Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Air Medical Journal 39 (2020) 317–323

Contents lists available at ScienceDirect

Air Medical Journal

journal homepage: http://www.airmedicaljournal.com/

Critical Care Update

The Virus II: Triage and Treatment

Mithun R. Suresh, MD, David J. Dries, MSE, MD

As coronavirus disease 2019 (COVID-19) and future respiratory viruses become a part of life, this issue of the journal will address two more topics of interest. The one obvious topic is that of *treatment*. We should be aware that approaches to management for COVID-19 will continue to evolve, and episodic updates may be found discussing different strategies in the journal. However, an important practical and ethical question comes when resources are limited and we have to decide where to send patients, should we transfer patients, and what treatment or transport resources can be made available to a particular individual. These issues come under the question of *triage*.

Triage

Hick JL, Einav S, Hanfling D, et al, on behalf of the Task Force for Mass Critical Care. Surge capacity principles: care of the critically ill and injured during pandemics and disasters: CHEST consensus statement. *Chest*. 2014;146(suppl):e1S-e16S.

Hick JL, Barbera JA, Kelen GD. Refining surge capacity: conventional, contingency, and crisis capacity. *Disaster Med Public Health Prep*. 2009;3(suppl):S59-S67.

Hick JL, Nelson J, Fildes J, et al. Triage, trauma, and today's mass violence events. *J Am Coll Surg*. 2020;230:251-256.

Fundamentally, triage refers to actions that occur when the demand for emergency and critical care resources exceeds the supply. During a medical disaster, such as a mass casualty incident or a pandemic, a primary goal of health system leadership should be to minimize the gap between demand and supply. This requires awareness of both demand and supply and, specifically, strategies to control the demand while augmenting supply. Several steps need to be taken to manage demand. These steps vary based on the medical disaster. For example, steps to control demand during a pandemic include public health initiatives, immunizations, and treatments short of critical care. Regarding supply, real-time awareness of staff, space, and equipment is imperative to delivering optimal critical care. The importance of triage cannot be overstated, and in recognition of its importance, many health systems will have named individuals or work groups (eg, incident commander or incident committee) whose primary responsibilities include monitoring and assessing the status of resources and personnel in response to a problem.

The demand for critical care resources is maximized in a disaster when a significant influx of patients presents to a health system. This phenomenon has been described to occur in the three stages that reflect the severity of the problem and the corresponding response of the health system. During the initial period of rapid patient accrual, health systems rely on conventional and contingency response strategies in order to match patient care demands with available medical resources. Examples of conventional care include using immediately available resources, such as filling all rooms of all intensive care units (ICUs), calling in ICU staff and personnel that may not be scheduled to work, and using equipment and supplies that have been stored in the hospital, with the overall goal of being able to expand critical care capacity to at least 20% over the typical maximum level within a few hours. Examples of contingency care include providing critical care in overflow units that have been repurposed (eg, postoperative units, operating rooms, etc), having non-ICU staff care for critically ill patients under the supervision of ICU personnel, and using adaptation and substitution of current supplies in order to meet patient care needs. The goal of these contingency care actions is to ultimately expand critical care capacity 100% beyond its typical maximum level within 24 hours. Beyond the conventional and contingency stages of a response to rapid patient influx or surge, the response will transition to the crisis stage, and it is at this stage when triage is needed to reallocate insufficient resources, including space, staff, and supplies, in order to provide the greatest good for the largest number of patients.

During a medical disaster, triage frequently begins in the prehospital setting, and emergency medical services (EMS) providers make primary triage decisions. Reassessment and re-evaluation is needed because triage decisions may need to be adjusted based on changes in patient status. EMS providers should have algorithms to help guide triage decisions, or algorithms may be modified in conjunction with a physician or senior health care provider working in the emergency department of the destination hospital. Upon arrival to the emergency department, patients may be directed to a designated area based on their condition. In a mass casualty scenario, areas of the emergency department may be delineated by color coding that corresponds to the following triage categories: the “green” zone for patients with minor injuries (the “walking wounded”), the “yellow” zone for patients with moderately severe injuries that are not life-threatening (delayed), the “red” zone for severe and life-threatening injuries (immediate), and the “gray” or “black” zone for patients expected to succumb or who are dead on arrival. During a pandemic, patients may be separated into areas of the emergency department based

1067-991X/$36.00
© 2020 Air Medical Journal Associates. Published by Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.amj.2020.06.009

on symptoms. For example, the COVID-19 pandemic has compartmentalized many emergency departments into areas for patients with fevers or respiratory symptoms suspicious for COVID-19 and areas for patients with other medical problems. With their arrival in the emergency department, patients will typically receive identification tags corresponding to their destination zone (eg, green, yellow, red, gray, or black during a mass casualty incident). Patients need to be registered into the electronic health record as quickly as possible so that documentation can be initiated. During a rapid influx of patients or surge, it may be useful to have a designated individual in the emergency department who is in charge of facilitating the immediate triage of patients after their arrival via EMS units. Typically, this individual should be an experienced provider in emergency medicine or critical care with knowledge of prehospital EMS triage protocols and workflows of the emergency department, operating rooms, and ICUs.

After primary triage is completed and after arrival to the hospital, secondary triage occurs. The goals of secondary triage are to determine if any advanced diagnostics or interventions are needed. Coordination and planning can be challenging during this phase because a large number of patients with varying levels of acuity may require transport or interventions in different areas of the hospital, including the resuscitation room, imaging department, or procedural sedation areas. During a mass casualty incident, an important triage decision is to determine which patients need to go to the operating room. Operating room triage can be challenging when many patients have serious traumatic injuries. The color-coded tagging system may provide guidance for prioritizing patients needing to go to the operating room. Moreover, preoperative areas may serve as an additional assessment point to help prioritize patients for the operating room. An added layer of coordination and planning may be needed if multiple subspecialty providers are needed for an operative case. Situational awareness of staff, space, and supplies and patient clinical status are essential to making accurate triage decisions, so secondary triage responsibilities will frequently be assigned to another experienced physician or provider. A strategy that may be used to assist with secondary triage decisions involves consideration of the following factors: task, time, and treater. This strategy is sometimes used by the military when prioritizing interventions and requires the individuals making triage decisions to consider the needed interventions, the time and resources consumed by those interventions relative to other priorities, and the expertise required to perform them. The ultimate goal of secondary triage is to ensure that patient flow is "1 way" through the emergency department because more patients will be arriving who need immediate medical attention. Accurate disposition planning is a vital component of secondary triage in order to prevent the emergency department from becoming a bottleneck for patient throughput. For small hospitals or those with limited critical care capabilities, disposition may include transferring a patient to another medical facility. During a pandemic, disposition may entail early identification of patients needing the ICU. Finally, and similar to primary triage, frequent reassessment and re-evaluation is needed in order adjust secondary triage decisions based on patients' current clinical status.

Christian MD, Sprung CL, King MA, et al, on behalf of the Task Force for Mass Critical Care. Triage: care of the critically ill and injured during pandemics and disasters: CHEST consensus statement. *Chest*. 2014; 146(suppl):e61S-74S.

Maves RC, Downar J, Dichter JR, et al, on behalf of the ACCP Task Force for Mass Critical Care. Triage of scarce critical care resources in COVID-19. An implementation guide for regional allocation: an Expert Panel Report of the Task Force for Mass Critical Care and the American College of Chest Physicians. *Chest.* 2020; 158:212-225.

Tertiary triage refers to decisions regarding definitive care, and, typically, these are decisions that are made regarding care in the ICU. During crisis scenarios, difficult decisions may be needed. For example, when patients are critically ill or injured and have a poor prognosis, should limited resources continue to be used to provide maximal care? Reallocation of resources may need to occur in these settings, and this may reflect withdrawal of care or delaying some definitive or noncritical aspects of care until additional resources are available. The current state of supply chains combined with ongoing assessment of patients' clinical condition will influence triage decisions at this stage. Unfortunately, even when additional resources become available, care restrictions may be needed if the number of patients is overwhelming. Ideally, decisions to restrict care should be implemented after consultation with other providers and in conjunction with the disaster command team.

An important aspect of tertiary triage is coordination with other health systems in a geographic or administrative area. This may include coordination with local or federal public health agencies. Before reallocating critical care resources during tertiary triage, plans should be initiated to conserve, substitute, adapt, and reuse resources if this is not already being performed. Hospitals should also reach out to other health systems or local agencies to identify resources to donate or share. Some areas may have a mass critical care plan for their region that assists with coordinating triage and supply chain decisions. Similar to primary and secondary triage, designated individuals may be responsible for tertiary triage decisions, and because these decisions affect the delivery of critical care, these individuals should have experience and training in critical care. Many guidelines and protocols are available to assist with decision making at this stage, and, generally, they should be followed in most cases rather than relying on arbitrary judgment. However, medical disasters are dynamic events, and deviation from predefined protocols may be needed as more information is obtained regarding resource demand and supply or the disaster itself (eg, new knowledge of the mass casualty incident, natural disaster, pandemic, etc). Likewise, if reassessment and re-evaluation of patients' clinical status determines that there have been significant changes, triage decisions may need to be adjusted if the protocols are no longer applicable or appropriate. Consequently, health systems should have a mechanism in place such that these deviations and breaks from protocols can be approved and implemented rapidly if needed.

When the patient burden during a disaster is so overwhelming that sufficient critical care resources are not available, tertiary triage may involve using inclusion and exclusion criteria regarding these resources. Broadly, these criteria call for admission to the ICU if patients need mechanical ventilator support or if hypotension and objective evidence of shock are present that cannot be managed on a general medical ward or that require vasoactive medications for resuscitation. With these criteria, an underlying objective is to provide critical care resources to individuals who would be likely to benefit from admission to the ICU. Likewise, exclusion criteria serve to identify individuals with a poor prognosis despite aggressive cares having a high likelihood of death or needing resources that are not available. Coinciding with the implementation of inclusion and exclusion criteria is incremental survival, where the likelihood of survival relative to the amount of resources used is maximized. There has been some interest in using prediction and prognostic scores to help guide tertiary triage. Prediction scores could be considered if they can reliably predict mortality, and, when used, a threshold

of 90% mortality could be an initial cutoff for exclusion from being admitted to the ICU. Regardless of the criteria or thresholds that are initially used to include or exclude individuals from ICU care, changes may be necessary based on reassessments of demand, supply, and patient clinical status. Reassessment should continue for at least the first 72 to 96 hours after admission to the ICU, and, accordingly, the inclusion and exclusion criteria should be re-evaluated in the context of patient response to care.

Ultimately, tertiary triage for critical care resources requires providers to make the following determination regarding their patients: 1) they are too well and do not need critical care, 2) they are too ill to benefit from critical care because of a low likelihood of survival, or 3) they are ill and would benefit from critical care. Triage decisions should serve to direct the use of critical care resources for patients in the third group. Because these decisions may entail withholding or withdrawing critical care from some patients, it is important to understand that during a medical disaster, triage protocols may constitute the standard of care. Communication is particularly important at this stage because decisions must be clearly explained to patients and family members so that they understand medical decision-making protocols and treatment strategies when triage steps are taken. Community-level communication and education may also be needed, and the advantages of these efforts include increased transparency and trust among the general public. Triage protocols should receive approval from health system administrative and regulatory bodies before implementation in order to minimize the risk of legal ramifications or liability. Furthermore, if these protocols can be presented to the public in advance of completion, opportunities for feedback and suggestions for improvement may further improve community relations and trust.

Frykberg ER. Triage: principles and practice. *Scand J Surg*. 2005;94:272-278.

Because triage decisions directly impact patient care, it important that accurate decisions are made. There are two types of errors pertaining to triage: undertriage and overtriage. Undertriage occurs when the degree of illness or injury severity is underestimated and results in delays in treatment, management with insufficient resources or prioritization, or treatment in a lower level of care when a higher level of care is needed. Overtriage occurs when the degree of illness or injury severity is overestimated, resulting in aggressive or immediate care that is unnecessary and excessive; management with an overabundance of resources; or treatment in a higher level of care when a lower level of care would be sufficient. Both undertriage and overtriage can lead to negative outcomes. During a mass casualty incident, accurate triage is critical to provide the greatest good for the greatest number of patients, and accurate decisions must be made starting in the prehospital setting during primary triage. Early identification of patients with life-threatening injuries is critical to ensuring that they are evaluated and treated immediately after arrival at the hospital. Individuals with minor injuries can wait to be evaluated and treated after arrival to the hospital, and recognition of these minor injuries is equally important so that valuable time is not wasted. In a mass casualty incident, avoiding undertriage and overtriage can be challenging simply because of the large number of patients who present to the hospital in a short period of time with very little accompanying information about their injuries or clinical status. Strategies to avoid these errors include having multiple points of triage, which would occur during secondary and tertiary triage after arrival to the hospital. Experienced and appropriately trained triage officers may also be helpful in minimizing the number of errors. During the initial stages of triage, the primary goal is to ensure that patients get to the correct destination based on the acuity of their illnesses and injuries and are evaluated and treated within the appropriate time frame. Later stages will focus on ensuring appropriate resource utilization based on injury severity, disease course, prognosis, current demand, and supply priorities. Accordingly, this process requires frequent reassessment.

Sprung CL, Joynt GM, Christian MD, et al. Adult ICU triage during the coronavirus disease 2019 pandemic: who will live and who will die? Recommendations to improve survival. *Crit Care Med*. doi:10.1097/CCM.00000000004419, accessed 2020 May 6.

Hick JL, Rubinson L, O'Laughlin DT, Farmer JC. Clinical review: allocating ventilators during large-scale disasters—problems, planning, and process. *Crit Care*. 2007; 11:217.

Patient care strategies for scarce resource situations. Available at: https://www.health.state.mn.us/communities/ep/surge/crisis/index.html. Accessed 2020 Jul 07.

During the COVID-19 pandemic, ICU triage has received significant attention because many health systems may not have enough critical care resources to care for a large number of patients. To begin, patients should be assessed to see if they meet any of the exclusion criteria, which include advanced directives specifying a wish to forgo intensive care practices, acute catastrophic injuries, terminal illnesses with poor prognoses, or simply refusing ICU admission. Inclusion criteria should be applied next, such as the presence of respiratory failure (severe hypoxemia, respiratory acidosis, or unstable airway) or shock (needing vasopressors or inotropes to avoid hypotension or clinical evidence of end-organ hypoperfusion). The remaining patients at this point are the cohort requiring admission to the ICU, and they should be admitted based on their priority for critical care. A recent consensus statement describes four categories of priority based on performance score, comorbidities, organ failure, and predicted survival, with admission priority given to patients in category 1 and the patients in category 4 having the last priority for admission. Health systems have multiple options to determine methodologies and scores that are used to determine priority. There are several options for performance scores, with examples including the Eastern Cooperative Oncology Group score or the Clinical Frailty Scale. The American Society of Anesthesiologists score is frequently used for describing comorbidities. Organ failure can be assessed by counting the number of failed organs or using a clinical score such as the Sequential Organ Failure Assessment (SOFA) score. Predicted survival varies among the categories, with category 1 typically greater than 80%, category 2 greater than 50%, category 3 less than 50%, and category 4 less than 20%. Reassessment should occur regularly; priority assessment should be performed every 24 hours for patients needing ICU admission and overall clinical course reassessment by no later than 10 to 14 days to determine if reallocation is needed. In situations in which a tiebreaker is needed (eg, more patients in a priority category than available ICU beds), then incremental ICU benefit (saving the most life years) could be used to determine admission followed by first come, first served if a second tiebreaker is needed. Health systems should modify this framework to create an algorithm that best aligns with their resources and patient population.

Another resource that has received significant attention is mechanical ventilation because many health systems may not have enough ventilators if they are required to care for a large number of patients with COVID-19 and respiratory failure. In this setting, reallocation of ventilators may be needed if the demand for ventilators becomes greater than the supply. For providers, making decisions regarding ventilator allocation can be ethically and morally

challenging. To assist with these decisions, predefined decision support protocols that have been vetted and approved by hospital administrators and local and regional health care leadership provide guidance. An example of one of these algorithms is described by Hick et al and also in a document from the Minnesota Department of Public Health titled "Patient Care Strategies for Scarce Resource Situations." The first step of this algorithm requires providers to assess multisystem organ failure by calculating the SOFA score, which provides an assessment of the overall severity of illness and prognosis. Next, providers should estimate the duration of benefit and need for mechanical ventilation. This may be a more subjective assessment because it will require incorporating prognoses, underlying comorbidities, and acute medical conditions. Providers should then determine if there has been clinical improvement or deterioration after initiating mechanical ventilation. Using the SOFA score as part of the decision matrix, providers decide if ventilator reallocation is needed from intubated patients with a lower likelihood of survival to patients with a higher likelihood of survival. This algorithm represents one strategy for ventilator reallocation. Providers should consult their institutions' protocols should they need to make decisions regarding ventilator reallocation. For health systems that do not have a process for ventilator reallocation, these references provide a framework from which they can develop their own protocol.

Treatment

Big Picture

Alhazzani W, Moller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Intensive Care Med*. 2020;46:854-887.

Murthy S, Gomersall CD, Fowler RA. Care for critically ill patients with COVID-19. *JAMA*. doi:10.1001/jama.2020.3633, accessed 2020 Mar 11.

COVID-19 is associated with severe disease requiring intensive care in approximately 5% of proven infections. Because this infection is becoming more common, like prior severe acute respiratory infection outbreaks, critical care will be an integral component of the global response to this problem. The rapid increase in the number of cases of COVID-19 in China in late 2019 demonstrated how quickly health systems can be challenged to provide adequate care. Fatality proportions were 7-fold higher in patients at the epicenter of the COVID-19 outbreak compared with areas outside of that immediate region. This emphasizes the importance of health system capacity to provide immediate local care to patients who are critically ill with COVID-19.

Patients who require critical care tend to be older with a median age of 60 years; 40% of these individuals have comorbid conditions, frequently diabetes and cardiac disease. Children have been observed to experience milder illness, although perinatal exposure may be associated with increased risk. There are limited data on pregnant women. Thus far, COVID-19 in pregnancy appears to be a mild problem. The median duration between the onset of symptoms and ICU admission has been 7 to 10 days, suggesting a gradual deterioration in the majority of cases. The most common reason for intensive care admission has been respiratory support, of which two thirds of patients have ultimately met the classic criteria for acute respiratory distress syndrome (ARDS).

Because there are many circulating respiratory viruses, differentiating COVID-19 from other pathogens, particularly influenza, is important and chiefly done using nasopharyngeal swabs or induced sputum, tracheal aspirates, or bronchoalveolar lavage respiratory tract samples for reverse transcriptase polymerase chain reaction testing and bacterial culture. Radiographic changes are suggestive but not specific. These include ground-glass opacities on computed tomographic (CT) imaging. Rapid access to diagnostic testing is a clinical priority allowing for efficient patient triage and implementation of infection control practices.

The management of severe COVID-19 is not different from the management of most viral pneumonias that cause respiratory failure. The principle features of patients with severe disease include the development of classic ARDS. However, intermediate stages, described later, have been observed frequently. Thus, careful screening for individuals best treated with classic ARDS management guidelines should take place as well as identifying individuals with less severe or earlier presentation in whom intervention short of aggressive mechanical ventilation may reduce the risk of progression of disease.

In settings with limited access to invasive ventilation or prior to patients developing severe hypoxemic respiratory failure, there may be a role for high-flow nasal oxygen or other noninvasive ventilation. However, the high gas flow of these techniques is less contained than in the closed circuit typical of invasive ventilators, which poses an additional risk of dispersion of an aerosolized virus in the health care environment, as may occur in the setting of a poorly fitting face mask.

Septic shock and specific organ dysfunction such as acute kidney injury appear in a significant proportion of patients with COVID-19 and are associated with increasing mortality. Mechanical hemodialysis needs may be significant, and, on occasion, emergent peritoneal dialysis may be used. At this point, firm management recommendations do not go beyond available evidence-based guidelines. There is no antiviral or immunomodulatory therapy for COVID-19 that has yet proven effective. Many patients have received trials of a variety of therapies. Unfortunately, much activity is outside the context of formal clinical research.

Mortality among infected patients may be in the range of 0.5% to 4% among patients requiring hospitalization. Mortality estimates vary for patients who become critically ill. The initial data from China suggest a wide mortality range from 22% to 62% in early Hubei Province cases. The exact cause of death is unclear. Hypoxia and multiorgan dysfunction are presumed causes. Clearly, there are wide knowledge gaps that remain to be filled.

Respiratory Care

Marini JJ, Gattinoni L. Management of COVID-19 respiratory disease. *JAMA*. doi:10:1001/jama.2020.6825, accessed 2020 Apr 24.

Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med*. 2020; 46:1099-1102.

COVID-19 is a systemic disease primarily affecting the vascular endothelium. Affected patients can progress from a respiratory infection to multiple organ failure. Thus, the vascular bed must be considered in the context of respiratory care of these patients.

Historically, ARDS has been characterized by noncardiogenic pulmonary edema, hypoxemia related to shunt, and a reduced aerated lung size, which account for low respiratory compliance. In this setting, increasing the lung size by reopening previously collapsed lung units may be achieved through the use of higher levels of positive end-expiratory pressure (PEEP), recruitment maneuvers, and prone positioning. Because high transpulmonary pressure induces stress across the lung that is poorly tolerated in ARDS, low tidal volumes, together with tolerance for hypercapnia, facilitate the goal of reducing ventilator-induced lung injury. In the early phases of ARDS, before the patient is fatigued or has been sedated, high transpulmonary pressures associated with vigorous spontaneous breathing may also contribute to lung damage.

Soon after respiratory distress associated with COVID-19 begins, patients retain good lung compliance despite poor oxygenation. Minute ventilation is characteristically high. Infiltrates are often limited and sometimes reflected in a ground-glass pattern on CT evaluation suggesting interstitial rather than alveolar edema. Many patients do not appear overtly short of breath. These patients can be described as having low lung elastance, high compliance, lower lung weight as estimated by a CT scan, and a low response to PEEP. In many patients, disease may stabilize at this stage without deterioration. In other patients, either because of disease severity or host response, a picture more consistent with typical ARDS may eventually be seen. When typical ARDS findings are noted, patients present with extensive CT evidence of lung consolidation, low lung compliance, higher lung weight, and better PEEP response. Obviously, these two descriptions reflect the extremes of the spectrum of disease, which includes a variety of intermediate stages, and characteristics may overlap. Another important feature is activation of the coagulation cascade with widespread micro- and macrothromboses in the lung and other organs. Elevated D-dimer levels are a finding associated with poor outcomes.

What is the best way to manage the patient with COVID-19 with good lung compliance? Contemporary recommendations include the acceptance of larger tidal volumes up to 7 to 8 mL/kg/ideal body weight. These tidal volumes are higher than those typically used with ARDS. Patients with high lung compliance in the setting of COVID-19 can be managed with a higher tidal volume, a lower PEEP, and a plateau pressure of approximately 20 cm H_2O yielding a driving pressure of approximately 10 cm H_2O if a PEEP of 10 cm H_2O is used. These thresholds are well below the standards for the typical management of ARDS. Accepting a slightly higher tidal volume could help avoid reabsorption atelectasis and hypercapnia caused by hypoventilation with lower tidal volumes.

The central issue in all stages of respiratory management is disrupted vasoregulation in which pulmonary vasoconstriction that normally occurs in response to hypoxia fails to occur because of an endothelial assault that does not match perfusion to ventilation and may result in profound hypoxemia. An initial response, boosting the fraction of inspired oxygen, may prove effective in the early stages. If increasing the oxygen content is insufficient, noninvasive ventilation such as a high-flow nasal cannula, continuous positive airway pressure, or bilevel positive airway pressure may stabilize the clinical course in mild cases provided that the patient does not expend excessive respiratory effort. If respiratory drive is not reduced by noninvasive support and oxygen, persistent strong spontaneous inspiratory efforts will increase tissue stress and raise pulmonary transvascular pressure, vascular flow, and fluid leakage. For these patients, early intubation, effective sedation, and possibly neuromuscular blockade may interrupt this destructive cycle. Initially, it may be appropriate to target a lower level of PEEP at 8 to 10 cm H_2O. Raising the mean transpulmonary pressure with higher PEEP or inspiratory time relative to expiratory time redirects blood flow away from overstretched open-air spaces, increases stresses on highly permeable pulmonary microvessels, and limits CO_2 exchange without the benefit of reopening of functional lung units.

If pulmonary edema increases with worsening lung disease, effective ventilating lung volume falls further, and low compliance presentation evolves. Concentrating the entire ventilation workload on already overtaxed lungs with reduced functioning volume increases the risk of progressive lung injury. Over time, superimposed aggressive ventilation and unchecked viral disease may lead to inflammation and edema promoting local and generalized thrombogenesis, cytokine release, right ventricular overload, and systemic organ dysfunction. In this advanced state of pulmonary injury, it is optimal to apply a more conventional lung-protective strategy including PEEP less than or equal to 15 cm H_2O, a lower tidal volume of 6 mL/kg or less, and prone positioning while attempting with medication administration to reduce the strenuous spontaneous breathing pattern and reduce oxygen consumption. Weaning from mechanical ventilation in these patients is likely to be time-consuming and should be done cautiously.

Cardiovascular

Tavazzi G, Civardi L, Caneva L, et al. Thrombotic events in SARS-CoV-2 patients: an urgent call for ultrasound screening. *Intensive Care Med*. 2020;46:1121-1123.

Oxley TJ, Mocco J, Majidi S, et al. Large-vessel stroke as a presenting feature of COVID-19 in the young. *N Engl J Med*. 2020;382:e60.

Marietta M, Ageno W, Artoni A, et al. COVID-19 and haemostasis: a position paper on Italian Society on Thrombosis and Haemostasis (SISET). *Blood Transfus*. 2020;18:167-169.

Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med*. 2020;46:1089-1098.

Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. 2020;191:145-147.

Multiple investigative groups draw particular attention to the link between cardiovascular disease, particularly thrombosis and embolic events, and COVID-19. An Italian group recently reported an exaggerated risk of acute pulmonary embolism, cardiac valve disease, and peripheral venous thrombosis. These findings relate to a link between inflammation and thromboembolic events. It is becoming clear that COVID-19 is associated with a diffuse vascular insult including activation of endothelial cells, platelets, and leukocytes, leading to triggering of the coagulation pathways. This phenomenon has also been reported as part of ARDS pathophysiology in which diffuse endothelial injury is seen. Patients reported by these Italian investigators had been sedated and mechanically ventilated in the critical care setting and received prophylactic low–molecular-weight heparin adjusted to body weight. Prophylaxis started with ICU admission. Despite prophylaxis, a variety of venous thromboembolic events were identified including pulmonary emboli leading to cardiac arrest in one patient. Another report cited by these investigators suggests a 40% incidence of pulmonary emboli in patients admitted with pneumonia associated with COVID-19. CT angiography was used to make the diagnosis of pulmonary embolism. Unfortunately, many patients did not receive early screening ultrasonography. These authors strongly recommend frequent venous ultrasound screening and monitoring for thromboembolic complications in patients hospitalized because of COVID-19. Right ventricular dysfunction was also identified in some patients suffering from pulmonary embolism. Any suggestion of right ventricular function changes without preexisting explanation should trigger consideration of venous thromboembolic complications of COVID-19.

Other reports note a disproportionate presentation of large vessel stroke in COVID-19 patients. Compared with the standard presentation of this severe complication, these writers report a clear increase in stroke compared with the incidence that would normally be expected. Often, these stroke patients had no COVID-19 symptoms or mild nonspecific disease. Again, a hypercoagulable state associated with COVID-19 may lead to disproportionally more large-vessel disease than small-vessel changes in

the presentation of stroke. Vascular bed inflammation is thought to drive thrombosis formation consistent with reports emerging from other investigators. Another recent report from the Netherlands found a 31% rate of thrombotic complications among 184 critical care patients with COVID-19 pneumonia.

Drugs

Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *JAMA*. 2020;323: 1582-1589.

Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med*. 2020;382: 1787-1799.

Vaduganathan M, Vardeny O, Michel T, et al. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. *N Engl J Med*. 2020;382:1653-1659.

Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe Covid-19. *N Engl J Med*. 2020;382: 2327-2336.

Gordon DE, Jang GM, Bouhaddou M, et al. A SARS-CoV2 protein interaction map reveals targets for drug repurposing. *Nature*. doi:10.1038/s41586-020-2286-9, accessed 2020 Apr 30.

Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. *JAMA*. doi:10.1001/jama.2020.6019, accessed 2020 Apr 13.

Many medication strategies are under investigation for COVID-19. There are no definitive results yet available. Following is a general list:

1. Angiotensin-converting enzymes/angiotensin receptor blockers: cardiovascular disease is a clear risk factor for complications related to COVID-19. Some investigators have linked this increase in risk to the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in patients with diabetes, hypertension, or heart failure. It is thought that these agents facilitate the entry of COVID-19 into the pulmonary epithelium through angiotensin-converting enzyme receptors. Prospective trials evaluating the safety for both of these agents are in progress. At present, a clear recommendation cannot be made. Patients who are taking these agents probably should continue these medications at present because they help manage recognized factors favoring poor outcome with COVID-19.
2. Nonsteroidal anti-inflammatory drugs: ibuprofen and acetaminophen are the classic agents in this group. At present, acetaminophen is the preferred agent because of the complication pattern seen with agents including ibuprofen such as gastrointestinal bleeding, fluid retention, and renal dysfunction. There are no trials supporting the recommendation to emphasize acetaminophen as an anti-inflammatory.
3. Repurposed agents: many existing drugs have been used outside the benefit of clinical trial data to treat COVID-19. Among these are neuraminidase inhibitors used to treat influenza, human immunodeficiency virus protease inhibitors, interferon, ribavirin, chloroquine or hydroxychloroquine, and azithromycin. Other drugs studied include corticosteroids and interleukin (IL)-6 inhibitors. There is limited evidence supporting the use of these agents; however, a theoretical benefit is present. In fact, chloroquine and hydroxychloroquine are associated with direct cardiac toxicity caused by rhythm changes.
4. Neuraminidase inhibitors: these agents are not expected to be effective for the prevention or treatment of COVID-19 because neuraminidase is not contained in this virus. A recently published trial with open-label drug administration randomized approximately 200 patients with severe COVID-19 illness to receive a human immunodeficiency virus protease inhibitor combination (lopinavir/ritonavir) as part of standard care. No benefit was demonstrated in comparison with standard care alone in rates of pathogen suppression, clinical improvement, or mortality. These agents may be associated with hepatotoxicity, pancreatitis, QT prolongation, skin eruptions, and gastrointestinal side effects. At present, these agents should not be used outside a clinical trial.
5. Immunosuppressive agents: the Centers for Disease Control and Prevention recommends that corticosteroids not be used routinely for the treatment of COVID-19 because they may prolong viral replication. This group recommends the use of steroids for COVID-19 patients with other indications for these drugs such as chronic obstructive pulmonary disease exacerbations and septic shock. The use of steroids in patients hospitalized with COVID-19 is not recommended in the setting of pneumonia and may be considered in the setting of a clinical trial for ARDS. IL-6 inhibitors may help control the cytokine storm released in response to COVID-19 and limit lung damage in patients with severe disease. Preliminary data suggest the control of pulmonary complications in COVID-19 patients with severe pneumonia and a lower rate of noninvasive or mechanical ventilation compared with placebo with IL-6 inhibition. The collection of trial data for IL-6 inhibitors in North America for patients with severe COVID-19 pneumonia is underway. For the most part, supportive care is recommended rather than reliance on these agents.
6. Remdesivir: this is an investigational broad-spectrum antiviral agent with preliminary data suggesting activity against COVID-19 and other coronaviruses in vitro and in animal models. Controlled trials are underway in multiple countries for the use of this agent as a treatment for severe COVID-19. Data from a compassionate use program, which have been published, showed a reduction in oxygen support requirements and subjective improvement in the ability to achieve extubation. The use of this drug has also been associated in a small trial with a faster time to recovery (11 days vs. 15 days with placebo, $P < .05$) and a trend toward improved mortality (8% vs. 11.6% with placebo).
7. Convalescent plasma: passive antibody therapy using pheresis serum from recovered patients having high titers of neutralizing antibodies may be considered for the treatment of COVID-19. A small data set from initial experience in China suggests that the use of convalescent plasma in severely ill patients may reduce the viral load and improve symptoms. Convalescent plasma may be used in the setting of a clinical trial or through an institutional access protocol. The Food and Drug Administration has also granted emergency access to convalescent plasma for individual patients with serious or life-threatening COVID-19 infection. Until a vaccine becomes available, convalescent plasma might be particularly beneficial for the prevention of infection in health care workers or relatives.

Summary Points

- Triage is fundamentally a supply and demand relationship examining available staff, material, and space in relationship to a situation that provides a significant drain on the health care resources of a community.

- Opportunities for triage begin in the field where decisions are made regarding transport status and continue in the emergency department where patients can be sorted from minimal to life-ending problems.
- When the burden of patient need during a disaster is so overwhelming that enough critical care resources are not available, a third level of triage involves inclusion and exclusion criteria, which may be based on the identification of individuals who are most likely to benefit from ICU resources.
- Two important errors made in the triage process are undertriage and overtriage. Undertriage occurs when the severity of patient problems is underestimated and treatment is delayed or given insufficient resources. Overtriage occurs when the degree of illness is overestimated, resulting in excessive use of essential resources. Both of these practices may lead to negative outcomes. Accurate triage brings the greatest good for the greatest number of patients.
- Critical care resources including mechanical ventilation and various forms of renal replacement therapy can be a limiting factor in the ability of a medical community to respond to COVID-19. Details on mortality and patterns of disease are still in evolution.
- Although COVID-19 was originally portrayed as a respiratory illness of varying degrees of severity, it is beginning to demonstrate a pattern of global vascular insults including the pulmonary circulation. Other end organs including the brain, kidney, and heart may be involved.
- Two phenotypes of respiratory insufficiency associated with COVID-19 have recently been reported. The first, and earliest presentation, is associated with a high compliance state and interstitial changes on chest imaging. The management of patients with this presentation includes acceptance of a higher tidal volume, lower levels of PEEP, increased levels of oxygen, and various forms of noninvasive ventilation. Prone ventilation, even in patients who have not been intubated, may be therapeutic.
- The second phenotype of respiratory insufficiency associated with COVID-19 is consistent with more traditional views of ARDS. Patients have a lower compliance state and significant areas of pulmonary consolidation. In these patients, prone ventilation, high PEEP, small tidal volumes, and other components of traditional ARDS management are appropriate.
- Many agents including repurposed drugs, which have been used in a variety of other applications, are under consideration as therapeutic modalities for COVID-19. Plasma from patients who have suffered this infection may also be a source of antibodies that could be used in treatment. At present, data supporting any of these interventions are scant. If at all possible, it is best to use these drugs in the context of a clinical trial. The core of management for patients with COVID-19 at present remains supportive care.

Acknowledgments

The authors gratefully acknowledge the assistance of Ms. Sherry Willett in preparation of this series for *Air Medical Journal*.

Dr. Suresh is a Hospitalist for Centracare based in St. Cloud, Minnesota. He may be reached at sure0015@umn.edu.

David J. Dries, MSE, MD, is a member of the Department of Surgery at HealthPartners Medical Group and a professor of surgery and an adjunct clinical professor of emergency medicine at the University of Minnesota in St Paul, MN, and can be reached at david.j.dries@healthpartners.com.