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The Antimicrobial Stewardship Publication of the Center for Antimicrobial Utilization, Stewardship, and Epidemiology (CAUSE)

BE ANTIBIOTICS AWARE
SMART USE, BEST CARE

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Respiratory Cultures: Change from Quantitative to Semi-Quantitative Reporting

By Elizabeth Palavecino, MD and Vera Luther, MD, FIDSA

Since the March 2024 Encompass go-live, the microbiology laboratory at Atrium Health Wake Forest Baptist (AHWFB) has standardized the respiratory culture workup and resulting categories to align with the other laboratories within our healthcare system. The quantitative culture method was replaced by a semi-quantitative culture method. This article describes the rationale for the change as well as information on how to interpret semi-quantitative culture results.

Diagnosis

There is no gold standard test for the diagnosis of ventilator-associated pneumonia (VAP). Clinicians must rely on a combination of clinical, radiologic, and laboratory data in severely ill patients. The actual necessity and utility of microbiologic cultures, and whether these should be performed on invasive or noninvasive specimens, remains controversial. Qualitatively, there is relatively good agreement among sample types, particularly when collected prior to initiating therapy for a new-onset infection.[1] The question then becomes whether a quantitative method offers any advantages over a semi-quantitative approach. The literature is not definitive on whether quantitative results of bronchoalveolar lavage (BAL) or endotracheal aspirate (EA) cultures are clinically reliable in the diagnosis of VAP, and there are widely varying opinions on what truly represents best practice.

Specimen quality

Another factor that must be considered is specimen quality. In BAL, for a quantitative result to be reliable, sampling must be standardized because variability in the volume of fluid, both instilled and retrieved, leads to differences in the bacterial load detected in culture. If a smaller amount of fluid is instilled and retrieved, this would overestimate bacterial burden, and the converse is true if a larger amount of fluid is used due to the increased dilution. Thus, a quantitative culture does not necessarily indicate the true bacterial load in the lung.[2] The quality of EA samples varies greatly as well. The viscosity or thickness of the sample makes it very difficult to homogenize it, and sampling cultures may not be representative of the disease process. Cultures of EA, although likely to contain the true pathogen, are more likely to grow mixtures of species of bacteria than specimens obtained by bronchoscopic techniques.

Quantitative versus semi-quantitative cultures

The microbiology laboratory at AHWFB had previously offered a quantitative culture for BAL and EA samples submitted for culture from patients suspected of VAP. For BAL samples, $\geq 10^4$ CFU/mL was considered significant, while for EA samples a threshold of $\geq 10^5$ CFU/mL was used.

Image: https://www.cdc.gov/antibiotic-use/

1. Masterton RG et al. *J. Antimicrob. Chemother.* 2008;62:5–34.
2. Fujitani S, Yu VL. *Clin. Infect. Dis.* 2006; 43(Suppl 2):S106 –S113.

Respiratory Cultures: Change from Quantitative to Semi-Quantitative Reporting, cont.

By Elizabeth Palavecino, MD and Vera Luther, MD, FIDSA

However, quantitative studies require extensive laboratory work and special procedures without providing an accurate result due to the variation in specimen quality as described above. Therefore, quantitative cultures are not endorsed by the IDSA/ASM guide to utilization of the microbiology laboratory for diagnosis of infectious diseases published in 2024 given there is no clear evidence that quantitative cultures improve the microbiologic diagnosis of VAP compared with semi-quantitative cultures.[3] For these reasons, the microbiology laboratory at AHWFB has replaced the quantitative culture method with a semi-quantitative culture method.

Previous and current reporting categories for respiratory cultures:

Quantitative culture resulting category (pre-Encompass): 10^3, 10^4, $\geq 10^5$ CFU/mL

Semi-quantitative resulting category (post-Encompass): Scant, Light, Moderate, Heavy.

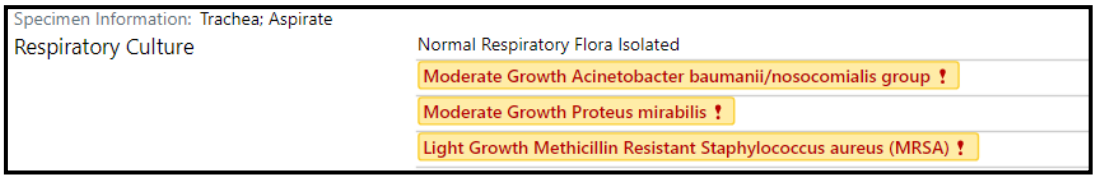

Figure 1: Semi-quantitative resulting category (post-Encompass)

Interpretation of respiratory culture results:

The microbiology laboratory has received many inquiries about the correlation between the semi-quantitative and the previously used quantitative culture. Because of the high variability in sample quality and amount and type of bacterial organisms present in the sample, strict correlation is challenging. An assessment performed by the microbiology laboratory found that samples growing one or two organisms (e.g., *S. aureus*, *P. aeruginosa*) in amounts of 10^4 or 10^5 CFU/mL by quantitative methods correlated with growth currently reported as moderate or heavy by the semi-quantitative method (Figure 2a). However, the correlation was lower between the two methods when multiple types of organisms in different amounts were present in the sample (Figure 2b).

A.

B.

Figure 2A: A BAL sample with heavy growth of *Klebsiella pneumoniae.* Organism is growing on all quadrants of the plate, and it is the predominant organism. **2B:** An endotracheal aspirate sample with moderate and heavy growth of several different organisms. Interpretation and reporting the amount of each organism is challenging.

It is important to remember that VAP is a clinical diagnosis. Culture results are helpful in identifying organisms. However, culture results alone do not form the basis for a diagnosis of VAP, and microbiologic culture results in respiratory samples should be interpreted in conjunction with clinical findings.

3. Miller JM et al. *Clin Infect Dis.* 2024;ciae104. doi: 10.1093/cid/ciae104. Online ahead of print.

Critical Shortage of Blood Culture Bottles

By Olivia Randazza, PharmD, CPP, BCIDP and Vera Luther, MD, FIDSA

There is a critical shortage of BD BACTEC™ bottles used for blood culture (BCx) collection. This shortage impacts aerobic, anerobic, acid-fast bacilli, and fungal culture bottles for both pediatric and adult patients in the Wake and Greater Charlotte markets. Due to a shortage of materials, blood culture bottle production will decrease by 50% over the next few months. Conservation of blood cultures bottles now is necessary to ensure adequate supply in the future. In response to the shortage, clinical guidance on blood culture ordering and utilization was developed. Facilities and providers should align their practices with recommendations found in the clinical guidance linked here: clinical guidance document.

Summary of Key Points

2 Blood Culture Sets	**1 Blood Culture Set Only**
	
Obtain 2 sets ONLY for initial blood cultures in adult patients with the following conditions: • Septic shock • Suspected endocarditis/ endovascular infection • High-risk immunocompromised conditions including febrile neutropenia **This is supported by clinical decision support in Encompass requiring documentation of initial BCx indication**	• **Obtain 1 set for initial blood cultures in adult patients with conditions associated with high probability of bacteremia** • Exception: conditions listed for 2 blood culture sets • **Obtain 1 set for follow-up blood cultures in adult patients to** document clearance of blood stream infection (BSI) only indicated for high-risk organisms (e.g. *Staphylococcus aureus or lugdunensis, Candida* species) or clinical syndromes • **For most pediatric patients** only 1 aerobic blood culture bottle should be sent for both initial and follow-up blood cultures

Do Not Check Blood Cultures

Do not repeat blood cultures more often than every 72 hours (hard stop in Encompass)

Do not order:

- **Blood cultures with low clinical utility** (e.g. with clinical syndromes rarely associated with bacteremia, comfort care or end-of-life care)
- **Initial fungal blood cultures** when Candidemia is suspected if also obtaining bacterial blood cultures
- **Anticipatory blood cultures** (i.e. drawn before clinical decision making is complete)
- **Surveillance blood cultures** (i.e. routine monitoring for bacteremia without clinical indication)
- **Future orders for blood cultures** (e.g. placing an order for follow-up blood cultures daily for multiple days)

- **Exceptions to the restrictions are only allowed via an Infectious Diseases provider**.
- For other clinical scenarios, see the guidance document for ADULTS and PEDIATRICS. **The guidance should be interpreted in the context of each patient's clinical scenario and does not substitute for clinical judgement.**

Images: Preventing Adult Blood Culture Contamination: A Quality Tool for Clinical Laboratory Professionals | CDC

Blood Culture Time to Positivity

By Alex Taylor, PharmD, CPP, BCIDP, AAHIVP

For over a decade the use of continuously monitored automated blood culture detection systems, like BD BACTEC™ FX Blood Culture System, has allowed for rapid and real time recognition of bacterial growth in blood cultures.[1] Prior to implementation of these systems, culture results were reported with colony-forming units per milliliter (CFU/mL). The quantification of these results correlated to the burden of infection and could be used to determine the source of bacteremia, to determine if the culture represented a contaminant, or to assign disease severity. While automated systems are not capable of providing a measure of CFU/mL**, time to positivity (TTP)**, defined as **the amount of time from the beginning of culture incubation to the detection of bacterial growth**, has become a diagnostic and prognostic tool.

A short TTP reflects a higher amount of bacteria in the blood culture sample and thus is generally associated with a higher disease burden.[2] Numerous studies have discovered certain clinical and microbiological factors associated with a short TTP, including immune status (e.g., neutropenia), source of bacteremia, biochemical properties of bacteria (e.g., lactose fermentation), bacterial species, cirrhosis, malignancy, and disease severity.[3-9] Additionally, **a short TTP has been shown to be a significant predictor of mortality and septic shock in Gram positive and negative bloodstream infections**.[10] In the modern area of rapid diagnostics, multiplex polymerase chain reaction (PCR) tests, like BioFire® Filmarray® Blood Culture Identification 2 Panel (BCID2), are used to identify organisms and key resistance genes within an hour of positive blood culture detection and to guide empiric antimicrobial therapy. The results from these rapid, multiplex PCRs have often eliminated the need for routine reliance upon tools like TTP for diagnostic purposes.[11-12] However, there are several examples where TTP maintains diagnostic utility. **Monitoring TTP** in multiple blood culture sets **can support the diagnosis of central line associated bloodstream infection (CLABSI)** when the TTP is shorter from the blood culture drawn from the central line compared to the simultaneously peripherally drawn blood cultures.[13] In serially drawn blood cultures from persistently bacteremic patients, TTP can also inform response to treatment, where increasing TTP would suggest the patient is progressing towards culture clearance. Alternatively, TTP has been used as a **diagnostic tool to assist in distinguishing contamination versus true infection (Figure 1)**.[14-18] Growth of pathogens, which are likely to be present in higher concentrations in blood from patients with true bacteremia, will be detected earlier than contaminants, where the burden of bacteremia is generally thought to be lower.

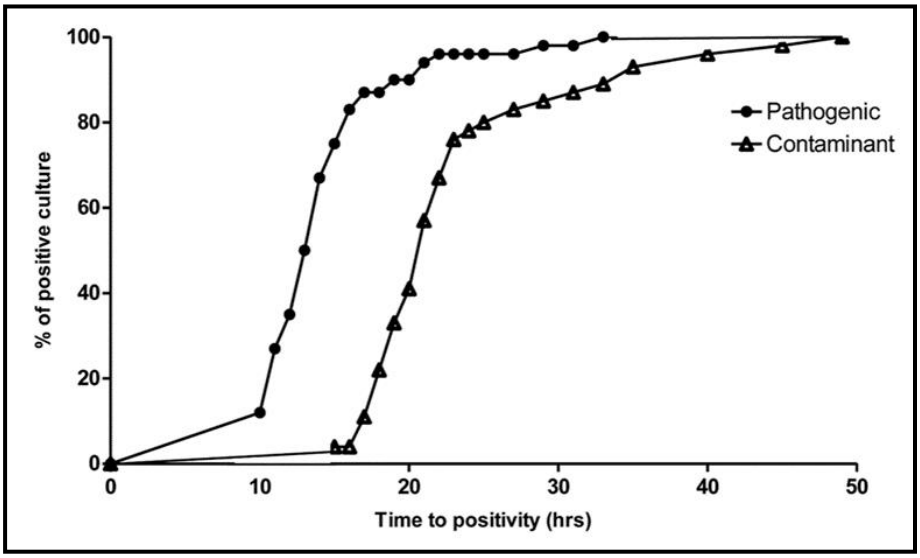

Figure 1: Graphic representation of blood culture time to positivity by pathogen and contaminant adapted from Lefebvre CE, Renaud C, Chartrand C. Time to Positivity of Blood Cultures in Infants 0 to 90 Days Old Presenting to the Emergency Department: Is 36 Hours Enough? *Journal of the Pediatric Infectious Diseases Society.* 2017;6(1):28-32.

See page 5 for references

Blood Culture Time to Positivity, cont.

By Alex Taylor, PharmD, CPP, BCIDP, AAHIVP

There are several limitations to the use of TTP. Cofounders that can effect organism growth, such as delays in time from culture collection to incubation or antibiotic exposure (Figure 2), can influence TTP and as a result it's utility.[1,2, 14] Continuously monitored blood culture systems and enhancements to culture media have improved the recovery and shortened the time to detection of both true pathogens and contaminants.[14, 19-20] Given these advances and the extensive overlap in detection times between pathogens and contaminants, length of TTP may be less informative and should not singularly be relied upon to accurately predict the clinical significance of individual blood culture isolates.[14] Instead TTP, if used, should be used in conjunction with a complete assessment of the patient and clinical scenario to inform decision making.

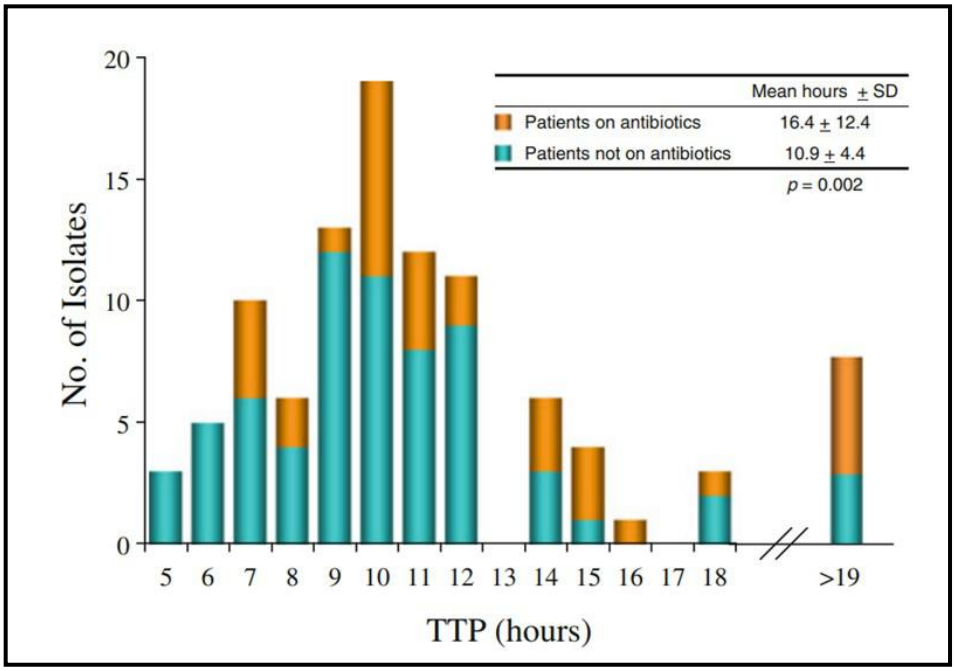

Figure 2: Time to positivity (TTP) histogram and impact of pre-existing antibiotics adapted from Palmer HR, Palavecino EL, Johnson JW, Ohl CA, Williamson JC. Clinical and microbiological implications of time-to-positivity of blood cultures in patients with Gram-negative bacilli bacteremia. *Eur J Clin Microbiol Infect Dis*. 2013; 32:955–959.

At Atrium Health Wake Forest Baptist facilities, TTP was historically reported for all positive blood cultures in the electronic medical record (EMR). Reporting of TTP in our health system required a manual calculation and subsequent manual documentation in the EMR by the microbiology lab technician. Beginning March 2024 as a part of harmonization efforts, **the microbiology lab no longer reports TTP for blood cultures within Encompass**. This change in practice was due to the availability of other diagnostic tools, the limitations discussed above, and the time intensive workflow it required. However, TTP can be requested by calling the microbiology lab at x62658 as it remains a prognostic and diagnostic tool in select scenarios.

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2. Rogers MS, Oppenheim BA. *J Clin Pathol.* 1998; 51:635–637.
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5. Peralta G et al. *BMC Infect Dis.* 2006;6:79.
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17. MacGregor RR, Beaty HN. *Arch Intern Med.* 1972; 130:84–88.
18. Lefebvre CE et al. *J Pediatric Infect Dis Soc.* 2017;6(1):28-32.
19. Krisher KK et al. *J Clin Microbiol.* 1993; 31:793–797.
20. Kennedy GT et al. *J Clin Pathol.* 1995; 48:912–914.

CAUSE Guideline Highlight

Did You Know?

- Institutional Antimicrobial Dosing Guidelines are available on the CAUSE website
- Includes:
  - Loading and maintenance dose recommendations based on the antimicrobial and select indications
  - Renal dose adjustments
  - Dose adjustments for dialysis modalities
  - Dosing weight recommendations

Atrium Health
Wake Forest Baptist
Center for Antimicrobial Utilization, Stewardship, and Epidemiology

P&T Formulary Updates

Drug	Action
Sulbactam/ durlobactam (Xacduro©)	• β-lactamase inhibitor—β-lactamase inhibitor combination antimicrobial indicated for use against *Acinetobacter baumannii-calcoaceticus* complex infection • Added to formulary; restricted to CAUSE/ID
Lenacapavir (Sunlenca©)	• HIV-1 capsid inhibitor indicated for use in combination with an optimized background antiretroviral regimen for salvage treatment of HIV • Added to formulary; restricted to outpatient use
Rezafungin (Rezzayo©)	• Long-acting echinocandin indicated for treatment of candidemia and invasive candidiasis • Added to formulary; restricted to CAUSE approval only

Meet the CAUSE Staff

The Center for Antimicrobial Utilization, Stewardship, and Epidemiology (CAUSE) is the Antimicrobial Stewardship Program of Atrium Health Wake Forest Baptist (AHWFB). CAUSE was established in 2000 to promote, administrate, and implement antimicrobial stewardship. Daily operation of CAUSE is directed by a core group of clinicians designated as CAUSE staff.

CAUSE activities are consistent with the IDSA/SHEA Antibiotic Stewardship Guidelines. In addition, CAUSE is compliant with TJC standards and the CDC Core Elements of Hospital Antibiotic Stewardship Programs.

It is CAUSE's philosophy to support and work through the clinicians practicing in various areas throughout the health-system. The program goals are to:

- Prevent or slow the emergence of antimicrobial resistance
- Optimize selection, dose, and duration of antimicrobial treatment
- Reduce adverse drug events
- Reduce morbidity and mortality
- Reduce length of stay
- Reduce health care expenditures

CAUSE Staff Members	
Vera Luther, MD, FIDSA CAUSE Medical Director ID Attending Physician	Christopher Ohl, MD, FIDSA CAUSE Associate Medical Director ID Attending Physician
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Olivia Randazza, PharmD, CPP, BCIDP ID Pharmacist	Courtney Jackson, PharmD ID PGY-2 Pharmacy Resident
Charles Hartis, PharmD, BCPS ID Pharmacist	Elizabeth Palavecino, MD Director of Clinical Microbiology Laboratory
Werner Bischoff, MD, PhD, FSHEA Health System Epidemiologist/Director of Infection Prevention and Health System Epidemiology	

The CAUSE Advisory Board (CAB) is a committee that serves to advise, approve, and communicate CAUSE activities and medical staff concerns. It is composed of CAUSE staff, medical staff from selected clinical services, and pharmacy, nursing, and informatics representatives from all Atrium Health Wake Forest market facilities.

Image: https://www.idsociety.org/clinical-practice/antimicrobial-stewardship/index.html

CAUSE Resources

CAUSE Website

CLICK HERE

Access to:

- Adult and pediatric infectious diseases resources:
  - Treatment guidelines
  - Antimicrobial dosing guidelines
  - Rapid diagnostic guidance
- Antimicrobial stewardship curriculum:
  - Didactic lectures
  - Exam questions
  - Small group activities
- Overview of the institution's antibiotic support team (AST)
- Adult and pediatric prior authorization processes and institutional restricted antimicrobials

Access all current and historical Wake Market Antibiograms on the Atrium Health Wake Forest Baptist Intranet by searching "Antibiograms"