Koronavirové infekce

MUDr. Roman Stebel, Ph.D.

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Principal points of the presentation

- Coronavirus family generally
- Severe Acute Respiratory Syndrome (SARS-CoV-1)
- Middle East Respiratory Syndrome (MERS-CoV)
- COVID-19 (SARS-CoV-2)
 - etiopathogenesis
 - clinical manifestations
 - diagnostics
 - treatment options



prevention and control

Coronaviridae

→ family of enveloped, single-strand, nonsegmented RNA viruses
 → circulate among mammals and birds, animal coronaviruses can rarely spread to humans and subsequently spread between people

- 2 humans serogroups (229E and OC43)
- \rightarrow cause usually mild to moderate **respiratory illnesses** (1/3 of "common colds")
- ightarrow able to survive in dry air for up to 3 hours, killed by exposure to UV light
- ightarrow mutate easily, each mutation triggers off an epidemic of respiratory disease
- \rightarrow bats are considered as **natural hosts** of these viruses

Virus structure

Envelope (lipid bilayer), **S** – spike protein, **M** – membrane protein, **E** – envelope protein, **N** – nucleocapsid with RNA

→ "coronavirus" refers to the protein molecules surrounding the virus, making it look like a crown (lat. "corona")



Classification and Taxonomy of CoV







Severe Acute Respiratory Syndrome

→ respiratory disease caused by SARS-associated coronavirus (SARSr-CoV or SARS-CoV-1)
 → first identified at the end of February 2003 during an outbreak in China and spread
 (2003 - 2004) to 4 other countries (Hong Kong, Taiwan, Canada, Singapore)
 → first severe and readily transmissible new infection to emerge in the 21st century and showed a clear capacity to spread along the routes of international air travel

→ characteristic clinical symptoms include fever above 38 °C, muscle pain, lethargy, cough, sore throat, complications were direct viral or secondary bacterial pneumonia \rightarrow in June 2003, the incidence was 8 422 cases with a case fatality rate of 11 %

→ measurement of body temperature at international airports, often using thermal imagers and subsequent targeted testing, was considered a key factor in stopping the spread of SARS-CoV-1

 \rightarrow chinese scientists traced the virus through the intermediary of Asian palm civets to cave-dwelling bats in Yunnan (province in the southwest China)

Severe Acute Respiratory Syndrome









Middle East Respiratory Syndrome

→ viral respiratory infection caused by the MERS-coronavirus (MERS-CoV)
 → first identified case occurred in June 2012 in Jeddah, Saudi Arabia, generally most cases have occurred in the Arabian Peninsula

 \rightarrow next outbreaks have occurred in **South Korea** (2015) and also in Saudi Arabia (2018)

→ most MERS patients developed severe respiratory illness with symptoms of fever, cough and shortness of breath, severe complications followed, such as pneumonia and kidney failure, 72% of patients required arteficial ventilation, 35 % of patients with MERS have died (ARDS + renal failure)

 \rightarrow relatively high lethality and targeted anti-epidemic measures taken in the Middle East have prevented the global spread of infection, but we will certainly encounter local outbreaks of MERS in the future as well

→ MERS-CoV may have originated in **bats** later transmitted via **dromedaries** (Arabian camels) to human

Middle East Respiratory Syndrome







COVID-19 - Introduction

→ at the end of 2019, a novel coronavirus (2019-nCoV) was identified as the cause of a **cluster of pneumonia** cases in Wuhan, a city in the Hubei, province of China → not previously identified virus in humans, natural host suspected to be **bats**, as intermediate hosts were considered **Pangolins**, first cases in China linked with an **animal market**

→ novel coronavirus rapidly spread, resulting in an epidemic throughout China, followed by a global pandemic (WHO declared a global pandemic on March 11, 2020)
 → in February 2020 WHO designated the disease COVID-19, the virus that causes COVID-19 is designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)





COVID-19 - Virology

→ SARS-CoV-2 is a **betacoronavirus** in the same subgenus (*Sarbecovirus*) as the severe acute respiratory syndrome (SARS) virus (as well as several bat coronaviruses) → the host receptor for SARS-CoV-2 cell entry is the same as for SARS-CoV-1, the **angiotensin-converting enzyme 2 (ACE2)**

→ the structural proteins of SARS-CoV-2 include membrane glycoprotein (M), envelope protein (E), nucleocapsid protein (N), and the **spike protein (S)**, the M protein of SARS-CoV-2 is 98,6% similar to the M protein of bat coronavirus, maintains 98,2% homology with pangolins coronavirus, and has 90% homology with the M protein of SARS-CoV-1; whereas, the similarity is only 38% with the M protein of MERS-CoV







COVID-19 - Virology

Variants of concern





COVID-19 - Pathophysiology

 \rightarrow SARS-CoV-2 binds to ACE2 through the receptor-binding gene region of its spike protein, density of ACE2 receptors in each tissue correlates with the severity of the inflammation and tissue demage

→ virus can affect the upper respiratory tract (sinuses, nose, throat) and the lower respiratory tract (windpipe and lungs), lungs are the organs most affected (ACE2 receptors are most abundant in type II alveolar cells)

→ SARS-CoV-2 also affects gastrointestinal organs (ACE2 is abundantly expressed in the glandular cells of gastric, duodenal and rectal epithelium) → virus can cause acute myocardial injury (perimyocarditis in 12% of infected people admitted to the hospital in Wuhan), ACE2 receptors are highly expressed in the heart and in vascular endothelium

→ blood vessel dysfunction and clot formation (high D-dimer levels) are thought to play a significant role in mortality, incidences of clots leading to pulmonary embolisms, and ischaemic events within the brain have been noted as complications leading to death

COVID-19 - Pathophysiology



COVID-19 - Routes of Transmission



Galbadage. Front Public Health. 2020;8:163. WHO. Scientific Brief. July 9, 2020.

Slide credit: clinicaloptions.com

COVID-19 – Clinical Manifestations

→ symptoms of COVID-19 are variable, ranging from mild "flu-like" symptoms to severe life-threatening illness with acute respiratory failure or MODS/MOF

The typical symptoms are:

- → Fever or Subfebrile > 37.3 °C (83-99%)
- → Dry cough (59-82%)
- \rightarrow Fatigue, collapse states (44-70%)
- \rightarrow Anorexia (40-84%)
- → Shortness of breath, dyspnoea (31-40%)
- \rightarrow Digestive symptoms (diarrhea) can be in up to 50%
- \rightarrow Runny nose, sore throat, loss of smell and taste

Symptoms last 5 - 6 days

Severe illness (complications) starts usually after day 5-8:

- → Intersticial bilateral pneumonia
- → Acute hypoxemic respiratory failure
- ightarrow Perimyocarditis, acute heart failure
- → Pulmonary embolism ("in situ")

→ Kidney failure, disseminated intravascular coagulation, secondary bacterial infection...



COVID-19 – Clinical Manifestations



Product Line	Parameter	Lab abnormalities
	Neutrophile count	•
Hematology	Lymphocyte count	•
	Erythrocyte sedimentation rate	•
	C-reactive protein	•
	Albumin	٠.
Clinical Chamistry	Liver enzymes (GOT (AST), GPT (ALT), GGT, ALP, Bilirubin)	4 1
Clinical Chemistry	Lactate dehydrogenase (LDH)	* *
	Kidney parameters (Creatinine, Urea/BUN)	A1
	Lactate	* *

	CK-MB	* *	
Cardiac Marker	Myoglobin	• *	
	Troponin	* *	
Coagulation	D-dimer	* *	
coagulation	Prothrombin time (sec)	* *	

* in severe cases, mainly

¹ Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7);

Released by National Health Commission & State Administration of Traditional Chinese Medicine; March 3, 2020 ² Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med 2020 Feb 24. doi: 10.1515/cclm-2020-0198

COVID-19 – Risk Factors

Risk factors for more severe illness:

- \rightarrow Age 65 and older
- \rightarrow People who reside in nursing homes or long-term care facilities

People of all ages with underlying medical conditions:

- → Chronic lung disease (asthma bronchiale, COPD)
- \rightarrow Serious heart conditions
- → Immunocompromise and **onkological patiens**
- \rightarrow Severe obesity (BMI > 35)
- \rightarrow Diabetes mellitus
- ightarrow Severe kidney disease
- \rightarrow Chronic liver disease

Outcomes of COVID-19 patients in USA:

- Adults > 65 represented:
- ightarrow 31% of COVID-19 cases
- ightarrow 45% of hospitalizations
- ightarrow 53% of ICU admissions
- \rightarrow 80% of deaths

COVID-19 – Risk Groups

LOW RISK

Contact studies indicate children and young adults do become infected, and can transmit infection. However, children rarely progress to serious illness

HIGH RISK

Risk of severe disease increases with age and in those with underlying medical conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, cancer & obesity

COVID-19 – Diagnostics

 \rightarrow COVID-19 can be diagnosed on the basis of **typical clinical symptoms** (fever, dry cough, shortness of breath, diarrea, loss of smell and taste) and confirmed using **polymerase chain reaction (RT-PCR)** with the detection of viral in RNA in collected biological \rightarrow test is typically done on respiratory samples obtained by a **nasopharyngeal swab**, however, a nasal swab, saliva or sputum sample may also be used

→ serologic tests detect **antibodies** (IgG, IgM, IgA) to SARS-CoV-2 in the blood and can help identify patients who **previously had COVID-19** as well as patients with current infection who have had symptoms **for three to four weeks**

 \rightarrow antigen detection tests detect viral antigens (nucleocapsid or spike protein), their advantage is speed and low price (can be performed at the point of care), the disadvantage is lower sensitivity

→ negative antigen test result (in a symptomatic patient) should be always confirmed by PCR test

COVID-19 – Diagnostics

Test category	Primary clinical use	Specimen type	Performance characteristics	Comments
NAATs (including RT- PCR)	Diagnosis of current infection	Respiratory tract specimens	 High analytic sensitivity and specificity in ideal settings. Clinical performance depends on the type and quality of the specimen and the duration of illness at the time of testing. Reported false-negative rate ranges from <5 to 40%, depending on the test used. [¶] 	 Time to perform the test ranges from 15 minutes to 8 hours.[△] Turnaround time is influenced by the test used and laboratory workflow. Some assays allow home collection of specimens that are mailed in.
Serology (antibody detection)	Diagnosis of prior infection (or infection of at least 3 to 4 weeks' duration)	Blood	 Sensitivity and specificity are highly variable. Detectable antibodies generally take several days to weeks to develop; IgG usually develops by 14 days after onset of symptoms. Cross-reactivity with other coronaviruses has been reported. Individual results should be interpreted with caution in settings of low seroprevalence; serologic tests that have high specificity still have a low positive predictive value. 	 Time to perform the test ranges from 15 minutes to 2 hours. Turnaround time is influenced by the test used and laboratory workflow. It remains uncertain whether a positive antibody test indicates immunity against future infection.
Antigen tests	Diagnosis of current infection	Nasopharyngeal or nasal swabs	 Data are limited. Antigen tests are generally less sensitive than nucleic acid tests. 	 Time to perform the test is <1 hour.



COVID-19 – Diagnostics





Is crucial to know how to collect the sample (nasophyryngeal swab) properly!



COVID-19 – Imaging Modalities







COVID-19 – Treatment Options

→ the management of COVID-19 includes especially supportive and symptomatic care,
 the possibilities of targeted therapy are limited, they are still in the research stage
 → treatment in mild forms of COVID-19 takes place in most cases in home isolation, in
 case of development of dyspnea or other complications, hospitalization is necessary

Non-specific therapy includes:

→ close monitoring for symptomatic patients with risk factors for severe disease (blood pressure, pulse, blood oxygen saturation level, GCS, qSOFA...)
 → empiric antibiotics (ceftriaxone, cotrimoxazole, meropenem) are administered if bacterial pneumonia strongly suspected (CRP > 100, positive prokalcitonin)
 → symptomatic care (antipyretics, fluid therapy, NSAIDs, antitussives and mucolytics)
 → supportive care (vitamins, probiotics, nutrition, rehabilitation, prone position)
 → prophylaxis of thromboembolic disease (LMWH) in all hospitalized patients + ASA

→ oxygen support: low-dose oxygen (nasal cannula, simple face mask, non-rebreather masks), high-flow nasal oxygen therapy (HFNO, Airvo), non-invasive ventilation, orotracheal intubation and artificial lung ventilation, ECMO

COVID-19 – Oxygen Therapy



















Glucocorticoids (dexamethasone)

→ data from randomized trials support the role of glucocorticoids for severe COVID-19, in a meta-analysis of seven trials that included 1703 critically ill patients glucocorticoids reduced 28-day mortality compared with standard care or placebo (32 % versus 40 %) and were not associated with an increased risk of severe adverse events

Proposed mechanism of action:

→ the sickest patients with COVID-19 suffer a hyperinflammatory state (cytokine storm) → immune suppression should help such patients, by contrast, immune suppression during the early phase of the viral infection might allow increased viral replication and aggravate the disease!

 \rightarrow inhaled glucocorticoids – in trials evaluating inhaled glucocorticoids, there was some benefit in the treatment of mild, early, COVID-19, although no mortality reduction was demonstrated

→ dexamethasone (or e.g. methylprednisolone) is recommended for severely ill patients with COVID-19 who are on supplemental oxygen or ventilatory support

Remdesivir (GS-5734, Veklury®)

→ a novel nucleotide analogue, inhibitor of the viral RNA-dependent RNA polymerase with in vitro inhibitory activity against SARS-CoV-2 (and SARS-CoV-1, MERS-CoV...) → remdesivir in ACTT-1 study (2020) resulted in a faster time to recovery, defined as discharge from the hospital or continued hospitalization without need for supplemental oxygen or ongoing medical care (median 10 versus 15 days), remdesivir reduced time to recovery whether patients were randomized within or after 10 days of symptom onset, however, in subgroup analysis, the reduced time to recovery was only statistically significant among patients who were on low-flow oxygen at baseline

 \rightarrow in the EU, remdesivir is indicated for the treatment of COVID-19 in adults and adolescents with intersticial pneumonia requiring supplemental oxygenotherapy, we prioritize remdesivir for those requiring low-flow oxygen because it may also reduce mortality in this population

 \rightarrow suggested adult dose is 200 mg intravenously on day 1 followed by 100 mg daily for 5 days total

Monoclonal antibodies

- 1) Monoclonal antibodies anti-SARS CoV-2:
- → developed to neutralize SARS-CoV-2 by targeting the SARS-CoV-2 proteins (e.g. spike protein) and preventing viral cell entry
- → bamlanivimab/etesevimab (Eli Lilly), casirivimab/imdevimab (Regeneron), sotrovimab
- \rightarrow therapy and also postexposure prophylaxis in patients who are at high risk for progression to severe COVID-19
- 2) Inflammatory pathways inhibitors:

 \rightarrow elevated inflammatory markers and elevated pro-inflammatory cytokines (e.g. IL-6) are associated with critical COVID-19 \rightarrow blocking the inflammatory pathway has been hypothesized to prevent disease progression (cytokine storm)

→ these include the IL-6 receptor blockers **tocilizumab** and sarilumab, the direct IL-6 inhibitor siltuximab, JAK (Janus kinase 1 and 2) inhibitor **baricitinib**

Approaches that target the virus itself are more likely to work early in the course of infection, whereas approaches that modulate the immune response may have more impact later in the disease course.

Convalescent plasma

 \rightarrow plasma obtained from individuals who have recovered from COVID-19 can provide **passive antibody-based immunity**, neutralizing antibodies are thought to be the main active component

 \rightarrow plasma that contains high neutralizing antibody titers is hypothesized to have clinical benefit when **given early in the course of disease** (first 3 - 5 days), and it may be of particular interest for individuals with deficits in antibody production

Favipiravir

→ RNA polymerase inhibitor that is available in Asian countries for treatment of influenza, is being evaluated in clinical trials for treatment of COVID-19 in the United States and elsewhere, favipiravir may hasten SARS-CoV-2 RNA clearance, although data are limited





Molnupiravir (Lagevrio)

ightarrow potent ribonucleoside analog that inhibits the replication of SARS-CoV-2

 \rightarrow exerts its antiviral action through introduction of **copying errors** during viral RNA replication

 \rightarrow I: treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19; CI: pregnancy, breastfeeding, people under 18

Tixagevimab/cilgavimab (Evusheld)

 \rightarrow long-acting monoclonal antibody combination

 \rightarrow I: pre-exposure prophylaxis of COVID-19 in adults and adolescents with moderate to severe immune compromise who may not mount an adequate immune response to COVID-19 vaccination

 \rightarrow duration of protection is estimated to be **at least 6 months**

Nirmatrelvir/ritonavir (Paxlovid)

 \rightarrow potent orally active 3C-like protease inhibitor

ightarrow a number of drug interactions (ritonavir induces CYP1A2 and inhibits CYP 3A4 and

2D6)

COVID-19 – Prevention and Control

 \rightarrow in locations where community transmission is **widespread**, preventive strategies for all individuals in a health care setting are warranted **to reduce potential exposures**!

Personal preventive measures:

- \rightarrow diligent hand washing, particularly after touching surfaces in public, use of hand sanitizer that contains at least 60% alcohol
- → social/physical **distancing** (CDC recommends a minimum distance of **two meters**)
- \rightarrow respiratory hygiene (covering the cough or sneeze)
- \rightarrow avoiding touching the face (in particular eyes, nose, and mouth)
- → cleaning and disinfecting objects and surfaces that are frequently touched
- \rightarrow adequate ventilation of indoor spaces

 \rightarrow optimize of health of individuals (quit smoking, minimize alcohol, healthy diet, get adequate sleep, regular physical activity...)

Wearing masks in the community:

- a surgical mask or respirators (FFP2)

- **in public spaces, inside buildings, in public transport** or when around individuals outside of their household

COVID-19 – Prevention and Control

Coronavirus Prevention

Take steps to protect yourself



Avoid close contact



Clean your hands often



Stay at home



Cover coughs and sneezes



Wear a facemask if you are sick



Clean and disinfect





Passive immunization - administration of **ready-made virus neutralizing antibodies** (immunoglobulins) to the human body



Passive immunization - administration of **ready-made virus neutralizing antibodies** (immunoglobulins) to the human body



+ convalescent plasma





Supply Vaccines to Eliminate Human Diseases











Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. NEJM, 2020; 383:2603-2615. DOI: 10.1056/NEJMoa2034577

A. Anaphylaxis (n = 21)



Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. NEJM, 2020; 383:2603-2615. DOI: 10.1056/NEJMoa2034577

How some of the Covid-19 vaccines compare



A GUIDE TO COVID-19 VACCINES

Updated 3/24/2021

0				
	Pfizer/BioNTech	Moderna	Johnson & Johnson	AstraZeneca
Vaccine Type	mRNA	mRNA	Adenovirus vector	Adenovirus vector
Number of Doses	2 doses about 3 weeks apart	2 doses about 4 weeks apart	1 dose	2 doses about 4 weeks apart
Age Requirement	16+	18+	18+	18+
FDA Emergency Use Authorization	Dec. 11, 2020	Dec. 18, 2020	Feb. 27, 2021	Not yet authorized
Disease Prevention in Clinical Trials	95%	95%	66%	70%
Hospitalization and Death Prevention	100%	100%	100%	100%
Storage Requirements	Standard freezer up to 2 weeks	Standard freezer	Standard refrigeration	Standard refrigeration

beaumont.org/covid-vaccine

Beaumont









Obdržel/a jste mRNA vakcínu CON onemocnění COVID-19 (modifikov	MIRNATY proti aný nukleosid) .
Jméno očkované osoby:	
Datum podání <u>29,12,20</u> •č.	šarže: 156796
Datum pro podání <u>19, 1, 21</u> 2. dávky:	Je důležité podat 2 dávky s minimálním odstupem 21 dní
Datum podání 2. dávky://*Č	.šarže:
Doplňte číslo šarže umístěné na štítku njekční lahvičky nebo nalepte štítek předtištěným číslem šarže.	COVID-19 mRNA Vaccine (nucleoside modified



Jméno a přijmení (Name and Surname) Kočka Testovací

Číslo pojištěnce (Health Insurance number)	Číslo	občanského pri (ID No.)		číslo pasu assport No.)
CZ1252156				
Datum na	rození / Date of birt	h (yyyy-mm-dd): 1	910-01-01	
Původce, proti kterému byla vakcinace provedena: (Agent vaccinated against)	SARS-CoV-2 (ICD	11 XN109, SNON	1ED CT 840533007)	
Typ očkovací látky: Vaccine:	mRNA vakcína proti onemocnění COVID-19 COVID-19 mRNA Vaccine, Severe acute respiratory syndrome coronavirus 2 mRNA only vaccine product(SNOMED CT 1119349			
Název produktu: (Name of medicinal product)	Comirnaty			
Držitel rozhodnutí o registraci: (Marketing Authorization Holder)	BioNTech Manufacturing GmbH			
Země vakcinace: (Country of vaccination)	cz			IČ 23833 PČZ
Vakcinace ukončena: Vaccination schedule completed:	Ano Dávka/celkový počet dávek Yes (Number in a series of vaccination/doses)		2/2	
Šarže (Batch number)	Dávka(dose) 1/2	CZ33333	Dávka(dose) 2/2	CZ33333
Vydavatel certifikátu: Certificate issued by:	Ministerstvo zdravotnictví České republiky Ministry of Health of the Czech Republic			
Datum vakcinace: (Date of vaccination YYYY-MM-DD)	2021-01-18 Datum vystavení certifikátu: 20		2021-01-18	



	Certifikát vystavil (Signature)
の語	

Identifikátor certifikátu (Unique identifier of the certificate):



EU Digital COVID Certificate

> Certifikát EU COVID-19



Place QR code here Minimum size 50 - 60 mm



Surname(s) and forename(s) Příjmení a jméno První František

Date of birth Datum narozeni 1990-01-01

Unique certificate identifier Unikátni identifikátor certifikátu su28rwka8kcbpzrctt9g2ayg9cx9nguh

COVID-19 – Prevention and Control

 \rightarrow public health measures aim at reducing contact rates in a population and thereby reducing transmission of the virus, throughout the world, countries have employed various nonpharmaceutical interventions to reduce transmission

Public health measures:

- → social/physical distancing orders
- \rightarrow stay-at-home orders (home office recommendation)
- \rightarrow school, venue, and nonessential business closure
- ightarrow bans on public gatherings
- \rightarrow travel restriction with exit and/or entry screening

→ aggressive case identification and isolation (separating individuals with infection from others)

 \rightarrow contact tracing and quarantine (separating individuals who have been exposed from others)

→ compulsory mask-wearing in public



THANK YOU FOR your ATTENTION ! ANY QUESTIONS ?

stebel.roman@fnbrno.cz



- → <u>https://www.uptodate.com/contents/coronavirus-disease-2019</u>
- \rightarrow <u>https://clinicaloptions.com/c19</u>
- → <u>https://www.cdc.gov/coronavirus/2019-ncov/index.html</u>
- → <u>https://www.who.int/emergencies/diseases/novel-coronavirus-2019</u>

Beigel JH, Tomashek KM, Dodd LE, *et al*. Remdesivir for the Treatment of Covid-19 — Final Report. *N Engl J Med*. 2020;383(19):1813-1826. doi:10.1056/NEJMoa2007764

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