Develop – DeVos Cardiovascular Research Program's Emergency Letter on the Pandemic

Scientific Stream Update on the COVID-19 Pandemic – 4.7.20 2200

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Multivariate Analysis Shows Age, SOFA score and D-dimer > 1 µg/L as Independent Predictors of Death In COVID-19 Patients

Article Title: Clinical course and risk factors for mortality of adult inpatients with COVID-19 in

https://www.thelancet.com/pb-assets/Lancet/pdfs/S014067362305663.pdf

Wuhan, China: a retrospective cohort study

Source: Lancet

Clinical Field: N/A

Article Type: Clinical Study

Study Type: Retrospective Study

Patient Group: COVID-19+

Intervention: Observational Study

Reviewer	Kathrine A. Kelly-Schuette
Study Design	Minor concerns
Study Design Concerns	retrospective cohort, enrolling all patients with definite outcome (death or discharge) at two hospitals in Wuhan 813 patients were hospitalized and 613 excluded (still hospitalized, inadequate medical records, no + RNA) RNA detection methods were reported, but only available starting in Jan 11, 2020 Only 171 patients were included in multivariate analysis (inadequate data).
Main Results	This study includes 191 COVID19 patients, comparing non-survivor vs. survivor (discharged from hospital). Non-survivors had significantly more comorbid conditions (67% vs. 40%; p=0.0010). The study provided a multivariable (log regression) on the

	outcome mortality. Age (1.10 CI1.03-1.17; p=0.043), SOFA score(5.65 CI 2.61-12.23; p<0.0001) and D-dimer (>1mikrog/L) (18.42 CI 2.64-128.55; p<0.0033) were significant independent predictors in the model while Coronary heart disease, Lymphocyte counts weren't identified as independent predictors. Male gender, diabetes, hypertension, respiratory rate >24, WBC > 10x10(9)/L, Creat >133 mikromol/L, LDH >245 U/L, CK >185 U/L, cTrop I >28 ng/ml, PTT > 16 s, Serum ferritin > 300 mikrog/L, IL-6 , Procalcitonin were all significant univariate variables significant in the analysis. Sustained viral detection occurred in both survivors and non-survivors
Comments	The median time from illness onset to discharge was 22.0 days (IQR 18.0-25.0), and median time to death was 18.5 days (15.0-22.0). Sepsis was the most common complication, followed by respiratory failure, ARDS, heart failure, and septic shock. For survivors, the median duration of viral shedding was 20.0 days (IQR 17.0-24.0) from illness onset, but the virus was continuously detectable until death in non-survivors The shortest observed duration of viral shedding among survivors was 8 days, whereas the longest was 37 days. The duration of viral replication may have important implications for isolation precautions. In this study, the disease course is long in survivors and non-survivors. Sepsis presenting on day 9 and day 10, discharge and death on day 22 and day 19 post the onset of symptoms. This was only a sample of the total patients with COVID19 at these two hospitals and excluded patients still hospitalized; therefore it is not clear if it is representative of true mortality rate of COVID19. However, one of the few multivariate analyses provided for the COVID-19 population. The size of the population and the outcome of death restricted the model to only include six predictors.

COVID-19 Convalescent Plasma Given to 5 Critical Ill COVID-19 Patients Was Safe and All Patients Improved WQithin seven Days

Article Title: Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma

https://jamanetwork.com/journals/jama/fullarticle/2763983?utm_campaign=articlePDF%26utm_medium%3darticlePDFlink%26utm_source%3darticlePDF%26utm_content%3djama.2020.4783

Source: JAMA

Clinical Field: Infectious Disease

Article Type: Clinical Report

Study Type: _____

Patient Group: Critical ill COVID-19

Intervention: Convalescent Plasma

Reviewer	Stefan Jovinge
Study Design	Major Concerns
Study Design Concerns	This is a five patients experience and thereby a report. It is an uncontrolled study.
Main Results	All five patients Improved, within 7 days post-transfusion in: temp, SOFA score, P/F ratio, viral load, CRP and pro-calcitonin
Comments	Since it is uncontrolled it is hard to say what would have happened in these patients without the plasma treatment. Patients not normalized for day of infection, rather day post transfusion only. But it serves as a feasibility, safety experience for future attempts. Other reports have shown that the mortality in this group of patients is about 30-50%. These five patients survived. Also, this strategy has indicated to be useful in other viral outbreaks of SARS, MERS and Ebola.

Editorial On Six Steps On Fighting an Pandemic Based on

Article Title: Ten Weeks to Crush the Curve

https://www.nejm.org/doi/full/10.1056/NEJMe2007263

Source: NEJM

Clinical Field: _____

Article Type: _____

Study Type: Other

Patient Group: N/A

Intervention: N/A

Reviewer	Meredith Busman
Study Design	N/A
Study Design Concerns	None. This is an editorial article from the New England Journal of Medicine written by Harvey V. Fineberg, M.D., Ph. D.
Main Results	Using the wartime experience as an analogy, the author proposes that instead of trying to flatten the curve (of the coronavirus pandemic), our goal should be "to crush the curve" with a goal of "defeating" COVID-19 by early June. He suggests this could be accomplished by taking the following steps: 1. Establish a unified command - designate a central commander with presidential authority to mobilize assets, and ask governors to do the same for their individual states. 2. Increase diagnostic testing - testing every person with symptoms could help to trace the scope of the outbreak, and testing should be done in physically separate facilities (ie drive-through tents). 3. Adequate supplies of PPE and equipment for health workers and hospitals - mobilize regional distribution centers to deploy ventilators, PPE, and other equipment, while recognizing "crisis standards of care" will be used to make ethically sound decisions about allotment. 4. Differentiate patient populations and treat accordingly - patients should be categorized as those who are infected; those presumed to be infected; those exposed to infection; those not know to be infected/exposed; and those who have recovered and are presumed immune. This stratification would allow for quarantining of exposed patients in separate

	facilities to reduce transmission, and to treat those with mild disease outside the hospital (ex. convention centers, hotels, etc) 5. Inspire and mobilize the public - everyone has a part to play and everyone needs to do their part, from researching a vaccine to distributing hand sanitizer and supporting neighbors. 6. Learn while doing real-time, fundamental research - treatment decisions, and when to reopen the economy, should be guided by science.
Comments	The author concludes that efforts to overcome the immediate pandemic should be extended to fight reoccurrences of coronavirus and novel pandemics as well. This includes developing a safe and effective vaccine, building strong public health infrastructure, and designing reliable predictive models.

Critical Ill COVID-19 Patients Could Benefit From VTE Prophylactic Treatment - But Be Aware of Bleeders.

Article Title: Risk assessment of venous thromboembolism and bleeding in COVID-19 patients

https://www.researchsquare.com/article/rs-18340/v1

Source: Research Square

Clinical Field: Internal Medicine

Article Type: Clinical Study

Study Type: Retrospective Study

Patient Group: COVID-19 patients

Intervention: Retrospective study

Reviewer	Mohammed Al-Charakh, MD
Study Design	Major Concerns
Study Design Concerns	-retrospective, observational with small sample size - portion of patient included in trial still hospitalized
Main Results	Design : -Number of patients: 138 , patient who are admitted with COVID-19 and identified in-hospital VTE and bleeding risk by Padua Prediction Score and Improve bleed risk assessment model. -Critically ill patients were defined as those admitted to the intensive care unit (ICU) who required mechanical ventilation or had a fraction of inspired oxygen (FiO2) of at least 60% or more. -A high risk of Bleeding is defined as a cumulative score ≥ 7. -A high risk of VTE is defined as a cumulative score ≥ 4. -Routine thromboprophylaxis was provided to patients whose Padua score > 4 . -intermittent pneumatic compression (IPC) or low intensive for improve score>7. - Lower extremity compression ultrasound (CUS) was performed for all critically ill patients and those with high risk of VTE and high level of D-dimer. If possible, these patients received computed tomography pulmonary angiogram (CTPA). Results : - 15 patients (10.9%) were critically ill. 81 patients (58.7%)

	patients were male. - The average age was 52.43 ± 16.68 years. - 40.6% had 1 or more coexisting medical conditions. Most common conditions were Hypertension 28% and diabetes 11.6%. - Compared non-critically ill patients(n = 123), critically ill patients were significantly older (60.07 ± 14.25 years vs 50.52 ± 15.97 years; P < 0.01) and were more likely to have underlying comorbidities and have elevated D-dimer levels on baseline, which was significantly higher than non-critically ill patients (0.74[0.44,135] vs 0.39[0.29,0.83], P < 0.01) -Thrombotic events were identified in four patients (2.9%) of all COVID-19 patients. All of them were diagnosed as DVT by ultrasound on the 3rd to 18th day of admission. -Three (75.0%) were critically ill patients, which means the incidence of VTE among critically ill patients was up to 20%. -Risk for developing thrombotic event include co-morbidities, elevated baseline D-dimer (identified in 3 of 4 patients) -The prediction risk of VTE (6.5%), as well as the incidence of VTE (0.8%), was low in non-critically patients. However, critically ill patients faced double high risk from thrombosis (Padua score more than 4 points in 100% of critically ill patients) and hemorrhage (Improve score more than 7 points in 60.0% of critically ill patients). -There was high incidence of VTE (20.0%) in critically ill patients with COVID-19, despite the use of universal, guideline-recommended thromboprophylaxis. Critically ill patients suffered a marked incidence of bleeding (26.7%)
Comments	The critical ill group have a significant risk of VTE but also, to a lesser degree risk for bleeding on VTE prophylaxis. Using individual assessment of VTE and bleeding risk is recommended. Padua Score (Need for AC) https://www.mdcalc.com/padua-prediction-score-risk-vte Improve Score (Risk for bleeding on VTE prophylaxis) The trial result consistent with our observation that critically ill patient with COVID 19 are at higher risk to develop thrombotic events. high index of suspicion and close monitoring required to identify and treat thrombotic events.

Fast Track for The IND Approval on an Individual Basis by FDA – This Is How.

Article Information

Article Title: Investigational COVID-19 Convalescent Plasma - Emergency INDs

https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds

Source: FDA

Clinical Field: Infectious Disease

Article Type: National Document

Study Type: Other

Patient Group: N/A

Intervention: FDA IND Document

Reviewer	Sihong Huang
Study Design	N/A
Study Design Concerns	This is not a study. FDA does not provide COVID-19 convalescent plasma for eINDs A licensed physician must request the Emergency IND (eIND) and obtain the COVID-19 convalescent plasma from a blood center.
Main Results	COVID-19 convalescent plasma must only be collected from recovered individuals if they are eligible to donate blood. Additional considerations for donor eligibility: 1. Prior diagnosis of COVID-19 documented by a laboratory test 2. Complete resolution of symptoms at least 14 days prior to donation 3. Female donors negative for HLA antibodies or male donors 4. Negative results for COVID-19 either from one or more nasopharyngeal swab specimens or by a molecular diagnostic test from blood. 5. Defined SARS-CoV-2 neutralizing antibody titers, if testing can be conducted (e.g., optimally greater than 1:320) 6. The container label of COVID-19 convalescent plasma units must include the following statement, "Caution: New Drug--Limited by Federal (or United States) law to investigational use"

	Eligible patients for use under expanded access provisions must have the following: 1. laboratory confirmed COVID-19 2. Severe or immediately life-threatening COVID-19 disease meeting definitions 3. must provided informed consent To obtain FDA authorization for use of COVID-19 convalescent plasma 1. If highly time sensitive emergency (response required in < 4 hours) - requesting providing may contact FDA's office of Emergency Operations at 1-866-300-4374 to seek verbal authorization - if verbal authorization is given, the requestor must agree to submit an expanded access application (e.g., form 3926) within 15 working days of FDA's authorization of the use. 2. For request that at not highly time sensitive (FDA provides response within 4-8 hours) - requesting physician will complete from 3926 by downloading from: https://www.fda.gov/media/98616/download (/media/98616/download - submitting the form by emailing to CBER_eIND_Covid-19@FDA.HHS.gov - FDA will review and provide confirmatory email including the emergency IND number
Comments	Convalescent plasma has been successful in other viral epidemias: Machupo virus (Bolivian hemorrhagic fever) , Junin virus (Argentinian hemorrhagic fever) , Lassa fever Ebola virus, West Nile encephalitis

American Society For Microbiology Summit Statement on COVID-19

Article Title: Report from the American Society for Microbiology COVID-19 International Summit, 23 March 2020: Value of Diagnostic Testing for SARS-CoV-2/COVID-19

https://mbio-asm-org.proxy2.cl.msu.edu/content/11/2/e00722-20.long

Source: American Society for Microbiology

Clinical Field: Other

Article Type: International Document

Study Type: _____

Patient Group: N/A

Intervention: _____

Reviewer	Stefan Jovinge
Study Design	N/A
Study Design Concerns	N/A
Main Results	Direct Viral detection by PCR: - The most common sample types being tested are swabs taken from the nasopharynx and/or oropharynx, with the former considered somewhat more sensitive than the latter. If both are taken - combine them. - Some patients with pneumonia may have negative nasal or oropharyngeal samples but positive lower airway samples - Because of sampling concerns a negative sample should never be considered 100% surely negative. False positives are less likely. -=Viral detection tests important to establish infectiousness of a patient Serology tests: - still under development - crucial to establish immunity on individual and population basis 1. Viral detection tests mainly important to evaluate infectiousness of patients.2. Antibody tests mainly to establish immunity. No guidance of treatment recommended in this document.
Comments	Summary statement and policy document.

Infected COVID-19 Mothers Do In the Vast Majority of Cases Not Infect Their Neonates. In They Do The Neonates Do Develop Mild Disease and Can Be Chest X-Ray Negative.

Article Title: Neonatal Early-Onset Infection With SARS-CoV-2 in 33 Neonates Born to Mothers With COVID-19 in Wuhan, China

https://jamanetwork-com.proxy2.cl.msu.edu/journals/jamapediatrics/fullarticle/2763787

Source: JAMA

Clinical Field: Other

Article Type: Clinical Report

Study Type: Other

Patient Group: Neonatal patients born by mothers with COVID-19

Intervention: Observational study

Reviewer	Sihong Huang
Study Design	Minor concerns
Study Design Concerns	Cohort study with small sample size of 33 neonates and 3 infected patients in the cohort. Incomplete laboratory data were presented and some without value even when reported being abnormal. Unclear what other laboratory studies were obtained. Did not report indication(s) for certain tests: for example an infant had elevated CK-MB but author did not report indications for the test, or state if CK-MB was obtained in all at risk neonates in this cohort for the study.
Main Results	33 neonates born to mothers with COVID-19 were recruited were identified from Wuhan Children's Hospital from 1/2020 to 2/2020. Diagnosis in neonates was by RT-PCR of nasopharyngeal and anal swabs. Overall 3/33 (9%) neonates was positive with COVID-19. No mortality reported. 2 infants were full term and 1 born at 31 weeks. All 3 infected infant delivered via C-section and all had reported pneumonia by chest CT. One full term infant had C-section for Meconium and

	developed fever and lethargy at 2 days old. CXR showed pneumonia, procalcitonin was reported elevated (0.09 ug/L), but otherwise normal LFT and CBC. RT-PCR was positive on day 2 and 4; and negative by day 6. 2nd infant born full term via C-section for maternal COVID-19 pneumonia. Presenting symptoms were fever, lethargy and vomiting. Leukocytosis, High CK-MB reported (no value reported) and unclear why it was obtained. RT-PCR was positive on day 2 and 4; and negative by day 6. 3rd infant was born at 31 weeks by C-section for fetal distress and maternal COVID-19 infection. Poor Agpar and Enterobacter sepsis required antibiotics. CXR and CT showed pneumonia. No intubation. RT-PCR was positive on day 2 and 4; and negative by day 7.
Comments	Author felt that overall neonates with or at risk of COVID-19 had milder disease and more favorable outcome. There was 9% infection rate in this cohort. Strict infection control with isolation and prevention procedure implemented during delivery. Author thought likely sources were from maternal transmission, and vertical-fetal transmission cannot be ruled out. It was not clearly stated by authors, but it appears their protocol maybe C-section for all mother with pneumonia due to COVID-19. No specific clinical physical exam findings in the infected neonates. Chest CT images provided were rather normal appearing, and did not demonstrate typical findings seen in older patients with ground-glass appearance of the small airway disease. All infants were tested 3 times: day of life 2, 4, and 6 or 7. Vital signs appeared to improve 2-3 days after RT-PCR test became negative for COVID-19.

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