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SPECIAL FEATURE

## The Opioid Crisis in the ICU

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**Dr. Chen reports no financial relationships relevant to this field of study.**

She started using opioids as a teenager after a painful sports injury. She had been traveling, working, and using heroin, but had recently returned to her family's home at age 21. She was hoping to stay clean, with plans to look for a job and go back to school. She had created a series of inspiration boards to help her focus. After going out with friends one evening, she injected heroin again. After she vomited and remained unresponsive, her friends called 911. She was resuscitated and brought to a local ED, then transferred to our tertiary care ICU. Over the next several days, despite maximal medical measures, she progressed to brain death.

He was 67 years old, living in a senior building. He presented with sepsis from a decubitus ulcer that had progressed to osteomyelitis. He had been addicted to heroin for decades, continuing to use it to numb the pain from his wound and escape the difficulties of his life. He required debridement for his infection and high doses of opioid medications to control his pain. He reported that he did not anticipate abstaining from heroin after he was discharged. Every critical care clinician has cared for patients with complications related to opioid use. The spectrum of conditions is broad. There are the heartbreaking overdose cases such as described above. There are patients who have survived many years of opioid use, misuse, and abuse, who may or may not have overcome their addiction, and who now live with complications of prior drug ingestion, inhalation, or injection. The long list includes complicating conditions such as COPD, chronic hypercapnia, dyspnea, debilitating joint pain, chronic kidney disease, hepatitis C and chronic liver disease, HIV infection, local site infections, and systemic infections such as endocarditis, malnutrition, and pressure ulcers.

### WHAT ARE OPIOIDS?

Opioids are medications that attach to and activate opioid receptor proteins. In the brain and spinal cord, they can reduce the intensity of pain signal perception, affect areas that control emotion,

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and activate reward regions that cause euphoria. Centrally, opioids also can induce respiratory depression, cough suppression, drowsiness, and confusion. Peripherally, opioids can affect receptors in the gastrointestinal tract, slow motility, and lead to nausea and constipation.[1]

Opium, cultivated from poppy seeds, has been described since ancient times. It has been used for relieving grief, for healing the sick, as a euphoriant in religious rituals, and for preventing excessive crying of children. Its use and abuse have been described in many cultures spanning several centuries. Morphine first was isolated in 1806 and began to be used for perioperative pain in the 1850s. Because opium and morphine were found to have significant abuse potential, efforts to develop a safer opioid led to the development of heroin, a semi-synthetic opioid, in 1898. Heroin was touted as a more potent and less addictive opiate than morphine, but its addictive potential soon was realized. Meperidine, an opioid with a structure different from morphine, first was synthesized in 1939 but is less commonly used today because of its side effect profile. Methadone, also structurally unrelated but with some similar pharmacologic properties, was synthesized first in 1946 and remains frequently prescribed for management of both pain and addiction.[2] More recently, opioid use began to increase rapidly in the 1990s when pharmaceutical companies marketed new formulations of prescription opioids as safe and effective analgesia without addiction potential. Over the subsequent two decades, diversion and misuse have increased as people realized that these medications are addictive.[3]

Opioids can be classified into prescription or nonprescription (illegal) forms, enteral or parenteral, or full or partial agonists. Prescription opioids include immediate-release and extended-release oral formulations, as well as transmucosal and transdermal fentanyl formulations. Opioids can be combined with nonopioid analgesics for synergistic effect. Occasionally, opioids can be combined with nonabsorbable opioid antagonists to deter abuse. Commonly prescribed enteral formulations include codeine cough syrups, hydrocodone combination analgesics, tramadol, morphine, oxycodone, and hydromorphone. Commonly available parenteral forms include morphine, fentanyl, and hydromorphone. Sufentanil and remifentanil are ultra fast-acting fentanyl analogues used more frequently for anesthesia purposes. Buprenorphine is a weak partial opioid agonist used for both chronic pain management and treatment of addiction.[1]

For many years, heroin has been the most commonly abused illicit opioid. Today, because of its high potentcy, fentanyl often is used to adulterate heroin and other street opioids.[4] Desomorphine, commonly known as krokodil, is cooked by combining codeine with household acid (which can include hydrochloric acid, gasoline, and paint thinner) similarly to methamphetamine. Developed in Russia, krokodil was created as a cheaper and more available alternative to heroin, so named because of the skin necrosis that develops at injection sites.[5]

## THE OPIOID CRISIS IN THE UNITED STATES

The White House has declared the opioid crisis a public health emergency. A national commission and a panel of state governors have issued recommendations for action. According to the CDC, more than 115 people die per day of opioid overdose in the United States. More than 350,000 people died from an overdose related to any opioid from 1999-2016.[3] Prescription opioid misuse is estimated to cost the United States $78.5 billion per year. In 2015, it was estimated that 2 million people suffer from prescription opioid misuse disorders, and 591,000 suffer from heroin use disorder.[6] In other reports, in 2016, more than 11 million Americans misused prescription opioids. Opioid overdose-related deaths have skyrocketed, tripling between 2002 and 2015, and more than quadrupling since 1999.[3,7]

Despite the rapid increases in overdoses and deaths, Americans may not recognize the severity of the crisis. Blendon et al compiled data from seven national polls conducted in 2016 and 2017. They found that Americans consider opioids a "second-tier" priority for the government, sixth on a 15-item priority list, and place most of the blame on prescribers (33%)

and those who sell prescription painkillers illegally (28%).[8] The public is uncertain about the effectiveness of treatment for opioid use disorder and ambivalent about whether it should be covered by insurance. However, most of those surveyed believe that anyone who is found to possess prescription opioids without a prescription should be treated rather than incarcerated. Even physicians and clinicians may not clearly understand the scope and details of the opioid crisis, thus highlighting the need for education.

The language sometimes can be confusing, with some reports using the term "opioid-related" to refer to prescription drugs, while other reports use the term to refer to prescription opioids, heroin, and other illicits. Drug dependence occurs when constant exposure to a drug leads to changes in the body. Rapid cessation or removal of the drug can lead to physiologic withdrawal symptoms. Misuse refers to any use of a prescription drug differently than it is prescribed or intended (e.g., using another person's medication or using a medication for a different reason, at a different dose, or more often than it was prescribed). Abuse refers to use of a drug to experience feelings associated with the drug, such as euphoria or relaxation. Addiction is considered a more serious condition. Now reclassified as a "drug use disorder," addiction is when ongoing drug use leads to changes in the brain and body. An individual compulsively seeks and uses drugs despite significant negative health and social consequences.[1,2]

Opioid use patterns have seen some shifts over time, but ongoing increase in use remains consistent. Over the past 50 years, the demographics of heroin use has changed substantially. This shift from an inner-city minority population to an affluent white suburban and rural population, attributed to the increase in availability of prescription opioids, has been reported frequently in mainstream media and corroborated by research. A mixed-methods retrospective data analysis study using surveys and statistics from substance use treatment programs showed that people who began using heroin in the 1960s were primarily young men (83% male; mean age, 16.5 years) whose first opioid of abuse was heroin (80%), with equal numbers of whites and non-whites. However, of those who began use in the 2000s, nearly 90% were white, with equal numbers of men and women (mean age, 22.9 years), and 75% of them were introduced to opioids through prescription drugs.[9]

From 2002-2010, opioid prescriptions increased substantially, then decreased from 2011-2013. Hypotheses for potential causes for this decrease include formulation changes in extended-release drugs, which decreased their desirability for abuse and injection, as well as improved programs for increasing the safety of opioid prescribing. When prescriptions decreased, abuse and diversion followed an associated decrease. However, there was a coincident increase in abuse (and overdose) of heroin in the United States.[10] These findings suggest that as prescription opioid use has waned, there have been significant increases in the numbers of people who concurrently abuse heroin with prescription opioids. In a qualitative online survey, of 126 respondents who reported abusing prescription opioids prior to heroin use, 73% primarily cited practical factors, such as accessibility and cost, when explaining their transition to heroin.[11]

One recent report by Jones et al described the recent significant rise in synthetic opioid involvement in the opioid crisis. This is primarily illicit fentanyl, which is found mixed with other illicit drug supplies frequently. In 2016, there were 42,249 opioid-related overdose deaths. Of those, 19,413 involved synthetic opioids, 17,087 involved prescription opioids, and 15,469 involved heroin. Synthetic opioid involvement in these deaths increased significantly from 14% in 2010 to 46% in 2016 ($P$ for trend < 0.01), and now it is the most common drug involved. Among synthetic opioid-related overdose deaths in 2016, 80% involved alcohol or another drug, most commonly another opioid or heroin. Because illicit synthetic opioid potency, variability, adulteration, and availability is poorly understood, and users often are unaware, its use poses significant risks to individuals and the public.[12]

## CRITICAL CARE COMPLEXITIES IN THE OPIOID EPIDEMIC

Given the breadth of clinical presentations, the total effect of the opioid crisis on the ICU is complex and not well-characterized. To better understand the effect of overdoses on ICUs, Stevens et al used a large national database of hospital admissions to study the epidemiology of opioid overdose admissions to ICUs.[13] Administrative data from 2009-2015 showed a near doubling in monthly opioid overdose deaths in the ICU over that period. Throughout that time, there were 21,705 overdose admissions to the ICU, with an average of 52.4 overdoses per 10,000 ICU admissions. Overdose admissions increased steadily at an average rate of 0.6% per month, with more admissions in summer months. Overall mortality increased during this period from 7.3% to 9.8%. Months with higher heroin overdose admissions were associated with higher mortality compared to months with higher prescription opioid overdose admissions. Additionally, admitted patients received significantly more intensive care in 2015 compared to 2009. This study was the first to describe the immense effect of the opioid crisis on the critical care community, showing significantly increased critical care use due to increasing opioid overdoses. The authors proposed that most, if not all, opioid overdose admissions to the ICU are preventable with upstream interventions and called for expanded primary prevention strategies and frontline responders.

Opioid intoxication and withdrawal also are important considerations in the ICU. It is vital to screen all confused, injured, or otherwise high-risk critical care patients with urine toxicology at the time of admission to assess for possible intoxication or withdrawal syndromes. While opioid withdrawal does not include the potential life-threatening complications of alcohol withdrawal syndrome, the withdrawal symptoms of diarrhea, vomiting, insomnia, muscle and joint pain, thermoregulation disturbances, tachycardia, and hypertension can affect management significantly. It is important to remember that opioid withdrawal symptoms can occur in patients maintained on opioids for the treatment of chronic pain. In patients with opioid dependence and tolerance, it may be difficult to achieve adequate analgesia and sedation. Medications such as methadone, buprenorphine, and alpha-agonists may be considered in the ICU for management of opioid dependence. However, treatment of the opioid use disorder and addiction may be better reserved for starting after the critical illness has resolved. Treatment of acute pain in patients maintained on buprenorphine may be especially challenging. Buprenorphine, with its partial agonist properties, has a very high affinity for mu-opioid receptors, rendering opioid analgesia less effective.[14]

As intensivists, it is our role to treat and support our patients who have been affected by opioids the best we can. This means best practice ICU care for all, managing pain and symptoms with possibly higher-than-expected doses of opioids. Consultative assistance of addiction support teams should be sought prior to transfer out of the ICU, if possible. For overdose survivors, the ICU stay may be a good time to engage their families and communities with future abstinence efforts.[7] Prescription of intranasal naloxone to those with opioid use disorder (so that first responders may have an option for treatment) has been increasing.[1] This has been shown to reduce death rates; paradoxically, this increase in naloxone use may be leading to increased ICU admissions, given that those overdoses now are surviving to hospitalization.[7] Advocacy, education, addiction treatment programs, and mental health services are important components in fighting the opioid crisis. The opioid crisis is complex, multidimensional, and must be approached not only at an individual, family, and community level, but also through healthcare institutions and public policy. ■

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ABSTRACT & COMMENTARY

# ECMO vs. Optimal Protective Ventilation and Ancillary Therapies in Severe ARDS


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**Mr. Kallet reports he is a major stockholder in the the Asthma & Allergy Prevention Company, is a consultant for Getinge Group, and receives grant/research support from Nihon-Kohden.**



SYNOPSIS: Treatment of very severe acute respiratory distress syndrome with venovenous extracorporeal membrane oxygenation vs. lung-protective ventilation with aggressive ancillary therapy use demonstrated only a trend toward improved 60-day mortality.


SOURCE: Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med* 2018;378:1965-1975.

The authors of this international, multicenter, prospective, randomized, controlled trial enrolled 249 subjects with very severe acute respiratory distress syndrome (ARDS) to receive either venovenous extracorporeal membrane oxygenation (ECMO) with lung-protective ventilation (LPV) or LPV using a higher positive end-expiratory pressure (PEEP) strategy. Both treatment arms apparently continued at least some ancillary therapies. Between intubation and randomization, approximately the same percentage of subjects received prone position, inhaled vasodilators, recruitment maneuvers, and neuromuscular blockade.

At randomization, there were no differences between treatments arms regarding time from intubation to randomization, pulmonary mechanics, ventilator settings, gas exchange, age, gender, ARDS etiology, presence of nonpulmonary organ dysfunction, or compromised immune status. Enrollment criteria included ARDS duration more than seven days and the presence of either profound hypoxemia or respiratory acidosis persisting for more than three to six hours (depending on severity). The authors of this trial used similar exclusion criteria as other large ARDS randomized, controlled trials.

Subjects in the ECMO arm were cannulated at 3.3 ± 2.8 hours of randomization, with an average therapeutic duration of 15 ± 13 days. Those managed in the LPV control arm continued to receive a low tidal volume ($V_T$) and higher PEEP strategy with encouragement to continue ancillary therapies. LPV goals were well-maintained in both treatment arms. However, those in the ECMO arm achieved a greater reduction in mean $V_T$ (< 300 mL), plateau pressure (< 25 cm $H_2O$), and driving pressure (< 14 cm $H_2O$) over the first seven study days.

The intention-to-treat design resulted in an extraordinarily high crossover (28%) to ECMO therapy, occurring at 6.5 ± 9.7 days. Sixty-day mortality in crossover subjects was 57% compared to 41% in those not failing LPV. Overall, subjects in the ECMO arm exhibited a lower-trend 60-day mortality compared to controls (35% vs. 46%; $P = 0.09$), which was not statistically significant. The ECMO arm subjects also experienced significantly more days without requiring either prone positioning or renal replacement therapy. However, subjects in the ECMO arm demonstrated significantly higher incidences of bleeding requiring transfusion as well as thrombocytopenia.

## ■ COMMENTARY

What was vexing about this trial was its early termination (at the third interim analysis for crossing futility criteria) despite a clearly positive outcome trajectory. This represents one of several nettlesome issues with conducting a randomized, controlled trial in a particularly challenging study cohort. These issues were discussed elegantly in the accompanying editorials.[1,2] Other problems included the high crossover and particularly slow enrollment rate (more than six years). The study was very well-designed and executed. Ethical considerations obviously and rightly dictated the need for crossover, which occurred at an appropriate juncture when acute cardiovascular failure became evident. The slow enrollment signified the earnest effort of investigators to test ECMO in precisely the appropriate patient population for whom this expensive and extraordinarily invasive therapy is indicated.

Notwithstanding the advances in medical science associated with evidenced-based medicine, it remains a human endeavor burdened with biases. Some of the most recent "negative" results in ARDS randomized, controlled trials have been dismissed outright by advocates, while simultaneously embraced by those inimical to a particular therapy (despite nuances in study design or execution that might preclude unequivocal acceptance). Thus, the initial hope that high-level evidence from large multicenter, randomized, controlled trials would engender a medical "Age of Reason" appears unfulfilled. Thus, a claim that this trial was underpowered downplays the fact that medical ethics dictates *a priori* boundaries, balancing competing needs to stop a trial early either for efficacy or to prevent unnecessary exposure to therapies carrying substantial risks. Moreover, the tacit assumption that strong statistical trends inevitably would result in efficacy "if only" more subjects were enrolled to increase study power represents perilous reasoning. It is plausible that with continued enrollment, the trend actually might reverse. One large randomized, controlled trial of which I am aware indicated clear therapeutic efficacy at the first interim analysis, which evaporated at the second interim analysis, only to reappear and cross efficacy boundaries at the third. Thus, trends and their magnitude can be deceiving. Further, the enrollment of approximately 42 subjects annually in more than 60 participating institutions raises ethical issues about expending limited economic and personnel resources on a therapy that, in a broader societal context, could be allocated for research that might benefit a more patients. It is improbable that ECMO will be abandoned in severe ARDS based on these results. The positive trend in mortality makes it reasonable to pursue ECMO as rescue therapy. Moreover, this trial reaffirmed the importance of minimizing parenchymal strain-stress, particularly in severe ARDS. ECMO's ability to enhance carbon dioxide ($CO_2$) excretion allowed a mean $V_T$ reduction that likely was ≤ 4 mL/kg and that also corresponded to plateau and driving pressures previously associated with improved outcomes. In this context, recent advances allowing extracorporeal $CO_2$ removal during renal replacement therapy[3] introduces the possibility to further reduce lung injury in severe ARDS in cases complicated by multiple organ dysfunction syndrome without further escalating the intensity of invasive therapy. ■


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## ABSTRACT & COMMENTARY

# Negative Fluid Balance on Day 3 Associated With Improved Outcomes in Critical Illness


***By Samuel Nadler, MD, PhD***

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**Dr. Nadler reports no financial relationships relevant to this field of study.**


SYNOPSIS: In critically ill patients, a negative fluid balance on day 3 either spontaneously or with deresuscitative measures may be associated with lower mortality.


SOURCE: Silversides JA, Fitzgerald E, Manickavasagam US, et al. Deresuscitation of patients with iatrogenic fluid overload is associated with reduced mortality in critical illness. *Crit Care Med* 2018 Jul 5. doi: 10.1097/CCM.0000000000003276. [Epub ahead of print].

Fluid administration to critically ill patients to ensure organ perfusion is widespread and supported by multiple guidelines. However, the ideal regimen, including which fluids and the duration of fluid administration, remains unclear. Excess fluid therapy is associated with pulmonary edema, renal congestion, and other negative physiologic effects. After the need for fluid administration has resolved, the question arises whether deresuscitative efforts such as diuresis or dialysis would be beneficial. The Role of Active Deresuscitation After Resuscitation (RADAR) investigators published a retrospective cohort study of 400 patients ≥ 16 years of age receiving mechanical ventilation for at least 24 hours and examined fluid balance. Exclusion criteria included drug overdose, subarachnoid hemorrhage, diabetic ketoacidosis, and other conditions for which specific fluid management is critical to management. Patients not expected to survive more than 24 hours and ICU transfers also were excluded. Demographic features were collected, and the primary outcome was 30-day mortality. Secondary outcomes included

ICU length of stay and duration of mechanical ventilation.

In this cohort, the overall 30-day mortality was 31%, with a median ICU length of stay of seven days. Overall, survivors demonstrated smaller positive fluid balance over the first week, with a maximum difference in means of 0.98 L on day 3 and 2.38 L overall. Within the first three days, 34.5% of fluid was due to medications compared to 26.5% due to maintenance fluids and 24.4% from bolus fluids. In univariate logistic regressions, fluid balance on day 3 was associated independently with 30-day mortality, with an odds ratio (OR) of 1.32 (95% confidence interval [CI], 1.17-1.5 per liter).

This association remained significant in multivariate logistic regression. A similar inverse association was observed between positive fluid balance and organ dysfunction scores, ICU length of stay, and duration of mechanical ventilation.

## ■ COMMENTARY

This study highlights the evolving notion that intravenous fluids are an intervention. Like many medications, these fluids require appropriate dosing and formulation to ensure benefit. The study also highlights the limitations of retrospective cohort studies. Compared with nonsurvivors in this cohort, 30-day survivors were younger (60 vs. 69 years of age; $P < 0.01$), were more likely to be surgical admissions (33.7% vs. 58.7%), had lower APACHE-II scores (16.8 vs. 22.4; $P = 0.01$), and had less severe disease overall.

In the multivariate regression model, spontaneous negative fluid balance was associated with decreased mortality (OR, 0.21; 95% CI, 0.08-0.56; $P < 0.01$), but this effect size was similar to surgery as the admission type (OR, 0.22; 95% CI, 0.09-0.53; $P < 0.01$). The OR for 30-day mortality in patients who achieved negative fluid balance with deresuscitative measures was 0.29 (95% CI, 0.12-0.69; $P < 0.01$). Those individuals in whom negative fluid balance was not achieved despite deresuscitative efforts had the highest crude mortality. Thus, patient factors may play a greater role than diuretics or dialysis.

The source of fluid input in this study deserves attention. The largest single input was medications. Over the first three days, the average fluid balance was 3,325 mL. Although volume of medications represented 34.5% of the input, overall, 50.9% represented maintenance and bolus intravenous fluids. Much of the positive fluid balance was "maintenance" fluid that often is started on admission without careful consideration of duration and dose. Furthermore, there was wide practice variation between sites in this study. Median fluid bolus volumes by site ranged from 0.75 L to 3.5 L, while median maintenance fluids ranged from 0 L to 5.77 L.

This study demonstrates the significant practice variability in fluid administration in critically ill patients and the opportunity for practice improvement. It adds to previous studies, such as the FACTT trial, that showed conservative fluid management decreased duration of mechanical ventilation and ICU length of stay.[1] A recent meta-analysis of conservative fluid management and deresuscitation in sepsis and ARDS also demonstrated decreased ventilator days and ICU length of stay but no change in mortality.[2] Although the current trial found negative fluid balance was associated with decreased mortality, the retrospective nature of the study, along with previous larger negative trials, raises doubt about a causal relationship. ■

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## CME/CE QUESTIONS

**1. The opioid crisis has affected intensive care in which of the following ways?**

a. Prescription opioid overdose admissions to the ICU are more common in winter months, and heroin overdose admissions are more common in summer months.
b. With increased naloxone available to first responders, opioid overdose mortality is improving.
c. With improved critical care in the past decade, mortality due to heroin overdose has decreased.
d. With decreased opioid prescriptions nationwide in the past few years, prescription opioid overdose admissions to the ICU have decreased.

**2. Which of the following is *true* of the opioid crisis?**

a. Over the past 50 years, heroin users have shifted from primarily younger urban males to primarily white suburban and rural females.
b. Decreasing opioid prescriptions has led to a decrease in abuse and overdose of heroin.
c. Those who switch from abusing prescription opioids to heroin cite practical factors, such as accessibility and cost, as the primary reasons for their transition.
d. Synthetic opioids such as fentanyl increasingly are involved in opioid overdose deaths, most commonly in combination with a benzodiazepine.

**3. Which of the following statements is *false* regarding the Combes et al trial?**

a. It took six years to enroll 249 subjects.
b. Only 8% of the control arm crossed over to the ECMO arm.
c. The control arm used a low tidal volume and higher PEEP strategy.
d. Prone positioning and other ancillary therapies were encouraged.

**4. The RADAR investigators' study of fluid balance in critically ill patients demonstrated which of the following?**

a. Negative fluid balance at day 3 was linked causally to decreased mortality.
b. Negative fluid balance at day 3 was associated with decreased mortality in a multivariate logistic regression analysis.
c. There was no change in mortality with changes in fluid balance.
d. There was an increased ICU length of stay with negative fluid balance.

**5. In the RADAR investigators' study, the decrease in mortality and negative fluid balance was associated with:**

a. negative fluid balance on day 3.
b. surgical rather than medical admissions.
c. lower severity of illness scores.
d. All of the above

## CME/CE OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- identify relevant topics in the practice of critical care medicine;
- utilize recommendations from current clinical guidelines; and
- manage common critically ill patient and ICU administration scenarios.