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# RAGE: a biomarker for acute lung injury

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Acute lung injury (ALI), and its more severe counterpart the acute respiratory distress syndrome (ARDS), are syndromes of acute respiratory failure associated with pulmonary oedema caused by increased permeability of the alveolar-capillary membrane. Many clinical scenarios are recognised as being associated with a high incidence of ALI, including the archetypal direct pulmonary and blood borne insults of pneumonia and severe sepsis, respectively. The internationally accepted diagnostic criteria<sup>1</sup> are non-specific to the point of including patients with relatively mild hypoxia and patients with lung pathology that may be different from the classical diffuse alveolar damage.<sup>2</sup> ALI is not uncommon but it is challenging to study, partly because the patients are heterogenous in the causes and severity of their illness. Furthermore,

patients die *with* rather than *from* respiratory failure in the majority of cases.<sup>3</sup> These issues partly account for the fact that only one intervention has been shown to affect the survival of patients with ALI. The National Heart, Lung and Blood Institute (NHLBI) ARDS Network ARMA study,<sup>4</sup> arguably the most important trial in respiratory medicine in the last 20 years, demonstrated an approximately 10% survival advantage in favour of a ventilation strategy that limited tidal volume (6 ml/kg predicted body weight) and plateau pressure ( $\leq 30$  cm H<sub>2</sub>O) compared with “standard” ventilatory parameters (12 ml/kg and  $\leq 50$  cm H<sub>2</sub>O).

A biomarker is a clinical parameter that is measured with a view to providing information about a disease process, in this case ALI (box 1). Apart from informing the diagnostic process, biomarkers might be used to predict which patients at risk of ALI develop severe ARDS, which of these will develop pulmonary fibrosis requiring prolonged ventilatory support<sup>5</sup> and ultimately who dies. Soluble receptor of advanced glycation end-products (RAGE), the cleaved form of the receptor, measured in plasma has been proposed as a biomarker of type I alveolar cell injury. Plasma RAGE concentrations

were elevated in samples from patients with ALI compared with healthy controls and patients with hydrostatic oedema.<sup>6</sup> In this issue of *Thorax*, Calfee and colleagues<sup>7</sup> from the NHLBI ARDS Network report the results of measuring soluble RAGE levels in plasma samples from 676 patients enrolled in the ARMA study, both at entry to the study and after 3 days of standard or protective ventilation (*see page 1083*). At entry, higher RAGE levels were associated with higher radiographic and physiological indices of ALI severity as well as the non-pulmonary Acute Physiology and Chronic Health Evaluation (APACHE 3) score.<sup>7</sup> These data suggest that RAGE may be a marker of disease severity but the potential predictive value of a raised plasma RAGE level needs to be tested in patients at risk of developing ALI in a prospective longitudinal study. Furthermore, in the group randomised to the “standard” mechanical ventilation but not the protective ventilation group, higher baseline RAGE was associated with increased mortality and fewer ventilator-free and organ failure-free days. Because ventilation using 6 ml/kg predicted body weight has become a standard of care,<sup>8</sup> this observation casts a shadow over the potential usefulness of RAGE although, as the authors state, such subgroup analyses should be viewed with caution.

In both groups plasma RAGE levels decreased 3 days after enrolment, but had fallen by 15% more in the protective ventilation group. Does this mean that RAGE joins the list of potential biomarkers of ventilator associated lung injury?<sup>9</sup> The

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### Box 1 Properties of an ideal biomarker for acute lung injury and the acute respiratory distress syndrome

Modified from Bucher and colleagues.<sup>27</sup>

- ▶ Has biological plausibility in terms of its role in the pathogenesis of disease
- ▶ Associated with a clinically important outcome such as mortality
- ▶ Modified by an effective intervention to change the target outcome of interest
- ▶ Measurement is safely, easily and reproducibly carried out in the critically ill

answer is *possibly*. Why would such a biomarker be so valuable? It is accepted that a low tidal volume and low airway pressure mechanical ventilation strategy confers a survival advantage and it seems likely that there is no safe threshold for these parameters.<sup>10</sup> In contrast, the best efforts to characterise the effects of other ventilatory parameters, for example the optimum level of positive end-expiratory pressure,<sup>11–13</sup> on the survival of patients with ALI have yielded inconclusive and for the most part negative results. An ideal biomarker of ventilator associated lung injury could, therefore, be used as a surrogate outcome measure in clinical studies and could guide ventilation strategy in individual patients. To be clinically useful, a biomarker would need to change significantly within hours rather than days of a change in a ventilatory parameter. Secondly, the biomarker should be specifically affected by ventilator associated lung injury, rather than its downstream consequences that can be affected by other variables, such as systemic inflammation and dysfunction of other organs.<sup>14</sup> Circulating RAGE levels respond rapidly after lung injury: in an animal model of ALI induced by intratracheal hydrochloric acid, RAGE was elevated in bronchoalveolar lavage fluid and to a lesser extent serum only 2 h after injury.<sup>6</sup> Secondly, RAGE is highly expressed in the lung compared with other organs and particularly on alveolar type I epithelial<sup>15</sup> and endothelial cells<sup>16</sup> and so the release of RAGE in the lung may follow alveolar epithelial and endothelial injury. Alternatively, it may occur as part of a pulmonary inflammatory response. Whatever the initiating stimulus, the movement of soluble RAGE into the systemic circulation may be enhanced by increased permeability of the alveolar–capillary membrane. While all of these processes are thought to be mediated by ventilator associated lung injury, none is specific for this mechanism of injury.<sup>17</sup>

Soluble RAGE shows considerable promise as a biomarker in ALI but is it just an epiphenomenon or do RAGE and its ligands contribute to the pathogenesis of ALI? RAGE is a member of the immunoglobulin superfamily whose ligands include advanced glycation end-product modified proteins,  $\beta$ -amyloid, S100A12 (also known as calgranulin C and EN-RAGE) and high mobility group box-1 (HMGB-1 or amphoterin).<sup>18</sup> Ligand binding to the intact receptor activates signalling pathways, including nuclear factor  $\kappa$ B, leading to induction of inflammatory cytokines, proteases and oxidative stress.<sup>19, 20</sup> When RAGE induced effects were suppressed by a neutralising antibody, survival in a mouse model of sepsis was improved<sup>21</sup> and inflammation in models of diabetes and chronic joint inflammation was reduced. Similarly, both HMGB-1 and S100A12 have been implicated in the overwhelming inflammatory response that characterises ALI<sup>22</sup> but the contribution of RAGE activation to alveolar inflammation in ALI is not well understood. However, recent data suggest that in a murine model of lipopolysaccharide induced lung injury, exogenous soluble RAGE reduced the inflammatory response, perhaps acting as a decoy receptor.<sup>23</sup> Hence increased soluble RAGE in a tissue compartment may actually reflect an anti-inflammatory response rather than a consequence of parenchymal lung injury, which suggests that an elevated soluble RAGE level would predict a favourable outcome from ALI.

Finally, RAGE expression is depressed in the lungs of patients with established idiopathic pulmonary fibrosis and those of mice treated with bleomycin, which induces a fibrosing alveolitis.<sup>24, 25</sup> An anti-fibrotic role for RAGE has been inferred from experimental models of fibrosing alveolitis in knockout mice lacking membrane RAGE.<sup>25, 26</sup>

The ARDS Network investigators have again used their unrivalled source of study material to produce more thought provoking insights into a means of improving the management of patients with ALI. Measurement of soluble RAGE in plasma joins an increasing list of candidate biomarkers of important processes that constitute ALI. It remains to be seen whether a single marker or a panel of markers will emerge to become robust outcomes for studies or useful tools in the management of individual patients.

**Competing interests:** None.

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## Thorax update: October 2007–September 2008

Jadwiga A Wedzicha, Sebastian L Johnston

We have now completed our sixth year as *Thorax* editors and are delighted that the Journal has continued to be so successful. As usual, the annual round of impact factor announcements was eagerly awaited by the editorial team and we were all delighted with the news that our impact factor for 2007, published in June 2008, had risen to the highest ever for *Thorax* at 6.226. The impact factor for 2007 reflects the number of citations in 2007 divided by the number of original papers and reviews published in *Thorax* in 2005 and 2006. We have thus maintained our position as the second highest ranked respiratory journal in terms of impact factor, behind the *American Journal of Respiratory and Critical Care Medicine*. This increase in the *Thorax* impact factor is a result of the high quality papers and reviews that you have all submitted to the journal for publication.

Perhaps the most visible change has been (we hope!) the change of front cover and our successful introduction of images to illustrate each issue (figs 1–3). These images were selected by the COPD research team at UCL Medical School, according to some democratic process! As they have to be of high quality, they come from the Science Photo Library. In addition, the inside page format has changed, and this is consistent with the new house style of BMJ Journals.

The number of submissions over the past year has remained steady compared with previous years at 1434, with 872 full original papers submitted to the journal. The time to the first decision on an original paper that has been through a full peer review is now a median of 50 days, but this also includes statistical review for all potentially acceptable papers. *Thorax* has a policy of rejecting papers without review that will not do well in the peer review

process or are outside the scope of the journal. This means that authors can rapidly submit their work to another journal for consideration. However, the large number of submissions—particularly for original papers—means that our acceptance rate for original research papers now stands at around 14%, although for case reports and Images in *Thorax* the acceptance rate is lower. During the past year we have also received an increased number of letters for publication at 115, and this has consisted of both correspondence about previously published papers and also research letters, all of which undergo peer review as for original papers.

We are grateful to all our reviewers who have taken time to review *Thorax* papers. The rigorous standard of peer review has helped to achieve the high quality of papers published in the journal. However, we have a significant number of review requests that are declined and sadly this figure is creeping up, with 37% of review requests declined over the past year.

Since the start of our editorship, we have always tried to ensure that there is something in *Thorax* each month of interest to all readers and thus educational features are important. The “Images in *Thorax*” series<sup>1</sup> and the Lung Alerts,<sup>2</sup> both published monthly, have proved very popular and the Alerts are serviced by our younger readers. In view of the large number of case reports submitted to the journal, we have decided to start a new feature called “Pulmonary Puzzles”.<sup>3</sup> These “Puzzles” consist of two parts, one providing details of the case and the other the answer, published in a different place in the journal. Over the last year we have had 47 articles submitted as “Pulmonary Puzzles” and a total of 117 articles for the “Images in *Thorax*” section, emphasising the popularity of these educational features.

A highlight of the past year was the 25th anniversary of the British Thoracic Society (BTS) and, to celebrate this event, *Thorax* published seven articles by BTS members highlighting achievements in respiratory medicine and some of our aspirations for the future.<sup>4–10</sup> We also published a report on the BTS Winter meeting held in London in December 2007.<sup>11</sup> A number of important guidelines and consensus statements have also been published, including the British guideline on asthma management,<sup>12</sup> BTS statement on malignant mesothelioma,<sup>13</sup> BTS criteria for specialist referral, admission, discharge and follow-up,<sup>14</sup> guidelines on the management of cough in children,<sup>15</sup> interstitial lung disease guideline<sup>16</sup> and a consensus statement on pulmonary hypertension.<sup>17</sup> We have published some excellent reviews during the past year; we have completed the series on exacerbations of cystic fibrosis<sup>18–19</sup> and interstitial lung disease<sup>20–24</sup> and started an interesting series on obesity and the lung.<sup>25–26</sup>

During our editorship we have had a series of very productive annual meetings for the Associate Editors, the most recent of which was held in November 2007 in London. We were delighted to be joined by editors of both the *British Medical Journal* and the *Lancet* who gave us

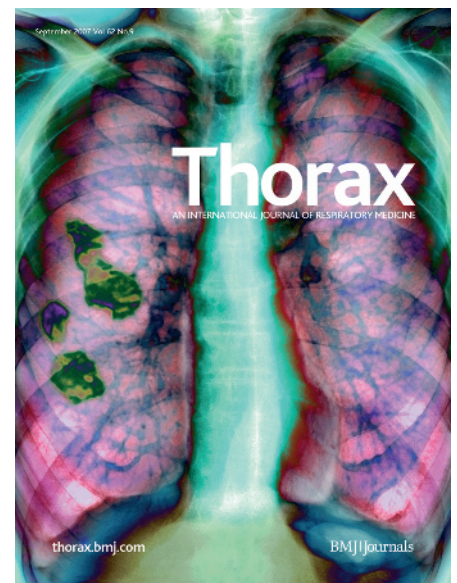


Figure 1 *Thorax* cover.

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