PROCESS AND SYSTEMS

The future of acute and emergency care

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ABSTRACT

Improved outcomes for acutely unwell patients are predicated on early identification of deterioration, accelerating the time to accurate diagnosis of the underlying condition, selection and titration of treatments that target biological phenotypes, and personalised endpoints to achieve optimal benefit yet minimise iatrogenic harm. Technological developments entering routine clinical practice over the next decade will deliver a sea change in patient management. Enhanced point of care diagnostics, more sophisticated physiological and biochemical monitoring with superior analytics and computer-aided support tools will all add considerable artificial intelligence to complement clinical skills. Experts in different fields of emergency and critical care medicine offer their perspectives as to which research developments could make a big difference within the next decade.

KEYWORDS: acute care, emergency care, precision medicine, stratified medicine

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Introduction

The events of the past year have brought into sharp focus the importance of research into acute and emergency care towards improving patient outcomes. With this in mind we present short perspectives from experts in different fields of emergency and critical care medicine as to what research developments could make a big difference to healthcare within the next 5–10 years. A consistent theme is improved patient stratification and characterisation to facilitate precision medicine (Fig 1). Breakthroughs in diagnostics, stratification, data analytics and treatments have the potential to lead to many exciting innovations which, in turn, will translate into better patient care and outcomes.

Stratification: the new frontier in emergency care

From the earliest days of medicine, doctors have tried to pick the best treatment for each individual patient. However, in emergency care, broad groups of patients are often treated in the same way as insufficient information is available to adopt a more precise approach. A 'sepsis bundle', for example, is applied to all patients who fulfil 'red flag' criteria. It is unlikely that any single approach is optimal for such a diverse group of patients. Guideline development provides treatment algorithms that are 'evidence

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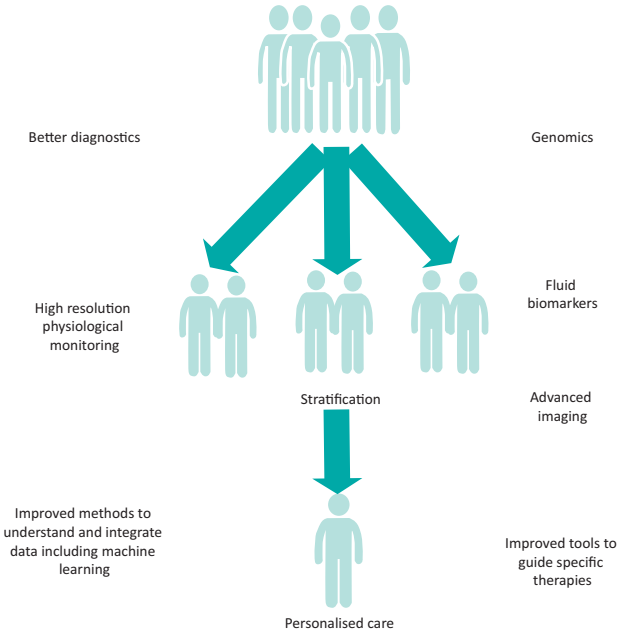

Fig 1. The advances which will enable precision medicine techniques to be used in acute and emergency care in the future.

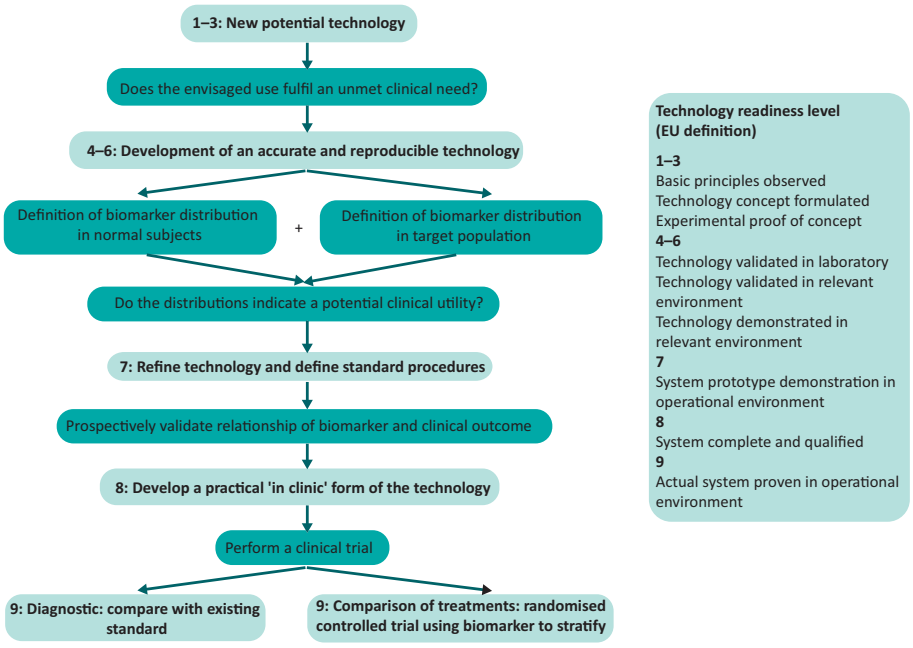

Fig 2. Development pathway for a biomarker in emergency care.

based', but these are designed for the average patient and so only constitute a best guess for any individual.

Greater stratification allows an increasingly precise approach with more individualised treatment. A large number of emergency point of care diagnostics are being developed, such as novel measures of physiology, novel biomarkers, measures of gene expression, new ways of using large data sets to make individual predictions and, on the horizon, rapid point of care genetic analysis.[1–4]

Development of novel stratification requires a series of research steps (Fig 2). This includes a wide range of research skills from technology development to validation studies, and then to pragmatic clinical trials and assessment of cost effectiveness. This pathway requires such a wide range of academic and methodological skills that success is only likely within a large multidisciplinary group. Future emergency care researchers need to develop the skills to play their part in these collaborative efforts as there may be more benefit from precise application of existing treatments than discovery of a novel treatment.

Rapid diagnostics for better antimicrobial use in acute care

Antimicrobial overuse leading to pathogen resistance is a leading global healthcare challenge, with considerable potential to impact on the effectiveness of future care pathways. There is an acknowledged overuse of high-potency, potentially toxic, broad-spectrum antimicrobial agents in acute care. This relates to limitations of time-critical diagnostic information regarding the likelihood of infection and identification of a causal pathogen. Advances in molecular science have led to newer technologies aimed at delivering rapid diagnostic information. Laboratory-based and point-of-care technologies include accurate rapid measurement of circulating host response inflammatory molecules (eg C-reactive protein and procalcitonin) and non-culture based multiplexed pathogen detection. However, it remains uncertain whether these rapid technologies, and the information they provide, can improve antimicrobial use while maintaining patient safety.

An ongoing portfolio of National Institute for Health Research-funded multicentre clinical research seeks to determine whether available technologies can improve antimicrobial use at key clinical decision points for patients with suspected severe infection syndromes.

Emergency antimicrobial therapy

Point-of-care procalcitonin is being investigated in the PRONTO trial to support the emergency assessment of suspected sepsis in adult patients.[5] This randomised controlled trial (RCT) aims to safely reduce patient antibiotic exposure in those who may not need them urgently, or not need them at all. A-STOP is investigating the clinical efficacy of rapid molecular fungal laboratory diagnostics to guide emergency use of antifungal therapy in high-risk critically ill adult and paediatric patients.[6]

Refining initial broad-spectrum antimicrobial treatments

Using respiratory samples from patients with pneumonia, multiplexed rapid pathogen identification technologies are being evaluated to improve antibiotic stewardship decisions. The INHALE programme includes a multicentre intervention trial in patients with severe healthcare-acquired pneumonia and ventilator-associated pneumonia, while BIPCAP is investigating a related technology in community-acquired pneumonia.[7,8]

Determining the most effective duration of antimicrobial treatment

Daily monitoring of host circulating inflammatory markers is being studied within routine NHS antimicrobial stewardship practice

in critically ill patients. ADAPT-Sepsis is investigating biomarker-guided decision protocols for antibiotic duration based on serial C-reactive protein and procalcitonin, aiming to safely shorten treatment duration in adult patients with sepsis.[9] BATCH is a similar study investigating serial procalcitonin in paediatric critical illness.[10]

Offering patients participation in these large-scale clinical antimicrobial stewardship trials is strongly encouraged to help establish definitive evidence for the clinical effectiveness of these technologies and treatment protocols embedded in routine NHS care.

Precision medicine

Modern medicine should aspire to give the right treatment to the right patient at the right time. RCTs provide the highest quality evidence to inform on the effectiveness of treatments, but they are limited to providing an average effect among a certain population. Critical care has classically used syndromic definitions to identify populations with similar signs and symptoms, but these syndromes contain very heterogenous groups of patients who are likely to have very different treatment needs.[11]

Attempting to use single biomarkers has not proven useful in guiding therapy.[12] Using multiple biomarkers and identifying patterns or signatures are, however, showing great promise. Using a combination of multiple biomarkers and clinical data, two distinct sub-phenotypes have been consistently identified among patients with ARDS.[13] Importantly, these two groups of patients appear to respond differently to different treatments, including ventilation, fluid strategies and drug treatments.[13–15]

In sepsis, RNA signatures can identify subphenotypes of patients with different outcomes.[16,17] Importantly, these signatures have been associated with different responses to treatment, notably to corticosteroids.[18] This may, in part, explain why different clinical trials have frequently yielded conflicting results.[19] To date, these differential treatment effects have only been demonstrated in retrospective analyses of clinical trials so prospective testing is required. The technology now exists and is being evaluated.[20]

Nevertheless, even using an '-omics' approach will still result in treating groups of patients, even if they are better defined and more homogeneous. The ultimate goal would be to individualise treatment for each patient. This will require techniques beyond just biomarker-guided clinical trials and will likely require machine learning / artificial intelligence (AI) techniques. Such approaches have already started to show promise to truly individualise clinical medicine within intensive care.[21]

Novel monitoring

While critical care currently uses a wide array of monitoring techniques assessing physiological and biochemical variables, there are some glaring deficiencies that need to be addressed. Prime among these are the inability to optimise antibiotic dosing and the early recognition of organ hypoperfusion and dysfunction.

With regard to antibiotics, abnormal drug handling in critical illness undermines the validity of fixed dosing regimens or simplistic algorithms based on estimates of glomerular filtration. Altered protein binding, distorted volumes of distribution, renal and/or hepatic dysfunction and augmented renal clearance may all conspire to produce significant under- or over-dosing.[22] Intriguingly, the so-called 'obesity paradox' in critical illness (ie lower mortality in the (morbidly) obese) may relate to excessive weight-adjusted doses of antibiotics and other treatments delivered to normal-weight patients.[23] While an important emphasis is directed towards administering an appropriate antibiotic, little attention has hitherto been paid to ensuring adequate yet not excessive dosing. Other than daily measurement of aminoglycosides and glycopeptides for toxicity, no other antibiotic classes are routinely measured, let alone continuously monitored to assess peak, trough and area under the curve concentrations. Perhaps of greater relevance is the need to assess tissue antibiotic levels as blood levels are poorly reflective; the need is to adequately treat tissue-based infection (such as pneumonia or peritonitis) rather than the scant amount of bacteria present within the circulation.[24] The concept of continuous therapeutic drug monitoring is being advanced, not just within blood but within tissues using a variety of techniques including microneedle biosensors, microdialysis and microfluidics.[25]

Current biomarkers used to detect organ hypoperfusion and dysfunction only become deranged when significant perturbations have occurred; for example, serum creatinine rises when glomerular filtration falls by at least 50%. Other blood biomarkers are often non-specific and reflect a balance of tissue production versus excretion or, as in the case of lactate, its utilisation as an important fuel source in stress states. Earlier, reliable identification of organ hypoperfusion/dysfunction, ideally using continuous monitoring, will prompt faster intervention with optimisation of treatment by titrating to sensitive endpoints. Hopefully, this will lead to prevention of organ dysfunction and better outcomes. A variety of monitoring technologies are being explored, such as tissue oxygen tension, mitochondrial redox status and mitochondrial PO_2 in animal models and early patient studies.[26–28] Their utility does, however, need to be validated in outcome studies.

Artificial intelligence

A discussion of medical research in the Google DeepMind era must soon turn to AI. Yet without resorting to randomisation, these tools can only optimise the observable and unmeasured confounding effects will occasionally lead us astray.[29] The rules of Go and the complexities of protein folding are transparent compared with bedside clinical medicine.[30]

The alternative, the RCT, is slow, expensive and cumbersome. Even with more efficient modern designs, such as those deployed during the COVID-19 pandemic, the answers are only 'true' on average.[31] Subtle endotypes create treatment heterogeneity not exposed by the RCT.[32]

Hitherto, the solution depends on the skill of the clinician to take that average answer and decide if it applies to their patient. Inevitably, this results in variation in practice; while we share expertise, each clinician's personal experience differs.

Such variation is normally considered a problem.[33] But it may hold the solution to the tension between observational and experimental research. Instead of just using clinical decision support (CDS) systems to reduce variation where strong evidence is available, they could be used to create randomisation opportunities where evidence is sparse and variation widespread. With both patient involvement to select topics suitable for opt-out consent and a flexible approach to randomisation that *nudges* rather than *mandates* treatment allocation, unbiased learning events can be generated without interrupting the delivery of care.

If I am uncertain whether to stop antibiotics today or tomorrow, then I could learn from my uncertainty. If I do know, I overrule the *nudge*, and the system learns from me.

Hundreds of millions of such decisions are made every day. Most are so small that the clinician does not always notice, eg prescribing paracetamol for a fever or setting a target oxygen saturation. It is inconceivable that the aggregate effect of all these small decisions is unimportant. However, to deliver personalised and not 'average' medicine, 'big data' needs to embrace experimental methods as well as observational ones.

Respiratory

In patients with acute respiratory failure, invasive mechanical ventilation is lifesaving, but also contributes to morbidity and mortality. Research into innovative approaches is needed to limit the harm associated with mechanical ventilation.

In the setting of COVID-19, the RECOVERY-Respiratory Support trial is evaluating the effectiveness of high-flow nasal oxygen or continuous positive airways pressure against standard oxygen therapy with a primary outcome of tracheal intubation or mortality within 30 days of randomisation. This trial should inform on the role of non-invasive respiratory support in COVID-19.

Prone ventilation is well established in the setting of mechanical ventilation patients with severe acute respiratory distress syndrome (ARDS). Although COVID-19 has prompted interest in the role of prone ventilation in awake patients, this concept is not new and the early reports of the use of prone positioning in the 1970s described its use both in patients who were invasively ventilated and also in awake patients to avoid intubation.[35,36] Given the potential for this simple intervention to improve outcomes in patients who are not intubated, trials in patients with acute hypoxaemic failure to avoid intubation as well as in patients following major surgery to avoid post-operative pulmonary complications are needed.

Airway pressure release ventilation (APRV) is a ventilation mode whereby pressure is alternated from a high level (Phigh) applied for a prolonged period (Thigh) to maintain lung volume and alveolar recruitment, to a low level (Plow) for a short period (Tlow). The underlying rationale is to maintain a pressure above the alveolar closing pressure for a sustained time, limiting the release time to allow carbon dioxide removal while avoiding lung de-recruitment. APRV also allows spontaneous breathing during any phase of the respiratory cycle. A systematic review suggested APRV resulted in a higher number of ventilator-free days and lower hospital mortality, although the underpinning evidence was low quality.[37]

Current approaches to weaning from mechanical ventilation require clinicians to gradually reduce ventilatory support. Emerging technologies can automatically adjust ventilation settings so these systems could both standardise and optimise the weaning process. A recent systematic review found that automated weaning methods may reduce the duration of ventilation.[38]

In recent years, the technology underpinning extracorporeal support has evolved and this may broaden indications for its use. Extracorporeal membrane oxygenation (ECMO) is increasingly established as an adjunct to protective mechanical ventilation for patients with severe ARDS.[39] Whether extracorporeal carbon dioxide removal offers a protective ventilatory strategy with improved patient outcomes remains uncertain.[40] Other potential indications for extracorporeal support include prevention of intubation, facilitation of extubation, and as an alternative to non-invasive ventilation.[41] Large-scale clinical trials are warranted to determine if these innovative technologies are clinically effective.

Finally, the findings of outcome benefit with steroids and IL-6 blockade in COVID-19 will renew interest in emerging pharmacological (including cell-based) therapies for patients with ARDS.[42–45] It is likely that a precision medicine approach using point-of-care testing will inform the design of future trials of such therapies.[46]

Cardiovascular disease

Cardiovascular disease remains the world's biggest killer.[47] The worldwide prevalence of heart failure is 64.34 million and increasing, accounting for 9.9 million years lost due to disability and $346 billion expenditure.[48] Evidence-based interventions have resulted in significant improvements in survival and quality of life in patients with long-term heart failure. However, outcomes remain persistently poor for those with its most severe manifestation, cardiogenic shock, with admission mortality rates of 27%–51%. The reasons are multifactorial and include variable syndrome definition, late recognition, lack of understanding of associated systemic pathophysiology, reliance on global rather than regional circulatory assessment/interventions, poor understanding of mechanisms of critical cardiac dysfunction, failure to tailor/individualise therapies and persistence in using interventions that are, at best, not beneficial and, at worst, harmful.[49,50]

Numerous factors have converged to fundamentally influence how research in this field is moving. First, technological evolution has led to a paradigm shift in approaches to circulatory support, using mechanical circulatory support (MCS) to 'rest' the heart rather than inotropes to drive contractility and, for non-reversible causes of severe heart failure, potentially providing an alternative to transplantation.[51,52] For acute MCS, research is required to understand the impact on the myocardium and wider circulation, and to determine which patients will benefit, from which support, and when and how to implement. Second, integrating high-content '-omics' to characterise each patient should allow for better understanding of the mechanisms of cardiac dysfunction in critical illness and lead to application of individualised therapies. Third, advanced imaging (including molecular) allows the potential for local drug delivery ('theranostics'). Finally, shock (as currently defined) is a late manifestation of a catastrophic cardiac insult. Here the rapid advance in technology (wearables, innables, outables, big data and related technologies) should define which metrics indicate the patient is early in their shock pathway and, potentially, how to intervene.

Acute brain injury

Traumatic brain injury (TBI) has been characterised as the most complex disease in the most complex organ.[53] Yet, despite this great heterogeneity, treatment guidelines have traditionally used a 'one size fits all' approach. Greater use of blood biomarkers, advanced magnetic resonance imaging and genomics, with improved integration of continuous high-resolution physiological monitoring, offers the opportunity for better patient characterisation and stratification.[54] This will enable improved patient selection and enrichment of clinical trials for subsets most likely to benefit, and avoid including those unlikely to benefit and/or suffer adverse consequences. Perhaps most importantly, these highly granular data offer the potential for more personalised

treatment approaches.

Improvements in knowledge and application of invasive neuromonitoring techniques will enable more widespread use outside academic centres with bespoke neuromonitoring programmes. This scale-up ability will facilitate previously not possible clinical trials. Two examples of such trials using invasive brain tissue oxygen-guided therapy are Brain Oxygen Optimization in Severe TBI, Phase 3 (BOOST3) and the Brain Oxygen Neuromonitoring in Australia and New Zealand Assessment (BONANZA).[55,56] Individualised cerebral perfusion pressure management based on cerebral autoregulation indices (such as cerebrovascular pressure reactivity) offer the opportunity to provide personalised dynamic targets to guide management; a feasibility study is now complete.[57] It is likely that more personalised approaches to TBI management will become the norm over the next few years. Similar approaches in other acute neurological and neurosurgical diseases also offer the potential to improve outcomes.

There is also an increasing recognition that all patients admitted to intensive care, even for primarily extra-cranial illnesses, have a vulnerable brain. Acute neurological dysfunction in the form of delirium is common, and is associated with long-term cognitive dysfunction.[58] One-third of survivors of acute respiratory failure or shock have significant cognitive impairment 1 year later.[59] Improvements in technology for non-invasive neuromonitoring and advances in analysis using machine learning (for example with bedside electroencephalography) may help to facilitate cross-over from neurocritical care concepts into general intensive care. This, in turn, may help to improve outcomes.

Long-term consequences of critical illness

Eighty per cent of critically ill patients survive to be discharged from intensive care. This survival is not without cost. Acute muscle wasting leads to profound weakness and significantly impaired function.[60] One-third of patients remain carer-dependent for basic activities of daily living at 1 year.[61] Compounding this, anxiety, depression and post-traumatic disorder are common. Forty per cent of young patients suffer from persistent cognitive deficit, akin to survivors of TBI or those with early-onset Alzheimer's disease.[62] At 5 years, one-third of previously employed patients have not returned to any form of work.[63] Rehabilitation from critical illness is recognised as a public health issue in National Institute for Health and Care Excellence guidance CG83; the poor understanding of the pathophysiology of muscle wasting was identified as a major therapeutic barrier.[64]

To date, no effective measures for primary or secondary prevention of these newly-acquired functional deficits exist. The field suffers from fundamental knowledge gaps. The underpinning biology of some aspects are being revealed, while others (such as that of cognitive decline) remain unclear. Biological heterogeneity is affected by pre-existing chronic disease states, but the impact of patient heterogeneity and sub-phenotypes on RCT outcomes are only now being realised.[20,65] To address this, translational research needs to be integrated into clinical trials to further reveal mechanisms of differential responses to interventions. Outcome measures in the field of critical illness have traditionally been related to mortality; there is an urgent need for patient-centred functional outcome measures with appropriate clinimetric properties.[20] Lastly, social, fiscal and cultural factors are tightly interlinked with patient outcomes.[66] Data regarding these factors are rarely recorded or used, and this gap is likely to be increasingly important in the post-COVID-19 world. ■

Conflicts of interest

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References

1 Elwan MH, Roshdy A, Elsharkawy EM, Eltahan SM, Coats TJ. The haemodynamic dilemma in emergency care: is fluid responsiveness the answer? A systematic review. *Scand J Trauma Resusc Emerg Med* 2017;25:25.
2 Czeiter E, Amrein K, Gravesteijn BY *et al*. Blood biomarkers on admission in acute traumatic brain injury: Relations to severity, CT findings and care path in the CENTER-TBI study. *EBioMedicine* 2020;56:102785.
3 Ducharme J, Self WH, Osborn TM *et al*. A Multi-mRNA host-response molecular blood test for the diagnosis and prognosis of acute infections and sepsis: proceedings from a clinical advisory panel. *Journal of Personalized Medicine* 2020;10:266.
4 Schinkel M, Paranjape K, Nannan Panday RS, Skyttberg N, Nanayakkara PWB. Clinical applications of artificial intelligence in sepsis: A narrative review. *Comput Biol Med* 2019;115:103488.
5 Euden J. *A point of care test to aid in diagnosis of suspected sepsis and optimal use of antibiotics in adults presenting to A & E: PROcalcitonin and NEWS2 evaluation for Timely identification of sepsis and Optimal use of antibiotics in the Emergency department*. ISRCTN registry, 2020. https://doi.org/10.1186/ISRCTN54006056 [Accessed 20 January 2021].
6 McMullan R. *Rapid diagnostic tests and treatment opportunities for fungal infection in critically ill patients*. ISRCTN registry, 2021. https://doi.org/10.1186/ISRCTN43895480 [Accessed 20 January 2021].
7 Enne V. *Inhale work package 3 – rapid versus standard testing to diagnose lung infections in intensive care, including COVID-19 observational sub-study: The impact of using film array pneumonia panel molecular diagnostics for hospital-acquired and ventilator-associated pneumonia on antimicrobial stewardship and patient outcomes in UK critical care: a multicentre randomised controlled trial and a COVID-19 related observational sub-study*. ISRCTN registry, 2021. https://doi.org/10.1186/ISRCTN16483855 [Accessed 20 January 2021].
8 Ross M. *Is it better to treat pneumonia by customising antibiotic treatment based on the PIBCAP test compared to the current standard NHS treatment?* ISRCTN registry, 2021. https://doi.org/10.1186/ISRCTN42850134 [Accessed 20 January 2021].
9 Dark P. *Biomarker-guided duration of antibiotic treatment for sepsis: the ADAPT-Sepsis trial*. ISRCTN registry, 2021. https://doi.org/10.1186/ISRCTN47473244 [Accessed 20 January 2021].
10 Waldron CA. *Using procalcitonin to guide duration of antibiotics*. ISRCTN registry, 2021. https://doi.org/10.1186/ISRCTN11369832 [Accessed 20 January 2021].

11 Singer M, Deutschman CS, Seymour CW *et al*. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315:801–10.
12 Reinhart K, Menges T, Gardlund B *et al*. Randomized, placebo-controlled trial of the anti-tumor necrosis factor antibody fragment afelimomab in hyperinflammatory response during severe sepsis: The RAMSES Study. *Crit Care Med* 2001;29:765–9.
13 Calfee CS, Delucchi K, Parsons PE *et al*. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. *Lancet Respir Med* 2014;2:611–20.
14 Famous KR, Delucchi K, Ware LB *et al*. Acute respiratory distress syndrome subphenotypes respond differently to randomized fluid management strategy. *Am J Respir Crit Care Med* 2017;195:331–8.
15 Calfee CS, Delucchi KL, Sinha P *et al*. Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomised controlled trial. *Lancet Respir Med* 2018;6:691–8.
16 Burnham KL, Davenport EE, Radhakrishnan J *et al*. Shared and distinct aspects of the sepsis transcriptomic response to fecal peritonitis and pneumonia. *Am J Respir Crit Care Med* 2017;196:328–39.
17 Davenport EE, Burnham KL, Radhakrishnan J *et al*. Genomic landscape of the individual host response and outcomes in sepsis: a prospective cohort study. *Lancet Respir Med* 2016;4:259–71.
18 Antcliffe DB, Burnham KL, Al-Beidh F *et al*. Transcriptomic signatures in sepsis and a differential response to steroids. From the VANISH randomized trial. *Am J Respir Crit Care Med* 2019;199:980–6.
19 Antcliffe DB, Gordon AC. Why Understanding Sepsis Endotypes Is Important for Steroid Trials in Septic Shock. *Crit Care Med* 2019;47:1782–4.
20 Puthucheary ZA, Gensichen JS, Cakiroglu AS *et al*. Implications for post critical illness trial design: sub-phenotyping trajectories of functional recovery among sepsis survivors. *Crit Care* 2020;24:577.
21 Komorowski M, Celi LA, Badawi O, Gordon AC, Faisal AA. The artificial intelligence clinician learns optimal treatment strategies for sepsis in intensive care. *Nat Med* 2018;24:1716–20.
22 Roberts JA, Paul SK, Akova M *et al*. DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? *Clin Infect Dis* 2014;58:1072–83.
23 Arabi YM, Dara SI, Tamim HM *et al*. Clinical characteristics, sepsis interventions and outcomes in the obese patients with septic shock: an international multicenter cohort study. *Crit Care* 2013;17:R72.
24 Kiang TK, Hafeli UO, Ensom MH. A comprehensive review on the pharmacokinetics of antibiotics in interstitial fluid spaces in humans: implications on dosing and clinical pharmacokinetic monitoring. *Clin Pharmacokinet* 2014;53:695–730.
25 Mabilat C, Gros MF, Nicolau D *et al*. Diagnostic and medical needs for therapeutic drug monitoring of antibiotics. *Eur J Clin Microbiol Infect Dis* 2020;39:791–7.
26 Parker T, Brealey D, Dyson A, Singer M. Optimising organ perfusion in the high-risk surgical and critical care patient: a narrative review. *Br J Anaesth* 2019;123:170–6.
27 Wu M, Pu K, Jiang T *et al*. Early label-free analysis of mitochondrial redox states by Raman spectroscopy predicts septic outcomes. *J Adv Res* 2021;28:209–19.
28 Mik EG, Balestra GM, Harms FA. Monitoring mitochondrial PO2: the next step. *Curr Opin Crit Care* 2020;26:289–95.
29 Vandenbroucke JP. Why do the results of randomised and observational studies differ? *BMJ* 2011;343:d7020.
30 Callaway E. 'It will change everything': DeepMind's AI makes gigantic leap in solving protein structures. *Nature* 2020;588:203–4.
31 Harris S, Palmer E, Fong K. Trials in pandemics: here we go again? *Br J Anaesth* 2021;126:e42–4.
32 Iwashyna TJ, Burke JF, Sussman JB *et al*. Implications of heterogeneity of treatment effect for reporting and analysis of randomized trials in critical care. *Am J Respir Crit Care Med* 2015;192:1045–51.
33 Wennberg JE. Time to tackle unwarranted variations in practice. *BMJ* 2011;342:d1513.
34 Perkins GD, Couper K, Connolly B *et al*. RECOVERY- respiratory support: respiratory strategies for patients with suspected or proven COVID-19 respiratory failure; continuous positive airway pressure, high-flow nasal oxygen, and standard care: A structured summary of a study protocol for a randomised controlled trial. *Trials* 2020;21:687.
35 Koeckerling D, Barker J, Mudalige NL *et al*. Awake prone positioning in COVID-19. *Thorax* 2020;75:833–4.
36 Douglas WW, Rehder K, Beynen FM, Sessler AD, Marsh HM. Improved oxygenation in patients with acute respiratory failure: the prone position. *Am Rev Respir Dis* 1977;115:559–66.
37 Carsetti A, Damiani E, Domizi R *et al*. Airway pressure release ventilation during acute hypoxemic respiratory failure: a systematic review and meta-analysis of randomized controlled trials. *Ann Intensive Care* 2019;9:44.
38 Neuschwander A, Chhor V, Yavchitz A, Resche-Rigon M, Pirracchio R. Automated weaning from mechanical ventilation: Results of a Bayesian network meta-analysis. *J Crit Care* 2021;61:191–8.
39 Griffiths MJD, McAuley DF, Perkins GD *et al*. Guidelines on the management of acute respiratory distress syndrome. *BMJ Open Respir Res* 2019;6:e000420.
40 Fitzgerald M, Millar J, Blackwood B *et al*. Extracorporeal carbon dioxide removal for patients with acute respiratory failure secondary to the acute respiratory distress syndrome: a systematic review. *Crit Care* 2014;18:222.
41 Boyle AJ, Sklar MC, McNamee JJ *et al*. Extracorporeal carbon dioxide removal for lowering the risk of mechanical ventilation: research questions and clinical potential for the future. *Lancet Respir Med* 2018;6:874–84.
42 Angus DC, Derde L, Al-Beidh F *et al*. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: The REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA* 2020;324:1317–29.
43 Investigators R-C, Gordon AC, Mouncey PR *et al*. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. *N Engl J Med* 2021;384:1491–502.
44 Gorman E, Millar J, McAuley D, O'Kane C. Mesenchymal stromal cells for acute respiratory distress syndrome (ARDS), sepsis, and COVID-19 infection: optimizing the therapeutic potential. *Expert Rev Respir Med* 2020;15:301–24.
45 Horie S, McNicholas B, Rezoagli E *et al*. Emerging pharmacological therapies for ARDS: COVID-19 and beyond. *Intensive Care Med* 2020;46:2265–83.
46 Reddy K, Sinha P, O'Kane CM, Gordon AC, Calfee CS, McAuley DF. Subphenotypes in critical care: translation into clinical practice. *Lancet Respir Med* 2020;8:631-43.
47 World Health Organization. *The top 10 causes of death*. WHO, 2020. www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death
48 Lippi G, Sanchis-Gomar F. Global epidemiology and future trends of heart failure. *AME Med J* 2020;5:15.
49 Thiele H, Zeymer U, Neumann FJ *et al*. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med* 2012;367:1287–96.
50 Tarvasmaki T, Lassus J, Varpula M *et al*. Current real-life use of vasopressors and inotropes in cardiogenic shock - adrenaline use is associated with excess organ injury and mortality. *Crit Care* 2016;20:208.
51 Combes A, Price S, Slutsky AS, Brodie D. Temporary circulatory support for cardiogenic shock. *Lancet* 2020;396:199–212.
52 Goldstein DJ, Naka Y, Horstmanshof D *et al*. Association of clinical outcomes with left ventricular assist device use by bridge to transplant or destination therapy intent: the multicenter study of MagLev technology in patients undergoing mechanical circulatory support therapy with HeartMate 3 (MOMENTUM 3) randomized clinical trial. *JAMA Cardiol* 2020;5:411–9.

53 Maas AI, Menon DK, Steyerberg EW *et al*. Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. *Neurosurgery* 2015;76:67–80.

54 Steyerberg EW, Wiegers E, Sewalt C *et al*. Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: a European prospective, multicentre, longitudinal, cohort study. *Lancet Neurol* 2019;18:923–34.

55 Barsan W. *Brain Oxygen Optimization in Severe TBI, Phase 3 (BOOST3)*. ClinicalTrials.gov, 2021. https://clinicaltrials.gov/ct2/show/NCT03754114 [31 January 2021].

56 Udy A. *The BONANZA trial- a randomised controlled trial that is testing whether a management strategy guided by early brain tissue oxygen monitoring in patients in with severe traumatic brain injury improves long term neurological and functional outcomes.* ANZCTR, 2019. http://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=378178

57 Roekaerts P. *CPPopt Guided Therapy: Assessment of Target Effectiveness (COGITATE)*. ClinicalTrials.gov, 2020. https://clinicaltrials.gov/ct2/show/NCT02982122 [Accessed 30 January 2021].

58 Mehta S, Cook D, Devlin JW *et al*. Prevalence, risk factors, and outcomes of delirium in mechanically ventilated adults. *Crit Care Med* 2015;43:557–66.

59 Pandharipande PP, Girard TD, Jackson JC *et al*. Long-term cognitive impairment after critical illness. *N Engl J Med* 2013;369:1306–16.

60 Puthucheary ZA, Rawal J, McPhail M *et al*. Acute skeletal muscle wasting in critical illness. *JAMA* 2013;310:1591–600.

61 Herridge MS, Cheung AM, Tansey CM *et al*. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med* 2003;348:683–93.

62 Pandharipande PP, Girard TD, Jackson JC *et al*. Long-term cognitive impairment after critical illness. *N Engl J Med* 2013;369:1306–16.

63 Kamdar BB, Huang M, Dinglas VD *et al*. Joblessness and lost earnings after ARDS in a 1-year national multicenter study. *Am J Respir Crit Care Med* 2017;196:1012–20.

64 National Institute for Health and Care Excellence. *Rehabilitation after critical illness in adults: Clinical guideline [CG83]*. NICE, 2009.

65 Puthucheary ZA, Astin R, McPhail MJW *et al*. Metabolic phenotype of skeletal muscle in early critical illness. *Thorax* 2018;73:926–35.

66 Lone NI, Lee R, Salisbury L *et al*. Predicting risk of unplanned hospital readmission in survivors of critical illness: a population-level cohort study. *Thorax* 2019;74:1046–54.

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