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Strategies to Optimize ICU Liberation (A to F) Bundle Performance in Critically Ill Adults With Coronavirus Disease 2019

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Objectives: The severe acute respiratory syndrome coronavirus 2 pandemic has stretched ICU resources in an unprecedented fashion and outstripped personal protective equipment supplies. The combination of a novel disease, resource limitations, and risks to medical personnel health have created new barriers to implementing the ICU Liberation (“A” for Assessment, Prevention, and Manage pain; “B” for Both Spontaneous Awakening Trials and Spontaneous Breathing Trials; “C” for Choice of Analgesia and Sedation; “D” for Delirium Assess, Prevent, and Manage; “E” for Early Mobility and Exercise; and “F” for Family Engagement and Empowerment (ABCDEF)) Bundle, a proven ICU care approach that reduces delirium, shortens mechanical ventilation duration, prevents post-ICU syndrome, and reduces healthcare costs. This narrative review acknowledges barriers and offers strategies to optimize Bundle performance in coronavirus disease 2019 patients requiring mechanical ventilation.

Data Sources, Study Selection, and Data Extraction: The most relevant literature, media reports, and author experiences were assessed for inclusion in this narrative review including PubMed, national newspapers, and critical care/pharmacology textbooks.

Key Words: ABCDEF bundle; agitation; ARDS; coronavirus disease 2019; delirium; intensive care

During the current severe acute respiratory syndrome coronavirus 2 pandemic, up to 5% of patients with coronavirus disease 2019 (COVID-19) will develop acute respiratory failure. Among patients needing ICU-level care, nearly 90% require intubation and mechanical ventilation, often for a prolonged period...
Solutions to Overcome Potential Global Barriers to Bundle Delivery

Barriers to Bundle delivery in mechanically ventilated adults with COVID-19 can be stratified by those affecting application of the bundle as whole (i.e., global barriers) and those primarily affecting delivery of individual bundle elements. Barriers to Bundle use, and the solutions to overcome them, are influenced by the degree to which the Bundle was implemented prior to the pandemic and the number of COVID-19 ICU admissions at any one time relative to institutional ICU capacity and staffing. This section of the paper highlights global barriers to Bundle use and practical solutions to overcome them.

Alterations in Critical Care Hierarchy and Care Priorities

Prior to the pandemic, Bundle implementation was a major focus of ICU critical care quality improvement at many hospitals (11, 23). Clinicians should remind themselves of the strong evidence behind the Bundle and take the opportunity to ensure the entire IPT refreshes their knowledge surrounding it. In the current crisis, where ICU beds and ventilator resources may be limited, the Bundle would seem to be tailor made to reduce duration of mechanical ventilation and shorten the ICU stay. However, the Bundle requires substantial clinician resources and time that many institutions often struggled to provide even before the pandemic (23, 24). Although ICU delirium assessment/reduction and rehabilitation/mobility are no less important than pain and sedation in optimizing ICU liberation and survivorship, it is realistic to assume these two former Bundle elements may be especially difficult to apply fully, particularly at centers experiencing a surge in COVID-19 admissions. Restrictions on visitation, even to dying patients, has substantially reduced the role of family as part of the ICU care team (30).

The importance of the intensivist-led IPT, in both academic and community hospitals, and its importance in facilitating Bundle completion, is well-established (25, 26). However, daily IPT rounds and interactions have been forced to change. The need to adopt social distancing and increased workload demands have pushed interprofessional team (IPT) rounds and collaboration from the ideal that promotes Bundle performance (25, 26).

This narrative review, which is intended neither as a guideline nor practice statement, is informed by authors with experience in managing critically ill COVID-19 adults admitted to both academic and community centers and builds on other recent COVID-19 papers focused solely on delirium (27, 28). This article does not address factors like clinician fear or ethical issues (e.g., ventilator shortages) that may influence Bundle use during the pandemic (29). Instead, we highlight key barriers to Bundle adoption during the pandemic and offer ways to reenvision ICU care using evidence-based strategies to optimize Bundle application to critically ill adults with COVID-19 requiring mechanical ventilatory support.
with a different range of baseline neurocognitive development and physiology. Optimal Bundle implementation in the PICU patient requires the same strategies of repeated assessments and IPT communication and collaboration needed with adults (32–34) but uses different tactical tools to accomplish these goals (Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/CCX/A205) (35–46).

Established ICU IPT members should embrace new team members and prioritize just-in-time training about the Bundle. Adult ICU specialists should partner with their PICU colleagues when adults are admitted to PICUs, both to provide support for adult-specific medicine and also to foster mutual learning about different approaches to Bundle element performance. The adult ICU team can provide just-in-time training, guidance, and coaching to non-ICU or PICU clinicians. The amount of training and coaching could be high for a non-ICU professional who has never heard of the Bundle or low for the PICU team member who has experience with the Bundle but requires guidance about the chronic medical comorbidities of adults.

**Care Delivery When Personal Protective Equipment Is Limited**

High quality critical care during a pandemic is predicated by adequate personal protective equipment (PPE); shortages can impact every stage of ICU care. Initial decisions about how supportive care for acute hypoxemia should be delivered (e.g., noninvasive vs invasive ventilatory support) continue to be clouded by concerns about viral aerosolization (47). If the frequency of bedside patient assessments and interventions are reduced, the increased use of hand restraints that invariably results may lead to greater use of deep sedation and NMB therapy outside of usual therapeutic goals. The loss of repeated bedside exams and assessments may force care to become more monitor-based, leaving clinicians to focus more on vital signs, cardiopulmonary status, and laboratory results than on neurologic and musculoskeletal function.

Restricted PPE availability has also resulted in an overlap of bedside responsibilities among available ICU IPT members (25); entry to the patient room by a single ICU clinician at a time is more common. As a result, the ICU team loses the added layers of safety based on profession-specific education and experience. Examples include non-respiratory therapists (RTs) making directed ventilator adjustments but without the RT’s implicit knowledge of how changes in one ventilator variable might impact another. Non-RNs may be asked to administer medications but without the RN’s ingrained process for cleaning central line hubs to mitigate risk of central line-associated bloodstream infections. The requirement to use PPE at all times also removes the all-important human face-to-face connection and touch of critical care. Patients can no longer see the nonverbal cues that convey communication, compassion, and empathy in ways that garbled words behind a N-95 mask can never hope to replace (48). Patient fear and anxiety, particularly if delirium is present, may increase and the ICU environment becomes that much more foreign.

Consider repurposing strategies that enhance efficiency of care for patient comfort, rethink the ideal number of in-room team members, and ask front line staff for outside-the-box ideas. Adherence to strong IPT communication along with robust just-in-time training and coaching can facilitate Bundle performance while also promoting judicious use of PPE (25, 26). As patients clinically improve, the bedside frequency of patient monitoring and care may be able to be reduced throughout the day, in a similar fashion to approaches increasingly being used at night to reduce sleep disruption (17). ICU teams can also reimagine in-room presence to two-person teams that enter the room together and work in tandem to provide “boluses” of patient care. This approach will reduce the time any-one clinician spends in the room, improve efficiency of care, and the in-the-moment clinician-clinician interaction will promote a sense of team rather than isolation. It may also reduce PPE use as the longer a single clinician stays in the room, the more likely they may need to temporarily leave the room to change PPE (e.g., a sweaty N-95 mask).

**SOLUTIONS TO OVERCOME POTENTIAL BARRIERS TO SINGLE ELEMENT BUNDLE DELIVERY**

A number of unique barriers, over and above those already discussed, exist surrounding the performance of individual Bundle components in critically ill adults with COVID-19. This section highlights these potential barriers and offers practical solutions to overcome them.

**A—Assess, Prevent, and Manage Pain**

Pain assessment of the mechanically ventilated COVID-19 patient may be compromised because patients may be more often deeply sedated and/or receiving NMB therapy and the nurse may be spending less time at the bedside. The risk factors and causes of pain may be different from those of less critically ill adults. Prolonged periods of high-dose opioid therapy are common. Strategies to overcome these barriers and optimize patient comfort are highlighted in Table 1 (10, 12, 13, 15–17, 49).

**B—Both Spontaneous Awakening Trials and Spontaneous Breathing Trials**

Sedation assessment is challenging during NMB therapy and may be reduced if the nurse is less frequently at the bedside. Although patients with acute respiratory distress syndrome can often safely be managed at a lighter sedation goal (50), COVID-19 patients may be maintained at a deep level of sedation for a prolonged period. Attempts at spontaneous awakening trials may be reduced due to concerns about patient-initiated device removal (e.g., self-extubation). Spontaneous breathing trials may be reduced due to deeper sedation and/or reduced lack of RT presence. Strategies to overcome barriers to wakefulness and mechanical ventilation liberation are presented in Table 2 (10, 12, 13, 15–17, 49, 50).

**C—Choice of Analgesia, Sedation, and Neuromuscular Blockade**

Use of analgescics, sedatives, and NMB, often for prolonged periods and at high doses, coupled with a high prevalence of multiple organ failure, will increase the risk for drug interactions, opioid/sedative withdrawal effects, and adverse drug events. Placement of IV infusion pumps in hallways and reduced room entry by
TABLE 1. Barriers and Solutions to A: Assess, Prevent, and Manage Pain in Critically Ill Adults With Coronavirus Disease 2019 (10, 12, 13, 15–17, 49)

<table>
<thead>
<tr>
<th>Potential Barriers</th>
<th>Potential Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain assessment may be compromised because patients are deeply sedated, sometimes on NMB therapy, and the RN is less frequently at the bedside</td>
<td>Pain should be assumed to be present and treated presumptively in the absence of pain assessments or in patients where pain assessment is not possible (e.g., receiving NMB). The use of behavioral pain assessment tools (e.g., CPOT, Behavioral Pain Score) should be considered for patients who are sedated. RNs should coordinate with other clinicians (e.g., physicians [medical doctor], respiratory therapists) providing bedside care on the use of nonverbal pain assessments. Certain CPOT domains (i.e., facial expressions, body movements, and ventilator compliance) may sometimes be detectable from outside the patient room.</td>
</tr>
<tr>
<td>Risk factors/causes for pain may be different in patients who are deeply sedated and/or receiving NMB therapy</td>
<td>The amount of pain experienced by medical and surgical patients are generally similar. Bedside procedures (e.g., chest tube insertion) are painful and usually require additional analgesia. Opioid tachyphylaxis may occur as soon as 2 d after opioid infusion initiation; increases in the infusion dose may be needed. Painful neuropathies due to viral invasion of peripheral nerves and/or prolonged immobility are prevalent and may require the addition of pregabalin or gabapentin.</td>
</tr>
<tr>
<td>High dose, long-term opioid infusions are common</td>
<td>Concerns about the potential risk for post-hospital opioid use disorder should be suspended. Consider higher initial opioid dosing if a history of chronic opioid use is known. Consider initiating a scheduled laxative protocol for all patients initiated on opioid infusions. Consider reducing opioid infusions prior to spontaneous breathing trial attempts given their effect on respiratory drive.</td>
</tr>
</tbody>
</table>

CPOT = Critical-Care Pain Observation Tool, NMB = neuromuscular blocker, RN = registered nurse.

TABLE 2. Barriers and Solutions to B: Both Spontaneous Awakening Trial and Spontaneous Breathing Trials in Critically Ill Adults With Coronavirus Disease 2019 (10, 12, 13, 15–17, 49, 50)

<table>
<thead>
<tr>
<th>Potential Barrier(s)</th>
<th>Potential Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation assessment may be compromised because patients are sometimes on NMB and the RN is less frequently at the bedside</td>
<td>Conduct sedation assessments with the Richmond Agitation-Sedation Scale or Sedation Assessment Score to coincide with other bedside care activities. Other clinicians (e.g., MDs, RTs) providing bedside care may be able to conduct sedation assessments in the absence of the RN. Bispectral index monitoring, if available, may helpful to titrate sedation in patients receiving continuous NMB therapy (17).</td>
</tr>
<tr>
<td>Severe hypoxemic respiratory failure requiring deep sedation and prolonged mechanical ventilation</td>
<td>Consider establishing a new sedation goal daily. Consider optimizing ventilator settings before increasing/initiating opioid, sedation, and/or neuromuscular blocker therapy. Not all patients with coronavirus disease 2019 acute respiratory distress syndrome require deep sedation (50). SATs should generally occur even when the patient is unlikely to be a candidate for an SBT. Non-RN clinicians providing bedside care can often help support SAT efforts. A protocolized approach to sedation titration is an effective alternative to SAT completion. Anticipate a prolonged time to wakefulness for patients receiving midazolam infusions. A daily SBT safety screen should occur daily regardless of perceived SBT success.</td>
</tr>
<tr>
<td>Clinicians (RN, RT, and MD) not routinely at the bedside</td>
<td>The RN may be able to adjust the ventilator (based on MD order) in the absence of the RT. Facilitated and efficient communication with the MD is needed when the SBT is passed and extubation decisions are being formulated.</td>
</tr>
</tbody>
</table>

MD = physician (medical doctor), NMB = neuromuscular blocker, RN = registered nurse, RT = respiratory therapist, SAT = spontaneous awakening trial, SBT = spontaneous breathing trial.
### TABLE 3. Barriers and Solutions to C: Choice of Analgesia, Sedation, and Neuromuscular Blockade in Critically Ill Adults With Coronavirus Disease 2019 (10, 12, 13, 15–17, 49, 51–54)

<table>
<thead>
<tr>
<th>Potential Barrier</th>
<th>Potential Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesic and sedative drug interactions and safety concerns may be greater</td>
<td>Hypertriglyceridemia may be due to a cytokine storm mimicking secondary hemophagocytic lymphohistiocytosis (51) rather than propofol. Consider checking serum triglyceride concentrations daily for patients receiving propofol, particularly at doses ≥ 40 µg/kg/min, but ignoring values ≤ 800 µg/dL. Many patients will have risk factors for PRIS; regularly evaluate patients receiving propofol for signs of PRIS (52). If fentanyl, methadone, and haloperidol are administered, particularly at high doses and/or in combination with other medications known to prolong the QTc interval, monitor the QTc interval regularly. Coronavirus disease 2019 treatment regimens known to be a substrate of one or more cytochrome P450 isoenzymes (e.g., lopinavir/ritonavir) may reduce fentanyl and midazolam clearance. IV acetaminophen may worsen hypotension, particularly in patients requiring vasopressor support. Nonsteroidal anti-inflammatory drugs should be avoided given their deleterious effects on prostaglandin synthesis and the high prevalence of coagulopathy and acute kidney injury in this population. Placement of IV infusion pumps in the hallway and frequency of room entry reduced. Longer lengths of IV extension tubing requires the administration of greater priming amounts when new opioid, sedative, and/or NMB infusion bags/bottles are hung. Use of larger bags/bottles will reduce the frequency of priming efforts. Use greater than normal IV flush volumes when administering opioids or sedatives as an IV bolus. Bundle oral/enteral medication administration times to preserve personal protective equipment use. Increased risk for opioid and sedative withdrawal. Oral/enteral administration of longer-acting opioids (e.g., methadone) and sedatives (e.g., diazepam) may reduce the risk for withdrawal reactions as continuous opioid and sedative infusions are weaned down/turned off. Note: Oral/enteral absorption may be unreliable until the gut is deemed to be “moderately functioning” (e.g., vasopressor requirements low and/or tube feeds initiated and being tolerated). Frequent use of continuous NMB therapy for prolonged periods to optimize mechanical ventilation/proning and/or to reduce self-extubation risk. Consider IV bolus dosing for NMB therapy before initiating continuous infusions. Note: NMB infusions should be administered using a weight-based approach. Infusions should be down-titrated (or stopped) at least once daily until ventilator dyssynchrony or some degree of patient movement is observed. Note: Early use of continuously-infused NMB has not been shown to improve 90-d mortality in patients with acute respiratory distress syndrome and is associated with safety concerns (53, 54).</td>
</tr>
<tr>
<td>Placement of IV infusion pumps in the hallway and frequency of room entry reduced</td>
<td></td>
</tr>
<tr>
<td>Increased risk for opioid and sedative withdrawal</td>
<td></td>
</tr>
<tr>
<td>Frequent use of continuous NMB therapy for prolonged periods to optimize mechanical ventilation/proning and/or to reduce self-extubation risk</td>
<td></td>
</tr>
</tbody>
</table>

NMB = neuromuscular blocker, PRIS = propofol-related infusion syndrome.

### TABLE 4. Barriers and Solutions to D: Delirium: Assess, Prevent, and Manage in Critically Ill Adults With Coronavirus Disease 2019 (10, 12, 13, 15–17, 25, 49)

<table>
<thead>
<tr>
<th>Potential Barriers</th>
<th>Potential Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium screening will be reduced due to deep sedation and reduced RN frequency at the bedside</td>
<td>With a prevalence close to 100%, delirium should be assumed to be present in the absence of assessment results. Prioritize delirium screening efforts during periods of greater wakefulness (Richmond Agitation-Sedation Scale ≥ –2). Other clinicians providing bedside care (e.g., physicians [medical doctor], respiratory therapists) can be trained to assess delirium using the Confusion Assessment Method-ICU or Intensive Care Delirium Screening Checklist in the absence of RNs being able to conduct assessments. If possible, ask patients if they are fearful or hallucinating; additional comfort efforts may be warranted.</td>
</tr>
<tr>
<td>Challenging to recognize and reduce potential modifiable risk factors for delirium</td>
<td>Systematically evaluate risk factors for delirium using an approach like 'Dr. DRE' (25). Newly occurring delirium may indicate worsening sepsis, a new acute neurologic injury, or the need for fluid or electrolyte replacement. Drug-associated delirium is generally dose-related; reductions in corticosteroid or benzodiazepine exposure may help facilitate delirium resolution. When feasible, consider providing potential delirium-reducing interventions such as eye glasses, hearing aids, reorientation efforts, favorite music, and/or phone/facetime/zoom calls with family.</td>
</tr>
<tr>
<td>Challenging to improve disrupted sleep</td>
<td>Simplify nocturnal interventions focused on reducing light and/or noise may help reduce delirium.</td>
</tr>
</tbody>
</table>

RN = registered nurse.
nurses raise important medication administration-related concerns. Strategies to optimize analgesic, sedative, and NMB use and reduce safety concerns with their use are presented in Table 3 (12, 13, 15–17, 49). Shortages of analgesic, sedative, and NMB medications are prevalent as the COVID-19 pandemic persists (55). Supplemental Table 3 (Supplemental Digital Content 3, http://links.lww.com/CCX/A206) provides suggestions for second-, third-, and fourth-line analgesics, sedatives, and NMB when first-line agents are not available (10, 17, 56–58). Supplemental Table 4 (Supplemental Digital Content 4, http://links.lww.com/CCX/A207) highlights the pharmacologic properties of these less commonly used ICU analgesics, sedatives, and NMB (57–59).

D—Delirium: Assess, Prevent, and Manage
The prevalence of delirium in critically ill adults with COVID-19 likely approaches 100% (27, 28, 60). Delirium screening may be compromised given the high proportion of patients managed at a very deep level of sedation and the reduced frequency of nurses at the bedside. In the potential absence of key IPT members and reduced entry into patient’ rooms, challenges to reducing potential modifiable delirium risk factors exist. Most COVID-19 patients will have disrupted sleep (17); multiple barriers prevent the routine application of nonpharmacologic strategies known to improve sleep and/or reduce delirium. Strategies to help better recognize and reduce delirium in this population are presented in Table 4 (10, 12, 13, 15–17, 25, 49).

E—Early Mobility and Exercise
Critically ill adults with COVID-19 are at high risk for ICU-acquired weakness and compromised post-ICU physical function. Deep sedation, with or without NMB therapy, precludes out-of-bed rehabilitation (17, 50). Physical and occupational therapists may not be present in the ICU; the truncated time nurses are at the patient bedside may reduce in-bed rehabilitation efforts. As patients recover, contact precautions may preclude out of ICU room mobility efforts. Strategies to optimize rehabilitation and mobility in light of these barriers are presented in Table 5 (10, 12, 13, 15–17, 49).

F—Family Engagement and Empowerment
In the face of contagion, evidence-based strategies known to support family engagement in ICU care have generally been abandoned (30). There is abundant sharing on social media by family members about their frustration, sadness, and grief over “not being there” for their loved ones. Families are rarely present in the hospital and almost never allowed at the bedside. For patients who are wakeful, daily telephone, facetime, or zoom communications with family is encouraged. Families should be encouraged to provide the ICU with family photos and provide clinicians with the E-stories and music the patient enjoys (30, 49).

CONCLUSIONS
The number of critically ill adults with COVID-19 requiring mechanically ventilatory support has dramatically affected the way critical care is delivered and has likely prompted a move at many centers away from evidence-based ICU practices such as ABCDEF Bundle delivery. Despite multiple factors affecting Bundle use in ICUs caring for COVID-19 adults, we have outlined multiple strategies to help operationalize the Bundle, regardless of PPE availability, the location of critical care, or patient severity of illness. Reemploying the use of evidence-based strategies developed over the past 20 years in critical care research, appropriately adapted for use in this new and trying time of the coronavirus pandemic, may be one of the best mechanisms by which to increase ventilator and ICU capacity and help critically ill adults with COVID-19 transition toward recovery and survivorship.

Table 5. Barriers and Solutions to E: Early Mobility and Exercise in Critically Ill Adults With Coronavirus Disease 2019 (10, 12, 13, 15–17, 49)

<table>
<thead>
<tr>
<th>Potential Barrier(s)</th>
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</thead>
<tbody>
<tr>
<td>Deep sedation prevalent, physiotherapists/OTs may not be in the hospital, the frequency of registered nurse room entry and time spent at bedside is limited</td>
</tr>
<tr>
<td>Contact precautions may preclude out of room mobility efforts</td>
</tr>
<tr>
<td>OT = occupational therapist.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Potential Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>For deeply sedated patients, range of motion exercises should be attempted at least daily and can be conducted by any bedside clinician</td>
</tr>
<tr>
<td>In the absence of physiotherapists/OTs availability (either live or virtual), bedside clinicians can still establish daily goals for rehabilitation/mobility efforts</td>
</tr>
<tr>
<td>If physiotherapists/OTs are not in the ICU but in the hospital, consider virtual consultation to guide rehabilitation/mobility efforts</td>
</tr>
<tr>
<td>Beneficial rehabilitation/mobility efforts can be achieved without the patient leaving their room</td>
</tr>
<tr>
<td>It may be possible to mask extubated ICU patients to facilitate hallway walking</td>
</tr>
</tbody>
</table>

Supplemental digital content is available for this article. Direct URL citations appear in the HTML and PDF versions of this article on the journal’s website (http://journals.lww.com/ccejournal).

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REFERENCES


59. Lexicomp Online; Lexicomp Corporation. Hudson, OH. Available at: https://www.wolterskluwercdi.com/lexicomp-online/. Accessed April 20, 2020