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When Is Critical Illness Not Like an Asteroid Strike?

For some time now, critical care research has had a dirty secret, albeit not one well kept. Our epidemiologic work was most feasible if we prospectively collected data after patients had already declared themselves to be critically ill. Our animal models were most feasible if we took healthy young mammals and then, at a time convenient for us, ligated and punctured their cecum or instilled bacteria into their trachea.

In brief, we have studied critical illness as if it were an asteroid strike. Everything is going fine, until—boom! Critical illness smites an otherwise well patient.

Yet asteroid strikes are rare events in our medical intensive care units. Our patients do not present in the prime of their life. Their past medical histories are long and complex. Critical illness often marks an important change in a patient's trajectory, but is usually understandable only in the context of that patient's prior trajectory.

So we all knew the asteroid strike model was not a very good one. It made things simpler, yes, but potentially at the risk of studying the wrong thing. But what were we going to do? Critical illness was a rare event, and we could not just sit around waiting for bad things to happen in a world of tenure clocks and tight funding cycles.

One important step was to begin embedding studies of critical illness back into the mainstream of longitudinal studies of aging. There is a noble and important tradition of National Institutes of Health–funded longitudinal studies—the Framingham Study began in 1948. These studies have proven essential to understanding, not just cardiovascular disease, but also lung disease, cancer, stroke, and diabetes. In 2010, Ehlenbach and colleagues added critical care to the mix (1). They published a key study where they looked at the incidence of cognitive impairment among patients who were followed longitudinally in the Adult Changes in Thought study prior to their onset of critical illness. This provided essential evidence suggesting that critical illness had a real, probably causative effect on blunting cognitive acuity. Others followed, including studies showing the returns possible from the National Institute on Aging's Health and Retirement Study (2–4).

Yet there was that nagging voice in the back of our heads. Yes, we were showing that critical illness often resulted in an independent and significant worsening in the patients' functioning. But we had not yet captured that interdependence that we experienced in our clinical work—the spiral of illness to decline and decline to illness that we labored to interrupt.

Into that breach step Dr. Shah and his 15 coauthors (pp. 586–592) in this issue of the *Journal* (5). They cleverly realized that there are new statistical techniques that allow one to simultaneously model the coevolution of cognitive decline

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and risk of pneumonia. They painstakingly pulled together data from 5,888 Cardiovascular Health Study participants in which they could assess both ongoing cognitive function and the onset of acute hospitalizations.

They show, quite carefully, that pneumonia is associated with worsened cognitive decline. They further show that the cognitive decline after pneumonia is not only a general posthospital effect that others have posited (6), but seems to be particularly worse than general hospitalizations. (This is not, of course, to say that pneumonia is the only hospitalization that leads to cognitive decline—but the authors strongly reinforce other work showing that infection is a key bad actor [7–11].)

They build on past work showing that a hospitalization for pneumonia is associated with an increased rate of transition to dementia (7). This is, at risk of being impolitic, "real" dementia, not a subtle defect visible only on extensive neurocognitive testing. The unadjusted hazard ratio of dementia is more than doubled. Even after adjustment—including correction for physical and cognitive decline trajectories prior to pneumonia—the hazard for dementia remains 57% greater after pneumonia.

Further, and clearly in need of future research, the authors show little evidence that the severity of the subsequent cognitive decline is driven by the severity of the acute illness. This raises fascinating questions about the mechanisms of long-term decline. It would be convenient if the organ dysfunctions that place one at greatest risk of death despite ca.-2010 medical care were also those that were most likely to lead to long-term adverse outcomes. This does not happen to be the case, and we need to understand the reasons for this divergence.

Beyond this important work on the risks of cognitive decline, the authors also look for the occurrence of asteroid strikes. Specifically, they ask how often pneumonia occurs among patients who were already experiencing cognitive decline. They show that approximately two-thirds of pneumonia occurs among patients without detectable cognitive abnormalities beforehand—suggesting that often pneumonia does come without a cognitive prodrome.

Nonetheless, one-third of pneumonia cases were in respondents *with* such abnormalities, and the risk of pneumonia increased impressively with declining cognitive function in the time before pneumonia. The authors, for the first time in the literature, carefully tease apart this interaction. In doing so, they open a new set of lovely questions about the specific physiological and behavioral mechanisms that diversely contribute, which will play out in the *Journal*'s pages in the coming years.

Beyond these specific findings, a critically important contribution of the paper may be its clear reminder that we do not live in a post–infectious disease era. Pneumonia is not a solved problem. Nor is the problem of pneumonia simply the residual problem of finding new antibiotics for ever-evolving microorganisms. There are fundamental questions in the pathogenesis of pneumonia to be addressed. What are the physiologic or behavioral mechanisms by which cognitive decline leads to increased rates of pneumonia?

Pneumonia, like severe sepsis, looks to be fundamentally life altering, not just acutely life threatening (12–15). We do not know why. We do not know how to prevent that damage. We do not have a balanced portfolio of prevention, treatment, and rehabilitation options that target patient-centered outcomes like cognitive decline after pneumonia and other acute infections. We do not even know what recovery looks like well enough to be able to properly test potential interventions.

When we look at scientific discussions driving public health efforts—and research allocation—too often infectious diseases are treated as if they were foreign aid. Although pneumonia and sepsis remain stubbornly in the top 10 causes of death, they are often ignored. For example, consider the Healthy People 2020 objectives (16). The respiratory disease objectives contain none about pneumonia. In the infectious disease recommendations, there are references to invasive pneumococcal disease and influenza, but not to other pneumonia—and the overwhelming focus is on vaccine prevention, not treatment or harm mitigation.

Shah and colleagues have provided an important service to our patients by reminding us of the important role of pneumonia in the arc of patients' lives. They illustrate the complex realities of pneumonia—sometimes an unforeseeable blow, other times a surprising sequela of an ongoing decline. They have expanded a growing literature showing that hospitalizations for acute infections often have lingering consequences—even when the acute infections do not require critical care in conventionally organized hospitals. Now the challenge is for us to take these insights—and the longitudinal perspective they demand—and move forward to both further discovery and urgently needed new treatments.

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IgG4-related Lung Disease

Despite the exponential increase in our knowledge in the last few decades, the now famous (and possibly apocryphal) quote "There is nothing new to be discovered in physics now, and all that remains is more and more precise measurement" attributed to the physicist William Thomson Kelvin more than a century ago reminds us that there is much that we still do not understand about the world around us.

Hamano and colleagues reported elevated serum IgG4 concentration in patients with sclerosing pancreatitis in 2001 (1). In 2003 Kamisawa and colleagues proposed the term systemic IgG4-related disease when they found that in addition to elevated serum IgG4 levels, patients with autoimmune pancreatitis had pancreatic, peripancreatic, bile duct, gallbladder, liver, stomach, colon, salivary gland, lymph node, and bone marrow infiltration with IgG4-positive cells (2). Pulmonary involvement was described 1 year later in a patient with IgG4-related disease and organizing pneumonia (3). We now recognize that other previously described conditions, including but not limited to Mikulicz's disease, Kuttner's tumor, Riedel's thyroiditis, inflammatory pseudotumor, and fibrosing mediastinitis, are or may be part of the IgG4-related disease spectrum (4). Multiorgan system involvement is common (>90%) in patients with IgG4-related disease, and virtually all organ systems, including eye, orbital soft tissue, extraocular muscle, salivary glands, pachymeninges, hypophysis, thyroid, aorta, arteries, mediastinum, retroperitoneum, mesentery, skin, lymph nodes, bile ducts, gallbladder, liver, pericardium, kidney, breast, prostate, lung, and the pleura, can be involved (4, 5).

The IgG4 antibodies form less than 5% of the IgG antibodies and are different from the other IgG antibodies in that they have a low affinity for the C1q protein complex and they are unable to activate complement via the classical pathway (6). The inter–heavy chain disulfide bond of the IgG4 molecule is susceptible to chemical reduction, allowing the heavy chains to separate and recombine randomly to form bispecific IgG4 molecules that cannot form immune complexes (6). IgG4 antibodies can, however, activate complement via the alternate pathway, activate leukocytes, and induce leukocyte-dependent tissue damage (7). Unlike antigen-specific IgG4 antibodies such as desmoglein 1 antibodies in pemphigus vulgaris and M-type phospholipase A2 antibody in membranous glomerulonephritis, no specific antigen targets for the IgG4 antibodies have been identified in patients with IgG4-related disease (6). It is unclear what role the antibody properties have in the pathogenesis of IgG4-related disease, or even whether the IgG4 antibodies are responsible for the pathogenesis of IgG4-related disease (6). IgG4-related disease is characterized by a preferential Th2-type response and an increase in expression of the Th2 cytokines IL-4, IL-5, IL-10, and IL-13 (8). Activated regulatory T cells secrete transforming growth factor-β, which is responsible for the fibrosis seen in IgG4-related disease (8).

An elevated IgG4 level (>140 mg/dl) has been found to be the most sensitive and specific laboratory test for the diagnosis of IgG4-related disease, but IgG4 levels are elevated in up to 5% of normal population, and in patients with many other unrelated disorders, including atopic diseases; bacterial, viral, and parasitic infection; Rosai-Dorfman disease; anti-neutrophil cytoplasmic antibody–related vasculites; autoimmune disorders, including systemic lupus erythematosus, rheumatoid arthritis, and polymyositis/dermatomyositis; pancreatic cancer; hepatobiliary cancer; and lung cancer (9). Histopathologic diagnosis of IgG4-related disease requires the presence of characteristic lymphoplasmacytic infiltrate with associated storiform (whorled) fibrosis (which may be minimal or absent in the lung), obliterative phlebitis, and IgG4-positive cells (>40% of plasma cells IgG4 positive, and >20–50 IgG4-positive cells/high-power field for lung) (10). The diagnosis of IgG4-related disease is furthermore confounded by the fact that a subset of patients with granulomatosis with polyangiitis and Churg-Strauss syndrome share clinical, laboratory, radiologic, and histopathologic characteristics with IgG4-related disease (11). Larger studies are needed to clarify these diagnostic criteria for pulmonary IgG4-related disease outlined in the recent consensus statement, which were based on expert opinion and two relatively short case series comprising less than 20 patients (10).

Case reports and registry data suggest that the rate of pulmonary and extrapulmonary malignancies in patients with IgG4-related disease is higher than the background rate; the reason for this increased incidence is not clear at this time (12). Patients with pulmonary and extrapulmonary malignancy can have an elevated IgG4 level and IgG4-positive plasmacytic infiltrate in regions primarily limited to areas in and around the tumor (13–15). Varying degree of IgG4-positive plasma cell infiltrate can be seen in a significant proportion of patients with lung cancer and cholangiocarcinoma, and the robustness of this IgG4 response in a subgroup of patients with lung cancer seems to correlate with improved survival (16, 17). These observations, which need to be confirmed, suggest that the IgG4 immune response at least in a subgroup of patients appears to be in response to yet unidentified antigen groups via mechanisms that await clarification.

Pulmonary involvement reportedly occurs in 12–50% of patients with IgG4-related disease, and this variation is a function of the meticulousness with which pulmonary involvement was sought after and the relatively small size of the case series (5, 18, 19). Hilar and mediastinal adenopathy is the most common (up to 80%) form of thoracic involvement in patients with IgG4-related disease (5, 20). Pulmonary involvement in IgG4-related lung disease can take the form of various sizes of lung nodules, lung masses, patchy ground-glass opacities, infiltrates resembling consolidation, reticular opacities, thickened bronchovascular bundles, central airway stenosis and obstruction, bronchiectasis, pleural effusion, nodular pleural lesions, and interstitial lung disease (5, 21, 22). Nodular