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SPECIAL ARTICLE

Therapeutic alternatives and strategies for drug conservation in the intensive care unit during times of drug shortage: a report of the Ontario COVID-19 ICU Drug Task Force

Alternatives thérapeutiques et stratégies pour la préservation des médicaments à l'unité des soins intensifs pendant les pénuries de médicaments : un compte rendu du Groupe de travail ontarien sur les médicaments à l'USI pendant la COVID-19

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Abstract *During the coronavirus disease (COVID-19) global pandemic, urgent strategies to alleviate shortages are required. Evaluation of the feasibility, practicality, and value of drug conservation strategies and therapeutic alternatives requires a collaborative approach at the provincial level. The Ontario COVID-19 ICU Drug Task Force was directed to create recommendations suggesting drug conservation strategies and therapeutic alternatives for essential drugs at risk of shortage in the intensive care unit during the COVID-19 pandemic. Recommendations were rapidly developed using a modified Delphi method and evaluated on their ease of implementation, feasibility, and supportive evidence. This article describes the recommendations for drug conservation strategies and therapeutic alternatives for drugs at risk of shortage that are commonly used in the care of critically ill patients. Recommendations are identified as preferred and secondary ones that might be less desirable. Although the impetus for generating this document was the COVID-19 pandemic, recommendations should also be applicable for mitigating drug shortages outside of a pandemic. Proposed provincial strategies for drug conservation and therapeutic alternatives may not all be appropriate for every institution. Local implementation will require consultation from end-users and hospital administrators.*

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Competing equipment shortages and available resources should be considered when evaluating the appropriateness of each strategy.

Résumé *Pendant la pandémie mondiale du coronavirus (COVID-19), des stratégies urgentes pour réduire les pénuries sont nécessaires. L'évaluation de la faisabilité, de l'aspect pratique et du mérite des stratégies de préservation des médicaments et des alternatives thérapeutiques nécessite une approche collaborative au niveau provincial. Le Groupe de travail ontarien sur les médicaments à l'USI pendant la COVID-19 a reçu comme mandat d'élaborer des recommandations proposant des stratégies de préservation des médicaments et des alternatives thérapeutiques pour les médicaments essentiels utilisés dans les unités de soins intensifs courant un risque de pénurie pendant la pandémie de COVID-19. Des recommandations ont été rapidement élaborées en utilisant une méthode Delphi modifiée, puis évaluées selon leur facilité de mise en œuvre, leur faisabilité et les données probantes les préconisant. Cet article décrit les recommandations quant aux stratégies de préservation des médicaments et aux alternatives thérapeutiques aux médicaments possiblement à risque de pénurie fréquemment utilisés pour les soins des patients en état critique. Les recommandations sont identifiées comme 'à privilégier' ou 'secondaires' si moins souhaitables. Bien que la pandémie de la COVID-19 ait été l'impulsion incitant la création de ce document, ces recommandations devraient également être applicables pour réduire les pénuries de médicaments en contexte normal. Les stratégies provinciales proposées pour la préservation des médicaments et les alternatives thérapeutiques pourraient ne pas être adaptées pour toutes les institutions. La mise en œuvre locale nécessitera la consultation des utilisateurs et des administrateurs hospitaliers. Il faudrait tenir compte des pénuries de matériel concurrentes et des ressources disponibles lors de l'évaluation de la faisabilité de chaque stratégie.*

Keywords drug shortage · COVID-19 · pandemic · therapeutic alternatives · conservation strategies

Drug shortages occur frequently because of manufacturing problems, regulatory issues, de-listing of drugs, and difficulties in sourcing raw materials.[1] Pharmacies, hospitals, and patients are forced to consider drug conservation strategies and possibly therapeutic alternatives. Many drug shortages are transient, and even predictable, so mitigation strategies can be coordinated, including stockpiling medications, planning for pre-determined drug allocations, and drug conservation strategies.[2] Nevertheless, during a global health crisis such as the coronavirus disease (COVID-19) pandemic, drug shortages are less predictable with little time for mitigation strategies. Drug supplies are also vulnerable to community-based consumer panic buying, prescribing, and stockpiling.[3,4] Managing a nation's drug supply chain during a pandemic requires collaboration between hospitals, drug manufacturers and distributors, advanced preparedness, and planning.[5,6] Typically, drug allocation at a hospital level is based on prior usage rates. At a time when high volumes of patients are expected to require critical care, usual allocations of certain drugs are projected to be insufficient without the means to rapidly increase allocations, production, or distribution. Relative drug shortages must be projected and anticipated to be able to continue to provide a high level of care.

In anticipation of drug shortages during the COVID-19 global pandemic, particularly in critical care and intensive care units (ICUs), several provinces have instituted measures to proactively address them. In Ontario, the Critical Care COVID-19 Command Center created the Ontario COVID-19 ICU Drug Task Force made up of hospital pharmacy administrators, government officials, pharmaceutical industry representatives, physicians, and clinical pharmacists (Appendix). The mandate was to 1) develop a list of critical ICU drugs anticipated to be in high use and at risk of shortage; 2) collate drug supply data from individual hospitals to prioritize procurement of key drugs and allocate them to institutions according to need; and 3) develop mitigation strategies including an approach to drug conservation and therapeutic alternatives should drug shortages be realized.

In this paper, we will focus on drug conservation strategies in critical care, and therapeutic alternatives when faced with drug shortages. While the impetus for these strategies was the COVID-19 pandemic, they are applicable for any global health crisis where sustaining maximal critical care capacity is required.

Development of drug conservation priorities and therapeutic alternatives

Based on experience in other jurisdictions, the Ontario COVID-19 ICU Drug Task Force initially determined that, during the COVID-19 pandemic, use of sedatives, analgesics, and neuromuscular blocking agents would be the essential ICU medications.[7,8] While these drugs became the focus, it was recognized that given the circumstances, other medications could also be at risk of shortage, including anticoagulants, vasoactive drugs, diuretics, antimicrobials, metred-dose inhalers (MDIs),

antiarrhythmic agents, and stress ulcer prophylaxis agents. Drug conservation strategies and therapeutic alternatives were considered separately for each class of medication.

Conservation strategies and proposed therapeutic alternatives were generated initially via solicited contributions from critical care pharmacists, nurses, and intensivists throughout the province. Regional pharmacy and ICU directors were contacted via email for their input. A draft document was created and refined by the Ontario COVID-19 ICU Drug Task Force using a modified Delphi method. Team members provided feedback related to prioritizing drug classes and individual recommendations and the feasibility of conservation strategies and therapeutic alternatives. Items were considered for inclusion if they were logical, practical, easy to implement, and had some supportive clinical evidence of efficacy and safety. Team members were asked to consider competing interests related to shortages of equipment including mechanical ventilators, personal protective equipment (PPE), and intravenous (IV) pumps when prioritizing strategies. Conservation strategies and therapeutic alternatives underwent three modified Delphi rounds (feedback was not anonymous) via teleconference followed by one round of feedback from pharmacy directors of Ontario hospitals and members of the Ontario Critical Care COVID-19 Command Centre. The final recommendations were tabulated and shared with critical care and pharmacy leaders across the province, made available to healthcare practitioners via document sharing websites, and shared via social media.

The Table collates strategies for drug conservation and recommends therapeutic alternatives in the face of drug shortages. The remainder of this document provides a narrative to accompany this table. It is important to recognize that, although the focus of these recommendations is the ICU, drug shortages will affect all areas of the hospital and conservation strategies should be considered both in and outside of the ICU. It is also important to note that strategies proposed here may not always represent best practices under ideal conditions, and as such, careful review of the toxicities and monitoring parameters must be reviewed in each case. Implementation at the local level requires consultation and collaboration from end-users (e.g., physicians, nurses, pharmacists) as well as pharmacy and clinical administrators. These collaborations ensure that proposed strategies are appropriate, feasible, and acceptable for each institution. Specific recommendations (e.g., dosing, drug selection) are purposely not provided here as such decisions should be made locally based on comfort and experience with new drugs in consultation with clinical pharmacists. Readers looking to use any of the proposed strategies are encouraged to use the references to guide local implementation and to consider local resources to help assess feasibility and safety.

General principles to address drug shortages

A general approach to drug shortages was adapted from the Multi-Stakeholders Tool Kit: A Toolkit for Improved Understanding and Transparency of Drug Shortage Response in Canada from Drug Shortages Canada.[6] When faced with anticipated drug shortages, the following questions should be considered:

1. Have all supply chain options been exhausted?
2. How critical is the medication?
3. Is there an interchangeable product available (e.g., different manufacturer, different routes of administration)?
4. Is there an alternative drug within the same medication class?
5. Is there an alternative drug class that would meet the patient's needs (e.g., non-dihydropyridine calcium channel blockers instead of beta-adrenergic blockers for rate control in atrial fibrillation)?
6. How can medication wastage be minimized (e.g., dose rounding, choosing appropriate vial size and concentrations)?
7. Is the lowest effective dose being used?
8. Can a therapeutic escalation strategy be implemented (e.g., for ICU sedation, intermittent oral dosing is preferred in eligible patients followed by intermittent IV dosing followed by continuous infusions of sedatives)?

Mitigating drug shortages is often easier when interchangeable products are already available within the same drug class or when reasonable alternatives are available from other drug classes. Nevertheless, in the era of electronic health records and prescriber order entry, changing drugs within existing order sets or altering the way IV medications are prepared (e.g., changing concentrations and IV bag sizes, altering dose rounding rules) will often require modification of electronic order entry pathways as well as workflow within pharmacy or in clinical areas that will require time and advanced planning. Using different drugs and administering drugs via alternative routes or methods may also require notification and education of end-users to ensure safe and effective prescribing, administration, and monitoring.

TABLE Strategies for drug conservation and proposed therapeutic alternatives in anticipation of critical care drug shortages

Conservation strategies to consider first:	Therapeutic alternatives to consider first:
ESSENTIAL DRUGS AT GREATEST RISK OF SHORTAGE	
Sedatives: propofol, midazolam, dexmedetomidine, ketamine	
• Consider an escalation strategy whereby intermittent enteral dosing is preferred followed by intermittent IV dosing followed by continuous infusions. • Analgesia-based sedation: mechanically ventilated patients who need only light sedation can receive infusions or intermittent doses of opioids alone (e.g., hydromorphone, fentanyl) that provide mild sedation. • Adjunctive use of intermittent sedatives (e.g., clonazepam, lorazepam, diazepam, clonidine, ketamine, atypical antipsychotics) with sedative infusions require lower doses of the IV infusion. • Nurse-managed sedation titration using a validated sedation scale (e.g., RASS[15]) and clearly defined sedation targets to ensure lowest effective dosing Other conservation strategies: • Daily sedative interruption or sedation vacations may reduce sedative requirements in select cases	• Intermittent clonazepam, lorazepam, diazepam clonidine, or atypical antipsychotics instead of continuous infusions of sedatives in patients who only need light sedation • Analgesia-based sedation • Ketamine infusions may be considered as an alternative sedative strategy for short-term sedation (e.g., 24–48 hr) Other potential therapeutic alternatives: • Phenobarbital can be administered enterally or intravenously in conjunction with benzodiazepines and titrated to provide sedation • Inhaled anesthetics can also be considered in select patients and settings (consider the risk of aerosolization in COVID-19 patients)
Opioid analgesics: hydromorphone, fentanyl, morphine	
• Nurse-managed analgesia titration using a validated pain assessment tool (e.g., NRS,[22] CPOT[23]) with clearly defined pain targets to ensure lowest effective dosing • Consider an escalation strategy whereby intermittent enteral dosing is preferred followed by intermittent IV dosing followed by continuous infusions • Multimodal approach to pain using non-narcotic medications such as acetaminophen, pregabalin, NSAIDS, ketamine, methadone, lidocaine, and tapentadol can reduce the need for opioids Other conservation strategies: • Analgesia vacations/interruptions in selected patients receiving continuous infusions to ensure the lowest effective dose is being used	• Intermittent enteral administration of hydromorphone, oxycodone, or morphine can be used in place of opioid infusions and titrated to the same pain score (e.g., CPOT[23]) • Fentanyl patches (although less easy to titrate) can be used in place of opioid infusions Other potential therapeutic alternatives: • Remifentanil or sufentanil may be considered as alternatives for continuous infusion • Lidocaine infusions can be used in combination with opioids for pain • Some long-acting preparations (e.g., Hydromorph Contin, M-Eslon) can be administered via large bore feeding tubes
Neuromuscular blocking agents (NMBAs): cisatracurium, rocuronium	
• Use both train-of-four monitoring and observed respiratory effort when titrating NMBA infusions to ensure the lowest effective dose is being used • Intermittent NMBA dosing (as opposed to continuous infusion) guided by train-of-four monitoring and respiratory effort may reduce total daily dosing and durations Other conservation strategies: • Magnesium infusions can boost the effect of neuromuscular blockers	• Limited options exist if these agents are no longer available. Succinylcholine could be used for intubation and procedural paralysis in select patients • Health Canada has permitted the importation of pancuronium and vecuronium
Vasopressors and inotropes: norepinephrine, epinephrine, vasopressin, dopamine, dobutamine, milrinone	
• Stress-dosed corticosteroid therapy (e.g., hydrocortisone) has been shown to reduce vasopressor requirements • Targeting lowest effective sedation dose can reduce vasopressor requirements • Concurrent enteral midodrine can reduce IV vasopressor needs Other conservation strategies: • For vasopressor dependent patients consider targeting a lower mean arterial pressure	• Phenylephrine can be administered as intermittent boluses or as a continuous infusion for patients in distributive shock • Intermittent dosing of oral midodrine can be used in patients in place of low dose vasopressors to improve vascular tone Other potential therapeutic alternatives: • Ephedrine can be used intravenously, enterally or intramuscularly

TABLE continued

Drugs used in cardiac arrest and rapid sequence intubation (RSI): ACLS drugs, propofol, rocuronium, succinylcholine, ketamine, fentanyl, phenylephrine

Conservation strategies to consider first:

- Code/crash carts and intubation kits should be designated as such; kept in COVID-19 areas so unused drugs can be reused in the same area
- Drugs in crash carts and intubation kits could be place in sealed plastic bags to minimize exposure in contaminated rooms
- Keeping code/crash carts outside of the room and having the drugs passed in as needed may reduce the risk of contamination

Therapeutic alternatives to consider first:

- Etomidate could be used in place of propofol for RSI induction
- Epinephrine, norepinephrine, or ephedrine can be administered as IV push in place of phenylephrine for RSI
- Lidocaine IV can be used in place of fentanyl for RSI pre-treatment
- Succinylcholine can be used in place of rocuronium for intubation paralysis in select patients

OTHER DRUGS POTENTIALLY AT RISK OF SHORTAGE

Metred-dose inhalers: salbutamol, ipratropium, and others

Conservation strategies to consider first:

- Avoid routine salbutamol and ipratropium dosing in the absence of bronchospasm
- Patients prescribed MDIs at home could be asked to bring them in to use as "patient's own medication"
- Salbutamol/ipratropium combination nebules could be used in place of individual nebules
- Long-acting beta-agonists (e.g., salmeterol, formoterol) could be used to reduce the need for salbutamol rescue therapy
- Long-acting anticholinergic agents (e.g., tiotropium) could be used in place of ipratropium in eligible patients

Other conservation strategies:

- Same MDIs theoretically could be used for multiple patients with a spacer device (e.g., aerochamber) that is changed for each patient. The mouthpiece would need to be sterilized between uses
- Upon discharge, rather than sending partly used MDIs home with the patient, these MDIs (or canisters) could potentially be redeployed after sterilization

Therapeutic alternatives to consider first:

- Salbutamol and ipratropium could be administered via nebulizer to COVID-19-negative patients while MDIs are reserved for patients with suspected or confirmed COVID-19
- Systemic corticosteroids could be used in bronchospastic or asthmatic patients
- Budesonide is available as a solution for nebulization
- Respimat® inhalers may be considered in lieu of nebulizers for concerns related to asymptomatic transmission of COVID-19
- Similarly, Turbuhalers®/Handihalers® may be used by non-ventilated patients with manual dexterity for self-administration

Other potential therapeutic alternatives:

- Salbutamol is available as oral tablets and could theoretically be used for maintenance dosing in bronchospastic COPD patients
- Theophylline could be used in asthmatic patients to reduce the use of salbutamol

Proton pump inhibitors (PPI) and histamine-2 receptor antagonists (H2RA): pantoprazole, lansoprazole, ranitidine

Conservation strategies to consider first:

- Twice daily PPI could be used instead of continuous infusions for the management of gastrointestinal bleeding
- Early enteral feeding could shorten the duration of pharmacologic stress ulcer prophylaxis
- Avoidance of pharmacologic stress ulcer prophylaxis in hemodynamically stable patients without coagulopathy and limited risk factors

Therapeutic alternatives to consider first:

- Several PPIs (e.g., pantoprazole, lansoprazole, omeprazole, esomeprazole, dexlansoprazole) and H2RA (ranitidine, famotidine, cimetidine) are available in Canada
- PPIs and H2RAs could be interchanged to manage stress ulcers, reflux, and gastrointestinal bleeding
- Antacids could be used in place of PPIs and H2RAs for reflux symptom management

Other potential therapeutic alternatives:

- Sucralfate is an alternative for stress ulcer prophylaxis

Diuretics: furosemide

Conservation strategies to consider first:

- Furosemide infusions can be a more efficient method of fluid removal while minimizing the total dose used
- Administering furosemide with metolazone can augment diuresis with theoretically lower doses of furosemide

Therapeutic alternatives to consider first:

- Using enteral furosemide can be as effective as IV dosing
- Ethacrynic acid is another loop diuretic that could be used in place of furosemide
- Thiazide diuretics could be used in the event that loop diuretics are no longer available

Other potential therapeutic alternatives:

- Low dose dopamine infusions theoretically could augment urine output
- Dialysis would be the definitive way to remove fluid in diuretic-refractory fluid overload or in the absence of other pharmacologic options

TABLE continued

Antimicrobials: antibiotics, antifungals	
Conservation strategies to consider first:	Therapeutic alternatives to consider first:
• Ensure duration of antimicrobial therapy adheres to best practice guidelines • Engage with antimicrobial stewardship program where available to assist with antimicrobial therapy • Step down from IV to oral antimicrobials as soon as appropriate	• For most classes of antibiotics more than one agent is available in Canada (e.g., in the event of a ceftriaxone shortage cefotaxime or ceftazidime could provide similar coverage) • Even for antimicrobials like vancomycin alternatives for gram-positive coverage exist such as linezolid, daptomycin, and trimethoprim-sulfamethoxazole • Antifungals options exist within the same class and between classes (e.g., fluconazole, itraconazole, caspofungin, micafungin, amphotericin, etc.)
Antiarrhythmic drugs: amiodarone	
Conservation strategies to consider first:	Therapeutic alternatives to consider first:
• Patients with hemodynamically stable new onset atrial fibrillation can be managed with rate control alone (e.g., beta blockers or non-dihydropyridine calcium channel blockers such as diltiazem) • Potentially reversible risk factors for supraventricular tachyarrhythmias should be addressed before resorting to pharmacologic antiarrhythmic therapy (e.g., electrolyte replacement, discontinuing pro-arrhythmic drugs, diuresis for fluid overload)	• Other agents besides amiodarone to consider for the management of atrial fibrillation (e.g., magnesium, procainamide, sotalol, propafenone) • Electrical cardioversion, when successful, can negate the need for antiarrhythmic drugs for hemodynamically unstable atrial fibrillation

COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease; CPOT = critical care pain observation tool; H2RA = histamine-2 receptor antagonist; IV = intravenous; MDI = metred dose inhaler; NRS = numerical rating scale; NMBA = neuromuscular blocking agent; PPI = proton pump inhibitor; RASS = Richmond Agitation and Sedation Scale; RSI = rapid sequence intubation.

Hydromorph Contin®, Purdue Pharma, Pickering, ON, Canada.

M-Eslon®, Ethypharm Inc., Montreal, QC, Canada.

Respimat® Boehringer Ingelheim Canada, Burlington ON, Canada.

Turbuhaler® AstraZeneca Canada, Mississauga, ON, Canada.

Handihaler® Boehringer Ingelheim Canada, Burlington ON, Canada.

Strategies for drug conservation and therapeutic alternatives in anticipation of drug shortages

Priority drugs identified at greatest risk of shortage either due to short supply or high anticipated usage in ICU included sedatives, opioids, neuromuscular blockers, vasoactive drug infusions, and medications used for cardiac arrest and intubation. Metred-dose inhalers, drugs used for stress ulcer prophylaxis, diuretics, antimicrobials, and antiarrhythmic drugs were also considered.

Sedatives

Inflammation-induced acute lung injury is a common complication of severe COVID-19 infection, particularly in patients in the ICU. This was also a complication seen with other viral pneumonias including severe acute respiratory syndrome (SARS), Middle East Respiratory Syndrome (MERS), H1N1 influenza, and seasonal influenza.[8,9] Pharmacologic sedation is required to facilitate mechanical ventilation and higher doses are often required in the setting of inflammation-induced acute lung injury, particularly associated with COVID-19.[7] In Canada, the most commonly used sedatives (via continuous infusion) are propofol, midazolam, and dexmedetomidine.[10] Nevertheless, not all ICU patients who require sedation suffer from acute lung injury or even COVID-19. It is likely that some patients will only require light sedation without a need for continuous infusions. An escalation strategy should be employed whereby intermittent enteral agents are preferred, then followed by intermittent IV agents and, if required, continuous infusions.[11–13] Such a strategy promotes use of alternative agents in patients with lower sedation needs and reserves the infusions for patients who need deeper sedation (e.g., patients receiving neuromuscular blockers or patients with acute respiratory distress syndrome [ARDS]). Similarly, rather than use both sedatives and opioid analgesics in intubated patients, some patients can be managed with opioids alone (analgesia-based sedation).[14] In patients who require infusions of sedatives, targeting the lowest effective dose is an important conservation strategy. Protocolized sedation with prescribed sedation targets based on a validated sedation scale (e.g., Richmond Agitation and Sedation Scale[15]) can prevent over-sedation of patients and unnecessary drug usage, and

shorten the duration of mechanical ventilation.[11] Daily sedation interruption in highly selected patients may also ensure the use of the lowest effective dose; this strategy may not be appropriate for patients in situations where increased agitation may lead to potential harm.[16] Ketamine infusions have also been shown to be an effective alternative sedative strategy in mechanically ventilated patients for short-term sedation.[17] Other potential alternatives involve the use of phenobarbital and inhaled anesthetics. Barbiturates were considered less desirable because of the risk of adverse events and drug interactions while inhaled anesthetics require technical expertise and specific equipment and ventilation requirements.[18]

Opioid analgesics

In the ICU, opioid analgesics are prescribed to manage pain and increase tolerance to mechanical ventilation. In Canada, hydromorphone, fentanyl, and morphine are the most commonly used agents.[10] Similar to sedatives, an escalation strategy should be employed where enteral agents (e.g., hydromorphone, oxycodone, and morphine) are preferred over intermittent IV agents followed by continuous IV infusions only if required.[11] During drug shortages, it is typically the IV products that are most vulnerable to supply issues, so using enteral agents as a first line not only preserves the IV agents but also promotes using lower doses of the IV products.[19] A multimodal, stepwise approach to pain management employs non-opioid adjunctive therapy (e.g., acetaminophen, pregabalin, non-steroidal anti-inflammatory drugs, methadone, ketamine, lidocaine, and tapentadol) to reduce opioid requirements.[20,21] While many of these strategies may already be employed in Canadian ICUs, reinforcement can still promote conservative opioid prescribing. Interruptions (or empiric dose reductions) in patients receiving continuous infusions of opioid analgesics as well as use of a validated pain assessment scale (e.g., Numerical Pain Rating Scale[22] or Critical Care Pain Observation Tool[23]) can assist the nurse in titrating infusions to the lowest effective dose.[11] Infusion interruption should be considered in highly selected patients. Interruption can result in severe pain or agitation and subsequently the need for higher doses of analgesics in some patients. Alternative dosage forms and delivery methods may represent both conservation strategies and therapeutic alternatives. Fentanyl patches may be appropriate for some stable patients in the ICU who require infrequent dose titration. Some long-acting opioid preparations (Hydromorph Contin®, Purdue Pharma, Pickering, ON, Canada; M-Eslon®, Ethypharm Inc, Montreal, QC, Canada) can be administered via large bore feeding tubes.[24] These capsules can be opened, and the coated granules administered via feeding tube without crushing, but they notoriously obstruct narrow bore feeding tubes. Remifentanil or sufentanil may also be reasonable alternatives for opioid infusions, but cost considerations may limit feasibility at some institutions. Finally, lidocaine may be used for pain alone or as an adjunct, but may not be appropriate for all centres because cardiac monitoring is required.

Neuromuscular blocking agents (NMBAs)

In the ICU, NMBAs as short-term infusions in combination with deep sedation are used in cases of ARDS to facilitate mechanical ventilation.[25] In Canada, the non-depolarizing agents cisatracurium and rocuronium are available, while the use of the depolarizing agent succinylcholine is limited because of concerns of hyperkalemia development in the ICU population. Both cisatracurium and rocuronium can be used interchangeably for continuous infusions in ARDS patients[26]; however, rocuronium is preferred for intubation because of shorter onset time. Other NMBAs are available in other countries, and Health Canada has recently permitted the importation of pancuronium and vecuronium during the COVID-19 pandemic.[27] Efforts to use the lowest effective dose for the shortest time possible should include dose titration according to both train-of-four monitoring and observed respiratory effort.[28] Often the desired effect can be achieved without full paralysis. Using a combination of both titration methods is useful to identify the lowest effective dose. Alternatively, intermittent dosing instead of continuous infusions may be effective in some patients.[29] Pharmacokinetically, it is impossible to achieve the same consistent drug exposure as continuous infusions because of the short half-lives of these drugs, but intermittent dosing may be sufficient for some patients who only need light or intermittent paralysis. Short-term magnesium infusions are known to boost the effect of NMBAs and this practice is best described in the anesthesia literature.[30] While possible in the ICU setting, this strategy is less desirable because large doses of magnesium are required as continuous infusions and there are associated risks in patients with kidney injury.

Vasopressors and inotropes

In Canada, the most commonly used agents for continuous infusions are norepinephrine, epinephrine, dopamine, vasopressin, dobutamine, and milrinone.[10] Phenylephrine can be administered as a continuous infusion but is more often used for intermittent IV bolus dosing in distributive shock. Drug shortages are likely to be less problematic in this field given the number of options. Conservation strategies for vasopressors should include targeting a

lower level of sedation in eligible patients. Many sedatives have direct vasodilating or myocardial depression properties, but lowering sedation targets can result in less blunting of patients' endogenous adrenergic drive. In patients with vasopressor refractory shock, stress-dosed steroids (e.g., hydrocortisone) can be considered as they reduce vasopressor dosing.[31] Enterally administered midodrine is used to mitigate hypotension during dialysis and can be given intermittently to ICU patients to reduce IV vasopressor requirements.[32] Finally, a lower blood pressure target could be considered in some patients provided they maintain evidence of end-organ perfusion.[33] Ephedrine may also be used as a less desirable alternative as it can be administered IV, enterally, or intramuscularly (IM), but rapidly results in tachyphylaxis thus limiting its role.[34]

Drugs used in cardiac arrest and rapid sequence intubation

Code carts (or crash carts) and intubation kits typically contain a large number of medications that are often a source of waste due to misuse, lack of use, or contamination. In the context of a pandemic such as COVID-19, contaminated carts/kits cannot be reused and result in significantly more waste. One strategy to minimize waste is to designate carts and kits for COVID-19 areas so unused drugs could be used in the same area. Drugs and other supplies could be sealed in plastic bags to minimize the risk of contamination. Alternatively (or in addition), code carts could be kept outside of the patient's room and the drugs could be passed in as needed to minimize waste and contamination. This strategy is less desirable during the COVID-19 pandemic because of the increased need for PPE and risks associated with opening and closing doors of isolation rooms. For rapid sequence intubation, combinations of drugs including propofol, rocuronium, succinylcholine, ketamine, fentanyl, and phenylephrine are often used and fall into multiple classes of drugs at risk of shortage. For most agents, alternatives within the same class or similar drugs exist. Etomidate could be used in place of propofol, lidocaine could be used in place of fentanyl, and succinylcholine could be used in place of rocuronium. A variety of alternatives that can be given via rapid IV injection can maintain blood pressure, such as norepinephrine, ephedrine, or epinephrine.

Metred-dose inhalers

Metred-dose inhalers deliver aerosolized drugs such as bronchodilators (e.g., salbutamol), anticholinergic agents (e.g., ipratropium), and corticosteroids (e.g., fluticasone). Although not exclusively used in the ICU, a shortage of these drugs or devices would affect many hospitalized patients, so a variety of conservation efforts should be considered for all hospitalized patients prescribed these drugs. Firstly, regular salbutamol and ipratropium prescriptions should be reserved for patients with evidence of bronchospasm. Often in the ICU, routine scheduled dosing is prescribed for mechanically ventilated patients who instead could tolerate "as needed" dosing. Nebulization of ampules could be used instead of MDIs in patients without COVID-19 because of potential virus aerosolization from respiratory secretions. The hospital could adopt a "patient's own medication" policy for MDI-delivered drugs. Typically, when a patient is prescribed an MDI in hospital, a full canister is dispensed (containing as many as 200 doses). These partly used MDIs are then typically sent home with the patient upon discharge, or are thrown away. If patients were advised to bring in and use their own MDIs, this could significantly reduce waste. Technically, MDIs could be redeployed if dispensed with a spacer device that is changed for each patient and/or have the MDI mouthpieces sterilized between patients. This strategy was felt to be less desirable given the resources required and the need to confirm that sterilization procedures are effective. Within these classes of drugs typically delivered by MDI, longer acting agents exist and are associated with better outcomes and reduced need for rescue therapy than shorter acting agents.[35] Long-acting beta-agonists (e.g., salmeterol and formoterol) could be used in place of more frequently dosed salbutamol. Long-acting anticholinergics (e.g., tiotropium) could be used in place of more frequently dosed ipratropium. In non-intubated patients, other delivery devices such as Turbuhalers® (AstraZeneca Canada, Mississauga, ON, Canada) or Handihalers® (Boehringer Ingelheim Canada, Burlington, ON, Canada) could be used instead. Salbutamol administered as an oral tablet and older drugs like theophylline were considered but were less desirable alternatives because of discomfort in prescribing, risk of adverse events, and drug interactions.

Proton pump inhibitors (PPI) and histamine2-receptor antagonists (H2RA)

In the ICU, PPIs (e.g., pantoprazole, lansoprazole) and H2RAs (ranitidine) are most often used for pharmacological stress ulcer prophylaxis and the management of gastrointestinal bleeding.[36] In Canada, therapeutic alternatives exist within each drug class; however, only pantoprazole, ranitidine, and famotidine are available intravenously. Practically, H2RAs and PPIs could be used interchangeably for stress ulcer prophylaxis although clinical equipoise exists regarding whether or not stress ulcer prophylaxis is required in all ICU patients.[37] One

conservation strategy would be to limit pharmacological stress ulcer prophylaxis to patients considered to be at high risk (e.g., not enterally fed, on vasopressors, signs of coagulopathy). Early feeding strategies may also reduce the duration of stress ulcer prophylaxis if discontinued once patients can tolerate enteral nutrition.[38] Sucralfate is an alternative for stress ulcer prophylaxis but is considered less desirable if other options are available.[37] While PPIs are a mainstay in the management of gastrointestinal bleeding, twice daily dosing has similar outcomes as traditional continuous infusion does, and would result in less drug being used.[39] A hospital-wide strategy of promoting first-line antacid therapy for gastrointestinal reflux before using other therapies may result in less H2RA and PPI prescribing as well.

Diuretics

Furosemide is the most widely used diuretic in the ICU as it is available intravenously and enterally. During previous shortages of the IV product, enterally administered furosemide (typically at double the IV dosage) proved to be both clinically and cost effective and should be the first alternative to consider in a shortage. Other alternatives such as ethacrynic acid (available both IV and enterally) and thiazide diuretics could also be considered. Conservation strategies, such as furosemide infusions titrated by the nurse to a fluid balance target, have also been shown to not only be more efficient but also result in lower drug exposure.[40] Furosemide co-administration with a thiazide diuretic such as metolazone can also augment diuresis and theoretically requires lower doses of furosemide to achieve the same diuretic effect. Other considered alternatives included low dose dopamine infusions to augment urine output although this was less attractive because of hemodynamic side effects and a pro-arrhythmic risk.[41] Ultimately, dialysis is the definitive method for fluid removal in ICU patients but should be reserved for diuretic-refractory fluid overload.

Antimicrobials

In Canada, most classes of antimicrobials and antifungals have more than one agent. For example, ceftriaxone, cefotaxime, and ceftazidime are all third-generation cephalosporins. For other drugs with limited within-class options, such as vancomycin, gram-positive coverage can be achieved with antimicrobials from different classes such as daptomycin, linezolid, and trimethoprim-sulfamethoxazole. Therapeutic alternatives for anti-viral agents are limited. Conservation strategies for antimicrobials should focus on responsible prescribing. Engaging with antimicrobial stewardship programs where available is encouraged to ensure that durations of antimicrobial therapy are not unnecessarily extended, narrowing of antimicrobial coverage is timely, and that step down to oral therapy is done when appropriate.[42]

Antiarrhythmic drugs

In the ICU, the most commonly encountered arrhythmias are supraventricular tachyarrhythmias and the most commonly used antiarrhythmic drug is amiodarone. In the event of a shortage of amiodarone, other antiarrhythmic agents would be suitable (procainamide, sotalol, propafenone), but familiarity with dosing and monitoring may require consultation with clinical pharmacists and cardiology consult services. Conservation efforts should reduce the need for therapeutic alternatives. Most ICU patients with hemodynamically stable atrial fibrillation can be managed with a rate controlling strategy alone.[43] Antiarrhythmic agents may not be necessary after addressing potentially reversible risk factors such as correcting electrolyte abnormalities, discontinuing pro-arrhythmic drugs when possible, and diuresing fluid overloaded patients.[44] Attempting electrical cardioversion in hemodynamically unstable patients is sometimes effective and could be tried prior to initiating antiarrhythmic therapy.[43]

Other considerations

Personal protective equipment shortages

The reality of a pandemic is that drug shortages and PPE shortages are expected to occur simultaneously. It is likely that some drug conservation strategies or use of therapeutic alternatives may have negative consequences on other equipment shortages. For example, using antacids multiple times per day for gastroesophageal reflux instead of a daily PPI would require the nurse to enter the patient's room more frequently and subsequently consume more PPE. Competing priorities must be considered when determining which drug conservation strategies are feasible and appropriate.

While hospitals struggle to manage PPE shortages, strategies involving drug therapy should be considered to minimize unnecessary PPE usage by nurses having to frequently enter and exit patient rooms. Consolidating medication administration times can minimize the frequency of room entries by the nurse. If medication administration times could be arranged to coincide with other activities (e.g., bloodwork, glucose checks, physical assessments) room entries could be further reduced. In rooms with multiple patients, the timing of medication

administration could be coordinated for all patients. Discontinuation of unnecessary drugs and reducing the frequency of medication administration can also minimize room entries. Daily review of medication lists and avoiding prescribing non-essential home medications (e.g., bisphosphonates, vitamins without a diagnosed deficiency, antihistamines) may be appropriate. Consider once daily low molecular weight heparin therapy for thromboembolism prophylaxis instead of twice or thrice daily heparin. Daily doses of amlodipine for hypertension can be as effective as hydralazine administered four times daily. In COVID-19 patients, ribavirin can be administered as a daily dose rather than in divided doses. In patients who can swallow tablets, long-acting formulations of drugs (e.g., hydromorphone, metformin) may be appropriate. Glycemic control can be achieved with intermittent doses of long and short acting insulins as opposed to insulin infusions which often require hourly glucose monitoring. Similarly, nitroglycerin and fentanyl can be administered transdermally instead of by titrated infusions or intermittent dosing. Some centres have used extended IV tubing to enable the pump to be kept outside the room thus allowing nurses to hang, remove, and titrate IV therapy without entering the room. For some patients in parts of the hospital, it may be appropriate to allow self-administration of oral medication. Similarly, in the ICU, patient-controlled analgesia or even patient-controlled sedation may be appropriate for highly selected patients.[45,46]

Intravenous pump shortages

Intravenous infusions are utilized in the ICU more than any other area of the hospital. In the event that hospitals and ICUs surge over capacity, it is possible that there may be a relative shortage of IV pumps. IV pumps used today are programmable, safely deliver IV medications and fluids at accurate infusion rates, and are programmed with a library of drug profiles with dose, concentration, and infusion rate limits that reduce the risk of drug administration errors. Shortages of IV pumps would represent a significant threat to patient safety. In the event that pumps have to be conserved within the hospital, a number of strategies could be considered relevant to drug therapy. These revolve around considering alternative dosing strategies, routes, and methods of drug administration. Where possible, intermittent IV dosing or (preferably) enteral dosing could be considered. Intermittent bolus dosing of drugs such as furosemide, insulin, labetalol, opioids, sedatives, and PPIs could be used instead of continuous infusions. Fentanyl patches could be used in place of opioid infusions. Electrolyte replacement should be done enterally when appropriate. Consultation with a dietitian may be appropriate to consider switching patients on parenteral nutrition to enteral nutrition or even cycling parenteral nutrition over night to free up the pump during the day. Patients requiring anticoagulation for venous thrombosis or pulmonary embolism could receive intermittent subcutaneous dosing of low molecular weight heparin rather than a heparin infusion. Antimicrobials with good bioavailability (e.g., ciprofloxacin and fluconazole) could be given enterally as opposed to IV. Early step down to enteral antimicrobial therapy may be appropriate and consultation with a clinical pharmacist or antimicrobial stewardship program would be warranted.

Local considerations for navigating drug shortages

While drug shortages under ideal conditions are often predictable, drug shortages during a pandemic are less so. Conservation strategies and therapeutic alternatives should be considered well in advance if possible and be part of the hospital's disaster/pandemic preparedness planning. The recommendations made by the Ontario COVID-19 Drug Shortage Task Force may not be appropriate for all hospitals and circumstances. Consultation with end-users, nurses, pharmacists, physicians, and administrators is strongly encouraged to ensure conservation strategies or therapeutic alternatives are feasible, safe, and practical for each institution. It is important to consider competing priorities (e.g., available resources and PPE or pump shortages) as implemented changes may have significant impacts on other vital resources. Finally, drug shortages during a pandemic are sometimes transient, unpredictable, and fluctuate rapidly. Frequent reassessment and adaptation are expected and necessary.

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