Risks of Intravenous Immunoglobulin in Sepsis Affect Trial Design

TO THE EDITOR: The meta-analysis by Turgeon and colleagues (1) on the use of intravenous immunoglobulin (IVIG) in adults with sepsis suggests that larger trials should be performed incorporating modern sepsis management techniques. However, the authors did not discuss the side effects of using IVIG in sepsis.

All immunologists recognize that immunoglobulin replacement therapy must be withheld in patients with infections because severe reactions commonly develop (2). An audit of adverse reactions in antibody-deficient patients showed that an intercurrent infection was the major cause of reactions to IVIG replacement therapy (3). This multicenter prospective study of 459 patients reported that the reaction rate would have been halved if infusions were not administered to patients with an intercurrent infection. Twenty-eight of 111 adverse reactions were attributed to underlying infections. Prophylaxis with antibodies and delaying IVIG infusion in patients with intercurrent infection is now the standard of care.

In view of this, future trials using IVIG in sepsis should not only consider reporting adverse events but also should consider effective antibiotics before considering treatment with IVIG. This may well prove to be crucial—the study by Rodriguez and colleagues (4) on IVIG in sepsis from abdominal infections had concluded that the initial choice of antibiotics had a dramatic effect on outcome.

A novel mechanism of action of IVIG can profoundly affect the outcome in sepsis. Naturally occurring anti–sialic acid–binding Ig-like lectin 9 autoantibodies in IVIG can cause accelerated apoptosis of neutrophils and may then lead to neutropenia (5). This effect is enhanced by high levels of interferon-γ and reactive oxygen species, which are present in sepsis.

Currently, manufacturers cannot provide a constant supply for the ever-increasing demand for IVIG, and this has resulted in escalating costs of the product (6). This particularly affects countries that rely on foreign sources of plasma, such as the United Kingdom. Off-label use must therefore be avoided, especially when alternatives are available. We recommend extreme caution in designing future trials of IVIG in patients with sepsis, paying close attention to adverse reactions. Trial designers must remember that the IVIG supply is limited and reduction in availability for licensed use will have tremendous effects on quality of life for patients with primary immunodeficiency disorders who have an absolute requirement for this drug.

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IN RESPONSE: We thank Drs. Khan and Sewell for their interest and relevant comments regarding our study. As pointed out in their letter, adverse reactions after IVIG administration have been observed in patients with severe infections. However, these severe adverse effects were described in patients with hypogammaglobulinemia who received their usual replacement treatment of IVIG during an intercurrent infection, who differ from the broad population of patients with sepsis of our study. Moreover, in the same observational study of more than 13,500 IVIG infusions, the incidence of adverse events was 0.8%, and none of these reactions were reported as severe (1). In our meta-analysis, adverse reactions were reported in only 6 studies. Of interest, most of these adverse effects were considered mild to moderate, and when severe (dyspnea or shock) they were thought to be secondary to the primary disease rather than to the treatment regimen. Neutropenia was also not reported as a consequence of IVIG use. However, ensuring the safety of participants with independent data safety monitoring committees and diligent reporting of adverse events within clinical trials is very important in general, as well as for future prospective trials evaluating the use of IVIG.

Costs and potential supply problems associated with the use of IVIG in a broad population of patients with severe sepsis and septic shock are crucial if considering recommending the use of IVIG. Albeit, important costs and supply should not supersede overall benefits, such as improvements in survival and quality of life; a clear survival benefit in any population should be given priority over other indications with lower evidence of a clinical benefit (2, 3). On the other hand, the estimated cost of IVIG (1 g/kg) is currently about half that of activated protein C in the same population. We agree that good management of IVIG supply should be prioritized by basing the use of IVIG on current evidence of clinical benefit. For these reasons and the potential benefit of the therapy, we believe that IVIG should be further evaluated in adult patients with severe sepsis and septic shock receiving current standard of care therapy.

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The Declining Number and Variety of Procedures Done by General Internists

TO THE EDITOR: We commend Wigton and Alguire (1) for their impressive and thought-provoking work. Although their findings certainly signify the evolution of the practice of general internists, the authors’ conclusion that “recommendations and practices for internal medicine residency training in procedures should be reexamined in light of these changes” fuels our growing concerns about procedural training in internal medicine residency. Previously, internal medicine residents were required to demonstrate proficiency in 15 common procedures (for example, central-line placement, lumbar puncture, and thoracentesis) before board certification. Recent changes made to the American Board of Internal Medicine (ABIM) procedural requirements include that residents are required to “safely and competently perform” four procedures and advanced cardiac life support, but they are required only to “know, understand, and explain” the remaining 11 procedures (2). We believe these changes do not take into account two major facts about internal medicine residents today.

First, because internal medicine residency continues to include major inpatient clinical responsibilities, residents are still primarily responsible for performing indicated procedures in a safe and timely manner for their hospitalized patients. This remains especially true during nights and weekends, when attending-led procedural services may not be staffed and patients may require critical diagnostic and therapeutic procedures. Ensuring that residents can adequately perform procedures remains critical to safe patient care at all times. Furthermore, delaying or forgoing procedural training in internal medicine residency invokes the “pay it forward” phenomenon, in which subspecialty fellowship training programs—notorious for already variable clinical curricula and training requirements (3)—may be unprepared to bear the brunt of basic procedural training for their fellows.

Second, the vast majority of internal medicine residents are not choosing to pursue a career as a general internist, whereas increasing numbers are pursuing hospitalist jobs, either as a temporary position before subspecialty training or as a long-term career (4). In either case, the ability to perform procedures independently remains a necessary skill for hospitalist practice. Not surprisingly, internal medicine residency programs often provide the proof of competence in procedural performance for necessary credentialing and medical staff appointments. For these reasons, the continued reliance on residents at the frontlines of hospital care, and the growing popularity of hospitalist careers, we encourage reexamining the needs and function of procedural training requirements in internal medicine residency.

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TO THE EDITOR: We read with interest the article by Wigton and Alguire (1) on the declining number and variety of procedures done by general internists. On the basis of experiences at our own institutions, we propose that this notable decline can be linked to the American Board of Emergency Medicine’s decision, in 1990, to restrict board certification to those who are emergency medicine residents (2). This has led to an increased number of emergency medicine residencies to fill the demand for emergency department (ED) physicians, which has, in turn, competed with the access that internal medicine residents have for ED experience during their residency. Emergency medicine rotations have traditionally been months where internal medicine residents had more opportunities to perform procedures (such as central-line placement, intubations, lumbar punctures, paracentesis, pulmonary artery catheter placement, and even chest tube placement in some institutions).

The original survey by Wigton and colleagues (3) was done at a time when physicians trained in internal medicine could still “grandfather” into emergency medicine by documenting 7000 hours of full-time ED practice and taking the American Board of Emergency Medicine certification examination (2). Those internal medicine residents interested in working in the ED probably sought out more opportunities to do emergency medicine procedures. Many large-county hospitals did not have emergency medicine residencies, and the bulk of ED cases were handled by internal medicine and general surgery residents, despite the ABIM requiring only 1 month of ED service throughout the 3-year residency.

The hospitalist movement, at least in academic practice, has been a route through which some general internists can maintain their procedural skills. However, hospitalists in private practice are often encouraged to consult specialty services, such as anesthesia or interventional radiology, to perform central-line placement, lumbar puncture, or paracentesis. Most procedures have already been performed in the ED once a patient has been admitted to an inpatient medicine service, thus obviating the need for the hospitalist to do them (Siddiq AA. Personal communication.).

With the replacement of internal medicine residents with emergency medicine residents competing for procedures in our nation’s EDs, internal medicine residents have lost a major source of procedural experience. Although internal medicine residency training was not designed for a career in emergency medicine, we cannot overlook the fact that for many decades before emergency medicine became a
recognized specialty in 1979, and for many years after, general internists, family practitioners, and general surgeons were taking care of patients and performing procedures in our EDs.

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TO THE EDITOR: Has Opportunity’s Door been opened a crack by this article (1) and its accompanying editorial (2)? The medical journals have been rife with articles on the death of internal medicine, or the salvaging of it. But no one seems to link its demise to the lack of procedural skills, and attendant income, for general internists. Nor do these 2 articles go that far. In Table 3 of Wigton and Alguire’s article (1), several procedures now performed by U.S. general internists are not listed: echocardiogram interpretation, hemodialysis, bronchoscopy, stress echocardiography, nuclear stress imaging, sleep studies, and even in a few cases, permanent pacemaker implantation and transesophageal echocardiography. Yet all of these procedures are performed capably by general internists—in Canada. That they are not in the United States is not because, as Duffy and Holmboe (2) maintain, general internists feel that their patients deserve better. It is because in the main, our residents are never given the opportunity to learn them. Procedures generate income. Procedures pay off burdensome student loans and relieve the pressure to see larger volumes of patients ever more quickly.

Procedures add spice to patient care. Patients do not demand that a subspecialist do the procedure. Uniformly, patients ask: “Why can’t you do it?” Cardiology is hardly more fascinating than rheumatology, except for the opportunity for large numbers of procedures and the income, power, and prestige that brings. Similarly, young people do not gravitate to gastroenterology because of any great magic in the splenic flexure.

If the Canadians can do it, so can we. But don’t ask permission from subspecialists who control training and credentialing. A greater politic must obtain. Both the ABIM and the American College of Physicians have foundations that exist in part to fund research of this type. Both should support impartial clinical research to answer this question posed by Duffy and Holmboe’s editorial: “What procedures should internists do?” Take it a step further. Just suppose this research shows that a well-trained general internist can read echocardiograms as well as, and more cheaply than, cardiologists. Who else might be interested? Finally, a caveat to you young students out there: If such research is not funded, if this profound question is not answered by funded clinical research, if the question is sent to committee and therefore to certain death, continue to avoid general internal medicine at all costs, as you have been.

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IN RESPONSE: We appreciate the interest in our study and are pleased that it has generated discussion about internists’ procedural skills. Drs. Farnan and Arora are concerned that the change in the ABIM requirements doesn’t consider the need for residents to perform procedures competently and safely during training. Resident
credentialing is a process for certifying residents who can do procedures independently while in training. Gabryel and Brierley (1) reviewed this topic and described its use in hospitals in New York State. The competency of residents in procedural skills remains an important issue even though Medicare requirements for direct supervision have limited the procedures that residents do independently. More information is needed about the procedures done during training by residents and their teachers.

Drs. Luh and Karnath propose that one cause of the decline in the number of procedures that internists do is that board certification in emergency medicine is now restricted to those trained in emergency medicine residencies. They point out that internal medicine residents have lost a major source of procedure experience to the emergency medicine residents. Our study provides no data on these questions, but we think that training opportunities in procedures for internal medicine residents have likely been lost because of the growth of many specialty-oriented residencies and fellowships.

Dr. LaCombe suggests that the declining popularity of general internal medicine is linked to the decrease in procedures done by general internists and the resulting loss of practice revenue. He contrasts the procedures done in the United States with those in Canada and suggests that U.S. internists do fewer procedures because they lack the opportunity to learn them as residents. Bodenheimer and colleagues (2) discuss this idea in their recent paper on the income gap between specialists and primary care physicians. They point out that the relative value scale rewards specialists disproportionately because of the number of procedures they do. Would general internists do more procedures if they learned to do more of them in residency and if higher reimbursements made it worthwhile? This would be a great area for study. Incidentally, according to a recent survey, Canadian internal medicine residency graduates also have difficulty finding adequate opportunities for learning some procedures in training (3).

Mr. Metkus asks whether a nonresponse bias could account for the differences between the 1986 and the 2004 surveys. Both city size and hospital size affected the number of procedures done in both surveys. The methods used in the 2 surveys were nearly identical, however, and a breakdown of the respondents and results by city size and hospital size in the 1986 survey (see Figure 2 of the 1986 survey [4]) and the 2004 survey (see Table 2 of the 2004 survey) shows that not only is the percentage in each subgroup quite similar, so is the decline in the number of procedures done within each subgroup. To estimate the maximum potential effect of such a bias, we reanalyzed the 2004 data with the rural sample completely excluded: The mean number of procedures done in practice decreased only from 8.5 to 8.0, which is still quite a contrast to the 16.0 procedures done in the 2004 data with the rural sample completely excluded: The mean estimate the maximum potential effect of such a bias, we reanalyzed not only is the percentage in each subgroup quite similar, so is the

Strategies for Timely and Effective Hospice Discussions: End-Stage Renal Disease

TO THE EDITOR: Casarett and Quill describe excellent strategies for discussing hospice and supportive (palliative) care with patients and families, including how to overcome the barriers to such discussions (1). Absent from Table 1 is a common condition with an increasing incidence and worse mortality rate than the other conditions listed: end-stage renal disease (ESRD). Incident dialysis patients have a 1-year mortality rate of 20% to 30% (2). The median survival for patients older than 80 years of age starting dialysis is 15.6 months; this is one fifth of the survival of an age-matched cohort without ESRD (3). Murray and colleagues (4) have demonstrated an alarming underutilization of hospice in this population (14% of all ESRD deaths). Only 40% of patients who stop dialysis (mean survival, 8 days) die with hospice care. Casarett and Quill discuss the regulatory barriers to hospice care, some of which, in their words, are “arguably unethical.” Patients with ESRD face even more extreme barriers. Despite the recent study (4) that demonstrates a cost savings for dialysis patients who die with hospice care, interpretation of the Medicare hospice benefit by the Centers for Medicare & Medicaid Services, their carriers, and the hospices themselves sometimes severely restrict access for this suffering population to hospice.

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IN RESPONSE: We thank Dr. Cennimo for bringing up this interesting point. The primary aim of our analysis was to assess the relationship between adherence and virologic outcomes on NNRTI regimen, and we caution that our finding of superior outcomes for efavirenz compared with nevirapine must be regarded as preliminary.

The homozygous \(CYP2B6\) position 516 TT genotype was found in 3.4% of European Americans and 20% of African Americans in the AIDS Clinical Trials Group study A5097s (1), close to 50% in participants in a study from Ghana (2), and 13.1% of participants in a recent South African study (3). The \(CYP2B6\) TT genotype increases the efavirenz half-life, but as pointed out in the article Dr. Cennimo cites (4), this would be expected to result in a higher risk for drug-resistant mutations in poorly adherent patients, because the interruption of other antiretroviral drugs with shorter half-lives will result in prolonged effective monotherapy with efavirenz.

The \(CYP2B6\) TT genotype is also associated with an increased incidence of efavirenz-induced neuropsychiatric symptoms (1), which may reduce adherence. Therefore, one could argue that efavirenz should be associated with poorer outcomes in populations, such as that in our study, with a relatively higher proportion of patients with the \(CYP2B6\) TT genotype. Finally, efavirenz has also been shown to be more effective than nevirapine in a collaborative study of 12 cohorts from Europe and North America (5) and in recent study of U.S. Veterans Affairs patients (6), populations in which the prevalence of the \(CYP2B6\) TT mutation is low. This suggests that population pharmacogenetic differences are not the likely explanation for our preliminary finding that efavirenz is more effective than nevirapine.

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IN RESPONSE: Dr. Quill and I fully agree with and appreciate the important comments by Dr. Germain and colleagues, and we regret not including this important group of patients who could potentially benefit from hospice.

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Pharmacogenetics of Efavirenz: Adherence and Virologic Outcomes

TO THE EDITOR: Nachega and colleagues (1) describe the virologic response to nonnucleoside reverse transcriptase inhibitor (NNRTI) use across a spectrum of adherence in a predominantly (96.9%) black, South African patient cohort. Their findings suggest a superiority of efavirenz-based regimens over nevirapine even after adjustment for adherence and other baseline variables. One potential confounding variable is the delayed hepatic clearance of efavirenz noted in some U.S. patients of African descent (2). This has been attributed to mutation in the \(CPY2B6\) gene (516G>T), which can prolong the efavirenz half-life to 48 hours in persons with TT homozygous mutations. In comparison, the half-lives in GG homozygotes and GT heterozygotes are 23 hours and 27 hours, respectively (3). This prolonged half-life, if present, could have ameliorated the effects of inconsistent adherence by maintaining effective levels until the next dose was taken. If this is the case, these effects may not be seen in alternate patient populations.

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CORRECTION

Correction: Update in General Internal Medicine

In the recent Update in General Internal Medicine (1), an error appeared in the Table. The Table erroneously included the word hemorrhagic in reference to the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) study (2). This should have read: “Consider prescribing atorvastatin, 80 mg/d, for secondary prevention of stroke in patients with transient ischemic attack or ischemic stroke.”

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