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REVIEW ARTICLE

DIAGNOSTIC STEWARDSHIP IN ANTIMICROBIAL STEWARDSHIP

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INTRODUCTION

On a global scale, infections are a leading contributor to morbidity and mortality. Use of diagnostic tests for patients with suspected infections are known to improve patient care. Hence, there has been an increasing use of acute phase reactants (APRs) to guide treatment of infections since the presence of these markers signify injury and inflammation.[1]

According to Zakhour et al there has been an overuse of diagnostic tests, particularly in patients who are critically ill or immunocompromised.[2] The overuse of tests applies even to mild infections where unnecessary testing lead to inappropriate treatment for colonizers identified through culture. Diagnostic stewardship plays a key role to help physicians request the right tests for the right patient at the right time. This involves providing coordinated guidance and interventions to ensure that tests especially cultures, are used appropriately and promptly to produce clinically relevant results. This guides medical decisions, while also conserving healthcare resources. Diagnostic stewardship therefore serves as a complement to Antimicrobial Stewardship (AMS).[3]

The objective of this review is to look into Diagnostic Stewardship as a component of Antimicrobial Stewardship. The discussion will focus on the use of inflammatory markers including erythrocyte sedimentation rate (ESR), C-Reactive Protein (CRP), and procalcitonin. The role of blood culture and a PCR based pneumonia panel in will also be examined.

DIAGNOSTIC STEWARDSHIP

Effective diagnostic stewardship entails a multidisciplinary collaboration between clinicians and microbiologists, to ensure that testing is timely and appropriate to optimize patient care and outcomes.

There are three pathways in diagnostic stewardship. The initial stage in the process is the pre-analytical phase, which involves the selection of an appropriate test based on clinical assessment and established guidelines.[2] This ensures that the diagnostic tools chosen are suitable for the disease, thereby guiding treatment decisions. [2] The analytical phase, ensures that the microbiology laboratory conducts tests only on suitable specimens by working closely with infectious disease specialists to establish clear criteria for acceptance of samples. The post-analytical phase, involves a collaboration between laboratory staff and physicians to accurately interpret results. Timely reporting of results is vital to reduce any delay in starting the most effective antimicrobial treatment.[2] Diagnostic stewardship aims to guarantee optimal treatment, resulting in decreased mortality-related infections, lower likelihood of negative side effects, reduced risk of antibiotic resistance, and cost savings through shorter hospital stays and unnecessary tests. [2]

In recent years, the availability of procalcitonin and other biomarkers has led to their increased use in diagnosing infections.[3] This review aims to examine the role of acute phase reactants in assisting clinicians in managing various infections.

ACUTE PHASE REACTANTS

Acute Phase reactants are a diverse set of plasma proteins that fluctuate in response to inflammatory triggers[1]. The acute phase reactants are typically elevated in both acute and chronic inflammatory states, which are linked to various infectious and non-infectious disorders. Identifying which conditions will benefit from these tests is crucial to practice diagnostic stewardship.

ERYTHROCYTE SEDIMENTATION RATE

Erythrocyte Sedimentation Rate (ESR) is a surrogate marker of inflammation, measuring the rate (expressed in mm/hour) at which erythrocytes suspended in plasma fall when placed in a vertical tube.[1] Red blood cells have a negatively charged cell surface and usually repel each other. If this charge is neutralized due to increased fibrinogen or acute phase proteins brought about by inflammation, the red blood cells clump together in chains, a phenomenon known as rouleaux formation. This leads to a faster sedimentation rate.[4] The presence of inflammation causes an increase in the ESR within 24-48 hours, reaching its peak in about a week and taking several weeks to return to normal levels. Conversely, CRP levels begin to rise within 6 hours, peak in 24-48 hours,

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and return to normal within 3 to 7 days[4]. An extremely high ESR value (>100 mm/hr) may indicate the presence of infection, malignancies, rheumatologic conditions, or vasculitis.[1]

ESR and CRP are commonly used in combination to differentiate between soft tissue and bone infections. In patients with soft tissue or bone infections, inflammatory markers decrease early with treatment and return to nearly normal levels within the first 3 weeks. Despite this, patients with osteomyelitis still exhibit elevated levels of ESR during this period. Since it is non-specific, the test is used to indicate disease activity in Osteoarticular infections. It aids in diagnosing and monitoring treatment response for chronic inflammatory conditions such as rheumatoid arthritis (RA), Hodgkin disease, and certain malignancies. A significantly high ESR level is frequently linked to a severe underlying illness such as infection, collagen vascular disease, or metastatic cancer. In cases of SLE, both ESR and CRP can be valuable, particularly when differentiating between infection and disease flare, wherein CRP levels remain unaffected during an SLE flare compared to ESR levels.[1]

Numerous processes that impact red blood cells or fibrinogen influence ESR results. The rate of sedimentation is affected by the size of red blood cells, with larger cells settling more quickly. Other factors such as age, pregnancy, medications, and obesity can also affect ESR.[1]

C-REACTIVE PROTEIN

C-reactive protein (CRP) is an acute-phase plasma protein and is a member of the pentraxin protein family. It is mainly produced in the liver when stimulated by cytokines like IL-6. This protein has been identified in various types of cells, including smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes.[1] It plays a role in the recognition and clearance of foreign pathogens and damaged cells. It acts as an opsonin by binding to phosphocholine on microorganisms, activating the complement pathway and removing cellular debris, apoptotic cells and pathogens.[1] CRP levels begin to rise within 6 hours, peak in 24-48 hours, and return to normal within 3 to 7 days.[4] Laboratory values may vary, and there is currently no standard, hence it is strongly recommended to clinically correlate when interpreting test results. Normal levels are under 0.3 mg/dL, while levels between 0.3 and 1.0 mg/dL are considered normal or mildly elevated, which can be seen in non-infectious conditions (e.g. obesity, pregnancy, depression, diabetes). Values exceeding 10.0 mg/dL, indicate significant elevation and is often indicative of acute bacterial infections, viral infections, systemic vasculitis, or major trauma.[1] Results seen over 50.0 mg/dL are typically associated with bacterial infections in 90% of cases. Moderate elevations between 1.0 and 10.0 mg/dL, strongly suggest systemic inflammation related to autoimmune diseases, malignancies, heart attack, or other conditions.[5] The rate of synthesis of circulating CRP increases proportionally with the intensity of the inflammatory process. CRP was found to be more sensitive than ESR, making it a better predictor of bacterial infection.[6]

CRP is extensively used in neonatal sepsis. As neonatal sepsis is a major cause of illness and mortality among newborns, diagnosing sepsis is a challenge because symptoms in neonates are often non-specific. A study conducted in 2012, examined its accuracy in neonatal sepsis.[7] CRP levels along with blood culture were analyzed upon admission and again after 72 hours. The results indicated that CRP demonstrated a sensitivity of 76.92% and a specificity of 53.49%, resulting in an overall accuracy of 70% for identifying neonatal sepsis. Although CRP testing can aid in the diagnosis of neonatal sepsis, it should not be solely depended upon because of its limited specificity. The American Academy of Pediatrics, recommend that in addition to clinical signs and infant risk factors, two normal CRP tests conducted 8-24 hours after birth and again 24 hours later reveal a negative predictive value (NPPV) of 99.7%. When levels remain consistently normal, the likelihood of bacterial sepsis is very low, allowing for the safe discontinuation of antibiotics.[8] When assessing a newborn for sepsis, it is essential to consider clinical findings, other diagnostic factors, and continuous monitoring of CRP levels. Although diagnostic tests do not effectively determine the need for empirical antibiotics, they can assist in deciding when to discontinue treatment.

PROCALCITONIN

There has been a shift in the focus to procalcitonin as a biomarker, and its use as a guide for antibiotic discontinuation in critically-ill patients or for initiation of antibiotics in mild or low risk cases.

Procalcitonin (PCT) is an early marker of infection with good specificity for distinguishing bacterial from non-bacterial infections.[9] As a prognostic marker it can be used to monitor treatment response and is used as a predictor of blood culture positivity.

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In healthy individuals, procalcitonin is produced within the thyroid. In this case, no procalcitonin enters the circulation since it is broken down to N-terminal procalcitonin, katacalcin and active calcitonin resulting in undetectable levels.[9] In the setting of inflammation and sepsis, procalcitonin production is stimulated by bacterial endotoxins, IL-6, and TNF-α activating the procalcitonin gene found in different tissues, resulting in its release into the bloodstream.[9] The normal level of PCT in healthy individuals is < 0.1 ug/mL. In the presence of bacterial infection PCT levels rise, the extent of which is proportional with the severity of infection. Levels can be detected as early as 3 hours, reaching its peak within 6 to 12 hours after an infection sets in.[10] Its half-life was observed to be approximately 24 hours hence when inflammation resolves, levels are expected to decrease by approximately 50% each day.[10] If the inflammation continues, PCT levels remain constant. Effective antibiotic treatment cause PCT levels to decrease daily, whereas ineffective treatment will lead to high or rising PCT levels.[10] This distinct feature of procalcitonin kinetics make it a useful tool for diagnosis and monitoring disease progression.

Multiple trials have been conducted to investigate the use of procalcitonin algorithms in clinical settings with the aim of reducing unnecessary antibiotic prescriptions and ultimately combating bacterial resistance. One notable study, the ProHosp Trial in Switzerland in 2009 sought to determine the effectiveness of a PCT algorithm in reducing antibiotic usage in patients with lower respiratory tract infections without increasing serious adverse outcomes.[11] The study looked at secondary endpoints such as antibiotic exposure, duration of therapy, and adverse effects from antibiotic treatment. Patients were divided into two groups, one where antibiotics were given based on a specific cut-off for initiating or discontinuing treatment depending on patient risk, and a control group that followed standard antibiotic guidelines.[11] In cases of lower respiratory tract infections, antibiotics were started if procalcitonin levels were above 0.25ug/L. Serial procalcitonin determinations were done during treatment and antibiotics were discontinued if levels decreased by 80-90% from the peak.[11] The study found that the group with procalcitonin-based antibiotic management had lower rates of antibiotic use with fewer antibiotic-related side effects, and no difference in mortality rates or ICU admissions compared to the control group.[11]

A similar PCT algorithm was employed in the PRORATA Trial in 2007 to assess whether a PCT-guided approach can reduce antibiotic use in the ICU. This study focused on critically ill patients suspected of having bacterial infections.[12] The algorithm involved using initial procalcitonin levels to guide decisions on when to start or stop antibiotics. Antibiotic initiation was suggested for patients with PCT levels between 0.5 to 1 ug/L, while criteria for discontinuation was having a PCT value of <0.5ug/L or an 80% decrease from peak levels.[12] The trial demonstrated that patients in the procalcitonin group received fewer antibiotic days compared to the control group, without significant differences in mortality rates between the two groups. There were instances of non-compliance among physicians, who showed reluctance to discontinue antibiotics in clinically unstable patients, even when procalcitonin (PCT) levels were low. Aside from this, the trial did not include patients who were immunocompromised, had poor prognosis, or required long-term antibiotic therapy. This highlighted the importance of an integrated approach to patient care, which considers both symptoms and biomarkers in clinical decision-making.

Procalcitonin and predicting blood culture result

A study was conducted in France between 2006-2012 examining the potential of procalcitonin to predict pathogens from blood culture results during suspected bloodstream infections.[13] The goal was to determine the accuracy of procalcitonin in predicting or excluding relevant pathogens and to identify organisms associated with specific procalcitonin levels. Most blood cultures yielded negative results however among positive cultures *Staphylococcus aureus* was most common, followed by *Escherichia coli, Enterococcus*, and *Pseudomonas*.[13] Patients with gram-negative bacteremia had the highest procalcitonin levels, while those with negative cultures or fungal infections had lower levels.[13] A procalcitonin concentration exceeding 10 ng/mL indicated an increased risk for both gram-positive and gram-negative pathogens, with no significant risk for fungal pathogens at this threshold.[13]

Procalcitonin in Neonatal Sepsis

Neonatal sepsis remains a significant concern in Neonatal ICUs worldwide, yet early detection remains challenging as initial symptoms can be subtle or absent. It was observed that there is a normal peak in procalcitonin

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levels in the first day of life due to physiologic changes after delivery according to Monneret et. al.[14] Similarly the reliability of procalcitonin for diagnosing neonatal sepsis in NICUs was assessed by Chiesa et al, and found an expected post-natal surge in procalcitonin levels among healthy infants, which reflected a normal adaptation process independent of infection. The study established that procalcitonin peaked at 10 ng/ml within 18 to 36 hours of life, decreasing to below 0.5 ng/ml by the second to third day.[14] Gestational diabetes was found to be the only significant factor causing deviation in procalcitonin levels. Thus, an abnormal procalcitonin level beyond 48 hours of life in the absence of gestational diabetes could serve as a marker for differentiating early onset infection from other neonatal conditions.[14]

Procalcitonin in Central Nervous system infections (CNSI)

Alkouli et al utilized PCT to help distinguish between children with bacterial and viral meningitis in Egypt.[15] Patients were divided into groups based on their CSF parameters along with PCT, CRP, and white blood cell counts. These were measured on admission and after three days of treatment. The study found that PCT levels were notably higher in those with bacterial meningitis compared to viral meningitis, and PCT levels decreased after three days of treatment for bacterial meningitis. Conversely, CSF parameters, blood leukocyte, and CRP values showed similar results in both groups.[15] Results are in agreement with a study by Chaudhaury in 2018, wherein serum PCT levels were higher in cases of bacterial meningitis using a cut off of > 0.5ng/mL.[16] This suggests that PCT can be a dependable indicator of bacterial meningitis, and aids in distinguishing between bacterial and viral causes, potentially reducing unnecessary antibiotic use. Furthermore, the sensitivity and specificity of serum PCT at the 0.5 ng/ml cut-off were 95.45% and 84.61% respectively, indicating its usefulness in monitoring treatment response for bacterial meningitis.[16] Various studies have examined the value of serum and CSF PCT levels to differentiate between bacterial meningitis and aseptic meningitis. A study by Makoo et al in 2010 found that a cutoff of > 0.5 ng/mL for serum PCT and CSF PCT demonstrated high sensitivity and specificity for bacterial meningitis.[17] A study in India in 2019, had similar conclusions for children with suspected meningitis. Values of serum PCT between 4 to 15 ng/mL and CSF PCT between 2.8 to 5 ng/mL were strongly indicative of bacterial meningitis, making them valuable as an additional diagnostic marker.[18] Findings do not hold true however for patients with brain abscess and subdural empyema as serum procalcitonin was not elevated in such patients,[19] thus the test may be of limited use in clinical scenarios where focal bacterial CNS infection is suspected.

Procalcitonin in the Post-operative period

It has been well studied that Systemic Inflammatory response syndrome (SIRS) with fever often follows after surgery. Research in adults indicate that procalcitonin levels measured during the post-operative period can increase based on the severity, type, and duration of procedure.[20] Specifically, in major abdominal operations, PCT levels could reach as high as 2 ng/mL, particularly in those classified as dirty procedures. This temporary elevation is expected to decline within 24 hours post-procedure.

The use of cardiopulmonary bypass can also trigger a SIRS response, with PCT levels rising in correlation with the duration of bypass.[20] Usually, the normal PCT value may be higher at 2 ng/mL in this scenario, but levels exceeding 10 ng/mL may indicate possible septic complications.[20] While there is limited research on PCT in neonates following cardiopulmonary bypass, findings suggest that PCT values surpassing 4 ng/mL at 24 hours and 5 ng/mL at 48 hours post-bypass should prompt clinicians to consider infectious complications. It was observed that in pediatric patients who have undergone liver transplant, a slower decline to normal PCT levels was seen, which could limit the usefulness of PCT in this setting. Daily monitoring of procalcitonin levels however could be beneficial in the early detection of infectious complications.[20]

No matter how useful PCT may be in discriminating bacterial infections, there are a few test limitations that should be kept in mind. Clinical situations that cause significant stress can lead to false elevations by triggering systemic inflammation, which results in an increase in cytokines. Such scenarios include severe trauma, shock, extensive burns, surgery, acute respiratory distress syndrome, and invasive fungal infections[21]. Likewise, falsely low PCT levels may be seen in localized infections such as abscesses, infective endocarditis or if blood was drawn too early in the course of infection.[22]

Procalcitonin Monitoring

In 2017, the Monitoring Sepsis Study (MOSES trial) conducted in the USA involved daily PCT measurements in adults with sepsis and severe sepsis in

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the ICU for 5 days.[22] For patients who did not show a decrease in procalcitonin levels by more than 80% from baseline to day 4, the mortality rate nearly doubled compared to those with decreasing PCT trends.[22] In clinical practice, monitoring the decline of PCT levels over time along with daily clinical assessments can guide clinicians in making informed decisions regarding treatment or early discharge from ICU care for sepsis [23]. As for Khilnani et al, there is no optimal time recommended as to when and how often PCT should be repeated. However considering the kinetic profile of this biomarker, it may be repeated every 72 hours while on treatment or earlier if warranted.[22]

In summary, PCT as a marker aids to refine our differential diagnoses especially in patients with non-specific symptoms and can assist healthcare providers in differentiating bacterial infections from non-infectious causes. For treatment monitoring, serial determination of PCT over time helps track resolution of infection and response to therapy. Decisions can also be made regarding early discontinuation of antibiotic treatment especially in patients in whom infection is deemed less likely. Nevertheless, procalcitonin is not a perfect biomarker, with its own limitations, and is not a substitute for culture.

PENTRAXIN, A NEW BIOMARKER

Pentraxin or PTX-3 behaves as an acute phase protein, in the setting of inflammation and is secreted by macrophages, dendritic cells, fibroblasts, mesangial cells and glial cells.[23] Under normal conditions, the level in humans was seen to be at < 2 ng/mL. The 2017 ALBIOS trial conducted in Italy examined the levels of plasma PTX3 in patients with sepsis or septic shock on Days 1, 2, and 7. They aimed to determine the relationship between PTX3 levels and disease severity, organ dysfunction, and mortality. PTX3 levels were elevated at the onset of sepsis and increased with the severity of illness and the number of organ involvement. Unfavorable outcome was predicted in patients where levels failed to normalize within the first few days of management.[23]

BLOOD CULTURE

Bloodstream infections continue to cause illness and death, even with the availability of antibiotics and improvements in supportive treatment. Blood cultures are the gold standard for diagnosing bloodstream infections. However, indiscriminate use of blood cultures leads to false positive results, unnecessary antibiotic use, increased length of stay, and increased cost.[24] This may also lead to anemia, patient discomfort, procedure-related adverse events and increased utilization cost associated with antibiotics started for a potential contaminant. Indications for the use of blood culture is often unclear, leading to frequent overuse and unnecessary testing.

A study by Shapiro et al. in 2006 established predictors of bacteremia in emergency cases and developed a rule to identify low-risk patients where blood cultures can be safely omitted.[24] The presence of certain features was linked to increased bacteremia risk. This led to the creation of a decision rule using major and minor criteria to determine when blood cultures are necessary. Patients with one major criterion or two minor criteria were seen to have a higher likelihood of bacteremia, and thus should have blood cultures taken. Parameters classified under major criteria where 3 points each was assigned included clinical presentation consistent with endocarditis, high-grade fever $\geq$39.4C and presence of an indwelling catheter. Parameters classified under minor criteria where 1 point each was assigned included fever <39.3C, chills, vomiting, hypotension, leukocytosis, elevated band, thrombocytopenia, creatinine >2mg/dL and age of >65 years. This study found that the low risk group (with score of 0-1) had a bacteremia rate of 0.6%. By considering the clinical scenario and patient presentation, along with the pretest probability, unnecessary blood cultures can be avoided. It is essential to emphasize that for high-risk groups, such as immunocompromised individuals or those with a history of infection with resistant bacteria, blood cultures should not be witheld.[24]

A Scoping Review of articles performed from 2004 to 2019 categorized bacteremia into low, moderate, and high pre-test probabilities.[25] Clinical scenarios with a pre-test probability of bacteremia above 50% include septic shock, meningitis, endovascular infections, ventriculo-atrial shunt infections, discitis, vertebral osteomyelitis, epidural abscess, and native septic joints. Positive blood culture results are likely to indicate infection from these conditions when organisms are isolated. For cases with moderate likelihood of bacteremia, blood cultures are recommended when specimen from the primary source of infection is unavailable for culturing or when prompt antibiotic treatment is necessary before obtaining culture samples (i.e. pyogenic liver abscess, cholangitis).[25] For scenarios having a low pre-test probability of bacteremia below 10%, such as those with uncomplicated cellulitis, lower UTI and non-severe community acquired

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pneumonia, blood culture results rarely changed management from empirical coverage.[25] In this study, fever and leukocytosis were the most prevalent indications for performing cultures, but neither of the two strongly predicted a true positive blood culture. Meanwhile for post-operative patients, among 746 patients whose blood cultures were taken within 10 days after surgery, those collected within the first 48 hours post procedure were linked to negative blood culture results.[25]

In this context, an algorithm was developed by Fabre et. al. for blood culture recommendations in non-neutropenic patients, which was adapted by a multidisciplinary team at Johns Hopkins Hospital based on the pre-test probability of bacteremia.[25] It was recommended that prior to ordering blood cultures, evaluation of the patient's clinical history and physical examination must be done to determine potential sources of fever. For patients who have no signs or symptoms indicative of sepsis, blood culture screening is not advised for patients at low risk of bacteremia (<10% probability).[25] If the patient is considered to have an intermediate probability based on clinical presentation and presence of certain risk factors such as unavailability of the primary site for culturing , risk for endovascular infection, and if blood culture result would impact treatment decisions, a blood culture sample should be taken. This is especially important for those with a high risk for bacteremia.[25]

The volume of blood gathered for each sample is essential for identifying pathogens. Collecting an extra 1 mL of blood can enhance the bacterial yield by 4.7%,[26] therefore it is advised that adults provide 20-30 mL of blood per culture set to improve sensitivity and distinguish between contaminants and true pathogens. The recommended amount of blood to be drawn should be determined from the patient's weight category, in accordance with existing guidelines.[26] The Clinical and Laboratory Standards Institute recommend that blood culture samples drawn from pediatric patients amount to less than 1% of their total blood volume.[26] The process of obtaining a blood culture specimen can be negatively impacted if one does not exercise caution. Observing sterile technique is crucial, as it reduces the likelihood of contaminating samples. The CDC recommends using alcohol to disinfect the skin over the venipuncture site, followed by the application of chlorhexidine then allowing the site to dry. Additionally, the tops of culture bottles should be sterilized with 70% alcohol.[27]

In summary, prior to obtaining specimen for blood culture, the indication for the test should be kept in mind, as well as the volume and technique in blood collection. Ideally, the collection should precede initiation of antimicrobials to increase test yield.

MULTIPLEX PCR ASSAY (BIOFIRE PNEUMONIA PANEL)

The pneumonia panel multiplex PCR, is a molecular, multiplex device that rapidly identifies viruses, bacteria, and antimicrobial resistance genes in sputum-like, bronchoalveolar lavage (BAL), and endotracheal aspirate specimens from individuals with signs of lower respiratory tract infection.[28] The panel identifies 15 common bacteria (4 gram-positive and 11 gram-negative), 3 uncommon bacteria, and 9 viruses, as well as 7 antibiotic-resistant genes. In contrast, the respiratory panel multiplex PCR detects 4 bacteria (*Bordetella* species, *Chlamydia*, and *Mycoplasma pneumoniae*, as well as a variety of viruses. The latter functions as a qualitative test, in contrast to the pneumonia panel.[29]

The semi-quantitative assessment of pneumonia pathogens, measured in genomic copies/mL for 15 common bacteria, helps quickly distinguish between infection and colonization. The estimated amount of the target gene is determined using real-time amplification curves from the bacterial tests compared to a quantified internal reference standard. The assays are designed to amplify genes that are present in single copies within the chromosome of the target bacterium and thus estimate a concentration of targeted bacterial genome equivalents in the specimen. The calculated value is rounded to the nearest 10 to the nth value and reported as a bin result. Assays without a measurable amplification or calculated value below $10^{3.5}$ are considered negative, and reported as “not detected.” A study by Webber indicated that using the pneumonia panel multiplex PCR assay for organism identification was approximately 40 hours quicker than traditional culture methods, along with prompt detection of antimicrobial resistance gene markers.[30] In adults diagnosed with lower respiratory tract infections (LRTI) concordance was assessed by having either single or multiple target genes detected in both multiplex PCR and standard culture, with the main target on the panel matching culture results. The pneumonia panel showed a qualitative detection performance of 96.2%, indicating that the same bacterial targets were found using the standard culture technique.[30]

Due to the uncertainty as to scenarios in which the test can be truly beneficial, more research is necessary to address this concern. The choice to start antibiotics

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should depend on the patient's clinical condition rather than solely on the panel results. Van Schooneveld et al. recommended that the pneumonia panel be used exclusively for patients exhibiting definite symptoms of pneumonia and should not be the sole criterion for diagnosis. The panel can identify organisms that may be present in the patient without being the actual cause of pneumonia. Consequently, a positive result from the pneumonia panel does not always indicate pneumonia or the necessity for antibiotics.[31] Recommended situations where the pneumonia panel should be considered where panel results may impact management, include severe community acquired pneumonia, use on patients who are already on broad-spectrum antibiotics, those who are not improving with initial treatment, and use in patients with hospital-acquired or ventilator-associated pneumonia.[32]

These multiplex PCR assays is not without limitations. Due to the panel's high sensitivity, challenges in interpreting results due to the presence of residual nucleic acids from colonizing organisms following treatment can be detected. Certain multidrug resistant organisms cannot be identified such as *Stenotrophomonas maltophilia, Burkholderia*, and *Elizabethkingia* spp[28], as well as fungal pathogens. Detection of multiple organisms in a single specimen is also a challenge, with the most abundant bacterial organism often becoming the primary target for therapy. It is essential to include clinical interpretation in cases where semi-quantitative results from the panel do not align with findings from standard culture techniques.

Given the expense of the pneumonia panel, it is recommended that appropriate specimens be collected with the decision to use the panel thoughtfully in scenarios that may impact management, such as in severe pneumonia that does not respond to initial antibiotic treatment, newly developed severe hospital-acquired pneumonia in patients receiving broad-spectrum antibiotics, and for patients exhibiting clinical deterioration who need prompt targeted antibiotic therapy.

DIAGNOSTIC STEWARDSHIP TO COMBAT ANTIMICROBIAL RESISTANCE

Diagnostic stewardship should be applied in all patient decisions, considering the test's diagnostic performance, turnaround time and cost, while correlating the results with the patient's clinical symptoms. Clinical impressions are based on history and physical examination and diagnostic tests should be utilized to support the impression. Acute phase reactants are supplementary tests that can reinforce our clinical assessments. While these tests have their limitations, they should be utilized judiciously, as they influence treatment choices.

The most specific biomarker highly suggestive of bacterial infection is PCT, which can be used as an adjunct to support the diagnosis when clinical evidence is unclear or when patient's signs and symptoms could be attributed to another condition. It can also be used to monitor response to antibiotic therapy. In our setting where resources are limited and cost of each test is of value, decisions regarding serial determination of PCT should be made at specific time-points where antibiotic decision making is affected. Awareness of its advantages, limitations, kinetics and cost should also be considered. However, use of procalcitonin is still not a replacement for culture.

Blood cultures should be obtained in clinical scenarios where there is a significant probability of bacteremia, ensuring that specimens are collected correctly to prevent contamination, and an adequate blood volume is obtained to increase the likelihood of isolating pathogens.

The pneumonia panel multiplex PCR assay is a valuable resource for aiding prompt clinical decisions by rapidly identifying pathogens and antibiotic resistance genes. Nonetheless, it is crucial to interpret the results within the clinical context while considering the panel's limitations. Recommendation for use is suggested among patients not responding to therapy, particularly those already receiving broad spectrum antibiotics with new onset nosocomial pneumonia and clinically deteriorating patients warranting immediate targeted antibiotic therapy.

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CONFLICT OF INTEREST

None declared.

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