

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

REFERENCES

1. **Challen K.** Severity scales in community-acquired pneumonia: what matters apart from death? *Thorax* 2011;**66**:1092–4.
2. **Chalmers JD, Singanayagam A, Akram AR, et al.** Severity assessment tools for predicting mortality in hospitalised patients with community-acquired pneumonia: systematic review and meta-analysis. *Thorax* 2010;**65**:878–83.
3. **Chalmers JD.** ICU admission and severity assessment in community-acquired pneumonia. *Crit Care* 2009;**13**:156.
4. **McGinn TG, Guyatt GH, Wyer PC.** Users' guides to the medical literature:XXII: how to use articles about clinical decision rules. Evidence based medicine working group. *JAMA* 2000;**284**:79–84.
5. **Chalmers JD, Akram AR, Hill AT.** Increasing outpatient treatment of mild community-acquired pneumonia: systematic review and meta-analysis. *Eur Respir J* 2011;**37**:858–64.
6. **Chalmers JD, Singanayagam A, Akram AR, et al.** Safety and efficacy of CURB65-guided antibiotic therapy in community-acquired pneumonia. *J Antimicrob Chemother* 2011;**66**:416–23.
7. **Charles PG, Davis JS, Grayson ML.** Rocket science and the Infectious Diseases Society of American/ American Thoracic Society (IDSA/ATS) guidelines for severe community-acquired pneumonia. *Clin Infect Dis* 2009;**48**:1796; author reply 1796–7.
8. **Phua J, See KC, Chan YH, et al.** Validation and clinical implications of the IDSA/ATS minor criteria for severe community-acquired pneumonia. *Thorax* 2009;**64**:598–603.

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 mouse model 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

REFERENCES

1. **Persson C, Uller L.** Transepithelial exit of leucocytes: inflicting, reflecting or resolving airway inflammation? *Thorax* 2010;**65**:1111–15.
2. **Corry DB, Kiss A, Song LZ, et al.** Overlapping and independent contributions of MMP2 and MMP9 to lung allergic inflammatory cell egression through decreased CC chemokines. *Faseb J* 2004;**18**:995–7.
3. **Li Q, Park PW, Wilson CL, et al.** Matrilysin shedding of syndecan-1 regulates chemokine mobilization and transepithelial efflux of neutrophils in acute lung injury. *Cell* 2002;**111**:635–46.
4. **Porter JC, Hall A.** Epithelial ICAM-1 and ICAM-2 regulate the egression of human T cells across the bronchial epithelium. *Faseb J* 2009;**23**:492–502.

Authors' response

We obviously agree with Porter¹ 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 models³ 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