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Insights into Critical Care and Post-ICU Opiate Administration

Opiate prescriptions skyrocketed over the last three decades and were followed by overdoses and deaths, which exceeded the mortality rate of motor vehicle accidents in the United States (1). In this context, Wunsch and colleagues in this issue of the *Journal* (pp. 568–575) examined whether adult ICU patients, whose ICU opiate prescriptions are estimated at 80%, continue receiving opiates after hospital discharge (2). The databases supporting their analysis describe a population in Ontario, Canada. This province accounts for 44% of Canadian opiate consumption in a country that ranks second worldwide in narcotic *per capita* prescription rates. In Ontario, 25% of opiate prescriptions fuel illicit use (3).

The investigators identified opiate prescriptions between 2013 and 2015 at 7 days, and 1 year after hospital discharge in opiate-naive adult ICU survivors who had been invasively mechanically ventilated and matched non-ICU patients. Prior substance use disorders and/or mental illnesses were identified through diagnostic codes. Logistical regression and odds ratio analyses also incorporated comorbidity, demographics, and receipt of at least one benzodiazepine prescription in the year preceding ICU admission.

Opioids were prescribed to 20% of ICU survivors at 7 days and to 2.4% of survivors 1 year after hospital discharge more often in surgical patients than medical patients (33% vs. 7.6% at 7 d and 4.1% vs. 1.6% at 1 yr). Interestingly, 21 patients received methadone or buprenorphine in the year after ICU admission. ICU survivors' opioid prescriptions rates were lower at 7 days (20% vs. 34%) and slightly higher at 1 year (2.6%) than those of non-ICU patients (1.5%).

The authors conclude an "analgesia-first" approach to ICU sedation does not result in high rates of subsequent long-term opioid use. Their findings echo preliminary results from a U.S. medical unit reporting 7% ICU survivors with opiate prescriptions at hospital discharge (4) and contrast with ICU survivors with traumatic brain injuries, in whom opiate prescriptions were 41% at 1 month and 21% at 12 months after ICU (5).

Thus, prescribing opiates to most ICU patients does not seem to lead to a high likelihood of long-term use. Beyond this, three aspects of the opiate administration described in the critically ill patients in this study warrant reflection.

The authors recognize the limitation of not having pain measurements, opioid doses, or the ability to determine opiate administration appropriateness during ICU care and hospitalization in these 25,085 opiate-naive ICU survivors, focusing instead on the postdischarge period. An analgesia-first approach in the ICU infers the documentation of pain and its resolution. In British Columbia, most ICUs enter pain, as well as sedation and delirium assessment data, into the British Columbia Patient Safety and Quality Council's critical care database (3). Such "granular" pain assessments, if compared with ICU opiate administration, may better identify not only appropriate opiate use but also drivers for subsequent long-term opiate exposure.

Effective pain management is a major preoccupation for ICU patients and their families (6). Recognizing pain, differentiating it from other symptoms, and administering effective analgesia remain significant challenges in critically ill patients (6). Pain assessments and opiate prescribing vary enormously and are greatly influenced by belief, bias, staffing ratios, and local culture (7). ICU physicians perform pain assessments in under 40%

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of patients receiving opiate infusions that they prescribe and do so inadequately (8). Nevertheless, over 85% of mechanically ventilated critically ill adult patients receive narcotics, perhaps because of the widely held belief they are effective analgesics, safe ICU sedatives, or both.

Data or observations to document who should receive opioids, and how useful or safe they are (7), in critically ill adults are scarce. Administration duration influences pharmacological effects; similar doses of morphine are half as effective analgesics after as few as 24 hours (9). Opiate tolerance occurs most predictably in circumstances that reflect practices in ICUs such as continuous exposure to high-dose high-potency opioids (9). Biological opiate dependence is established after one week. After the mean of 6 ICU days described in this study, pain-associated discomfort may be indistinguishable from opiate withdrawal symptoms. Regrettably, no opiate withdrawal scale is validated for critically ill adults (10).

Pediatric ICU studies provide richer data on effective analgesia and opiate administration. An elegant randomized controlled trial in neonates and infants undergoing major noncardiac surgery suggests paracetamol and morphine are equipotent as first-line analgesics (11). Nonsteroidal anti-inflammatories, a second-line pediatric ICU analgesic choice (12), palliate pain and reduce opiate exposure. Both pharmacological variability and the long-term impact of ICU opiate administration in pediatric ICUs, including longitudinal effects on school performance, have been studied (13). Finally, in contrast to the adult world, withdrawal screening is routinely implemented in pediatric ICUs.

Beyond the ICU, pain assessments during hospitalization and after discharge are the second unexplored aspect of the long-term opiate administration question. Poor pain control during admission and subsequent chronic pain are the best predictors of opiate prescribing in the hospital and beyond. Opiate-dependence determinants (habitual use at any time of regular benzodiazepines, nicotine, alcohol, and cannabis) (14) may identify high-risk groups. Interest in long-term post-ICU outcomes has risen; researchers and providers now understand the burden and cost of post–intensive care syndrome (15). Whether chronic pain and opiate exposure, both manageable conditions, correlate with post–intensive care syndrome remains unexplored.

Finally, the authors suggest preferring opiates for sedation may be warranted because of the purported harms associated with propofol and benzodiazepine administration, a belief that contrasts with the dearth of sedative studies incorporating drug-level sampling. The pharmacodynamic and pharmacokinetic differences among individual ICU patients and the characteristics of various sedatives are complex. Moreover, many biases and emotional convictions drive sedation practice. In addition, sedation level confounds delirium screening. Although sedatives are studied more extensively than analgesics in critically ill patients, how necessary they are in the majority of ICU patients and the harm when they are given are not well established. Using opiates as sedatives ("analgosedation") has imprecise and overlapping definitions in recent guidelines (6) and remains unsupported by convincing data.

Instituting granular practice evaluations, incorporating accurate pain assessments, prompting opiate adjustment to symptoms, and lowering their administration when analgesia is adequate may be of interest in the ICU and beyond. E-prescribing has been proposed as a solution to track overall hospital-discharge opiate prescriptions and inform prescribers (16).

At the end of the day, our limited understanding of how to provide effective ICU analgesia and the harm of exposing patients to opiates, leading to opiate habituation or misuse, remains a physician-driven problem. The 2.4% of ICU admissions with ongoing prescribed opioids after 12 months may seem like a small number; however, these long-term opioid users may be burdened by ongoing unresolved pain, undetected addiction, and the stigma associated with the long-term opiate prescriptions provided by their physicians (17). Beyond the dimensions of functionality and dignity, managing complex chronic pain or opiate-consuming patients is cost-effective. The healthcare resource use in this cumulative group should drive adaptations to better manage physician-driven opiate use and misuse. ■

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Transforming Diagnostics in Lung Transplantation: From Bronchoscopy to an Artificial Intelligence–driven Approach

Transbronchial biopsies to obtain lung tissue specimens remain the gold standard to identify acute lung allograft rejection. However, bronchoscopic biopsy practices, including biopsy schedule, frequency, follow-up after abnormal results or results suggesting rejection, and the role and composition of a biopsy review panel, differ between transplant centers (1). Because of this heterogeneity, there have been few studies for at least a decade analyzing posttransplant biopsy data collected prospectively from multiple centers. A study by Todd and colleagues (pp. 576–585) published in this issue of the *Journal* is a welcome exception (2).

In this multicenter study, Todd and colleagues present a careful and extensive analysis of 2,026 lung biopsies obtained during surveillance (83.4%) and for-cause (16.6%) transbronchial biopsies from 400 lung transplant recipients to determine the incidence and severity of acute rejection within the first year after transplant with a focus on identifying potential risk factors for acute rejection. Results were obtained from five high-volume transplant centers in North America that used nonidentical but congruous biopsy schedules, which increases the priority of this study. Todd and colleagues report an incidence of acute rejection of 53.3%, with the majority of patients experiencing mild A1 rejection. High-level HLA mismatch between donor and recipient was associated with an increased risk for acute rejection. Double lung transplantation and the use of induction immunosuppression were associated with a decreased risk for acute rejection during the first year after transplantation. When Todd and colleagues normalized for number of biopsies performed during the first year after transplant and analyzed time-independent variables associated with acute rejection, they found that patients with double lung transplantation and patients with fewer than four HLA mismatches continued to have a decreased risk for acute rejection (2).

These results are consistent with previous findings, highly reproducible, and clinically useful based on the solid study design with prospective data collection from multiple centers. However, surveillance transbronchial biopsy has inherent limitations. It is invasive and costly, is subject to sampling errors, and is not capable of anticipating alloimmune events (3). Therefore, new diagnostic venues that can be combined with available pathological data should be explored.

An evolving body of recent evidence consistently supports that antibody-mediated rejection is an important contributor to acute and chronic lung allograft rejection after lung transplantation and that $Foxp3^+$ regulatory $CD4^+$ (cluster of differentiation 4–positive) T lymphocytes play a central role in recovery from acute injuries in lung allografts regardless of the cause of the injuries (4, 5). Indeed, since their discovery in 1995, regulatory T cells have been characterized as master regulatory cells with simultaneous, multidirectional functions in immune tolerance that are involved in both innate and adaptive immunity (6–8). These findings should be duly translated into clinical practice in a "bench-to-bedside manner" for assessment of regulatory T-cell function along with the routine tests currently utilized throughout the lung transplant process, including transbronchial biopsies.

Our increased understanding of the underlying immunology along with evolving analytic technologies provide the basis for new surveillance approaches with the aim of better predicting immune-mediated allograft damage that will determine whether the patient will suffer chronic lung allograft dysfunction (CLAD) or be free of CLAD. For instance, noninvasive biomarkers, including regulatory T cells circulating in the blood (9) and immune-cell–based assays that replicate antidonor alloimmune responses *ex vivo* (10), have recently been described and are associated with short-term and long-term transplant outcomes. The evaluation of key cellular events and signaling pathways underlying detectable posttransplant immunologic processes will help to more accurately quantify lung injuries associated with acute rejection in lung allografts. This includes evaluation of acute rejection with biomarkers identified with the evolving "-omics" technologies, including direct genome sequencing, genomics, transcriptomics, proteomics, and metabolomic analyses. Most notably, molecular measurement of gene expression using machine-learning–based microarray analysis has been developed over the last 3 years to overcome the limitations of conventional diagnostics used after abdominal organ transplantation (11, 12).

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