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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Statement of Interest: None declared.

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DOI: 10.1183/09031936.00218811

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.

Even more importantly, what is the fate of disease-driving neutrophils dwelling in the pulmonary tissues? This latter aspect is often overlooked [3], and MORET *et al.* [1] are no exception. We appreciate that proper tissue samples cannot be obtained in order to follow the fate of infiltrated neutrophils during the resolution phase of CAP. However, the fate of inflammatory cells in the tissue remains an important issue. In this regard, the reader may need to be reminded of the fact that apoptotic (dead) cells cannot migrate. Hence, the examination of neutrophil apoptosis in accessible samples from airway lumen (BAL) cannot tell anything about apoptosis of these cells in the diseased pulmonary tissue [3]. Interestingly, MORET *et al.* [1] show lack of correlation between BAL and blood neutrophil apoptosis. They thus make a point of location-specific neutrophil apoptosis yet fail to mention anything about the pulmonary tissue neutrophils. Or, is it their view that neutrophils located in the air space rather than in pulmonary tissues are pathogenic?

Perhaps the most important issue concerns alternative paths of elimination of the pulmonary neutrophils. Discussion of other modes of leukocyte elimination is warranted since the *in vivo* evidence for a role of neutrophil apoptosis in inflammation resolution is not overly strong. Inconsistent rates of BAL neutrophil apoptosis in CAP stand out. DROEMANN *et al.* [4] found that only 0.3% of BAL neutrophils are apoptotic in CAP soon after admission, whereas MORET *et al.* [1] give a 40 times greater figure, of about 12% apoptotic neutrophils. MATUTE-BELLO and MARTIN [5], who originally demonstrated reduced neutrophil apoptosis in patients with adult respiratory disease syndrome (ARDS), have since suggested that neutrophil apoptosis may have nothing to do with outcome of ARDS. Furthermore, data obtained *in vivo* by several groups, including our own, also fail to support a resolving role of apoptosis in different inflammatory respiratory diseases [3]. With regard to an alternative route, we have discussed observations favouring the possibility that pulmonary tissue leukocytes in human diseases are eliminated by swift and non-injurious transepithelial migration followed by lumen clearance. Our notion is based largely on *in vivo* findings in human diseased airways. We have put particular weight on such studies that address cell kinetics in airway lumen and tissue when patients recover from respiratory tract inflammation. Previously puzzling data, for example demonstrating that neutrophils increase markedly in the bronchial lumen along with clinical improvement, have thus received an explanation [3]. There is no information in the study by MORET *et al.* [1] that can shed light on any contribution by transepithelial elimination of neutrophils during resolution of CAP. However, further studies in this disease, as well as in other inflammatory mucosal diseases, seem warranted to explore the possibility that non-injurious migration of disease-driving tissue leukocytes across the epithelial lining is a significant resolving mechanism. While future clinical *in vivo* data are still awaited in this field, we need to interpret the number of cells, and their features, in the accessible lumen samples with caution. This is particularly important during resolution of inflammation, when cells appearing in the lumen may simply reflect the elimination of a corresponding number of cells from the diseased mucosal tissue [3]. The hegemonic apoptosis-phagocytosis paradigm of inflammation resolution is largely based on findings *in vitro*. Currently available human *in vivo* data may not provide compelling support for its

suggested role in resolution of inflammatory diseases involving mucosal lined tissues [3].

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Statement of Interest: None declared.

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DOI: 10.1183/09031936.00189511

From the authors:

We would like to thank C.G.A. Persson and L. Uller for their interesting observations and suggestions concerning our recently published article [1]. Also, we would like to comment the issues they have raised.

As they point out, we performed our study in patients (and controls), using blood and bronchoalveolar lavage (BAL) neutrophils for *in vivo/ex vivo* experiments. We did not include tissue samples due to the difficulty of obtaining them, just as C.G.A. Persson and L. Uller acknowledge. We analysed neutrophils from BAL fluid from non-responding community-acquired pneumonia (NCAP) patients to whom bronchoscopy was indicated and had signed informed consent. Bronchoscopy has the advantage of being a technique that is able to sample around 106 alveoli and, in addition, it is indicated for patients with NCAP [2]. All this could give relevant information about NCAP and, in fact, it did, as reflected in results that shed light on the relationship of some cytokine levels (interleukin (IL)-6, -8 and -10) and apoptosis rates in NCAP patients with clinical outcome.

We agree that more studies are needed to address several issues that emerge from our findings. Specifically, the engulfment of apoptotic neutrophils in NCAP patients is one of them. As they indicate, the lack of engulfment of apoptotic neutrophils can imply secondary necrosis which, in turn, can also be an important pathogenic event to analyse. We also agree that apoptosis alone is not sufficient to resolve inflammation; therefore, in our study