concentration is Key

- Recommended final concentration is 1.0% NaOH
- Concentration of NaOH can be adjusted based on contamination rate in individual laboratories
- NaOH at a FINAL concentration of $\geq 2.0\%$ can be lethal to mycobacteria (may see decrease culture sensitivity in smear negative specimens)

Amount of NaOH in 100 ml water	% NaOH	% NaOH when added to equal volume Na citrate	Final concentration of NaOH when added to specimen
4.0g	4.0%	2.0%	1.0%
6.0g	6.0%	3.0%	1.5%
8.0g	8.0%	4.0%	2.0%

Timing is CRITICAL

- **15 MINUTES**

- Time in contact with NALC-NaOH is critical since the high pH rapidly kills microorganisms in the specimen including mycobacteria
- Over processing results in reduced recovery of mycobacteria
- The importance of timing must be considered when deciding how many specimens can be processed in one run

Specimen Processing QC

- A Negative Processing Control (10 ml sterile water or buffer) should be included with each batch of specimens processed
- Negative control is put through entire specimen processing procedure and inoculated to media
 - Determines if contamination is introduced during processing or culture handling
 - Assures that isolates are coming from patients and not from any other source

Definition of Cross Contamination

Cross contamination: the transfer of *M. tuberculosis* complex bacilli (or other mycobacteria) from one specimen to another specimen that does not contain viable bacilli, causing a false positive result.

- The phenomenon of misdiagnosis of tuberculosis due to cross contamination has been widely reported and has significant clinical and therapeutic impact on the patient.

To reduce the possibility of Cross Contamination:

- Use daily aliquots of processing reagents and buffers. Any leftover should be discarded.
- Never use common beakers or flasks when processing.
- Keep the specimen tubes tightly closed and clean the outside of the tube prior to vortexing or shaking.
- Pour decontamination reagents or buffers slowly on the side of the tube without causing any splashing. Do not touch the container of reagents to the lip of the tube at any time during addition.

To reduce the possibility of Cross Contamination:

- Open the specimen tubes very gently to avoid aerosol generation.
- When adding reagents to the tube, open one tube at a time. Do not keep all the tubes open at the same time.
- Do not place tubes too close to each other in the rack
- Change gloves often
- Avoid manipulation of PT specimens
- Disinfect biological safety cabinet work surfaces routinely.

Specimen Processing Proficiency

- Digestion, decontamination, and concentration procedures should only be performed by trained laboratory staff.
- Mycobacteriology laboratories should participate in an approved proficiency testing program.
- Proficiency in culture and identification of MTV may be maintained by digestion and culture of 15-20 specimens per week.

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**SPECIMENS FROM CYSTIC FIBROSIS
PATIENTS AND EXTRAPULMONARY SITES**

Cystic Fibrosis (CF) Patients

- Specimens from CF patients are often heavily contaminated with *Pseudomonas aeruginosa*.
- If it is known or discovered specimen is from a patient with CF or notable media contamination you can process concentrated sediment using only the 5% oxalic acid method.

Oxalic Acid Processing Method for Specimens from CF Patients

- Add an equal amount of 5% oxalic acid to:
 - 5-10 ml of primary respiratory specimen or
 - NALC-NaOH processed concentrated sediment
- Vortex specimen and allow to incubate at room temperature for 30 minutes, mixing every 10 minutes
- Neutralize with buffer solution
- Concentrate specimen by centrifugation for 15 minutes at $\geq 3000 \times g$
- Decant supernatant into splash-proof container and resuspend pellet with buffer solution
- Inoculate media

Processing Gastric Lavage and Urine

- Centrifuge for 30 minutes at $\geq 3000 \times g$
- Discard supernatant carefully into splash-proof container
- Re-suspend pellet in sterile distilled water
- Process suspension as for sputum (NALC-NaOH)

Processing Aseptically Collected Fluids

- Cerebral spinal fluid (CSF), synovial, pleural, peritoneal, pericardial
- No decontamination required
- Concentrate specimen to maximize the yield of mycobacteria
- Inoculate directly to culture media

Processing Tissue Specimens

- Lymph node, lung tissue, biopsies
- Tissue submitted in formalin is unsatisfactory for culture
- No decontamination required
- Process tissue specimens using a sterile tissue grinder, or mortar and pestle
- Inoculate directly to culture media

Processing Blood or Bone Marrow Aspirates

- Specimens inoculated directly into MYCO/F LYTIC bottles or BacT/ALERT MB blood medium
- Direct inoculation of blood onto a solid medium is not recommended
- If transport is necessary, sodium polyanethol sulfate, heparin, or citrate may be used as anticoagulants
- Blood collected in EDTA and coagulated blood are not acceptable

Specimen Collection, Handling, Transport and Processing

PRINCIPLES OF CENTRIFUGATION

Concentration of Specimens

- Since mycobacteria do not readily sediment, centrifugation force and time are important for maximal concentration
- Specimens should be centrifuged for at least 15 minutes at 3000 x g
- *Revolutions per minute* (rpm) is a measure of speed for a particular centrifuge head and not a measure of concentration efficiency or *relative centrifugal force* (RCF)
- The relative centrifugal force is measured in units and is expressed in multiples of the earth's gravitational field abbreviated as *g*
- Use of a refrigerated centrifuge at 8 to 10°C may help to eliminate heat build-up which could be lethal to mycobacteria

Calculation of Centrifugal Force

Formula for calculating a particular centrifugal force is:

$$RCF = 1.12r (\text{RPM}/1000)^2$$

where r is the radius, which is the distance in mm from the center of rotation to a point within the rotor, and RPM (revolutions per minute), which is the speed of rotation

- This information should be published in many of the centrifuge manufacturers instruction manuals

Note: Nomogram attached in Resources section

Specimen Collection, Handling, Transport and Processing

QUALITY INDICATORS

Quality Indicators: Contamination Rate

- “Contamination” occurs when inoculated media is completely compromised due to overgrowth with non-acid fast organisms.
- Contamination Rate monitors specimen preparation and the decontamination process
- Calculation of contamination rate in Liquid media:
 - Numerator: number of inoculated broth cultures discarded or re-decontaminated in 1 month due to contamination
 - Denominator: total number of broth cultures inoculated in one month
- Calculation of contamination rate in Solid media:
 - Numerator: number of inoculated solid media slants or plates discarded in 1 month due to contamination
 - Denominator: total number of solid media slants or plates inoculated in one month

Contamination Rates

- Acceptable overall rates of contamination
 - Solid media (LJ) is 2-5%
 - Liquid media (MGIT960) is 7-8%
 - Contamination rates for the individual laboratory can be affected by the type of media used (i.e. media containing antibiotics)
- A contamination rate less than that of the acceptable rate indicates that processing methods are too harsh
 - NaOH concentration too high
 - Specimen exposure time to NALC-NaOH too long
- A contamination rate greater than that of the acceptable rate could indicate a pre-analytical problem, an inadequate decontamination process, or both

Potential Causes of High Contamination Rates

- Lack of appropriate sputum collection guidance for patients
- Delays in transport
- Lack of refrigeration prior to transport
- Inappropriate storage conditions or processing delays upon receipt in the laboratory
- Decontamination process is ineffective
 - NaOH concentration too low
 - Specimen exposure time to NALC-NaOH too short

Quality Indicators: Positivity (Recovery) Rate

- Establishes a baseline for a given population or geographic area
- Assists in identifying potential false positive or false negative cultures (MTB)
- Assists in identifying environmental contamination
- Calculation of positivity rate:
 - Numerator: number of cultures reported as MTB in one month
 - Denominator: total number of cultures reported (TB, NTM, negative, contaminated) in one month.

Quality Indicators: Positivity (Recovery) Rate

- Expectation: Population/geographic region dependent
- Increases may be due to:
 - Shift in patient population
 - Cross contamination/false positives
 - Contaminated reagents, media, water (NTM)
 - Specimens contaminated during collection
- Decreases may be due to:
 - Shift in patient population
 - Problems with specimen quality
 - Problems with specimen processing
 - Problems with equipment or media
 - Increase in contamination

What should I do if Quality Indicators or Controls are out of range?

- Ensure quality specimens are being received in the laboratory
- Ensure quality reagents and media are being used
- Ensure water used for specimen processing is sterile and filtered
- Ensure laboratory equipment (e.g. incubators, BSCs) is functioning properly
- Ensure protocols are followed
- Ensure staff are trained and proficient

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