INFOLETTER 4 – COVID-19

31 March 2020

Content overview

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

Case series of 5 critically ill patients with COVID-19 and ARDS who met the following criteria: **severe pneumonia** with rapid progression and continuously **high viral load** despite antiviral treatment; **Pao_2/Fio_2 <300**; and **mechanical ventilation**. Patients received a transfusion of convalescent plasma with a SARS-CoV-2–specific antibody **(IgG) binding titer greater than 1:1000** that had been obtained from 5 patients who recovered from COVID-19. Convalescent plasma was administered between 10 and 22 days after admission. All 5 patients (age range, 36-65 years; 2 women) all had received antiviral agents and methylprednisolone. Following plasma transfusion, body t**emperature normalized within 3 days in 4 of 5 patients**, the **SOFA score decreased**, and **Pao_2/Fio_2 increased within 12 days** (range, 172-276 before and 284-366 after). **Viral loads also decreased** and became negative within 12 days after the transfusion, and SARS-CoV-2–specific ELISA and neutralizing antibody titers increased following the transfusion (range, 40-60 before and 80-320 on day 7). **ARDS resolved in 4 patients at 12 days** after transfusion, and 3 patients were weaned from mechanical ventilation within 2 weeks of treatment. **Of the 5 patients, 3 have been discharged from the hospital** (length of stay: 53, 51, and 55 days), and **2 are in stable condition** at 37 days after transfusion.
The limited sample size and study design preclude a definitive statement about the potential effectiveness of this treatment, and these observations require evaluation in clinical trials.

Convalescent Plasma to Treat COVID-19: Possibilities and Challenges

The use of convalescent plasma is not new; it was used for SARS, pandemic 2009 influenza A (H1N1), avian influenza A (H5N1), several hemorrhagic fevers such as Ebola, and other viral infections. For instance, in 2005, Cheng et al reported outcomes of patients who received convalescent plasma in Hong Kong during the 2003 SARS outbreak. Although this investigation was not a randomized trial, **the 80 who received convalescent plasma had a lower mortality rat**e (12.5%) compared with the overall SARS-related mortality for admitted patients (n = 299 [17%]). The antibody titers and plasma transfusion volumes varied and did not appear to correlate with a clinical response; however, patients receiving transfusion within 14 days of symptom onset had better outcomes. No adverse events were reported among patients receiving convalescent plasma. **Convalescent plasma** has the advantage over **hyperimmune globulin** (H-Ig) that while its antibodies limit viral replication, **other plasma components** can also exert beneficial effects such as replenishing coagulation factors. On the other hand, plasma demonstrates **donor-dependent variability in antibody specificities and titers**. H-Ig preparations contain **standardized antibody doses**, although **fractionation removes IgM**, which may be necessary against some viruses. While

H-Ig (like plasma) can be stored for years, **a new collection may be needed the next season**, especially as passive antibody efficacy wanes due to accumulated viral mutations.

Association of Coronavirus Disease 2019 (COVID-19) With Myocardial Injury and Mortality

https://jamanetwork.com/journals/jamacardiology/fullarticle/2763844

Journal: JAMA *Published Online: March 27, 2020*
Authors from: USA

Acute coronary events during acute infection could result from the severe increase in **myocardial demand** that precipitates myocardial injury or infarction, akin to type 2 myocardial infarction. Alternatively, **circulating cytokines** released during severe systemic inflammatory stress could lead to atherosclerotic plaque instability and rupture. Similarly, patients with heart failure are also prone to **hemodynamic decompensation** during the stress of severe infectious illnesses. In addition, acute/fulminant myocarditis as well as heart failure have been reported with MERS and could be expected to occur with COVID-19, given the similar pathogenicity. **Direct viral infection of the myocardium** is another possible causal pathway of myocardial damage. SARS-CoV-2 has a high affinity for the host angiotensin-converting enzyme 2 receptor, raising the possibility of direct viral infection of vascular endothelium and myocardium. Shi et al present a **cohort study of 416 hospitalized patients** with COVID-19 in Wuhan, out of whom 19.7% had evidence of myocardial injury manifested by elevation of hs-TnI. Patients with **myocardial injury had a significantly higher in-hospital mortality** rate compared with those without myocardial injury (51.2 vs. 4.5%), and among those with myocardial injury, greater degrees of TnI elevation were associated with higher mortality rates. Similar observations were reported by Guo et al, where' the highest mortality rates were observed in those with **elevated TnT levels who had underlying cardiovascular disease** (69.4%], but mortality rates were also considerable in those with elevated TnT levels without prior cardiovascular disease (37.5%). Patients with known cardiovascular disease without elevation of TnT levels had a mortality of 13.3%. TnT levels were significantly associated with levels of CRP and NT-proBNP, thus **linking myocardial injury to the severity of inflammation and ventricular dysfunction**. Their data also show progressive serial increases in both TnT and NT-proBNP levels during hospitalization in patients who follow a deteriorating clinical course toward death.

Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19)

https://jamanetwork.com/journals/jamacardiology/fullarticle/2763845

Journal: JAMA Cardiology *Published Online: March 27, 2020*
Authors from: China

Information regarding the impact of cardiovascular complications of COVID-19 on the fatal outcomes is scarce. This **retrospective single-center case series** analyzed 187 patients with confirmed COVID-19. 77% were discharged and 23% died. The mean age was 58.5 yrs. Overall,

35.3% had underlying CVD including hypertension, coronary heart disease, and cardiomyopathy, and **27.8% exhibited myocardial injury as indicated by elevated TnT levels**. The mortality during hospitalization was 7.62% for patients without underlying CVD and normal TnT levels, 13.33% for those with underlying CVD and normal TnT levels, 37.50% for those without underlying CVD but elevated TnT levels, and **69.44% for those with underlying CVD and elevated TnTs.** Patients with underlying CVD were more likely to exhibit an elevation of TnT levels compared with the patients without CVD (54.5% vs 13.2%).

Plasma TnT levels demonstrated a high and significantly positive linear correlation with plasma high-sensitivity CRP and NT-proBNP levels. Plasma TnT and NT-proBNP levels during hospitalization and impending death increased significantly compared with admission values in patients who died, while no significant dynamic changes of TnT and NT-proBNP were observed in survivors. During hospitalization, patients with elevated TnT levels had more frequent **malignant arrhythmias**, the **use of glucocorticoid therapy** and **mechanical ventilation.** The mortality rates of patients with and without the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers were 36.8% (7 of 19) and 25.6% (43 of 168).

Aggressive treatment may be considered for patients at high risk of myocardial injury.

Potential Effects of Coronaviruses on the Cardiovascular System

https://jamanetwork.com/journals/jamacardiology/fullarticle/2763846

Journal: JAMA   *Published Online: March 27, 2020*
Authors from: USA

Coronaviruses are known to affect the cardiovascular system. A large proportion of patients with COVID-19 have underlying cardiovascular disease and/or cardiac risk factors. Factors associated with mortality include male sex, advanced age, and presence of comorbidities including hypertension, diabetes mellitus, cardiovascular diseases, and cerebrovascular diseases. **Acute cardiac injury** determined by elevated high-sensitivity troponin levels is commonly observed in severe cases and is strongly associated with mortality. COVID-19 is associated with a high inflammatory burden that can induce **vascular inflammation, myocarditis, and cardiac arrhythmias.** Cardiovascular risk factors and conditions should be judiciously controlled per evidence-based guidelines.

SARS-CoV-2 appears to affect the myocardium and cause myocarditis. Sporadic autopsy cases suggest infiltration of myocardium by **interstitial mononuclear inflammatory cells.** In parallel, cases of severe myocarditis with **reduced systolic function** have been reported after COVID-19. Cardiac biomarker studies suggest a high prevalence of cardiac injury in hospitalized patients. Myocardial injury is likely associated with infection-related myocarditis and/or ischemia and is an important prognostic factor in COVID-19.

A prospective registry of patients with COVID-19 with a systematic recording of clinical variables and cardiovascular complications will be beneficial to identify the pattern of cardiovascular

complications, to develop a risk model for cardiac complications, and to identify and/or predict response to various treatment modalities.

Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy

https://onlinelibrary.wiley.com/doi/abs/10.1111/jth.14817

Journal: Journal of Thrombosis and Haemostasis   *Published Online: March 27, 2020*
Authors from: China

The use of heparin in COVID-19 has been recommended by some expert consensus due to the risk of disseminated intravascular coagulation (DIC) and venous thromboembolism (VTE). However, its efficacy remains to be validated. Coagulation results, medications, and outcomes of 449 consecutive severe COVID-19 patients in Tongji hospital were **retrospectively analyzed.** Heparin (mainly LMWH) was given to 99 patients for 7 days or longer. The **D-dimer, prothrombin time and age were positively correlated,** while the **platelet count was negatively correlated with 28-day mortality** in multivariate analysis. No **difference in 28-day mortality was found between heparin users and nonusers** (30.3% vs 29.7%, P=0.910). But the 28-day mortality of heparin users was lower than nonusers In patients with SIC score ≥4 (40.0% vs 64.2%, P=0.029), or D-dimer > 6 fold of upper limit of normal (32.8% vs 52.4%, P=0.017).
Anticoagulant therapy mainly with LMWH appears to be associated with better prognosis in severe COVID-19 patients meeting SIC criteria or with markedly elevated D-dimer.

Disseminated intravascular coagulation in patients with 2019-nCoV pneumonia

https://onlinelibrary.wiley.com/doi/full/10.1111/jth.14781

Journal: Journal of Thrombosis and Haemostasis   *Published Online: March 24, 2020*
Author from: Canada

In the 2003 SARS epidemic, 63% of patients demonstrated isolated transient elevations of the activated partial thromboplastin time in the first 2 weeks of infection, but most patients had normal prothrombin times and no elevation of D-dimers. A total of 2.5% of SARS patients showed evidence of disseminated intravascular coagulation (DIC), and this was frequently associated with mortality. Tang and colleagues from Wuhan described their experience with the association of 2019-nCoV pneumonia and DIC over the first 6 weeks of the epidemic. Their findings highlight that **DIC is a strong predictor of mortality** in patients developing pneumonia with this virus. At the time of reporting, 42.6% of patients had been discharged from the hospital, 45.9% remained as inpatients, and the overall mortality was 11.5%. Patients were tested for PT, aPTT, antithrombin, fibrinogen, D-dimer, and fibrin degradation products every 3 days for the first 2 weeks of hospital stay. Applying the validated International Society on Thrombosis and Haemostasis DIC score, **71.4% of nonsurvivors and 0.6% of survivors showed evidence of overt DIC, with the median time to DIC detection being 4 days.** The authors concluded that DIC is a frequent occurrence in worsening 2019-

nCoV pneumonia and is often associated with mortality. Evidence of DIC, especially elevated D-dimer levels, may be used in therapy considerations.

Whether this particular virus is more prone to DIC development will need to be followed closely as this epidemic evolves. The pathophysiology of DIC is complex and multifactorial, involving an interplay between cellular and plasmatic elements and components of the innate immune response to the infecting pathogen. Activation of the vascular endothelium, platelets, and leukocytes results in dysregulated thrombin generation that occurs both systemically and locally in the lungs of patients with severe pneumonia, resulting in the **deposition of fibrin with subsequent tissue damage** and **microangiopathic pathology**. There is evolving evidence that a combination of activation events initiated by exposure of the endothelium, platelets, and leukocytes to pathogen- and damage-associated molecular patterns are the primary instigators of this pathophysiology. To date, the treatment of DIC has been focused on strategies to target the primary associated pathology. Trials of natural anticoagulant infusions have met with variable outcomes, although recent experience with a **soluble thrombomodulin product** appears promising.

Immunosuppression for hyperinflammation in COVID-19: a double-edged sword?

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30691-7/fulltext#%20
Journal: The Lancet   *Published Online: March 24, 2020*
Authors from: UK

Hyperinflammation in COVID-19 could be a driver of severity and **systemic inflammation is associated with adverse outcomes**. However, correlation does not equal causation, and it is equally plausible that increased virus burden (secondary to failure of the immune response to control infection) drives inflammation and consequent severity rather than augmented inflammation being an inappropriate host response that requires correction.

The authors hypothesize that approaches such as corticosteroids or Janus kinase (JAK) inhibitors could be considered if hyperinflammation is present. **Broad immunosuppression in patients with overwhelming viral illness might be inadvisable.** Beneficial anti-inflammatory effects should be weighed up against the potentially detrimental effects of inhibiting anti-viral immunity, thereby delaying virus clearance and perpetuating illness. Accordingly, findings from multiple studies in humans and animals indicate that inhaled and systemic **corticosteroid immunosuppression impairs the induction of anti-viral type-I interferon responses to a range of respiratory viruses**, effects that are likely to also occur in the context of COVID-19. Selective therapies with JAK inhibitors could be expected to have similar effects. JAK-STAT signaling is a major component of the type-I interferon pathway. Tofacitinib has been shown to inhibit interferon-α production in vitro. Suppression of interferon or other mediators (eg, Il-6) could also **promote secondary bacterial infection** and further complicate the disease course. The decision to pharmacologically immunosuppress a critically unwell patient with COVID-19 remains a difficult one. Possible beneficial effects of reducing inflammation should be carefully weighed up against the potential for deleterious impairment of anti-microbial immunity.

Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019

173 patients with SARS-CoV-2 infection were enrolled. Their serial plasma samples (n=535) collected during the hospitalization were tested for total antibodies (Ab), IgM and IgG against SARS-CoV-2. The dynamics of antibodies with the disease progression was analyzed. **The seroconversion rate for Ab, IgM, and IgG was 93.1%, 82.7%, and 64.7%,** respectively. The reason for the negative antibody findings in 12 patients might be due to the lack of blood samples at the later stage of illness. The **median seroconversion time** for Ab, IgM and then IgG were **day-11, day-12, and day-14**, separately. The presence of antibodies was <40% among patients within 1-week since onset, and rapidly increased to 100.0% (Ab), 94.3% (IgM) and 79.8% (IgG) since day-15 after onset. In contrast, **RNA detectability** decreased from 66.7% (58/87) in samples collected before day-7 to 45.5% (25/55) during day 15-39. **Combining RNA and antibody detections** significantly improved the sensitivity of pathogenic diagnosis for COVID-19 (p<0.001), even in the early phase of 1-week since onset (p=0.007). Moreover, a **higher titer of Ab was independently associated with a worse clinical classification** (p=0.006).

Quantitative Detection and Viral Load Analysis of SARS-CoV-2 in Infected Patients

The widely used RT-PCR method has limitations for clinical diagnosis and treatment. A total of **323 samples from 76 COVID-19 confirmed patients** were analyzed by droplet digital PCR (ddPCR) and RT-PCR based on two target genes (ORF1ab and N). Nasal swabs, throat swabs, sputum, blood, and urine were collected. Clinical and imaging data were obtained for clinical staging. The viral load of respiratory samples was compared and the **average viral load in sputum** (17429 ± 6920 copies/test) **was found to be significantly higher than in throat swabs** (2552 ± 1965 copies/test, p < 0.001) **and nasal swabs** (651 ± 501 copies/test, p < 0.001). Furthermore, the viral load in the early and progressive stages was significantly higher than that in the recovery stage (46800 ± 17272 vs 1252 ± 1027, p < 0.001) analyzed by sputum samples. Quantitative monitoring of viral load in lower respiratory tract samples helps to evaluate disease progression, especially in cases of low viral load.

The Italian coronavirus disease 2019 outbreak: recommendations from clinical practice

https://onlinelibrary.wiley.com/doi/full/10.1111/anae.15049

Journal: Anesthesia   *Published Online: March 27, 2020*
Authors from: Italy, Switzerland

The authors report the impact of the coronavirus disease 2019 outbreak on regional and national healthcare infrastructure. They also share **first-hand experience and recommendations**. In particular, they describe key elements of clinical management, including **safe oxygen therapy; airway management; personal protective equipment; and non-technical aspects** of caring for patients diagnosed with coronavirus disease 2019. **A pocket chart summarizing the airway management guidelines** is part of the article.

GVA — GESTIONE VIE AEREE — SIAARTI

AIRWAY MANAGEMENT
Rev. 1.2

COVID-19

One of the most critical issues regarding 2019 nCoV patients is the transitory phase between initial symptoms and potentially severe evolution requiring critical care, while taking into account the comorbidities. The choice of supplementary oxygen delivery interface and the decision to provide invasive ventilatory support is crucial.
These decisions have the potential of impacting outcome and may lead to consequences on saturation of critical care beds.
Non-invasive support methods (CPAP, BiPAP, NIV, HFNO) might correct hypoxemia and counterbalance respiratory failure (though univocal data are missing) and may either delay or avoid endotracheal intubation (with potential complications and effects on outcome). Nevertheless, data from the SARS epidemic provide evidence showing that these ventilatory techniques might favor the risk of airborne viral spreading. Given the nature of nCoV 19 in terms of contagiousness, should the patient require, or be expected to necessitate

invasive ventilator support, an elective endotracheal intubation should be preferred, or even anticipated, rather than waiting for an emergency procedure (in the precipitating patient) as to minimize complications of intubation itself and also to reduce both the risks of procedural errors and the contamination of healthcare providers.
Adoption of early warning scores (EWS), shared and predefined strategies, multidisciplinary team training and simulation of possible scenarios are highly recommended, taking also into account the available levels of care and feasibility of critical care levels of assistance in a non-ICU environment.
The decisional elements for airway management, oxygenation and invasive ventilator support thus include competencies and organization and available human and environmental resources.
Vigilance in prevention, strict adhesion of donning/doffing of PPE, preparedness for the care of infected patients remain priority and of utmost importance.

HIGHLIGHTS
- ► INTEGRATED COMPETENCIES FOR EVERY PHASE/STEP
- ► AIRBORNE PROTECTION FOR EVERY EVERY PHASE/STEP IN CRITICAL CARE SETTINGS (IF POSSIBLE)
- ► ANTICIPATE NEEDS, MAXIMIZE FIRST-PASS SUCCESS

DOUBLE-CHECK INDICATIONS FOR ENDOTRACHEAL INTUBATION
- ► Adopt **Early Warning Scores** for intubation/quod vitam prognosis (consider DNR cases)
- ► Identify **Isolated room/(negative pressure environment if possible)**
- ► Balance benefits of CPAP/BiPAP/NIV/HFNO **versus risks of airborne diffusion**
- ► IF INTUBATION is required, prefer **ELECTIVE** procedure (in emergency >> patient risk)

TEAM PREPARATION
► Minimize the number of team members:
1. The most expert team member should perform the intubation and advanced airway control/ventilation (with donned PPE) [INSIDE the chamber]
2. EXPERT assistant on protocols and devices (doctor/nurse with donned PPE) [INSIDE the chamber]
3. Second doctor with donned PPE if complex maneuver/difficult airway is expected/planned [INSIDE the chamber]
4. Doctor available with donned PPE [OUTSIDE the chamber]
5. PPE donning/doffing Observer [OUTSIDE]

CARRY OUT PRELIMINARY BRIEFING FOR ROLE DEFINITION, STRATEGY DEFINITION, IDENTIFICATION OF DONNING/DOFFING OBSERVER

PPE DONNING
Airway Management (including NIV) is considered aerosol generating procedure requiring airborne level protection, or the maximum available level of protection taking account of WHO/ECDC/ISS interim guidance for availability and rational PPE use.

[Legend: ⬇ = if not available]

1. HELMET (Powered Air Purifying Respirator - *PAPR*) ⬇ PROTECTIVE SUIT ⬇ HAIR COVERS/HOODS
2. GOGGLES/FACE SHIELD (nothing if PAPR)
3. FFP3 respirator ⬇ FFP2 or N95 respirator (nothing if PAPR)
4. PROTECTIVE SUIT ⬇ LONG-SLEEVED FLUID-RESISTANT GOWN
5. PROTECTIVE SUITE ⬇ OVERSHOES
6. DOUBLE GLOVES (possibly in different colors)
7. Decontamination - Dedicated Donning & Doffing Area
8. Clear separation of Clean/Contaminated pathways, adequate disposal

DONNING/DOFFING OBSERVER EXTERNALLY CHECKING, INDIVIDUAL DONNING

CLINICAL CHECKLIST (wearing PPE)
- ► COMPLETE EVALUATION OF AIRWAYS AND OXYGENATION (accept difficult airway management risk overestimation)
- ► HEMODYNAMIC EVALUATION ⬇ PRE-EMPTIVE HEMODYNAMIC OPTIMIZATION

AIRWAY INSTRUMENTATION
- ► HEPA FILTER ON EVERY OXYGENATION INTERFACE (face mask, circuit, endotracheal tube, supraglottic airway devices, introducer, airway exchange catheters, respiratory circuit)
- ► AIRWAY CART READY (DISPOSABLE devices preferable)
- ► SUCTION: CLOSED SYSTEM
- ► ANTIFOGGING
- ► MEDICATIONS: PREPARED AND DOUBLE-CHECKED
- ► EMERGENCY CART READY (DISPOSABLE devices preferable)

AWAKE INTUBATION NOT INDICATED:
- ► PREOXYGENATION (according to respiratory and hemodynamic status)
  - 3min' at TV FiO_2=100%
  - or 1min' at FVC 8 breaths FiO_2=100%
  - or CPAP/PSV 10 cmH_2O + PEEP 5 cmH_2O FiO_2=100%
- ► RSI in all patients (limit BMV **unless** unavoidable and **apply** Cricoid Pressure only in case of ongoing regurgitation)
- ► NASAL PRONGS 1-3 lt/min FiO_2=100% FOR APNOIC PHASE (NODESAT)
- ► FULL DOSE NEUROMUSCULAR BLOCK **RESPECT** onset time for laryngoscopy
  > 1st LARYNGOSCOPY: prefer **VIDEOLARYNGOSCOPE with separate screen + endotracheal tube pre-loaded on introducer**
  > Re-oxygenate with low TV/pressure between attempts -Early switch (after failed second attempt) to supraglottic airway devices **(prefer second generation - intubable SADs)**
  > INTUBATION THROUGH SUPRAGLOTTIC AIRWAY DEVICES: flexible endoscope with **separate screen** (prefer DISPOSABLE)
- ► EARLY CRICOTHYROTOMY IF CI-CO

AWAKE INTUBATION INDICATED *(only if really mandatory):*
- ► AIRWAY TOPICALIZATION: no aerosol/vaporization
- ► TITRATED SEDATION (INFUSION PUMP) - sedation depth monitoring
- ► FLEXIBLE ENDOSCOPE WITH **SEPARATE SCREEN** (PREFER DISPOSABLE)
- ► RESCUE: INTUBATION THROUGH SUPRAGLOTTIC AIRWAY DEVICES (see above)
- ► EARLY CRICOTHYROTOMY if CI-CO

ENDOTRACHEAL TUBE POSITION CONTROL - PROTECTIVE VENTILATION
- ► CAPNOGRAFIC CURVES repeated and with standard morphology *(if in doubt take it out)*
- ► AVOID unuseful circuit disconnections (if needed: ventilator on stand-by/clamp endotracheal tube)
- ► CONSIDER indications for advanced techniques: ECMO - experts advise

PPE DOFFING
- ► During and after PPE doffing, hands hygiene mandatory
- ► Donning/doffing observer externally checking, individual doffing
- ► Waste disposal

TRANSPORT
- ► Follow bio-containment regulations

STOP COVID
- **S** - Secure airway: anticipated intubation
- **T** - Team briefing
- **O** - Organize (competencies - team - pathways)
- **P** - Prepare (devices)
- **C** - Checklist - controls- crisis management
- **O** - Optimize (hemodynamics - oxygenation)
- **V** - Vigilated donning/doffing
- **I** - Invasive airways - evaluation and integrated airway management
- **D** - Debriefing

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PRO VITA CONTRA DOLOREM SEMPER

M. Sorbello, I. Di Giacinto, F. Bressan, R. Cataldo, G. Cortese, C. Esposito, S. Falcetta, G. Merli , F. Petrini
on behalf of SIAARTI Airway Management Research Group

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Indicazioni ad interim per un utilizzo razionale delle protezioni per infezione da SARS-CoV-2 nelle attività sanitarie e sociosanitarie (assistenza a soggetti affetti da COVID-19) nell'attuale scenario emergenziale SARS-CoV-2. https://www.epicentro.iss.it/coronavirus/sars-cov-2-i-pc-rapporti-tecnici-iss

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New therapeutic opportunities for COVID-19 patients with Tocilizumab: Possible correlation of interleukin-6 receptor inhibitors with osteonecrosis of the jaws

https://www.sciencedirect.com/science/article/pii/S1368837520300956?via%3Dihub

Journal: Oral Oncology   *Published Online: March 21, 2020*
Authors from: Italy

Excessive and aberrant immune responses in COVID-19 lead to **fibrosis and lung damage**, causing functional disability and reduced quality of life. Considering the absence of specific drugs, a range of existing host-directed therapies could potentially be repurposed to treat COVID-19. **Tocilizumab is a humanized antiinterleukin-6-receptor (IL-6R)** monoclonal antibody that inhibits Il-6 signaling. It is used as a treatment in rheumatoid arthritis (RA).

Tocilizumab was experimentally administered in the treatment of COVID-19 in China and Italy with encouraging results. Whether tocilizumab can **restore T cell counts in COVID-19 patients by suppressing IL-6 signaling** remains uninvestigated.

The authors of the present article evaluated the possible correlation between tocilizumab and **medication-related osteonecrosis of the jaws** (MRONJ), an infectious complication of antiresorptive and antiangiogenic drugs. In a recent review on MRONJ unrelated to bisphosphonates and denosumab, a wide range of medications have been implicated in MRONJ, **but tocilizumab is not reported**. However, anecdotally MRONJ after tocilizumab was reported in isolated case studies. Efficacy and safety of tocilizumab in COVID-19 is, therefore, to be investigated. The manufacturer has made the drug **available free of charge to continue the experimentation on COVID-19 patients in Italy**.

Herd immunity – estimating the level required to halt the COVID-19 epidemics in affected countries

https://www.journalofinfection.com/article/S0163-4453(20)30154-7/fulltext

Journal: Journal of Infection   *Published Online: March 21, 2020*
Authors from: China (Hong Kong), UK

Extensive social distancing measures have been taken within most European countries. An alternative strategy would be to allow the causal virus to spread to increase the population herd immunity, but at the same time protecting the elderly and those with multiple comorbidities, who are the most vulnerable. The basic reproductive number (R0) and the more 'real-life' effective reproductive number (Rt) for a given population can be estimated. R0 is the number of secondary cases generated by the presence of one infected individual in an otherwise fully susceptible, well-mixed population. **Rt is a more practical real-life version of this, which uses real-life data** (from diagnostic testing and/or clinical surveillance) to estimate the reproductive number for an ongoing epidemic. **The minimum ('critical') level of population immunity** (Pcrit) can be calculated, acquired via vaccination or naturally-induced (i.e. after recovery from COVID-19), to halt the spread of infection in that population. The estimated values for various countries are summarised in the table within the article. For example, for the Czech Republic, Rt is 3.57 and Pcrit 72,0 %.

Profile of Specific Antibodies to SARS-CoV-2: The First Report

Currently, there is a paucity of data on the profile of specific antibodies to SARS-CoV-2 infection. The authors of the present study evaluated the **profile of IgM and IgG for SARS-CoV-2 from 34 COVID-19 patients**. Blood samples were obtained at different dates after onset of symptoms to detect the specific antibodies to SARS-CoV-2. IgM and IgG were analyzed by chemiluminescent immunoassay. **In week 3 after symptoms onset, all patients were tested positive for IgM and IgG**, with the mean value of 322.80AU/ml and 112.40AU/ml (Reference:<10AU/ml) respectively. **In week 5, all patients were positive for IgG, while 2 patients (16.7%) got negative results for IgM.** IgM level kept going down to 78.03AU/ml and IgG continued up to 163.56AU/ml. At the end of observation (7 weeks), 2 **patients (33.3%) got negative results for IgM, while all patients positive for IgG**, with the mean value of 21.83AU/ml and 167.16AU/ml respectively. Detectable and continuous high levels of IgM indicated the acute phase of infection. Furthermore, IgM lasts more than a month indicating the prolonged virus replication in SARS-CoV-2 infected patients. IgG responded later than IgM and persisted high in the study, **indicating the humoral immune reaction** to protect the body against the SARS-CoV-2 virus.

The detection and profile of specific antibodies to SARS-CoV-2 will provide valuable information for the rapid screening of suspects, assist diagnosis and evaluate the disease course. Furthermore, the concentrated IgG antibody may be informative in vaccine development and treatment for SARS-CoV-2.

Covid-19: trials of four potential treatments to generate "robust data" of what works

The World Health Organization (WHO) is to coordinate the **SOLIDARITY clinical trial,** an international study of treatments for COVID-19. While multiple small trials with different methodologies may not yield strong evidence, a large trial like SOLIDARITY can achieve that. The study will focus on **four treatment options**: the novel antiviral drug **remdesivir**, developed by Gilead in response to Ebola; **lopinavir and ritonavir,** antiretroviral drugs used against HIV; **lopinavir and ritonavir in combination with the immune system regulator interferon β**; the antimalarial drug **chloroquine**, which has reportedly been effective in China. The drugs and combinations will be tested against standard care, which is supportive treatment with supplementary oxygen and respiratory support as required. Countries reported to be taking part in SOLIDARITY are Argentina, Bahrain, Canada, France, Iran, Norway, South Africa, Spain, Switzerland, and Thailand. European hospitals are also being invited to take part in a similar trial, **Discovery**, coordinated by the French research institution INSERM. The trial organizers plan to include 3200 patients from Belgium, France, Germany, Luxembourg, the

Netherlands, Spain, Sweden, and the UK. It will study the same drugs and drug combinations as the WHO trial. It will be **randomized but open-label** and will assess outcomes at 15 days. The great strength of this trial is its adaptive nature. This means that **ineffective experimental treatments can very quickly be dropped and replaced by other molecules that emerge from research efforts**.

Could chloroquine /hydroxychloroquine be harmful in Coronavirus Disease 2019 (COVID-19) treatment?

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Authors from: Italy

In vitro activity of hydroxychloroquine (HCQ) in inhibiting SARS-CoV-2 has been reported, but **in vivo data are still limited**. Taking into account the antiviral in vitro effect, chloroquine (CQ) has been considered as a valuable candidate, alone or in combination with Lopinavir, for further testing in animal models or direct off-label use for COVID-19. It has been postulated that CQ/HCQ may have some effect on SARS, in particular by inhibiting the production of TNF-α and IL6 and consequently blocking the subsequent cascade of events that lead to ARDS. Due to the aforementioned evidence, the negligible cost, the large worldwide use, and the known safety profile, CQ/HCQ has been considered as a potentially useful drug in patients affected by SARS-CoV-2. Despite in vitro activity in inhibiting the growth of several viruses, to date, **no acute virus infection has been successfully treated by CQ/HCQ.** Moreover, CQ showed a **paradoxical effect when administered in treating Chikungunya virus** Infection: in a prophylactic study in a non-human primate model the infection was enhanced by CQ treatment; in a curative study on a human cohort, CQ **did not affect the acute phase** of the disease, in term of symptoms and viral clearance, but the **chronic complications of Chikungunya were more frequent** in the treated group with respect to the control group. This paradoxical effect has been explained by a delay in an immune adaptive response to the virus provoked by CQ administration that could nullify the antiviral activity shown in vitro.
As a matter of fact, the **pathogenesis of SARS-CoV-2 is still unknown**, however, preliminary studies show differences with respect to SARS pathogenesis: in particular, with different effects on the **T-helper function**. It has been demonstrated that CQ inhibits T-cell proliferation by reducing IL-2 production and IL-2 responsiveness and it seems that IL2 plays a crucial role in "priming" T cells for TH-2 differentiation. Thereafter if TH -2 response could play a role in suppressing inflammation in SARS-CoV-2 infection, it cannot be excluded that CQ/HCQ negatively impacts the immune response to the virus.
For the aforementioned points, CQ/HCQ not only could be useless in treating COVID-19 patients but even harmful, as it was for Chikungunya Virus infection. Hence, nevertheless, the proved in vitro efficacy, **before clinical trials result in publication and/or further clarification about COVID-19 pathogenesis, clinicians should use it cautiously.**

Coronavirus disease 2019 (COVID-19): update for anesthesiologists and intensivists March 2020

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Authors from: Germany

Practical German guidelines and recommendations on diagnosis and management of severe COVID-19 cases. Summary for clinical practice

1. In most cases, the course of the disease is mild, but around 5% of patients develop severe ARDS.
2. It is necessary to establish structures for providing outpatient care for as many mild cases as possible.
3. Pathogen identification is done by PCR, in critically ill patients preferably from the lower respiratory tract.
4. NIV therapy or even high-flow oxygen must be assessed critically due to the high risk of infection for staff.
5. If NIV is nonetheless applied, early intubation is needed in case of failure.
6. Unlike other severe infectious diseases, COVID-19 patients often deteriorate only with a certain delay in the course of the disease.
7. Avoiding nosocomial COVID infection is crucial, above all by consequent use of personal protective gear.
8. Apart from challenges regarding patient care, staff absences and lack of resources can cause considerable problems in hospitals' operational processes.
9. Structures that provide the care of other medical conditions, e.g. trauma, myocardial infarction or births, need to be maintained at all costs.

Considerations for Cardiac Catheterization Laboratory Procedures During the COVID-19 Pandemic

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Authors from: USA

COVID-19 infection likely promotes pathways leading to acute coronary syndrome (endothelial activation, oxidation of low-density lipoproteins, platelet activation, expression of tissue factor). Whether there are additional pathogenic aspects specific to COVID-19 (interaction with ACE/ARB medications, NSAIDs, lymphocytic myocarditis, etc.) will require further investigation.
The authors, therefore, described strategies for triage and management of care in the **Cardiac Catheterization Laboratory** (CCL). **Guiding Principles for Confirmed or Suspected COVID-19 Patients**

1. All STEMI patients including transfers should initially undergo **clinical and COVID-19 screening evaluation** in the Emergency Department.

2. 2. Currently, all **STEMI patients should be brought to the CCL for primary PCI**. Although several reports are advising fibrinolytic therapy in these patients if the prevalence of COVID-19 is high or system resources are in danger of becoming overwhelmed, the prevalence globally currently favors continuing a primary PCI approach. As the prevalence of COVID-19 increases causing systematic and infrastructural bottlenecks for care, especially given regional variations, the primary therapeutic options may have to change.

3. Alternative therapeutic options such as **systemic fibrinolytic therapy may be considered for low-risk STEMI** (e.g. inferior STEMI without right ventricular involvement or lateral myocardial infarction without hemodynamic compromise) depending on local availability of expertise and the prevalence and effects of the COVID-19 disease burden at the institution; a potential downside is that these patients then often require prolonged ICU level of care and may end up utilizing vital finite resources.

4. When possible, **bedside procedures are preferable** (e.g., intra-aortic balloon pump, pericardiocentesis, ECMO, temporary venous pacemakers); CCLs should create COVID-19 carts with all potential supplies for these procedures.

5. For treatment in the CCL, maximal protection to prevent staff exposure should be employed including effective **personal protective equipment** (PPE).

6. Percutaneous coronary intervention (PCI) should **only be performed to the culprit vessel** unless a non-culprit lesion is deemed unstable or multiple culprit lesions are present.

7. Performing **endotracheal intubation in the CCL should be avoided** to the extent as possible. In patients with respiratory distress, early intubation (prior to transfer to the CCL) should be considered in order to minimize aerosolization. Similarly, high-flow nasal cannula, non-invasive ventilation, and use of an Ambu bag should be avoided to minimize potential aerosolization and dissemination of the virus. If intubation is required in the CCL, all personnel not essential to the act of intubation should exit the room to avoid the associated higher risk of virus exposure during the process. If cardiopulmonary resuscitation (CPR) is required in the CCL, consider using automated CPR devices for chest compression to minimize personnel exposure.

8. Within the CCL, a **single procedure room should be designated for the care of COVID-19** patients, airflow modified to negative pressure if possible (though this is controversial), and strategies for safe containment and elimination of the virus should be developed. In some cases, this may involve the utilization of HEPA filters in the room.

Temporal Profiles of Viral Load in Posterior Oropharyngeal Saliva Samples and Serum Antibody Responses During Infection by SARS-CoV-2: An Observational Cohort Study

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Authors from: China (Hong Kong)

Comprehensive data for serial respiratory viral load and serum antibody responses from patients infected with SARS-CoV-2 are not yet available. Nasopharyngeal and throat swabs are usually obtained for serial viral load monitoring of respiratory infections but gathering these specimens can cause discomfort for patients and put health-care workers at risk. The authors aimed to **ascertain the serial respiratory viral load in posterior oropharyngeal** (deep throat) saliva samples from patients with COVID-19, and **serum antibody responses** in a cohort study. They obtained samples of **blood, urine, posterior oropharyngeal saliva, and rectal swabs**. Serial viral load was ascertained by RT-qPCR. Antibody levels against the SARS-CoV-2 **internal nucleoprotein** (NP) and **surface spike protein receptor-binding domain** (RBD) were measured using EIA. Whole-genome sequencing was done to **identify possible mutations** arising during infection. **23 patients were included** median age 62 years. The median viral load in posterior oropharyngeal saliva or other respiratory specimens **at presentation was 5.2 log10 copies per mL**. Salivary **viral load was highest during the first week after symptom onset and subsequently declined with time**. In one patient, viral RNA was detected 25 days after symptom onset. Older age was correlated with higher viral load. For 16 patients with serum samples available 14 days or longer after symptom onset, rates of **seropositivity were 94% for anti-NP IgG**, **88% for anti-NP IgM**, **100% for anti-RBD IgG, and 94% for anti-RBD IgM.** Anti-SARS-CoV-2-NP or anti-SARS-CoV-2-RBD IgG levels correlated with virus neutralization titer. No genome mutations were detected on serial samples.

Posterior oropharyngeal saliva samples are a non-invasive specimen more acceptable to patients and health-care workers. Unlike SARS, patients with COVID-19 had the **highest viral load near presentation**, which could account for the fast-spreading nature of this epidemic. This finding emphasizes the importance of stringent infection control and early use of potent antiviral agents, alone or in combination, for high-risk individuals. The serological assay can complement RT-qPCR for diagnosis.

Expanded Umbilical Cord Mesenchymal Stem Cells (UC-MSCs) as a Therapeutic Strategy in Managing Critically Ill COVID-19 Patients: The Case for Compassionate Use

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Authors from: USA

Expanded umbilical cord mesenchymal stem cells or (UC-MSCs) may have a role and are being studied in COVID-19. The cure for COVID-19 is essentially dependent on the patients' own immune system. When the immune system is over-activated in an attempt to kill the virus, this can lead to

the production of a large number of inflammatory factors, resulting in a severe cytokine storm. The cytokine storm may induce organ damage followed by the edema, dysfunction of air exchange, ARDS, acute cardiac injury, and secondary infection, which may lead to death. Thus, at this point, the **avoidance of the cytokine storm may be the key to the treatment**. Several patients were treated with expanded UC-MSCs in China. Additionally, the Italian College of Anesthesia, Analgesia, Resuscitation and Intensive Care has reported guidelines to treat coronavirus patients with stem cells in the hope of decreasing the number of patients going to the ICU, and, also relatively quickly getting them out of ICU. MSCs have been widely used in cell-based therapy, from basic research to clinical trials. Safety and effectiveness have been documented in the **immune-mediated inflammatory diseases**, such as graft-versus-host disease (GVHD) and systemic lupus erythematosus (SLE). MSCs play a positive role mainly in two ways, namely **immunomodulatory effects** and **differentiation abilities**. MSCs can secrete many types of cytokines by paracrine secretion or make direct interactions with immune cells including T cells, B cells, dendritic cells, macrophages and natural killer cells leading to immunomodulation. MSCs are thought to regulate the inflammatory response and promote tissue repair and regeneration. MSCs may also directly influence the infection, by the secretion of antimicrobial peptides and proteins (AMPs), and by the expression of molecules such as indoleamine 2,3-dioxygenase (IDO) and interleukin (IL)-17.

In a recently published tiny clinical trial, the investigators compared 7 patients (1 critically serious, 4 serious and 2 common) with COVID-19 who received one dose of stem cell therapy with 3 patients in the control group (3 serious) who did not. All these patients were not responding to standard treatment. They were followed for 14 days. **All patients with stem cell therapy recovered**. However, in the control group, one patient died while another patient developed ARDS. Only one patient in the control group was stable. No complications were noted in the treatment group. In the treated group within a few days, the oxygen saturation, biomarkers for inflammation and tissue injury like CRP, aspartic aminotransferase, creatine kinase activity, and myoglobin normalized. Significant improvements were seen in the radiological signs in the follow-up CT scans of the lungs. Limitations of this study include the small sample size and short-term follow-up. More trials are registered and ongoing.

Antibodies in Infants Born to Mothers With COVID-19 Pneumonia

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Authors from: China

A previous study of 9 pregnant women and their infants found no vertical transmission of SARS-CoV-2 based on RT-PCR. The authors of the present study retrospectively applied new serologic testing criteria to 6 pregnant women with confirmed COVID-19 and their infants. Blood samples were collected **from the mothers at delivery** and **neonatal blood and throat swab samples were collected at birth**. The sensitivity and specificity reported by the manufacturer for IgM are 88.2% and 99.0% respectively, and for IgG are 97.8% and 97.9%. All 6 mothers had mild clinical manifestations. All had **cesarean deliveries** in their third trimester in negative pressure isolation rooms. All mothers

wore masks, and all medical staff wore protective suits and double masks. The infants were isolated from their mothers immediately after delivery.

All infants had 1-minute Apgar scores of 8 to 9 and 5-minute Apgar scores of 9 to 10. **Neonatal throat swabs and blood samples all had negative RT-PCR test results. All 6 infants had antibodies detected in their serum**. Two infants had IgG and IgM concentrations higher than the normal level (<10 AU/mL). One infant had an IgG level of 125.5 and IgM level of 39.6 AU/mL; the second infant had an IgG level of 113.91 AU/mL and IgM level of 16.25 AU/mL. Their mothers also had elevated levels of IgG and IgM. Three infants had elevated IgG levels (75.49, 73.19, 51.38 AU/mL) but normal IgM levels; all 3 mothers had elevated IgG and 2 also had elevated IgM levels. **Inflammatory cytokine IL-6 was significantly increased in all infants**. **None of the infants presented any symptoms.** The IgG concentrations were elevated in 5 infants. **IgG is passively transferred across the placenta** from mother to fetus beginning at the end of the second trimester and reaches high levels at the time of birth. However, **IgM, which was detected in 2 infants, is not usually transferred from mother to fetus** because of its larger macromolecular structure. In a study of mothers with SARS, the placentas of 2 women who were convalescing from SARS-CoV infection in the third trimester of pregnancy had abnormal weights and pathology. **Whether the placentas of women in this study were damaged and abnormal is unknown.** Alternatively, **IgM could have been produced by the infant if the virus crossed the placenta.** This study is limited by the small sample size, lack of cord blood, amniotic fluid, and breast milk and by incomplete information on the outcome of the infants.

Management of Critically Ill Adults With COVID-19

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Authors from: USA

Selected major recommendations:
Infection Control and Testing

1. For health care workers performing **aerosol-generating procedures** (eg, endotracheal intubation, nebulized treatments, open suctioning) use of fitted **respirator masks is recommended (N95 respirators, FFP2)**, instead of surgical masks, in addition to other personal protective equipment (PPE) (best practice statement).
2. For usual care of nonventilated patients, or for performing non−aerosol-generating procedures on patients receiving mechanical ventilation, the use of **medical masks is recommended**, instead of respirator masks, in addition to other PPE (weak recommendation, low-quality evidence [LQE]).
3. **Diagnostic lower respiratory tract samples (endotracheal aspirates) are preferred** over bronchial washings, bronchoalveolar lavage, and upper respiratory tract (nasopharyngeal or oropharyngeal) samples (weak recommendation, LQE).

Hemodynamic Support

1. For acute resuscitation of adults with shock, the following are suggested: measuring dynamic parameters to assess fluid responsiveness (weak recommendation, LQE), using a conservative fluid administration strategy (weak recommendation, very LQE), and using crystalloids over colloids (strong recommendation; moderate QE). Balanced crystalloids are preferred over unbalanced crystalloids (weak recommendation, moderate QE).

2. For adults with shock, the following are suggested: **using norepinephrine as the first-line vasoactive** (weak recommendation, LQE), use of either vasopressin or epinephrine as the first line if norepinephrine is not available (weak recommendation, LQE). **Dopamine is not recommended** if norepinephrine is not available (strong recommendation, high QE). Adding vasopressin as a second-line agent is suggested if the target (60-65 mm Hg) mean arterial pressure cannot be achieved by norepinephrine alone (weak recommendation, moderate QE).

Ventilatory Support

1. Starting supplemental oxygen is recommended **if the Spo$_2$ is less than 90%** (strong recommendation, moderate QE). Spo$_2$ should be maintained no higher than 96% (strong recommendation, moderate QE).

2. For acute hypoxemic respiratory failure despite conventional oxygen therapy, the use of a **high-flow nasal cannula (HFNC) is suggested** relative to conventional oxygen therapy and noninvasive positive pressure ventilation (NIPPV) (weak recommendation, LQE). **If HFNC is not available, a trial of NIPPV is suggested** (weak recommendation, very LQE). Close monitoring for worsening of respiratory status and **early intubation if worsening** occurs is recommended (best practice statement).

3. For adults receiving mechanical ventilation who have acute respiratory distress syndrome **(ARDS), the use of low tidal volume ventilation** (4-8 mL/kg of predicted body weight) is recommended and preferred over higher tidal volumes (>8 mL/kg) (strong recommendation, moderate QE). **Targeting plateau pressures of <30 cm H$_2$O** (strong recommendation, moderate QE) is recommended. Using a **higher positive end-expiratory pressure (PEEP)** strategy over the lower PEEP strategy is suggested (weak recommendation, LQE).

4. For adults receiving mechanical ventilation who have moderate to severe ARDS, **prone ventilation for 12 to 16 hours** is suggested over no prone ventilation (weak recommendation, LQE). Using **as-needed neuromuscular blocking agents** (NMBAs) instead of continuous NMBA infusion to facilitate protective lung ventilation is suggested (weak recommendation, LQE).

5. For adults receiving mechanical ventilation who have severe ARDS and hypoxemia despite optimizing ventilation, a **trial of inhaled pulmonary vasodilator** is suggested. If no rapid improvement in oxygenation is observed, the treatment should be tapered (weak recommendation, very LQE). The **use of lung recruitment maneuvers** (intended to open otherwise closed lung segments, such as 40 cm H$_2$O inspiratory hold for 40 seconds) is suggested, over not using recruitment maneuvers (weak recommendation, LQE), **but using staircase (incremental PEEP) recruitment maneuvers is not recommended** (strong recommendation, moderate QE). Use of veno-venous circulation for extracorporeal

membrane oxygenation (ECMO) or referral to an **ECMO center is suggested, if available, for selected patients** (weak recommendation, LQE).

Therapy

1. In adults receiving mechanical ventilation who do **not have ARDS, routine use of systematic corticosteroids is suggested against** (weak recommendation, LQE). In those **with ARDS, the use of corticosteroids is suggested** (weak recommendation, LQE).
2. In COVID-19 patients receiving mechanical ventilation who have respiratory failure, the use of **empiric antimicrobial/antibacterial agents is suggested** (no evidence rating); assess for de-escalation.
3. In critically ill adults with fever, the use of pharmacologic agents for **temperature control** is suggested over nonpharmacologic agents or no treatment. Routine use of standard **IV immunoglobulins is not suggested**. **Convalescent plasma is not suggested.** There is **insufficient evidence** to issue a recommendation on use of any of the following: antiviral agents, recombinant interferons, chloroquine/hydroxychloroquine, or tocilizumab.

Tilorone: a Broad-Spectrum Antiviral Invented in the USA and Commercialized in Russia and beyond

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Authors from: USA

A broad-spectrum agent tilorone dihydrochloride is known for over 50 years. Tilorone is a small-molecule orally bioavailable drug that was originally discovered in the USA and is currently used clinically as an antiviral in Russia and Ukraine. Over the years there have been numerous clinical and non-clinical reports of its **broad spectrum of antiviral activity**. More recently we have identified additional promising antiviral activities against MERS, Chikungunya, Ebola, and Marburg which highlights that this old drug may have other uses against new viruses. This may, in turn, inform the types of drugs that we need for virus outbreaks such as for SARS-CoV-2. Tilorone has been **long neglected by the west** in many respects but it **deserves further reassessment** in light of current and future needs for broad-spectrum antivirals. Besides this track record of use in Russia and neighboring countries, tilorone has never been evaluated and tested for safety and efficacy under studies that meet current ICH and FDA guidelines and regulations, and previous nonclinical data (if any) are not readily available.

The SARS-CoV-2 Vaccine Pipeline: an Overview

One of the major hurdles in the early development of SARS coronavirus vaccines has been the finding of **undesired immunopotentiation** in the form of eosinophilic infiltration or increased infectivity, which is noted to occur following challenge infections after immunizations with whole virus vaccines or even complete spike protein vaccines. Safety of the COVID-19 vaccine is, therefore, paramount. Unfortunately, vaccines developed and produced for global health security or biodefense are often considered **less profitable than traditional childhood and adult vaccines**. For that reason, very few of the major multinational pharmaceutical companies appear to have expressed upfront commercial interest in entering this space.

Whole Virus Vaccines:

Live-attenuated or inactive whole virus vaccines represent a classic strategy for viral vaccinations. According to an industry newsletter, Johnson & Johnson is one of the few multinational companies embarking on COVID-19 vaccines]; similar to their Ebola vaccine platform, they are employing Janssen's AdVac® adenoviral vector and manufacturing in their PER.C6® cell line technology. In addition, researchers at the University of Hong Kong have developed a live influenza vaccine that expresses SARS-CoV-2 proteins. Finally, Codagenix has developed a "codon deoptimization" technology to attenuate viruses and is exploring SARS-CoV-2 vaccine strategies. A major advantage of whole virus vaccines is their **inherent immunogenicity** and **ability to stimulate toll-like receptors**. However, live virus vaccines often require extensive additional testing to confirm their safety. This is especially an issue for coronavirus vaccines, given the findings of increased infectivity following immunization with live or killed whole virus SARS coronavirus vaccines.

Subunit Vaccines

Subunit vaccines for both SARS coronaviruses rely on eliciting an immune response **against the S-spike protein** to prevent its docking with the host ACE2 receptor. Already, under funding from the Coalition for Epidemic Preparedness (CEPI), the University of Queensland is synthesizing viral surface proteins, to present them more easily to the immune system. Moreover, Novavax has developed and produced immunogenic virus-like nanoparticles based on recombinant expression of the S-protein, while Clover Biopharmaceuticals is developing a subunit vaccine consisted of a trimerized SARS-CoV-2 S-protein using their patented Trimer-Tag® technology, although some full-length S-proteins for SARS also elicit increased infectivity and eosinophilic infiltration. Accordingly, a consortium led by Texas Children's Hospital Center for Vaccine Development at Baylor College of Medicine (including the University of Texas Medical Branch and New York Blood Center) has developed and tested a subunit vaccine comprised of **only the receptor-binding domain** (RBD) of the SARS-CoV S-protein. When formulated on alum, the SARS-CoV RBD vaccine elicits high levels of protective immunity on the homologous virus challenge. An advantage of the RBD-based vaccine is its ability to minimize host immunopotentiation. Initial findings that the SARS-CoV and SARS-CoV-2

RBDs exhibit more than 80% amino acid similarity and bind to the same ACE2 receptor offer an opportunity to develop either protein as a subunit vaccine.

Nucleic Acid Vaccines
Several major biotechs have advanced nucleic acid vaccine platforms for COVID-19. For example, Inovio Pharmaceuticals is developing a DNA vaccine, while others, such as Moderna Therapeutics and Curevac, are exploring RNA vaccine platforms. The concept of immunizing with DNA began with promising results in mice in 1993 showing protective immunity against influenza, but for decades, these findings have not translated to similar findings in humans. More recently, new modifications and formulations have improved nucleic acid performance in humans, with an expectation that this approach might eventually lead to the first licensed human nucleic acid vaccine.

There are now at least a **half-dozen candidates**, including live viruses, recombinant protein subunits, and nucleic acids that may ultimately offer promise as preventive vaccines against COVID-19. However, each of these vaccines may require additional manufacturing steps and formal toxicology testing before submitting a regulatory package to national regulatory agencies and be able to commence the clinical development, first with phase 1 clinical trials for safety and immunogenicity, and later, phase 2 and phase 3 trials for both safety and efficacy.