Garib Unnayan Sangstha (GUS)
Humanitarian Cooperation- according to need

COVID-19 Protocols & Guidelines Policy
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Common Symptoms

UpdatedDate:May,2020
LiteratureReview: GalleryView, GridView
Tool: *CDC Symptom Self-Checker*

Many patients are asymptomatic. Among patients with symptoms, most present with an influenza-like illness (fevers, myalgias, respiratory symptoms), but many do not present with this classic combination. Some may present with less-usual findings such as perniosis (COVID toes) or anosmia. These ranges are pulled from the following articles, and symptom prevalence varies greatly depending on testing and survey methodology (Arentz et al; Chen et al; Guan et al; Li et al; Wu et al; Zhou et al; WHO-China Joint Mission on COVID-19; Young et al; Yan et al; Jiang et al; Huang et al; Tostmann et al).

Incubation and Window Period

Updated Date: December 19, 2020

Incubation period is the time from exposure to symptom onset. Latency period is the time from exposure to infectiousness (or viral detection, depending on the definition). COVID-19 has a relatively long incubation period, and typically at least 2 days of infectivity before symptoms develop.

Incubation
Window Period

Prognostic Indicators

Updated Date: May, 2020

Demographic and Health Factors

1. Children are less likely to have severe disease, but pediatric deaths have been reported (Bialek et al).
2. Children appear to be as likely to contract the infection as adults, although symptomatic cases of children are more rare (Bi et al).

3. **Comorbidities and other health factors**: Multiple comorbidities and/or health factors are associated with increased risk of severe COVID-19 illness. Evidence-based knowledge on this topic is continuing to develop; for ongoing updates, see the CDC's living document. The comorbidities and other health factors associated with the strongest bases of evidence for increased risk are listed below. This list is not inclusive of all conditions which may be associated with increased risk; other common conditions which may be associated with increased risk include hypertension, moderate to severe asthma, liver disease, and others (CDC).

1. Chronic Kidney Disease
2. Chronic Obstructive Pulmonary Disease (COPD)
3. Type 2 Diabetes Mellitus
4. Pregnancy
5. Sickle Cell Disease
6. Smoking
7. Cancer
8. Down Syndrome
9. Immunocompromised status associated with solid organ transplant
10. Obesity (BMI of 30kg/M2 or higher)
11. Multiple heart conditions, including heart failure, coronary artery disease, and cardiomyopathies

4. **Race**: Please see Health Equity for a discussion on racial differences in COVID infection and severity.
5. **Sex:** Men appear to be more severely affected by COVID-19 than women. Conclusive evidence related to sex differences is limited by methodology of existing studies (Schiffer et al).
6. **Smoking**: Smoking may offer a small risk reduction for COVID infection, though it is not clear why and this finding may be subject to confounding. It does appear to be associated with worse outcomes. See Smoking for more details.

Laboratory Indicators

The most significant laboratory abnormalities associated with severe COVID-19 disease and death include the following:

Mortality

UpdatedDate:December16,2020

Literature Review: Gallery View, Grid View

Cause of Death

- **Cause of Death**: This is usually the acute medical diagnosis that caused a patient to die, and often relates to a medium-term or long-term diagnosis as well. It will often include other diseases as co-morbid or contributing factors (e.g. pneumonia due to COVID-19 infection or Acute Myocardial Ischemia due to COVID-19 infection and Coronary Artery Disease).
- **Mechanism of Death**: Defined as the immediate physiologic issue resulting in death (for example, hypoxemia).

A significant number of COVID-related deaths do not have clear delineation of cause of death (CEBM). The majority of people who die from COVID-19 die from respiratory failure. Because definitions of cause of death are reported differently it can be hard to determine exact numbers, but here are estimates (Ruan et al, 68 cases), (Zhang et al, 82 cases):

Case Fatality Rate

Pathophysiology

UpdatedDate:December16,2020
LiteratureReview(ACE2): GalleryView, GridView
Literature Review (Human Genetics) Gallery View, Grid View

Blood type: There is evidence that A blood type is a risk factor for COVID-19 respiratory failure, and O may be protective. This was based on a genome-wide association study (GWAS) of 835 patients and 1255 control participants from Italy and 775 patients and 950 control participants from Spain. Respiratory failure was defined as a patient requiring supplemental oxygen or mechanical ventilation (Ellinghaus etal).

Histology and Autopsy

Updated date: December 18, 2020
Literature Review (Autopsy): Gallery View, Grid View
Literature Review (Histology): Gallery View, Grid View

- Autopsy studies indicate universal damage to pulmonary tissue (Falasca et al; Elsoukkary et al). Pulmonary histology of COVID-19 shows bilateral diffuse alveolar damage, desquamation of pneumocytes, pulmonary edema, hyaline membrane formation, inflammatory cell infiltrates, and multinucleated giant cells, as well as some evidence of direct viral injury (Xu et al; Geng et al). Vascular involvement in the lung is also quite common, with microthrombi, endotheliitis, severe capillaritis, vascular complement deposition, and pulmonary thromboemboli, often in small and mid-sized vessels (Calabrese et al).
- Cardiac injury and thrombotic complications are widely prevalent, including cardiac inflammatory infiltrates, epicardial edema, and pericardial effusion in some autopsies (Falasca et al; Elsoukkary et al; Geng et al).
- Acute kidney injury, while common in hospitalized COVID patients, was found to be mild in post-mortem patients with theoretical potential for recovery (Santoriello et al).
- Neurologic lesions in autopsy series of 43 patients (not necessarily with neurologic manifestations) showed fresh ischemic lesions in 14%, and neuroinflammatory changes with infiltration of cytotoxic T lymphocytes most pronounced in the brainstem (also cerebellum and meninges) (Matschke et al). In patients with significant neurologic decline, more severe findings have been noted including hemorrhagic lesions through the cerebral hemispheres, marked axonal injury, areas of necrosis, and pathology similar to Acute Disseminated Encephalomyelitis (ADEM). (See e.g. Reichard et al).

Origins

Updated date: June, 2020
Literature Review: Gallery View, Grid View

COVID-19 transmission is primarily human-to-human following a suspected animal-to-human initiating event (Li et al). It is thought that it may have emerged from raccoon dogs or civets, but this is still being investigated (Mallapaty). The virus was initially recognized in December 2019 by Chinese authorities in the setting of cases of pneumonia that seemed to be clustered around a seafood market in Wuhan, Hubei Province (Wuhan Municipal Health Commission, 2019). Laboratory samples collected in December 2019 yielded evidence of a novel betacoronavirus, genetically-distinct from previously identified SARS-CoV and MERS-CoV but genetically-similar to previously-published coronavirus strains collected from bats from southwestern China (Zhu et al).

Major New Variants
Infectiousness and Severity
Testing, Vaccine, and Antibody Efficacy

Infectivity

Updated Date: August 30, 2021

Viral Load, PCR Clearance, and Infectiousness Timeline
Asymptomatic Patients

Asymptomatic, minimally symptomatic (paucisymptomatic), and pre-symptomatic patients can all transmit the virus (Bai et al; Rothe et al; Furukawa et al), though presence of symptoms is probably associated with increased frequency of transmission. Though it is hard to estimate the prevalence of asymptomatic cases due to testing bias and few population-level studies, one metanalysis found that asymptomatic patients represented 17% or cases, and were 42% less likely to transmit than symptomatic cases (Byambasuren et al). In one study in Beijing, face masks worn by family members of pre-symptomatic COVID-19 patients were shown to be 79% effective (OR = 0.21) at reducing transmission, suggesting that presymptomatic transmission is an important mode of transmission and that masks can be effective at preventing it (Wang et al).

Recovered Patients
Vaccinated People

Transmission

Updated Date: December 18, 2020
Literature Review: University of Washington Literature Report (Transmission)

Basic Reproduction Number (R_0)

The R_0 for COVID-19 is likely similar to, or slightly higher than, many other respiratory viruses, but because it is so highly influenced by human behavior, it can be changed. The initial R_0 of COVID in Wuhan in the absence of containment measures was thought to be about 2.5 (Majumder et al). However, R_0 declines with control measures (Zhao et al; Riou et al; Flaxman et al; Read et al; Shen et al). As variants of COVID develop, the R_0 is likely to change.

Aerosol, Droplet and Fomite Transmission

COVID-19 transmission primarily occurs through liquid respiratory particles (droplets, 50-100 micrometers particles) that travel through the air between people who are within a distance of about 2 meters of one another. Early in pandemic there was debate about whether transmission also occurs via aerosols (small particles under <5 micrometers), which can hang in the air for far longer and travel longer distances. Growing evidence indicates that aerosol transmission is possible, especially in poorly-ventilated spaces and with periods of exposure exceeding 30 minutes (Lancet Editorial), and the World Health Organization and US CDC both changed their guidance to include aerosol spread in spring of 2021.

Airborne/Aerosol Transmission: Very small respiratory droplets, often called aerosols, remain suspended in the air and travel a distance exceeding 2 meters (Lancet Editorial). The risk of producing aerosols is heightened during coughing, sneezing, and certain medical procedures (WHO-China Joint Mission on COVID-19).

See concerns about aerosolization to see a list of procedures and devices and the effect they may have on aerosols. Aerosolized particles appear to remain in the air for at least 3 hours (Van Dorelmalen et al), with some laboratory studies indicating it can be as long as 16 hours (Fears et al)

Bodily Fluids

1. **Feces and whole blood** have been shown to contain viral ribonucleic acid (RNA) on PCR studies (Wölfel et al; Young et al). Significance for transmission is unclear (Chen et al), though in one systematic review of smaller studies, replication-capable virus was found in 35% of samples (van Doorn et al), meaning that fecal transmission may be possible.
2. **Urine** does not appear to contain viral ribonucleic acid (Wölfel et al).
3. **Semen and vaginal secretions:** COVID-19 virus has not been detected in vaginal secretions (Qiu et al). It is detectable in semen, but transmissibility is unclear. Likelihood of transmission via respiratory secretions during sexual encounters, however, is likely (Sharun et al).
4. **Tears:** a few studies have indicated presence of COVID-19 virus in tears, while others have not. Current evidence is limited, but risk of transmission through tears is thought to be low (Seah et al).
5. **Cerebrospinal Fluid:** Rarely, CSF has been noted to be positive by PCR (in 2 of 578 samples in one study, but not at levels that are infectious) (Destras et al).

Household and Community Transmission

Super-Spreading Events (SSEs)

Super-Spreading Events are when an individual directly spreads an infection to an unusually large number of others. Several cases of superspreading have occurred at choirs (Hamner et al), weddings (including a Maine wedding that led to 177 linked cases, including seven deaths), churches Daegu, South Korea, where "Patient 31" infected at least 40 others (Ryall), and even within the White House. SSEs are believed to be disproportionately responsible for COVID-19 cases globally, with several studies suggesting that ≈80% of secondary transmissions have been caused by a small fraction (≈10%) of initially infected individuals. (Althouse et al; Endo et al). SSEs are heavily dependent on sociobiological mechanisms, including individual viral load, numbers of susceptible contacts per person, residence or employment in congregate settings, and 'opportunistic' scenarios including temporary clustering of individuals in mass gathering events. Environmental factors also are very important with closed places, crowded places, and poor ventilation playing a significant role in SSEs. Because SSEs play such an outsized role in fueling the pandemic, they amount to a significant concern, but also serve as an opportune area for public health interventions, particularly the prevention of transmission events where over 10 people are infected (Althouse et al).

Schools

Schools are unique settings and are likely to contribute to COVID-19 transmission between households and within communities. However, sustained closure of in-person schooling is expected to have an adverse effect on life outcomes for children and to worsen existing inequalities.Multiple studies have shown that **mitigation measures like masks, distancing, and ventilation** have a significant impact on reducing transmission in schools (Lessler et al, Doyle et al, Dawson et al, Falk et al).

Schools without mask mandates are 3.5 times more likely to have COVID-19 outbreaks than schools with mask mandates based on data from early in the 2021-2022 school year in the USA (CDC). A simulation study indicates that opening windows may significantly reduce transmission, as much as 14 fold, and masks may reduce transmission as much as 8 fold (Villers et al). The exact repercussions of novel variants on these interventions has yet to be determined, but it is likely that they will continue to reduce risk.This thorough Review of the Literature on School Transmission and Safety summarizes some of the unique challenges and recommendations (Massachusetts General Hospital COVID-19 Resource Library). Decisions on whether or not to open schools depends significantly on local policy and local epidemiology.

Air Travel

The risk of contracting COVID-19 on airplanes is low. 50% of the air circulated in the cabin is brought in from the outside, and the remaining 50% is filtered through HEPA filters. Air enters the cabin from overhead inlets and flows downwards toward floor-level outlets. There is relatively little airflow forward and backward between rows, making it less likely to spread respiratory particles between rows (Pombal et al). To avoid transmission, it is advised to avoid moving up and down the aisles as much as possible, and to wear a mask for the duration of the flight. A laboratory study (not real-world) designed to mimic spread within airplanes indicated that the lack of physical distancing when middle seats were permitted for occupancy may increase transmission, but this model did not account for mask wearing or vaccination (CDC).

Pets and Animals

Seasonality

Antibody Response

Updated Date: August 30, 2021

Rates of Antibody Response

The majority of patients with RT-PCR-confirmed COVID-19 develop antibodies against the virus within 4 weeks, with most studies ranging from 90-99% (Zhao et al; Wang et al, Arkhipova-Jenkins et al). In most patients these are neutralizing antibodies: over 90% of people seropositive for SARS-CoV-2 appear to have detectable neutralizing antibody responses (Wajnberg et al).

Types of Antibodies and Seroconversion

Duration of Immunity

Updated date: August 23, 2021

Duration of Antibodies

Correlation of Antibodies with Protection

Waning Protection from Infection

The effectiveness of vaccine-based immunity at preventing ***infection*** may start to wane around 5-6 months, based on data from four studies in the USA which showed a declines in efficacy from 91.7% to 79.8% (Rosenberg et al), 74.7% to 53.1% (Nanduri et al), 91% to 66% (Fowlkes et al) and 86% to 76% (Moderna) 76%-42% (Pfizer) (Puranik et al) across 5-6 month followups. Slide 14 from this CDC summary shows an excellent graphical representation of these trials. The vaccines studied were the ones available in the USA (Pfizer, Moderna, J&J). The decline in efficacy also may correspond somewhat to the emergence of new viral variants like Delta,

however the above CDC analysis suggests it is likely a combination of both the new variant and waning immunity. Similarly, the spike of new infections in Israel in August 2021, which has a very high vaccination rate and vaccinated most of its population around February 2021, may be a sign of waning immunity (Goldberg et al).

However, the waning in immunity appears to apply mostly to mild or moderate disease and not severe disease, hospitalization, or death. This CDC study looked at hospitalizations at 21 medical centers in the USA over 24 weeks and found no decline in vaccine effectiveness against COVID-19 ***hospitalization*** regardless of time of vaccination or "high risk" status.

Reinfection and Breakthrough Infection

Updated Date: August 30, 2021

Literature Review: Gallery View, Grid View

- **Reinfection is different from** (NICE guidelines 2020-12-18, Yahav et al)**:**
  - **Prolonged symptoms from Post-COVID-19 syndrome or relapse/reactivation** (also called recrudescence) of symptoms from initial infection
  - **Repositivity**, or residual shedding of RNA fragments or viral particles (not necessarily infectious; see Infectivity) from the initial infection
  - **Breakthrough infection**, or infection after vaccination in a patient who has not ever had evidence of viral replication

Efficacy

Updated date: August 30, 2021

1. ***Preventing hospitalization, critical illness, and death:***
   1. **All vaccines seem to offer excellent efficacy against hospitalization, critical illness, and death.**
   2. A large CDC/MMWR study indicated that vaccination was associated with a **29 fold reduction in risk of hospitalization** compared with no vaccine.
   3. AstraZeneca and Johnson & Johnson appear to be 95-100% effective at preventing severe disease and death.
   4. mRNA vaccines (Pfizer and Moderna) have near 100% efficacy at preventing severe disease and death, though case reports of breakthrough, critical illness, and death do occur (US CDC)
2. ***Preventing all symptomatic infection:***
   1. The following are the efficacies of the most commonly globally-available vaccines at preventing symptomatic infection *at the time of local regulatory authorization*, which typically meant with the ancestral strain (not more virulent strains like Delta).
      1. **Pfizer/BioNTech (mRNA).** FDA EUA cited efficacy of 95% at preventing symptomatic infection. (Pfizer EUA). Full FDA approval on August 23, 2021, cited 91% efficacy (FDA).
      2. **Moderna (mRNA).** FDA EUA cited 94% efficacy against symptomatic infection (Moderna EUA).
      3. **Oxford/AstraZeneca (viral vector).** The Oxford/AstraZeneca vaccine had an initial efficacy of 90% (Ledford; Knoll et al).
      4. **SinoPharm (whole virus inactivated).** 79% effective against symptomatic SARS-CoV-2 infection (WHO)

5. **Gam-COVID-Vac aka Sputnik (viral vector).** The vaccine is the only vaccine that uses two different serotypes, and it appears to have 91.6% efficacy based on a phase 3 trial (Longunov). It is used in about 70 countries. However, it has yet to gain approval from the EMA or the WHO (as discussed in this Nature article).
6. **Covaxin (whole virus inactivated).** 77.8% efficacy against symptomatic disease. The vaccine is approved in 15 countries but has yet to gain approval from the WHO (GAVI).
7. **Janssen/Johnson & Johnson (viral vector).** FDA EUA reports an efficacy of 85% against severe disease, and around 70% for symptomatic disease (Janssen EUA).

Mixing Different Vaccines

1. A study of 458 individuals were sorted to get the initial full series of J&J, Moderna, or Pfizer vaccinations followed by a booster of one of the three four to six months later (Atmar et al). This study formed the basis of the ACIP recommendation to allow mixing and matching for booster shots. *Notably, this study was performed using a 100ug booster for Moderna, not the 50ug booster that is currently recommended.*
    1. The safety profile appears similar to boosting with the same vaccine, and includes mild reactions like fever, fatigue, and cutaneous reactions.
    2. After primary J&J series:
        1. Moderna booster gave 56.1 fold increase in IgG and 76.1 fold increase in neutralizing antibodies.
        2. Pfizer booster gave 32.8x IgG and 35x neutralizing antibody increases
        3. J&J booster gave a 4.2x igG and 4.6x neutralizing antibody increases
    3. After a primary Moderna series:
        1. Moderna booster gave 7.9 fold increase in IgG and 10.2 fold increase in neutralizing antibodies.
        2. Pfizer booster gave 9.7x IgG and 11.5x neutralizing antibody increases
        3. J&J booster gave a 4.7x igG and 6.2x neutralizing antibody increases
    4. After a primary Pfizer series:
        1. Moderna booster gave 17.3 fold increase in IgG and 31.7 fold increase in neutralizing antibodies.
        2. Pfizer booster gave 14.9x IgG and 20.1x neutralizing antibody increases
        3. J&J booster gave a 6.2x igG and 12.5x neutralizing antibody increases

Efficacy on New Viral Variants

Efficacy may change as different viral variants become more predominant, as the antibodies produced by the vaccines may have different neutralizing effects on different strains, especially if the virus mutates the area targeted by the vaccine. However, most vaccines seem to retain at least partial effect against new variants, and most of the time retain excellent protective benefit. Please see this link for a curated chart of the efficacy of six major vaccines or vaccine candidates against major variants, including links to the original literature (compiled by Dr. Katelyn Jetelina). Notably, for the Delta Variant data is still emerging, but as of August 2021 the CDC estimates that unvaccinated people have 5x more COVID infections and 29x more hospitalizations (Griffin et al). Study estimates for effectiveness against symptomatic disease are currently around 59% for the Astrazeneca vaccine, 67% for J&J, 66-95% for Moderna, and 39-96% for Pfizer. (Nasreen et al, Sheikh et al, Puranik et al, Pouwels et al, Elliott et al, Fowlkes et al, Sadoff et al, Israel health minister as cited in WSJ).

Booster Shots

Updated Date: October 24, 2021

Boosters for Immunosuppressed Patients

Boosters for Patients with Normal Immune Systems

- Eligibility criteria for boosters varies by country, so please consult your local health department for guidance. In the USA recommendations (see full guidance here) are currently:
  - For those who received an initial **Pfizer or Moderna** series, a booster is recommended those who are:
  - For those who received an initial **J&J vaccine**, a booster is recommended for everyone >2 months after the initial dose
  - Note, Moderna boosters are approved for a 50mcg dose, different from the 100mcg initial series dose

Adverse Events and Reactogenicity

Most observed adverse events during vaccine trials were injection-related or reflected an expected immune response. Many people feel ill following vaccine administration for about 1-3 days, especially after the second dose of the vaccine This is *not* a sign of infection by the coronavirus.

Contraindications

Routine Vaccinations

The CDC now states that COVID-19 vaccines and other vaccines may now be administered without regard to timing. This includes simultaneous administration of COVID-19 vaccine and other vaccines on the same day, as well as co-administration within 14 days. Other public health guidance may vary.

Vaccine-Induced Immune Thrombotic Thrombocytopenia

There have been reports of rare (tens of cases globally) of venous thrombotic disease -- and particularly cerebral venous sinus thrombosis -- in recipients of the widely deployed Oxford/AstraZeneca and Janssen/Johnson & Johnson adenovirus vector vaccines. For both vaccines, the frequency of these events appears to be far lower than the risk of severe thromboembolic complications of COVID-19 itself. As of April 15, 2021, the benefits of both Oxford/AstraZeneca and Janssen/Johnson & Johnson vaccines are thought to outweigh potential risks. From Cines et al:

Myocarditis

- The benefits of vaccination (specifically preventing ICU admission and death) outweigh risks in both girls and boys age 12-17 according to US CDC guidance (CDC update August 2021). See this link for a graphical representation of the CDC's estimates of risks of myocarditis compared with COVID cases/hospitalizations/deaths for both boys and girls (as of June, 2021). (Mostly mRNA vaccines but also J&J vaccine)
- The UK Joint Committee on Vaccination and Immunization also determined that the benefit of vaccination outweighs the risks in adolescent males, but their statement describes a more marginal difference. The reported risk of myocarditis in the UK is 3 to 17 per million for the first dose; and 12 to 34 per million for the second dose (Astrazeneca vaccine).

- Exact data on the risks of myocarditis differentiated by vaccine type is not yet available. This is an evolving area of research.
- Risk of myocarditis with boosters is actively being studied. Israel has administered 3.7 million boosters and to date their incidence of myocarditis with boosters is lower than with the initial series (presumably as there has been longer between doses).

Special Populations

Prior Infection or Antibody Therapies

Obstetrics

- **Vaccines are not associated with infertility or pregnancy loss**
- In one study of 3,958 pregnant people there were no unexpected outcomes related to COVID-19 vaccination, regardless of trimester. Of the 827 people who completed pregnancy, pregnancy loss, preterm birth, babies size, congenital problems, and death were the same as background rate (Shimabukuro et al). Miscarriage rates are also the same as background rates. (Zauche et al)
- Preliminary findings of the US Vaccine Adverse Events Reporting System (VAERS) find no specific safety concerns to the mRNA vaccines in pregnant and lactating women (Shimabukuro et al).

Pediatrics

Immunosuppressed Patients

Immunosuppressed people should get vaccinated against SARS-CoV-2, as all currently approved vaccines do not include live virus. However, vaccination may not be as efficacious as in those who are not immunosuppressed. Guidelines as to timing of vaccination and holding of certain immunosuppressive medications vary among expert panels in different specialties.

- Vaccine Timing and Immunosuppression Adjustment
  - No modifications for most drugs are suggested at present, though if starting new immunosuppression, vaccination should be completed at least two weeks prior to initiation if possible. The International Organization for the Study of Inflammatory Bowel Disease, as well as the National Psoriasis Foundation, suggest immediate vaccination for all patients currently on immunosuppression, with no alterations in timing and no holding of immunosuppressive medications (Siegel et al; National Psoriasis Foundation 2021). The American College of Rheumatology differs in opinion and makes the suggestions below:
    - For anti-CD-20 monoclonals (e.g. rituximab and ocrelizumab), vaccination should occur at the end of the dosing interval, with the second dose for 2-dose vaccines occurring at least 2-4 wks before the next infusion if possible (ACR guidelines).
    - Hold treatment for 1 week after each vaccine dose for methotrexate, cyclophosphamide, and JAK inhibitors (ACR guidelines, Feb 2021).
    - Hold subcutaneous abatacept for one week before and one week after the first vaccine dose only (ACR guidelines).
    - For intravenous abatacept, time COVID vaccination so the first shot occurs 4 weeks after infusion, with the next infusion delayed a week after the shot (ACR guidelines).

Autoimmune Conditions and History of Guillain-Barre

Vaccine Equity

While approval of the first vaccine marked the culmination of a tremendous scientific effort, the fight against COVID-19 now faces a new challenge: a massive worldwide vaccination campaign.

The same embedded structural forces driving inequities in the burden of COVID-19 must also be considered within the context of vaccine access and distribution.

Vaccine Prioritization: It is essential that COVID-19 vaccines be distributed equitably. People who should be prioritized for vaccination include (adapted from the National Academies of Sciences, 2020).

- High-risk of COVID-related Morbidity and Mortality
  - Medical Comorbidities
  - Over the age of 65
- High-risk of Contracting COVID-19

COVAX, a global coalition including the WHO to assure vaccination, has proposed that all countries receive an adequate supply to inoculate at least 20% of their population before any nation receives additional vaccines. This will ensure that high-risk groups are vaccinated regardless of where they live. Following this initial roll-out, vaccines should be distributed based on the vulnerability of the country's health system and the impact of COVID-19 on the country, prioritizing countries most in need (COVAX, 2020).

What is Health Equity?

Updated Date: December 17, 2020

The COVID-19 pandemic has disproportionately affected historically oppressed populations around the world. Due to long-standing structural inequities, people from these communities are: 1) more likely to be exposed to disease, working essential jobs and living in crowded conditions; 2) less likely have to have access to quality healthcare, including COVID-19 testing and treatment; and 3) more likely to suffer from preexisting health conditions, as a result of adverse social determinants of health, putting them at increased risk of complications and death (Warren et al).

Providers should **screen for and Address Social Determinants of Health (SDOH):** SDOH are the conditions under which people are born, grow, live, work, and age (AAFP's The EveryONE Project) which act to shape the health and well-being of people in complex ways. In the context of COVID-19, living situations coupled with job insecurity increase the risk of infection and then make safe isolation and quarantine difficult. In some neighborhoods in the United States, as many as 70% of positive cases required social support to safely isolate and quarantine (Kerkhoff et al).

Resource Inequity

Updated Date: January 20, 2021

It should be noted, despite facing significant barriers to containment and treatment, a number of low- and middle-income countries have prevented COVID-19 cases and fatalities from reaching the astronomical levels seen in many wealthier nations.

Economic Consequences

Racial Disparities

Updated Date: December 17, 2020

Literature Review: Gallery View, Grid View

In the United States and United Kingdom multiple sources have demonstrated that Black and Latinx populations are disproportionately likely to be infected and/or die from COVID-19 (Garg; NYSDOH Fatalities, NYC DOH). A systematic review and meta-analysis of over 18

million patients across 50 studies from these two countries found higher COVID infection rates within Black, Latinx, and Asian communities (Sze et al). As of late November, 2020 Black and Latinx Americans have had 1.57 and 1.69-fold, respectively, as many cases as white Americans. Black deaths have been at 2.05-fold the rate of white Americans, and Latinx at 1.38-fold the white case fatality rate (Covidtracking). In the United States, rates of hospitalization among Black and Latinx COVID patients are approximately 4.7 times than among non-Hispanic white patients (Mayo Clinic; Pan et al). In terms of years of potential life lost before age 65, Black Americans are 6.7 times higher, Latinx people 5.4 times higher, Indigenous populations 4.0 times higher, and Asians 2.6 times higher compared to whites (Bassett Working Paper).

Indigenous Communities

Indiginous communities are particularly affected by COVID-19. The cumulative incidence of COVID-19 among American Indian and Alaska Native persons is 3.5 times that among non-Hispanic white persons (CDC) Rates of infection often significantly exceed those in major metropolitan outbreaks (like New York City in April, 2020). As of July, 2020 in New Mexico, American Indians represented 53% of COVID deaths but only 11% of the population (Sequist et al).

Immigrants and Migrants

Updated Date: December 17, 2020

Literature Review: Gallery View, Grid View

- Compared with citizens, noncitizens are more likely to live in larger multi-family households where bedrooms may be shared.
- Non-citizens are also more likely to perform work that cannot be done remotely and depend on public transit.
- Non-citizens are not currently eligible for public financial and food assistance programs such as Social Security, TANF, and SNAP. Paradoxically, eligible documented immigrants who receive support from these public assistance programs are ineligible for citizenship based on the "public charge" test.
- Immigration and Customs Enforcement (ICE) has detained over 50,000 undocumented immigrants in holding facilities in the United States. Detainees in such facilities are subject to all of the same infection risks as prison inmates (see People who are Incarcerated), but may be more prone to poor outcomes since ICE's operational COVID-19 containment protocols do not consistently reflect evolving CDC recommendations (Openshaw et al; Meyer et al; Keller et al).
- International Medical Graduates (IMGs) make up roughly 25% of the specialist workforce in America but many are serving on H-1B (temporary employment) visas that disqualify them from disability benefits if they were to get COVID at work. This also exposes family members to forcible relocation in the event of their deaths (Tiwari et al).
- Immigrants are also at risk of being systematically overlooked or underserved in public vaccination campaigns (Foppiano et al).

People Who Are Incarcerated

Updated Date: November, 2020

Literature Review: Gallery View, Grid View

People who are imprisoned are particularly vulnerable to COVID-19 infection due to overcrowding, poor ventilation, poor sanitation, lack of medical care, violence, and increased rates of chronic medical conditions (U.S. Department of Justice Special Report). Early data from the COVID-19 pandemic demonstrated up to 5 times higher rates of death among incarcerated people, despite disproportionately younger age distributions relative to nearby communities (Saloner et al). Since the start of the pandemic across all states, incarcerated persons have >3 times the per-capita number of cases as the general population (The Marshall Project). Dormitory housing has been shown to be a strong risk factor for infection (Kennedy et al).

- Since COVID-19 was identified, over 25 states in the United States have engaged in early release efforts, 14 states have reduced jail and prison admissions, and 47 states have suspended medical co-pays for incarcerated individuals (Prison Policy Initiative: Responses to the COVID-19 Pandemic).

People with Disabilities *Updated Date: November, 2020*

Literature Review: Gallery View, Grid View

People with disabilities may be disproportionately marginalized by COVID-19 response efforts due to inadequate recognition of their unique needs. People with disabilities may not have equitable access to safe living situations or healthcare resources. Some disabilities do not affect severity or prognosis with COVID infection, but some disabilities may (generally due to related comorbidities such as structural heart disease). For example, if infected, individuals with Down Syndrome are five times more likely to be hospitalized and 10 times more likely to die (Wadman M).

- Alternative **support structures** should be considered for patients with disabilities who are unable to participate in standard public health protocols, such as home-based COVID testing for people with autism spectrum disorder (Eshraghi et al).
- Health policy leaders must be attentive to inequities in access to care and resources, disproportionate hardships imposed by pandemic mitigation strategies, and increased risk of harm from COVID infection in the context of pre-existing health disparities (Armitage et al).
- Creation of **equitable resource allocation protocols**, especially when considering Crisis Standards of Care, should be guided by near-term survival calculations and objective measures to avoid bias against people with physical and intellectual disabilities in allocating resources (Solomon et al).

Tool: COVID-19 response: Considerations for Children and Adults with Disabilities, UNICEF

Tool: COVID-19 and persons with psychosocial disabilities, Pan African Network of Persons with Psychosocial Disabilities, et al

People Living in Congregate Housing

Updated Date: November, 2020

Literature Review: Gallery View, Grid View

- In the United States, as of April 23, "there have been over 10,000 reported deaths due to COVID-19 in long-term care facilities (including residents and staff), representing 27% of deaths due to COVID-19 in those states (Kaiser Family Foundation).

- COVID has impacted long-term care facilities around the world, with data from many countries showing 40% of COVID deaths to be connected to long-term care facilities. Rates in some higher-income countries are 80% (WHO).

People with Substance Use Disorders (SUDS)

Updated Date: November, 2020

Literature Review: Gallery View, Grid View

Possible explanations include higher rates of comorbid pulmonary and cardiac pathologies in people with SUD, as well as disparities in access to healthcare associated with stigma and marginalization. Black Americans with a recent diagnosis of opioid use disorder were four times more likely to become sick with COVID-19 than white peers (Wang et al).

Tool: *Harm Reduction Strategies* For people who use substances during the COVID-19 pandemic (Harm Reduction Coalition, English/US Focus)

Intimate Partner Violence (IPV)

Literature Review: Gallery View, Grid View

Current impact data are limited, but one study comparing rates of physical IPV during the COVID-19 pandemic to rates of physical IPV during the preceding three years indicated a 1.8-fold increase in incidents, accompanied by a higher rate of severe injuries and a lower rate of reporting (Gosangi et al).

In the context of the COVID-19 pandemic, it is important to support programs that prevent IPV. Social support, cash transfer, food distribution, housing, availability and accessibility to health care, and health insurance coverage are critical to mitigating the impact of COVID-19 and preventing increasing IPV.

Tool: Identifying & Mitigating Gender-based Violence Risks within the COVID-19 Response, UNICEF, IASC

CHAPTER 3

Diagnostics

Read full Chapter →

Types of Tests

Please see COVIDProtocols 2.0 (Global Health Version) for detailed descriptions of testing modalities, their use case,

Whom to Test

1. BWH-Specific **Outpatient guidance** can be found in the ambulatory testing section.
2. Full BWH-specific **inpatient** COVID-19 testing pathways and infection control guidelines can be found here (Partners login required). Major points are as follows:
    1. **PCR-based testing:**
    2. **On Admission:** All ED patients are tested prior to admission so that test results will be back before deciding inpatient disposition.
        1. **Transfers** coming from non-MGB hospitals are only accepted for asymptomatic ruleout if done within 3 days of transfer. Additional testing should be completed with one swab on arrival.
        2. **Direct admissions** also need testing, initial isolation depends on symptoms, reason for isolation, and other risk factors.

3. **Perioperative testing:** if ndergoing a procedure that will or could potentially involve an aerosol-generating procedure, patients should be tested for Covid-19 within 3 days prior to the procedure.

2. **Repeat testing**:
   1. **All inpatients** must undergo a repeat PCR test 72 hours after admission via AN swab.
   2. Patients with **new symptoms** (since admission) suggestive of possible COVID should be tested when they develop those symptoms
   3. **Symptomatic or high-suspicion patients patients with negative initial testing** should be kept on precautious and undergo at least one additional test, ideally on an ET aspirate or sputum sample.
   4. **Patients during recovery period** (positive testing within 90 days) typically do not need repeat testing unless they have worsening or new symptoms.
3. **Complex decisions about isolation** should involve infection control, and a cycle threshold may be used to determine infectiousness (generally cycle threshold >34 is not considered infectious, though this may change with different viral variants).
4. Testing can be ordered through the symptomatic and asymptomatic testing pathways in Epic. (Partners login required)

1. **Serology testing**
   1. Further guidance about sending and interpreting SARS-CoV-2 serology can be found here. (Partners login required)
   2. Two types of serology tests are available:
      1. **Anti-nucleocapsid antibody assay.**
         1. **Symptomatic**: The anti-nucleocapsid antibody test orderable in Epic can be considered in select patients with symptoms consistent with COVID-19 who have had negative NAAT testing and at least 7 days have passed since symptom onset at the time of the test.
         2. **Asymptomatic**: Use of serology to assess for evidence of prior infection is *not routinely recommended*; use of this assay is at provider discretion. The duration of antibodies is widely variable in patients and thus interpretation can be very difficult.
      2. **Anti-spike protein antibody assay.**
         1. **Use of serology to assess response to COVID-19 vaccination.** The anti-spike antibody assay is not recommended for use in assessing response to COVID-19 vaccination; correlation between result and level of protection is not known. This assay is currently only available at MGB through approved clinical research protocols when ordering through a research encounter; the ordering provider will be prompted to select the indication "Approved Research Study" and enter the IRB protocol number when ordering the test in Epic.

Radiology

1. **Findings**: Please see CEBI COVID Protocols, the HMS Library of Evidence and Radiopedia.

For Radiologists

1. Guidelines for Radiologists reading and reporting COVID lung imaging
2. Guidelines for precautions for radiology studies (in radiology suite as well as bedside ultrasound and portable chest X-Ray)

Cardiac Testing

1. **Telemetry:**
    1. Telemetry should be used for all critically-ill patients
    2. At BWH, COVID-19 intermediate-care patients also have telemetry.
    3. For hospitals, with resource-limitations, telemetry is most important for patients who meet AHA criteria (Sandau et al, *Circulation*, 2017).
2. **ECGs:**
    1. Daily ECGs are reasonable for individuals with severe COVID-19.
3. **Bedside TTE:**
    1. Do not order routine TTEs on COVID-19 patients.
    2. Indications for POCUS:

CHAPTER 7

Respiratory

Read full Chapter →

Pathophysiology

1. Histology of COVID-19 associated lung disease most often shows bilateral diffuse alveolar damage with cellular fibromyxoid exudates, desquamation of pneumocytes, pulmonary edema, hyaline membrane formation, microthrombi ., organizing fibrosis and superimposed pneumonia. There is evidence of direct viral injury to lung tissue, as well as inflammatory sequelae. (Xu et al, Lancet Respir Med, 2020, Hariri et al, Chest, 2021).
2. The SARS-CoV-2 virus binds to the ACE2 receptor as its target receptor for cell entry which may be an explanation for many of the pathophysiological manifestations of infection. The ACE2 receptor is expressed by select populations of cells including the pulmonary endothelium, Alveolar Type 2 cells, proximal renal tubule cells, gastrointestinal epithelial cells, and many other others. The cells that express ACE2 may be the cell populations injured by infection or targeted by the immune response.

Definition of Acute Respiratory Distress Syndrome (ARDS)

1. Most patients with COVID-19 who require ICU level of care develop ARDS.
2. The Berlin definition of ARDS requires the following four criteria:

Supplemental Oxygen Support

4. **Pulmonary consultation:**
    1. Contacting the correct pulmonary consultation service
        1. Tower/CWN: Covered by “Pulmonary consult”
            1.Pulmonary consult fellow (pager 11957)
            2.Pulmonary consult attending (listed in Partners Phone Directory [PPD])
        2. Shapiro: Covered by “Pulmonary vascular consult”
            1.Pulm. Vascular consult fellow (pager 16513)
            2.Pulm. Vascular consult attending (listed in PPD)
    2. Availability
        1. The consult services are on-site from approximately 8am to 6pm daily and available for calls in the early evening.
        2. The consult service may not be immediately available for emergent issues during the day (e.g., if performing a procedure); for emergent issues during the day, if the consult service does not respond, the MICU attending can be contacted.

3. Overnight issues should be directed to the MICU attending (pager 36648), who is on-site.

3. Possible indications for seeking consult input
    1. Covid-19 patients on HFNC.
    2. Respiratory decline raising the question of ICU transfer.
    3. Questions of therapeutics (e.g., steroids) or interventions (e.g., NIPPV).
    4. Typical non-Covid-19 reasons for consultation (e.g., complicated asthma/COPD exacerbations, ILD exacerbations)

6. **Considerations for ICU transfer:**
    1. Several resources can assist with evaluating a Covid-19 patient for ICU transfer:
        1. Pulmonary or Pulm Vasc. consultation service (see above for directions on which service to consult)
        2. Covid-19 ICU triage pager (pager 39999, activated only during a surge)
        3. MICU attending (pager 36648)
        4. Medical consult senior resident (pager 17762)

High-Flow Nasal Cannula (HFNC)

1. **Concerns about aerosolization**
    1. Early in the COVID-19 pandemic, our institution avoided HFNC in COVID-19 confirmed and PUI patients given the indeterminate data on aerosol and HCW transmission risk. Since then, we have demonstrated that our PPE and isolation protocols have effectively prevented HCW transmission of COVID-19 in several types of aerosol generating procedures, both short-term (*e.g.*, intubation, nebulizer in non-intubated patient) and prolonged (*e.g.*, coughing, 12L oxymizer) (Rhee et al, *JAMA Network Open*, 2021).
        1. Many partner organizations and other major medical centers that use HFNC with similar PPE have so far not reported increased viral transmission when using HFNC
    2. Evidence suggests that HFNC (and NIPPV) does not increase aerosol or particle production.
        1. A study of ten healthy volunteers demonstrated that NIPPV (or HFNC) did not increase aersolization compared to to nasal cannula or face mask supplemental oxygen. In all oxygen delivery methods, coughing did increased particle generation (Gaeckle et al, *AJRCCM*, 2020)
        2. Studies of simulated patient models suggest that a surgical mask placed over the HFNC or other nasal oxygen apparatus significantly reduces exhaled gas flow and droplet dispersion (Leonard et al, *Chest*, 2020; Li et al, *Eur Resp J*, 2020)
        3. A non-peer reviewed preprint in healthy volunteers concluded that there was no variation in aerosol level among room air, 6L/min NC, 15 L/min NRB, 30L/min HFNC and 60 L/min HFNC regardless of coughing.(Iwashyna et al. *MedRxivPreprint*, 2020)
2. **COVID-19 Confirmed or PUI patients**
    1. **HFNC can be used if it would clinically benefit patients as determined by the primary team.** Early data shows COVID-19 patients *might* avoid intubation using HFNC, though no mortality benefit has been found in this population (Demoule et al. AJRCCM, 2020)
        1. Indications for High-Flow Nasal Cannula are the same as for COVID-19 negative patients
        2. The primary hypoxemia management pathway is as described above. HFNC can be added to the pathway for select patients at the discretion of the primary team
        3. Contraindications are the same as for COVID-19 negative patients

3. **If HFNC is used:**
    1. Discuss risks and benefits with MD, RN, and RT
    2. Follow infection control guidance, with strict airborne precautions including N95s and a negative pressure room.
    3. Setup is the same as for COVID-19 negative patients

Intubation

1. **If appropriate, call airway team for intubation:**
    1. Use the similar criteria for intubation as used for non-Covid-19 ARDS, such as work of breathing that cannot be sustained, concern for volutrauma or escalation to maximal supplemental oxygen requirements (e.g., marginal SpO2 on Non-breathing mask)
    2. Procedure for intubation:
2. Pre-oxygenation for patients on advanced supplemental oxygen support:
    1. Non-rebreathing Mask prior to intubation.
3. Avoid initiation of NIPPV or HFNC solely for pre-oxygenation just before intubation
4. Rapid Sequence Induction (RSI) should be performed by the most experienced airway provider without bag-valve masking and using a video laryngoscope

Non-invasive Positive Pressure Ventilation (NIPPV)

1. **NIPPV does not significantly increase aersolization**
    1. A study of ten healthy volunteers demonstrated that NIPPV (or HFNC) did not increase aersolization compared to nasal cannula or face mask supplemental oxygen. In all oxygen delivery methods, coughing did increase particle generation (Gaeckle et al, *AJRCCM*, 2020)
2. **COVID-19 Confirmed or PUI patients**
    1. **NIPPV should be utilized for the same indications as used in COVID-19 negative patients:**
        1. Obstructive Sleep Apnea or Tracheobronchomalacia: Patients on home nocturnal CPAP or BiPAP should continue nocturnal NIPPV.
        2. Pulmonary edema
        3. COPD exacerbation and other reversible hypercapnia
        4. NIPPV should be generally avoided in the same situations that NIPPV is avoided in COVID-19 negative patients (*e.g.*, severe ARDS without short-term reversibility; the presence of relative contra-indications such as altered mental status, aspiration risk, secretions).

Self-proning

1. **Potential benefits of self-proning:**
    1. Proning is thought to provide physiologic benefits for patients with COVID infection: it may improve recruitment of alveoli in dependent areas of the lungs, perfusion to ventilated areas, and V/Q matching. Typically proning is used in ventilated ICU patients, however the same benefits may accrue to non-ventilated patients.
    2. Intubated proning: Proning is one of the mainstays of ARDS therapy for intubated patients, showing both 28 day and 90 day mortality benefit in the PROSEVA 2013 trial (Guerin et al, NEJM, 2013).
    3. Self-proning (non-intubated) in non-Covid-19 patient cohorts: ARDS, after lung transplant, and post-surgery. These small studies showed that self-proning was associated with lab, radiographic, or clinical improvement:

    1. In one observational study, (Scaravilli et al, *J of Critical Care*, 2015) 15 patients with pneumonia underwent a total of 43 self-proning procedures , with an average of 3 hours, range 2-8 hours. They found improvement in P/F ratio and PaO2 without complications.
    2. In another limited study of 20 patients (Ding et al, *Critical Care*, 2020) with ARDS who underwent self-proning for at least 30 minutes, many fewer (45%) required intubation than would have been expected based on previous data (75%)
2. **Use in COVID-19:**
    1. Numerous small, observational studies and one randomized trial have shown that prone positioning in non-intubated patients with COVID-19+ hypoxemic respiratory failure rapidly improves SpO2, PaO2 and/or respiratory rate (Elharrar et al, *JAMA*, 2020; Thompson et al, *JAMA Internal Med*, 2020; Damarla et al, *AJRCCM*, 2020; Kharat et al, *Eur Resp J Open Research*, 2021; Caputo et al, *Acad Emerg Med*, 2020). This benefit has not been shown to reliably persist after a return to the supine position.
3. **Recommendation:**
    1. Based the well-tolerated, low-risk, low-cost nature of prone positioning, we recommend self-proning as tolerated in all hospitalized, non-intubated patients with COVID-19 on supplemental oxygen.

Determining PEEP and mechanics

1. **Titrate FiO2 and PEEP for oxygenation**
    1. Initiate PEEP based on BMI, per above, and then titrate PEEP and FiO2 to target oxygenation SpO2 92-96% as per the following guidelines:

Pain, Agitation, Delirium model

1. **Pharmacologic therapy is chosen to target pain, agitation, and delirium in that order (both assessment and treatment).**
    1. Please see the chart below for details, and the BWH Guidelines for Pain Agitation and Delirium in Mechanically Ventilated Patients for full detail (Partners login required)

General management of ventilated patients

1. Consider whether patient requires daily CXR:
    1. CXR clearly indicated for:
        1. Clinical change
        2. Concern for displaced ET tube:
            1.Sudden increase in peak inspiratory pressure or resistance
            2.Decreased, unilateral breath sounds (usually on the right)
            3.RN or RT concern for change in depth of ET tube at teeth
2. COVID-19 ICU Bundle:
    1. Ventilated patients should all have a daily ICU "Bundle" of best practices. See here for our COVID-19 ICU Bundle.

Changing oxygenation parameters

1. **Minimize oxygen toxicity:** PEEP and Fi02 drive oxygenation
    1. The goal is to deliver a partial pressure of oxygen to perfuse tissues ($PaO2 \geq 65$, $Sp02 \geq 92\%$) while limiting lung injury from high distending pressures ($Ppl \leq 30$) and hyperoxia (**$FiO2 \leq 60\%$**, $SpO2 \leq 96\%$).

2. **PEEP Optimization:**
    1. COVID-specific data:
        1. Preliminary anecdotal reports suggest a common phenotype of high compliance with PEEP-sensitive hypoxia. The pathophysiology of this phenotype has yet to be determined but it may reduce the efficacy of the ARDSNET PEEP tables to guide FiO2 and PEEP management.
    2. PEEP should be set and titrated as explained above using the ARDSNET PEEP tables to guide FiO2 and PEEP determination
    3. Optimal PEEP methods: significant efforts to determine a physiologically optimal PEEP are described in the literature but no specific method has demonstrated improved outcomes in large studies. In the setting of persistent hypoxemia or deviation from the ARDSNET PEEP tables, there are several methods employed at BWH for determining optimal PEEP.
        1. Best PEEP: BWH employs a "Best PEEP" protocol to optimize PEEP in selected patients in which the RT iterates changes in PEEP and compliance measurements to determine the physiologically optimal PEEP.
            1. However, to minimize demands on RT time, we will avoid routine use of "Best PEEP" protocol for COVID-19 ICUs.
        2. PV Tool: For patients on the Hamilton G5 ventilator, the Pressure-Volume (PV) tool may be used to determine the optimal PEEP as described below:
            1. Set the Pstart = 0 and Pmax = 40 and Pstop = prior PEEP
            2. Set the time step at 2 seconds with time hold at 0 seconds
            3. On completion of the maneuver, a PV loop is displayed demonstrating the inspiratory and expiratory limbs of the hysteretic loop
                1. The optimal PEEP is selected as slightly greater (1 to 2 cm H2O) above the lower inflection point (considered to reflect alveolar collapse and risk of "atelectrauma")
            4. *Note:* test is optimally performed when patients are not making voluntary respiratory effort (eg deeply sedated or paralyzed).
        3. Esophageal balloon: Use of esophageal balloons to measure transpulmonary pressure will not be routinely performed on COVID patients due to infectious risk to staff.
    4. In other contexts, some patients in severe, fibrotic stage ARDS require very low PEEP (even <5 occasionally). Anecdotally, this very low compliance phenotype may be less common in COVID-19, but should not be missed (*e.g.,* by tracking respiratory mechanics).

Refractory Hypoxemia

1. **Refractory Hypoxemia pathway**
    1. If patient is hypoxic (PaO2 <75) despite PEEP optimization as above); and FiO2 >= 0.6 or PaO2 / FiO2 ratio < 150 then perform the following in this order:
        1. Assess volume status. Diurese or remove volume (e.g. RRT) if indicated.
        2. Assess ventilator synchrony and sedation. Adjust ventilator and sedation to achieve ventilator synchrony.
            1. If still dyssynchronous, consider neuromuscular blockade
        3. Initiate prone ventilation early: Discuss proning when PaO2/FiO2 < 150 and FI02 >=0.6 or if you think the patient may clinically benefit

1. Strongly consider early in severe ARDS (<36 hrs from ARDS onset, *we prone earlier than typical in non-COVID-19 ARDS)*
4. If persistent PaO2<75 on FIO2>0.75, initiate trial of continuous inhaled epoprostenol (veletri). Note that inhaled nitric oxide is NOT available for non-COVID-19 or COVID-19 ARDS (see "pulmonary vasodilators" below).
5. If goals are not met with the above, consider a trial of continuous neuromuscular blockade.

Prone Ventilation

2. **Eligibility criteria for proning:**
    1. The only absolute contraindications are spinal cord injury, open chest, and unstable airway; BMI and patient size are not contra-indications
    2. For tracheostomy, we recommend that patients have their tracheostomy replaced by oral endotracheal intubation (ETT) while recognizing that some institutions prone patients with a tracheostomy. In the setting of COVID-19, decannulating a tracheostomy and placing an ETT is higher risk and the ICU team and anesthesiology should carefully discuss the risks.
    3. RRT can be performed while proned (*e.g*, typically via femoral vein catheter due to frequent neck turns while proned) but should be discussed with renal consultation prior to proning

Inhaled Pulmonary Vasodilators

1. There is no evidence of survival benefit of inhaled vasodilators in ARDS, and it can demand significant respiratory therapist resources (Fuller et al, *Chest*, 2015; Gebistorf et al, *Cochrane Database Syst Rev*, 2016; Afshari et al, *Cochrane Database Syst Rev*, 2017).
2. There is currently no evidence of the survival benefit in COVID ARDS, though data is still very limited.
    1. In a retrospective cohort study of BWH intubated COVID-19 patients, inhaled epoprostenol did not significantly alter PaO2/FiO2. PaO2/FiO2 increased by >10% in 40% of patients (N=38), but clinical outcomes were not changed. 11 patients who failed to respond to inhaled epoprostenol were trialed on inhaled nitric oxide (iNO). On iNO, PaO2/FiO2 increased by >10% in 60% of patients (N=11). There was no change in outcome. This study was limited by a small sample size and retrospective design (DeGrado et al, *Crit Care Explor*, 2020, in press).
3. Inhaled Nitric Oxide:
    1. Limited *in vitro* data notes that iNO at high doses inhibits replication of SARS-CoV, but this has not been studied *in vivo* (Akerstrom et al, *J Virol*, 2005; Gebistorf et al, *Cochrane Database Syst Rev*, 2016) although clinical trials are in progress.
    2. Given the lack of clinical evidence supporting its use, inhaled nitric oxide is NOT available at BWH for ARDS patients (either non-COVID-19 or COVID-19 related).

1. Initiating epoprostenol:
    1. Exclude contraindications: Alveolar hemorrhage (epo has mild antiplatelet effect), LV systolic or diastolic CHF (vasodilators cause ↑ pulm blood flow → ↑ LV filling pressure → ↑ pulmonary edema & ↓ PaO2 → consider CHF if pt gets worse after starting).
    2. Measure baseline ABG for PaO2
    3. Start continuous nebulization at 0.05 mcg/kg/min based on IBW (MDcalc online calculator).
    4. Do not change ventilator settings, sedation, paralysis, patient position or other care that could affect oxygenation.
    5. Re-check ABG 2 hrs after initiation of inhaled epoprostenol.
    6. If PaO2 increased by >10% from baseline, continue inhaled epoprostenol.

7. If PaO2 not increased by >10% from baseline, discontinue inhaled epoprostenol.

ECMO consultation

1. **BWH ECMO guidelines**
    1. BWH ECMO consult pager is 35010.
    2. BWH ECMO guidelines are linked here (BWH log-in required).
    3. BWH participates in the New England ECMO consortium to discuss regionally ECMO availability and policies during COVID-19.
    4. The information below conveys general principles used by many medical centers and is NOT meant to reflect current BWH specific policies (linked above).

CHAPTER 8

Critical Care

Read full Chapter →

Workup

3. Assess for **cardiogenic shock**
    1. Assess extremities: warm or cool on exam
    2. Assess patient volume status: JVP, CVP, edema, CXR
    3. Assess pulse pressure: If < 25% of the SBP, correlates highly with a reduction in cardiac index to less than 2.2 with a sensitivity of 91% and a specificity of 83% (Stevenson and Perloff, *JAMA*, 1989)
    4. Perform POCUS, if able, to assess for gross LV/RV dysfunction (upload to PACS/Centricity)
        1. For TTE protocols see *"Other Tests"*

Management

2. **Pressors and Fluid Management:**
    1. **Goal MAP > 65mmHg**
        1. While there is emerging data that lower MAP thresholds may be beneficial, we recommend following this threshold for now.
    2. **Pressors**
        1. Start Norepinephrine while determining the etiology of undifferentiated shock
        2. Unless new evidence emerges, standard choices for distributive shock (*i.e.*, norepinephrine then vasopressin) are recommended, with high vigilance for the development of cardiogenic shock, addressed in the next section
    3. **Conservative fluid management:**
        1. **Do not give conventional 30cc/kg resuscitation**
            1.COVID-19 clinical reports indicate the majority of patients present with respiratory failure without shock. ARDS is mediated in part by pulmonary capillary leak, and randomized controlled trials of ARDS indicate that a conservative fluid strategy is protective in this setting (Grissom et al, *Crit Care Med*, 2015; Famous et al, *Am J Respir Crit Care Med*, 2017; Silversides et al, *Int Care Med*, 2017)
            2.Conservative fluid management is also part of the most recent WHO guidelines. WHO, *COVID-19 Interim guidance*, March 2020).
        2. **Instead, give 250-500cc IVF and assess in 15-30 minutes** for:
            1.Increase > 2 in CVP
            2.Increase in MAP or decrease in pressor requirement

1. Use isotonic crystalloids; Lactated Ringer's solution is preferred where possible. Avoid hypotonic fluids, starches, or colloids

3. **Repeat 250-500cc IVF boluses; Use dynamic measures of fluid responsiveness**
   1. Pulse Pressure Variation: can be calculated in mechanically ventilated patients without arrhythmia; PPV >12% is sensitive and specific for volume responsiveness
   2. Straight Leg Raise: raise legs to 45° w/ supine torso for at least one minute. A change in pulse pressure of > 12% has sensitivity of 60% & specificity of 85% for fluid responsiveness in mechanically ventilated patients; less accurate if spontaneously breathing
   3. Ultrasound evaluation of IVC collapsibility should only be undertaken by trained personnel to avoid contamination of ultrasound
   4. For further guidance, Conservative Fluid Management protocols are available from from FACCT Lite trial (Grissom et al, *Crit Care Med*, 2015).

Mechanical Support

1. The benefit of mechanical circulatory support in COVID-19 is not yet clear.
2. Patients who experience the following should prompt an immediate call to the cardiovascular medicine consult service for consideration of mechanical support:
   1. Dobutamine gtt at 5mcg/kg/min (or unable to tolerate dobutamine due to tachyarrhythmias) and ScvO2 < 60% or CI < 2.2
   2. Lactate > 4 after medical therapy
3. The criteria for VA ECMO and other mechanical circulatory support varies among centers and are difficult to develop even under typical circumstances. The unclear trajectory of the COVID-19 pandemic makes these evaluations even more difficult.
   1. VA- ECMO guidelines are available here (Partners login required)
   2. For the purposes of general education, a ***hypothetical*** set of inclusion criteria for VA ECMO or MCS could cover:

Pathophysiology

1. **Categories of Cytokine Storm Syndrome (CSS).** Also called cytokine release syndrome, CSS is an umbrella term used for many different cytokine-driven illnesses that share certain aspects of pathophysiology but differ in serum cytokine patterns, timing, and other factors. However, treatment is similar. These fall into four main categories (reviewed in Henderson et al, *Arthritis Rheumatol*, 2020):
   1. Familial hemophagocytic lymphohistiocytosis (fHLH) - associated with genetic mutations in granule-mediated cytotoxicity by NK cells and CD8 T cells (Brisse et al, *Br J Haematol*, 2016)
   2. Secondary HLH, also called macrophage activation syndrome (MAS), seen in patients with systemic juvenile idiopathic arthritis and other systemic autoimmune diseases and malignancies (Brisse et al, *Br J Haematol*, 2016)
   3. Chimeric antigen receptor (CAR) T-cell therapy (Fitzgerald et al, *Crit Care Med*, 2018, Shimabukuro-Vornhagen et al, *J Immunother Cancer*, 2018)
   4. **Viral infections**, especially EBV and influenza but also others (Schulert et al, *J Infect Dis*, 2016)

1. Cytokine storm contributing to ARDS has been implicated in SARS and MERS (Kim et al, *J Korean Med Sci*, 2016)

2. **Cytokine Storm Syndrome in COVID.** A subgroup of patients with severe COVID-19 have an immune hyperactivation that resembles CSS (Mehta et al, *Lancet*, 2020, Henderson et al, *Arthritis Rheumatol*, 2020).
   1. Evidence of cytokine storm syndrome in COVID-19 includes correlation of elevated D-dimer, ferritin (a marker of macrophage activation), and soluble IL-2 receptor (a marker of T lymphocyte activation) with severe disease course (Zhou, *Lancet*, 2020, Chen, *JCI*, 2020)

Workup

2. **Lab work-up:**
   1. **General markers:** neutrophilia, lymphopenia, elevated hepatic transaminases, elevated LDH
   2. **Disseminated Intravascular Coagulation markers**: elevated D-dimer, thrombocytopenia, falling fibrinogen, prolonged PT / PTT
      1. D-dimer is an acute phase reactant and can be elevated even in the absence of VTE. However, given the thrombotic propensity of patients with COVID-19, imaging or other studies to evaluate for DVTs or other clots should be considered.
      2. Fibrinogen is also an acute phase reactant, so it may be elevated in CSS. If fibrinogen levels fall rapidly from baseline, or fall below the normal range, consider active DIC.
   3. **Readily available inflammation markers:** Elevated C-reactive protein (CRP), ESR, ferritin (all of these markers are non-specific)
      1. CRP
         1. CRP is predominantly regulated by IL-6, so it is a good surrogate marker of IL-6 signaling pathways.
         2. After IL-6 blocking therapy (e.g. tocilizumab or sarilumab), CRP levels usually drop by about 50% each day, reflecting its half-life of about 19 hours (Pepys and Hirschfield, *JCI*, 2003).
      2. ESR
         1. ESR tends to change more slowly than CRP - days to weeks, not hours to days
         2. It is affected by a number of factors relevant in COVID-19, including fibrinogen levels, anemia, renal function, immunoglobulin levels, which makes it a little more difficult to interpret
      3. Ferritin
         1. In CSS in COVID-19, ferritin levels are only moderately elevated, even in severe cases (typically no higher than low 1000s).
         2. This is in contrast to other types of CSS, including macrophage activation syndrome, where ferritin can be >10,000.
   4. **Targeted immune cell activation markers:**, sIL2R (sCD25), IL-6
      1. These tests may take several days to result and should not delay clinical care.
      2. Large serum cytokine panels are commercially available but are not recommended for patients with COVID-19 due to the turnaround time and the uncertainty of how to interpret the results, as serum cytokine levels often do not correlate with their importance in pathogenic mechanisms
   5. Keep in mind that **procalcitonin** is downstream of IL-6 and IL-1, so it is not a specific marker of infection in the setting of cytokine storm

3. **Screening:** All hospitalized patients with COVID-19 should receive laboratory screening for CSS
    1. Please see Inpatient Laboratory Workup for screening recommendations
    2. There are currently no validated risk calculator to predict risk of CSS in COVID-19.
    3. CSS may show up in the labs before it appears clinically, and suggestive lab findings merit early consideration of immunomodulators as patients with laboratory evidence of CSS exhibit higher risk of progression to ARDS, shock, and multiorgan failure (Chen et al, *Lancet*, 2020).

Management

1. The management of CSS in COVID-19 has evolved significantly during the course of the pandemic and continues to change over time.
2. Corticosteroids are now recommended for patients with COVID who require supplemental oxygen.
    1. The mechanism through which steroids provide benefit is not clear, but it is likely that they help prevent cytokine storm.
3. For patients hospitalized with several COVID-19, especially patients with escalating oxygen requirements early during their admission, treatment with *Anti-IL6 Agents* or *Jak inhibitors* is also recommended.
    1. The strategy is summarized in this Overview table.
    2. More information is available in appendix A of the ID treatment guidelines (only accessible on the BWH internal network).
    3. Currently, *Anti-IL6 Agents* (tocilizumab, sarilumab) and *Jak inhibitors* (baricitinib, tofacitinib) are most commonly used.

Minimizing Healthcare Worker Risk of Exposure

1. Code Responses to COVID-19 patients are high-risk events for healthcare worker exposure due to the aerosolization that occurs with chest compressions and intubation
    1. Use PPE:
        1. CDC guidelines recommend N95 respirator, face shield, gown and gloves be used by all code responders during code events (CDC Guidelines, 2020) as well as Face Shield, Gown and Gloves).

In-Hospital Cardiac Arrest Management

5. **Breathing**
    1. **Initial Ventilator Settings**
        1. Patients should be placed on the following settings, consistent with AHA_ACLS guidelines (Edelson et al, *Circulation*, 2020) unless clinical information suggests different ventilator settings be used
9. **Post-Resuscitation Care**
    1. Dispose of, or clean, all equipment used during CPR. Any work surfaces used for airway/resuscitation equipment will also need to be cleaned.
    2. After the resuscitation has ended adhere to strict doffing procedure to limit exposure.
    3. If ROSC is achieved, provide usual post-resuscitation care consistent with current recommended guidelines including targeted temperature management (Donnino et al, *Circulation*, 2015).

CHAPTER 9

Infectious Disease

Read full Chapter →

Diagnostics

1. BWH-specific inpatient COVID-19 testing pathways and infection control guidelines can be found here (Partners login required)
2. Please reference the *Diagnostics* chapter

Biothreats, Flags and Infection Control

1. Please see the *Biothreats* section and *Infection Control* section for further details
2. Testing and Infection Control Guidelines (Partners login required)

Infectious Diseases Consultation

1. Infectious diseases consult may be considered in inpatients who have been diagnosed with COVID-19
2. Infectious diseases e-consults are available for outpatients

COVID-19 Treatment with Antivirals

1. A breakdown of the potential therapeutic options for COVID-19 can be found in the *Therapeutics* chapter
2. The BWH Infectious Diseases COVID-19 treatment guidelines can be used to access current BWH protocols based on enrolling clinical trials (available on-site or off-site via VPN)

Secondary Infections

1. **Viral**: viral co-infection data suffers from inconsistencies, but the incidence is likely ~3% among hospitalized patients with COVID-19
    1. A study in San Francisco found ~20% of symptomatic COVID-19 patients were also PCR positive for another viral pathogen (Kim et al, *JAMA*, 2020)
    2. In contrast, two studies in San Francisco and Wuhan, China where hospitalized COVID-19 patients tested for influenza and RSV found that none of these patients had evidence of viral co-infection (Myers et al, *JAMA*, 2020; Chen et al, *Lancet*, 2020)
    3. A meta-analysis of 1014 hospitalized COVID-19 patients found a viral co-infection rate of 3% (95% CI 1-6%, I^2=62.3%), with RSV and influenza being the most common coinfections (Lansbury et al, *J Infect*, 2020)
    4. MGB influenza treatment guidelines, which include guidance on how to manage patients with concomitant COVID-19 and influenza, can be found here
2. **Bacterial**: The incidence of nosocomial infections is 7-8% among hospitalized patients with COVID-19. It is important to differentiate co-infection from secondary infection
    1. One meta-analysis of 2183 hospitalized COVID-19 patients found 7% had a bacterial coinfection (95% CI 3-12%, I^2=92.2%) (Lansbury et al, *J Infect*, 2020)
    2. Another meta-analysis of 806 hospitalized COVID-19 patients found 8% developed bacterial and/or fungal infections during admission (Rawson et al, *Clin Infect Dis*, 2020).
    3. A separate meta-analysis of 3448 COVID-19 patients broke bacterial infections down into co-infection and secondary infection and found the risk of co-infection on presentation to be 3.5%, while the risk of secondary infection after presentation was 15.5%. In this same cohort,

71.3% of patients received antibiotics, despite only 7.1% of patients overall having a bacterial infection (Langford et al, *Clin Microbiol Infect*, 2020)

1. This particular group out of the University of Toronto created a living systematic review of the data at https://www.tarrn.org/covid

4. Two smaller cohort studies have reported similar nosocomial infection rates: 8% of 150 hospitalized patients (Ruan et al, *Intensive Care Med*, 2020) and 13.5% of 52 mechanically ventilated patients (Yang et al, *Lancet Resp Med*, 2020). In contrast, one study of 339 COVID-19 patients over 60 years of age with severe and critical disease found bacterial secondary infection rates of 42.8% (Wang et al, *J Infect*, 2020)
5. The most common reported infections are pneumonia (32%), bacteremia (24%), and urinary tract infections (22%) (He et al, *Infect Control Hosp Epidemiol*, 2020)
6. Nosocomial infections are associated with increased COVID-19 severity and mortality (He et al, *Infect Control Hosp Epidemiol*, 2020; Wang et al, *J Infect*, 2020)
    1. Patients with severe COVID-19 suffer a higher rate of secondary infection compared to those with non-severe COVID-19 (Zhang et al, *J Clin Virol*, 2020)
    2. Organisms reported include those commonly seen with hospital-acquired infections
        1. Bacterial pathogens include *Mycoplasma* sp., *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Klebsiella* sp., *Enterobacter* sp., *Staphylococcus aureus*, *Acinetobacter* sp., and *E.coli*, and *Enterococcus* sp. (Langford et al, *Clin Microbiol Infect*, 2020; Lansbury et al, *J Infect*, 2020)

3. **Fungal**: fungal pathogens such as *Aspergillus* sp., *Candida albicans*, *Pneumocystis jirovecii*, and Mucorales have been described in a subset of patients with COVID-19 (Lansbury et al, *J Infect*, 2020; Menon et al, *Am J Respir Crit Care Med*, 2020)
    1. Consensus criteria on the definition and management of COVID-19-associated pulmonary aspergillosis (CAPA) has been published by the European Confederation of Medical Mycology and the International Society for Human and Animal Mycology (Koehler et al, *Lancet Infect Dis*, 2020)
    2. In a prospective Italian cohort of 108 mechanically ventilated COVID-19 patients, probable pulmonary aspergillosis was diagnosed in 30 patients (27.7%) after a median of 4 days from ICU admission, and these patients had a much higher risk of 30-day mortality (OR 3.53 (95% CI 1.29-9.67, p=0.014). Of note, most patients received tocilizumab or steroids in this cohort (Bartoletti et al, *Clin Infect Dis*, 2020)
    3. Some case series have reported COVID-19 associated pulmonary aspergillosis rates of 15-35% (Prattes et al, *Intensive Care Med*, 2021; Arastehfar et al, *J Fungi*, 2020), while others are as low as 3.8% (Lamoth et al, *Clin Microbiol Infect*, 2020). Risk factors for CAPA were explored by a group out of Johns Hopkins (Permpalung et al, *Clin Infect Dis*, 2021)
    4. Mucormycosis has been reported in patients with COVID-19, with the majority of data being generated from India (Kumar Singh et al, *Diabetes Metab Syndr*, 2021; Garg et al, *Mycopathologia*, 2021)
4. Risk factors for secondary bacterial and fungal infections
    1. In a single center study of 65 COVID-19 patients, invasive devices (OR 4.28, 95% CI: 2.47–8.61), diabetes (OR 3.06, 95% CI: 1.41–7.22), and the use of one or more class of antibiotic (OR 1.84, 95% CI: 1.31–4.59) were significant predictors of nosocomial infection (He et al, *Infect Control Hosp Epidemiol*, 2020

2. Glucocorticoid treatment was also found to be positively associated with secondary infection (38% in He et al, *Infect Control Hosp Epidemiol*, 2020)
3. There is a disproportionate high use of antibiotics despite paucity of evidence for bacterial secondary infection in COVID-19 (He et al, *Infect Control Hosp Epidemiol*, 2020; Zhou et al, *Infect Control Hosp Epidemiol*, 2020; Rawson et al, *Clin Infect Dis*, 2020)

Choice of agent

1. Clinical reports indicate that rates of bacterial superinfection with COVID-19 **are low** (see *Secondary Infections* section above), but when present, increase mortality risk. Reports suggest less MRSA superinfection than is often seen with influenza. Unnecessary antibiotics carry risks of toxicities, fluid overload, and potential drug resistance.
2. If antibiotics are to be used, they should reflect IDSA guidelines based on presumed source and multi-drug resistant risk factors

HIV-Positive Patients

1. The U.S. Department of Health & Human Services released Interim Guidance for COVID-19 and Persons with HIV
2. The NIH COVID-19 Treatment Guidelines also include a section on Special Considerations in People with HIV
3. It's not entirely clear if, and how, HIV infection affects risk or severity of COVID-19
    1. Multiple studies have found that HIV-positive patients develop COVID-19 at a similar rate as the general population. The patients included in these studies were largely on antiretroviral therapy (ART) with well-controlled HIV (Richardson et al, *JAMA*, 2020; Sigel et al, *Clin Infect Dis*, 2020; Karmen-Tuohy et al, *J Acquir Immune Defic Syndr*, 2020; Vizcarra et al, *Lancet HIV*, 2020; Guo et al, unpublished report, 2020)
    2. A large Spanish cohort study of people with well-controlled HIV found that the rate of COVID-19 diagnosis and hospitalization in HIV patients was decreased to 30.0 cases per 10,000, compared with 41.7 per 10,000 in the general population (Del Amo et al, *Annals Intern Med*, 2020).
    3. Conversely, a WHO analysis found that persons with HIV were at an increased risk of severe or critical disease at hospital admission (aOR 1.06, 95% CI 1.02–1.11) compared to HIV-negative individuals. HIV infection was also independently associated with a higher risk of death (aHR 1.29, 95% CI 1.23–1.35) compared to the HIV-negative population (WHO Report July 2021)
4. Some antiretroviral therapy may be protective against COVID-19
    1. A large Spanish cohort study of over 77,000 people with HIV, 236 of whom were diagnosed with COVID-19, found that patients taking tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) had a significantly decreased risk of COVID-19 diagnosis and hospitalization compared with those taking tenofovir alafenamide (TAF)/FTC or abacavir (ABC)/lamivudine (3TC). This may be an effect of increased blood concentrations of tenofovir with TDF compared with TAF, though may also reflect that patients taking TDF are typically younger and healthier than those on TAF (Del Amo et al, *Annals Intern Med*, 2020)
    2. Conversely, a smaller observational Spanish study of 2873 HIV-positive individuals, 51 of whom had COVID-19, found that tenofovir (either TDF or TAF) use was disproportionately enriched among COVID-19 cases (Vizcarra et al, *Lancet HIV*, 2020)

3. A randomized controlled trial of lopinavir-ritonavir in treatment of severe COVID-19 in hospitalized, HIV-negative patients found no benefit (Cao et al., *NEJM* 2020). This treatment also did not reduce duration of viral shedding in mild COVID-19 in a Taiwanese study (Cheng et al, *J Microbiol Immunol Infect*, 2020)
4. For further information about antiretroviral agents under investigation for treatment of COVID-19, please see the *Therapeutics* Chapter

5. There is speculation that lymphopenia and immune dysfunction in HIV-positive individuals may protect from the hyperinflammatory state thought to contribute to severe COVID-19 disease (Mascolo et al, *J Med Virol*, 2020), but no evidence currently exists to support this theory
6. Summary and recommendations:
    1. Studies to date suggest that well-controlled HIV does not substantially increase the risk or severity of COVID-19, but data on patients with low CD4+ counts remains sparse. Given the limitations of the existing evidence at this time, we recommend that **HIV-positive patients be considered high risk**, in accordance with existing CDC guidelines, and be counseled on precautions accordingly
    2. Per existing standard of care, **all patients with HIV should remain on a daily ART regimen** under the supervision of a trained HIV provider
    3. We **do not recommend changing an existing ART regimen** for the purposes of prophylaxis or treatment of COVID-19 in HIV-positive patients
    4. HIV-positive patients who develop COVID-19 **do not require any change from standard protocol** in management or treatment strategies
    5. People with HIV are **eligible to receive any COVID-19 vaccine** currently available in the U.S. as long as there are no contraindications. HIVMA has posted an FAQ on COVID-19 Vaccines and People with HIV

CHAPTER 11

Hematology

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Incidence

1. In ICU patients, cumulative incidences range from 9% to 70% in patients on varying levels of prophylactic anticoagulation, and whether patients were screened with compression ultrasonography or imaged for change in clinical status (Klok et al, Thrombosis Res 2020.; Middeldorp et al, Preprint 2020.; Klok et al., Thrombosis Res April 30 2020; Llitjos et al, J Thromb Haemostat 2020; Nahum et al. JAMA Net Open 2020.; Moll et al. CHEST 2020).
2. We found that in 102 COVID-19 positive ICU patients, there were 9 radiographically-confirmed DVT or PE, based on imaging obtained for a change in clinical status; all patients received standard dose prophylactic anticoagulation (enoxaparin 40 mg daily or unfractionated heparin 5000 IU three times daily). No events occured in 108 wards patients (Moll et al., CHEST 2020). Similar findings were reported in Indianapolis (Maatman et al. Crit Care Med 2020).
3. Higher D-dimer and FDP levels track with multi-organ dysfunction syndrome and poorer prognosis (Wang et al, *JAMA*, 2020; Zhou et al, *Lancet*, 2020).

Pathophysiology

3. There is evidence that A blood type is a risk factor for COVID-19 respiratory failure, and O may be protective. This was based on a genome-wide association study (GWAS) of 835 patients and 1255 control participants from Italy and 775 patients and 950 control participants from Spain. Respiratory failure was defined as a patient requiring supplemental oxygen or mechanical ventilation (Ellinghaus et al. NEJM 2020).

Prophylaxis Management

1. **Rationale:** As stated above, VTE incidence is elevated in patients with COVID-19. ICU patients are at additionally elevated risk for VTE events even on standard prophylaxis (Klok et al, Thrombosis Res 2020.; Middeldorp et al, Preprint 2020.; Klok et al., Thrombosis Res April 30 2020; Llitjos et al, J Thromb Haemostat 2020; Nahum et al. JAMA Net Open 2020.; Moll et al. CHEST 2020). Therefore, several observational studies and randomized clinical trials have addressed the use of **intermediate** and **therapeutic** dose heparin prophylaxis in ICU and non-ICU patients.
    1. **Intermediate dosing:** The INSPIRATION randomized controlled trial (INSPIRATION Investigators, JAMA 2021.) compared **intermediate** to **standard** dose heparin prophylaxis in ICU patients and reported no difference in venous or arterial thromboses, need for ECMO, or 30-day mortality. The intermediate dose group had more thrombocytopenia, but no significant differences in major bleeding. We observed similar findings at our institution (Moll et al., Throm Res 2021).
    2. **Therapeutic dosing:** A multi-platform response-adaptive randomized controlled trial was undertaken to evaluate **therapeutic** versus **standard** dose heparin prophylaxis in COVID-19 patients, and the results were published separately for ICU and ward patients (The REMAP-CAP, ACTIV-4a, and ATTACC Investigators, NEJM 2021 (Critically-ill), The REMAP-CAP, ACTIV-4a, and ATTACC Investigators, NEJM 2021 (Non-critically ill). The primary outcome was a composite of organ support-free days (including in-hospital death on the ordinal scale) and number of days free of cardiovascular or respiratory organ support up to 21 days among patients who survived to hospital discharge. Respiratory organ support included non-invasive ventilation and high flow nasal cannula. Participants were further divided into subgroups based on D-dimer levels.
        1. **For ICU patients,** the trial was stopped early for futility (The REMAP-CAP, ACTIV-4a, and ATTACC Investigators, NEJM 2021 (Critically-ill)).
        2. **For ward patients,** the therapeutic heparin arm appears to have an beneficial effect with a Bayesian adjusted OR of 1.27 (95% credible interval 1.03 - 1.58). The authors reported major bleeding events to be 1.9% in the therapeutic arm compared to 0.9% in the standard dose arm (The REMAP-CAP, ACTIV-4a, and ATTACC Investigators, NEJM 2021 (Non-critically ill)).

            1.This result is **controversial for several reasons:**
                1. First, the proportions of participants assigned to each trial arm were recalculated based on a single interim analysis performed on December 15, 2020 to favor randomization to the therapeutic dose arm. This approach is called response-adaptive randomization. While this approach theoretically provides therapeutic advantages to study participants and could be more ethical, it can also introduce selection bias, counteract the benefits of initial randomization, actually reduce total

absolute numbers of individuals assigned to the favored arm, and can lead to challenges in interpreting the final results (Proschan, et al. Clin Inf Dis 2020, Park, et al., Clin Epidemiol 2018) The chance for bias is greater when based on fewer or a single interim analysis, as was done in this trial.

2. Second, it is challenging for a clinician to gauge whether an individual patient would have qualified for the trial. For example, participants who were thought not to need hospitalization for more than 72 hours were excluded, and some platforms only enrolled patients within 72 hours of hospital admission, while others enrolled patients within 14 days of hospital admission.
3. Third, given these issues, it is difficult to weigh the benefits and risks of therapeutic dose prophylaxis for individual patients, especially since major bleeding events were higher in the therapeutic dose arm. For these reasons, guidelines vary widely.

3. **For moderately-ill COVID-19 patients**, the difficulty in determining which individual patients might benefit from this strategy, the possibility of bias explaining the observed beneficial effects, and the elevated major bleeding risks render it challenging to recommend this strategy. Therefore, we **do not** recommend initiating therapeutic dose prophylaxis in all non-critically ill hospitalized COVID-19 patients at this time. Rather, we recommend standard prophylaxis, but encourage clinicians to weigh individual risk factors for VTE when deciding whether to start therapeutic dose heparin prophylaxis. The difference in treatment effect was 4% favoring therapeutic dose, with a 0.7% difference in major bleeding, resulting in an approximately 3% difference in outcome. **Planned analyses to assess factors associated with benefit are underway.**

2. **For floor patients:**
   1. Given BWH data do not support significantly increased VTE risk in this population (1%, see above), prophylaxis for SPU (Covid-19) patients remains the same:
   2. We do not recommend therapeutic anticoagulation for all floor patients (see **Rationale** above). Clinicians can consider existing VTE risk factors and opt to initiate therapeutic prophylaxis if the perceived risk of VTE is high. However, therapeutic dose heparin is not likely needed for all hospitalized patients. All admitted patients should at least get prophylactic dose heparin as below:
3. **For ICU patients and post-ICU patients:**
   1. Given the elevated VTE risk relative to baseline (1.5-2 fold, see above), our recommendation for prophylaxis doses for ICU patients and post-ICU patients is ***higher*** (see table below). Randomized controlled trial data do not suggest that intermediate dose heparin reduces the risk of progression of COVID-19 or death but does decrease VTE death, but there was also no increase in major bleeding events. We will continue to give intermediate dose prophylaxis given that there does not appear to be harm associated with this strategy.
   2. Inclusion:
      1. Covid-19 confirmed and PUI patients requiring ICU level of care during ICU course and after transfer to the floor
      2. Platelets > 25

Therapeutic anticoagulation

1. Recommendations for therapeutic anticoagulation of patients with known DVT or PE remain the same as prior.
    1. While some institutions are considering full dose anticoagulation in severe COVID disease without known VTE, our interpretation of the data is that the risks outweigh the benefits at this time, unless documented DVT or PE. See the **Rationale** section above.
    2. A propensity score-matched cohort study of 3,772 participants compared COVID-19 patients receiving anticoagulation/anti-thrombotic therapy prior to diagnosis to patients without prior anticoagulation/anti-thrombotic therapy; no statistically significant difference in survival or time to mechanical ventilation was observed (Tremblay et al. Blood, 2020.)
2. If the patient is on direct oral anticoagulants (DOACs) or Warfarin for Afib or VTE, assess on an individual basis whether to switch to a parenteral anticoagulant with a shorter half-life (LMWH or heparin) based on clinical status.
    1. Consider the same clinical criteria used for non-COVID-19 patients. For example:
        1. Consider LMWH or heparin in COVID-19 patients with AKI, procedures that require time off therapeutic anticoagulation or clinical instability (e.g., patients requiring critical care).
        2. Continue home anticoagulation regimen in clinically stable COVID-19 patients without other contra-indications, with close monitoring of factors that could influence pharmacokinetics (e.g., antibiotics that could increase the effect of Warfarin; renal function for DOACs).

Speculative use of therapeutic anticoagulation or tissue plasminogen activator (TPA)

1. While therapeutic anticoagulation has been used empirically in some severe COVID-19 patients in Wuhan given the possible microthrombi in pulmonary vasculature (see *"Pathophysiology"* above), our interpretation of the data is that the risks outweigh the benefits at this time, unless documented DVT or PE (Hardaway et al, Am Surg 2001).

Prognosis

1. DIC is associated with worse survival in COVID-19 patients. Out of 183 COVID-19 patients in Wuhan, 71% of non-survivors had DIC (ISTH score ≥ 5; MDcalc online calculator) compared to 0.6% of survivors (Tang et al, *J Thromb Haemost*, 2020).

Incidence

1. Many patients with COVID-19 have either normal WBC or leukopenia
    1. Leukocytosis (>10,000/µL) in 13% and leukopenia (<4000/µL) in 15.5% (Goyal et al, *N Engl J Med*, 2020)
2. Lymphocytopenia, or lymphopenia, typically defined as an absolute lymphocyte count < 1000/µL, is the most common abnormality on the CBC in COVID-19 and is found in over 80% of hospitalized patients (Guan et al, *N Engl J Med*, 2020, Huang et al, *Lancet*, 2020)
    1. In 393 adult patients hospitalized with COVID-19 in New York City, 90 percent had a lymphocyte count <1500/µL (Goyal et al, *N Engl J Med*, 2020)
    2. ICU patients with COVID-19 had a median lymphocyte count of 800 cells/mm (Wang et al, *JAMA*, 2020)

Prognosis

1. In COVID-19, the degree of lymphopenia correlates with disease severity and survival (Tan et al, *Signal Transduct Target Ther*, 2020; Yang et al *Lancet Respir Med*, 2020; Ruan et al, *Intensive Care Med*, 2020).

Pathophysiology

1. Numerous possible explanations for lymphopenia in COVID-19 have been proposed.
    1. Invasion/ destruction of lymphocytes via ACE2 receptor
        1. ACE2 receptor is expressed on lymphocytes, mainly those within oral mucosa, digestive system, and the lungs
    2. Acidemia, nutrition, bone marrow suppression
        1. In critically ill patients, all of these factors may suppress proliferation of lymphocytes
    3. Cytokine Storm
        1. Cytokines (such as TNFα, IL-6) may induce apoptosis of lymphocytes and has been previously documented in critical patients with SARS (Lam, *The Clinical Biochemist Review*, 2004). However, this explanation is likely inadequate, as in Cytokine Release Syndrome with CAR-T therapy there are elevated cytokine levels but not consistent documented lymphopenia
    4. Lymphatic organ damage (thymus, spleen)
        1. This possibility still requires pathological evidence and remains speculative (Tan et al, *Signal Transduct Target Ther*, 2020)
    5. Host Endothelial function
        1. With age and chronic disease, there is more leukocyte adhesion and extravasation (Bermejo-Martin, *Journal of Infection*, 2020)
    6. Sequestration of lymphocytes
        1. Cytokine release leads to movement of the lymphocytes to the site of infection, the lung tissue, which could contribute to peripheral lymphopenia (Rahimmanesh, *Preprint*, 2020)
        2. Cytotoxic T lymphocytes decline sharply in COVID-19, which could be due to movement of these cells to the lower respiratory tract (Rahimmanesh, *Preprint*, 2020)
2. Lymphocyte Subgroups
    1. Increased $CD8^+$ T cells tended to be an independent predictor for COVID-19 severity and treatment efficacy, which is likely due to their known function of helping to mediate clearance of viruses. (Wang, Journal of Infectious Disease, 2020)

Management

1. No current treatment regimen management changes based on lymphopenia
    1. There is no evidence for giving pneumocystis jiroveci prophylaxis given the transient nature of lymphopenia with COVID-19

Incidence

1. Thrombocytopenia has been described in hospitalized patients with COVID-19 with variable reported incidence:

Pathophysiology

1. Multiple proposed mechanisms of thrombocytopenia (Xu et al, *Ann Hematol*, 2020; Amgalan & Othman, *J Thromb Haemost*, 2020)

Diagnosis and workup

2. Initial workup
    1. Labs: PT, aPTT, fibrinogen, LDH, LFTs, B12, folate
    2. Peripheral blood smear
        1. Useful to exclude platelet clumping (pseudothrombocytopenia) and to evaluate for other contributing causes

3. Pretest probability of HIT can be calculated by 4Ts score (MDCalc 4Ts calculator)
    1. Laboratory testing for HIT should typically only be sent in patients with at least intermediate probability of HIT (4 or more points on 4Ts score), although need to consider clinical context.
    2. If send PF4, use a non-heparin anticoagulant (e.g. bivalirudin or other direct thrombin inhibitor per institutional protocols) while awaiting PF4 results. Serotonin release assays may be necessary to confirm positive PF4 results.

CHAPTER 13

Neurology

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Incidence

1. While much is still to be learned about the CNS involvement of COVID-19, lessons from scientific and clinical experience from other human coronaviruses suggest neuroinvasive potential of SARS-CoV-2.Experience from prior coronavirus infections and emerging cases of COVID-19 both suggest that clinically-relevant direct CNS involvement of SARS-CoV-2 is likely to be rare.
2. Neurologic manifestations may occur in 36.4%-69% of hospitalized COVID-19 patients (Mao, *JAMA Neurology*, 2020; Helms, *NEJM*, 2020). Manifestations can include:
    1. Delirium, confusion, or executive dysfunction (Helms, *NEJM*, 2020).
    2. Smell or taste abnormalities (5-98%, see anosmia section)
    3. Headache (6.5-71%, see headache section)
    4. Corticospinal tract signs (67%) (Helms, *NEJM*, 2020)
    5. Dizziness (16.8%) (Mao, *JAMA Neurology*, 2020)
    6. Stroke (2.5-5%) (see stroke section).
    7. GBS, Miller Fisher syndrome (case reports) (see neuromuscular disorders section)
    8. Encephalitis, acute necrotizing encephalopathy, myelitis, CNS demyelinating lesions (case reports) (see encephalitis section)
3. Neurological care is complicated by COVID-19:
    1. Patients with underlying neurological disorders may be vulnerable to infections and respiratory complications (due to immunosuppression, aspiration, respiratory weakness, poor cough) and often have impaired communication.
    2. Patients with COVID-19 often have impaired communication with providers owing to oxygen delivery devices, proning, and the need for PPE

Pathophysiology

1. Illness from SARS-CoV-2 can provoke states that increase risk of neurological disease. The pathophysiology of the various neurological manifestations of COVID-19 is currently unknown, but possible mechanisms include (Wu, *Brain Behav Immun*, 2020):

PPE considerations

1. See PPE section for standard guidelines
2. **Convulsive seizure and agitated delirium should be considered aerosol-generating**
3. Patients who are unable to be screened due to encephalopathy or neurologic deficits should be treated as COVID-19 rule-out patients

COVID-19 Direct Neurologic Effects

Anosmia

1. Incidence:
    1. Changes in smell and taste perception have been reported in a wide range of patients with COVID-19 (5-98%).
        1. A meta-analysis of 10 studies (1627 patients) demonstrated olfactory dysfunction in 53% and gustatory dysfunction in 44% of COVID-19 patients (Tong, *Otolaryngol Head Neck Surg*, 2020).
        2. Table of studies measuring frequency of anosmia
    2. Anosmia may precede COVID-19 diagnosis (Kaye, *Otolaryngol Head Neck Surg*, 2020), and when anosmia/ageusia occur they most frequently precede hospitalization (Giacomelli, *Clinical Infectious Disease*, 2020).
3. Clinical course:
    1. 66-80% of patients with COVID-19-associated smell impairment report spontaneous improvement or resolution within days-weeks of recovery from clinical illness (Yan, *Int Forum Allergy Rhinol*, 2020; Lechien, *Eur Arch Otorhinolaryngol*, 2020; Hopkins, *J Otolaryngol Head Neck Surg*, 2020; Vaira, *Head Neck*, 2020).
    2. In a study of 3191 patients, median time to recovery for anosmia and ageusia was 7 days, and most patients recovered within 3 weeks (Lee, *J Korean Med Sci*, 2020).
4. Management: No indication for corticosteroids to treat hyposmia/anosmia, as frequently recovers without intervention.
    1. For persistent anosmia, please see prolonged anosmia and ageusia in the global health version of COVIDProtocols.

Encephalitis and Myelitis

2. Incidence of brain and CSF abnormalities in case series:
    1. MRI brain abnormalities may be present in 37-62% of COVID-19 patients with neurologic symptoms requiring imaging (excluding stroke).
4. Pathophysiology
    1. Evidence for autoimmune involvement
        1. Case report of presumed COVID-19 related autoimmune meningoencephalitis, with improvement in 4/6 patients after plasmapheresis (Dogan, *Brain Behav Immun*, 2020).
        2. Case report of acute necrotizing encephalopathy, a presumed auto-immune inflammatory condition (Poyiadji, *Radiology*, 2020).
6. Work-up and management
    1. Consult neurology for guidance.
    2. *General approach to work-up and management of encephalitis and myelitis*
    3. Published cases of meningitis/encephalitis in COVID-19 patients report variable presence or absence of MRI or CSF abnormalities.
    4. In cases where CNS involvement of COVID-19 is suspected, save extra CSF from LP and discuss with neurology and infectious disease possibly sending for next-generation sequencing or COVID-19 RT-PCR

Incidence

1. Patients with COVID-19 may have an increased risk of stroke related to a systemic inflammatory and prothrombotic state (Klok, *Thromb Res*, 2020), possible endothelial dysfunction related to ACE2 depletion (Hess, *Trans Stroke Res*, 2020), and/or medical comorbidities.
2. In case series of patients with COVID-19, 2.5%-5.0% have strokes (Mao, *JAMA Neurology*, 2020; Li, *Preprint in Lancet*, 2020; Lodigiani, *Thromb Res*, 2020)
    1. Ischemic stroke (5%) is more common than intracerebral hemorrhage (0.5%) or cerebral venous sinus thrombosis (0.5%) (Li, *Preprint in Lancet*, 2020).
    2. Stroke was associated with older age, risk factors (hypertension, diabetes, prior cerebrovascular disease), elevated C-reactive protein, elevated D-dimer, and more severe COVID-19 disease (Li, *Preprint in Lancet*, 2020, Aggarwal, *Int J Stroke*, 2020, Mao, *JAMA Neurology*, 2020)

3. Case reports have suggested that COVID-19 infection may predispose to large-vessel occlusion strokes, including in young patients, though more data from larger studies are required to determine the presence and magnitude of increased risk (Beyrouti, *J Neurol Neurosurg Psychiatry*, 2020; Oxley, *NEJM*, 2020; González-Pinto, *Eur J Neurol*, 2020; Valderrama, *Stroke*, 2020; Viguier, *J Neuroradiol*, 2020).
4. Case reports have also documented COVID-19 positive patients presenting to care with acute ischemic stroke or intracranial hemorrhage, reinforcing the need for consideration of COVID-19 testing for patients presenting with neurologic syndromes (Oxley, *NEJM*, 2020; Avula, *Brain Behav Immun*, 2020; Muhammad, *Brain Behav Immun*, 2020)
5. Some patients may have asymptomatic strokes incidentally discovered on brain MRI (Helms, *NEJM*, 2020)
6. Limited data from COVID-19 positive patients with stroke or intracranial hemorrhage have found CSF to be negative for SARS-CoV-2 (Al Saiegh, *J Neurol Neurosurg Psychiatry*, 2020; Muhammad, *Brain Behav Immun*, 2020)

Transient Ischemic Attack (TIA) and minor stroke pathway

1. Our management approach to minimize TIA- and stroke-related admissions during the COVID-19 pandemic can be found here.

Work-up

1. If acute stroke is suspected:
    1. Protocols for acute stroke work-up and management: IV tPA, endovascular therapy, and 2018 AHA guidelines. Consult neurology for any acute stroke evaluation.
    2. COVID-19-specific considerations:
        1. Imaging should focus on use of CT scans, and neurology should be involved in discussion regarding the need for inpatient or acute MRI, given comparative ease of CT sterilization.
        2. In patients being ruled out for COVID-19, consider CT chest in addition to CTA head and neck as part of initial imaging
    3. As reference, multiple published guidelines exist addressing how to best manage acute stroke during the COVID-19 pandemic (Khosravani, *Stroke*, 2020; AHA/ASA Stroke Council, *Stroke*, 2020; Baracchini, *Neurol Sci*, 2020; Qureshi, *Int J Stroke*, 2020)

Management

1. See linked guidelines above for acute stroke work-up and management.
2. COVID-19-specific considerations:
    1. tPA increases D-dimer levels and decreases fibrinogen levels for at least 24 hrs (Skoloudik, *J Thromb Thrombolysis*, 2010). D-dimer should not be used for COVID-19 prognostication post-tPA.
    2. If IAT is being considered, strongly consider intubating COVID-19 positive and rule-out patients in discussion with the stroke team to minimize risk (including patient movement and agitation, airborne respiratory droplets, vomiting, etc.) (Alqahtani, *Cureus*, 2020; Smith, *Stroke*, 2020; Nguyen, *Stroke*, 2020)
    3. Post-tPA recommended neurological exam frequency is q15 min for the first two hours after administration; we recommend the same provider remain in the room to perform serial exams to minimize PPE use and exposure risk during this period
    4. Given likely hypercoagulable state (see *Thrombotic Disease*) in many COVID-19 patients, consider therapeutic anticoagulation for confirmed stroke in a COVID-19 patient if stroke mechanism is unclear (discuss with neurology)

Incidence

1. In early studies, the frequency of seizures appears low (<1%) in COVID-19 patients relative to other coronaviruses (8-9% for MERS-CoV and other HCoV [Saad, *Int J Infect Dis*, 2014; Dominguez, *J Med Virol*, 2009]).
    1. In a series of 214 patients, 1 patient had a generalized seizure lasting 3 minutes (Mao, *JAMA Neurology*, 2020)
    2. In a series of 304 COVID-19 positive patients in Hubei, China, none had seizures despite many with systemic and metabolic risk factors for lowering the seizure threshold (Lu, *Epilepsia*, 2020)
2. Case reports exist of COVID-19 positive patients developing new-onset seizures (Moriguchi, *Int J Inf Dis*, 2020; Xiang et al. unpublished, 2020; Duong, *Brain Behav Immun*, 2020; Zanin, *Acta Neurochir (Wien)*, 2020; Sohal, *IDCases*, 2020; Bernard-Valnet, *Eur J Neurol*, 2020; Karimi, Iranian Red Crescent Medical Journal, 2020).
3. Limited evidence to date does not suggest that patients with epilepsy are at higher risk of COVID-19 infection or severe disease manifestations (French, *Neurology*, 2020)
4. Epileptic patients with COVID-19 infection may have a higher than normal level of breakthrough seizure activity given changes in medication adherence, metabolism, and active infection (Lai, *Seizure*, 2005; Vollono, *Seizure*, 2020; Zubair, *JAMA Neurology*, 2020). There should be a low threshold to check levels of home AEDs and check for medication interactions.

Work-up and management

1. General seizure work-up and management regardless of COVID-19 status
2. Note that convulsive seizure should be considered **aerosol generating**, providers should don appropriate PPE
3. COVID-19-specific considerations:
    1. Patients with new or worsening seizure activity should be ruled out for COVID-19
        1. Infection can lower seizure threshold
        2. Post-ictal confusion often impedes accurate symptom screening
    2. Diagnostic testing:

1. Self-limited, first-time seizure
    1. If COVID-19 rule-out: Defer MRI brain with and without contrast (seizure protocol), and routine EEG until rule-out complete
    2. If COVID-19 positive: Defer MRI brain with and without contrast (seizure protocol), and routine EEG until infection cleared unless likely to change immediate management; initiate AEDs based on clinical history
2. Status epilepticus and non-convulsive status epilepticus
    1. Obtain inpatient MRI and LTM-EEG regardless of COVID-19 status
3. A helpful resource of medication interactions specific to COVID-19 patients can be found here.

Incidence

1. Altered mental status (AMS) in patients with COVID-19 may be caused by systemic infection, toxic-metabolic derangements or medication effects, or primary CNS dysfunction (e.g. seizure, stroke). See "Direct neurological effects" section for a discussion of evidence to date of direct neuroinvasion by SARS-CoV-2.
2. Delirium, characterized by waxing and waning arousal and impaired attention, is common in hospitalized patients of advanced age and with multiple comorbidities.
3. In early studies of COVID-19 patients, rates of AMS (including delirium) have been relatively high (7.5-66%), with variability likely related to differences in assessment of mental status and definitions of deficits.

Work-up

1. Initial evaluation:
    1. General evaluation for AMS, regardless of COVID-19 status
    2. Note that agitated delirium should be considered **aerosol generating**, providers should don appropriate PPE
    3. COVID-19 positive and rule-out patients often have multiple potential etiologies for AMS not due to a primary CNS process, detailed below.
        1. Metabolic derangements are common:
            1. Hypoxemia or hypercarbia due to respiratory failure
            2. Renal or hepatic dysfunction that may present with COVID-19
            3. Nutritional deficiencies (e.g. thiamine) in patients with poor nutritional status
        2. Infection: Any systemic infection can lead to encephalopathy. In addition to COVID-19, consider other concurrent or hospital-acquired infections (e.g. HAP, CAUTI, CLABSI)
        3. Medication effects:
            1. Sedation required for prolonged intubation
            2. Antibiotics used for empiric pneumonia or sepsis treatment, especially cephalosporins and quinolones (Bhattacharyya, *Neurology*, 2016)
    4. If a general evaluation for causes of altered mental status is unrevealing, or if abnormalities are corrected and mental status remains altered, recommend neurology consultation to discuss further possible diagnostic studies:
        1. MRI brain: recommend obtaining to evaluate for structural etiologies such as encephalitis or stroke (see *encephalitis* and *stroke* sections).
        2. Routine EEG: consider deferring until patient off COVID-19 precautions unless high suspicion for seizure and/or likely to change immediate management.

3. Lumbar puncture: recommend pursuing especially if patient has headache, meningeal signs, or focal neurologic findings not explained by above studies.

Management

1. Treat specific causes as discovered in work-up
2. Treat for delirium as discussed in the psychiatry section (or palliative care section for terminal delirium).
3. Further guidelines regarding ICU treatment of sedation, pain, agitation, and delirium can be found here. A summary of medications to treat agitation is available here.

Incidence

1. Estimates of headache incidence in COVID-19 patients range from 6.5-71% (Mao, *JAMA Neurology*, 2020; Lai, *Int J Antimicrob Agents*, 2020; Tian, *J Infect*, 2020; Zeng, *medRxiv*, 2020; Xu, *BMJ*, 2020; Huang, *Lancet*, 2020; Tostmann, *Euro Surveill*, 2020; Gupta, Monaldi Arch Chest Dis, 2020; Jin, *Gut*, 2020; Borges do Nascimento, *J Clin Med*, 2020). The wide variability in reported incidence may relate to method of assessment (self-report, spontaneous report versus specific symptom assessment), as well as the patient population studied.

Work-up

3. Features of history or exam that suggest distinct headache etiologies can be found here
4. Laboratory evaluation: CBC with diff, BMP, LFTs, TSH, PT-INR, PTT, hCG (females)
5. If there are red flag features:
    1. Consult neurology
    2. If headache onset is acute (pain is maximal within seconds to minutes of onset): Obtain non-contrast head CT to rule out acute emergencies (e.g. subarachnoid hemorrhage). Otherwise, consider MRI brain with and without contrast
    3. Consider CT or MR venography in appropriate clinical context
    4. Consider CT or MR angiography in appropriate clinical context
6. Recommend deferring fundoscopy in COVID-19 positive or rule-out patients given high risk of transmission, unless required to determine management
7. Consider lumbar puncture after imaging, especially if concern for:

Management

1. In COVID-19 positive patients whose headache is thought to be due to general systemic infection OR related to their history of migraine/tension type headache:
    1. Initial management (Orr, *Headache*, 2016)
        1. Antipyretic or NSAID:
            1.There is not data to support avoidance of NSAID use in COVID-19 (see discussion of NSAIDS in the therapeutics section)
            2.Anti-inflammatory:
                1. Acetaminophen 950 mg PO Q8H
                2. OR Toradol 15-30 mg IV Q8H PRN
                3. OR Naproxen 440-500 mg PO Q8H
                4. OR Indomethacin 50 mg (PO/suppository) Q8H
        2. AND Antidopaminergic medication (PO or IV) every 8 hours for 24-72 hours
            1.Metoclopromide 10 mg IV/PO q86h PRN (+/- Benadryl 25 mg)
            2.OR Prochlorperazine 10 mg IV/PO

3. AND Fluids
    1.500 cc normal saline or lactated ringers if signs of dehydration, and contingent upon pulmonary status as COVID-19 patients with lung injury are fluid-sensitive

Guillain Barré syndrome (GBS)

2. Incidence:
    1. Unknown incidence, however case reports of GBS and its variants are emerging in COVID-19 positive patients.
3. Presentation:
    1. Neuromuscular symptom onset usually occurs 3-10 days after initial COVID-19 symptoms
    2. Symptoms can include:
4. Work-up:
    1. Recommend neurology consult if clinically concerned for GBS. General work-up guidelines for GBS can be found here.
    2. Covid-19 specific considerations:
        1. Lumbar puncture: If COVID-19 positive, consider sending CSF COVID-19 PCR via CDC or requesting next-generation sequencing.
        2. EMG/ NCS: Guidance from the AANEM recommends EMG/NCS be performed only for urgent requests during the COVID-19 pandemic, with acute or rapidly evolving clinical presentation and if needed to determine management (AANEM 2020).
        3. Spine/ brain imaging: Often not required for clinical diagnosis and can be deferred until patient off COVID-19 precautions unless likely to distinguish from other etiologies or change management.
5. Management:
    1. General guidelines for GBS management independent of COVID-19 status can be found here.
    2. COVID-19-specific considerations:
        1. In contrast to COVID-19-associated ARDS, respiratory failure with GBS will manifest as hypercarbia before hypoxemia. Providers should maintain a low threshold for ABG if concerned for worsening respiratory *weakness*.
        2. Although there is a theoretical risk of thrombotic complications with IVIG, which may be compounded by the inflammatory state observed in COVID-19 patients, case reports to date have demonstrated use of IVIG in post-COVID-19 GBS without complications. Patients should be maintained on DVT prophylaxis if able and monitored carefully for thrombotic complications while on IVIG.

Myasthenia Gravis (MG)

1. Patients with MG may be at higher risk of contracting COVID-19 or developing severe disease because they are often on immunosuppressive therapies and have respiratory muscle weakness. Limited case reports have described MG patients with exacerbations or myasthenic crisis in the setting of COVID-19 (Anand, *Muscle Nerve*, 2020; Delly, *J Neurol Sci*, 2020)
2. Clinical presentation:
    1. Fluctuating skeletal muscle weakness, which can affect extraocular muscles, facial muscles, and/or appendicular muscles.
    2. Muscles of respiration can be affected; if severe, this leads to “myasthenic crisis” with respiratory failure requiring artificial ventilation

3. Exacerbations can be triggered by infections, medications, surgery, medication non-adherence and pregnancy / the postpartum period.
    1. It is expected that the COVID-19 pandemic will be associated with increased incidence and disease flares (Guidon, *Neurology*, 2020).
3. General management guidelines for all inpatients with Myasthenia Gravis are linked here
4. For COVID-19 positive patients and PUIs (International MG/COVID-19 Working Group, *J Neurol Sci*, 2020; Guidon, *Neurology*, 2020):
    1. Please consider reporting cases to CARE-MG, a physician-reported registry
    2. Avoid the following COVID-19 exploratory therapies known to exacerbate MG flares: Chloroquine, hydroxychloroquine, azithromycin
    3. Discuss continuation of home MG medications with outpatient neurologist. In general:
        1. Hold immune-depleting agents (e.g. rituximab) during illness
        2. Immunosuppressive agents (e.g. mycophenolate, azathioprine) may be continued given prolonged effects, and extended dosing needed to take effect each time medication is resumed
        3. Adjustment of steroid doses should be discussed with neurology
        4. Consider holding maintenance IVIG during illness given risk of thrombotic complications
    4. If concern for MG exacerbation, consider increased steroid dosing and/or IVIG in consultation with Neurology. Although there is a risk of thrombotic complications with IVIG, limited case reports have described its use in MG patients with COVID-19 without complication (Anand, *Muscle Nerve*, 2020; Delly, *J Neurol Sci*, 2020)
    5. Neuromuscular blockade

Critical illness polyneuropathy and myopathy

1. Incidence:
    1. ICU-acquired weakness has been observed in 25-46% of ICU patients. Duration of ventilation, corticosteroid administration, multi-organ dysfunction, sepsis, hyperglycemia, and renal replacement therapy have all been correlated with ICU-acquired weakness (De Jonghe, *JAMA*, 2002; Stevens, *Intensive Care Med*, 2007).
    2. Unknown incidence to date in patients with SARS-CoV-2 infection
    3. Rare case reports of critical-illness polyneuropathy and/or myopathy have been described in patients with SARS-CoV-1 and MERS-CoV, though this may underreport frequency related to prolonged ICU stays (Tsai, *Arch Neurol*, 2004; Kim, *J Clin Neurol*, 2017; Algahtani, *Case Rep Neurol Med*, 2016)
    4. Prone ventilation can lead to increased incidence of brachial plexopathy in the context of increased pressure to anterior portions of the arm and shoulder (Scholten, *Chest*, 2017; Goettler, *Crit Care*, 2002)
2. General guidelines on the presentation and evaluation of critical illness neuropathy and myopathy are linked here

Muscle injury

3. Work-up:
    1. CK, BMP, Phosphate, LFTs, TSH, UA
        1. If CK elevated, ddx includes muscle injury due to: viral myositis, patient positioning, muscle activity (e.g. shivering, seizure), medication toxicity

2. Note that CK levels are normal in steroid myopathy and may be normal in other toxic myopathies
3. AST and ALT are found in both liver and muscle. If elevated, consider checking GGT to distinguish muscle from hepatic injury (Rosales, *J Child Neurol*, 2008)

2. Check for medications that may contribute to toxic myopathy (Doughty, *Continuum*, 2019)
   1. Includes: statins , propofol, chloroquine, hydroxychloroquine, amiodarone, labetalol, colchicine, immune checkpoint inhibitors, certain antivirals.
   2. Toxic neuromyopathy associated with chloroquine and hydroxychloroquine typically occurs after prolonged treatment, and is unlikely to develop with the short medication courses being investigated for COVID-19 infection (Guidon, *Neurology*, 2020)

Brain death in COVID-19 patients

Determination of brain death

1. Brain Death Examination and Checklist Tool
2. COVID-19-specific considerations:
   1. We recommend completing COVID-19 testing prior to brain death examination, with a negative result obtained within 48 hrs of examination if possible
   2. The New England Organ Bank (or regionally appropriate center) should be consulted early regardless of COVID-19 status to issue a formal declaration regarding acceptance or refusal of case.
   3. Brain death testing involves aerosol-generating procedures (AGPs), requiring appropriate PPE use:
      1. Noxious stimulation of the nares
      2. Testing of cough and gag reflexes
      3. Apnea testing
         1. We recommend considering ancillary testing (defined in linked page above) in place of apnea testing for COVID-19 positive patients.
   4. If apnea testing is required for determination of brain death in a COVID-19 positive patient based on specific clinical context or available resources and expertise, would consider the following:

Management of patients with baseline neurologic symptoms

1. **Disease Modifying Therapy (DMT) and Risk of COVID-19 infection**
   1. It is not known whether patients with MS have increased **incidence** of COVID-19
      1. Patients with MS may be at higher risk of infection, including pneumonia and influenza, but do not appear to be at higher risk of all upper respiratory infections (Wijnands, *Multiple Scler*, 2017; Brownlee, *Neurology*, 2020; Willis, *J Neurol*, 2020).
   2. Most patients with MS or NMO are on DMTs to reduce progression to disability. DMTs can be classified as immunomodulatory (which may or may not increase infection risk) or immunosuppressive (which are associated with increased infection risk).
      1. This table summarizes a list of DMTs, their effects on the immune system, and the possibility of increased infection risks (Winkelmann, *Nat Review Neuro*, 2016).
      2. An excellent resource for DMT management has been assembled by the National Multiple Sclerosis Society
2. **COVID-19 positive patients with baseline neurologic symptoms:**

1. It is not known if MS patients with COVID-19 have a more **severe course** of disease

1. Very limited data have *not* shown that patients with MS have an increased risk of severe disease (Sormani, *Lancet Neurol*, 2020)

2. Mild COVID-19 Infection:
   1. In general, during mild viral infections DMTs are usually continued, as the benefit of preventing relapse outweighs the risk from the infection (Brownlee, *Neurology*, 2020).
      1. If COVID positive not requiring hospitalization, continue medication and FYI neurologist
      2. If COVID positive requiring hospitalization, page neurology
   2. If a patient has only mild symptoms and is a candidate for outpatient management, would discuss DMT management with outpatient neurologist
3. Moderate or Severe COVID-19 infection:

Management of patients with new or worse neurologic symptoms

1. Worsening symptoms may be due to recrudescence or relapse/new CNS demyelination. COVID-19 could trigger either of these, **so all patients with new or worsening symptoms should undergo COVID-19 PCR testing.**
   1. **Recrudescence:** URIs are known to lead to recrudescence of prior neurologic symptoms in patients with demyelinating disease (Berkovich, *Continuum*, 2016). Case reports are emerging in COVID-19 (Barzegar, *Neurol Neuroimmunol Neuroinflamm*, 2020)
   2. **CNS Demyelination:** The inflammatory state associated with COVID-19 infection could in theory trigger onset of demyelinating disease, formation of antibodies associated with demyelinating disease (e.g. anti-AQP4 or MOG), or exacerbate known disease.
2. Work-up and management of MS/NMO patients with worsening symptoms (regardless of COVID-19 status)
   1. For patients who are SARS-CoV-2 infected:
      1. Please consider reporting cases to COVIMS, a de-identified patient data repository.

      2. If neurologic symptoms are severe, new, or different than prior, obtain MRI w/wo contrast. If symptoms are mild or if they are fully consistent with worsening of known prior neurological deficits, may defer MRI studies (which are used to help distinguish recrudescence from relapse) until cleared, or COVID-19 precautions are discontinued.
3. If a new demyelinating lesion is found:
   1. COVID-19 negative patients, asymptomatic / minimally symptomatic COVID-19 positive patients:
      1. MS patients:
         1.Consider a 3-5 day course of high-dose steroids (with or without taper) to hasten recovery if benefits are felt to outweigh risks
         2.Although methylprednisolone 1000 mg IV daily is typically used, given efficacy of similar doses of PO methylprednisolone in MS and optic neuritis, can consider either PO steroids or outpatient IV steroid infusions to minimize risk associated with hospitalization if there is no other indication for admission (e.g. need for PT, OT, or rehab placement) (Burton, *Cochrane Database Syst Rev*, 2012; Le Page, *Lancet*, 2015; Morrow, *JAMA Neurol*, 2018).
      2. NMO patients:
         1.Recommend 3-5 day course of IV high-dose steroids and concurrent plasmapheresis (Weinshenker, *Annals of Neurol*, 1999; Bonnan, *J Neurol Neurosurg Psychiatry*, 2018)

2. Moderate-severely symptomatic COVID-19 positive patients:

Inclusion Criteria/ Temperature Target/ Procedure

1. Please see attached guidelines for discussion of these topics

CHAPTER 16

Rheumatology

Read full Chapter →

Managing COVID in Rheumatic Disease

1. *Please enroll patients with rheumatologic/autoimmune disease who are diagnosed with COVID-19 into the COVID-19 Global Rheumatology Alliance Registry and/or the EULAR – COVID-19 Database.*
2. **Clinical Presentation:**
    1. Patients with rheumatologic disease are not known to differ from other patients in terms of clinical presentation of COVID-19, though further information will be elucidated from the studies of the Global Rheumatology Alliance Registry.
3. **Outcomes:**
    1. Studies looking at outcomes for COVID patients with rheumatic disease indicate that immunosuppressed patients are at risk of more severe disease.
        1. **Incidence** appears to be similar to the general population
            1. In one prospective case series of 86 patients in New York City with a variety of immune-mediated inflammatory diseases. (Haberman et al, *NEJM*, 2020)
        2. **Hospitalization and mortality rates** appear similar to the general population
            1. In one comparative cohort study of 52 patients with rheumatic disease (75% on immunosuppressive medications) hospitalization and mortality rates were similar.

               However, rheumatic patients were more likely to require mechanical ventilation than healthy comparators, though the number of patients was low (11 patients [48%] vs 7 patients [18%], multivariable OR with 95% CI 1.07 to 9.05).(D'Silva K et al. *Ann Rheum Dis*, 2020)
            2. In a case series from the Global Rheumatology Research Alliance of 600 patients with rheumatic disease and COVID-19 from 40 countries, glucocorticoid exposure >= 10mg daily was associated with modestly higher odds of hospitalization (OR 2.05, 95% CI 1.06-3.96) while use of anti-TNF agents was associated with lower odds of hospitalization (OR 0.40, 95% CI 0.19-0.81). Neither use of DMARDs nor NSAIDs changed odds of hospitalization. (Gianfrancesco M et al. *Ann Rheum Dis* 2020)
            3. In a larger case series from the Global Rheumatology Research Alliance of 600 patients with rheumatic disease on baseline disease-modifying treatments (DMARDs) and COVID-19 from around the world, baseline use of Jak inhibitors and sulfasalazine conferred increased risk of worse outcomes compared with other disease-modifying therapies. (Sparks J et al. *Ann Rheum Dis* 2021)

4. **Management:**
    1. Data are evolving. We have included our recommendations below based upon guidelines as developed by the American College of Rheumatology. The authors also have outlined a helpful resource on UptoDate.
    2. *General Management*
        1. Patients should be counseled on general measures to prevent infection including physical distancing, hygiene, and wearing masks.
        2. For physician follow-up, telemedicine or video visits should be used when possible.
        3. Decrease frequency of routine laboratory testing or other in-person health care exposures where possible and safe.
    3. *Pharmacologic treatment for patients without infection with or exposure to COVID-19*
        1. Most anti-inflammatory and immunosuppressive medications including DMARDs and biologics may be continued or started.
            1. This recommendation applies to hydroxychloroquine, chloroquine, sulfasalazine, methotrexate, leflunomide, tacrolimus, cyclosporine, mycophenolate mofetil, azathioprine, tocilizumab, anakinra, and NSAIDs.
            2. In patients with systemic inflammatory or organ-threatening disease, glucocorticoids and immunosuppressants in high doses can be started.
            3.
        2. Doses of most anti-inflammatory and immunosuppressive medications should not generally be reduced
            1. This is especially in instances where the patient has a history of organ-threatening rheumatic disease
            2. Glucocorticoids should be reduced to the lowest safe dose as deemed by the treating physician, though should not be abruptly stopped.
    4. *Pharmacologic treatment for stable patients after exposure to COVID-19 (without symptoms)*
        1. Continue glucocorticoids and NSAIDs.
        2. If safe to do so, stop other immunosuppressive medications temporarily for 2 weeks of observation without symptoms.
            1. The panel noted that it is not clear whether to stop methotrexate or leflunomide.
            2. In certain cases, IL-6 inhibitors may be continued pending shared decision-making with the patient's provider.
    5. *Pharmacologic treatment in rheumatic patients with confirmed or suspected COVID-19 infection*

Rheumatic Manifestations of COVID-19

1. COVID-19 can cause a number of symptoms that may overlap with those seen in rheumatologic diseases as outlined below. For patients with established rheumatologic disease who have confirmed or suspected COVID-19, careful evaluation will be required to determine if their symptoms are due to flare of the disease or are sequelae of viral infection. Other patients who have persistent or unexplained rheumatic symptoms may benefit from a rheumatology consult to determine if there are additional concerns for underlying rheumatologic disease.
    1. Arthralgias, Myalgias, Myositis
        1. Myalgia or arthralgia occur in approximately 15% of patients.

1. 14.8% of patients (based on analysis as of 2/20/2020 on 55924 cases. (WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) 2020)
2. Myalgia or arthralgia in 14.9% of 1099 patients in mainland China (Guan et Al, NEJM, 2020)

2. Occasionally arthralgia can be a presenting feature.
   1. Observation of one female patient in Thailand who presented with fever and low platelet count, initially misdiagnosed as Dengue. (Joob et al, *Rheum Int*, 2020)
3. Rhabdomyolysis is also a potential late complication of Covid-19. (Tong et al, *Emerg Infect Dis*. 2020, Ronco et al, *Nat Rev Nephrol*, 2020)
   1. Please see Muscle Injury under *Neuromuscular Disorders*

2. Parenchymal Lung Disease
   1. Please see *Radiology* and *Acute Lung Injury*
3. Pericarditis and Myocarditis
   1. Please see *Pericarditis and Myocarditis*
4. Cytokine Storm / Secondary HLH
   1. Please see *Cytokine Storm*
5. Kawasaki-like Multisystem Inflammatory Syndrome in Children
   1. Please see section below
6. Livedo Reticularis
   1. Please see *Vasculopathies and Livido*
7. Pernio- or Chilblain-like lesions of hands and feets ("COVID toes")
   1. Please see *Perniosis*
8. Fever
   1. Please see *Clinical Course*
9. Coagulopathy
   1. Please see *Thrombotic Disease*
10. Elevated levels of inflammatory markers
    1. including CRP, ESR, and ferritin as well as elevated levels of cytokines including IL-1 and IL-6. Please see *Diagnostics*
11. Lymphocytopenia and thrombocytopenia
    1. Can be present in active lupus, is also be seen in COVID-19 infection. Please see *Lymphocytopenia* and *Thrombocytopenia*

Multisystem Inflammatory Syndrome in Children (MIS-C)

1. Multisystem Inflammatory Syndrome in Children (MIS-C) is covered in greater detail in this section of the global health version of COVIDProtocols.
2. Multisystem Inflammatory Syndrome in Children (MIS-C), also known as Pediatric Inflammatory Multi-System Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS or PIMS), is a relatively rare manifestation of COVID-19 that has been described now in children and some young adults in multiple case series. (Panupattanapong et al, *Cleve Clin J Med*, 2020, Riphagen et al, *Lancet*, 2020, Verdoni et al, *Lancet*, 2020, Toubiana et al, *BMJ*, 2020, Pouletty et al, *Ann Rheum Dis*. 2020, Jones et al, Hosp Pediatr, 2020)
   1. It appears to be a late (i.e. post-viral) manifestation that occurs as a reaction to COVID-19 rather than directly by the virus, as many of the patients presented 2-3 weeks after the peak of infection in the area and had negative COVID-19 PCR testing but positive serologies. (Panupattanapong et al, *Cleve Clin J Med*, 2020)

2. MIS-C has manifestations that overlap with Kawasaki disease and toxic shock syndrome.
3. MIS-C compared to Kawasaki disease
    1. Typical Kawasaki disease is a generally self-limited febrile illness affecting young children characterized by symptoms that, in addition to fever, can include a diffuse polymorphic rash, erythema and edema of the palms and soles, conjunctivitis, oral mucosal changes (classic "strawberry tongue"), and cervical lymphadenopathy. It can cause coronary artery aneurysm if left untreated.(Panupattanapong et al, *Cleve Clin J Med*, 2020)
    2. Kawasaki disease was suspected to be a post-viral phenomenon even before COVID-19
3. MIS-C occurs in an older patient population than Kawasaki disease. Kawasaki disease tends to occur in very young children, mean age of 2 years, but essentially always < 5 years old, whereas the average age of MIS-C patients is 8 years old. Symptoms include:
    1. Fever, rash, conjunctivitis, distal extremity edema, and GI symptoms including abdominal pain, nausea, vomiting, and non-blood diarrhea. In some cases, the GI symptoms occurred 1-2 weeks prior to their presentation for clinical care and may represent the period of acute infection with COVID-19.
    2. Severe cases can cause cardiac dysfunction and shock. Unlike the case in adults, respiratory symptoms are rare.
5. Management
    1. Treatment guidelines have been released by the American College of Rheumatology
    2. Current treatment recommendations include low-dose aspirin and IVIG. In more severe cases, glucocorticoids are also recommended. In IVIG- and glucocorticoid-refractory cases, high-dose anakinra (IL-1 blockade) can also be considered.

CHAPTER 17

Oncology

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General Oncology

1. **Data:**
    1. Based on early descriptive studies from China, patients with cancer - particularly those on active treatment for cancer - appear to have a worse prognosis. This includes higher prevalence, higher risk of severe disease, and higher risk of death from COVID-19 in patients with cancer compared to those without. (WHO-China Joint Mission on COVID-19, Yu et al, *JAMA Oncology* 2020, anecdotal reports)
9. **Anticoagulation:**
    1. Patients with solid tumors are at very high risk of thrombosis but at lower risk of infection than most heme malignancy patients.
    2. Thrombosis prophylaxis for all unless contraindicated
        1. Hold pharmacologic prophylaxis if platelet count < 30K, use pneumoboots
        2. Both COVID-19 infection and malignancy increase thrombotic risk, particularly with solid tumors.
        3. See "*Thrombotic Disease*" section for guidelines on both prophylactic and therapeutic anticoagulation.

Immune Checkpoint Inhibitors

2. **Immune toxicity**
    1. If patient develops organ dysfunction, it may be due to immune toxicity
        1. Consult the service team of the involved organ system and inform primary oncologist.
    2. Common immune toxicities include pneumonitis / respiratory failure (may be difficult to distinguish between COVID19 disease or may be aggravated by COVID19 infection), colitis, endocrine dysfunction (thyroid, pituitary / hypothalamic, adrenal), nephritis. Less common hepatitis, meningitis, dermatitis.
        1. Check TSH, ACTH, cortisol if hypotension or concern for endocrine dysfunction.
        2. Check T-spot, HIV, HBV, HCV serologies if immune toxicity is suspected, in case additional immunosuppression (particularly TNF-alpha blockade) is required.
    3. Immune toxicities are usually treated with high dose steroids
        1. risks and benefits must be weighed immediately with primary oncologist and ID consult teams if immune toxicity is suspected concurrent with COVID19 infection.
    4. BWH/DFCI iTox guidelines can be found here (Partners login required)

CHAPTER 18

Palliative Care

Read full Chapter →

Dyspnea & Acute Pain

General principles

2. Symptom management
    1. Should follow the guidelines provided in sections above
    2. Intensive Comfort Measures Guidelines (BWH Policy 5.5.5) (Partners login required)

Intensive Palliative Care Unit

1. The Palliative Care Service has opened the COVID-19 Intensive Palliative Care Unit (COVID-IPCU) and suspended the usual oncology IPCU service. The COVID-IPCU is intended as a unit for end of life care during the COVID pandemic. The Palliative Care Team aims to leverage the interdisciplinary expertise of the IPCU team and Palliative Medicine clinicians to provide symptom management and psychosocial support quickly and effectively for patients likely to die from COVID-19, whether or not they have cancer.
2. The admission criteria to the COVID IPCU are as follows:
    1. COVID-19+ or pending results
    2. Experiencing organ failure such that the patient would be expected to die without life sustaining treatments and an estimated prognosis of less than a week
    3. Patient/family assenting to comfort-focused care
    4. Code Status is “DNR/DNI/LLST (Comfort)” or “DNR/DNI” with no escalation of care to the ICU
    5. Communication with the COVID-IPCU team is required prior to transfer; page “IPCU” in the Partners Paging Directory

Terminal Delirium

3. **Treatment:**
    1. Non-pharmacologic:

1. Daytime lights, nighttime dark. Frequent reorientation. Reverse contributing medical conditions as able.
2. Consult Psychiatry; for terminal delirium, consult Palliative Care

2. Pharmacologic
   1. Additional information available at: Guidelines for Acute Hospital Acquired Delirium (Partners login required)
   2. Alter existing medications and treat comorbid symptoms.
   3. QTc prolonging agents <65 yo or DNR/I +LLST Comfort Measures

Communication Skills

1. **Skills for COVID-19 Scenarios**
   1. The BWH Division of Palliative Medicine has created brief videos outlining common communication tasks in COVID-19 across settings
      1.ICU Conversation #1: Sharing concern illness may get worse
      2.ICU Conversation #2: Discussing Illness getting worse/GOC
      3.ICU Conversation #3: Talking about Dying
      4.Hospital Medicine #1: GOC & Code Status (goals c/w intubation)
      5.Hospital Medicine #2: GOC & Code Status (goals not c/w intubation)
      6.ED #1: GOC & Code Status (goals not c/w intubation)
   2. Experts at VitalTalk have created a COVID-19 Communication Guide. See also: *Suggested Language for COVID-19 scenarios*
2. **Important Skills for All Conversations**
   1. **Respond to emotion with empathy**
      1. Key Skill: NURSE Statements (Back et al. *CA Cancer J Clin* 2005)
         1.Name, Understand, Respect, Support, Explore
         2.*NURSE Skills for Responding to Emotion*
   2. **Assess Understanding & Delivering Information**
      1. Key Skill: *ASK-TELL-ASK* (Back et al. *CA Cancer J Clin* 2005)
      2. For COVID, it is important to make patients and families aware that patients with significant comorbid illnesses or who have poor baseline functional or health status may decompensate rapidly and have very high mortality due to COVID-19.

Documenting Important Conversations

1. The **Advance Care Planning (ACP) Module in Epic** is the single BEST place to document serious illness conversations for patients with COVID-19 and their families. *Where to find and how to use the ACP Module in Epic*.
2. In conscious patients, review or sign Health Care Proxy form.

Please send suggestions and questions: covidprotocolsv2@gmail.com

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