Clinico-virological profile, intensive care needs, and outcome of infants with acute viral bronchiolitis: A prospective observational study.

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Abstract

Objectives: To describe clinico-virological profile, treatment details, intensive care needs, and outcome of infants with acute viral bronchiolitis (AVB). Methodology: In this prospective study, 173 infants with AVB admitted to Pediatric emergency and Pediatric intensive care unit (PICU) of a tertiary care teaching hospital in North India during November 2019 to February 2020 were enrolled. The data collection included clinical features, viruses detected, complications, intensive care needs, treatment, and outcome. Multivariate analysis was performed to determine independent predictors for PICU admission. Results: Patients had rapid breathing (98.8%), cough (98.3%), and fever (74%). On examination, tachypnea (98.8%), chest retractions (93.6%), respiratory failure (84.4%), wheezing (49.7%), and crepitations (23.1%) were observed. RSV and rhinovirus were predominant isolates. Complications were noted in 25% cases as encephalopathy (17.3%), transaminitis (14.3%), shock (13.9%), AKI (7.5%), myocarditis (6.4%), MODS (5.8%), and ARDS (4.6%). More than one-third cases required PICU admission requiring nasal cannula oxygen (11%), continuous positive airway pressure (51.4%), high flow nasal canula (14.5%), and mechanical ventilation (23.1%); nebulization (74%); antibiotics (35.9%); and vasoactive drugs (13.9%). The mortality was 8.1%. Underlying comorbidity; chest retractions, respiratory failure, and low oxygen saturation at admission; presence of shock; and need of mechanical ventilation were independent predictors of PICU admission. Isolation of virus or co-infection were not associated with disease severity, intensive care needs, and outcome. Conclusion: Among infants with AVB, RSV and rhinovirus were predominant; >1/3rd required PICU admission; and comorbidity; chest retractions, respiratory failure, low oxygen saturation; shock; and need of mechanical ventilation independently predicted PICU admission.

Introduction:

Acute viral bronchiolitis (AVB) is the leading cause of hospitalization among infants in developed and developing countries and associated with significant morbidity[1-4]. AVB is defined as the first episode of wheezing in a child younger than 12-24 months with physical findings of a viral respiratory infection and has no other explanation for the wheezing (pneumonia or atopy)[3,4]. The common clinical presentation includes prodrome of rhinorrhea, cough, low-grade fever, followed by paroxysmal cough, dyspnea, chest retractions, wheezing, and lung hyperinflation with patchy atelectasis on chest radiograph. Respiratory syncytial virus (RSV) is the main cause of AVB worldwide and accounts for 30-80% of cases. Other viruses implicated are influenza viruses, parainfluenza viruses (PIV 1-3), human metapneumovirus (hMPV), rhinovirus, enterovirus, adenovirus, and bocavirus[2,4-11]. AVB is characterized by acute inflammation, edema, and necrosis of epithelial cells lining of small airways, increased mucus production, and bronchospasm[4,12]. The severity of AVB varies from asymptomatic exposures to severe lower respiratory tract infection leading to emergency room (ER) visit, Pediatric intensive care unit (PICU) admission, and sometimes mortality[4]. The reason

for variable course in children is not well understood but it is believed that in children with severe disease, the enhanced inflammatory response may be a contributing factor rather than virus induced cytopathy.[13]. Children with RSV infection in early life have a higher risk of developing asthma and recurrent wheezing in later childhood[4,14,15]

The literature on clinical characteristics, viral profile, intensive care needs, and outcome of infants with AVB is limited. Therefore, this prospective observational study was planned to investigate clinico-virological profile, treatment details, intensive care needs, and outcome infants with AVB.

Materials and methods:

This prospective study was conducted in Pediatric emergency room (ER) and Pediatric intensive care unit (PICU) of a tertiary care teaching hospital in North India during the season of AVB for the year 2019-20 (November 2019 to February 2020). The study was approved by the Institute Ethics Committee and patients were enrolled after written informed consent from the parents or legal guardians. All infants admitted to ER and PICU with AVB were included. The AVB was defined as the first episode of wheezing in a child younger than 12-24 months who has findings of a viral respiratory infection on examination and absence of pneumonia or atopy[3,4]. Patients were managed following the protocol for AVB in ER and PICU.

In Pediatric ER, there are 20-30 admissions per day. The ER is manned 24X7 by 6-8 junior residents (undergoing MD Pediatrics training), 2-3 senior residents (undergoing Pediatric critical care fellowship), and one Pediatric critical care consultant. The 15-bedded PICU is manned 24X7 by 4-5 junior residents, 2-3 Pediatric critical care senior residents, and one Pediatric critical care consultant. For management of AVB, there are facilities for administration of heated humidified oxygen, continuous positive airway pressure, high flow nasal cannula, nebulization, and multipara monitors in ER and PICU; and non-invasive and invasive ventilation in PICU.

The data was collected on a pre-designed study proforma regarding demographic variables like age, sex, presenting complaints, duration of illness, gestation and birth weight, pre-referral treatment details, underlying illness or comorbidity (congenital cardiac disease, chronic lung disease, neurological disease, neuromuscular disorder, etc.), and clinical findings. The chest radiograph findings, extra-pulmonary manifestations or complications [(myocarditis, encephalitis/encephalopathy, transaminitis, shock, acute respiratory distress syndrome, (ARDS), acute kidney injury (AKI), and multiple organ dysfcuntion syndrome (MODS), pulmonary artery hypertension (PAH)], treatment details [oxygen support, mechanical ventilation, nebulization, antibiotics, steroids, vasoactive agents, intravenous immunoglobulin (IVIG)], and outcome (duration of PICU and hospital admission, and mortality) were noted.

Viral testing:

For viral testing, nasopharyngeal aspirates (NPA) were taken by a trained health personnel within 12 hours of admission by passing 6-8 Fr feeding tube into the nasopharynx and applying gentle suction with a syringe. The secretions were rinsed into viral transport medium (VTM) and transported under cold chain to Regional viral research and diagnostic laboratory (VRDL), Department of Virology for testing of RSV, rhinovirus, influenza A, PIV 2, PIV 3, and hMPV. The samples were subjected to nucleic acid extraction using QIAamp Viral RNA Mini Kit (Qiagen, Heidelberg) and extracted RNAs were reverse transcribed utilizing high capacity cDNA reverse transcription kits (Applied Biosystems). Matrix gene of Influenza A and nucleocapsid gene of RSV, PIV 2 and PIV 3 were targeted to screen the respective RNA according to the protocol by Bharaj et al[5]. Amplification of Influenza A and RSV were done on monoplex single tube format whereas for the amplification of PIV 2 and PIV 3, multiplexing PCR was used. Viral genome of hMPV was detected in clinical samples by using primers as described by Bouscambert-Duchamp et al[16]. For the detection of human rhinovirus, highly conserved 5' un-translated region of the genome was amplified using a previously described nested PCR strategy according to Wisdom et al[17]. The amplified DNA fragments were identified on a 2% agarose gel with ethidium bromide and visualized under UV transilluminator. For the confirmation, PCR amplified products were purified and sequenced bi-directionally using BigDye Terminator v3.1 Cycle sequencing kit (Applied Biosystems, Foster, CA) with an ABI 3500xL genetic analyzer (PE Applied Biosys-

tems Inc., Foster City, CA) and further checked by BLAST tool with already available reference database of NCBI website.

Our study was carried out with the aim to describe the clinical and virological profile, treatment details, intensive care needs, and outcome of infants with AVB.

Statistical analysis:

Appropriate data entry and statistical analysis was performed on Microsoft Excel 2010 (Microsoft, Redmond, WA) and SPSS software version 20 (SPSS, Inc, Chicago, IL). Descriptive statistics [number (percentages) and median (interquartile range, IQR)] was used for baseline variables. The infants admitted to PICU were compared with those who do not required PICU admission by using Chi square test for categorical variables and Mann Whitney U test for continuous variables. Multivariate analysis was done to find out independent predictors of PICU admission. All tests were two-tailed and p value <0.05 was taken as significant.

Results:

A total of 173 infants with AVB were enrolled with median age of 3 (2-7) months with male preponderance (65.9%, n=114). The number of cases admitted during each month are shown in Figure 1. Majority (75.7%, n=131) were born by vaginal delivery, 13.3% (n=23) were preterm, 28.9% (n=50) were low birth weight, and median birth weight was 2.6 (2.3-3) kgs. The median duration of illness was 4 (3-7) days and common clinical features were rapid breathing (98.8%), cough (98.3%), and fever (74%). One-third cases (n=59) had one or another underlying comorbidity. Before referral, 56.1% (n=97) cases were admitted at local hospitals for 24 (24-72) hours where they received oxygen support (51.4%) and antibiotics (50.3%). The examination findings at admission were tachypnea (98.8%), chest retractions (93.6%), respiratory failure (84.4%), wheezing (49.7%), crepitations (23.1%), and oxygen saturation on room air was 88% (82-91%). The chest radiographs were performed in 65.3% (n=113) cases and common abnormalities included hyperinflation (75.2%), micro-atelectasis (54.9%), and para-hilar infiltrates (13.3%) (Table 1).

All infants underwent virological testing for RSV, rhinovirus, influenza A, PIV 2, PIV 3, and hMPV and 75% (n=128) tested positive for one or more viruses with total of 166 virus RNA positivity. The most common viruses identified were RSV (51.2%, n=85), rhinovirus (39.7%, n=66), influenza A virus (5.4%, n=9), and PIV 3 (3%, n=5), and hMPV (0.6%, n=1). PIV 2 was not isolated in any case. One-fifth of infants (20.8%, n=36) had >1 virus isolated (co-infection) and common combinations were RSV with rhinovirus (14.5%, n=25), and RSV with influenza A virus (2.3%, n=4) (Table 2).

One-fourth cases developed one or more complications in form of encephalopathy (17.3%), transaminitis (14.3%), shock (13.9%), AKI (7.5%), myocarditis (6.4%), MODS (5.8%), and ARDS (4.6%). All cases were managed with oxygen support. The highest level of oxygen support received was in form of nasal cannula (11%), nasal continuous positive pressure (CPAP) (51.4%), high flow nasal canula (HFNC) (14.5%), and mechanical ventilation (23.1%). Other treatment included nebulization (74%, n=128) [3% saline (66.5%), adrenaline (15%), and salbutamol (13.9%)], intravenous fluids (55.5%, n=96), intravenous antibiotics (35.9%, n=96), steroids (11.6%, n=20), vasoactive drugs (13.9%, n=24), and IVIG (1.7%, n=3). The PICU admission was needed in 36.4% (n=63) cases for 3 (2-6) days. The duration of hospital stay was 5 (3-9) days and the mortality was 8.1% (n=14) (Table 3).

On univariate analysis, infants who required PICU admission had higher rates of comorbidity (55.6% vs. 21.8%, p=0.001), pre-referral admission (68.3% vs. 48.2%, p=0.01), fever (84.1% vs. 74%, p=0.02), chest retractions (100% vs. 90%, p=0.009), respiratory failure at admission (92.1% vs. 80%, p=0.026), encephalopathy (25.4% vs. 12.7%, p=0.03), transaminitis (22.2% vs. 10%, n=0.02), shock (20.6% vs. 1%, p=0.04), MODS (11.1% vs. 2.7%, p=0.029); requirement of mechanical ventilation (39.6% vs. 13.6%, p<0.001), intravenous fluids (71.4% vs. 46.4%, p=0.001), and vasoactive drugs (20.6% vs. 1%, p=0.04); and lower SpO2 at admission [85% (80-90%) vs. 88% (84-93%), p=0.04] compared to those who did not required PICU admission (Table 4). The duration of hospital stay was longer in those who required PICU admission (9 vs. 3 days, p=0.001). On multivariate analysis, underlying comorbidity (p<0.001); presence

of chest retractions (p<0.001), respiratory failure (p=0.03), lower oxygen saturation on room air at admission (p=0.01); presence of shock (p=0.02); and need of mechanical ventilation (p=0.04) were independent predictors of PICU admission.

There was no difference in demographic details, clinical features, complications, treatment details, intensive care needs, and outcome among infants who had atleast one virus detected compared to those with no virus; and in whom >1 virus detected (co-infection) compared to those in whom no virus or atleast 1 virus detected (data not shown).

Discussion:

In this prospective observational study, we noted that the number of cases with AVB were higher in the months of November-December 2019. The common symptoms included rapid breathing, cough, and fever. The common findings at admission were tachypnea, chest retractions, respiratory failure, low SpO2, wheezing, and crepitations. RSV and rhinovirus are most commonly detected. The extra-pulmonary manifestations were described in 25% cases in form of encephalopathy, transaminitis, shock, AKI, myocarditis, MODS, and ARDS. More than 1/3rdcases needed PICU admission and common treatment included oxygen support (nasal prong oxygen, CPAP, of HFNC), mechanical ventilation, nebulization (3% saline, adrenaline, and salbutamol), vasoactive drugs, and steroids. One-third cases also received intravenous antibiotics. The mortality rate observed to be 8%.

The impact of AVB on the health of young children is huge and approximately 2-3% of infants require hospitalization due to AVB[4]. Characteristically, in a winter month a child presents with 2-4 days history of low-grade fever, rhinorrhea, nasal congestion; and symptoms of lower respiratory tract involvement (cough, tachypnea); increased respiratory effort (grunting, nasal flaring, and intercostal, subcostal, or supraclavicular retractions); and inspiratory crackles and expiratory wheezing on auscultation[4,10].

Despite the high burden of disease, there is lack of effective treatment for AVB. None of the commonly practised modalities shown to shorten the disease course or hastens the resolution of symptoms of AVB leaving the clinicians to go for supportive therapy in form of heated humified oxygen, adequate hydration, and respiratory monitoring for improvement or worsening. With supportive treatment, majority of infants with AVB do well. The American Academy of Pediatrics published clinical practice guidelines based on Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system to standardize the diagnosis and management of AVB[18]. As per the guidelines, the suspicion of AVB should be based on the history and physical examination. There is no need of routine radiographic, laboratory studies, and viral testing. The supplemental oxygen is needed if oxyhemoglobin saturation (SpO2) falls below 90%. Intravenous or nasogastric fluids to be administered to maintain adequate hydration. Epinephrine, short-acting β2-agonists, systemic glucocorticoids, chest physiotherapy, and antibiotics are not recommended for the treatment of AVB. Nebulization with hypertonic saline may be used as it improves symptoms of mild-to-moderate AVB, if length of stay is >3 days[18].

Due to tertiary care referral hospital, commonly the infants with severe illness are referred with respiratory failure, higher rates of extra-pulmonary complications (25%), more cases required PICU admission (36.4%), and mechanical ventilation (23%), vasoactive drugs (14%); and had higher mortality (8%).

PICU admission is needed in 15-25% of children with AVB. About 25-40% of those admitted to PICU require endotracheal intubation and mechanical ventilation which is associated with various complications including ventilator induced lung injury, infection, airway trauma, vocal cord dysfunction, need for prolonged sedation, and overall a financial burden to the family[19-22]. Various non-invasive modes of oxygen delivery are being increasingly used including CPAP, HFNC, non-invasive positive pressure ventilation (NPPV), and bilevel positive airway pressure (BiPAP) which may obviate the need for invasive mechanical ventilation and complications related to it[23-27]. The infants deteriorating on non-invasive modes of oxygen delivery required intubation and mechanical ventilation because of apnea, severe lower airway disease, or ARDS and usually need a shorter mechanical ventilation (<5 days)[3, 28]. Appropriate sedation and analgesia should be provided to infants with AVB. There is substantial variability in diagnosis and management of infants with AVB in

different PICUs[22].

In index study, 36.4% cases needed PICU admission. Underlying comorbidity; presence of chest retractions, respiratory failure, and lower oxygen saturation at admission; presence of shock; and need of mechanical ventilation were independent predictors of PICU admission on multivariate analysis.

In AVB, the use of antibiotics does not lead to change in course or outcome and are not routinely recommended[4,18]. Despite these facts, antibiotics has been used in AVB inappropriately. Papenburg et al[29] noted that about 25% infants with AVB were given antibiotics, 70% of them had no documented bacterial co-infection, and 38% received macrolides. Therefore, efforts are needed to reduce inappropriate and unnecessary use of antibiotics in AVB.

With the availability of molecular techniques, it has been possible to identify viruses causing AVB. The most common viruses identified are RSV (50-80%), rhinovirus (5-25%), PIV (5-25%), hMPV (5-10%), coronavirus (5-10%), adenovirus (5-10%), and influenza (1-5%)[4,11,30,31]. The proportion of virus causing AVB differ according to geographical location and time of the year. The clinical features of AVB caused by different viruses are generally indistinguishable. However, it has been noted that AVB caused by rhinovirus may be less severe and associated with shorter duration of hospitalization than RSV[4,32]. Also, there are not much differences in response to medical treatment among infants with AVB caused by different viruses[4]. The reported rates of co-infection varied widely among different studies ranging from 6% to more than 30%[4,32,33]. Few studies noted greater severity of disease, longer hospital stay, more severe hypoxemia, and greater risk of relapse in children with co-infection[32,34,35]; whereas, other studies showed no difference on disease severity and outcome in those with co-infection[33,36-38]. In index study, atleast one virus was isolated in 74% cases with RSV and rhinovirus as commonest. One-fifth cases had co-infection with >1 virus. However, isolation of virus or co-infection was not associated with any differences in clinical features, complications, treatment, PICU needs, and outcome.

The strengths of this study include prospective study with large sample size. All the enrolled cases underwent viral testing which is important to determine etiology but did not have much significance in determining disease severity, prognosis, and short-term outcome. The details of treatment, intensive care needs, and outcome has been described. The predictors of PICU admission were determined. The limitations included single centre study and lack of long-term follow-up.

Conclusion:

AVB is common cause of hospitalization among infants, RSV and rhinovirus commonly detected viruses, and 1/3rd cases required intensive care admission. Underlying comorbidity; presence of chest retractions, respiratory failure, lower oxygen saturation at admission; shock; and need of mechanical ventilation were independent predictors of PICU admission. Isolation of virus or co-infection were not associated with disease severity, PICU admission, or outcome.

Figure legend:

Figure 1: Month wise distribution of acute viral bronchiolitis cases from November 2019 to February 2020.

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