Preparing for COVID-19 Related Drug Shortages

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The COVID-19 pandemic has dramatically impacted all aspects of healthcare delivery.[1] There is widespread concern that increased clinical demands due to the virus will outstrip available resources. Much attention has focused on how to view these suddenly urgent issues of distributive justice through the established lens of public health ethics.[2] The majority of these discussions have focused on how to prioritize and ration selected resources, namely personal protective equipment, intensive care unit beds, and ventilators.[3] While these are indeed critical conversations, the pharmaceutical drug supply, historically threatened, remains incredibly vulnerable at this time.[4] Indeed, providing care to those who are critically ill both with and without COVID-19 presupposes the availability of essential medications to treat their pain, sedate them, address secondary infections, and maintain their blood pressure.

Drug shortages represent an ongoing public health crisis that predates COVID-19. The unavailability of life-saving medications engenders incremental expenses, patient harm, and increased medical errors, causing widespread trepidation in oncology, critical care, infectious disease, and innumerable other settings.[5] A recent FDA report summarizes and contextualizes the underlying root causes and potential solutions, highlighting economic drivers as the primary cause of drug shortages.[6] Recent legislative attention promised incremental steps for mitigation.[7] The current pandemic caused disruptions to domestic and international supply chains as well as globally increased demand, further straining an already-broken system. While the federal government and other groups continue to work on potential solutions[8], the impact at the bedside will be formidable, and its scope remains as uncertain as the evolution of the pandemic itself. Herein, we provide guidance for clinicians and the institutions tasked with

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preventing, mitigating and managing potential scarcities of essential medications in the current pandemic.

Collaboration

Formulating a plan and response to impending drug shortages requires information. Given that drug shortages have been an extant reality for the past decade, pharmacists and health systems have become adroit at monitoring and responding to them; in fact, it has even become a component of pharmaceutical training.[9] Much of this information is available online in formats that are easily synthesized by institutions and clinicians. Both the FDA[10] and the American Society of Health-system Pharmacists[11] maintain dynamic databases of current drug shortages, and these resources can be invaluable. Independent healthcare companies may also provide guidance and data regarding how specific drugs are impacted in real-time.[12]

Regional communication can determine how local supply chains are impacted, and potential coordination and sharing mechanisms are also critical.[13] Ideally, information sharing should occur via a central repository or clearing house. For example, in many states, the local government requires individual health systems to report the number of ventilators and reserves the right to re-allocate these ventilators to communities and hospitals in need. Similarly, at the federal level, the Department of Health and Human Services (HHS) is responsible for allocating the limited remdesivir supply to individual states. Although this process has been far from perfect, such a model of distribution holds promise and should not be abandoned.

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Sharing *information* is an important first step; the second and more difficult step involves actual sharing of *medications* across hospitals and health systems. Despite calls to allow such care coordination,[14] barriers remain, including the need for cooperation by competing health systems, concerns about potential liability, and legal regulations that affect transfer of drugs. In the state of Maryland, in an effort to promote uniform and consistent prioritization of scarce resources, e.g., ventilators, ICU beds, and medications, competing hospital systems have aligned to create an agreed upon joint allocation framework. Importantly, such an approach assures the public that allocation will occur in a thoughtful, transparent, and fair manner.[15]

In the COVID-19 era, siloed information as well as manpower is a real threat. Thus, in this time of crisis, it is critical to rely upon and expand these resources and networks. Many larger institutions maintain dedicated resources to identify and mitigate shortages, yet may still struggle to communicate real-time information across service lines and disciplines. Communication may be easier at smaller institutions, yet these organizations may lack resources with clear implications for patients and further aggravating disparities in access to basic and critical medications. Given the need for rapid redeployments and massive changes in manpower assignments, ensuring that increased efforts focus on drug shortage responses will be critical. Tantamount to this effort is facilitating communication between pharmacists – those tasked with maintaining supplies, as well as those embedded with clinical teams – in order to inform the clinical team of how supply may impact care delivery.

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Conservation and Flexibility

Evidence-based preservation of drugs that are in limited supply, even before critical shortages occur, is a necessary component of a cohesive rationing strategy. Often informed by the pharmacists serving within the interprofessional group,[16] critical care providers are all-too-familiar with shortages of medications that are an essential part of their day-to-day management, and thus, are accustomed to improvising in selected circumstances. The parenteral opioid shortage and shortage of small volume saline has similarly required workarounds and alternatives. Proactively implementing some of these strategies even prior to critical shortages is of value, especially because of the disruption of supply chains that may engender shortages with even less notice than before COVID-19.[17] Pandemic-era strategies for conservation of commonly used critical care agents at-risk of shortages are presented in Table 1, recognizing that these shortages are often regional and unpredictable, and intensive care protocols and strategies are highly individualized. As another example, while intravenous solutions are liberally administered in acute care settings,[18] novel strategies that safely maintain fluid balance while conserving resources are worth considering.[19] Anesthesia providers are also adept at selecting alternative regimens during shortages. As organizations balance critical and elective surgeries with current or presumptive planned needs, flexible anesthetic and sedation techniques are vital.

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Communication

Scarce resource allocation committees are being engaged at many institutions to manage anticipated critical shortages related to COVID-19, in many cases informed by statewide guidance.[20] However, many may be centering on ventilators, ICUs and other specific high-ticket resources. We call upon stakeholders, from governments to clinicians, to refocus some of these efforts on essential medications. Established workflows and rationing criteria that predate COVID-19 enumerate clear prioritization schema for scarce medications that consider ethical, logistical, and legal components.[21,22,23] Many of these will need to be updated and amended to be applied appropriately to the current pandemic. This relates to the types of shortages we anticipate, as well as to the reality of medical practice in the midst of a pandemic.

As one component of this effort, pharmacists and institutional scarce resource allocation groups will need to transparently consider the triggers to formally consider a drug supply threatened, limited, or subject to rationing. The lines between routine care, evidence-based conservation, and rationing are important. There is a lack of consensus as to the definition of a drug shortage with the FDA and ASHP, each defining the threshold for a drug shortage differently. The first step in addressing drug shortages is need for agreement on an accepted and common definition. As ASHP's drug shortage definition is broader in scope, we prefer this approach. Given the unique nature of local supply chain and distribution, arguably, decisions regarding mitigation and conservation strategies inevitably will occur differently by individual hospitals and health systems. Irrespective, altering the standard of care must be

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discussed openly with patients. In fact, supporting transparency, some have argued that hospitals should publicly post when they are faced with drug shortages.[24]

Even if there are sufficient ventilators, a critical shortage of sedatives, paralytics and/or opioids will obviate the ability to safely keep patients intubated; data suggest that these shortages have already been associated with inadvertent extubations.[25] Moreover, shortages of vasopressors and inhalers may limit ability to support critically ill patients regardless of disease-state or respiratory status, and will need to be more explicitly built into rationing schema.

Scarce resource allocation teams must also consider the understandable, yet nonetheless troubling rush to adopt putative treatments for COVID-19 despite no proof of safety or effectiveness, such as hydroxychloroquine and azithromycin, among many others.[26,27] In the case of hydroxychloroquine, hoarding has prompted shortages, jeopardizing the well-being of patients for whom hydroxychloroquine is a proven intervention. Once viable and effective treatments and/or vaccines for COVID-19 are available, prioritizing nascent supplies will present a formidable ethical and logistical challenge, albeit one that will depend upon unknown clinical and logistical factors (who stands to most benefit, oral versus parenteral dosing, among a litany of others). The initial experience with remdesivir is a deeply troubling harbinger.[28] Beyond the scope of this paper, in the coming days and months, this matter demands global attention.

Those in charge of institutional pandemic responses must integrate with extant resources and individuals to determine how best to plan for these eventualities. Moreover, ensuring that such plans are shared broadly – from clinical pharmacists to hospital executives to

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policymakers and beyond – will be critical in order to be able to respond to critical shortages in real-time, and adjust clinical workflow and appropriate prioritization accordingly.

Conclusion

COVID-19 has upended an already-vulnerable medication supply chain and risks engendering devastating shortages of life-saving drugs, regardless of whether patients suffer from this virus. Clinicians and the institutions for which they work will need to communicate at local, regional, and national levels to appropriately respond. Whenever feasible, they will need to use best available evidence to conserve existing supplies and they will need to plan for contingencies such as how to prioritize patients in the event of critical shortages. Only with clear lines of communication and a proactive, collaborative approach can we weather this impending storm.

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Table 1: Stepwise Approach to Conserving Commonly Used Critical Care Agents

Preference	Analgesia	Sedation	Neuromuscular blockade
First-Line	Fentanyl	Dexmedetomidine or Propofol Consider adding ketamine	Cisatracurium
Second-Line	Hydromorphone	Lorazepam	Vecuronium
Third-Line	Morphine	Midazolam	Rocuronium
Comments	Consider adjunctive acetaminophen, gabapentin, oxycontin	Do not use dexmedetomidine alone for deeper sedation (Riker <3)	Ensure appropriate sedation and pain control before initiating

These recommendations align with the Surviving Sepsis Campaign: Guidelines on the Management of the Critically Ill Adults with Coronavirus Disease 2019 (COVID-19) and 2018 PADIS clinical practice guidelines.[29,30]

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