

ICS treatment are sicker (13). Similarly, those with a history of more exacerbations showed a larger reduction in mortality with 320 BGF. It is becoming clearer that the effect of either starting or stopping ICS on exacerbation risk is influenced by the blood eosinophil count (14, 15). In ETHOS, this appears to be true for mortality as well, with patients with a higher eosinophil count being at greater risk of dying when receiving GFF compared with 320 BGF. Further analysis of this potentially important observation is needed.

Several important lessons come from these positive studies of ICS and COPD mortality. First, large studies allow for more complex analyses than small ones, but to properly test their primary hypothesis, trials need to focus on patient groups at the greatest risk of experiencing the events under study. Treatment that reduces mortality will only be seen to work in patients who are at risk of dying. Second, neither the drug, the delivery system, nor the dosage regime is crucial to preventing death with ICS–LAMA–LABA treatment, but the dose of the corticosteroid chosen may be. Finally, mortality is not different from other endpoints in COPD studies, and a therapy that decreases exacerbations is likely to reduce mortality if sufficient numbers of the right kind of patient are studied. So, belatedly, the flame lit by TORCH is burning brightly again and does offer hope to all those who have COPD after all. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Peter Calverley, M.B. Ch.B., D.Sc.*
Institute of Ageing and Chronic Disease
University of Liverpool
Liverpool, United Kingdom

*P.C. is Associate Editor of *AJRCCM*. His participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.

References

- Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al.; TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;356:775–789.
- Calverley P, Vlies B. A rational approach to single, dual and triple therapy in COPD. *Respirology* 2016;21:581–589.
- Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. *Thorax* 2012;67:957–963.
- Celli BR, Anderson JA, Cowans NJ, Crim C, Hartley BF, Martinez FJ, et al. Pharmacotherapy and lung function decline in patients with chronic obstructive pulmonary disease: a systematic review. *Am J Respir Crit Care Med* [online ahead of print] 23 Sept 2020; DOI: 10.1164/rccm.202005-1854OC.
- Vestbo J, Anderson JA, Calverley PM, Celli B, Ferguson GT, Jenkins C, et al. Bias due to withdrawal in long-term randomised trials in COPD: evidence from the TORCH study. *Clin Respir J* 2011;5:44–49.
- Nici L, Mammen MJ, Charbek E, Alexander PE, Au DH, Boyd CM, et al. Pharmacologic management of chronic obstructive pulmonary disease: an official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med* 2020;201:e56–e69. [Published erratum appears in *Am J Respir Crit Care Med* 2020;202:910.]
- Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, et al.; IMPACT Investigators. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med* 2018;378:1671–1680.
- Rabe KF, Martinez FJ, Ferguson GT, Wang C, Singh D, Wedzicha JA, et al.; ETHOS Investigators. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. *N Engl J Med* 2020;383:35–48.
- Lipson DA, Crim C, Criner GJ, Day NC, Dransfield MT, Halpin DMG, et al. Reduction in all-cause mortality with fluticasone furoate/umeclidinium/vilanterol in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2020;201:1508–1516.
- Martinez FJ, Rabe KF, Ferguson GT, Wedzicha JA, Singh D, Wang C, et al.; ETHOS investigators. Reduced all-cause mortality in the ETHOS trial of budesonide/glycopyrrolate/formoterol for chronic obstructive pulmonary disease: a randomized, double-blind, multicenter, parallel-group study. *Am J Respir Crit Care Med* 2021; 203:553–564.
- Suissa S, Ariel A. Triple therapy trials in COPD: a precision medicine opportunity. *Eur Respir J* 2018;52:1801848.
- Calverley P. Angels dancing on the tip of a needle: interpreting clinical trials in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2020;202:1206–1207.
- Calverley PM, Tetzlaff K, Dusser D, Wise RA, Mueller A, Metzendorf N, et al. Determinants of exacerbation risk in patients with COPD in the TIOSPIR study. *Int J Chron Obstruct Pulmon Dis* 2017;12:3391–3405.
- Calverley PMA, Tetzlaff K, Vogelmeier C, Fabbri LM, Magnussen H, Wouters EFM, et al. Eosinophilia, frequent exacerbations, and steroid response in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2017;196:1219–1221.
- Singh D, Bafadhel M, Brightling CE, Sciruba FC, Curtis JL, Martinez FJ, et al. Blood eosinophil counts in clinical trials for chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2020;202:660–671.

Copyright © 2021 by the American Thoracic Society



Learning from the First Wave of the Pandemic in England, Wales, and Northern Ireland

The year 2020 has been one like no other for intensive care medicine owing to the coronavirus disease (COVID-19) pandemic. Many

Ⓞ This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). For commercial usage and reprints, please contact Diane Gern (dgern@thoracic.org).

Originally Published in Press as DOI: 10.1164/rccm.202101-0089ED on January 21, 2021

countries experienced unprecedented demand on critical care resources during the first half of the year, with some respite over the summer, only to see demand rise again toward the end of the year (1).

In this issue of the *Journal*, Doidge and colleagues (pp. 565–574) describe how the characteristics and outcomes of patients with COVID-19 admitted to ICUs in England, Wales, and Northern Ireland changed over the first wave of the pandemic (2). This large study from the well-established United Kingdom registry group

ICNARC (Intensive Care National Audit and Research) describes over 10,000 ICU admissions to 223 hospitals between February 1, 2020, and July 31, 2020. They examined patients in three time epochs corresponding to the prepeak, peak, and postpeak periods. Remarkably, almost half (43%) of all COVID-19 ICU admissions in the 6-month period occurred during the 2-week “peak” period in April, demonstrating the burden on United Kingdom ICUs at that time. They also investigated regional variation, recognizing that London suffered the greatest burden of COVID-19. They describe improved mortality outcomes and declining use of mechanical ventilation and renal replacement therapy despite similar overall baseline severity of illness over the whole time period. The in-hospital mortality of 39.2% (44.5% in those requiring mechanical ventilation) for the 6-month study period covers a progressive decline from 43.6% in the earliest phase to 33.6% in the latest phase, a trend that persists after risk adjustment. Similar trends in outcome have been reported from other countries (3–5). However, the changes in demographics and processes of care provide additional lessons for us as we deal with present and future phases of the pandemic.

Calls for “early institution” of invasive mechanical ventilation of patients with COVID-19 were common and supported by many national guidelines during early 2020—even if some have been updated or modified since (6, 7). This was, in part, due to the belief that this was best practice and because of concerns about the risks of self-induced lung injury or aerosol generation by noninvasive ventilatory techniques. The reduction in rates of invasive ventilation reported by Doidge and colleagues mirrors anecdotal experience of many clinicians as we “relearned” the place of therapies such as noninvasive ventilation and high-flow oxygen therapy, as we became comfortable in accepting hypoxia in otherwise well patients (8), and as we realized the value of strategies such as proning even in those who were not invasively ventilated (9).

The ICU is a complex environment reliant on well-trained experienced staff who can use invasive technologies to safely treat patients. The pandemic has brutally demonstrated that ICU resources can become rapidly overwhelmed. Lack of access to critical care services and high community prevalence of COVID-19, which in turn places excess demand on hospital services, have been associated with worse patient outcomes (4, 10, 11). Outcomes of patients with COVID-19 admitted to ICUs in countries or regions with greater ICU capacity or lower demand through more effective community control of COVID-19 have typically been better than those reported from the United Kingdom (12–14). Many of the trends reported by Doidge and colleagues are consistent with a system under extreme strain in which improved outcomes are achieved partly by changes in processes of care (rather than by “magic bullet” therapies) and partly by resources becoming eventually available to meet the needs of patients as demand subsides.

COVID-19 has been spread internationally by those with the means to travel, mainly through the world’s major transport hubs such as London, but it has often then disproportionately affected more disadvantaged and socially deprived local populations (15). The findings of Doidge and colleagues are consistent with this sobering theme.

As the authors recognize, we should be cautious about extrapolating the implications of the findings too far without

knowledge of overall (non-COVID-19) ICU admission numbers and without knowledge of the demographics of individuals infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in different regions of the United Kingdom. Although expanded bed occupancy was reported to remain below 60%, this may not reflect “real-world” ICU capacity, taking into account staff illness, equipment and consumable supplies, or how the expansion in ICU beds may have directly influenced the ability to deliver care to other critically ill patients. A number of countries, including the United Kingdom, reported an excess of deaths during this period beyond that explained by COVID-19 deaths alone (16). If nothing else, the abrupt and marked rise in ICU admissions during the peak and sustained “tail” of bed occupancy well into the months afterward demonstrates how rapidly normal systems may become disrupted, with potential for lasting impacts on care.

Variation in individual hospital outcomes was outside of the scope of the paper but has been reported by others (17). It is extremely unlikely that outcomes were uniform. In addition, it is possible that this paper underestimated the number of ICU admissions with COVID-19. Some critically ill patients treated in surge areas outside of established ICUs may not have been submitted, and testing for the SARS-CoV-2 virus in the United Kingdom was less comprehensive in the earlier months.

However, there are also other strengths of this paper, which go beyond the findings themselves. The ability to “stand up” and maintain comprehensive high-quality national data collection at a time when resources to care for patients were at their most strained is a testament to the robust processes of the ICNARC registry and to the dedication of data collectors, researchers, and clinicians at all sites. The authors should be commended for this.

At the time of writing this editorial, the United Kingdom is experiencing ICU admission numbers similar to those described by Doidge and colleagues (18) and has just reentered a “national lockdown” in an attempt to control spread of infection and reduce demand on the healthcare system. The findings of this comprehensive and well-analyzed paper make us think about how changes in processes of care and availability of resources impact outcomes and how societal and socioeconomic factors affect ICU demand. Ultimately, it highlights how vital it is to both have adequate resources to maintain the best patient outcomes during the pandemic and also be able to collect the data to measure these outcomes. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

David Pilcher, M.B. B.S., M.R.C.P., F.C.I.C.M., F.R.A.C.P.
Department of Intensive Care
The Alfred Hospital
Melbourne, Victoria, Australia
Department of Epidemiology and Preventive Medicine
Monash University
Melbourne, Victoria, Australia
 and

The Australian and New Zealand Intensive Care Society Centre for Outcome and Resources Evaluation
Camberwell, Victoria, Australia

Matthew Durie, M.B. B.S., M.D., F.A.N.Z.C.A., F.C.I.C.M.
 Department of Intensive Care
 The Alfred Hospital
 Melbourne, Victoria, Australia
 and

Department of Epidemiology and Preventive Medicine
 Monash University
 Melbourne, Victoria, Australia

ORCID IDs: 0000-0002-8939-7985 (D.P.); 0000-0002-4473-9005 (M.D.).

References

- World Health Organization. COVID-19 weekly epidemiological. 2021 [updated 2021 Jan 5]. Available from: <https://www.who.int/publications/m/item/weekly-epidemiological-update--5-january-2021>.
- Doidge JC, Gould DW, Ferrando-Vivas P, Mouncey PR, Thomas K, Shankar-Hari M, et al. Trends in intensive care for patients with COVID-19 in England, Wales, and Northern Ireland. *Am J Respir Crit Care Med* 2021;203:565–574.
- COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. *Intensive Care Med* 2021;47:60–73.
- Asch DA, Sheils NE, Islam MN, Chen Y, Werner RM, Buresh J, et al. Variation in US hospital mortality rates for patients admitted with COVID-19 during the first 6 months of the pandemic. *JAMA Intern Med* [online ahead of print] 22 Dec 2020; DOI: 10.1001/jamainternmed.2020.8193.
- Armstrong RA, Kane AD, Cook TM. Decreasing mortality rates in ICU during the COVID-19 pandemic. *Anaesthesia* [online ahead of print] 10 Aug 2020; DOI: 10.1111/anae.15230.
- NHS. Guidance for the role and use of non-invasive respiratory support in adult patients with coronavirus (confirmed or suspected) [updated 2020 Mar 26; accessed 2020 Mar 29]. Available from: https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/03/CLEARED_Specialty-guide_-_NIV-respiratory-support-and-coronavirus-v2-26-March-003.pdf. Version no longer accessible. Updated version available at <https://www.nice.org.uk/media/default/about/covid-19/specialty-guides/specialty-guide-niv-respiratory-support-and-coronavirus.pdf>.
- Australian and New Zealand Intensive Care Society. COVID-19 guidelines: version 1 [accessed 2020 Mar 16]. Available from: <https://www.anzics.com.au/wp-content/uploads/2020/03/ANZICS-COVID-19-Guidelines-Version-1.pdf>.
- Tobin MJ, Laghi F, Jubran A. Caution about early intubation and mechanical ventilation in COVID-19. *Ann Intensive Care* 2020;10:78.
- Koeckerling D, Barker J, Mudalige NL, Oyefeso O, Pan D, Pareek M, et al. Awake prone positioning in COVID-19. *Thorax* 2020;75:833–834.
- Rimmelé T, Pascal L, Polazzi S, Duclos A. Organizational aspects of care associated with mortality in critically ill COVID-19 patients. *Intensive Care Med* 2021;47:119–121.
- Bauer J, Brüggmann D, Klingelhöfer D, Maier W, Schwettmann L, Weiss DJ, et al. Access to intensive care in 14 European countries: a spatial analysis of intensive care need and capacity in the light of COVID-19. *Intensive Care Med* 2020;46:2026–2034.
- Burrell AJ, Pellegrini B, Salimi F, Begum H, Broadley T, Campbell LT, et al. Outcomes for patients with COVID-19 admitted to Australian intensive care units during the first four months of the pandemic. *Med J Aust* 2021;214:23–30.
- Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation. Report on COVID-19 admissions to intensive care in Australia 01 January 2020 - 30 September 2020 [accessed 2020 Nov 16]. Available from: https://www.anzics.com.au/wp-content/uploads/2020/11/Covid_Report_All-Australia_JAN_SEPT_2020.pdf.
- Fadel FA, Al-Jaghbeer M, Kumar S, Griffiths L, Wang X, Han X, et al. Clinical characteristics and outcomes of critically ill patients with COVID-19 in Northeast Ohio: low mortality and length of stay. *Acute Crit Care* 2020;35:242–248.
- Niedzwiedz CL, O'Donnell CA, Jani BD, Demou E, Ho FK, Celis-Morales C, et al. Ethnic and socioeconomic differences in SARS-CoV-2 infection: prospective cohort study using UK Biobank. *BMC Med* 2020;18:160.
- Kontis V, Bennett JE, Rashid T, Parks RM, Pearson-Stuttard J, Guillot M, et al. Magnitude, demographics and dynamics of the effect of the first wave of the COVID-19 pandemic on all-cause mortality in 21 industrialized countries. *Nat Med* 2020;26:1919–1928.
- Qian Z, Alaa AM, van der Schaar M, Ercole A. Between-centre differences for COVID-19 ICU mortality from early data in England. *Intensive Care Med* 2020;46:1779–1780.
- Intensive Care National Audit & Research Centre. ICNARC report on COVID-19 in critical care: England, Wales and Northern Ireland. 2021 Jan 22 [accessed 2021 Jan 28]. Available from: <https://www.icnarc.org/DataServices/Attachments/Download/7673eac0-ed5c-eb11-912d-00505601089b>.

Copyright © 2021 by the American Thoracic Society



⊗ Mechanical Ventilation in the Obese Patient: Compliance, Pleural Pressure, and Driving Pressure

Obesity is increasingly common in Western societies (1). When critically ill, obese patients present many management challenges, especially during mechanical ventilation (2). As a consequence of the large abdominal and chest wall loads on the diaphragm, they have more atelectasis and hypoxemia and require higher pleural pressure (Ppl) and airway pressure to maintain

adequate oxygen saturation as measured by pulse oximetry (Sp_{O₂}). These higher pressures have the potential to decrease \dot{Q} . This can negate the benefit of an increase in Sp_{O₂} and result in no change or even a decrease in O₂ delivery (DO₂), which ultimately is what matters for tissues. There is little information on airway pressure management in obese patients because they usually are left out of clinical trials. Accordingly, in this issue of the *Journal*, to evaluate the hemodynamic consequences of higher levels of airway pressure in obese patients with acute respiratory distress syndrome (ARDS), De Santis Santiago and colleagues (pp. 575–584) (3) performed clinical and animal studies to determine if higher positive end-expiratory pressure (PEEP) can improve gas exchange without compromising hemodynamics.

⊗This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). For commercial usage and reprints, please contact Diane Gern (dgern@thoracic.org).

Originally Published in Press as DOI: 10.1164/rccm.202009-3607ED on September 30, 2020