

# Prematurity is a significant predictor of worse outcomes in viral bronchiolitis: A comparative study in infancy

Original  
Article

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## ABSTRACT

**Background:** The rate of admissions to hospital with bronchiolitis has increased over the past years. The reasons for this are likely to be multifactorial including improved survival of preterm infants.

**Aim:** To assess the severity of viral bronchiolitis in preterm compared with term infants admitted at a tertiary hospital in Cairo, Egypt, based on the outcome.

**Materials and Methods:** This prospective study was conducted throughout a 3-year period from September 2011 to October 2014. It included 153 infants, 74 healthy preterm and 79 healthy term infants, admitted with clinical diagnosis of bronchiolitis at a tertiary hospital in Cairo, Egypt. Bronchiolitis severity score (BSS) was recorded, and nasopharyngeal swabs were obtained from each patient at the time of presentation. Viruses were identified using reverse transcription PCR. The clinical course and patient's outcome were recorded.

**Results:** This study recorded a significantly more severe BSS for preterm compared with term infants. The preterm group had an increased mean length of hospital stay and oxygen therapy and were more likely to need ICU admission and mechanical ventilation compared with the term group. The mean  $\pm$ SD BSS for infections with human metapneumovirus, respiratory syncytial virus, parainfluenza 3 was more significantly severe in preterm compared with term infants. Bacterial co-infection was significantly correlated with severity scoring in both groups.

**Conclusion:** Prematurity significantly affects the severity of bronchiolitis, and this underscores the importance of early categorization of these infants as a high-risk group on their first visit. Physician should be aware that their illness runs a more severe course, even if they have no underlying disorders.

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## INTRODUCTION

Bronchiolitis is the most common lower respiratory tract infection in children less than 1 year of age and is usually of viral etiology<sup>[1]</sup>. Human respiratory syncytial virus (RSV) is the most commonly affecting virus and identified in 60–70% of hospitalized infant with bronchiolitis<sup>[2]</sup>. Bronchiolitis by itself accounts for the greatest number of hospitalization in infancy during the fall and winter season<sup>[3]</sup>.

Bronchiolitis is a self-limiting condition but may be life-threatening causing significant severe illness<sup>[4-6]</sup>; it is the most common cause of hospital admission for infants beyond the neonatal period, with rate varying between 1 and 3%. Furthermore, ~10% of hospitalized infants will need intensive care admission<sup>[7-10]</sup>.

The rate of admissions to hospital with bronchiolitis has increased over the past 10 years. The reasons for this are not fully understood and are likely to be multifactorial

and include improved survival of preterm infants<sup>[11]</sup>. Epidemiological evidence revealed that young age (<6–12 weeks) and premature birth (<37 weeks) are associated with high risk of severe bronchiolitis<sup>[7,12,13]</sup>.

The aim of the present study was to assess the severity of viral bronchiolitis in healthy preterm compared with healthy term infants in terms of the duration of hospital stay, oxygen saturation, duration of oxygen requirement, and ICU and/or mechanical ventilation (MV) requirement.

## MATERIALS AND METHODS

### Study design and patients

This prospective study was conducted throughout a 3-year period from September 2011 to October 2014. It included 153 infants in the first year of life with clinical diagnosis of bronchiolitis, according to American Academy of Pediatrics<sup>[14]</sup>. All were admitted to inpatient departments at Cairo University Specialized Pediatric Hospital.

Seventy-four of those infants were healthy preterm (<37 weeks) and 79 infants were healthy term. The following specific groups were excluded: neonates, recurrent wheeze, and association of underlying chronic diseases.

### **Methods**

All patients were subjected to thorough history taking, including demographic data, and also, full physical examination was performed with emphasis on signs of respiratory tract infection. The respiratory severity score that has been used in this study is the modified Tal score. This score ranges from 0 to 12, with a higher score indicating more severe disease. Each score is an aggregate of assigned values ranging from 0 to 3 in categories of respiratory rate, retractions, wheezing, and oxygen saturation in room air<sup>[15]</sup>. Bronchiolitis severity score (BSS) was recorded for each patient at the time of presentation. Subsequently, during inpatient management, the following data were recorded: the clinical course was observed during the hospital stay, including the need for ICU admission, need for MV, duration of oxygen therapy, and duration of hospital stay.

### **Clinical specimens**

Complete blood count and C-reactive protein were determined at the time of study enrollment for each patient. Oropharyngeal and nasopharyngeal swabs were obtained for PCR at the time of presentation and put in viral transport media.

### **Molecular identification of respiratory viruses**

Total nucleic acid was extracted from the nasopharyngeal/oropharyngeal swabs by the automated KingFisher Flex Magnetic Particle Processor (Thermo Scientific, Waltham, Massachusetts, USA) using MagMAX Total Nucleic Acid Isolation Kit (Cat No. AM 1840; Applied Biosystems, Foster City, California, USA) according to the manufacturer's instructions. All the viral targets were amplified using specific primers and probes produced by the Center of Disease Control and Prevention (CDC), Atlanta, Georgia, USA, and following the standard protocol for quantitative reverse transcription PCR detection.

Detection of influenza viruses was conducted in the Cairo University Hospital Laboratory and confirmed by the Naval Medical Research Unit No.3 (NAMRU-3) Laboratory. The samples were screened for the presence

of influenza A and B using the CDC kit for influenza following CDC protocol<sup>[16]</sup>. Samples positive for influenza A were further subtyped according to the CDC protocol to the following types: pandemic influenza 2009 A(H1N1), seasonal H1, and H3.

Testing for adenovirus, human parainfluenza viruses 1, 2, and 3, RSV, and human metapneumovirus (hMPV) was done at NAMRU-3 laboratory by reverse transcription-qPCR using CDC-specific primers and probes and following a CDC protocol for the detection of noninfluenza viruses. Samples were considered positive to the viral target if the amplification curve crossed the threshold line before cycle 40. All clinical samples had to be positive for the human RNase P gene (RP), with a Ct value less than or equal to 37, for validation. A positive control for each virus was added to each run to ensure adequate amplification of the target genes.

### **Statistical analysis**

Pre-coded data were entered on the statistical package of social science software program, version 23 (IBM SPSS Statistics for Windows, version 23.0; IBM Corp., Armonk, New York, USA) to be statistically analyzed. Data were presented using mean and SD for quantitative variables and frequency and percentage for qualitative ones. Comparison between groups was performed using independent sample t-test or Mann-Whitney for quantitative variables and  $\chi^2$ -test and Fisher's exact test for qualitative ones. Spearman's correlation coefficient was used to estimate the association between different quantitative variables. P values less than 0.05 were considered statistically significant.

### **Ethical considerations**

This study was approved by Cairo University Clinical Research Ethics Committee, and informed verbal consents were obtained from parents of the included children. The study design conformed to the Revised Helsinki Declaration of Bioethics.

## **RESULTS**

The study included 153 infants with a clinical diagnosis of acute bronchiolitis in otherwise healthy infants. Seventy-nine of them were term and 74 were preterm infants. The detailed demographic characteristics including risk factors for bronchiolitis of both preterm and term infants are summarized in Table 1. Preterm infants were significantly younger than term infants ( $P=0.001$ ).

**Table 1:** Demographic characteristics of preterm and term infants with bronchiolitis, Cairo University Specialized Pediatric Hospital

| Variables                   | Preterm infants (n=74)<br>[n (%)] | Term infants (n=79)<br>[n (%)] | P value |
|-----------------------------|-----------------------------------|--------------------------------|---------|
| Age (mean ±SD) (months)     | 5.2±4.1                           | 7±4.2                          | 0.001*  |
| Sex                         |                                   |                                |         |
| Male                        | 36 (48.6)                         | 41 (51.9)                      | 0.747   |
| Female                      | 38 (51.4)                         | 38 (48.1)                      |         |
| History of passive smoking  | 46 (62.2)                         | 41 (51.9)                      | 0.253   |
| Nonexclusive breast feeding | 32 (43.2)                         | 27 (34.2)                      | 0.319   |

\* $P < 0.05$ , statistically significant.

Clinical findings at the time of presentation, BSS, and outcomes of both groups are shown in Table 2. BSS (mean ±SD) was significantly more severe for preterm compared with term infants at the time of presentation ( $P=0.045$ ). Moreover, preterm group had an increased

mean length of hospital stay and mean duration of oxygen therapy compared with term group ( $P=0.002$  and  $0.001$ , respectively). Preterm infants were significantly more likely to need ICU admission ( $P=0.007$ ) and MV ( $P=0.033$ ) than term infants.

**Table 2:** Clinical findings on presentation and outcomes of the preterm and the term infants with bronchiolitis

| Variables                             | Preterm infants [n (%)] | Term infants [n (%)] | P value |
|---------------------------------------|-------------------------|----------------------|---------|
| Respiratory rate (mean ±SD)           | 54.7±10.2               | 47.8± 10.5           | <0.001* |
| Respiratory distress [n (%)]          |                         |                      |         |
| No RD                                 | 10 (13.51)              | 28 (35.4)            | 0.003*  |
| Grade 1                               | 10 (13.51)              | 12 (15.2)            | 0.821   |
| Grade 2                               | 16 (21.62)              | 13 (16.5)            | 0.536   |
| Grade 3                               | 30 (40.55)              | 24 (30.4)            | 0.236   |
| Grade 4                               | 8 (10.81)               | 2 (2.5)              | 0.051   |
| Lethargy                              | 28 (37.8)               | 9 (11.4)             | <0.001* |
| No drink                              | 34 (45.9)               | 46 (58.2)            | 0.147   |
| Seizures                              | 4 (5.4)                 | 2 (2.5)              | 0.431   |
| Vomiting                              | 16 (21.6)               | 36 (45.6)            | 0.002*  |
| Oxygen saturation (mean ±SD)          | 85.4±13.1               | 90.6± 9.7            | 0.016   |
| Duration of oxygen therapy (mean ±SD) | 4.4±1.7                 | 2.9± 1.4             | 0.001*  |
| PICU admission [n (%)]                | 18 (24.3)               | 6 (7.6)              | 0.007*  |
| Duration of PICU admission (mean ±SD) | 3.8±1.3                 | 3.2±0.4              | 0.186   |
| Mechanical ventilation [n (%)]        | 12 (16.2)               | 4 (5.1)              | 0.003*  |
| Duration of MV (mean ±SD)             | 3.3± 1.0                | 2.5± 1.0             | 0.128   |
| Duration of hospital stay (mean ±SD)  | 5.4±1.6                 | 4.0±1.6              | 0.002*  |
| Bronchiolitis severity score          |                         |                      |         |
| Mean ±SD                              | 9.6± 3.8                | 8.3± 3.3             | 0.045*  |
| Severe bronchiolitis [n (%)]          | 36 (48.6)               | 26 (32.9)            | 0.051   |

MV: mechanical ventilation, RD: respiratory distress.

\* $P < 0.05$ , statistically significant.

Viral screening results are summarized in Table 3. Respiratory viruses were detected in 36 (48.6%) preterm patients and in 53 (67%) term patients with acute bronchiolitis. RSV was the most commonly detected virus in both groups, although more significantly frequent in term infants (57%) than preterm infants (32.4%) ( $P=0.003$ ). On the contrary, adenovirus was more significantly frequent in preterm than term infants (16.2 and 5.1%, respectively;  $P=0.033$ ). Concomitantly with the viral respiratory

infection, preterm patients had more frequent concomitant bacterial infections than term, despite nonsignificance ( $P=0.221$ ).

On comparing BSS of different viral agents in preterm and term infants, the mean  $\pm$ SD score for hMPV, RSV, parainfluenza 3 was more significantly severe in preterm compared with term infants ( $P=0.003$ , 0.009, and 0.013, respectively), as shown in Table 4.

**Table 3:** Viral PCR results among preterm and term infants with bronchiolitis, Cairo University Specialized Pediatric Hospital

| Viruses                     | Viral positive in preterm infants (n=36)<br>[n (%)] | Viral positive in term infants (n=53)<br>[n (%)] | P value |
|-----------------------------|---|--|---------|
| RSV                         | 24 (32.4)   | 45 (57)  | 0.003*  |
| Adenovirus                  | 12 (16.2)   | 4 (5.1)  | 0.033*  |
| hMPV                        | 4 (5.4)   | 1 (1.3)  | 0.198   |
| Influenza A                 | 8 (10.8)  | 2 (2.5)  | 0.051   |
| Influenza B                 | 0 (0.0)   | 0 (0.0)  | –       |
| Parainfluenza 1             | 0 (0.0)   | 0 (0.0)  | –       |
| Parainfluenza 3             | 2 (2.7)   | 6 (7.6)  | 0.278   |
| Mixed viral infection       | 12 (16.2)   | 5 (6.3)  | 0.071   |
| Co-infection with bacterial | 12 (16.2)   | 7 (8.9)  | 0.221   |

hMPV: human metapneumovirus, RSV: respiratory syncytial virus.

\* $P<0.05$ , statistically significant.

**Table 4:** Correlation between screened viruses and bronchiolitis severity score in preterm and term infants

| Virus           | Outcomes       |                | P value |
|-----------------|----------------|----------------|---------|
|                 | Preterm        | Term           |         |
| RSV             | 9.7 $\pm$ 3.9  | 7.4 $\pm$ 3.1  | 0.009*  |
| Adenovirus      | 9.5 $\pm$ 4.0  | 10.3 $\pm$ 2.6 | 0.717   |
| hMPV            | 11.0 $\pm$ 1.2 | 5 $\pm$ 0.0    | 0.003*  |
| Influenza A     | 10.0 $\pm$ 3.4 | 13.5 $\pm$ 2.1 | 0.212   |
| Parainfluenza 3 | 13.0 $\pm$ 0.0 | 6.7 $\pm$ 2.4  | 0.013*  |

hMPV: human metapneumovirus, RSV: respiratory syncytial virus.

\* $P<0.05$ , statistically significant.

On correlating BSS to screened viruses and outcome in both groups, mixed viral infection did not correlate with severity scoring of bronchiolitis in preterm and term groups ( $P=0.723$ , 0.537, respectively). However, bacterial co-infection was significantly correlated with

severity scoring in both groups ( $P<0.001$ ). Moreover, we found significant correlation between BSS and need for admission. In addition, there were significant correlations between severity and duration of hospital stay and oxygen therapy, as shown in Table 5.

**Table 5:** Correlation of bronchiolitis severity score with screened viruses and outcome in preterm and term infants

| Variables                      | BBS in preterm | P value | BSS in term    | P value |
|--------------------------------|----------------|---------|----------------|---------|
| Screened virus (mean $\pm$ SD) |                |         |                |         |
| hMPV                           | 11 $\pm$ 1.2   | 0.721   | 5 $\pm$ 3.3    | 0.329   |
| RSV                            | 9.7 $\pm$ 3.9  | 0.676   | 7.4 $\pm$ 3.1  | 0.015*  |
| Adenovirus                     | 9.5 $\pm$ 4    | 0.953   | 10.3 $\pm$ 2.6 | 0.233   |
| Parainfluenza 3                | 13 $\pm$ 00    | 0.214   | 6.7 $\pm$ 2.4  | 0.189   |
| Influenza A                    | 10 $\pm$ 3.4   | 0.7     | 13.5 $\pm$ 2.1 | 0.042*  |
| Mixed viral infection          | 9.8 $\pm$ 3.6  | 0.723   | 9.2 $\pm$ 3.8  | 0.537   |
| Co-infection with bacterial    | 13.7 $\pm$ 1.0 | <0.001* | 13.7 $\pm$ 2.0 | <0.001* |
| Outcome (r) <sup>a</sup>       |                |         |                |         |
| Duration of oxygen therapy     | 0.653          | <0.001* | 0.721          | <0.001* |
| Duration of hospital stay      | 0.644          | <0.001* | 0.803          | <0.001* |
| Duration of PICU admission     | 0.304          | 0.220   | 0.310          | 0.550   |

BSS: bronchiolitis severity score, hMPV: human metapneumovirus, RSV: respiratory syncytial virus.

<sup>a</sup>r is coefficient correlation.

\*  $P < 0.05$ , statistically significant

## DISCUSSION

We identified a viral etiology in 48.6% of preterm infants and in 67% of term infants hospitalized with acute bronchiolitis; one or more viral pathogens were detected. RSV was the most frequently isolated respiratory virus in both preterm and term infants with bronchiolitis, and adenovirus was the second most frequently detected virus in the current study. The predominance of RSV is in concordance with the assertion that this virus is the single most frequently identified lower respiratory tract pathogen in hospitalized infants worldwide<sup>[17–20]</sup>. Although RSV significantly affects more term infant in this study, yet it is likely to be associated with more severe disease in preterm infants; this observation is important in planning protocols for bronchiolitis prophylaxis and management in such high-risk preterm infants. Similarly, hMPV and parainfluenza 3 infections were more severe in preterm than term infants. So, physicians treating preterm infants with RSV, hMPV, and parainfluenza 3 bronchiolitis should be aware that their illness is more protracted and runs a more severe course than term infants, even if otherwise healthy. The low prevalence of virus detection among preterm compared with term infants with acute bronchiolitis in this study could be attributed to other respiratory viruses, which were not included in this study, such as coronaviruses, bocaviruses, and rhinoviruses, and may be also, explained by the fact that only patients admitted with severe infections were included in our study.

Although there were no significant differences in the length of stay in PICU and the duration of MV among preterm and term infants, these preterm patients had more frequent need to be managed in PICU, more frequent need

for MV, and more prolonged oxygen therapy and hospital stay than term ones. These findings were in accordance with the study by Howidi *et al.*<sup>[21]</sup>. These differences may be explained by smaller airway and/or suboptimal immune response in preterm infants. In addition, the significant difference in age between the two groups could partly explain the higher severity among preterm group.

We found also significant correlation between bronchiolitis severity scoring and need of hospital admission, the same as for the duration of hospital stay and duration of oxygen therapy. This was similar to results reported by Ricart *et al.*<sup>[22]</sup>, who found that severe bronchiolitis had more mean length of hospital stays compared with nonsevere and more prolonged duration of oxygen and MV. We documented that preterm infants have a more severe form of illness than term infants, where we found that prematurity significantly affects the severity score of bronchiolitis. Increased illness severity in infants who had bronchiolitis was discussed in several researches<sup>[1,23]</sup>. In this study, we found that preterm infants were significantly younger than those born term, similar to that reported by Fleming *et al.*<sup>[1]</sup>.

Mixed viral infection and bacterial co-infection in the present study were more frequently observed in preterm compared with term infants with acute bronchiolitis. However, bacterial co-infection was significantly correlated with severity scoring, whereas mixed viral infection did not correlate with severity scoring of bronchiolitis, and this was in consistence with what was reported by others<sup>[22,24,25]</sup>. This indicates that infection with multiple viruses in infants is a common situation that does not change the clinical course of bronchiolitis. However, some studies have

reported an increased risk for severe bronchiolitis in dual viral infection<sup>[26–28]</sup> or even in some specific viral infections such as RSV and hMPV co-infection<sup>[29–31]</sup>.

Although respiratory viruses seem to be related to increased risk of severe disease, our data suggest that prematurity has more specific weight in predicting bronchiolitis outcome. So, understanding host susceptibility and immune response of preterm infants to these viruses, as well as targeting the prevention of infection with these viruses in preterm infant may have even broader implications than only focusing on their role in disease morbidity.

### LIMITATIONS OF STUDY

Limiting this study is a possible underestimation of viral etiologies of acute bronchiolitis because testing for rhinoviruses, coronaviruses, and other viruses was not done, and these viruses were previously detected in such patients<sup>[32–35]</sup>. Moreover, the enrolled patients were from a single tertiary institution, which is a referral center for many local hospitals, so enrolled cases may be more ill than those at other hospitals. The enrolled patients were inpatients only, whereas patients with mild respiratory symptoms did not undergo diagnostic testing for viral infections; they were treated in outpatient clinics and this could further direct results toward a more severe population and could influence the scores.

### CONCLUSION

Prematurity is one of the risk factors that significantly affect the bronchiolitis severity, and this underscores the importance of early categorization of these infants as a high-risk group on their first visit. Physicians treating preterm infants with bronchiolitis should be aware that their illness runs a more severe course than term infant, even if they have no underlying disorders.

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### CONFLICT OF INTEREST

There are no conflicts of interest.

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