and recurrent post-bronchiolitis wheezing, defined as at least two episodes, was reported in 138 (52.7%) cases *versus* four (10.3%) in controls. Although the difference was highly significant statistically, the estimate in controls must be rough, since only 39 controls (infants hospitalised for an acute disease unrelated to the respiratory system) were enrolled. The results in controlled studies are highly dependent on how the controls have been selected and collected; for example, from the general population or from hospital patients, and with infants at risk included or excluded.

When children with and without recurrent post-bronchiolitis wheezing were compared using logistic regression as the multivariate model, rhinovirus infection (OR 3.3), family history of asthma (OR 2.6) and absence of infiltration in chest radiograph (OR 2.5) were independently significant risk factors for recurrent wheezing. Blood eosinophil count $>0.4 \times 10^9$ cells per L was not significant, though eosinophils were significant as both continuous and categorised variables in univariate analyses. Since the absence of radiological infiltration was a risk factor, the severity of infection may have less impact, and the host factors and the properties of causative viruses may have more impact on outcome.

The age distributions of different viruses were not presented [1]. In the earlier paper from the same authors covering the first three study years, the mean $\pm$ SD age was 2.0 ± 1.8 months in the 60 sole respiratory syncytial virus (RSV), 3.1 ± 2.4 months in the 16 sole rhinovirus and 3.5 ± 3.1 months in the 15 RSV- and bocavirus-positive cases [3]. In the Finnish studies, RSV has been the major cause of bronchiolitis at age <6 months, and both RSV and rhinoviruses have caused bronchiolitis at age 6–12 months [4]. Thereafter, rhinoviruses have been the predominant wheezing-inducing viruses. Compared with these previous observations, the mean age of the sole rhinovirus cases was rather low [3], highlighting the role rhinoviruses also have in young infants aged <6 months, or even in those aged <3 months. In our recent study on bronchiolitis at <6 months of age, RSV caused 70.5% and rhinovirus 12.7% of the 168 cases [2]. The proportion of bocavirus was $<5\%$, and all cases were mixed infections with other viruses. Post-bronchiolitis wheezing was present in 34.6% and repeated post-bronchiolitis wheezing (at least two episodes) in 18.1% of those 127 children, who were prospectively followed up using diaries filled in by parents and/or doctors on duty until the age of 1.5 yrs [5]. These figures in <6 -month-old bronchiolitis patients are lower than the 52.7% proportion of recurrent wheezing in the Italian children admitted at <12 months of age [1]. Thus, the risk of post-bronchiolitis wheezing is associated with age and causative virus on admission, which interact with each other.

There is some preliminary evidence on differences in clinical severity (lower oxygen saturations in RSV-positive cases), air trapping or patchy infiltrates in chest radiographs (RSV-positive cases) and association with atopy and eosinophilia (rhinovirus-positive cases) in relation to viral aetiology [1, 4]. In line with this, RSV-associated and rhinovirus-associated bronchiolitis/wheezing could not be separated by clinical characteristics, but patients with RSV infection had lower oxygen saturations and patients with rhinovirus infection more often had atopy and eosinophilia in our previous study [4].

The upper age limit of bronchiolitis cannot be 24 months and that limit should be 12 months [1], or even lower [2, 5]. The children who wheeze at 1–2 yrs of age form a heterogeneous group of patients with different wheezing phenotypes [4]. The research on the presence and impact of genotypes is so far at an early stage. The results of the study of MIDULLA *et al.* [1], in line with the results of the previous and recent Finnish studies, call for clinical studies including only patients aged less than 12 months on admission. Genetic properties, clinical characteristics, viral identifications and subsequent outcomes should be incorporated in the same model, and the analyses should be carried out and adjusted for age and sex.

Currently available evidence suggest that RSV and rhinovirus at least should be studied in children hospitalised for bronchiolitis or wheezing at <12 months of age. The identification of viruses in wheezing infants, evaluated in relation to the age of the patient, may be more important than, for example, “allergy studies”, which seem to be “*à la mode*” in paediatric clinical practice.

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REFERENCES

- 1 Midulla F, Pierangeli A, Cangiano G, *et al.* Rhinovirus bronchiolitis and recurrent wheezing: 1-year follow-up. *Eur Respir J* 2012; 39: 396–402.
- 2 Koponen P, Helminen M, Paasilta M, *et al.* Preschool asthma after bronchiolitis in infancy. *Eur Respir J* 2012; 39: 76–80.
- 3 Midulla F, Scagnolari C, Bonci E, *et al.* Respiratory syncytial virus, human bocavirus and rhinovirus bronchiolitis in infants. *Arch Dis Child* 2010; 95: 35–41.
- 4 Korppi M, Kotaniemi-Syrjänen A, Waris M, *et al.* Rhinovirus-associated wheezing in infancy: comparison with respiratory syncytial virus bronchiolitis. *Pediatr Infect Dis J* 2004; 23: 995–999.
- 5 Nuolivirta K, Koponen P, Helminen M, *et al.* Weight gain in infancy and post-bronchiolitis wheezing. *Acta Paediatr* 2012; 101: 38–42.

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From the authors:

We thank M. Korppi and co-workers for their correspondence regarding our article [1]. In our prospective study, we identified rhinovirus (RV) infection and a positive family history for asthma as substantial risk factors for recurrent wheezing during 1-yr follow-up after the initial episode of bronchiolitis. The distinctive point of our study was that all the infants enrolled had clinically well-characterised bronchiolitis, defined as the first episode of acute lower airway infection that appears with a history of upper respiratory tract infection followed by acute

onset respiratory distress with cough, tachypnoea, retraction and diffuse crackles on auscultation in infants <12 months of age [2]. Another strength of our study is that we also assayed nasal washes simultaneously for 14 different respiratory viruses, rather than just including infants with respiratory syncytial virus bronchiolitis.

We agree with M. Korppi and co-workers that some controversies remain in defining bronchiolitis. The North American definition of bronchiolitis includes the first episode of acute viral wheeze occurring in infants <2 yrs of age [3], thus probably overlapping early asthma manifestations. Defining bronchiolitis according to strict clinical criteria that exclude wheeze ensured the availability of homogeneous studies suitable for investigating epidemiological, clinical and prognostic factors in infants with bronchiolitis. As JARTTI *et al.* [4] underlined, if poorly defined, the diagnosis of bronchiolitis is likely to include various disease entities differing in immunopathogenesis according to viral aetiology, wheezing phenotype and preceding inflammatory state (atopy or no atopy). Another future research direction could be whether the aetiology differs in infants <12 months of age with lower respiratory infections with and without wheeze.

As M. Korppi and co-workers mention, the virus detection rate in our study was rather low (55.6%). Although possible reasons include difficulties in nasal washing or sample storage, we cannot exclude a pathogenetic role in bronchiolitis of viruses other than the 14 investigated. M. Korppi and co-workers noted that only 39 infants were prospectively enrolled as controls. These were consecutive unselected infants with an acute disease unrelated to the respiratory system, hospitalised in our paediatric department. We agree that the small number of patients could be a limitation, but our study was not designed as a community-based control study. All 39 control families and 83.7% of the 313 families of infants with bronchiolitis contacted replied. The only reason for dropout was a change in telephone number.

Our previous study provides reliable data that infants with RV bronchiolitis seem to be those predisposed to asthma, as suggested by the high blood eosinophil counts and heredity for asthma [2]. The question of whether RV is directly involved in the development of asthma or preferentially infects infants prone to wheeze remains unanswered. RV bronchiolitis might serve to disclose infants who are already predisposed to asthma owing to

abnormal lung physiology or cytokine dysregulation, or both. Indeed, RV seems preferentially to affect the lower airways, causing bronchiolitis in atopic children prone to wheezing [5].

The lower blood C-reactive protein concentration and fewer radiologically documented lung consolidations in infants with recurrent wheezing than in nonwheezing infants also suggests that the two groups of infants differ not only in having risk factors for atopy and asthma, but also in their pathogenetic response to the different viruses.

In conclusion, we think the time is right to reach an agreement on how to define bronchiolitis. Only by speaking the same language can we understand the pathophysiology and find the optimal therapy for this disease.

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REFERENCES

- 1 Midulla F, Pierangeli A, Cangiano G, *et al.* Rhinovirus bronchiolitis and recurrent wheezing: 1-year follow-up. *Eur Respir J* 2012; 39: 396–402.
- 2 Midulla F, Scagnolari C, Bonci E, *et al.* Respiratory syncytial virus, human bocavirus and rhinovirus bronchiolitis in infants. *Arch Dis Child* 2010; 95: 35–41.
- 3 Wainwright C. Acute viral bronchiolitis in children – a very common condition with few therapeutic options. *Paediatr Respir Rev* 2010; 11: 39–45.
- 4 Jartti T, Lehtinen P, Vuorinen T, *et al.* Bronchiolitis: age and previous wheezing episodes are linked to viral etiology and atopic characteristics. *Pediatr Infect Dis J* 2009; 28: 311–317.
- 5 Gern JE. The ABCs of rhinoviruses, wheezing, and asthma. *J Virol* 2010; 84: 7418–7426.

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Increased lung neutrophil apoptosis and inflammation resolution

To the Editors:

MORET *et al.* [1] have studied bronchoalveolar lavage fluid (BAL) and blood neutrophils in patients with nonresponding community-acquired pneumonia (CAP). Their stated aim is to highlight the importance of neutrophil apoptosis as a central factor in resolution of CAP. This is in accord with the current belief that apoptosis, when followed by engulfment of apoptotic neutrophils, constitutes the resolving mechanism in conditions of

neutrophilic inflammation. Importantly, the authors focus on features of these cells *in vivo*. We also read with interest the authors' discussion, in which they exclusively treat their data within the frame of the apoptosis–phagocytosis dictate. Unfortunately, occurrence of engulfed neutrophils was not studied. Apoptotic neutrophils that are not engulfed undergo secondary necrosis. This potentially is a major pathogenic event [2]. Hence, apoptosis alone is not a safe cell clearance mechanism that resolves inflammation.