Improved understanding of ARDS mechanism of disease may offer an opportunity to advance patient care

Acute respiratory distress syndrome (ARDS) is a life-threatening lung condition seen in intensive care units (ICUs), where fluid from surrounding blood vessels leaks through the endothelial barrier into the lungs. It is a complicated, heterogeneous condition associated with many different causes (e.g. pneumonia, sepsis and major trauma) that make it difficult to diagnose.

With such challenges, it is no wonder that ARDS is one of the key focal areas at the ISICEM meeting this year.

An estimated >300,000 people develop ARDS in the USA and EU annually.[3] It is a major cause of death, with mortality rates 27–45%, and has long-term health and social implications for survivors, which can persist for at least five years.[4–6] The physical impact of ARDS can also result in significant impairments to quality of life,[4] with survivors reporting high rates of depression (17–43%), post-traumatic stress disorder (PTSD; 21–35%) and anxiety (23–48%).[7]

"While the primary focus in ICUs is to save the life of the patient, in treating ARDS, we cannot ignore that different interventions can lead to long-term complications for the patient," Geoff Bellingan (Medical Director for Surgery and Cancer, specializing in critical care at University College London Hospitals, London, UK), told ISICEM News ahead of his presentation today on the role of interferon-beta in ARDS.

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>
> *Geoff Bellingan*

"Some people will have persistent breathlessness that may recover with time. They may also experience polyneuropathy involving weight loss and weakening of the muscles. Furthermore, the psychological impact is another concern."

The complex and varying sequelae after critical illness, including cognitive, psychological and physical effects, have been described as post-intensive care syndrome, which affects many patients treated in the ICU, and increases with duration of stay.[8] Therapies reducing the ICU length of stay will also help reduce these additional problems for patients.

Significant economic burden for patients and hospitals

Therefore, it is not surprising that ARDS places a considerable economic burden on ICUs and hospitals. The average stay in the ICU is 25 days, and the average length of hospitalization is 47 days.[9] In terms of economic burden, approximate UK costs for treating ARDS patients during their initial hospitalization and during the first year after their illness are £40–45,000 per patient,[10] and the direct hospital costs from ARDS are estimated at approximately $82,000.*[11]

The impact on long-term quality of life also has economic implications, with depression and PTSD being significant factors affecting a patient's ability to return to work and maintain employment.

Commenting on the economic implications of treating ARDS effectively, Professor Bellingan explained that, "Since ARDS impacts people of all ages, in caring for ARDS you are saving the lives of both young and old. Saving young people means they can get back to work eventually. However, depression, anxiety and PTSD may be lessened by being in intensive care for a shorter period." These factors highlight the need for the development of an effective treatment for ARDS, a goal that has, so far, eluded researchers.

Failed trials of investigative compounds

Professor Bellingan referred to a multicenter, randomized, placebo-controlled trial of salbutamol for the treatment of ARDS, the so-called 'BALTI' study (The β-Agonist Lung Injury Trial).[12]

The BALTI study found that absorption of sodium via apical epithelial sodium channels (ENaC) is essential for fluid clearance in the lung; activation of ENaC is regulated by cyclic adenosine monophosphate (cAMP), and enhanced intracellular cAMP is stimulated by intravenous salbutamol that accelerates the resolution of alveolar edema. In their conclusions, the study authors wrote that, "The trial provides the first proof of principle that, in humans with ALI/ARDS, sustained treatment with intravenous β-agonists reduces extravascular lung water."

Yet, despite these results, the BALTI trial was stopped early due to harm. "β-2 agonists were tried – and improved the capillary leak – but had significant side effects in ARDS," said Professor Bellingan. "But new options exist and studies are ongoing. Targeting the capillary leak is still of interest.

"Compared with heart disease or cancer, ARDS occurrence is not that common, but in the specific field of critical care, it is common, and a key unmet medical need," Professor Bellingan pointed out.

"Given this situation, it's not easy to do a trial with 20,000 ARDS patients and show a 5% difference – you're looking for bigger percentage changes in a condition that is so variable," he added, outlining the difficulties in doing trial work in this field. "To add to the complications you have many variables as you're treating several different elements: capillary leak, fibrosis and inflammation."

Setting these difficulties aside, it is clear that we need novel approaches to managing ARDS. For Professor Bellingan, one area of interest could be the common issue of vascular leakage.

Understanding mechanisms driving ARDS

Researchers are beginning to make promising inroads into better understanding of the mechanisms that drive the occurrence of ARDS.[4,13] Regardless of the etiology, all patients with ARDS have the same underlying problem, a compromised endothelial barrier that allows protein-rich fluid from surrounding blood vessels to leak into the lungs. This fluid impairs the absorption of oxygen into the blood stream, starving vital organs and leading to hypoxia.

Professor Bellingan explained further: "If the patient has edema, cellular enzymes and pores in the lungs try to re-absorb the fluid. It's not just a capillary leak, there will be inflammation – in ARDS these pathophysiological processes swamp the ability of the lung epithelium to clear that fluid."

Research has elucidated some of the molecular mechanisms driving ARDS:

- Transport capacity of the alveolar epithelium is markedly diminished in ARDS and increasing severity is associated with higher mortality
- Excessive hydrostatic pressures and unfavorable ventilatory strategies exacerbate the problem
- ARDS is associated with cellular inflammatory and immune responses, with accumulation of neutrophils, macrophages and red blood cells in the alveoli[5,13]
- Studies have shown that the enzyme, CD73 contributes to the maintenance of the endothelial barrier, reduces inflammation and increases fluid clearance, through generation of adenosine[14,15]

"The usual understanding of ARDS is to treat inflammation, but we need to look at other key problems, of which lung leakage is key, and which is a new approach," remarked Professor Bellingan.

> *"ARDS is a heterogeneous condition with a variety of outcomes, and because of this it is not straightforward to provide a treatment. We need a drug that works on the inflammatory processes, capillary leakage processes and the thrombotic processes – all of which happen in ARDS."*
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No licensed therapy for ARDS treatment

"ARDS is a heterogeneous condition with a variety of outcomes, and because of this it is not straightforward to provide a treatment," said Professor Bellingan. "We need a drug that works on the inflammatory processes, capillary leakage processes and the thrombotic processes – all of which happen in ARDS. If we can develop this, then it should help us reduce the high mortality rate, which is where we have been stuck for the past five years or more."

Patients are currently managed with mechanical ventilation to maintain their breathing and oxygen levels and provide the lungs with support to allow the body itself to rectify the vascular leakage. However, mechanical ventilation has the potential to cause further damage to the lungs and, therefore, needs to be carefully managed, with research ongoing to optimize its use, and reduce the damaging effects. However, if the opportunity that our greater understanding of the role of the endothelial barrier can be used to develop an effective treatment for ARDS, without undue side effects, it could significantly improve patient management, and ultimately outcomes, for those affected by this devastating syndrome.

Professor Bellingan's talk is one of a number of ARDS presentations that are taking place during today's 'Managing ARDS' session, being held in the Gold Hall between 13:45–17:00.

Note

* Calculated from the original Canadian dollar amount to US dollars based on the 2002 average exchange rate of 1.57 CAD to 1 USD.

Table 1. The Berlin Definition of Acute Respiratory Distress Syndrome[1]

	Acute Respiratory Distress Syndrome
Timing	Within one week of a known clinical insult or new or worsening respiratory symptoms
Chest Imaging[a]	Bilateral opacities – not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild	200 mm Hg < PaO_2/FIO_2 ≤ 300 mm Hg with PEEP or CPAP ≥5 cm H_2Oc
Moderate	100 mm Hg < PaO_2/FIO_2 ≤ 200 mm Hg with PEEP ≥ 5 cm H_2O
Severe	PaO_2/FIO_2 ≤ 100 mm Hg with PEEP ≥ 5 cm H_2O

Abbreviations: CPAP, continuous positive airway pressure; FIO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.
a Chest radiograph or computed tomography scan.
b If altitude is higher than 1000 m, the correction factor should be calculated as follows: [PaO_2/FIO_2 x (barometric pressure/760)].
c This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

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Diagnosing ARDS

- ARDS is diagnosed based on the Berlin definition (Table 1): occurring within one week of known clinical insult, new or worsening respiratory symptoms; bilateral opacities not fully explained by effusions; lobar/lung collapse or nodules and respiratory failure not fully explained by cardiac failure or fluid overload (with objective assessment to exclude hydrostatic edema); and reduced oxygenation
- The severity of ARDS is then classified as follows: mild, 200 mmHg < PaO_2/FIO_2 ≤300 mmHg with positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) ≥5 cm H_2O; moderate, 100 mmHg < PaO_2/FIO_2 ≤200 mmHg with PEEP ≥5 cm H_2O; and severe, PaO_2/FIO_2 ≤100 mmHg with PEEP ≥5 cm H_2O.[1] Historically, the phrase, 'acute lung injury (ALI)' has been used but this refers most commonly to the mild severity of ARDS[2]

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