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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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

we also investigated inflammatory local and systemic cytokine profiles and clinical resolution of infectious parameters. In fact, our results clearly show that neutrophil apoptosis is associated with lower proinflammatory cytokine levels and faster clinical stability. This is a finding that would probably not have been changed if we had obtained lung biopsies.

Another comment refers to transepithelial elimination of neutrophils during resolution of NCAP. The interesting proposed hypothesis of inflammatory resolution through egression of leukocytes is very attractive [3]. C.G.A. Persson and L. Uller argue that elimination of leukocytes from the airways with bronchial inflammation (transepithelial egression) is a mode of resolving inflammation. This challenging interpretation is nicely presented in human and animal models in asthma and chronic obstructive pulmonary disease. However in pneumonia, the acute inflammatory response of host against microorganisms is a completely different model of airway inflammation. In pneumonia, innate responses and alveolar macrophages orchestrate the inflammatory response in lung parenchyma, and neutrophils exit the pulmonary circulation at the capillary level, that is, mainly in alveolar air spaces. Obviously, our design was not directed to evaluate the neutrophil migration across the alveolar or epithelial lining, although this topic merits attention.

Referring to the comments that evidence of neutrophil apoptosis in inflammation resolution is not very strong, it is worth mentioning that our results and those from other researchers seem to indicate the contrary [4–6]. We have found a significant correlation between neutrophil apoptosis and pneumonia outcome. Our results agree with the comment made by MATUTE-BELLO and MARTIN [7], indicating that studies in humans suggest that neutrophil apoptosis is inhibited early in acute respiratory distress syndrome but returns to normal as inflammation resolves. These authors also indicate other steps that must be explored to understand all the process, but they were not the objective of our present work. DROEMANN *et al.* [8] have results in concordance with ours, and the differences in the rate of neutrophil apoptosis are probably due to the initial phase of pneumonia (24 h).

So, we consider that the study of cytokine patterns and neutrophil apoptosis in BAL fluid from NACP is currently an excellent available option to evaluate the ongoing inflammatory process *ex vivo*. With regard to the role of the transepithelial exit of leukocytes from the airway proposed by C.G.A. Persson and L. Uller for asthma and chronic obstructive pulmonary disease, it should not be directly translated to pneumonia, an acute infection with a completely different *restitutio in integrum*. Finally, we totally agree that regarding the host response against microorganisms and resolution of inflammation, there are still many missing important pieces and new approaches are welcome.

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Chest radiotherapy to achieve lung volume reduction

To the Editors:

We read with great interest the letter from O'MEARA *et al.* [1] regarding the mechanism of dyspnoea relief following radiation treatment in a patient with severe chronic obstructive pulmonary disease and presumed bronchogenic malignancy. Our group has long been interested in the potential for lung radiotherapy to noninvasively result in lung volume reduction, after we have observed dyspnoea relief in similar patients. The clinical and physiological benefit of lung volume reduction in select patients with obstructive lung disease has been demonstrated. The benefits of lung volume reduction surgery, however, are offset by the surgical morbidity. Varied non-surgical and bronchoscopic procedures are under evaluation, including endobronchial valves, biological agents, thermal airway ablation and airway bypass. Unfortunately, the goal of collapsing overinflated emphysematous lung with non-surgical techniques has had mixed results to date [2–4].

We propose (again) that lung radiotherapy has similar potential physiological benefit in patients similar to those presented by O'MEARA *et al*. [1], and this is an area which is ripe for clinical