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Biomarker-Guided Antibiotic Stewardship in Acute Respiratory Infection - A Review

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ABSTRACT: Background: Antimicrobial over use in clinical setting is largely due to uncertainty in differentiating bacterial and viral infections**.** We have reviewed the potential role of serum biomarkers; C-Reactive Protein(CRP), Procalcitonin(PCT), Myxovirus Resistance Proteins (Myx A) and Tumor necrosis factor-related apoptosis-inducing ligand(TRAIL) in differentiating Viral from Bacterial respiratory Infections and to guide antimicrobial stewardship practices.

Main body: In an outpatient setting, decision on empirical therapy is based on diagnostic suspicion of pulmonary infection. Atleast 2-3 days is required for routine culture results and molecular test detection lack sensitivity to distinguish between infecting pathogens and colonizing organisms in acute respiratory infection. The prognostic role of blood and respiratory secretion biomarkers, has been analyzed with variable results with data on procalcitonin guided strategies used by clinicians to guide antibiotic discontinuation after clinical stabilization in critically ill patients.

Methods: A comprehensive literature search was performed to identify studies on the role of serum biomarkers in differentiating acute bacterial and viral respiratory tract infection and relevant articles were selected after thorough screening of the articles.

Conclusion:C-reactive protein and Procalcitonin show inadequate specificity to discriminate between viral and bacterial etiology of respiratory infection. Combination of TRAIL, with CRP displayed the highest diagnostic accuracy for discriminating respiratory

pathogens of bacterial and viral etiologies. Combination of C-Reactive Protein or Procalcitonin with MxA will assist to detect viral infection in patients and greatly enhance antibiotic stewardship.

INTRODUCTION:

Acute respiratory infections (ARI) accounts for majority of oral antibiotic prescriptions in the outpatient setting.[1] Approximately 30-50% of antibiotic prescribed in the outpatient settings for acute respiratory tract infections are unnecessary, primarily from antibiotics misuse for viral upper respiratory tract (URI) infection [2,3,4]. Overreliance on antibiotics for Acute respiratory infections (ARI) has been linked to the development of antibiotic resistance, secondary infections, increased healthcare expenditure and drug toxicities.[5] Antibiotic stewardship practices for Upper Respiratory Tract Infections requires definitive evidence of a bacterial infection before prescribing antibiotics .The lack of prompt diagnostic tests has hampered antibiotic stewardship efforts of clinicians to identify bacterial respiratory infections.[6]

Current testing approaches such as traditional culture and molecular diagnosis has varied diagnostic accuracy and turnaround time. [7,8] While culture remains as standard method for pathogen identification for acute respiratory infections, but the turnaround time varies from 48 hours to 3 days, limits its utility for rapid diagnosis. Low pathogen detection rates in adults with respiratory symptoms and colonization of non-pathogenic commensals in respiratory tract limits the use of PCR for diagnosis, despite decreased turnaround time. This scenario is challenging where timely antibiotic treatment is crucial for patients, prescription of empirical antibiotics results in overuse of last resort antibiotics, exacerbating resistance rate or inadequate therapeutic coverage, leading to poor outcomes.[9] Having access to pathogen-specific biomarker test, capable of identifying specific bacterial/viral pathogens with less turnaround time could optimise empiric therapy targeting.

Recent advancements in Point of Care testing for diagnostic laboratories aids to rapidly detect systemic inflammatory response improving decision making for bacterial or viral infections. Serum biomarkers serve as valuable tool for monitoring therapeutic response in acute respiratory infections. These tools offer clinical guidance for Outpatient antibiotic prescription.

The widely used serum biomarker, Procalcitonin, has been extensively evaluated in clinical trials for bio marker-guided drug therapy protocols for severely ill cases, including those with pneumonia. [10-12] C-Reactive Protein is a established cytokine responsive blood biomarker. The levels of CRP in blood elevates following non -specific response to infection. A high C-Reactive Protein elevation generally differentiates bacterial from viral infection, providing reliable measure to assess disease severity.[13] Myxovirus Resistance Proteins typically increases during most active acute viral infections. Evidence suggest that Myxovirus protein A could serve as a sensitive and specific viral indicator across diverse populations and clinical settings [14] TRAIL is recognised as a biomarker for cardiovascular autoimmune disease but recent studies highlights its use as a promising viral biomarker, where its expression is up regulated in viral infection and down regulated in bacterial infection. [15]

The prognostic value of blood and respiratory secretions biomarkers, yielded inconsistent results across studies. The adoption of these biomarkers in clinical settings for discriminating viral from bacterial infections is restricted by its narrow applicability to clinical syndromes, settings and certain population. Our study aimed to review the potential role of serum biomarkers; C-Reactive Protein, Procalcitonin, Myxovirus Resistance Proteins and Tumor necrosis factor-related apoptosis-inducing ligand in differentiating Viral from Bacterial Infections and guiding antimicrobial stewardship practices.

1.Diagnostic profile of CRP and Clinical outcome

As a nonspecific acute-phase protein, CRP undergoes rapid elevation during inflammatory process and severe infection. CRP begins to rise within 4–6 hours of infection, doubles every 8 hours, and peaks between 36–50 hours. In severe infection or inflammation, CRP concentration can increase more than 500 mg/L whereas the normal levels of CRP is below 3 mg/L. Studies show that CRP effectively improves diagnostic accuracy of bacterial infection identification.[13,16]

CRP concentration of more than 20 mg/L supports diagnosis of bacterial sinusitis in acute rhinosinusitis.[13] CRP concentration showed an increased level, exceeds 20 mg/L across nearly all observations of infections due to Group A beta haemolytic streptococci , indicating a clinically significant bacterial infection.[16] Putto et al. found a CRP concentration of more than 20 mg/L in 89% positive bacterial cultures in febrile children indicating clinically significant infection and 75 % Patients with probable viral infection had CRP level less than 20mg/L.[17] Higdon et al. found that CRP concentration of

≥40 mg/L is highly specific to rule out most Respiratory Synctitial Virus pneumonias among children aged less than 5 years.[18]. When compared with patients unchanged levels, patients with an average CRP levels of 1 mg/dl during the first 6 days of mechanical ventilation were 62% more likely to develop VAP. In severe Community acquired Pneumonia, a CRP level above 50% post 5 days of antibiotic therapy signals poor outcome. CRP levels above 100 mg/dL at the onset of therapy signals adverse outcomes in Community acquired Pneumonia [19] Alex Pizzini et al found positive correlations between the duration of hospitalization and CRP [20] .Results of clinical trial suggest that testing CRP for acute cough significantly reduce antibiotic prescription rates for acute respiratory tract infections without an increase in adverse outcomes or therapeutic failures.[21] Typically, bacterial infection elevates CRP but similar levels may be observed in patients with some viral strains such as adenovirus and influenza.[22] CRP increases in both bacterial infection and non-infectious inflammation and viral infection such as enterovirus, respiratory syncytial virus and SARS Cov-2.Hence CRP is not a specific marker to correctly differentiate between infectious or inflammatory etiologies in a febrile patient.[23]

2.Diagnostic profile of PCT and Clinical outcome

Procalcitonin serves as a peptide precursor of calcitonin, this diagnostic marker elevates in bacterial infections but stay low in viral infections.[24] Procalcitonin synthesis is independent of liver function, its levels remain unaltered by cirrhosis and fulminant hepatic failure.[25] In adults and paediatric cases older than 72 hours, the standard value of Procalcitonin is ≤0.15 ng/ml. Following inflammation linked to bacterial endotoxin or inflammatory cytokines, Procalcitonin rises within 2–6 hours and peaks at 12–24 hours, and declines with a half-life of 25–40 hours.[26] A procalcitonin cut off of more than 0.8 ng/ml best identified patients with bacterial/co- infection with 100%, sensitivity and 62.5%, specificity.[27] A Procalcitonin value of <0.25 ng/ml. indicates unlikely bacterial infection in patients whereas Procalcitonin value of ≥0.25 ng/ml signals Viral–bacterial co-infections [28] Rise in procalcitonin levels during bacterial sepsis correlates with increased risk of severe sepsis, septic shock, and low chance of survival.[29] Respiratory colonization or carrier states without a systemic host response do not significantly raise procalcitonin and levels remains stable. Procalcitonin cut off level of 0.15–0.25 ng/mL could be used in clinical decision making where the growth of bacterial colonizers or a negative bacterial culture rules out active bacterial infection in patients without viral infection.[29] Procalcitonin value remains low and typically do not exceed 0.75 ng/mL in conditions like autoimmune disease and chronic inflammatory processes.[11] Existing evidence imply that Procalcitonin levels rarely spike after pure viral infection.[27] Procalcitonin is the best marker for clinical judgment in severely ill patients or patients with sepsis particularly when using a baseline value of 0.3 ng/ml.[30] Reduction in Procalcitonin concentration greater than 30% between days 2 and 3 independently predict survival outcomes in sepsis patients secondary to ventilator-associated pneumonia (VAP), community acquired pneumonia (CAP) or bloodstream infection.[31] Serum procalcitonin values were significantly elevated in cases with pneumonia compared to COPD exacerbation.[23] Schützle H et al found that in acute respiratory infection, no clinically relevant variation was observed for PCT values across cases of RSV, adenovirus or rhinovirus as these viruses may enhance bacterial adherence to respiratory epithelial cells which lead to bacterial superinfection.[28] A low concentrations of procalcitonin (<1.0 ng/mL), does not provide adequate discrimination between viral and bacterial causes.[32]

3.Diagnostic profile of Myx A and Clinical outcome

Exclusively upregulated by type I Interferons, MxA, an interferon (IFN) inducible proteins is expressed in blood mononuclear cells or in local tissues. [14,33] MxA suppresses viral activity by inhibiting the translation of viral proteins and or impedes the nuclear translocation of newly synthesized viral proteins. MxA level in peripheral blood of healthy individuals is below 50 ng/mL. MxA protein is induced within 1.2 hours of virus exposure. It remains detectable in serum for as long as 10 days post infection with a half-life of 2.3 days. [34] MxA levels peak at 16 hours and remains sustained along with increased Interferons level. Clinically, the expression of MxA in peripheral blood has emerged as a sensitive and specific indicator of viral infection [14] Unresponsive to inflammatory cytokines such as IL-1 and TNF-α, MxA gene levels are not elevated in healthy subjects.[33] Bacterial infections fail to induce elevation either type I IFN or MxA.[14] Human MxA functions as intracellular blood protein that exhibit wide antiviral spectrum against diverse viruses, irrespective of their intracellular replication site. MxA protein elevates during a wide spectrum of acute active viral respiratory infections such as Adenovirus, Influenza A/ B, Respiratory syncytial virus, Parainfluenza viruses, Coronavirus, Rhinovirus, and Metapneumovirus infections and herpes virus including Epstein-Barr virus, Herpes simplex virus and Cytomegalovirus [35]

In children with respiratory symptoms, Evaluating MxA levels aids in discriminating active viral infection from asymptomatic cases. [36] Elevated MxA expression correlates with viral etiology in febrile children consequently MxA levels serve as a promising biomarker to detect viral etiology in febrile respiratory infection than afebrile infections [37] The levels of MyxA in children with single virus infection was comparable to that of multiple virus coinfection. Rhedin, S et al observed higher blood MxA cut off levels in 81% of children with symptomatic viral respiratory infection. Myx A level of 175 µg/L demonstrated 92% sensitivity and 77% specificity in identifying infections due to influenza virus, rhinovirus, respiratory syncytial virus, parainfluenza virus, coronavirus, and human metapneumovirus in symptomatic cases. [38] Iliopoulou K et al found that MxA levels of 15 ng/mL could discriminate viral infection from no infection yielding a sensitivity of 79.7% and specificity of 80.0%.[39]. Zhu M et al observed MxA levels rise in both the viral infection and co-infection groups relative to the healthy cohorts and bacterial infection group.[40]

Significant levels of MxA was found in paediatric cases with viral Lower Respiratory Tract Infection as compared to bacterial Lower Respiratory Tract Infection. The highest MxA levels were seen in cases positive for influenza virus, Respiratory Synctitial virus and human metapneumovirus.[41] MxA level detection in capillary blood, make it an ideal biomarker for pediatrics cases.[34]

4.Diagnostic profile of TRAIL and Clinical outcome

TRAIL belongs to the tumor necrosis factor (TNF) family induces extrinsic cell death. In immune system, TRAIL may have a dual function, by eliminating infected cells while contributing to the pathogenesis of multiple infections.[42]

Papan C et al observed correlation between Influenza and Respiratory Synctitial viral load from nasopharyngeal swabs of children with TRAIL. [43] In a prospective observational study, among cases with respiratory infections and pyrexia of unknown origin, TRAIL exhibited high diagnostic performance for discriminating bacterial from viral etiologies. TRAIL was induced in response to a diverse viral infections and exhibited significantly low levels in bacterial infected patients [44] In influenza virus infection , selective expression of TRAIL occurs on virus-specific cytotoxic T cells, whereas increased TRAIL receptor (DR5) selectively expressed on virus-infected pulmonary epithelial cells [45,46] Reinout A et al reported soluble TRAIL levels in bronchoalveolar lavage fluid significantly elevated with RSV-associated respiratory failure compared to mechanically ventilated controls [47] Morissette MC et al found elevated TRAIL levels in the lungs of COPD cases.[48] Higher levels of TRAIL was observed in specimens obtained via airway epithelial brushing of COPD patients versus healthy controls[49] In a prospective, cohort study conducted for the evaluation of the diagnostic performance of TRAIL in paediatric patients with suspicion of Respiratory Tract Infection, it was observed that TRAIL complements multiplex PCRs assay result for viral infection diagnosis .[50] TRAIL was differentially expressed in sera of severe Covid 19 cases versus non-severe Covid. [51] Circulatory TRAIL was positively correlated with the severity scores in Community acquired Pneumonia patients and circulatory TRAIL expression on admission significantly increased the probability of requiring ICU care, mechanical ventilation, extended hospitalisation, or hospital mortality.[52] Elevated TRAIL levels, even though indicates a distinctive immune response in Mycoplasma pneumoniae Community acquired Pneumonia cases, may misdiagnose bacterial atypical pneumonia as viral infections.[53]

Dandon Hu et al compared the diagnostic performance of TRAIL with conventional laboratory indicators and found that TRAIL has a sensitivity of 91% and specificity of 65%. The complementary diagnostic value of TRAIL to detect bacterial infection was observed in their study.[54] Pagano F et al observed significant variation in the diagnostic performance of TRAIL and CRP in children who received prior antibiotics treatment when compared to the group who were naïve to antibiotics.[55]

Antibiotic stewardship approaches in Acute respiratory infection

Evidence suggests that point of care testing for biomarkers reduces antibiotic prescription and guide antibiotic utilization in primary care .[56] The sensitivity and specificity of point of care testing that use respiratory samples ranges between 80-100%.[57] Multiple biomarker test provide high accuracy for assessing people with lower respiratory tract infection than test which detect single biomarker.[4] However diagnostic inaccuracy can arise as inflammatory biomarkers are not exclusive for infection ; underlying health conditions or individual-level variation can leads to elevated levels in blood there by increase the risk of diagnostic misinterpretation [56]

In the outpatient setting, the most important step of antibiotic stewardship is to efficiently reduce the risk of missing clinically significant bacterial infection requiring antibiotic therapy. While C-reactive protein or procalcitonin serves as independent markers for bacterial infection, both lack adequate specificity to discriminate between viral and bacterial infection leading to antibiotic overuse for viral infections.[14]

Viral infections with Adenovirus, Parainfluenza virus, Influenza, Respiratory syncytial virus, Epstein-Barr virus, Herpes simplex virus, and Varicella zoster virus can drive CRP levels above 20 mg/ L, mimicking bacterial infection confounding clinical decision making. [58]

While antibiotic initiation is strongly discouraged for Procalcitonin between ≤0.1 and 0.24 ng/mL and concentrations below 1.0 ng/mL lack accuracy to discriminate viral from bacterial etiology and to prospectively guide treatment decision. Antibiotic treatment is encouraged for procalcitonin values between 0.25 and 0.49 ng/mL and for values more than ≥0.5 ng/mL strongly mandates antibiotic initiation.[12] Hence Procalcitonin guided intervention effectively lowers antibiotic exposure without adverse outcomes. Procalcitonin levels are increasingly used by clinicians for antibiotic discontinuation following clinical stabilization, especially among critically ill and sepsis cases. [59,60]

Numerous studies comparing serum CRP and PCT levels, shows that CRP raises in response to bacterial, viral and autoimmune diseases, while PCT typically raises in bacterial infection. Hence, serum CRP levels provide better sensitivity and specificity for detecting nonspecific inflammation.[61]

In emergency departments, Procalcitonin driven antibiotic stewardship protocols have been shown to reduce overall antibiotic exposure in community-acquired pneumonia by 40%-50% initial antibiotic prescription rates by 40%-50% in lower respiratory infection, and 70%-80% ambulatory patients, [62-64]

Integrating C-Reactive Protein or Procalcitonin assessments with rise in MxA serves to reliably detect patients experiencing viral infection, assisting physicians to restrict antibiotics usage and proceed with a watchful, waiting approach[14] While bacterial infection trigger marked CRP levels, leaves no impact on MxA levels.[65] Elevated MxA presenting independently or alongside elevated CRP indicates a viral etiology and the absence of bacterial etiology in children [36] When CRP is evaluated independent of MxA,CRP led to overtreatment of viral infection in 38% cases[66] Within an ambulatory care setting, using multimarker test system that pair CRP with MxA or Procalcitonin with MxA enables health care professionals to specifically detect suspected cases of viral and/or bacterial infection immune response and optimise antibiotic stewardship. Multimarker panel combining TRAIL with CRP yielded highest diagnostic accuracy for distinguishing between bacterial and viral etiologies of respiratory infections and fever of unknown origin.[44]

Utilising biomarkers can assist clinician on necessity and timing of antibiotic initiation for patients with acute respiratory infection, acute exacerbation of chronic obstructive pulmonary disease and pneumonia. [67] However it provides no better clinical outcome compared to control groups. In a randomised controlled trial result, the role of CRP-based and Procalcitonin-based algorithms for discontinuation of antibiotic treatment showed reduced antibiotic exposure in Community acquired pneumonia.[68] The impact of Myx A protein and TRAIL test on antibiotic prescription rates still needs to be demonstrated [69]

In clinical setting, facilitating the selection of targeted antibiotic therapy depends upon most likely etiological agent. [70-72] Although real-time PCR and other molecular assays, successfully identifies potential pathogens they lack the ability to differentiate colonizing organisms from infectious agents. Biomarkers are a promising tool to support antibiotic decision-making in respiratory infections. Biomarkers reduce unnecessary antibiotic use without risking adverse outcome. Biomarkers are especially useful in resource-limited settings, guiding escalation/de-escalation and monitoring trends alongside clinical signs.[73]

CONCLUSION

- No single biomarker can replace clinical judgment in acute respiratory infection, even though Procalcitonin guided strategies are increasingly integrated into clinical workflow to guide antibiotic discontinuation once clinical stabilization is achieved, particularly in critically ill patients. By accelerating bacterial or viral identification through reduced turnaround time, pathogen specific biomarkers offer a valuable tool to target empiric antibiotic treatment. Integrating MxA with conventional markers

like CRP or PCT can assist healthcare providers in differentiating viral and bacterial etiologies, providing a robust framework to drive precision antibiotic stewardship.

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