

**Editorial**

Pathogen vs Non-pathogen from a Culture-positive Report: How to Distinguish and Who Will?

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KEYWORDS: Pathogen; Commensal; Colonizer; Contaminant; Culture

INTRODUCTION

Recognizing microorganisms isolated in culture is one of the most challenging issues microbiologists and physicians face in infectious diseases.¹ The crucial inquiry is to determine whether the microorganism under investigation is a genuine pathogen necessitating prompt medical attention, a commensal organism coexisting peacefully with the host, a colonizer perhaps dormant, or an unintentional contaminant brought in during specimen collection.

A pathogen is an organism that satisfies Koch's postulates and serve as the definitive causative agent of disease.^{2,3}

A non-pathogen is an organism that does not cause the host disease, harm, or death.⁴ Therefore, its presence does not warrant treatment with an antimicrobial agent.

Commensal, in contrast to a pathogen, engages in a symbiotic relationship with the host that does not result in perceptible, ongoing, or persistent harm.⁵ They are part of the microbiome; however, if the microbiota of one body area gains access to other areas, they may initiate pathogenesis at the new site.

Colonization denotes a state where a microorganism is present within the host for a variable duration without causing localized damage. Colonizers are microorganisms that do not belong to the host's normal flora but do not inflict local damage to the host.⁶ Some

patient characteristics contributing to the transformation of these microorganisms into pathogens are age ≥ 60 years, diabetes mellitus, acquired immunodeficiency syndrome, malignancy, foreign body in the urinary tract, or loss of vesicoureteral reflux on voiding cystourethrogram. Specific organism risk factors are also present.⁷

Contaminants include the unintended or accidental introduction of saprophytic organisms into clinical specimens, including bacteria, fungi, viruses, prions, protozoa, or their toxins and by-products.⁸

Bacteria involved in infectious diseases exist on a continuum, ranging from normal flora to external flora as bystanders, and finally to true pathogens. However, when a clinician receives a culture growth report on a provided sample, there is no distinction between these classified organisms in most cases. In rare instances, microbiologists and clinicians talk with each other before or after providing the report and finalize the true meaning of this growth. Sometimes, reports mention that contaminants cannot be ruled out; clinical co-relation needs to be done. Hence, microbiological diagnosis by culture is paramount to the clinician but sometimes without any real clinical significance.

Sterile body samples or fluids are biological samples that do not typically contain microorganisms, while non-sterile fluids may contain microorganisms. Infections in sterile body sites can be life-threatening

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diagnostic accuracy and patient care will improve while minimizing unnecessary antimicrobial use.¹¹

Blood cultures and multiplex sepsis polymerase chain reaction are vital diagnostic tools in managing patients, especially for identifying underlying infectious processes. A significant challenge arises when blood cultures test positive, as it can be difficult to determine whether the isolated organism is a true pathogen or merely a contaminant or colonizer from a blood-bathed device. This dilemma mainly concerns increased healthcare costs and potential harm to patients.¹³ To address this issue, clinicians use a key approach: collecting blood samples in duplicate. This increases the test's sensitivity and helps confirm the presence of a true pathogen.¹⁴ Additionally, microbiologists often advise a repeat blood sample to ensure that samples are collected under strict aseptic techniques when contamination is suspected.¹⁵ If the same organism is detected in the second sample, it is more likely to be a true pathogen rather than a contaminant. However, there is no definitive way to confirm colonization when a blood-bathed device is present and another source of infection exists, which often occurs in critically ill patients. However, clinician and microbiologist teams may use a bundle, checklist, or stepwise approach to solve this crucial dilemma (Figure 2), as evidenced by these recent studies.¹²

The patient's clinical context plays a significant role in this decision-making process. Clinicians carefully evaluate the patient's signs and symptoms, along with other laboratory findings such as complete blood count, procalcitonin, other infective biomarkers, erythrocyte sedimentation rate, and C-reactive protein levels, to determine whether the isolated organism is consistent with a true pathogen. Also, they use various sepsis scores to determine host-dysregulated responses such as Sequential Organ Failure Assessment (SOFA) score, Modified Early Warning Score (MEWS), etc.¹⁶ Certain organisms are generally considered contaminants, especially Gram-positive bacilli, common skin commensals. These bacteria can easily be introduced into culture plates during the laboratory processes. Additionally, if blood cultures become positive more than 72 hours after collection, the likelihood of contamination increases, depending on the organism. The use of antibiotics before obtaining blood cultures can also complicate the interpretation by delaying or preventing bacterial growth, making it essential to consider the presence of fastidious organisms like *Kingella*, *Eikenella*, *Cardiobacterium*, and species of *Haemophilus*, which require specific conditions for growth.¹⁶ Despite these challenges, some organisms are always regarded as true pathogens when

isolated from blood cultures, such as *Staphylococcus aureus*, *Group A streptococci*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, members of *Enterobacteriaceae*, *Bacteroidaceae*, and *Candida* species.¹⁷

Figure 2: Various checklists used in both stepwise models to decide pathogen vs non-pathogen in culture-positive samples (I-IX).

CHECKLIST I ANY LOCAL SYMPTOMS / SIGNS OF URINARY TRACT INFECTION (UTI)? Any local symptoms/signs of urinary tract infection? 1. Is there increase in frequency to pass urine? 2. Is there urgency to pass urine? 3. Is there dysuria? 4. Is there pus in urine? 5. Is there blood in urine? 6. Is there flank pain/tenderness? 7. Any other local symptoms/signs of urinary tract infection?	CHECKLIST II ASYMPTOMATIC BACTERIURIA NEEDED TO BE TREATED? Asymptomatic bacteriuria needed to be treated? 1. Is patient a pregnant female? 2. Is patient undergoing urological procedure? 3. Is patient in first month after renal transplantation?	CHECKLIST III SOFA Score <table> <tr> <th>Organ System</th><th>Assessment</th><th>0</th><th>1</th><th>2</th><th>3</th><th>4</th></tr> <tr> <td>Respiratory System</td><td>MMV (ml/kg/min)</td><td>10-15</td><td>16-20</td><td>21-25</td><td>26-30</td><td>>30</td></tr> <tr> <td>Coagulation System</td><td>INR</td><td><1.5</td><td>1.5-1.8</td><td>1.8-2.5</td><td>2.5-3.5</td><td>>3.5</td></tr> <tr> <td>Renal System</td><td>Cr (mg/dl)</td><td><1.2</td><td>1.2-1.9</td><td>2.0-2.9</td><td>3.0-3.9</td><td>>4.0</td></tr> <tr> <td>Neurological System</td><td>Cr (mg/dl)</td><td><1.2</td><td>1.2-1.9</td><td>2.0-2.9</td><td>3.0-3.9</td><td>>4.0</td></tr> <tr> <td>Cardiovascular System</td><td>MAP (mmHg)</td><td>>65</td><td>60-64</td><td>55-59</td><td>50-54</td><td><45</td></tr> <tr> <td>Other Systems</td><td>Cr (mg/dl)</td><td><1.2</td><td>1.2-1.9</td><td>2.0-2.9</td><td>3.0-3.9</td><td>>4.0</td></tr> </table> Source: 1. SOA UTI Guideline 2019 2. http://www.ncbi.nlm.nih.gov/books	Organ System	Assessment	0	1	2	3	4	Respiratory System	MMV (ml/kg/min)	10-15	16-20	21-25	26-30	>30	Coagulation System	INR	<1.5	1.5-1.8	1.8-2.5	2.5-3.5	>3.5	Renal System	Cr (mg/dl)	<1.2	1.2-1.9	2.0-2.9	3.0-3.9	>4.0	Neurological System	Cr (mg/dl)	<1.2	1.2-1.9	2.0-2.9	3.0-3.9	>4.0	Cardiovascular System	MAP (mmHg)	>65	60-64	55-59	50-54	<45	Other Systems	Cr (mg/dl)	<1.2	1.2-1.9	2.0-2.9	3.0-3.9	>4.0
Organ System	Assessment	0	1	2	3	4																																													
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CHECKLIST IV ANY POSSIBLE CAUSE RESPONSIBLE FOR INCREASE IN SOFA OTHER THAN UTI? Any possible cause responsible for increase in SOFA other than UTI? 1. Any clinical feature suggesting cause responsible for increase in SOFA other than UTI? 2. Any lab parameters cause responsible for increase in SOFA other than UTI? 3. Any imaging evidence suggesting cause responsible for increase in SOFA other than UTI?	CHECKLIST V IS MICROORGANISM PART OF NORMAL FLORA? Is microorganism part of normal flora? 1. E.coli 2. Candida 3. Klebsiella 4. Proteus 5. Alpha hemolytic streptococci 6. S. epidermidis 7. E. faecalis 8. Corynebacteria 9. Any other commensals as suggested by microbiologist https://www.nip.edu/india/11669/chapter/5	CHECKLIST VI ANY PATIENT CHARACTERISTICS CONTRIBUTING TO GROWTH OF MICROORGANISM? Any patient characteristics contributing to growth of microorganism? 1. General 2. Old age > 60 years 3. Immunosuppression 4. Acquired immune deficiency syndrome 5. Any long-term use of antibiotics 6. Foreign body in urinary tract 7. Use of vesico-urinary catheter/urethral catheter 8. Any other characteristics contributing to growth of microorganism? Source: Harrison's Principles of Internal Medicine, Twenty-first Edition Copyright © 2015 McGraw-Hill Education, Inc. All rights reserved. ISBN: 978-0-07-182473-0 McGraw-Hill Education, Inc. All rights reserved. ISBN: 978-0-07-182473-0 McGraw-Hill Education, Inc. All rights reserved. ISBN: 978-0-07-182473-0																																																	
CHECKLIST VII ANY POSSIBILITY OF CONTAMINATION? Any possibility of contamination? A1. Was the site cleaned? A2. Was it clean catch and mid-stream? A3. Was it via Suprapubic method? B1. Was the load/weight condition maintained? B2. Was the temperature maintained? B3. Was the sterility maintained? C1. How long was it stored before processing? C2. Was the temperature maintained? C3. Was aseptic condition maintained? Source: UpToDate	CHECKLIST VIII Local site symptoms and signs of infections Meningitis Headache, Altered sensorium UTI Increased frequency, urgency, dysuria Skin Soft tissue swelling, redness, increased warmth, tenderness, pus discharge GI Pain abdomen, Diarrhea, Vomiting Osteomyelitis Bone pain, Local swelling, warmth, pus discharge Other local site infections presenting as bacteremia Any other signs and symptoms	CHECKLIST IX Risk factors for colonization in blood stream infections: 1. Central Venous Catheter (CVC)/PICC line 2. Catheter implanted electronic devices (CED) Source: Vetter S, Kumar A, Singh VA, Tripathi AK, Kumar H. Central venous catheter-related blood stream infections: incidence, risk factors and associated pathogens in a tertiary hospital (a). Jt Science. 2020 Apr; 12(2):55-60.																																																	
CHECKLIST VII	CHECKLIST VIII	CHECKLIST IX																																																	

In the laboratory, samples are screened for quality. For example, those containing too many squamous epithelial cells in respiratory samples are often rejected due to possible contamination. Bartlett's scoring, indicating more than 25 polymorphonuclear leukocytes and fewer than ten squamous epithelial cells per low-power field, strongly suggests the presence of a true pathogen.¹⁸ Similarly, in urine, the Kass Criteria are applied, which consider a bacterial count of $\geq 10^5$ organisms per milliliter as indicative of significant bacteriuria.¹⁹ Pathogens isolated from fine needle aspirations and biopsies are always deemed significant. Pathogens like *Aspergillus* and *Candida* found in sputum are usually considered colonizers and are treated only if there is evidence of invasive disease. Any indwelling device in the respiratory or urinary tract always risks colonizer growth.⁸ For accurate diagnosis, semi-quantitative cultures are performed on lower respiratory tract or urine specimens. Depending on the specimen type and patient profile, growths with specific colony counts are considered significant.²⁰

Urine is an excellent medium for bacterial growth, and any delay in processing can lead to bacterial proliferation, resulting in false-positive results.²¹ Hence, accurate diagnosis depends on proper specimen collection and prompt transportation and processing of samples to the laboratory, as evidenced in these recent studies.¹²

Although the above models look promising, there are a few limitations. The single-centre study had a small sample size and considered limited factors to decide the colonizer. Also, there were limitations of sepsis scores, an absolute method to determine contamination and a need to validate each step and its flow. Further, human assessment errors are a few apparent limitations.

CONCLUSIONS

Sterile and non-sterile body fluid infections are critical due to their life-threatening nature and high risk of morbidity and mortality. However, incorrect diagnoses can lead to unnecessary antimicrobial use, contributing to antimicrobial resistance (AMR), drug toxicity, and higher healthcare costs. Distinguishing between true pathogens and non-pathogens is of utmost importance. Clinician and microbiologist teams can collaboratively answer this complex decision-making process to categorize organisms and determine appropriate treatment strategies accurately. Adopting a structured stepwise model like the one mentioned above could be beneficial in addressing these challenges. Each hospital should consider implementing a flowchart tailored to its infection control program, antimicrobial stewardship practices, and local antibiograms. This model may include essential steps: *Any local signs/symptoms suggestive of infection, any signs of septicemia (by using SOFA/MEWS/any other score), any risk factors for the growth of the organism, what are commensals present in the sample site, any possibility of contaminants, and lastly response to empirical/culture guided treatment.* This should remain adaptable, allowing for future modifications based on emerging evidence and evolving clinical needs. Establishing and refining such a model will improve patient outcomes and combat AMR.

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CONFLICTS OF INTEREST STATEMENT

The authors declare no conflict of interest

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Not applicable

AUTHOR'S CONTRIBUTION

All authors are qualified for authorship as per ICMJE criteria. They approved the manuscript.

AI DECLARATION

No AI tool was used to generate research data, perform data analysis, interpret findings, formulate scientific conclusions, or make editorial decisions. All AI-assisted content was critically reviewed, verified, and revised by the authors. The authors take full responsibility for the accuracy, originality, integrity, and final content of the manuscript.

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