In the context of uncertainties related to the future of COVID-19 and other pandemics, we must consider whether no-visitor policies are essential for continued infection prevention and to what extent restricted visitation and changes in communication practices might unintentionally foster poor health outcomes, inequity, and animosity toward health care (13). ■

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Monitoring Research Blood Sampling in Critically Ill Patients: Avoiding Iatrogenic Anemia

To the Editor:

As members of the Pathogenesis Subcommittee of the NHLBI Prevention and Early Treatment of Acute Lung Injury (PETAL) Network (referred to herein as “Network”), we write to share our experience in navigating a growing concern about possible excess blood draw volumes in critically ill patients enrolled in multiple clinical studies. The Network’s Data Safety Monitoring Board (DSMB) observed that requests for enrollment of patients in ICU-based clinical studies along with potentially multiple PETAL clinical trials posed a potential risk for iatrogenic anemia, especially at centers with multiple ongoing ICU studies. Review of the existing literature revealed limited guidance for blood volume draw limits in critically ill patients. For example, the Canadian Medical Research Council Institutional Review Board (IRB) limits allowable total blood draw volumes (for both clinical and research purposes) to 140 ml in a single draw and 280 ml in a 30-day period in a 70-kg individual and requires a minimum Hb of 7.0 g/dl (or 9.0 g/dl for subjects with respiratory or cardiovascular compromise) (1). The U.S. Department of Health and Human Services guideline recommends a comparable research blood volume draw limit over an 8-week period (2). A number of IRBs have adopted similar recommendations without specific guidance for critically ill subjects (3, 4). These recommendations are generally based on expert opinion rather than data-driven patient outcomes.

Our committee noted that existing guidelines are impractical for ICU patients for a number of reasons, including 1) the time frame of blood draws for both clinical and research purposes generally occurs over a 7- to 10-day period in ICU patients rather than a 30- or 60-day period; 2) an Hb of 7.0 g/dl is the generally accepted transfusion threshold in the ICU, and drawing blood at that level without additional clinical considerations might precipitate the need for a

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Table 1. NIH NHLBI PETAL Network–recommended Maximum Allowable Research Blood Draw Volumes for PETAL Subjects Coenrolled in Other Network-approved Critical Illness Studies

Body Weight (kg)	Body Weight (lb)	Estimated Total Circulating Blood Volume (ml) (1)	Recommended Maximal Research Blood Volume in a 24-h Period (ml)	Recommended Maximal Research Blood Volume in a 7-d Period (ml)	Recommended Minimum Hb (g/dl) Required at Time of Blood Draws in the Absence of Active Bleeding or Active Cardiac Ischemia*
31–35	68–77	2,480–2,800	50	110	≥7.5
36–40	79–88	2,880–3,200	60	130	≥7.5
41–45	90–99	3,280–3,600	70	150	≥7.5
46–50	101–110	3,680–4,000	80	170	≥7.5
51–55	112–121	4,080–4,400	90	190	≥7.5
56–60	123–132	4,480–4,800	100	210	≥7.5
61–67	134–143	4,880–5,200	110	230	≥7.5
>67	>143	5,280–5,600	120	250	≥7.5

Definition of abbreviation: PETAL=Prevention and Early Treatment of Acute Lung Injury.

These guidelines apply to the volumes collected in the first week of critical illness in studies approved by the PETAL Network for coenrollment for PETAL subjects and for centers in which the local IRB does not monitor blood volumes. PETAL Network and ancillary studies are monitored by the central IRB. *For Hb values in the 7–7.5 g/dl range, we recommend discussion among investigators at the site to consider prioritization of studies and then considering a lower volume threshold of 50 ml maximal research blood volume over a 24-hour period. These limits may not apply to certain types of critically ill patients, such as trauma patients or other patients with active bleeding or anemia enrolled in approved studies in this setting.

transfusion; 3) asking investigators or IRB committees to monitor total blood volumes that include both research as well as clinical blood draw volumes would prove difficult; and 4) the existing guidelines do not take into account ICU-specific issues, such as trauma and other patients with active bleeding enrolled in approved studies in this setting.

At the request of the Network's DSMB, we therefore developed guidelines for monitoring blood draw volumes in patients coenrolled in PETAL Network and other ongoing ICU studies. We first surveyed the 12 clinical participating centers in the PETAL Network and found that local IRBs at 8 of the centers (or participating hospitals) approve coenrollment of subjects in concurrent clinical trials, whereas only 3 centers had IRB-directed guidance for specific blood volume limits or Hb thresholds for drawing blood in place for subjects enrolled in PETAL studies. In general, monitoring blood volumes drawn from patients was the responsibility of the principle investigators directing the studies and was not monitored by the IRB.

Thus, based on the literature reviewing safety of blood draw volumes, we developed a recommended limit for total research blood volume drawn in a 24-hour and 1-week period for PETAL subjects (see Table 1). We focused our deliberations on this early time period given the frequency of critical illness trials targeting the early phases of the illness. A goal of the committee was to avoid blood transfusions that are purely the result of research blood draws. As an example of our proposed guideline, a limit of 120 ml of research blood taken from a 70-kg adult within a 24-hour period would still put them within the Canadian Medical Research Council's recommended maximum of 140–200 ml over that time frame if clinical sample blood volumes are included (which can average 40 ml/d for critically ill adults [5]). We recommended that the Hb be at least 7.5 g/dl, instead of 7.0 g/dl, in the absence of active bleeding or active cardiac ischemia to proceed with research draws, with additional contingencies as listed in Table 1. The Network required that investigators requesting

coenrollment with PETAL studies provide documentation of local IRB approval (if that site's IRB grants such permission) as well as approval from one of the requesting site principle investigators acknowledging awareness of the request and plans to monitor total blood volumes drawn from patients included in PETAL studies. If the local IRBs approve coenrollment and monitor blood draw volumes, then oversight of blood draw volumes for research purposes was deferred to the local IRBs. In addition, once our Pathogenesis Committee approves ancillary or coenrollment studies requesting additional blood collection from PETAL-enrolled subjects, final approval is also required from the Network Steering Committee and DSMB. In addition, approval by our central IRB is required for ancillary studies to proceed.

The PETAL Network has adopted this blood volume sampling policy, and approvals from the Network for ancillary or coenrollment studies that require additional blood draws are accompanied by a reminder that adherence to the policy is required. We acknowledge the significant complexities of monitoring blood draw volumes in critically ill patients, especially in large clinical centers with multiple ongoing studies in the ICU setting. However, given the lack of literature in this area, we write to share our experience in drafting and enacting a policy with the hope that this information can be of use to the broader community. In addition to the need for ongoing research studies in critically ill subjects, we anticipate a growing need for additional biospecimens to more comprehensively phenotype patients with the complex and heterogeneous syndromes encountered in the ICU (6), and appropriate monitoring to safeguard the health of an already compromised patient population will be increasingly important. We note that the Network will make research biospecimens collected from PETAL studies available to the general community, and we encourage that current and future studies using these specimens be performed by using the lowest volumes possible to conserve this valuable resource to maximize the possibility of unforeseen future science while maintaining the safety of our patients. ■

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Mild to Moderate Sleep Apnea Is Linked to Hypoxia-induced Motor Recovery after Spinal Cord Injury

To the Editor:

Acute intermittent hypoxia (AIH) is a novel treatment to enhance respiratory and nonrespiratory motor function after chronic incomplete spinal cord injury (SCI) (1–3). Despite promising findings, uncertainties in optimal AIH delivery to a heterogeneous population of persons with SCI remain a challenge to clinical translation. Beneficial AIH responses are variable between individuals, and we lack useful biomarkers to determine which individuals benefit most from treatment. AIH-induced functional benefits rely on mechanisms of AIH-induced neuroplasticity. Multiple factors modify AIH-induced plasticity in rodent models, including intermittent hypoxia preconditioning and systemic inflammation, among others (4, 5). One factor not accounted for in human AIH trials, to date, is the incidence of sleep-disordered breathing (SDB). Many individuals with SCI exhibit mild to moderate SDB (6), leading to extended periods of nocturnal high-dose intermittent hypoxia. Because chronic intermittent hypoxia (CIH) elicits both neuroplasticity and inflammation (5), SDB after SCI may contribute to between-person variations in response to AIH therapy.

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