Original Research Paper

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TO DETERMINE BEST CLINICAL CHARACTERISTICS AND BIOMARKERS THAT GUIDE IN CASE MANAGEMENT AND IMPROVE ANTIBIOTIC STEWARDSHIP FOR CHILDREN ATTENDING PEDIATRIC CLINIC WITH ACUTE RESPIRATORY INFECTIONS

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ABSTRACT **Back ground and objectives :** Acute Respiratory Infections (ARI) are one of the most causes for evaluation and management at pediatric outpatient clinics. Most common of these ARIs are self limiting viral illnesses but majority are prescribed with antibiotics which is one of the major contributory factor for development of antibiotic resistance. So the aim of this study was to determine the ideal combination of clinical signs and biomarkers measured in resource limited settings and to facilitate accurate diagnosis and management and inturn antibiotic stewardship.

Methods: From June 2021 to Jan 2022, children between one month and 5 years of age presenting with fever and at least one respiratory symptom to the OPD MIMS are included in the study. Patients with pneumonia and severe pneumonia basing on IMNCI guidelines and no exclusion criteria were included in this study. Participants underwent total leukocyte count (WBC), Absolute neutrophil count (ANC), C - reactive protein (CRP), procalcitonin (PCT), chest X-ray. A multiplex polymerase chain reaction (PCR), Sputum blood and urine cultures and sputum microscopy was done to identify the pathogen. Demographic and clinical characteristics of the participants were recorded. We studied the predictive accuracy by combining best clinical signs and biomarkers using statistical analysis.

Results: In 15% of cases there was evidence of a mixed viral/bacterial infection, viral infection alone was detected in 52% and bacterial infection alone in 31% of patients. Children aged >2 years had a bacterial pneumonia more often than children aged <2 years. Among clinical markers Respiratory rate and oxygen saturation (92%) could discriminate accurately between bacterial LRTI and other LRTI. The proportion of patients with an increased WBC (>15.0 × 10^9/1) or increased ESR (>40 mm/h) was similar in bacterial and non bacterial RTI (48% v 47% and 66% v 60%, respectively). The differences in the CRP levels were significant at the selected levels of >40 mg/l (p=0.005), >80 mg/l (p=0.001). PCT > 0.25 µg/L showed the best discriminating ability (AUROC 0.92; 96% CI 0.88–0.98), followed by CRP > 80 (0.80; 0.72–0.88). The combination of tacypnea and procalcitonin had the better predictive value (AUROC 0.98, 97% CI 0.94–1.00).

Conclusions: Strict adherence to national guidelines and training physicians in assessment of clinical signs will reduce antibiotic use but still leads to over or under treatment. Although ideally point of care testing for respiratory pathogens like influenza and RSV would be employed, this is unlikely to be feasible at peripheral health centers and pediatric clinics in India in the near future. Therefore, it remains important to consider use of Procalcitonin that can be quickly and easily adopted even less effective than rapid tests for pathogens.

KEYWORDS : Antibiotic stewardship; Biomarkers; Procalcitonin; point of care testing.

INTRODUCTION:

Acute respiratory infection is the most common illness in children and still one of the leading causes of under five mortality in developing countries. Most of these children will have self limiting respiratory infections, likely of viral etiology and only few of them require antibiotics and admission[1]. As there is a lack of rapid and commercially available laboratory tests for most pathogens the etiology is rarely established in clinical practice and antibiotic treatment is empirical in most cases. In up to 70 percent of respiratory infections unnecessary or ineffective antibiotic treatment may often be used leading to antimicrobial resistance. Antibiotics prescribed in outpatient clinics for respiratory tract infections (RTI) account for the majority of unnecessary prescriptions. Acute respiratory tract infections of bacterial origin require antibiotic treatment while others such as bronchiolitis, bronchitis and viral pneumonias does not require. Biomarkers along with clinical characteristics and chest x ray can support clinical decision making in children with RTI. Timely accurate diagnosis and treatment is critical to avoid morbidity and mortality associated with bacterial RTIs.

Accurately identifying the children with bacterial RTI in resource limited settings, where diagnostic imaging (e.g., chest X-RAY) and sophisticated laboratory equipment are not routinely available, is challenging. Furthermore, outpatient providers at peripheral health centers, where most patients first seek care, are generally are not pediatricians with limited clinical training... The WHO, UNICEF, Ministry of health and family welfare govt. of India, Integrated Management of Childhood and Neonatal Illnesses (IMNCI) [2] guidelines, recommend antibiotic treatment based only on symptoms of fever and fast breathing. While there is no definitive gold standard for diagnosing bacterial pneumonia, previous studies have established that clinical symptoms are not specific to a causative organism. In addition, Tachypnea, a clinical sign for classification of pneumonia, can be difficult to measure accurately and precisely by untrained physicians. This leads to both (i) An excess and inappropriate use of antibiotics leading to antimicrobial resistance and (ii) Unable to recognize children with high risk for bacterial infection[3] leads to increased morbidity and mortality.

The important step for reducing childhood mortality and improving antibiotic stewardship in pediatric clinics is to develop and validate a method to identify the patient in whom antibiotic is not required. To evaluate the potential impact of adding Point of care testing of biomarkers[4] such as total leukocyte count(WBC), Absolute neutrophil count(ANC), C-reactive protein (CRP), procalcitonin(PCT), Erythrocyte sedimentation rate(ESR) along with chest X-ray to the existing clinical management guidelines, we conducted this prospective observational cohort study in children attending pediatric outpatient clinic, Maharaja institute of medical sciences , Vizianagaram, Andhra Pradesh, India.

MATERIALS AND METHODS:

Study design and population:

BetweenJune 2022 and January 2022, 810 children less than five years of age attending OPD with Acute respiratory tract infections (fever with any respiratory symptom) were enrolled in the study. 110 patients with pneumonia and severe pneumonia basing on IMNCI and ministry of health and family welfare India[2] guidelines were included in this study. Patient demographics, co-morbidities, symptoms, as well as vital and other clinical signs were collected at inclusion using a standardized electronic case report form.

Microbiological investigations, chest X-ray and biomarker testing:

Blood, sputum and urine cultures were sent to identify specific bacterial pathogen. Rapid diagnostic tests were done for dengue, malaria, typhoid, HIV, scrub typhus. Sputum or gastric lavage sent for staining, culture and CBNAAT. A nasopharyngeal swab was collected in all patients and sent for multiplex polymerase chain reaction (PCR) for common respiratory pathogens. All children with Tachypnea had a chest X-ray and based on radiological findings they were divided into Bacterial (bronchopneumonia, consolidations, alveolar infiltrates) and Non bacterial (interstitial infiltrates, hyper aeration) pneumonias. Follow up X-rays were taken in relevant cases. Biomarkers [4] WBC, ANC, ESR, CRP and PCT were determined using routine laboratory methods.

Statistical analysis:

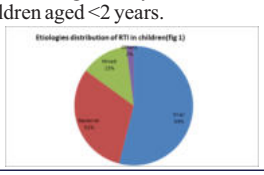
Differences in characteristics, vital signs, management, outcome and biomarkers between the bacterial and non bacterial groups were evaluated by Chi-square test. Differences between bacterial RTI and patients with other RTIs were evaluated using chi-square, or Fisher tests as appropriate. P values were adjusted for multiple comparisons using Bonferroni correction. Using univariate logistic regression, the area under the receiver operating characteristic curve (AUROC) was calculated for all clinical signs and biomarkers to predict bacterial infection among patients with RTIs. Variables with excellent predictive value (AUROC≥0.80) were selected for the multivariate analysis[5] . The linearity of the continuous variables with respect to the logit of the dependent variable was assessed via the Box-Tidwell (1962) procedure and by inspecting the partial residuals. Nonlinear variables were transformed for the multivariate logistic regression. A maximum of two variables at a time were tested to avoid over fitting. The predictive validity of a multivariate model adding biomarkers to vital signs was measured using logistic regression, and the predicted probabilities were used to generate AUROC. The multi-variate models were compared using the Delong method [6]. The identified algorithm was tested to predict bacterial RTI versus RTI of other etiology (viral or unknown). To evaluate the accuracy of recommendation regarding antibiotics, we compared children who received antibiotics during routine care with children in whom antibiotics were not prescribed using chi-square test.

All analyses were performed with IBM SPSS version 26 (IBM Corporation, Armonk, New York, USA), STATA software (version 13.1, Stata Corp, College Station, TX, USA) MedCalc version 19.1 and GraphPad Prism 8.

RESULTS:

Etiology:

Among 810 children prospectively enrolled in the fever etiology cohort, 110 patients with a clinical pneumonia and no exclusion criteria were included in this study. A potential causative agent was found in 88% of the cases... A respiratory virus was found in 62% (RSV 29%, influenza 24%, para influenza viruses 10%, rhinovirus 7%, adenoviruses 4%, other viruses 8%) and a bacterial agent in 53% (Streptococcus pneumoniae 42%, Haemophilus influenzae 12%, Mycoplasma pneumoniae 2%, Moraxella catarrhalis 1%, Chlamydia pneumoniae 1%,Pseudomonas 2% other bacteria 2%). In 15% of cases there was evidence of a mixed viral/bacterial infection, viral infection alone was detected in 54% and bacterial infection alone in 31% of patients (fig 1). Children aged >2 years had a bacterial pneumonia more often than children aged <2 years.



Clinical presentation and management:

The most common reported symptoms were fever, cough, and rhino rhea. Danger signs, including chest indrawing, coma, and convulsions, were uncommon. Among clinical markers Respiratory rate(RR) (Tachypnea basing on IMNCI guidelines) is better than others in discriminating between bacterial LRTI and other LRTI .All but one child(109/110, 99%) received antibiotic treatment, including all of the children with RR documented who did not meet clinical criteria for pneumonia. The most commonly prescribed antibiotics were amoxycillin (68%) and cefpodoxime (22%). Children who received amoxycillin were slightly older than those who received cefpodoxime, although the difference was not statistically significant (median age, 4.5 versus 3 years; P = 0.086). Six of the seven children admitted to the inpatient ward received parenteral ceftriaxone. Nine children (8%) were prescribed more than one antibiotic. The predictive accuracy of clinical characteristics are shown in table 1.

Table 1:showing predictive accuracy of clinical signs and symptoms

SYMPTOMS AND SIGNS	%	P value
Fever	100	NS
Cough and rhino rhea	95	NS
Rapid breathing	88	< 0.003
Refusal of feeds	2	NS
Convulsions	1	NS
Cyanosis	0	NS
Wheezing	18	NS
Hypoxia	1	NS

Radiographic findings:

Evidence of a bacterial infection was found in 71% of 68 children with alveolar infiltrates on the chest radiograph (64% of the 110 patients in the study). In children with solely viral pneumonia 49% had alveolar changes (p=0.001 compared with bacterial pneumonias). The alveolar infiltrate was lobar in 36% of cases with bacterial pneumonia and in 15% of with viral pneumonia (p=0.001). Half of the 77 children with sole interstitial infiltrates on the chest radiograph had evidence of viral infection and half had evidence of bacterial infection. The 110 patients were divided into two subgroups according to age (2 years). In children aged >2 years, 78% of those with bacterial infection had alveolar infiltrates compared with 56% of those with viral infection (p=0.02). (TABLE 2)

Laboratory findings:

The proportion of patients with an increased WBC (>15.0 × 10^9 /l) or increased ESR (>30 mm/h) was similar in bacterial and viral pneumonia (48% v 47% and 66% v 60%, respectively). The differences in the CRP levels were significant at the selected levels of >40 mg/l (p=0.005), >80 mg/l (p=0.001), We choose a CRP concentration of >80 mg/l as a screening limit for bacterial pneumonia (sensitivity 0.52, specificity 0.72) because there were too many false positives at the level of >40 mg/l and too many false negatives at the level of >120 mg/l.. Among biomarkers, PCT > 0.25 µg/L showed the best discriminating ability (AUROC 0.92; 96% CI 0.88–0.98), followed by CRP > 80 (0.80; 0.72–0.88). (TABLE 2)

Table 2 Laboratory findings and chest radiographic characteristics of ARI children

Parameter	Total (n)	Bacterial(%)	Viral(%)	P value
WBC (>15000)	47	48	39	NS
ESR(>40)	64	66	60	NS
CRP < 40	27	33	22	NS
CRP >40	59	66	47	0.004
CRP>80	43	52	18	0.001
Alveolar infiltrates	64	72	49	0.001
Alveolar infiltrates + CRP	37	46	18	0.001
RR + CRP>80	48	78	38	0.001
RR+Procalcitonin	46	82	19	0.001

Combination of different biomarkers and of clinical signs/ scores with biomarkers:

We assessed the diagnostic accuracy with combinations of different biomarkers two at a time but none improved the diagnostic performance over using a single marker. We combined vital best predicting clinical sign tachypnea with the best predicting biomarkers Procalcitonin and CRP (AUROC≥0.80). The combination of clinical sign tachypnea and biomarker procalcitonin (0.25ng/ml) had the highest predictive value (AUROC 0.98, 97% CI 0.94–1.00) and next is tachypnea and CRP >80mg/l.

DISCUSSION:

We found that the vast majority of children presenting to a peripheral health facility and pediatric clinics in India with febrile acute respiratory infections had only mild illness but majority received antibiotic treatment. So to improve antibiotic stewardship in management of RTI our study recommends addition of simple point-of-care test ideally procalcitonin to current guidelines is required which is feasible in pediatric clinics and peripheral health centers with basic infrastructure.

Biomarkers like WBC, ANC, ESR, CRP, PCT etc can be used to take antibiotic treatment decision[8, 9]. Past studies shown the ability of CRP and PCT testing to differentiate bacterial from non bacterial illness are variable[10, 11], these investigations are limited by the lack of a reference standard for diagnosis of bacterial pneumonia .In this prospective cohort of 810 children attending outpatient clinics with a clinical RTI in northern Andhra, an approach combining Tachypnea and PCT (cutoff>0.25 µg/L) performed well to differentiate bacterial and nonbacterial RTI. We estimated that by using this approach in treatment of RTI we could have reduced antibiotic use by nearly 90%. Our findings also suggest that use of rapid influenza and RSV testing at peripheral health centers in India in future that will further help in antibiotic stewardship and appropriate case management. Laboratory technicians were able to collect nasopharyngeal (NP) swabs and conduct influenza testing for all participants, and almost every fourth children tested positive.

Radiographic findings of pneumonia have traditionally been classified into lobar pneumonia, bronchopneumonia and interstitial pneumonia[12] Lobar and Bronchopneumonia pneumonia in children is most commonly caused by Streptococcus pneumoniae, Klebsiella pneumonia, Staphylococcus aureus, Pseudomonas etc. Interstitial pneumonia is mostly caused by viruses[12].Viral LTRI include bronchiolitis, pneumonia and bronchitis in older children. Radiographic features of these conditions include increased/blurred bilateral lung markings and double contour[12]. Common radiographic features in viral pneumonia include bilateral patchy consolidation, lobar consolidation; diffuse areas of air space consolidation or interstitial lung disease.[13] Many studies shown identification of the specific organism causing pneumonia cannot be made on the basis of radiological findings without laboratory testing[14].

Our study shows that most children with an alveolar pneumonia and lobar infiltrates have laboratory evidence of a bacterial infection. The observation is clinically important because two thirds of the hospitalized patients in our study had alveolar infiltrates on the chest radiograph had evidence of bacterial infection. Some children with interstitial infiltrates as the sole radiographic finding had bacterial infection. This supports the view that interstitial infiltrates are not a reliable indication of solely viral pneumonia, although significant.

The total leukocyte count is variable in the pediatric population, especially in the early period of life. The reference values differ between the age groups [15]. Elemraid et al.[16] showed that almost 40% of viral pneumonia cases presented with WBC > 15 × 10^9/L. Esposito et al. [17] highlighted that WBC had the lowest positive predictive value compared to PCT and CRP. According to Zhu et al.[18] the percentage of neutrophils compared to a total WBC count was to some extent better at discriminating viral from bacterial infection. In the study by Elemraid et al[16] 25% of viral CAP cases had CRP over 80 mg/L, and nearly 23% of bacterial cases had CRP less than 20 mg/L . It is evident that a low reference point for CRP will diagnose almost all cases of bacterial etiology but will include a significant number of false-positive cases. Procalcitonin is a precursor to calcitonin produced in the parafollicular cells of the thyroid gland by the transcription of CALC-1 gene. During an infection, CALC-1 gene is activated and unregulated to increase the production of procalcitonin in not only endocrine glands but also many parenchymal tissues [19]. The sudden and marked increase in PCT within four to six hours is a key indicator of bacterial infection [20]. It is found that viruses are not able to increase PCT to such a concentration. Esposito et al. [17] study shown the mean PCT was very low in viral CAP compared to bacterial CAP cases.

WBC, ANC, ESR, CRP and procacitonin -all of which may be available to a clinician when deciding on treatment- added very little to the differential diagnosis. A serum procalcitonin more than 0.25 ng/ml and serum CRP > 80 were found to be the most practical laboratory tests for bacterial RTI. We show that PCT is a good predictor of RTI with a bacterial pathogen detected among patients with RTIs. PCT is now available as the point of care test which makes it suitable for implementation in daily care in India. By adding procalcitonin or CRP to clinical signs definitely there will be a added value.Furthermore, having a approach or guideline combining an easy-to-measure vital sign respiratory rate with PCT adds value since it has a high negative predictive value. The combination of clinical signs and biomarkers to predict bacterial RTI added value to the clinical assessment study in Swiss cohort of LRTI patients.[21,22.]

The limitation of this study were biomarkers and X-ray were done only once at the starting of the study and our study cohort is small.

CONCLUSION:

There is need for improvement in regard to antibiotic stewardship[22] in treatment of pediatric ARI in developing countries. Better adherence to national guidelines based on clinical signs and symptoms would reduce antibiotic use, but may lead to excess or inappriopriate use of antibiotics leading to Antimicrobial Resistance or not using when needed leads to increased morbidity and mortality. Although ideally point of care testing for respiratory pathogens like influenza and RSV would be employed, this is unlikely to be feasible at peripheral health centers in India in the near future. Therefore, it remains important to consider use of Procalcitonin that can be quickly and easily adopted, even less effective than pathogen testing. Here we provide new data supporting a simplified approach[23] combining an easy-to-measure vital sign, respiratory rate, with a biomarker easily measurable at the point-of-care, PCT, that shown an excellent predictive accuracy in identifying RTI patients with documented bacterial infection. Findings from our study support the potential use of biomarkers for antibiotic stewardship and management of patients with RTIs in developing countries like India. However, our results need confirmation in larger cohorts of patients with respiratory tract infections.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee.

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