without a huge expansion of critical care beds that could not be justified without evidence of benefit to patients. It should be noted that most of the studies reported by Dr Challen failed to exclude patients with do not attempt resuscitation orders or with directives not to be admitted to the ICU. Therefore, these percentages and the pooled performance characteristics do not necessarily reflect their 'real life' clinical utility.

Expanding on Dr Challen's statement that application of these tools 'should be with caution', we would suggest that severity scores should only be used to predict outcomes for which they have been validated and, as suggested by McGinn,[4] scoring systems should have their impact assessed in clinical studies before being applied to guide clinical decisions.

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Competing interests None.

Provenance and peer review Not commissioned; not externally peer reviewed.

Accepted 24 November 2010
Published Online First 21 December 2010

Thorax 2011;**66**:1094–1095.
doi:10.1136/thx.2010.156554

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Exit of leucocytes across the alveolar epithelium worsens lung injury

Persson and Uller are to be commended for their review highlighting the important role of leucocyte egression in the resolution of airway inflammation.[1] They go on to speculate that egression across the alveolar epithelium may be detrimental, because, unlike for the airways, there is no mucociliary escalator, and luminal cells that are not removed will interfere with gas exchange. They allay this concern citing work from Cory *et al*[2] using a mousemodel of asthma. In this model a deficiency of matrix metalloproteinase (MMP)-2 and/or MMP-9 inhibits leukocyte egression across the airway epithelium and leukocytes accumulate in the interstitium around the bronchial wall. The MMP-2/MMP-9 knock-out (KO) mice died from asphyxia (presumably from bronchoconstriction). The wild type (WT) mice survive with less peribronchovascular inflammation, but more mild diffuse alveolar inflammation than the KOs.[2]

Persson and Uller present this as evidence that egression into the alveolar airspace, as for the airway lumen, may also be beneficial. But it would be dangerous to extrapolate this to other inflammatory diseases for two reasons. First, the leucocytes may have reached the alveolar space not by crossing the alveolar epithelium, but from overspill of the exuberant egression into the airway lumen. Second, in the asthma model described death is by bronchoconstriction and modest alveolar inflammation may be tolerated. In addition, the hazards of egression have been convincingly demonstrated in a murine model in which bleomycin inhalation is used to induce alveolar (rather than airway) inflammation.[3]

Li and colleagues found that MMP-7 deficiency was protective against death following bleomycin lung injury. They went on to show, very elegantly, that MMP-7 is required to establish the chemoattractant gradient that drives leucocyte egression across the alveolar wall.[3] The protective effect of the MMP-KO was reversed when n-formyl-nle-leu-phe (nFNLP) was instilled with bleomycin, and egression of leucocytes into the alveolar airspace was re-established.[3]

There is still much to be learnt about egression, and in particular the complex regulation and interplay of extravasation and egression in inflammation and resolution of disease. Our own research examines the molecular differences involved in egression across distinct epithelial barriers (alveolar vs bronchial), with a view to enhance the transepithelial exit of leucocytes across the bronchial epithelium (beneficial) while limiting their exit across the alveolar epithelium (detrimental).[4] The ability to differentially alter the exit of leucocytes across distinct epithelial barriers may be essential when designing drugs and biological compounds to enhance the resolution of inflammation.

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Competing interests None.

Provenance and peer review Not commissioned; not externally peer reviewed.

Accepted 17 December 2010
Published Online First 20 April 2011

Thorax 2011;**66**:1095.
doi:10.1136/thx.2010.157065

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Authors' response

We obviously agree with Porter[1] on the need to make a distinction between egression of infiltrated leucocytes across mucosal epithelia, where a swift further elimination of the lumen cells can be expected to occur (nasal, tracheobronchial, gut, bladder), and the bronchiolar–alveolar epithelial linings where there is a risk of undesirable accumulation of lumen cells. We repeat this cautionary note in an extended review on resolution of cell-mediated respiratory diseases where we discuss a role of egression in the elimination not only of granulocytes and lymphocytes but also of mast cells and dendritic cells.[2] We further discuss how elimination of leucocytes through egression can be compatible with the use of sputum cell counts to adjust treatment in asthma.[1] The concept developed in our two reviews is underpinned foremost by clinical observations and experimental findings in patients. We were indeed surprised to find that numerous, human, so far little understood, in vivo data supported the resolving role of transepithelial egression whereas little support for the role of leucocyte apoptosis, the accepted paradigm, emerged. However, Porter's comments mainly concern mouse model findings. Of interest are supporting findings in murine (mouse and rat) models of 'asthma' indicating that inhibition of egression can have serious respiratory consequences. We are aware of severe limitations of mouse models[3] but felt that these data should be discussed. We also speculated that cell traffic in mouse airways, better than cell activation, could be relevant. However, the distinction between bronchial and

alveolar cell traffic, that Porter highlights, may not be readily made in mice. In sharp contrast to humans, mice lack a bronchial circulation. The dominance of the pulmonary circulation is reflected in the work carried out by Corry *et al*. These authors repeatedly emphasise that their studies concern parenchymal leucocytes. When egression is inhibited, leucocytes accumulate in pulmonary parenchymal tissues 'causing' severely impeded gas exchange.[4] Oxygen is an effective remedy in these lethally affected mice.[3] Corry *et al*[3] particularly underscore that 'differences in smooth muscle or other contractile cell function cannot explain the increased mortality observed.' Hence, Porter's statement that death in this model is by 'bronchoconstriction' is puzzling. Then Porter discusses data suggesting that mouse lung injury evoked by intratracheal bleomycin is caused by transepithelial neutrophil egression. We are not equally convinced. For example, n-formyl-neoleucyl-leucyl-phenylalanine (nFNLP) may not be used as a specific inducer of neutrophil egression, as quoted by Porter. nFNLP-like peptides are multipotent agents and avidly induce neutrophil toxicity as well.

Nearly 130 years have passed since Julius Cohnheim held classic lectures on inflammation.[5] He discussed the resolution of inflammatory infiltrates in mucosally lined organs, specifically noting the advantageous outward transport available to bronchi and lung alveoli. Cohnheim's contemporary and perpetual authority, Henry Hyde Salter, observed cell-rich sputum production at resolution of severe asthma. Salter intriguingly analysed how the most peripheral airways could be cleared of cellular exudates since coughing would have little impact here.[6] It seems overdue to fill in the large gaps in our knowledge concerning clearance of cells from the human bronchiolar–alveolar lumen.

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Funding From Swedish Medical Research Council.

Competing interests None.

Provenance and peer review Not commissioned; not externally peer reviewed.

Accepted 5 January 2011
Published Online First 20 April 2011

Thorax 2011;**66**:1095–1096.
doi:10.1136/thx.2010.158220

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Can cells other than Th17 lymphocytes be important sources of IL-17 in the lungs?

We read with interest the recent paper by Facco *et al* which showed that Th17 cells are present in blood, bronchoalveolar lavage (BAL) and lung tissue from people with sarcoidosis. The authors conclude that Th17 cells are involved in the pathogenesis of sarcoidosis as a multisystem disorder.[1]

Interestingly, the paper mentions expression of interleukin (IL)-17 protein by macrophages. Currently, a strong emphasis exists in the literature on the role of Th17 lymphocytes in the production of IL-17 in the lungs. However, Th17 cells are not the only source of IL-17 identified.[2] IL-17 is also known to be produced by γδ and natural killer T cells.[3 4] It has also been suggested that in human alcoholic liver disease, atherosclerosis and rodent models of lipopolysaccharide-induced airway inflammation IL-17 can be localised to neutrophils.[5–7] Furthermore, we have recently demonstrated that IL-17 protein expression is raised in the lower airway of people with advanced cystic fibrosis lung disease.[8] This IL-17 protein expression was immunolocalised to both neutrophils and mononuclear cells.[8]

It is known that granulocytes may be part of the inflammatory process in sarcoidosis.[9 10] The BAL method used by Facco *et al* was referenced, via the online supplement, to an original paper that used a 200 ml lavage. A differential cell count seems to have been produced from a cytospin, but in the table listing differential BAL data the percentage of neutrophils was not stated.

It would therefore be of interest if the authors could clarify the methodology used for the BAL and differential cell counts, whether any neutrophils were detected in BAL from people with sarcoidosis, and if so, did neutrophils demonstrate IL-17 immunolocalisation? Such data may support a paradigm indicating that IL-17 expression may involve cells in addition to Th17 lymphocytes in sarcoidosis. This may also be relevant to other lung pathologies where IL-17 is implicated.

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Funding Medical Research Council, Cystic Fibrosis Trust.

Competing interests None.

Provenance and peer review Not commissioned; not externally peer reviewed.

Accepted 4 January 2011
Published Online First 15 March 2011

Thorax 2011;**66**:1096.
doi:10.1136/thx.2010.157941

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Authors' response

We thank Dr Brodlie and coworkers for their letter[1] and fully agree on the necessity to evaluate whether cells other than lymphocytes and macrophages are involved in IL-17 release in sarcoid lungs. The main manifestation of sarcoidosis is an accumulation of mononuclear inflammatory cells, mostly $CD4^+$ T cells and monocytes/macrophages in involved organs, including the lungs.[2] As specified in our 'Materials and methods' section, we evaluated cells obtained by filtering bronchoalveolar lavage (BAL) fluid through gauze. A standard morphological and immunological analysis of BAL cellular components was performed. The analysis included cell recovery and differential count of macrophages, lymphocytes, neutrophils