SIMLPE PREDICTORS TO DIFFERENTIATE ACUTE ASTHMA FROM ARI IN CHILDREN : IMPLICATIONS FOR REFINING CASE MANAGEMENT IN THE ARI CONTROL PROGRAMME

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ABSTRACT

There is a considerable overlap in the clinical presentation of acute asthma and ARI. According to the current ARI Control Programme recommendations, a child with cough and rapid breathing is overtreated for ARI (pneumonia) with antibiotics and undertreated for asthma with bronchodilators. The present study, therefore, evaluated simple predictors to differentiate these two conditions to refine the recommended case management.

In a case control comparison, children between 6 to 60 months age who presented with cough and rapid breathing due to acute asthma (n=100) and ARI (n=100) were evaluated.

Only 34% of asthmatics had an audible wheeze. Significant independent predictors on multiple logistic regression analysis were number of earlier similar attacks and fever (or temperature). The best predictor for asthma was two or more earlier similar episodes (sensitivity 84%, specificity 84%) followed by temperature <37.6°C (sensitivity 73% and specificity 84%). Absence of fever, audible wheeze and a family history of asthma had excellent specificities (98-100%) but low sensitivities (20-34%).

It is concluded that simple clinical predictors can differentiate acute asthma and ARI. The recommended case management can, therefore, be refined by either: (i) Prescribing bronchodilators and no antibiotics with two or more earlier similar episodes of cough and rapid breathing; or (ii) To further minimize undertreatment for pneumonia, prescribing bronchodilators as above, but denying antibiotics in such cases only if there is audible wheeze or family history of asthma or no fever.

Key words: *Acute respiratory infections, Acute asthma, ARI Control Programme, Brochodilator, Antibiotic.*

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Acute respiratory infections (ARI) are one of the principal causes of morbidity and mortality in children under five years of age in developing countries. Reduction of child mortality is a priority goal of the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF), and the strategy for dealing with ARI constitutes a critical component of this objective(l).

Since almost 60% of the episodes in developing countries are bacterial in etiology (1,2) and can be treated with antibiotics, pneumonia can be taken as the practical equivalent of ARI for interventional purposes. Clinical experience and intervention studies in these countries have indicated that early appropriate treatment can significantly reduce mortality from pneumonia(3,4). The key to reducing mortality from

ARI is early diagnosis and appropriate management by paramedical workers in the community, based on clinical signs that are easily detectable. The WHO Programme for Control of Acute Respiratory Infections has, therefore, formulated simple clinical guidelines for the diagnosis and case management of ARI(5). These guidelines are intended to rationalize referral and the use of antimicrobials so that children who may benefit receive them sooner and also there is less over prescribing of antibiotics to those who do not need them.

There is a considerable overlap in the clinical presentation of an acute exacerbation of bronchial asthma and ARI in children below five years of age. However, for logistic reasons the concern in this context in the WHO recommended case management has been biased towards overtreatment as ARI(5,6). It is warned that wheezing can occur during pneumonia and therefore, care must be taken when treating wheezing children not to miss treating pneumonia with an antibiotic(5). Further, the need for bronchodilator therapy is guided by the presence of a wheeze; and for paramedical workers this pertains to only a small proportion of wheeze which may be audible without the aid of a stethoscope. Thus, according to the current guidelines, in a child with cough and rapid breathing;" there is a predilection for overtreatment for ARI with antibiotics and for undertreatment for asthma with bronchodilators. In this context, it is also important to visualize that although morbidity and mortality due to acute asthma may be rare in comparison to ARI in developing countries, the prevalence of asthma is increasing globally and asthma related fatalities do occur, which can largely be prevented by an accurate diagnosis and early institution of appropriate therapy including bronchodilators(7,8).

There is an obvious need to further rationalize the antimicrobial and bronchodilator prescription in the recommended ARI case management regimen. The present study was, therefore, designed to explore the possibility of recommending simple practical guidelines to differentiate ARI from an acute exacerbation of asthma in preschool children.

Subjects and Methods

In a 1:1 case control design, 200 children in the age group of 6 months to 5 years who presented with cough and rapid breathing of less than 5 days duration, were enrolled for the investigation. The lower limit of 6 months was used since a diagnosis of acute asthma below this age is rare.

A detailed clinical evaluation of these subjects was recorded on a pretested proforma by a single investigator (BV). Due emphasis was given to pertinent symptomatology, namely, cough, fever, nasal discharge, tachypnea, chest indrawing, refusal of feeds, cyanosis, history of previous attacks, family history of allergic disorders and history of respiratory distress in the neighbourhood. On physical examination, the following aspects were specially looked for: (i) Toxic look (investigator's impression); (ii) Temperature-axillary temperature was measured with a[1] thermometer for 60 seconds; *(iii)* Pulse rate-counted by palpating the radial pulse for 60 seconds; (iv) Respiratory rate-counted by observing the movements of chest and abdomen for 60 seconds in an awake but quiet child; (v) Audible wheeze-hearing for the characteristic sound in proximity to the subject's mouth; *(vi)* Subcostal retraction-by observing the inward movement of the bony structures of the lower chest wall with respiration in a quiet child for 60 seconds. Similarly, flaring of *alae nasi* and suprasternal and intercostal

retractions were looked for; *(vii)* Chest examination-percussion, breath sounds and added sounds like crepitations and wheeze; and *(viii)* Liver and splenic size. All the patients were subjected to chest roentgenogram and differential leucocyte count.

On the basis of clinical presentation and laboratory investigations, the children were started on therapy for acute bronchial asthma or ARI. The specific therapy for the former comprized of bronchodilators only (adrenaline, aminophylline, deriphylline, salbutamol, terbutaline or hydrocortisone) either singly or in various combinations given orally and/or parenterally. Nebulised bronchodilator therapy could not be used due to non-availability of a nebulizer, as is common in several areas of the developing world. For ARI, the specific therapy used was antimicrobials. However, in 10 subjects with ARI, additional bronchodilator therapy was instituted for auscultable wheeze. Other supportive measures like intravenous fluids and oxygen were utilized, as and when required.

The following subjects were not recruited for the study: *(i)* if antibiotics had been empirically started by the treating physician in the hospital in a child with an acute exacerbation of bronchial asthma; and *(ii)* children with a diagnosis of bronchiolitis. These exclusions were done so that in this preliminary exploratory study, the clinical differentiating features which emerged were between definitely diagnosed ARI and acute asthma.

In under five children, there are till date no universally applicable criteria to objectively (100%) define either ARI or acute asthma(9). ARI is known to occur without cough, respiratory distress or radiological abnormalities while conversely infiltrative changes in the X-ray are possible even in bronchiolitis or asthma. Since the intent was to further rationalize bronchodilator and antibiotic usage in the community by a health worker on the basis of simple criteria, an objectified diagnosis by experienced pediatricians in a tertiary referral centre, as detailed below, was considered adequate.

The patient was diagnosed to have asthma if there were: *(i)* wheeze, *(ii)* absence of pulmonary infiltration on X-ray, and *(iii)* rapid response to bronchodilator therapy alone without antimicrobial use. However, in one such case, the oral antibiotic (ampicillin) prescribed prior to recruitment in the investigation was inadvertently continued for 24 hours. A diagnosis of ARI was made if there were: *(i)* features of pulmonary infiltration on X-ray, and *(ii)* crepitations and/or signs of consolidation on auscultation.

Statistical methods included univariate analysis (Chi square test, Fisher's exact test or Student's 't' test) to determine the clinical features significantly different between the two groups. Subsequently, a multiple logistic regression analysis was done to find out the factors independently differentiating the two groups. Sensitivity and specificity values were calculated for the. significant predictors. In the case of continuous variables, different cut off levels were screened to determine the best amongst them, namely, the value which maximized the sum of sensitivity and specificity. Various combinations of the significant independent predictors were also tried to arrive at the best predictive model.

A sample size of 100 cases and 100 controls was perceived to be adequate on the basis of following considerations for an alpha of 0.05 (95% confidence level) and beta of 0.1 (90% power): *(i)* For predictor

variable prevalences of 75% and 25% in the two groups (for example, history of earlier similar attacks, temperature below 37.6°C) the requisite sample size is 23 cases and 23 controls; *(ii)* The corresponding figure for prevalences of 20% and 2% (for example, fever, family history of asthma, audible wheeze) is 72 cases and 72 controls; *(iii)* The required sample size is 91 cases and 91 controls for prevalences of 15% and" 1% (unexpected variable).

Results

Table I compares the relevant historical events and the examination findings in the two groups. Within the specified age range, subjects in the ARI group were slightly younger, predominantly due to an over representation in the 6 to 11 months age groups (39 *vs* 19). Subjects in the asthma group presented earlier by almost a day; the duration of illness, cough, fever, respiratory distress and nasal discharge were all significantly ($p < 0.001$) lower. Although, the mean respiratory rate in the two groups was comparable ($p > 0.05$), children with asthma had a severer degree of respiratory distress. Using the WHO Programmed) recommended cut off limits, a significantly greater proportion of cases in the asthma group had fast breathing (90 *vs* 74; p=0.006) and perceptible subcostal or intercostal recession (p=0.001). Only 34% of subjects with asthma had wheeze which was audible without the aid of a stethoscope.

To determine the factors which were independent predictors in differentiating the two groups, a multiple logistic regression analysis was done. The variables included in the model were age, number of earlier similar attacks of cough and fast breathing, fever (or axillary temperature in the second model), positive family history of asthma, audible wheeze and toxic look. Features like historical evidence of tachypnea or chest indrawing, and examination findings related to pulse rate, respiratory rate, subcostal and intercostal recession and accessory muscle use were not included in the model since the subjects with either of the two illnesses could have a moderate or severe presentation at the time of the examination. Consequently, these features would have limited predictive ability in an individual child cough and rapid respiration. Multiple logistic regression analysis revealed that number of earlier similar attacks [OR (95% CI) for ≥ 2 similar attacls-25.1 (11.1, 56.8); p=0.0000] and history of fever [37.5 (4.4, 319.9); p=0.0013] were the only significant independent predictors. In the second model too, earlier similar attacks [18.7 (8.2, 42.7); p=0.0000] and axillary temperature [8.6 (3.7, 19.8); p=0.0000) were the only significant independent predictors.

Table II compares the sensitivity and specificity values of the significant univarfate predictors derived from *Table I* and various combinations of the independent factors derived from the multiple logistic regression analysis. The best predictor was a history of two or more earlier similar episodes which had both high sensitivity (84%) and specificity (84%) for the diagnosis of asthma. A temperature below 37.6°C was almost as good a predictor with a specificity of 84% and a sensitivity of 73%. Absence of toxic look was highly sensitive but had a very low specificity (10%). The other individual predictors had very high specificities (98 to 100%) but low specificities (20 to 34%). Serial combinations of the independent predictors tended to maximize the specificity at the expense of sensitivity whereas the converse was true for parallel

TABLE I—*Univariate Comparison of Historical Events and Examination Findings [Mean (SD) or number]*

	Parameter	ARI (n=100)	Asthma (n=100)	p value
1.	Age (mo)	23.4(18.5)	29.5(17.6)	0.016
2.	Males	54	62	0.316
3.	Duration (days)	3.4(1.2)	2.4(1.5)	<0.001
4.	Nocturnal cough#	13	55	<0.001
5.	Fever			
	Intensity	99	68	<0.001
	Low	17	34	
	Moderate	16	11	<0.001
	High	66	23	
6.	Previous similar episode	30	96	<0.001
7.	Family history of asthma	2	20	<0.001
8.	Personal/family history of other allergies	0	3	0.246
9.	Toxic look	10	0	<0.001
10.	Temperature (°C)	38.5(1.0)	37.3(0.5)	<0.001
11.	Pulse rate (per min)	131.1(22.2)	124.4(22.5)	0.035
12.	Nasal discharge	35	31	0.652
13.	Audible wheeze	0	34	<0.001
14.	Respiratory rate (per min)	52.1(12.6)	54.9(11.6)	0.100
(*i*)	Tachypnea per WHO@			
	6-11 mo	29/39	17/19	0/162
	12-60 mo	45/61	73/81	0.019
(*ii*)	Subbcostal or intercostal recession*	88	99	0.001
(*iii*)	Accessory muscle use	34	40	0.464
15.	Liver size	2.4(0.8)	2.1(1.1)	0.051
16.	Palpable spleen	29	36	0.365

\# - Nocturnal cough refers to coughing more frequently and/or intensely at night.

@ - Tachypnea (fast breathing) as per WHO recommended(5) guidelines, namely, ≥50 breaths/min from 2 upto 12 mo age and ≥40 breaths/min from 12 up to 60 mo age.

* - Includes mild/perceptible recession.

TABLE II–*Summary of the Sensitivity (%) and Specificity (%) Values*

	Predictor(s)	Sensitivity	Specificity	OR (95% CI)#
1.	Earlier similar* attacks (≥2)	84	84	27.6 (12.2, 63.6)
2.	Absence of fever	32	99	46.6 (6.5, 954.3)
3.	Family history of asthma + ve	20	98	12.3 (2.6, 44.0)
4.	Absence of toxic look	100	10	-
5.	Temperature* (<37.6°C)	73	84	14.2 (6.7, 30.3)
6.	Audible wheeze	34	100	-
7.	Earlier similar (≥2) *and* no fever	27	99	36.6 (5.1, 740.6)
8.	Earlier similar (≥2) *or* no fever	89	84	42.4 (17.4, 106.6)
9.	Earlier similar (≥2) *and* temp (<37.6°C)	62	94	25.5 (9.6, 72.0)
10.	Earlier similar (≥2) *or* temp (<37.6°C)	95	74	54.1 (18.5, 119.8)

* - Refers to best cut off point.
\# - Refers to crude (unadjusted) odds ratio.

combinations. However, a combination of earlier similar attacks (≥2 in number) *or* no fever was marginally better than the former alone.

The diagnosis of bronchial asthma below the age of one year is relatively uncommon and the selected sample had more representation for the infants (6 to 11 mo old) in the ARI group. A similar analysis was,, therefore, attempted for children aged one year or more. Almost identical results were documented after exclusion of children below 12 months. The independent predictive factors on multiple logistic regression analysis were earlier similar attacks and fever (or axillary temperature). The best predictor again was ≥2 earlier similar episodes (sensitivity 88%, specificity 79%). Axillary temperature below 37.6°C was almost as good a predictor (sensitivity 75%, specificity 82%). Absence of toxic look was highly sensitive (100%) but had a low specificity (7%). Conversely, the other remaining predictors (absence of fever, positive family history of asthma, audible wheeze) had a high specificity (82-100%) but low sensitivity (22-33%). A combination of earlier similar attacks (≥2 in number) *or* no fever was marginally better (sensitivity 92%, specificity 78%) than the former alone.

Discussion

In the current investigation, even a trained pediatric resident would have failed to identify two thirds of the subjects with acute asthma, if the sole criterion of audible wheeze had been utilized. In the context of a peripheral health centre, therefore, according to the current recommendations for case management(5), a child with cough and rapid breathing has a substantial probability of being overtreated for ARI with antibiotics and undertreated for asthma with bronchodilators. However, our study indi-

cates that despite considerable overlap in the clinical presentation, simple predictors can reliably differentiate an acute exacerbation of bronchial asthma from ARI and these features can be profitably employed to further rationalize the ARI case management.

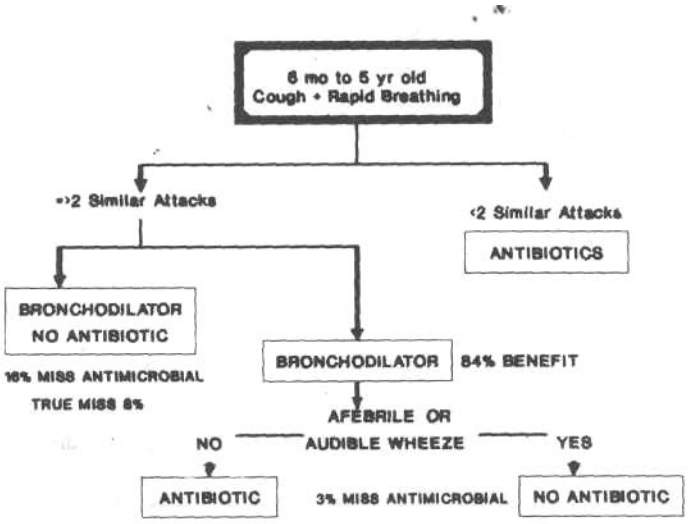
The observation that the children in the ARI group were younger is not surprising since the diagnosis of asthma is relatively uncommon in infancy(5). The shorter symptom duration in the asthma group at recruitment could be due to the following reasons: *(i)* It may simply have been a reflection of recruitment of subjects unrelated to other causes; *(ii)* Parents of asthmatics were possibly more disease educated and consequently sought medical care earlier; *(iii)* Children with asthma had more severe respiratory distress which could have stimulated the parents to seek attention sooner. It could also be argued that asth matics develop respiratory distress faster in comparison to ARI. However, the present study design does not permit a test of these possibilities. The variations in liver size and pulse rate in the two groups are primarily a reflection of the differences in age and/or temperature.

The present trial validated the sensitivity of the WHO recommended cut off levels of respiratory rate for diagnosing ARI and hence the prescription of antibiotics. When the ARI Control Programme recommended(5) cut off respiratory rate per minute (>50 from 2 up to 11 months age and >40 from 12 up to 60 months age) was considered, the sensitivities for diagnosing ARI were 73% and 74%, respectively. The observed sensitivity for the younger children is at the upper limit of the earlier experience (34-75%) whereas for older subjects it is at the lower end of the reported (77-90%) range(10-13). Thus almost a quarter of subjects with ARI may not receive antibiotics with the recommended cut off levels. The 'gold standard' for the diagnosis of ARI in these investigations varied from a radiologically confirmed pneumonia to a clinical evidence of pneumonia or bronchopneumonia as judged by the treating doctor (crepitations or features of consolidation). However, it is important to note that none of these studies had incorporated subjects with recurrent wheezing and only one report(11) had included cases with evidence of wheeze for that particular episode. It is obvious that the reported predictive values for pneumonia, based on respiratory rate, would alter in the actual field situation since children with acute asthma or similar conditions (for example, bronchiolitis) would also be included as controls.

In conformity with the concern of not to miss treating ARI with antibiotics and simplicity of-the criteria, the following suggestions emerge for further rationalizing both bronchodilator and antibiotic usage in a particular child ≥ 6 months age with cough and rapid breathing: *(i)* Subjects with two or more earlier similar attacks (cough and rapid breathing) should receive bronchodilators and no antibiotics (sensitivity 84%, specificity 84%). This would certainly reduce undertreatment for asthma to a great extent. Also, amongst 10 children with wheeze in the ARI group, 2 had a history of more than 1 earlier attack and required bronchodilator therapy in addition. With this predictor, therefore, some children with ARI who also require bronchodilators may be selected. However, with this proposal one would miss 16% of cases with ARI requiring antibiotics, a figure that may be unacceptable currently. Amongst these 16 children, 8 would anyhow not have been

prescribed antibiotics as per the recommended cut off respiratory rate(5). With this correction, therefore, only 8% of cases would actually have been denied antibiotics; *(ii)* If the concern for missing antibiotic therapy in 16% (or corrected figure of 8%) of children with ARI is overriding, one could resort to an alternative strategy. All subjects with two or more earlier similar attacks (cough and rapid breathing) may be given bronchodilators, thereby reducing undertreatment for asthma. Amongst these children, various combinations of three highly specific predictors (absence of fever, audible wheeze, a positive family history of asthma) can be further utilized to minimize the misclassification. It would be practical to avoid antibiotics in subjects who have any of these three predictors (over-prescription of antibiotics for asthma 31%, antibiotics not given for ARI 3%). However, if this figure of 3% of subjects with ARI not given antibiotics is still not acceptable, then a reasonable compromise would be presence of either audible wheeze or absence of fever (overprescription of antibiotics for asthma 39%, antibiotics not given for ARI 1%). The different options outlined above for refining the recommended case management are summarized in *Fig. 1*.

It would be pertinent to caution that the present study was only a preliminary attempt in this direction. The utility of clinical predictors depends upon not only the health functionary eliciting information but also the ability of the respondent. These conditions may vary from place to place and therefore, validation of the findings is required in different settings. Further, the current investigation had included only



children with clear cut differentiation into the two groups, namely, ARI and asthma. The reported sensitivities and specificities are, therefore, representative only of a comparison between these two clear cut groups. The predictive value could alter when all conditions resulting in cough and rapid breathing are considered.

It is concluded that despite considerable overlap in the clinical presentation, simple predictors (two or more earlier similar attacks, fever, audible wheeze, positive family history of asthma) can reliably differentiate an acute exacerbation of bronchial asthma from ARI and a combination of these features can be profitably amalgamated in the recommended case management to further rationalize the antibiotic and bronchodilator prescription.

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