EBMT European Society for Blood and Marrow Transplantation

COVID-19 in stem cell transplant patients.

What do we know?

e-learning

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Disclosures

- No disclosures on this topic

I’m not ashamed to confess that I’m ignorant about what I don’t know.

Cicero

Learning objectives

Larning objectives

a) Define the virus SARS-CoV-2 and the disease COVID-19

b) Update information on the virus and the disease

c) Discuss option for prevention and management

d) Become familiar with options to ensure stem cell graft availability

Definitions

- SARS-CoV-2 is the virus
- COVID-19 is the disease.

The virus

- SARS-CoV-2 is a coronavirus spread from animals – a zoonosis
- Coronaviruses are RNA viruses
- There are many coronaviruses of which three are common in humans causing usually mild upper respiratory disease
- Two coronaviruses of animal origin have passed into humans the last 15 years – SARS-CoV-1 and MERS-CoV.
- SARS-CoV-2 is genetically close to SARS-CoV-1.

The virus

- The virus has been identified in:
  - Respiratory tract specimens
  - Faeces
  - Whole blood
  - Serum
  - Saliva
  - Urine
  - Conjunctival secretion

The virus

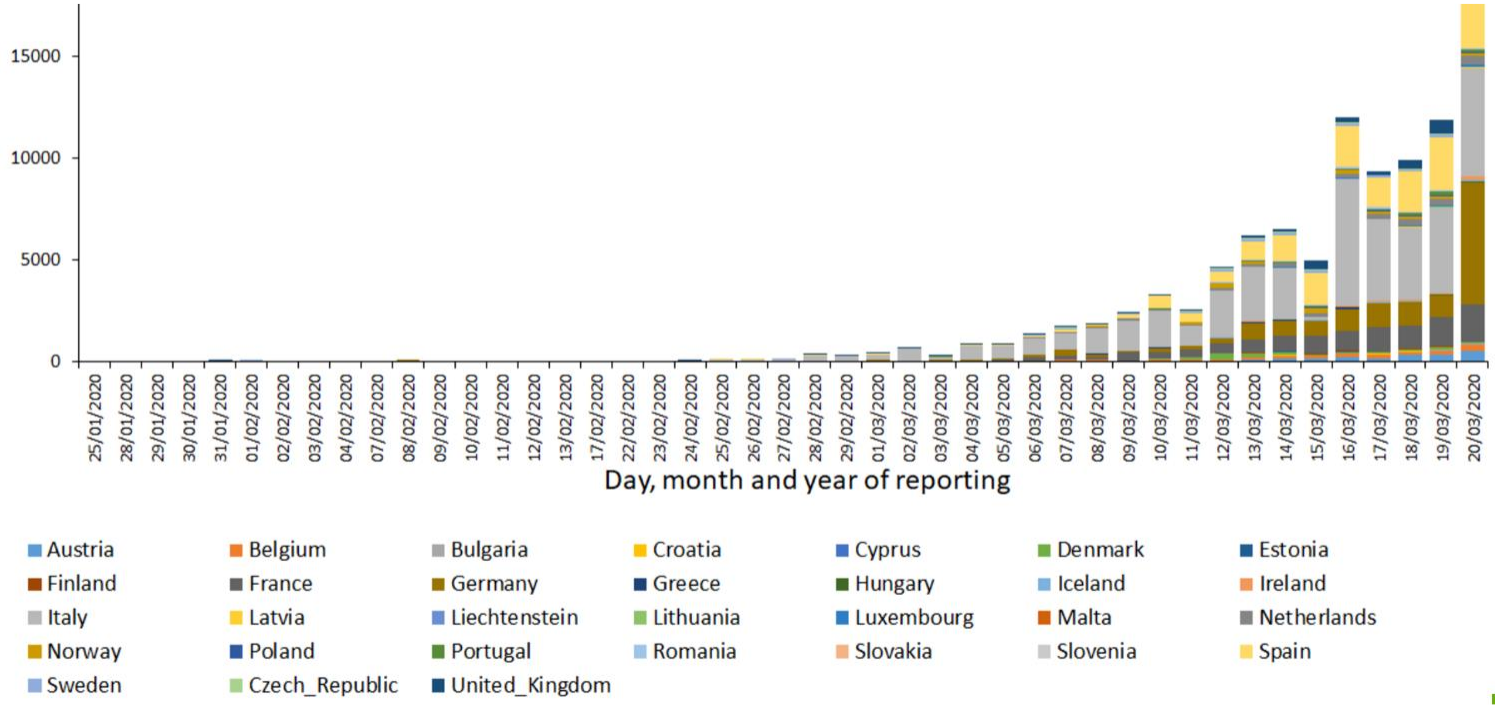
- The virus is transmitted from human-to-human by droplets spread by coughing or sneezing or exhaled by infected persons as well as by touching of droplets-contaminated surfaces or objects – and then touching the eyes, nose or mouth
- Other ways of transmission has not been proven although viable virus can be found on surfaces after up to 72 hours (laboratory experiments; van Doremalen et al; NEJM 2020).
- A major question is how infectious a person is in the asymptomatic early phase of the infection
- There is evidence of molecular development of the virus. Whether this will result in less or more severe disease is currently unclear

The disease

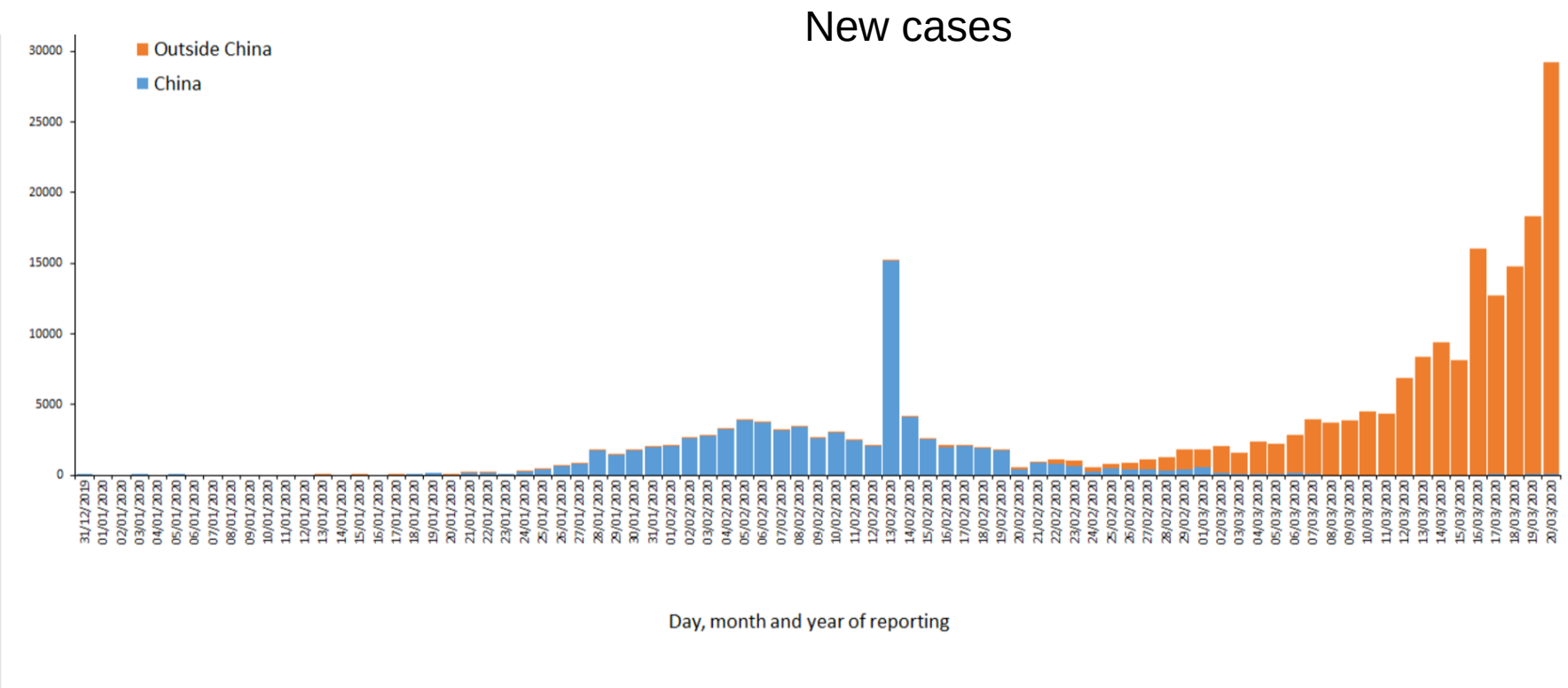
The disease

- The disease is called COVID-19 by WHO
- It first appeared in the city of Wuhan, Hubei province in China in the end of December 2019 and spread rapidly first in China and then to neighboring countries including Japan, South Korea, and Singapore
- In the end of February it was documented in the north of Italy and quickly spread in the population.
- It is now classified as a pandemic with major clusters in Korea, Europe, and the US
- The situation in China seems to be under control with few new cases.

No of cases in the EU (ECDC); March 20



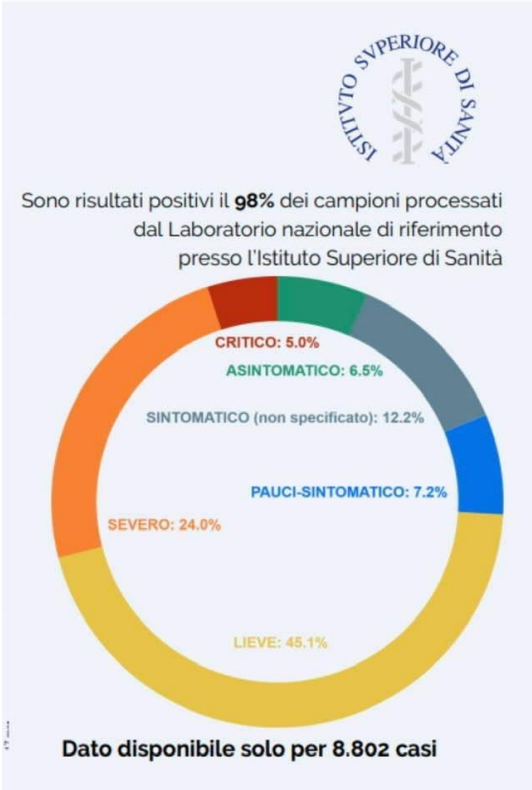
Data from the ECDC March 20



The disease

- There is a great variability in the symptoms from none to fatal ARDS
- Risk factors for severe disease are primarily high age but also co-morbidities including heart- and lung disease and cancer
- Pregnant women seem not to be at high risk
- Children seem to have milder disease
- The incubation period is usually 2 -14 days (median 5 days) but occasional cases have been documented with a both shorter and longer incubation period (Lauer et al, Ann Intern Med 2020).
- This is, however, difficult to verify today since the virus is so widespread that exact time of contracting the infection is almost impossible to prove.

The disease



- There is a great variability in the symptoms from none to fatal ARDS

The disease

- The most commonly reported clinical symptoms in laboratory-confirmed cases are:
  - fever (88%)
  - dry cough (68%)
  - fatigue (38%)
  - sputum production (33%)
  - dyspnoea (19%)
  - sore throat (14%)
  - headache (14%)
  - myalgia or arthralgia (15%) [11].
  - Less common symptoms are diarrhoea (4%) and vomiting (5%)

The disease

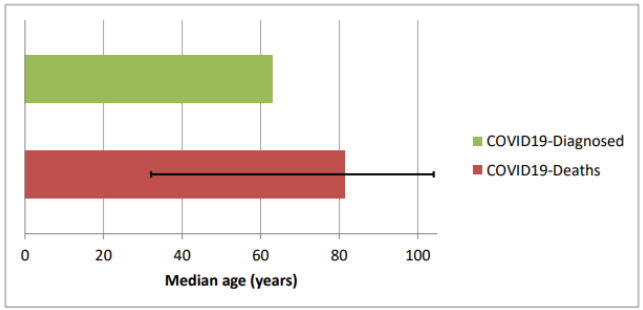
- The information from China suggests that approx. 80% have mild disease, 14% severe disease, and 6% critical illness.
- The case fatality rate has varied between countries.
    - China 2.3%
    - Italy 2.8%
    - Korea 0.5%.

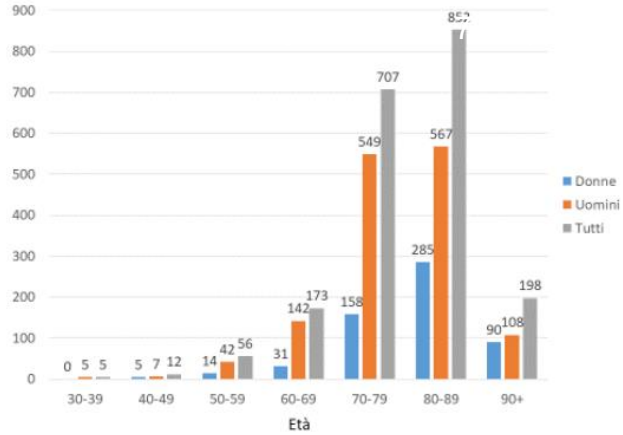
Data from ECDC

Characteristics of Italian deaths for COVID19 update at 17.3.2020,

Official report released by Institute of Health (ISS)

2003 patients deceased





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What is the impact in Stem Cell Transplant recipients?

The recipient - risks

- Risk for postponement of a life saving therapy in a patient intended to undergoing HSCT either due to that the patient becoming infected or by the donor being unavailable
- Risk for contracting severe disease similar to what is the case with other respiratory viral infections such as RSV or influenza.
- Risk for not receiving stem cells at the intended time point after start of conditioning due to the donor becoming available

The recipient

- 15 cases known in Europe with COVID-19 after HSCT so far (Spain 5, France 2, Belgium 2, Italy 3, Sweden 2, Greece 1).
- Median age 59; 12 allo and 3 auto.
- 10 were diagnosed as upper respiratory and 5 as lower respiratory
- At the time of reporting 1/15 has died. More data will be collected.
- Ongoing EBMT survey to learn more and get information to distribute as fast as possible. Please, report with the registration form ASAP if you have a case since we need information as quickly as possible
- Mixed reports from China that we are trying to verify

The recipient - diagnosis

Should be according to national guidelines.

Symptomatic patients, who reside in an area with high risk of transmission of SARS-CoV-2, should be tested for the virus.

Nasal samples have a better yield than oral samples

It is important to note that a test for SARS-CoV-2 can be false negative and needs to be repeated if there is a strong suspicion of COVID-19 such is case of pneumonia or severe illness.

It is also important to test for other respiratory viral pathogens including influenza and RSV preferably by multiplex PCR.

Patients positive for SARS-CoV-2 in an upper respiratory tract sample with lower respiratory tract symptoms should undergo chest imaging.

Routine bronchoalveolar lavage (BAL) is not recommended if patient tested positive with SARS-CoV-2 given risk of transmission amongst health care workers, unless a co-infection is suspected.

The recipient

Stem cell transplanted patients should restrict their risk of exposure to infected individuals as much as possible and to be very thorough following strict hygienic routines including hand washing and use of alcohol containing hand sanitizers.

Stem cell transplant patients should refrain from non-necessary travel according to national guidelines.

The transplant candidate

It is recommended that all patients are tested for SARS-CoV 2 before start of conditioning regardless of symptoms.

In case of close contact with a person diagnosed with COVID-19 any transplant procedure (PBSC mobilization, BM harvest, conditioning) shall not be performed within at least 14 preferably 21, days from the last contact. Patient should be closely monitored for the presence of COVID-19, with confirmed PCR negativity.

Patients with proven COVID-19 should be deferred for transplant for at least 30 days if possible considering the urgency of the transplant.

In case of having been to a high risk area or having been in close contact with person travelling from a high risk area for COVID-19 as defined by national authorities, ECDC, or WHO, any transplant procedures (PBSC mobilization, BM harvest, conditioning) should not be performed within at least 14 preferably 21 days from the last contact

The donor

SARS-CoV-1 and 2 and MERS-CoV have been detected in blood, although there have not been any reports of transmission from donor to recipient either in transfusion of blood products or cellular therapies.

WMDA has produced recommendations and the EBMT endorses these.

The donor

In case of diagnosis of COVID-19, donor must be excluded from donation. At this time it is not possible to give recommendations when such an individual can be cleared for donation but at least three months deferral can be considered unless the need for donation is urgent when individual consideration should be made.

In case of close contact with a person diagnosed with SARS-CoV-2, the donor shall be excluded from donation for at least 28 days. Donor should be closely monitored for the presence of COVID-19.

If the patient's need for transplant is urgent, the donor is completely well and there are no suitable alternative donors, earlier collection may be considered subject to careful risk assessment if local quarantine requirements permit

In case of travel to high risk areas for COVID-19 (as defined by health authorities*) or being a close contact with person travelling from such an area, donor shall be excluded from donation for at least 28 days.

Donors within 28 days before donation should practice good hygiene (see: Box 1. The WHO recommendations) and avoid crowded places and large group gatherings.

The donor

- Logistical problems with donation are likely.
    - The donor might become infected between clearance and harvest
    - The harvest center staff might become infected making it difficult to perform a harvest
    - Problems with moving stem cells over closed borders and/or caused by cancelled travel options
- Based on these considerations, it is strongly recommended to have cryopreserved cells before start of the conditioning

Prevention

Prevention

- It should be recognized that the SARS-CoV-2 will most likely infect a large proportion of the human population of the world
- It is too late for successful containment as was obtained for SARS-CoV-1
- The aim of prevention in the HSCT recipient population should therefore at this stage of the pandemic be to avoid infection in the most vulnerable most likely being those patients early after HSCT, in patients with GVHD and in those with chronic pulmonary complications.
- However, this is an assumption due to lack of data,.

Prevention

- Hand hygiene
- Cough etiquette
- Social isolation
- Personal protective equipment
- Cleaning of surfaces, avoid sharing objects etc.

Prevention

- Intensive work is being conducted to develop a SARS-CoV-2 vaccine and human trials have been initiated.
- It is, however, likely that there will be at least several months before a vaccine can be introduced.
- Iv. Ig is, at least currently, unlikely to work for protection since there are no blood donors with antibodies, which could provide protection.

Information available

KNOW

What is the novel coronavirus?

Coronaviruses are a large family of viruses that cause illness ranging from the common cold to more severe diseases. The novel coronavirus is a new strain, not previously identified in humans. COVID-19 is the infectious disease caused by the latest discovered coronavirus (SARS-CoV-2).

How does the virus spread?

People can catch COVID-19 from others who have the virus through inhaling small droplets from people with COVID-19 who cough or sneeze or through touching contaminated surfaces.

What are the symptoms?

Many people who become infected experience mild illness and recover, but it can be more severe for others.

The symptoms include a combination of:

- Fever
- Cough
- Difficulty breathing
- Muscle pain
- Tiredness

ecdc

Insert national link here
www.ecdc.europa.eu/en/novel-coronavirus-china

KNOW, PREPARE, PROTECT

Information on COVID-19 for people with immunocompromising condition, their family members and care givers

PREPARE

What to do if you have immunocompromising condition?

How can you prepare yourself

- Educate yourself on COVID-19 from trusted sources.
- Refill your prescription medicines or consider using a mail-order for your medications.
- Continue practicing specific preventive measures, as prescribed by your health provider, in connection to your ongoing treatment.
- Have over-the-counter medicines and medical supplies (e.g. tissues, thermometer) to treat fever.
- As much as feasible, keep physically active to ensure good physical condition.
- Have enough groceries and household items, approximately 2-4 weeks. Prepare gradually and avoid panic buying.
- Activate your social network. Contact family, friends, neighbours or community health care workers in advance and make joint plans on what to do when COVID-19 is spreading in your community or if you become ill.
- Follow instructions from national authorities on how to prepare for emergencies.
- Continue to practice general hygiene.

What do you do if you fall ill?

If you become ill with symptoms of cough, fever and difficulty breathing:

1. Stay home and call your local health care services for advice.
2. Mention what immunocompromising condition you have.

PROTECT

How can you protect yourself and others

Clean your hands often. Wash your hands with soap and water or, if not available, use an alcohol-based hand sanitizer:

- Before eating, after using the toilet;
- After blowing your nose, coughing or sneezing;
- After having been in public places;
- After having touched surfaces in public places;
- After having touched other people.

Avoid contact with sick people, in particular those with a cough.

Avoid touching your face, nose and eyes.

Avoid meetings, events and other social gatherings in areas with ongoing community transmission.

Practice social distancing if COVID-19 is spreading in your community:

- Avoid crowds, especially in confined and poorly ventilated spaces.
- Do your grocery shopping at off-peak hours.
- Avoid using public transport during rush hours.
- Exercise outdoors instead of indoor settings.

If you develop cough, once COVID-19 is spreading in your community, use disposable facemasks. This will protect those around you from getting infected.

Management

Management

There is currently no approved drug for treatment of COVID-19

There are several ongoing trials with different drugs.

Some drugs might be available for compassionate use in critically ill patients.

Management

Upper respiratory tract infection (URTI)

- Consider chest imaging to evaluate for lower respiratory tract infection.
- If chest imaging is normal and no symptoms (ie testing done for surveillance), no therapy is recommended at this time. Future clinical trials may enroll patients at the asymptomatic phase.
- If chest imaging is normal and there are mild upper respiratory symptoms (rhinorrhea, sore throat, etc), patients should be considered for clinical trials if available. Specific agents can be considered if symptoms progress

Management

Lower respiratory tract infection (LRTI)

Given challenges around obtaining imaging and bronchoalveolar lavage fluid (BALF), we propose the following definitions of LRTI:

> Proven LRTI: Detection of SARS-CoV-2 by PCR in BAL fluid with consistent radiographic changes
>
> Possible LRTI: Consistent radiographic changes OR presence of LRTI symptoms (hypoxia, significant cough, shortness of breath with a positive upper tract SARS-CoV-2 PCR test.

LRTI may be complicated by severe lung inflammation and the development of ARDS.

LRTI from SARS-CoV-2 may be complicated by subsequent bacterial co-infection. Viral co-infection should also be considered and treated if agents available.

Therapy should be considered in patients with LRTI; agents may be added as combination therapy as severity increases

Management - remdesivir

a. Mechanism of action: Nucleotide analogue, inhibits RNA-dependent RNA polymerase

b. Efficacy demonstrated in in vitro and mouse model of MERS-CoV and in in vitro models of SARS-CoV-2

c. Clinical trials underway

d. Compassionate use information: https://rdvcu.gilead.com/
    i. Key Inclusion criteria: Hospitalization, Confirmed SARS-CoV-2 by PCR, Invasive mechanical ventilation
    ii. Key Exclusion criteria: Evidence of multi-organ failure, pressor requirement to maintain blood pressure, ALT levels > 5 X ULN, Cr Clearance <30 mL/min or dialysis or continuous veno-venous hemofiltration, use of other experimental antiviral agents for COVID-19

e. Adverse events: Transient elevations of transaminases, hypotension during infusion,

a. Drug-drug interactions: AVOID acetaminophen/paracetamol, otherwise no anticipated drug-drug interactions

Can be considered in patients requiring mechanical ventilation

Management – lopinavir/ritonavir

a.Mechanism of action: Protease inhibitors

b.Efficacy: In SARS-CoV, early LPV/r (with ribavirin) associated with increased survival and lower need for pulse steroids· ARDS or death as outcome reduced, progressive decrease in viral load, early rise in lymphocyte count, reduction in cumulative dose of pulsed steroids, and fewer nosocomial infections.

c.Clinical trials underway

d.Adverse events: Moderate diarrhea and nausea, LFT abnormalities

e.Drug-drug interactions: including but not limited to amiodarone, cyclosporine, tacrolimus, phenytoin, rifampin, voriconazole,
simvastatin and others); consult pharmacy for specifics

A randomized study with lopinavir/ritonavir used as monotherapy in patients with lower respiratory tract disease failed its primary endpoint (time to clinical improvement). No effect on viral shedding. Slightly lower number of deaths in the active treatment arm (Cao et al, NEJM March 18, 2020)

Management – chloroquine /hydrocloroquine

a.Mechanism of action: Heme polymerase inhibitor; increases endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV

b.Efficacy: Inhibits SARS-CoV-2 *in vitro* (Wang et al. Cell Res 2020) , hydroxychloroquine more potent; antiviral effect in newborn mice with MERS-CoV; no antiviral effect seen in mice with SARS-CoV Reported success in 100 subjects in China with COVID-19: showed inhibited the exacerbation of pneumonia, improved lung imaging findings, promoted virus negative conversion, and shortened the disease course. (Reviews: Cortegiani et al; J Crit Care: 2020; Gao et al; Biosci Trends 2020)

c.Clinical trials underway

d.Adverse events: Nausea and diarrhea, both mild; bone marrow suppression; renal dysfuction, liver dysfunction; retinopathy with prolonged use (>5 years)

e.Drug-drug interactions: Caution with concomitant QTc prolonging drugs

Management – favipiravir

i. Mechanism of action: RNA polymerase inhibitors

ii. Developed for influenza but has been used for Ebola, Lassa, and other severe infections.

iii. Efficacy: Tested in China and Japan. Media reports suggest efficacy regarding viral shedding (11 days compared to 4) and possibly improvement of patients with pulmonary symptoms. (Review: Dong et al; Drug Discov Ther 2020)

iv. Clinical trials underway

v. Adverse events: Limited

Management – ribavirin

i. Mechanism of action: Nucleoside inhibitor

ii. Used for HCV and also off label for RSV.

iii. Efficacy: Used in several reviews as combination therapy, no clear added benefit

iv. Clinical trials underway as combination with IFN-beta and lopinavir/ritonavir

v. Adverse events: Hemolysis

Management – tocilizumab

Tocilizumab is a recombinant humanized monoclonal antibody against IL-6 receptor that inhibits IL-6 mediated pro-inflammatory response.

Used for treatment of cytokine release syndrome after CAR-T cell therapy

In an open-label study in 20 patients in China with documented COVID-19 and moderate to severe oxygenation impairment, including high flow oxygen and intubation, tocilizumab reduced oxygen requirement, normalized the CRP, and increased the lymphocyte count to normal; 19 of the 20 patients were discharged. Tocilizumab has been approved in China for use in sever COVID-19 cases.

Adverse reactions: LFT abnormalities, increased risk of serious infections, loss of fever as response to infections.

Routine use is not recommended. Tocilizumab can be considered in severely ill patients balancing risks and benefits. Future clinical trials are needed to assess efficacy and toxicity profile in treatment of COVID-19.

Management – corticosteroids

In SARS-CoV, any steroid therapy was associated with increased need for ICU admission or mortality,

Lower mortality and shorter hospitalization was seen among critical case and pulse steroids resulted in lower oxygen requirements and better radiographic outcomes compared to non-pulsed steroids.

In MERS-CoV, steroid therapy was evaluated both by dose and duration and no effect was seen on mortality.

One study of SARS-CoV-2 suggests, delayed use of steroids may increase risk of death in the ICU.

In another COVID-19 cohort, the use of methylprednisolone in patients who developed ARDS was associated with decreased risk of death.

Given the uncertainty of optimal timing of steroid therapy, and potential for steroid therapy to worsen disease severity and lead to secondary infections in the immunocompromised population**,** routine use of steroids is not recommended at this time in patients with mild disease.

Use of steroids in patients with severe disease (requiring oxygen support or mechanical ventilation) could be considered as part of the supportive care regimen for patients with ARDS on a case-by-case basis

Management – other possible options

JAK-1 and 2 inhibition

Mesenchymal stem cells have been used in some cases with ARDS (Leng et al; Liang et al)

Immunoglobulins for treatment (anti-inflammatory) has been used in China.S.

Umifenovir (currently available only in China and Russia) is a drug with efficacy against influenza.

There are other options being tested – watch this space for more!

Recommendations

At this point no recommendations can be made on specific therapies due to limited data and unknown risk vs benefit

Even less data is available for pediatric patients.

Treatment for viral, bacterial, and fungal co-pathogens should be optimized.

Report data to the EBMT survey!

We will also collect data on patients treated with CAR-T cells

Thanks to!

Jan Styczynski, Malgorzata Mikulska, Rafael de la Camara, Simone Cesaro, Alpana Waghmere, and Nicolaus Kroeger

Any questions?