could be the use of prophylactic *Pneumocystis*-active agents in patients receiving long-term, high-dose inhaled or oral corticosteroid therapy. Unraveling these complex issues ought to be possible in larger longitudinal cohort-based studies.

A possible weakness of the current study is that it employed crude extracts from murine *P. murina* infections, which may not be entirely consistent with human *P. jirovecii* antigen sensitization and are not suitable for skin hypersensitivity testing. To further develop the tools and approaches needed to further define the role on *Pneumocystis* in asthma, systematic definition of human *Pneumocystis* antigens could be very useful, opening a door to direct sensitization studies, assessment of individual cellular responses, and therapeutic vaccination. ■

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

Anand Shah, M.R.C.P., M.B. B.S.
Darius Armstrong-James, M.R.C.P., Ph.D.
National Heart and Lung Institute
Imperial College London
London, United Kingdom

ORCID ID: 0000-0002-1014-7343 (D.A.-J.).

References

1. Armstrong-James D, Copas AJ, Walzer PD, Edwards SG, Miller RF. A prognostic scoring tool for identification of patients at high and low risk of death from HIV-associated *Pneumocystis jirovecii* pneumonia. *Int J STD AIDS* 2011;22:628–634.
2. Armstrong-James D, Meintjes G, Brown GD. A neglected epidemic: fungal infections in HIV/AIDS. *Trends Microbiol* 2014;22:120–127.
3. Issa NC, Fishman JA. Infectious complications of antilymphocyte therapies in solid organ transplantation. *Clin Infect Dis* 2009;48:772–786.
4. Katsuyama T, Saito K, Kubo S, Nawata M, Tanaka Y. Prophylaxis for *Pneumocystis* pneumonia in patients with rheumatoid arthritis treated with biologics, based on risk factors found in a retrospective study. *Arthritis Res Ther* 2014;16:R43.
5. Dutz W, Jennings-Khodadad E, Post C, Kohout E, Nazarian I, Esmaili H. Marasmus and *Pneumocystis carinii* pneumonia in institutionalised infants: observations during an endemic. *Z Kinderheilkd* 1974;117:241–258.
6. Alonso-Vargas R, González-Alvarez L, Ruesga MT, Carrillo-Muñoz AJ, Martín-Mazuelos E, Wallace TL, Cossum PA, Pontón J, Quindós G. In vitro activity of a liposomal nystatin formulation (Nyotran) against *Cryptococcus neoformans* [in Spanish]. *Rev Iberoam Micol* 2000;17:90–92.
7. Aliouat-Denis CM, Chabé M, Demanche C, Aliouat M, Viscogliosi E, Guillot J, Delhaes L, Dei-Cas E. *Pneumocystis* species, co-evolution and pathogenic power. *Infect Genet Evol* 2008;8:708–726.
8. Choukri F, Menotti J, Sarfati C, Lucet JC, Nevez G, Garin YJ, Derouin F, Totet A. Quantification and spread of *Pneumocystis jirovecii* in the surrounding air of patients with *Pneumocystis* pneumonia. *Clin Infect Dis* 2010;51:259–265.
9. de Boer MG, de Fijter JW, Kroon FP. Outbreaks and clustering of *Pneumocystis* pneumonia in kidney transplant recipients: a systematic review. *Med Mycol* 2011;49:673–680.
10. Lowe DM, Rangaka MX, Gordon F, James CD, Miller RF. *Pneumocystis jirovecii* pneumonia in tropical and low and middle income countries: a systematic review and meta-regression. *PLoS One* 2013;8:e69969.
11. Eddens T, Campfield BT, Serody K, Manni ML, Horne W, Elsegeiny W, McHugh KJ, Pociask D, Chen K, Zheng M, et al. A novel CD4⁺ T cell-dependent murine model of *Pneumocystis*-driven asthma-like pathology. *Am J Respir Crit Care Med* 2016;194:807–820.
12. Crothers K, Huang L, Goulet JL, Goetz MB, Brown ST, Rodriguez-Barradas MC, Oursler KK, Rimland D, Gibert CL, Butt AA, et al. HIV infection and risk for incident pulmonary diseases in the combination antiretroviral therapy era. *Am J Respir Crit Care Med* 2011;183:388–395.
13. Casadevall A, Pirofski LA. The damage-response framework of microbial pathogenesis. *Nat Rev Microbiol* 2003;1:17–24.
14. Castanhinha S, Sherburn R, Walker S, Gupta A, Bossley CJ, Buckley J, Ullmann N, Grychtol R, Campbell G, Maglione M, et al. Pediatric severe asthma with fungal sensitization is mediated by steroid-resistant IL-33. *J Allergy Clin Immunol* 2015;136:312–322.
15. Denney L, Byrne AJ, Shea TJ, Buckley JS, Pease JE, Herledan GM, Walker SA, Gregory LG, Lloyd CM. Pulmonary epithelial cell-derived cytokine TGF-β1 is a critical cofactor for enhanced innate lymphoid cell function. *Immunity* 2015;43:945–958.
16. Walzer PD. The ecology of pneumocystis: perspectives, personal recollections, and future research opportunities. *J Eukaryot Microbiol* 2013;60:634–645.
17. Summah H, Zhu YG, Falagas ME, Vouloumanou EK, Qu JM. Use of real-time polymerase chain reaction for the diagnosis of *Pneumocystis* pneumonia in immunocompromised patients: a meta-analysis. *Chin Med J (Engl)* 2013;126:1965–1973.
18. Stevens DA, Schwartz HJ, Lee JY, Moskovitz BL, Jerome DC, Catanzaro A, Bamberger DM, Weinmann AJ, Tuazon CU, Judson MA, et al. A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis. *N Engl J Med* 2000;342:756–762.
19. Agbetile J, Bourne M, Fairs A, Hargadon B, Desai D, Broad C, Morley J, Bradding P, Brightling CE, Green RH, et al. Effectiveness of voriconazole in the treatment of *Aspergillus fumigatus*-associated asthma (EVITA3 study). *J Allergy Clin Immunol* 2014;134:33–39.
20. Fishman JA. Prevention of infection due to *Pneumocystis carinii*. *Antimicrob Agents Chemother* 1998;42:995–1004.

Copyright © 2016 by the American Thoracic Society

Muscle Regeneration after Critical Illness: Are Satellite Cells the Answer?

In 1985, Op de Coul and colleagues reported 12 patients who had developed profound skeletal muscle weakness without sensory

Supported by the National Institute for Health Research Respiratory Biomedical Research Unit at the Royal Brompton and Harefield National Health Service Foundation Trust and Imperial College, which partially fund the authors' salaries. The views expressed in this publication are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research, or the Department of Health.

impairment after mechanical ventilation for 6 days or longer (1). They attributed the weakness to the use of neuromuscular blockade, but in fact their patients were also exposed to other factors now believed to contribute to intensive care unit-acquired weakness (ICUAW), including corticosteroids, aminoglycosides, and, most importantly, multiorgan failure. These patients followed a variable course: three died during follow up, and only seven made a full recovery over 2 to 6 months.

In the intervening 30 years, an explosion has occurred in the number of patients receiving intensive care, their illness severity, and the effectiveness of organ support. As a consequence, an increasing number of survivors, recently estimated to be approximately 75,000 patients annually in the United States (2), develop ICUAW. Critical illness is followed, even up to 5 years later, by functional disability, including impaired exercise capacity (3). The etiology is probably multifactorial, but it is at least in part ascribable to ICUAW and may persist despite exercise training; therefore, effective therapeutic approaches have great potential to improve quality of life in survivors and to be economically attractive. However, identifying these approaches has been hampered by the fact that patients with ICUAW are typically heterogeneous in terms of their comorbidities, their reason for ICU admission, and (in this context) the potentially damaging therapies (e.g., neuromuscular blocking agents) to which they might have been exposed. Similarly, at a physiological level controversy remains regarding the extent to which ICUAW should be considered a muscle disorder or of neurogenic origin.

The molecular mechanisms underlying ICUAW have been recently studied; the strength of this approach is that it moves focus toward maximizing function in the face of multiple etiological factors. As a result of the work of Puthucherry and coworkers, we have greater insight into the early changes taking place in the skeletal muscle of patients admitted to the ICU (4). Briefly, myonecrosis was observed in approximately half the patients, and rates of muscle protein breakdown were increased throughout the first week of ICU admission; interestingly, rates of muscle synthesis were reduced at the point of ICU admission but were similar to fasted healthy control subjects by Day 7. Until now, however, we had very little insight into mechanisms determining skeletal muscle mass over longer periods. In this issue of the *Journal*, dos Santos and colleagues (pp. 821–830) studied a prospectively recruited cohort of patients who required mechanical ventilation for 1 week or longer after discharge from their index admission, which had lasted between 9 and 88 days (5). From an initial pool of 82 eligible and 27 consented patients, 11 were studied at both 7 days and 6 months. Strengths of these unique data include the prospective way in which they were gathered and the comprehensive clinical and histological data obtained. As expected, quadriceps strength improved, to a variable extent, between Day 7 and 6 months and was universally reduced at Day 7 compared with published normal values. Recovery of quadriceps muscle bulk, assessed as computed tomography–defined midthigh cross-sectional area, was similarly variable, and in three patients the authors report that at 6 months there was a marked diminution of the ratio between voluntary contraction force and cross-sectional area (termed muscle-specific force), suggesting the interesting hypothesis that the regenerated muscle is of “poor quality.” At 7 days, there was evidence of increased ubiquitination (suggesting an increased rate of muscle breakdown), but this had reduced at 6 months to levels that were not different from library samples obtained from healthy volunteers. Why then should quadriceps weakness and atrophy be present at 6 months, if there is neither increased breakdown nor reduced synthesis?

Here the authors provide new data by determining the number of satellite cells. Satellite cells are muscle progenitor cells that differentiate into myoblasts and fuse to myofibers, as part of the

process of muscle regeneration. Thus, for example, patients with chronic obstructive pulmonary disease (COPD) receiving exercise training exhibited increased satellite cell numbers within 24 hours, which persisted for 2 months of training (6). Satellite cells are sparse, and it has been estimated that a minimum of 50 type I and 75 type II fibers should be assessed to draw meaningful conclusions even in young adults (7). dos Santos and colleagues were obliged to accept those specimens with 50 or more visible fibers only, presumably because biopsies from patients in the ICU are necessarily difficult to obtain (5). With this reservation, their finding that patients with demonstrable muscle atrophy at 6 months had fewer satellite cells than those without atrophy at this time point is relevant, because it implies that a reduced ability to regenerate impairs restoration of muscle mass after critical illness and explains variation between individuals.

A loss of muscle bulk may be considered to be a function both of the magnitude of the insult and the susceptibility to that insult. MicroRNAs (miRs) are noncoding RNAs that exert biologically important effects. miR-1 promotes myotube formation, and thus one candidate mechanism determining the magnitude of the insult may be reduced miR-1 expression, which we found to be substantially suppressed in a study of 20 patients with a median length of stay of 20 days (8) and also in patients with COPD (9). Reduced regeneration was observed by Thériault and colleagues (10) and by ourselves (11) in patients with COPD with a low fat-free mass index. In our studies, reduced regeneration was associated with differential expression of genes from imprinted genetic loci, suggesting a role for epigenetics and DNA methylation in determining the rate of regeneration in response to the stress of disease (11).

Understanding the mechanisms by which patients recover muscle in response to the loss associated with critical illness is important in developing appropriate therapeutic approaches to relieve the burden of ICUAW on patients. By identifying satellite cell number as a potential factor contributing to the longer-term response of individuals to ICUAW, the study by dos Santos and colleagues raises the possibility that the capacity of individuals to regenerate may determine recovery of skeletal muscle function after critical illness (5); the contribution of epigenetic factors to this recovery may be an interesting avenue of exploration. ■

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

Michael I. Polkey, Ph.D.
Mark J. Griffiths, M.D.
*National Institute for Health Research Respiratory Biomedical Research Unit
Royal Brompton and Harefield National Health Service Foundation Trust and
Imperial College
London, United Kingdom*

Paul R. Kemp, Ph.D.
*National Institute for Health Research Respiratory Biomedical Research Unit
Royal Brompton and Harefield National Health Service Foundation Trust and
Imperial College
London, United Kingdom*
and
*National Heart and Lung Institute
Imperial College
London, United Kingdom*

References

- Op de Coul AA, Lambregts PC, Koeman J, van Puyenbroek MJ, Ter Laak HJ, Gabreëls-Festen AA. Neuromuscular complications in patients given Pavulon (pancuronium bromide) during artificial ventilation. *Clin Neurol Neurosurg* 1985;87:17–22.
- Fan E, Cheek F, Chlan L, Gosselink R, Hart N, Herridge MS, Hopkins RO, Hough CL, Kress JP, Latronico N, *et al.*; ATS Committee on ICU-acquired Weakness in Adults; American Thoracic Society. An official American Thoracic Society Clinical Practice guideline: the diagnosis of intensive care unit-acquired weakness in adults. *Am J Respir Crit Care Med* 2014;190:1437–1446.
- Herridge MS, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, Cooper A, Guest CB, Mazer CD, Mehta S, Stewart TE, *et al.*; Canadian Critical Care Trials Group. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011;364:1293–1304.
- Puthucherry ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, Hopkinson NS, Phadke R, Dew T, Sidhu PS, *et al.* Acute skeletal muscle wasting in critical illness. *JAMA* 2013;310:1591–1600.
- dos Santos C, Hussain SNA, Mathur S, Picard M, Herridge M, Correa J, Bain A, Guo Y, Advani A, Advani SL, *et al.*; MEND ICU Group; RECOVER Program Investigators; Canadian Critical Care Translational Biology Group. Mechanisms of chronic muscle wasting and dysfunction after an intensive care unit stay: a pilot study. *Am J Respir Crit Care Med* 2016;194:821–830.
- Menon MK, Houchen L, Singh SJ, Morgan MD, Bradding P, Steiner MC. Inflammatory and satellite cells in the quadriceps of patients with COPD and response to resistance training. *Chest* 2012;142:1134–1142.
- Snijders T, Nederveen JP, McKay BR, Joannisse S, Verdijk LB, van Loon LJ, Parise G. Satellite cells in human skeletal muscle plasticity. *Front Physiol* 2015;6:283.
- Bloch SA, Lee JY, Syburra T, Rosendahl U, Griffiths MJ, Kemp PR, Polkey MI. Increased expression of GDF-15 may mediate ICU-acquired weakness by down-regulating muscle microRNAs. *Thorax* 2015;70:219–228.
- Lewis A, Riddoch-Contreras J, Natanek SA, Donaldson A, Man WD, Moxham J, Hopkinson NS, Polkey MI, Kemp PR. Downregulation of the serum response factor/miR-1 axis in the quadriceps of patients with COPD. *Thorax* 2012;67:26–34.
- Thériault ME, Paré ME, Maltais F, Debigaré R. Satellite cells senescence in limb muscle of severe patients with COPD. *Plos One* 2012;7:e39124.
- Lewis A, Lee JY, Donaldson AV, Natanek SA, Vaidyanathan S, Man WD, Hopkinson NS, Sayer AA, Patel HP, Cooper C, *et al.* Increased expression of H19/miR-675 is associated with a low fat-free mass index in patients with COPD. *J Cachexia Sarcopenia Muscle* [online ahead of print] 5 Jan 2016; DOI: 10.1002/jcsm.12078.

Copyright © 2016 by the American Thoracic Society

Advancing a Third Revolution in Critical Care

By the 1970s, a revolution was underway in critical care. The field distinguished itself professionally, claiming that critical care medicine was a distinctive body of expertise. The closed intensive care unit (ICU) was born (1). This revolution argued that a well-organized approach, not merely individual excellence, could save the lives of the very sick.

By the 1990s, a second revolution began in critical care. Through a tumultuous series of debates, we recognized that prolonging life ought not to be the sole goal of critical care. ICU practitioners assumed ownership of acute care of the dying (2). Excellence in family meetings, shared decision making, and symptom palliation were recognized as core ICU competencies, alongside resuscitation and ventilator management. This second revolution argued that a well-organized approach can provide a good death (or a good dying process) to those we cannot save.

This decade, a third revolution is underway in critical care. It is born of dissatisfaction with the simple dichotomization of alive versus dead. It builds on our growing expertise in both resuscitation and end-of-life care, but extends the ambition of the ICU to helping patients thrive after surviving their critical illness. This third revolution argues that a well-organized approach can help those

who survive critical illness live full new lives; lives not the same as they were before, necessarily, but also not necessarily less.

Each revolution is unfinished, but no less important for that. Each combines ambition, partnership, practice innovation, and science. Helping each revolution are useful conceptual simplifications that cognitively organized previously disparate problems and practices. In the first revolution: “shock” (3), “resuscitation,” and “acute respiratory distress syndrome” (4); in the second: a “good death” and “acute care of the dying” (5).

The third revolution in critical care is still searching for that grand simplification to help us improve survivorship. One area of particular interest is those patients who linger in the ICU, neither thriving nor dying (6). Although they comprise a minority of those we serve, they may account for a disproportionate number of bed-days and, given their emotional salience to many clinicians, even more of our recalled experience of providing ICU care.

Herridge and colleagues and the Canadian Critical Care Trials Group began the RECOVER program in 2007 to study these patients. In this issue of the *Journal* (pp. 831–844), they report that they recruited ICU patients for 7 years, from 2007 through 2014, at ICUs across Canada (7). They found 1,013 patients aged 16 years and older who had been mechanically ventilated for at least 7 days and were anticipated to survive at least another 24 hours, and who were not in ICU with brain injury. (Other exclusions are documented in Figure 1 of their article.) The 7-day mark was chosen, it appears, on the basis of expert clinical judgment and plausibility. Of the 534 participants enrolled, 398 survived the ICU, and 391 survived the ICU by at least a week to become the cohort.

This work was supported by Department of Veterans Affairs, Health Services Research & Development Investigator-Initiated Research Award 13-079.

This work does not necessarily represent the views of the U.S. Government or the Department of Veterans Affairs