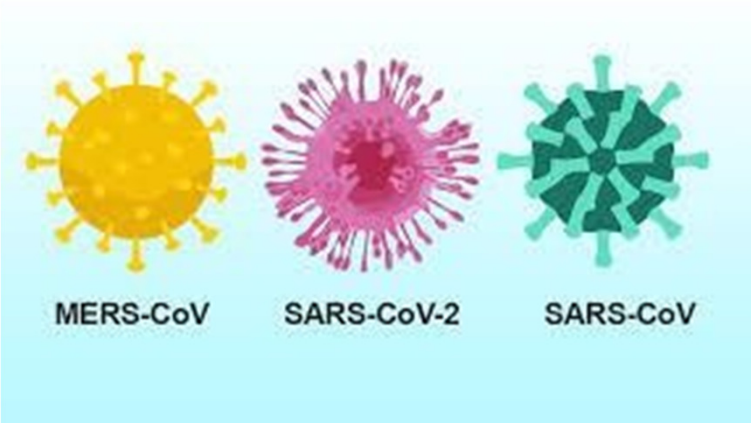
COVID-19:
aspetti clinici ed epidemiologici

Francesco Di Gennaro

DOCTORS WITH AFRICA CUAMM | USAID FROM THE AMERICAN PEOPLE | UPO UNIVERSITÀ DEL PIEMONTE ORIENTALE RESEARCH CENTER IN EMERGENCY AND DISASTER MEDICINE CRIMEDIM

La famiglia CORONAVIRUS



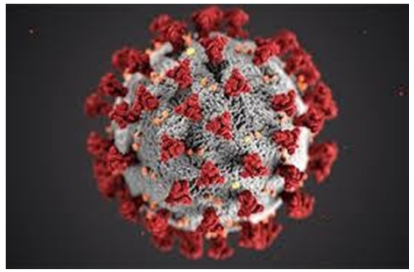
- Virus con capsula a RNA a singolo filamento
- Clinicamente
  - virus respiratori noti dai primi anni ’30
  - Spettro clinico dal raffreddore comune alle gravi infezioni delle basse vie respiratorie spec. in lattanti, anziani, immunodepressi
- Già noti in passato:
  - SARS-CoV, 2003 focolaio di sindrome respiratoria acuta grave iniziato in Cina nel 2002, letalità 10%
  - MERS-CoV, 2012 = sindrome respiratoria del Medio Oriente (Arabia Saudita, Quatar… letalità 34%)

SARS-CoV2 e COVID-19

- Dicembre 2019 nuovo coronavirus causa di un cluster di casi di polmonite a Wuhan, nella provincia cinese di Hubei.
- 11 Marzo 2020, WHO ha dichiarato Pandemia
- Verosimilmente di origine zoonotica. Trasmissione predominante uomo–uomo
- La *malattia* è designata come **COVID-19:** (COrona Virus Disease)-19
- Il *virus* che causa COVID-19 è designato come **sindrome respiratoria acuta grave- da CoronaVirus- 2** (SARS-CoV-2: Severe Acute Respiratory Syndrome – COronaVirus – 2)

Infezione da SARS-CoV2 è condizione estremamente complessa

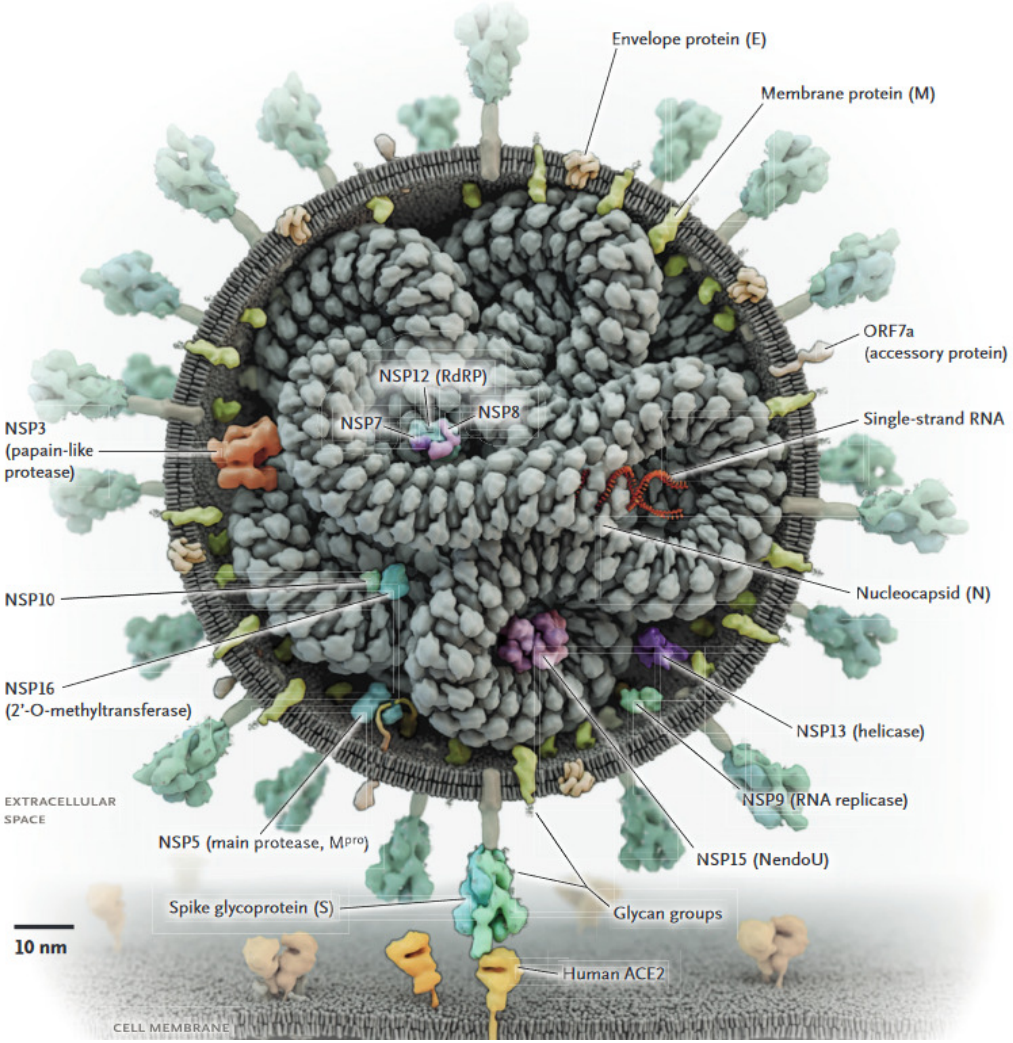
- per i meccanismi fisiopatogenetici connessi
- per la molteplicità delle manifestazioni cliniche
- per il ruolo giocato dalla risposta immunitaria dei soggetti



Struttura del virus SARS-CoV2

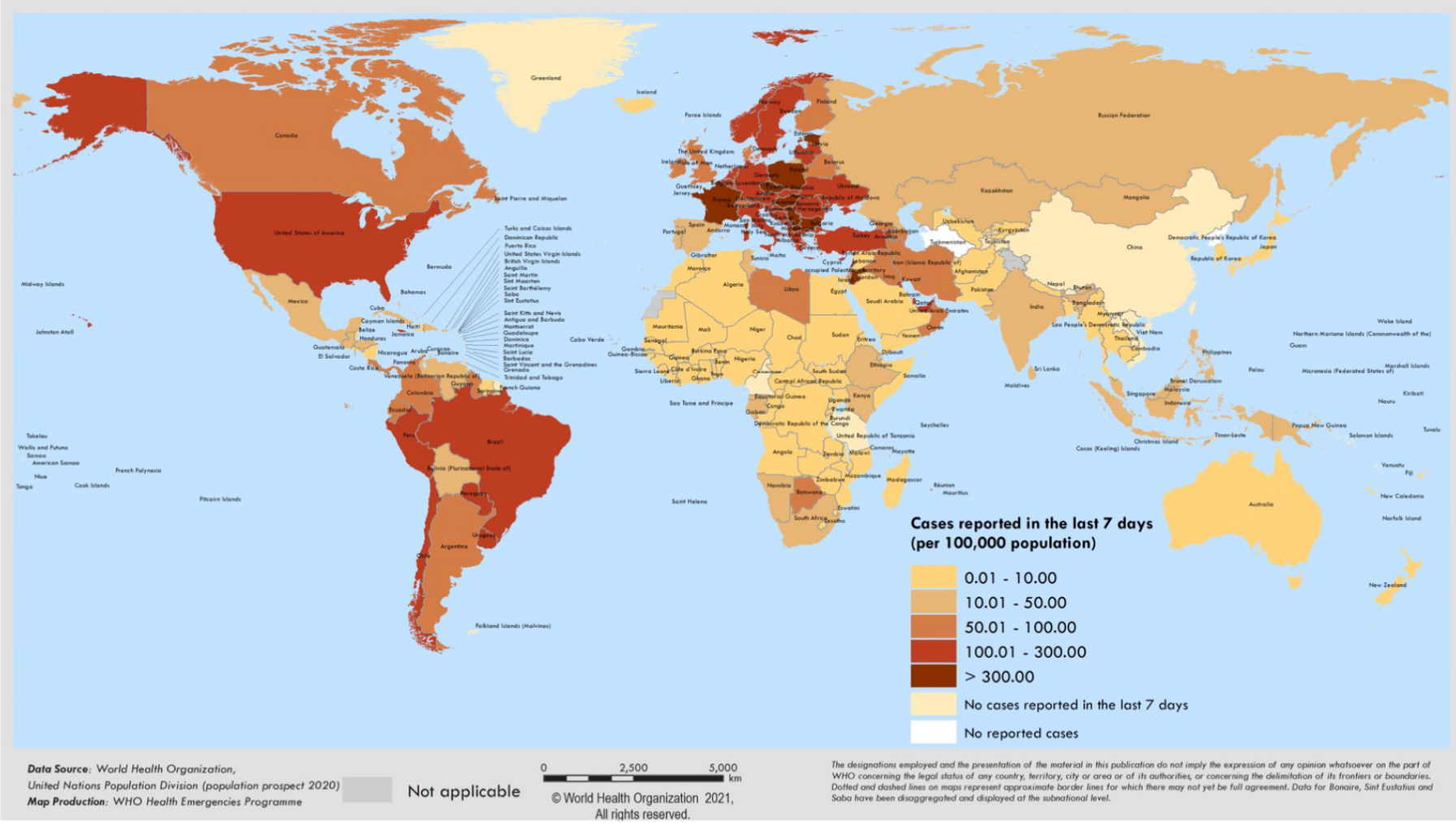
La provincia di Wuhan

SARS-CoV-2 STRUTTURA E CICLO VITALE



- Singolo filamento di RNA a polarità positiva (28-32 Kb), RNA polimerasi RNA-dipendente
- Proteina S (*Spike*) lega il recettore sulla cellula ospite (ACE 2 identificato come recettore)
- Iniziale traduzione poliproteina non strutturale che forma il complesso di replicazione-trascrizione
- 4 proteine strutturali (*Spike,* di membrana, *envelope* e nucleocapside)
- S (Spike, permette al virus di attaccarsi alle membrane della cellula ospite), E (Involucro), M (Membrana), tutte e tre creano il CAPSIDE
- N (Nucleocapside) , contiene il genoma

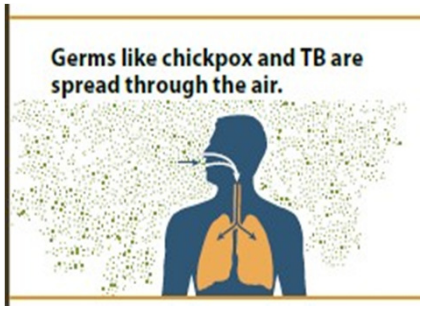
Figure 2. COVID-19 cases per 100 000 population reported by countries, territories and areas, 15-21 March 2021**



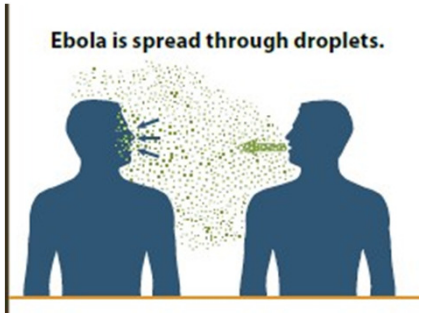
Modalità di trasmissione del virus

COVID-19 si trasmette per droplets/ per contatto con superfici contaminate

- *attraverso la saliva, tossendo e starnutendo*
- *contatti diretti personali, attraverso le mani, ad esempio toccando con le mani contaminate non ancora lavate bocca, naso o occhi*



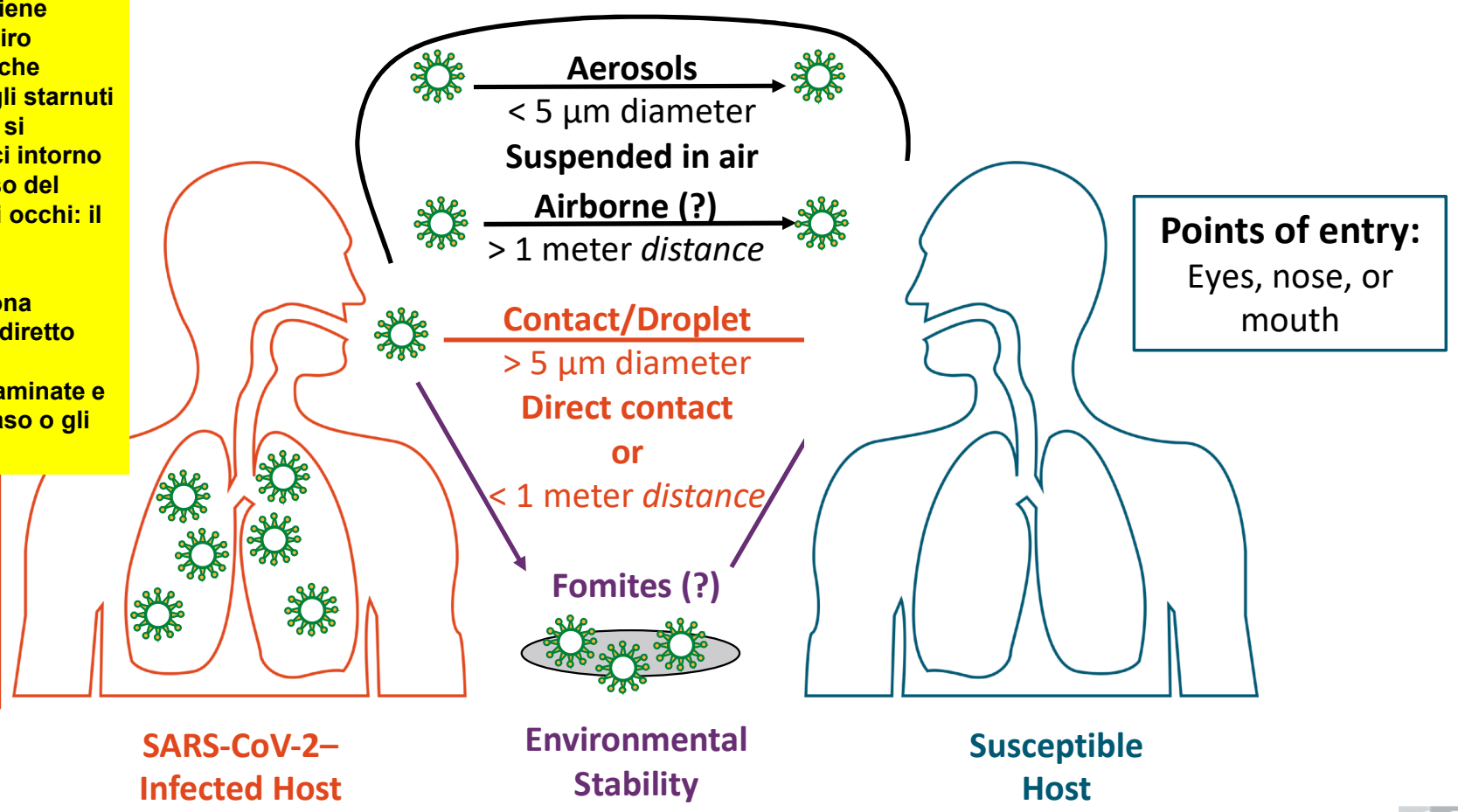
Diffusione per via aerea	Trasmissione attraverso droplets
Germe fluttua nell´aria dopo che una persona parla, tossisce, starnutisce NON è necessario il contatto diretto con la persona infetta perché qualcun altro si ammali	Goccioline respiratorie che si emettono starnutendo, tossendo o parlando, dette goccioline di Flügge
Tubercolosi, Morbillo, Varicella	Ebola



Proposed Routes of SARS-CoV-2 Transmission

La trasmissione interumana avviene attraverso le goccioline del respiro (droplets) della persona infetta, che vengono espulse con la tosse, gli starnuti o la normale respirazione, e che si depositano su oggetti e superfici intorno alla persona. Le porte di ingresso del virus sono la bocca, il naso e gli occhi: il contagio avviene
inalando attraverso il respiro le goccioline emesse da una persona malata, oppure tramite contatto diretto personale,
oppure toccando superfici contaminate e quindi toccandosi la bocca, il naso o gli occhi con le mani.

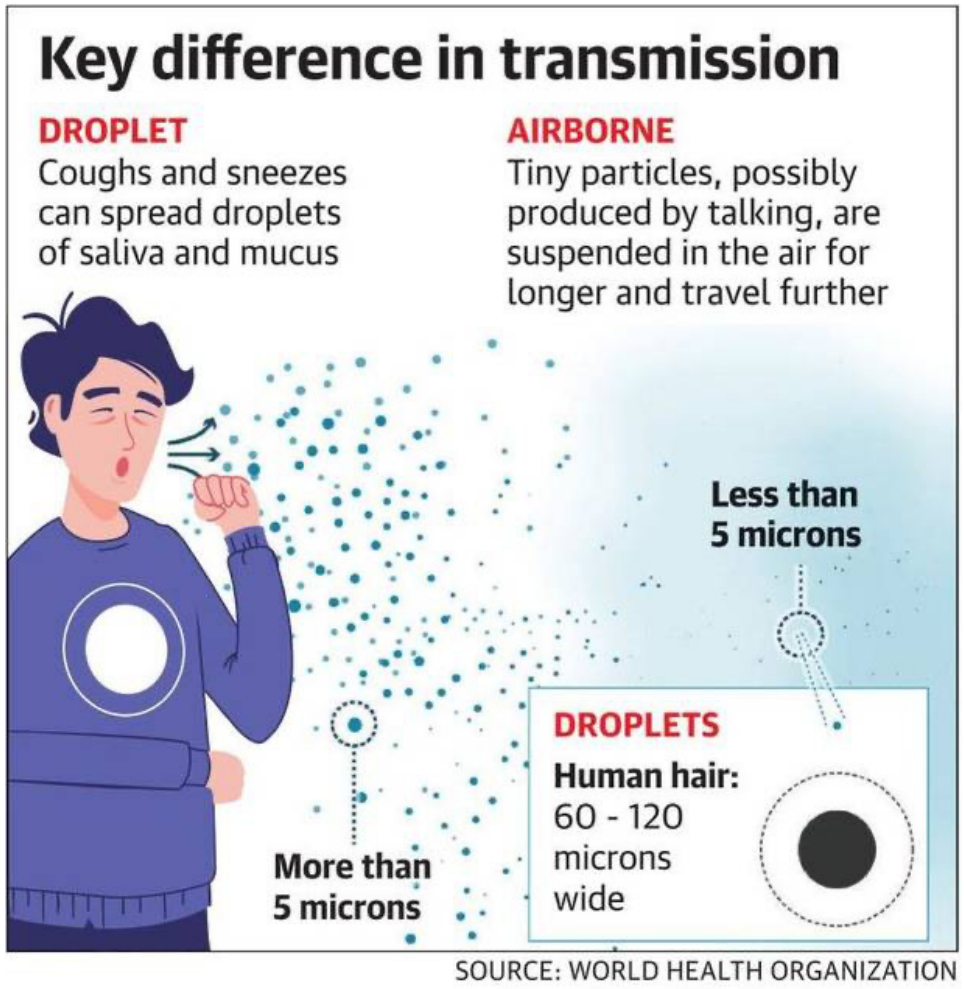
Urine/feces:
RNA found in both; live virus cultivated from few specimens



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

Slide credit: clinicaloptions.com

IRC-19 Italian response to COVID-19



Recentemente l'OMS ha pubblicato un documento nel quale sottolinea come la **trasmissione airborne** non possa essere esclusa in ambienti affollati e inadeguatamente ventilati in cui sono presenti persone infette, come chiese, ristoranti e locali notturni in cui le persone gridano, parlano o cantano.
La possibilità di trasmissione del virus tramite aerosol è supportata da un numero sempre maggiore di evidenze scientifiche. Gli US Centers for Disease Control and Prevention (CDC), nelle loro linee guida recentemente aggiornate, riconoscono che in determinate condizioni le persone con COVID-19 possono infettare altre persone che si **trovano a più di 6 piedi (oltre 180 centimetri) di distanza**, soprattutto se ci si trova all'interno di **spazi chiusi** con ventilazione inadeguata, e la persona infetta respira pesantemente, oppure canta o svolge attività fisica

Hallmarks of COVID-19 Clinical Picture

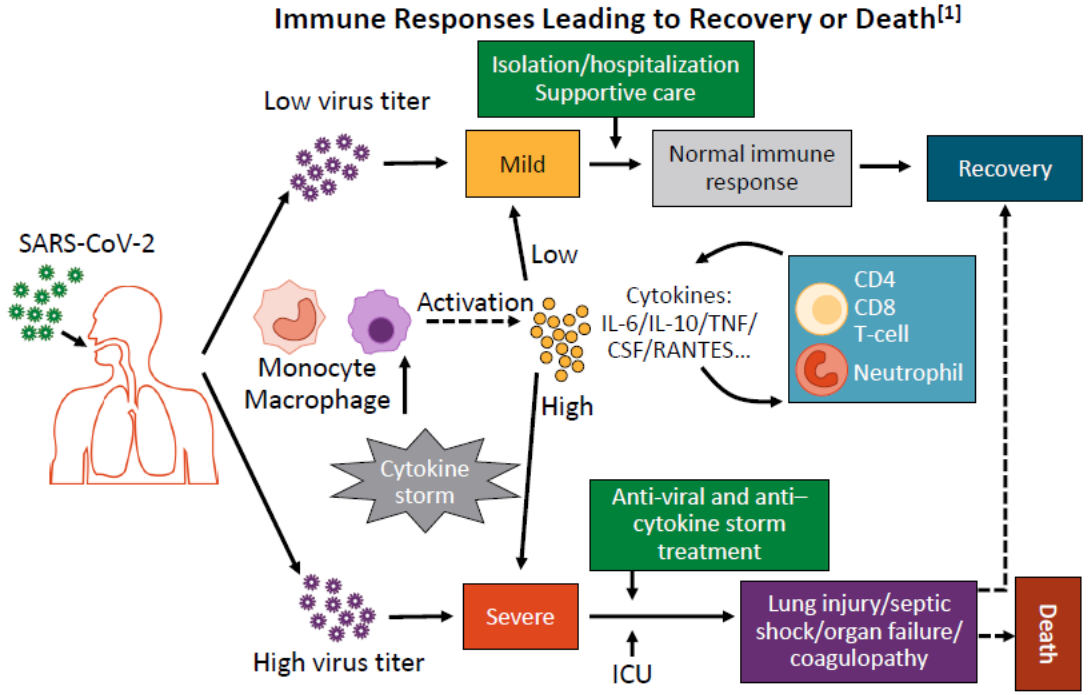
1.Cytokine Storm: **Dysregulated and excessive immune responses** may lead to significant systemic damage. Mononuclear cells such as neutrophils and monocytes in the patient's lung tissues and peripheral blood produce elevated levels of pro-inflammatory cytokines such **as interleukin-6 (IL-6), interleukin-1 and tumor necrosis factors**, **directly related to the severity and mortality of the disease**

2.Hypoxemic Respiratory Failure: Direct cytopathic effects of the virus and virus-induced decrease in surfactant levels causing atelectasis are some of the unique pathologic findings seen in patients with COVID-19. **Hypoxemia is the hallmark of the pulmonary derangement of the disease**, with no signs of respiratory distress **("silent or happy hypoxemia")**

3.COVID-19-related Hypercoagulability: A distinct **prothrombotic state** as opposed to a consumptive coagulopathy has been described in COVID-19 patients, secondary to a **markedly increased levels of fibrin and fibrinogen**. **This mechanism is synergistic with the cytokine storm and the virus-induced endothelial dysfunction**.
Consequently, **serum levels of D-dimer are a strong prognostic factor of poor outcomes**

1.Cytokine Storm

Immune Response to SARS-CoV-2



Adequate immune responses[2]

- Timely innate/adaptive responses
- Quick type 1 IFN response
- Activation of efficient antiviral response (clearance by macrophages)
- Activation of Th1 cells and B-cells for production of neutralizing antibodies

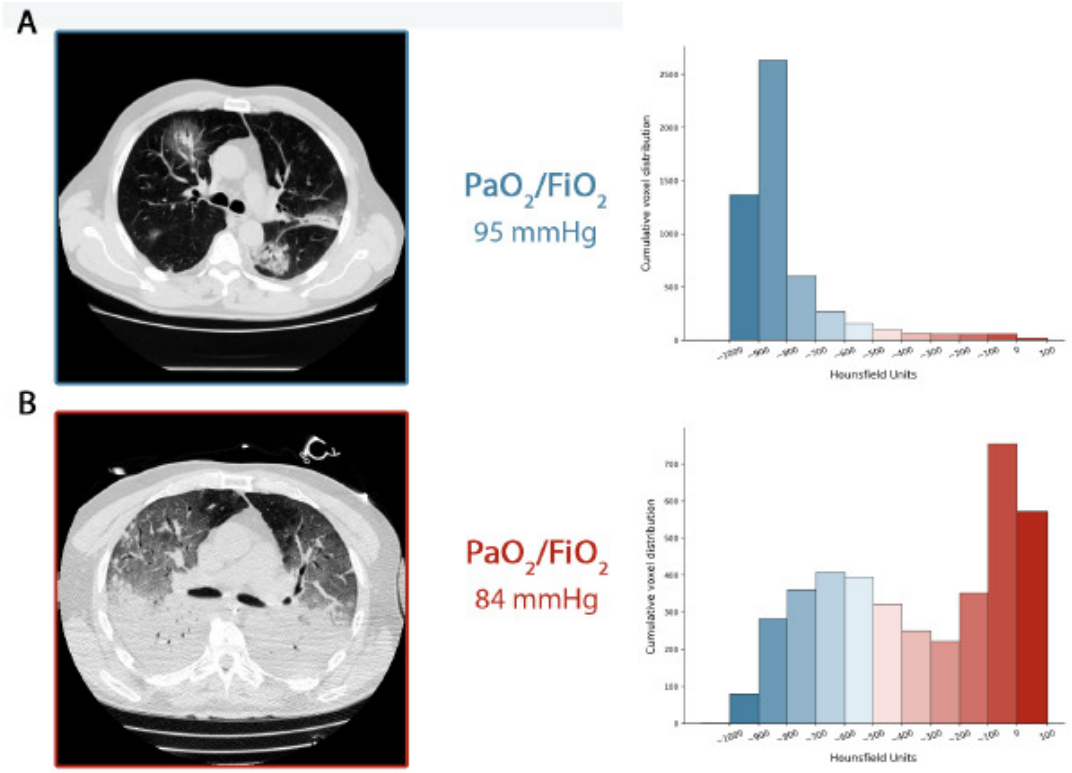
Inadequate immune responses[2]

- Delayed/limited type 1 IFN
- Endothelial cell death
- Epithelial/endothelial leakage
- Overactivation/exhaustion T-cells and NK cells
- Accumulation of activated macrophages → cytokine storm

1. Wang. 2020; J Leukoc Biol. 2020;[Epub]. 2. Sokolowska. EAACI. 2020[Epub].

Slide credit: clinicaloptions.com

2.Hypoxiemic Respiratory Failure



Panel A: CT scan acquired during spontaneous breathing. The cumulative distribution of the CT number is shifted to the left (well aerated compartments), being the 0 to -100 HU compartment, the nonaerated tissue virtually 0. Indeed, the total lung tissue weight was 1108 g, **7.8% of which was not aerated** and the gas volume was 4228 ml. Patient receiving oxygen with Venturi mask, **inspired oxygen fraction of 0.8**. (**TYPE L**)

Panel B: CT acquired during mechanical ventilation at end-expiratory pressure at 5 cmH2O of PEEP. The cumulative distribution of the CT scan is shifted to the right (non-aerated compartments) while the left compartments are greatly reduced. Indeed, the total lung tissue weight was 2744 g, **54% of which was not aerated** and the gas volume was 1360 ml. The patient was ventilated in Volume Controlled mode, 7.8 ml/kg of tidal volume, respiratory rate of 20 breaths per minute, **inspired oxygen fraction of 0.7**. (**TYPE H**)

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EDITORIAL Open Access

COVID-19: a hypothesis regarding the ventilation-perfusion mismatch

Mario G. Santamarina[1,2], Dominique Boisier[3], Roberto Contreras[4], Martiniano Baque[5], Mariano Volpacchio[6] and Ignacio Beddings[7*]

We believe that a severe V/Q mismatch underlies the pathophysiology of moderate to severe COVID-19 cases, in which downregulation of ACE2 secondary to viral endocytosis plays a key role.

Il rapporto **ventilazione/perfusione** (V/Q) rappresenta il principale determinante della concentrazione di ossigeno nel sangue che esce dalla circolazione **polmonare** per raggiungere i tessuti attraverso il circolo sistemico.

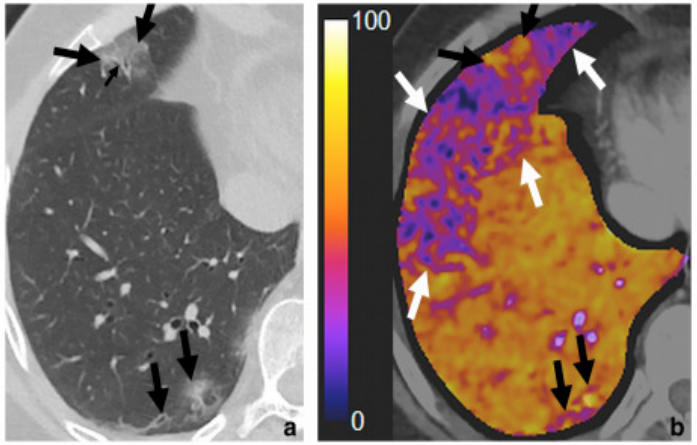

Fig. 1 a, b Slight hypoperfusion in the well-aerated lung, hyperemia, and small zones of hypoperfusion in the areas of injured lung. Fifty-nine-year-old male patient, RT-PCR-confirmed COVID-19, 11 days since symptom onset, without hypoxemia, (PaO_2/FiO_2) 538, D-dimer 340 ng/mL. There are isolated foci of ground-glass opacities associated with septal thickening, with a predominantly subpleural distribution, which correlate with areas of hyperemia (middle lobe) and small zones of hypoperfusion (lower right lobe) in subtraction CT iodine maps (large black arrows). There is an evident area of hypoperfusion in the middle lobe and lower right lobe (white arrows) that correlates with the apparently normal lung parenchyma in conventional chest CT images. The conventional CT image also shows pulmonary arterial vascular dilatation in the periphery of the ground-glass opacity in the middle lobe (small black arrow). These slight perfusion abnormalities do not impact the PaFi ratio. The ground-glass opacity in the lower right lobe shows slight peripheral hypoperfusion, probably due to compensatory vasoconstriction, an expected regulatory mechanism when vasoplegia is not fully established

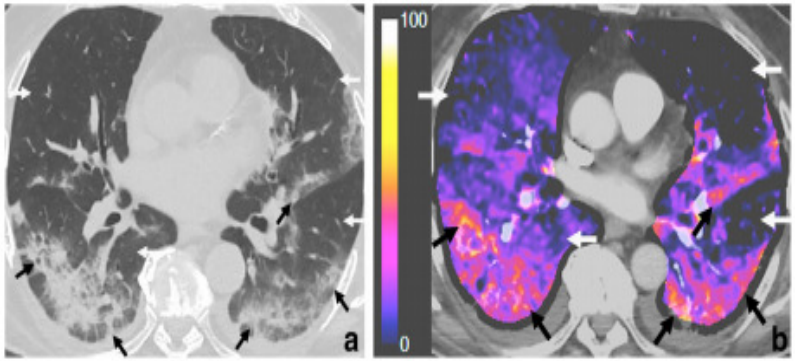

Fig. 2 a, b Prominent hypoperfusion in the well-aerated lung and hyperperfusion in areas of injured lung. Seventy-eight-year-old male patient, RT-PCR-confirmed COVID-19, 10 days since symptom onset, with hypoxemia, (PaO_2/FiO_2) 206, D-dimer 1600 ng/mL progressively increasing. There are extensive foci of consolidation and ground-glass opacities, associated with septal thickening, with a predominantly posterior and subpleural bilateral distribution, which correlate with the areas of hyperemia and iodine pooling in subtraction CT iodine maps (black arrows). There are areas of markedly decreased perfusion in both lungs, which correlate with the apparently healthy lung parenchyma in conventional chest CT images (white arrows). Bilateral pleural effusion. This could be explained by an increased blockage of ACE2 receptors in the lung endothelium, leading to increased local levels of angiotensin II, which leads to vasoconstriction and ventilation/perfusion mismatch. This patient was managed with invasive mechanical ventilation, with highly compliant lung parenchyma, in accordance with the type 1 or L phenotype described by Gattinoni et al.

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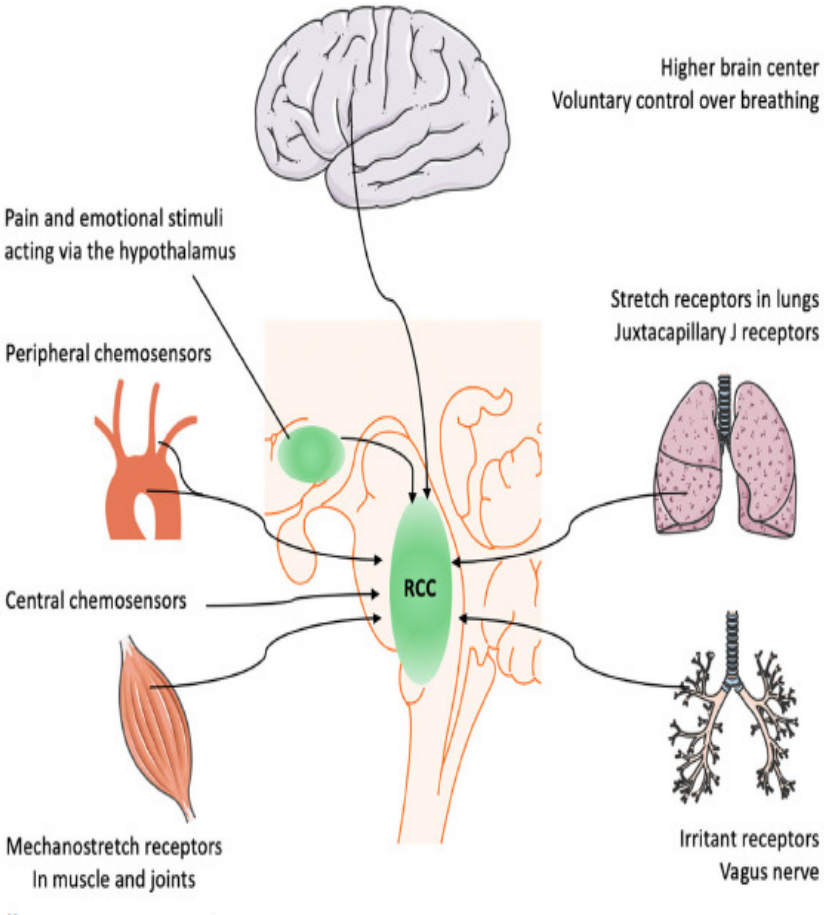
IRC-19 Italian response to COVID-19



Dhont *et al. Respiratory Research* (2020) 21:198
https://doi.org/10.1186/s12931-020-01462-5

Respiratory Research

REVIEW Open Access

The pathophysiology of 'happy' hypoxemia in COVID-19

Sebastiaan Dhont[1*], Eric Derom[1,2], Eva Van Braeckel[1,2], Pieter Depuydt[1,3] and Bart N. Lambrecht[1,2,4]

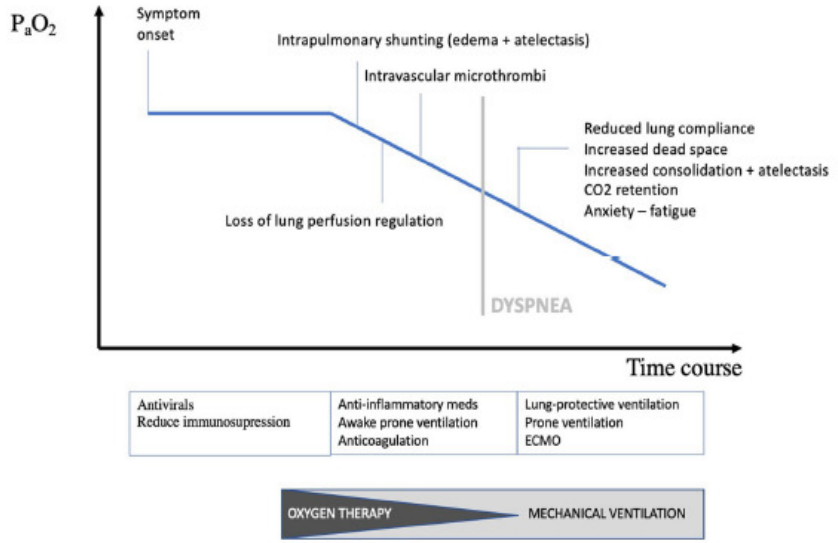


Fig. 2 Mechanisms of hypoxemia in COVID-19

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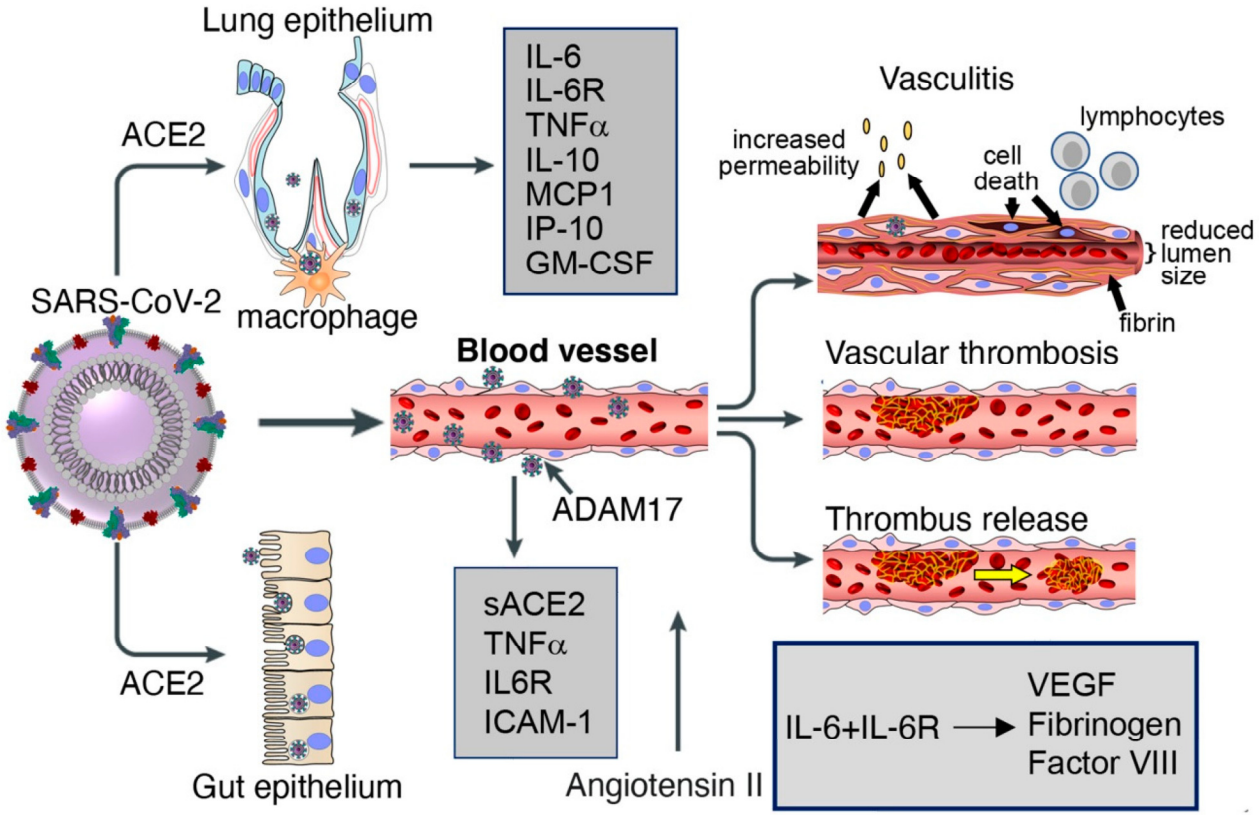
3. COVID-19-related Hypercoagulability

Stato protombrotico sia dovuto al virus + tempesta citochinica



IRC-19 Italian response to COVID-19

Angiogenesis
https://doi.org/10.1007/s10456-020-09753-7

ORIGINAL PAPER

Microvascular dysfunction in COVID-19: the MYSTIC study

Alexandros Rovas[1] · Irina Osiaevi[1] · Konrad Buscher[1] · Jan Sackarnd[2] · Phil-Robin Tepasse[3] · Manfred Fobker[4] · Joachim Kühn[5] · Stephan Braune[6] · Ulrich Göbel[7] · Gerold Thölking[1,8] · Andreas Gröschel[9] · Hermann Pavenstädt[1] · Hans Vink[10] · Philipp Kümpers[1]

Received: 16 September 2020 / Accepted: 28 September 2020

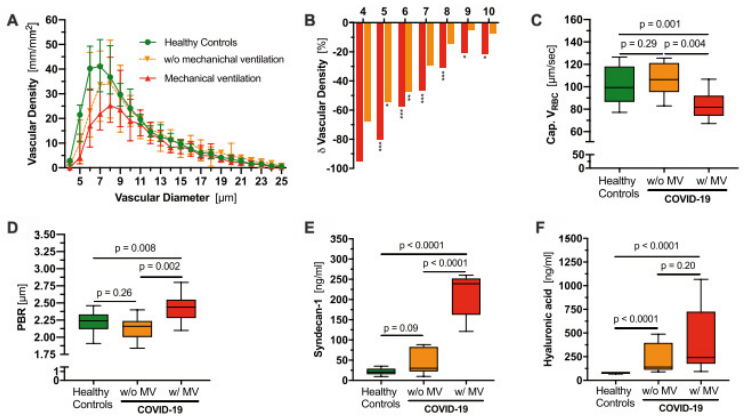


Fig. 1 Endothelial glycocalyx dimensions in vivo and in vitro and capillary density in COVID-19 patients with (w/) and without (w/o) mechanical ventilation (MV) and healthy controls.**a** Median and IQR values of vascular density of healthy controls and COVID-19 patients based on the diameter class from 4 to 25 µm. **b** Bar charts showing the percentage of loss of vascular density in COVID-19 patients with (red) and without (orange) mechanical ventilation compared to healthy controls (diameter class from 4 to 10 µm). $*q < 0.05$, $**q < 0.01$, $***q < 0.001$ Boxplots of **c** of capillary V_{RBC}, **d** PBR values, and endothelial glycocalyx constituents **e** syndecan-1 and **f** hyaluronic acid of healthy controls (green) and COVID-19 patients with (red) or without (orange) mechanical ventilation (MV) $*p < 0.05$, $**p < 0.01$, $***p < 0.001$

"Our data **clearly show severe alterations of the microcirculation and the endothelial glycocalyx in patients with COVID-19**. Future therapeutic approaches **should consider the importance of systemic vascular involvement in COVID-19**"

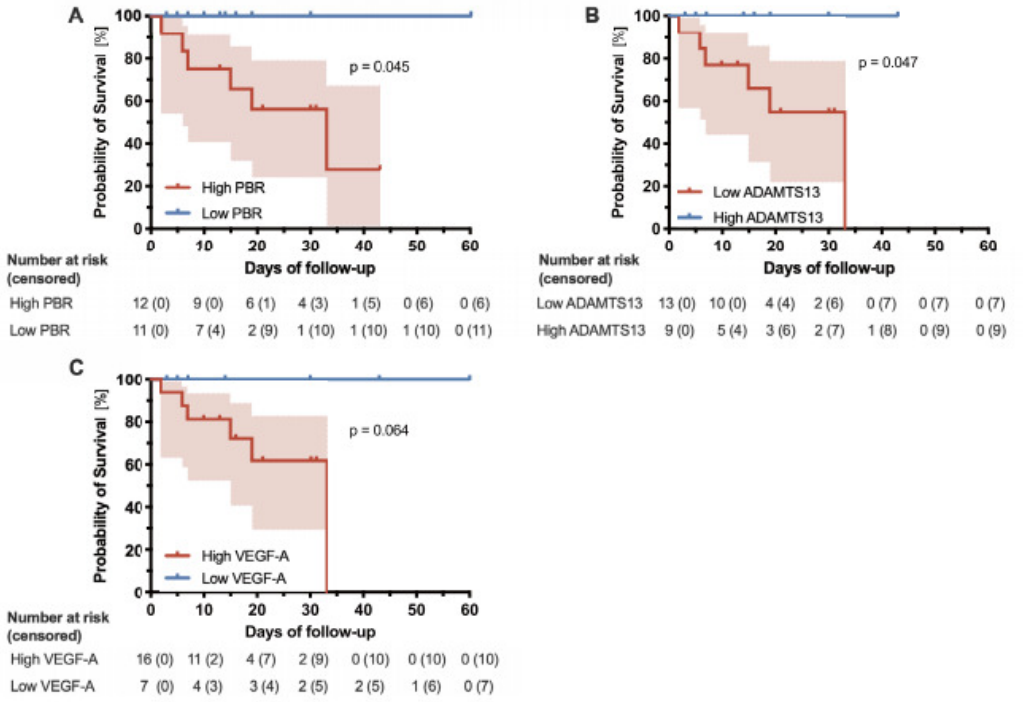


Fig. 3 Survival probability of COVID-19 patients according to different endothelial markers.Kaplan–Meier curves with 95% CIs showing survival probability of COVID-19 patients with **a** low/high PBR, **b** low/high ADAMTS13, and **c** low/high VEGF-A.#ADAMTS13 of one patient could not be measured due to technical reasons

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Decorso clinico

Fase iniziale

- Legame a ACE2 penetrazione all'interno delle cellule dell'ospite replicazione.
- Fase dei sintomi generali, aspecifici.
- Se sistema immunitario dell'ospite riesce a bloccare l'infezione decorso benigno

Seconda fase

- Alterazioni morfo funzionali a livello polmonare
- Effetti diretti + risposta immunitaria dell'ospite
- Polmonite interstiziale sintomatologia respiratoria generalmente limitata nella fase precoce
- Possibile evoluzione a progressiva instabilità clinica con insufficienza respiratoria
- "Ipossiemia silente" bassi valori diossigenazione ematica in assenza di sensazione di dispnea soggettiva

Tempesta citochinica

- Possibile evoluzione a quadro clinico ingravescente dominato da tempesta citochinica e da stato iperinfiammatorio

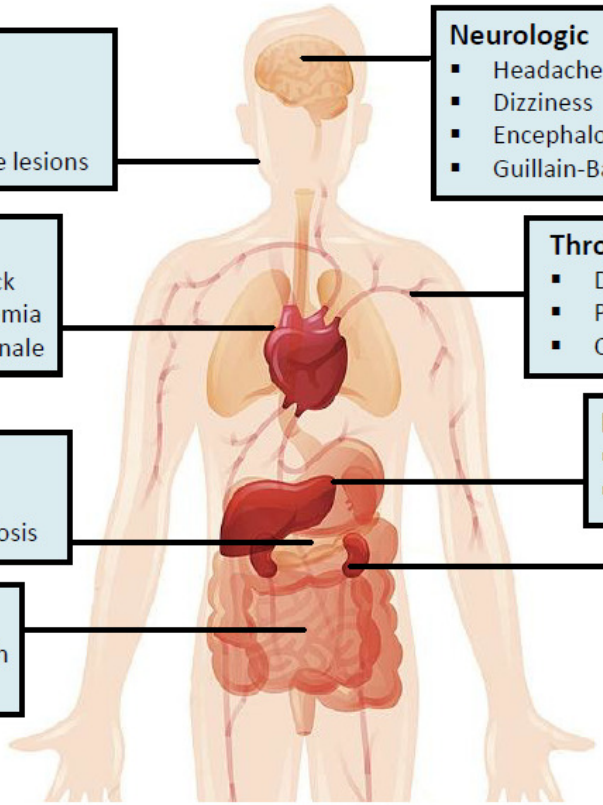
- A livello polmonare
  - quadri di vasculopatia arteriosa e venosa con trombizzazione dei piccoli vasi ed evoluzione verso lesioni polmonari gravi e, talvolta, permanenti (fibrosi polmonare).

ARDS

Alterazione progressiva di parametri:

- infiammatori come PCR, ferritina, citochine pro-infiammatorie (IL2, IL6, IL7, L10, GSCF, IP10, MCP1, MIP1A e TNFα)
- Parametri coagulativi come aumentati livelli dei prodotti di degradazione della fibrina, il D-dimero, consumo di fattori della coagulazione, trombocitopenia.

Extrapulmonary Manifestations



Dermatologic
- Petechaie
- Livedo reticularis
- Erythematous rash
- Urticaria
- Vesicles
- Pernio-like lesions

Neurologic
- Headaches
- Dizziness
- Encephalopathy
- Guillain-Barré
- Ageusia
- Myalgia
- Anosmia
- Stroke

Cardiac
- Takotsubo cardiomyopathy
- Myocardial injury/myocarditis
- Cardiac arrhythmias
- Cardiogenic shock
- Myocardial ischemia
- Acute cor pulmonale

Thromboembolism
- Deep vein thrombosis
- Pulmonary embolism
- Catheter-related thrombosis

Endocrine
- Hyperglycemia
- Diabetic ketoacidosis

Hepatic
- Elevated ALT/AST
- Elevated bilirubin

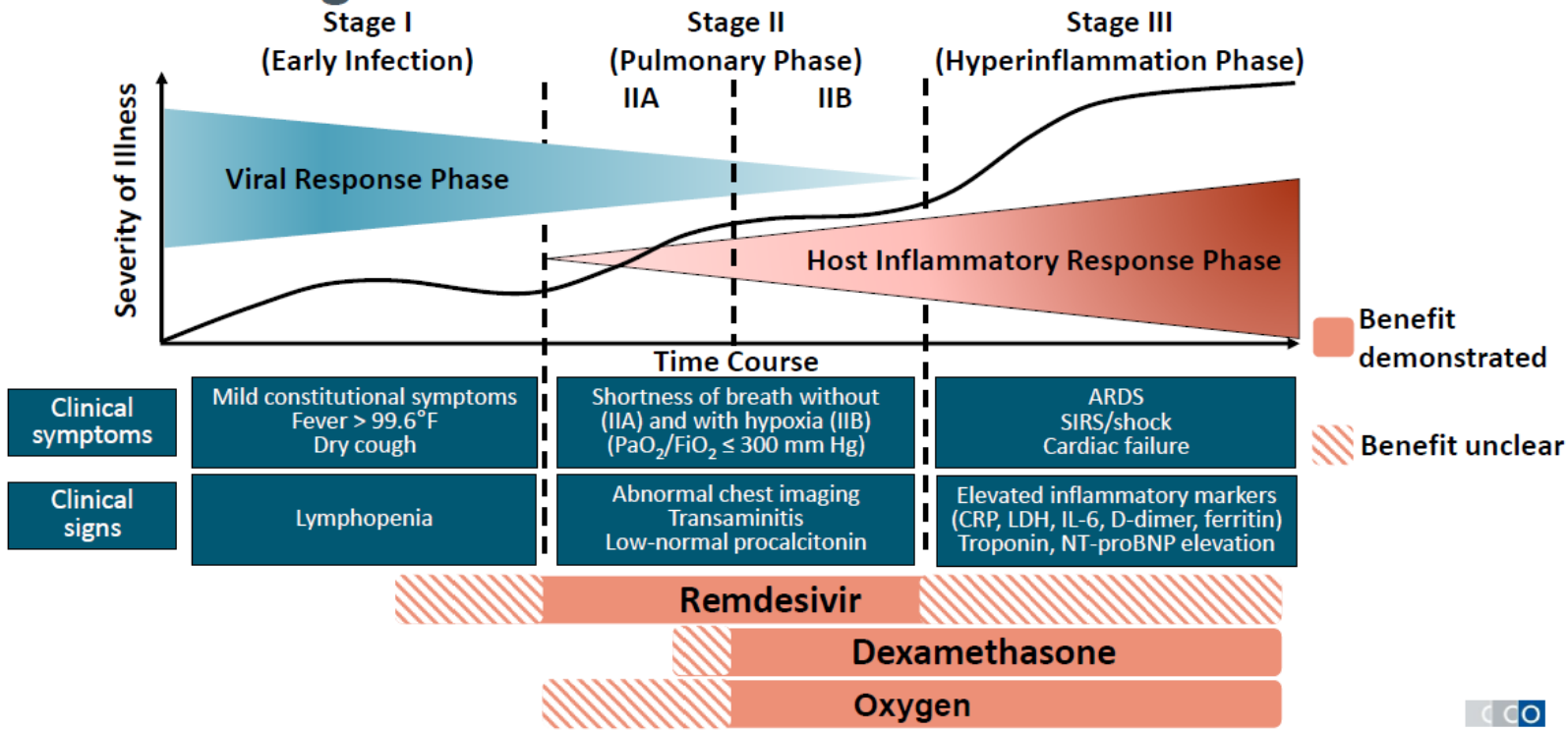
Gastrointestinal
- Diarrhea
- Nausea/vomiting
- Abdominal pain
- Anorexia

Renal
- Acute kidney injury
- Proteinuria
- Hematuria

Gupta. Nat Med. 2020;26:1017.

Slide credit: clinicaloptions.com

COVID-19 Therapies Predicted to Provide Benefit at Different Stages



Siddiqi. J Heart Lung Transplant. 2020;39:405.

Slide credit: clinicaloptions.com

Sintomi e segni di malattia

SINTOMI	%
Febbre *4-12 gg* (Tc > 38°C)	**44-94%**
Tosse *19 gg*	**68-93%**
Anosmia e/o Ageusia	79%
Sintomi delle alte vie respiratorie (mal di gola, rinorrea, congestione nasale o dei seni paranasali)	5-61%
Dispnea *13 gg*	**11-40%**
Astenia	23-38%
Mialgie	11-15%
Cefalea	8-14%
Confusione	9%
Sintomi GI (nausea, vomito, diarrea)	3-17%

Il 20% dei casi è asintomatico

L´importanza della misurazione dei parametri vitali

PARAMETRI VITALI

1. Pressione arteriosa – PA
2. Frequenza cardiaca – FC
3. Saturazione periferica - SpO2 %
4. Frequenza respiratoria – FR
5. Stato di coscienza - GCS

SEGNALI DI ALLARME

- Tachipnea (FR> 22 atti/min)
- Desaturazione
  - SpO2 < 94%
  - Ipossiema all'EGA
- Grave alterazione dello stato di coscienza

CAVE!

I pazienti COVID non "sentono" la dispnea

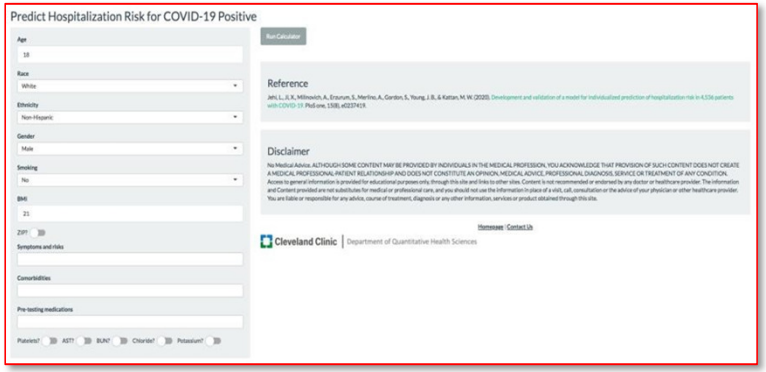
Fondamentale la frequenza respiratoria!

Fattori di rischio (per malattia severa)

- Sesso M
- Età > 60
- Ipertensione arteriosa
- Obesità BMI > 30
- Diabete
- Malattie cardiovascolari, cerebrovascolari
- Malattie degenerative neuro-muscolari
- BPCO
- Insufficienza renale
- Neoplasia maligna attiva
- Latenza tra inizio sintomi e prima valutazione medica

CRITERI DI SEVERITÁ

- Ospedalizzazione
- Trasferimento in TI
- IOT o ventilazione meccanica
- Mortalità aumentata



Cleveland Clinic: Studio su ca. 5000 Pz. per stimare il rischio di ospedalizzazione

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Caratteristiche dei pazienti deceduti positivi all'infezione da SARS-CoV-2 in Italia

Dati al 16 dicembre 2020

2. Caratteristiche demografiche dei deceduti

L'età media dei pazienti deceduti e positivi a SARS-CoV-2 è 80 anni (mediana 82, range 0-109, Range InterQuartile - IQR 74-88). Le donne sono 25.185 (42,4%). La figura 1 mostra che l'età mediana dei pazienti deceduti positivi a SARS-CoV-2 è più alta di oltre 30 anni rispetto a quella dei pazienti che hanno contratto l'infezione (età mediane: pazienti deceduti 82 anni – pazienti con infezione 48 anni). La figura 2 mostra il numero dei decessi per fascia di età. Le donne decedute dopo aver contratto infezione da SARS-CoV-2 hanno un'età più alta rispetto agli uomini (età mediane: donne 85 – uomini 80).

Figura 1. Età mediana deceduti e diagnosticati positivi a SARS-CoV-2

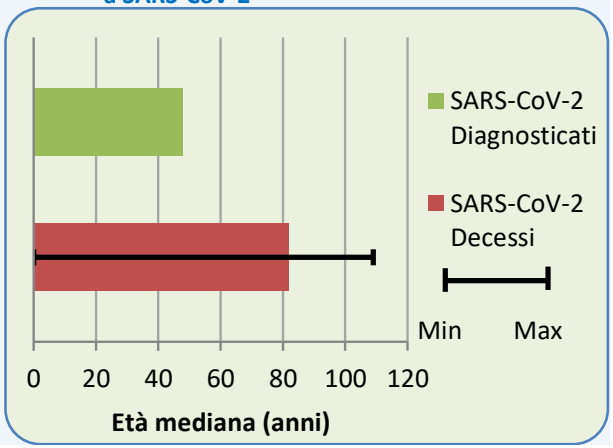


Figura 2. Numero di decessi per fascia di età

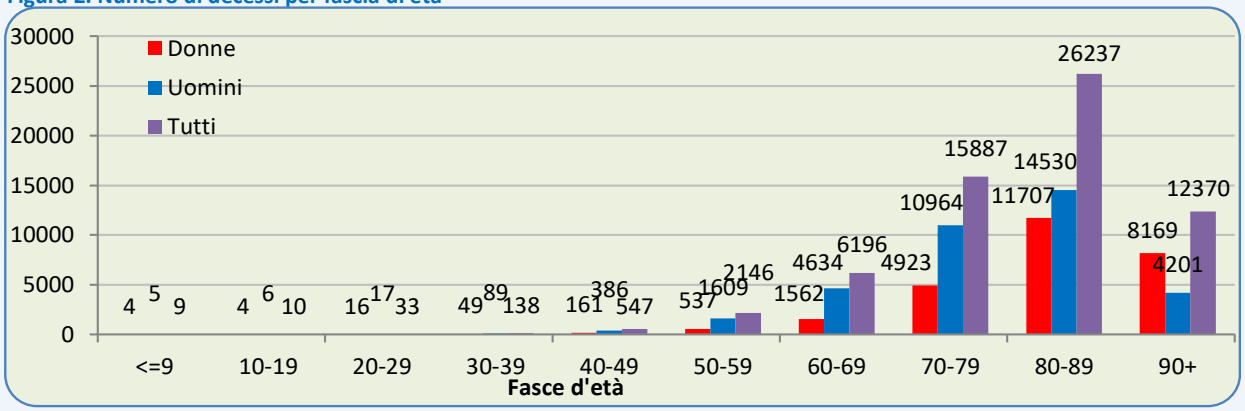
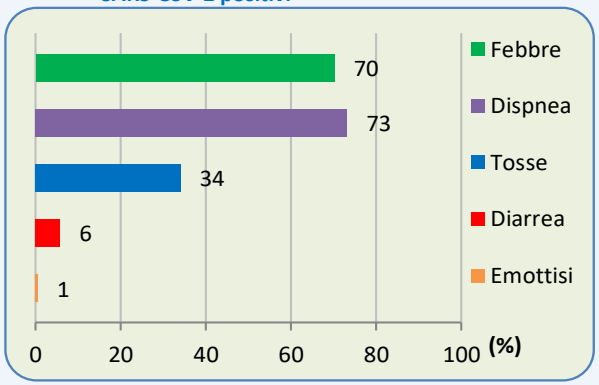


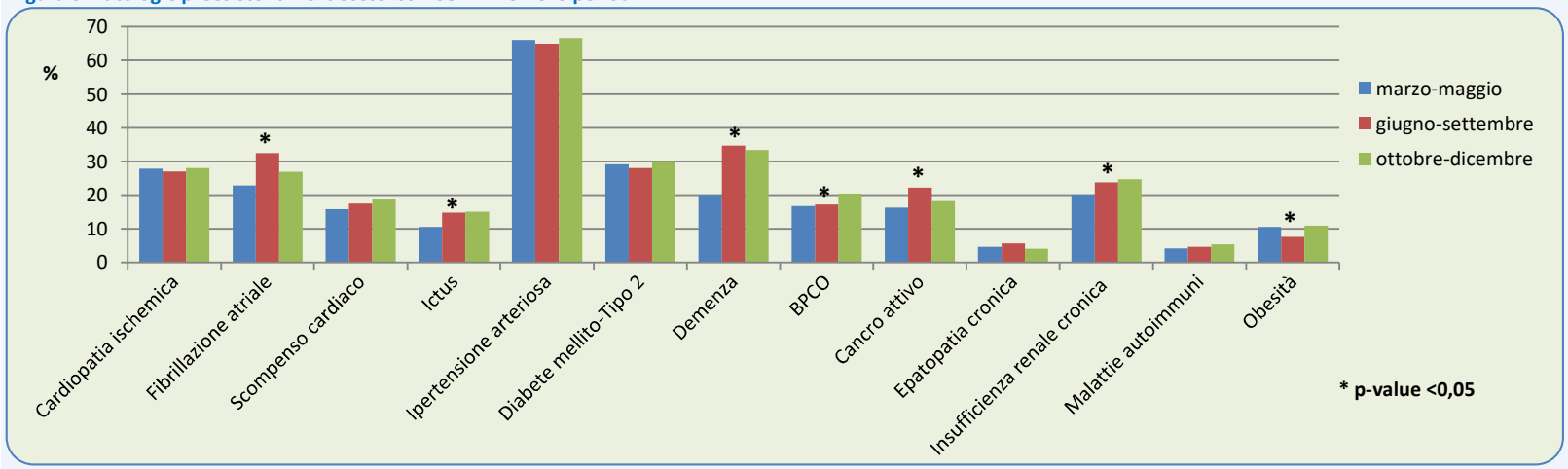
Figura 4. Sintomi più comuni nei pazienti deceduti SARS-CoV-2 positivi



Caratteristiche dei pazienti deceduti positivi all'infezione da SARS-CoV-2 in Italia

Dati al 16 dicembre 2020

Figura 6. Patologie preesistenti nei decessi con COVID-19 nei 3 periodi



Definizione di caso

Caso confermato

Conferma di laboratorio indipendentemente dai segni e dai sintomi clinici

Caso sospetto

Persona con sintomi sospetti +contatto stretto con COVID+ nei 14 giorni precedenti la comparsa di sintomi

Caso probabile

Laboratorio inconcludente + sintomi (o epidemiologia) sospetti

Caso esposto

Individui asintomatici con esposizione nota a COVID-19

Collegamento epidemiologico

< 14 giorni prima dell'insorgenza della malattia

Definizione di contatto stretto

- Chi vive nella stessa casa di un caso di COVID-19
- Una persona che ha avuto un contatto fisico diretto
  - con un caso di COVID-19 (per esempio la stretta di mano)
  - con le secrezioni di un caso di COVID-19
- Contatto diretto (faccia a faccia, ambiente chiuso) con un caso di COVID-19, <2 metri e > 15 minuti
- Un operatore sanitario, o altra persona che fornisce assistenza diretta
- Personale di laboratorio addetto alla manipolazione di campioni di casi COVID-19 senza DPI raccomandati o idonei
- Condivisione di spazi durante un viaggio (treni, aerei)

Diagnosi: test di laboratorio

RT-PCR

- **Tampone Nasofaringeo** (80% sensibilità 3 giorni dopo l'insorgenza dei sintomi)

- **Lavaggio broncoalveolare (BAL)**: dati ancora non conclusivi, suggeriscono un aumento del 5% nella diagnosi

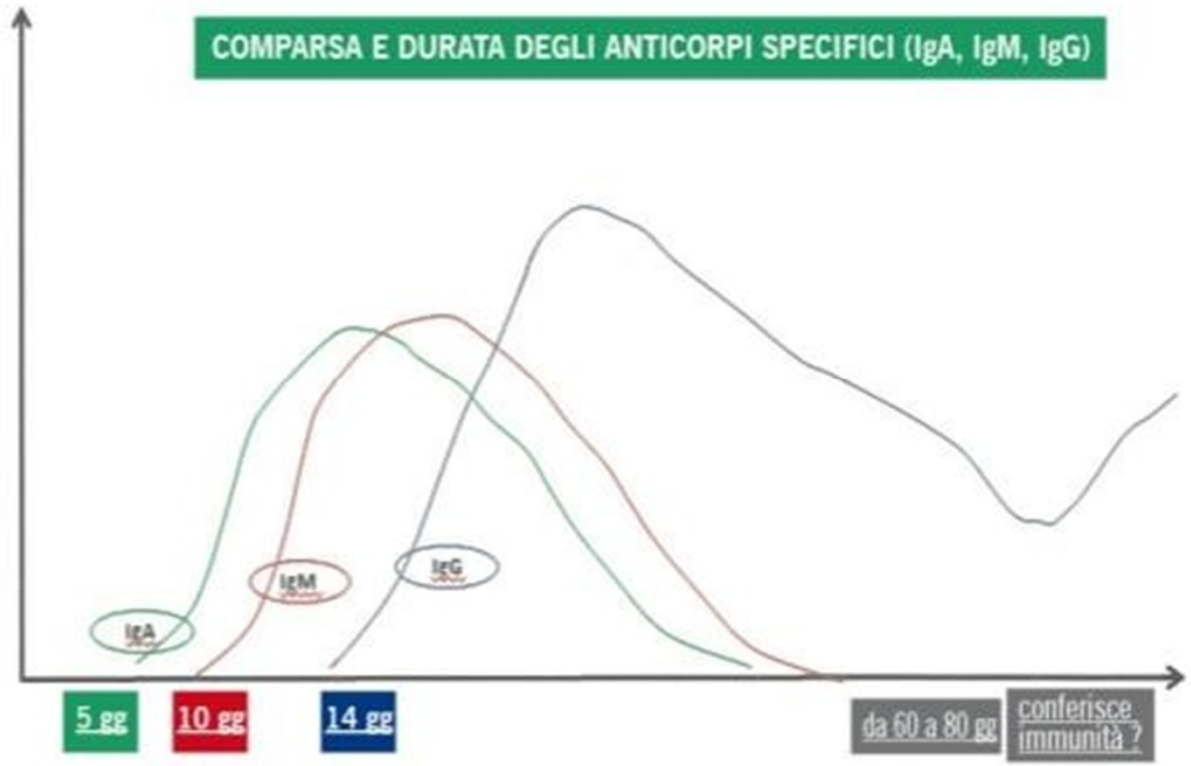
Antigen test ("rapido")

- rapido, point of care, possibili falsi negativi

TEST ANTIGENICO	PROBABILITA' PRE-TEST di infezione da SARS- CoV-2	
	BASSA *	ALTA °
NEGATIVO	INFEZIONE SARS-CoV-2 ESCLUSA / MOLTO IMPROBABILE	INFEZIONE SARS-CoV-2 INCERTA
	Non indicati test ulteriori	Ripetizione test Ag o effettuazione test RT-PCR
POSITIVO	INFEZIONE SARS-CoV-2 INCERTA	INFEZIONE SARS-CoV-2 CONFERMATA/ MOLTO PROBABILE
	Effettuazione test RT-PCR	Non indicati test ulteriori per motivi clinico-epidemiologici

Test sierologici

- Prestazioni e precisione **variabili**
  - IgA: le più precoci
  - IgM: da 5-10 giorni dall'infezione fino a 3 settimane
  - IgG: 14 giorni dopo l'insorgenza dei sintomi; alti titoli in caso di malattia severa



Esami di laboratorio di routine

Leucociti	< 4000 o > 10000/µL	**Lattati**	> 2
Linfociti	< 800/µL	**LDH**	> 250 U/L
Neutrofili	> 8000/µL	**PCR**	> 10 mg/L
PLT	< 150000/µL	**Creatinina**	> 1.5 mg/dL
Troponina	> 99° percentile	**AST/ALT**	> 40 U/L
D-dimero	> 1.5 µg/mL	**Ferritina**	> 1000 ng/mL

Fattori prognostici: Linfopenia, LDH, PCR, PCT, D-dimero, Ferritina, Troponina, IL-6

EGA: pH, P/F, PCo2, Lac

Stage	Characteristics
Asymptomatic or presymptomatic infection	▪ Positive test for SARS-CoV-2 but no symptoms
Mild illness	▪ Varied symptoms (eg, fever, cough, sore throat, malaise, headache, muscle pain) but no shortness of breath, dyspnea, abnormal imaging
Moderate illness	▪ $SpO_2 \geq 94\%$ and lower respiratory disease evidenced by clinical assessment or imaging
Severe illness	▪ $SpO_2 < 94\%$, $PaO_2/FiO_2 < 300$, respiratory rate > 30 breaths/min, or lung infiltrates > 50%
Critical illness	▪ Respiratory failure, septic shock, and/or multiorgan dysfunction

MEWS: Modified Early Warning Score

DATI FISIOLOGICI (indicare un solo valore per ogni fattore)							
Punteggio	3	2	1	0	1	2	3
Frequenza respiratoria (atti/minuto)		< 9		9-14	15-20	21-29	≥ 30
Frequenza cardiaca (battiti/minuto)		≤ 40	41-50	51-100	101-110	111-129	≥ 130
Pressione sistolica (mmHg)	< 70	71-80	81-100	101-199		≥200	
Temperatura corporea (°C)		≤ 35 °C		35.1-38.4		≥ 38.4°C	
Sintomi neurologici				Vigile	Risponde alla voce	Risponde al dolore	Non risponde (GCS < 9)

PUNTEGGIO TOTALE |__|__| legenda MEWS: 0-2 paziente stabile, 3-4 instabile, ≥ 5critico

Saturazione O_2 ____ in Aria ambiente |__| in O_2 terapia |__| _____ Lt/min

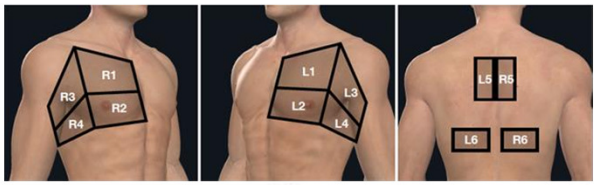
Rapporto PaO_2/FiO_2 _____

DOCTORS WITH AFRICA CUAMM | USAID FROM THE AMERICAN PEOPLE | UPO CRIMEDIM

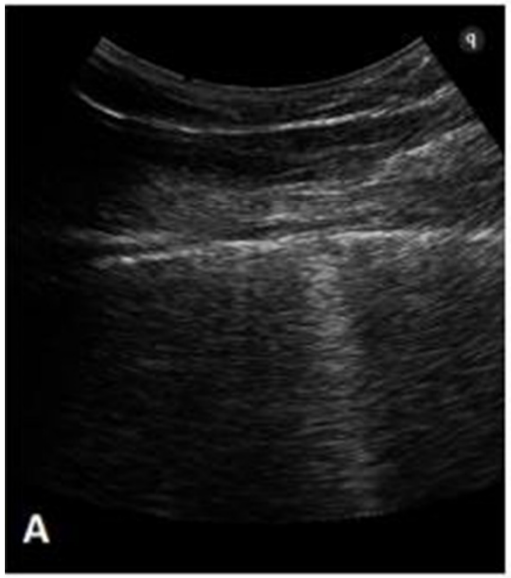
Diagnostica d´immagine

- **Ecografia polmonare**

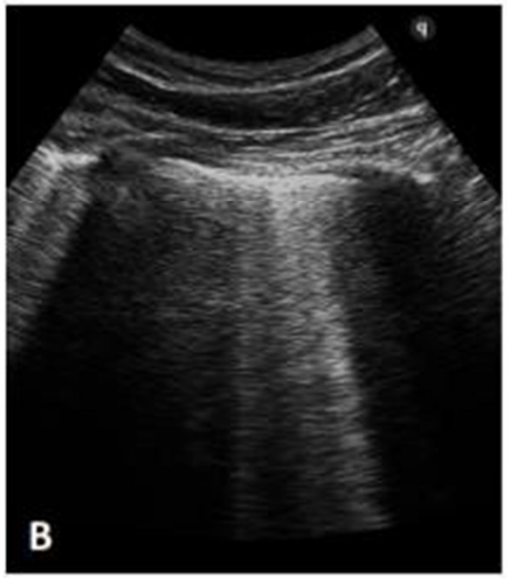
  12 aree da esaminare



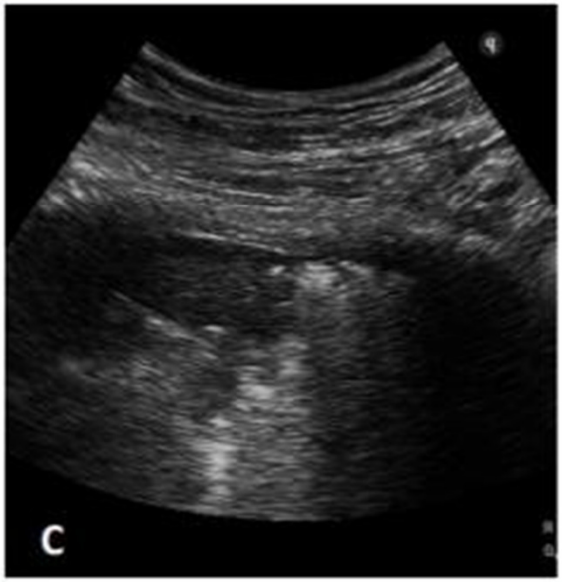
SCAN ME



A. Rare linee B, iniziale coinvolgimento interstiziale



B. Coinvolgimento interstiziale con linee B confluenti e iniziali addensamenti subpleurici



C. Multipli addensamenti subpleurici

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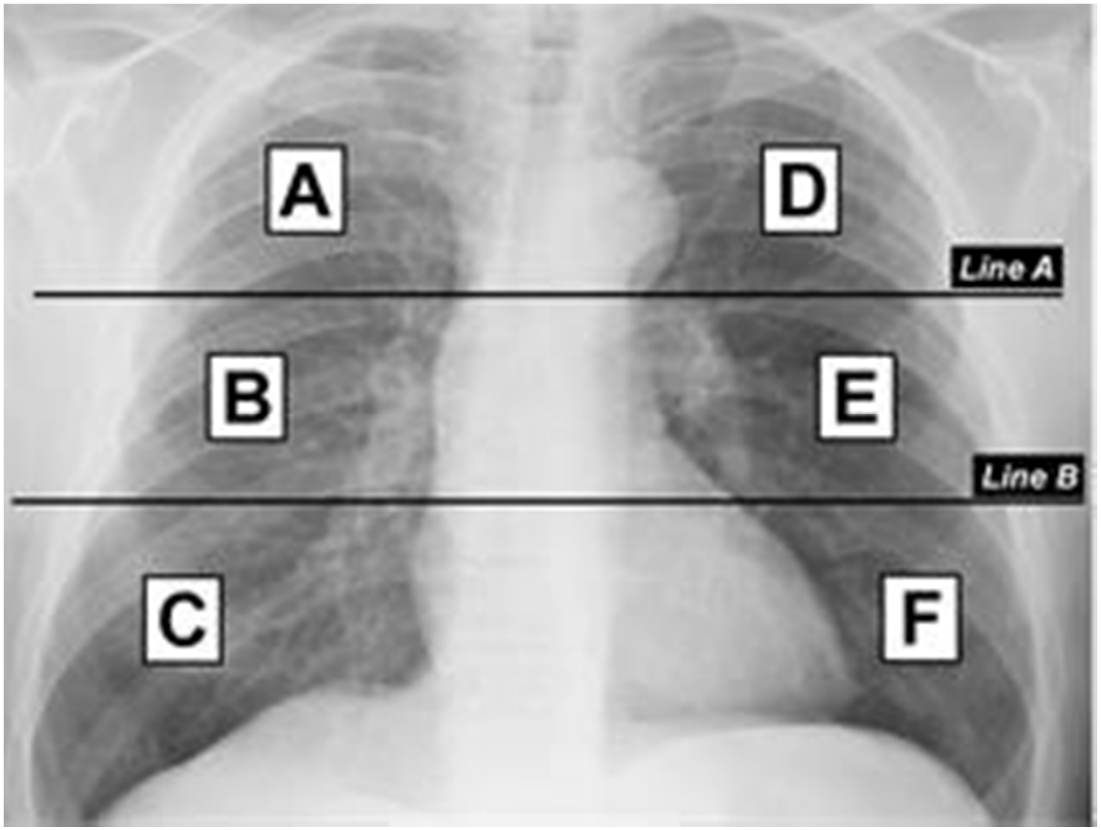
Diagnostica d´immagine

- **RX torace**
  - Valutazione del *grado di impegno parenchimale*
  - **BRIXIA score** valuta semiquantitativamente il grado di impegno parenchimale in ogni area (con punteggio totale variabile da 0 a 18):
    - 0 – nessuna alterazione
    - 1 – infiltrati interstiziali
    - 2 – infiltrati interstiziali e alveolari
    - (predominanza interstiziale)
    - 3 – infiltrati interstiziali e alveolari
    - (predominanza alveolare)



Diagnostica d' immagine: TC torace con studio ad alta risoluzione: HRTC

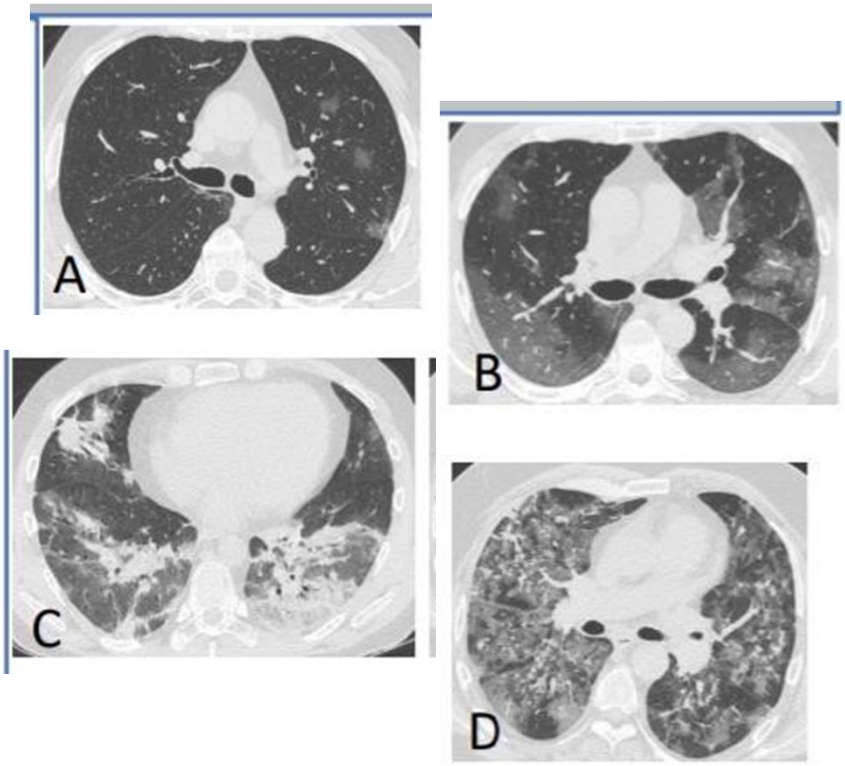
Gold standard

Fase pre-sintomatica (A): piccole aree di iperdensità con aspetto "ground glass", spesso unilaterale, pochi segmenti coinvolti

Prima settimana (B): lesioni bilaterali, più estese, più segmenti coinvolti, tipico pattern GG a distribuzione prevalentemente periferica/posteriore. Rari VPL e linfadenopatia

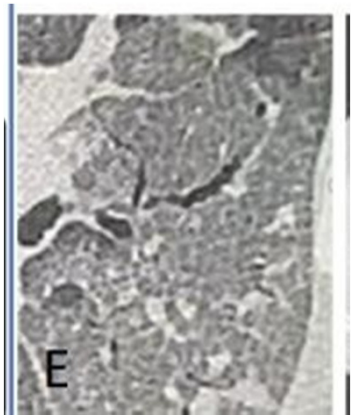
Peggioramento (C): aumento del pattern GG e comparsa di consolidamento parenchimale.

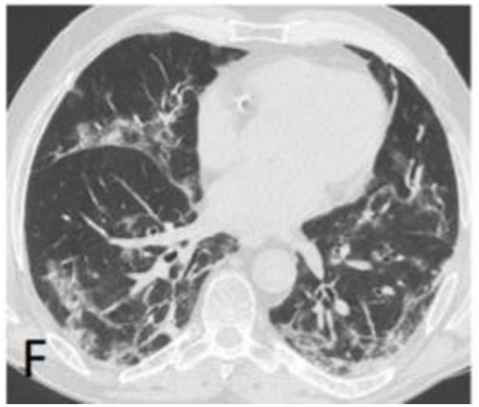
Possibile anche evoluzione a pattern ARDS **(D)**



Diagnostica d' immagine: TC torace con studio ad alta risoluzione: HRTC

Evoluzione: casi non severi mostrano riduzione delle aree GG **(E)**. Ispessimento dei setti interlobulari. Nelle aree di consolidamento, sono le porzioni più periferiche che rimangono consolidate più a lungo → "old spiderweb" **(F)**





SCAN ME

IRC-19 Italian response to COVID-19

- Antiviral therapy
- Oxygen therapy
- Anti-inflammatory therapy
- Anti-thrombotic therapy
- Antimicrobial therapy
- Plasma/monoclonal antibodies therapy

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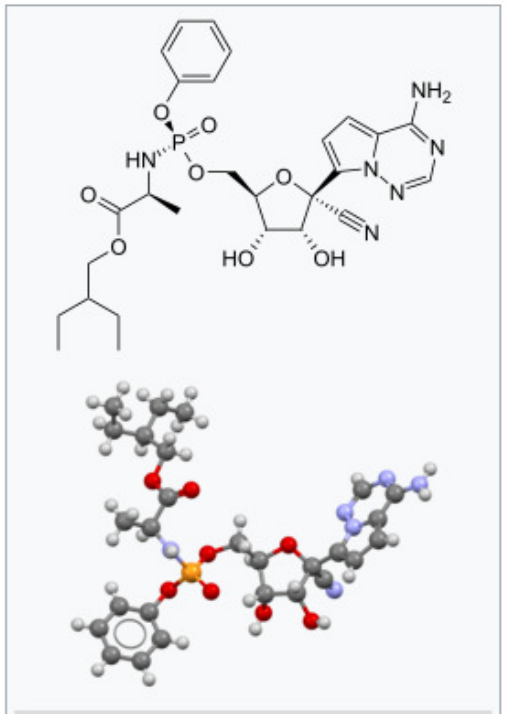
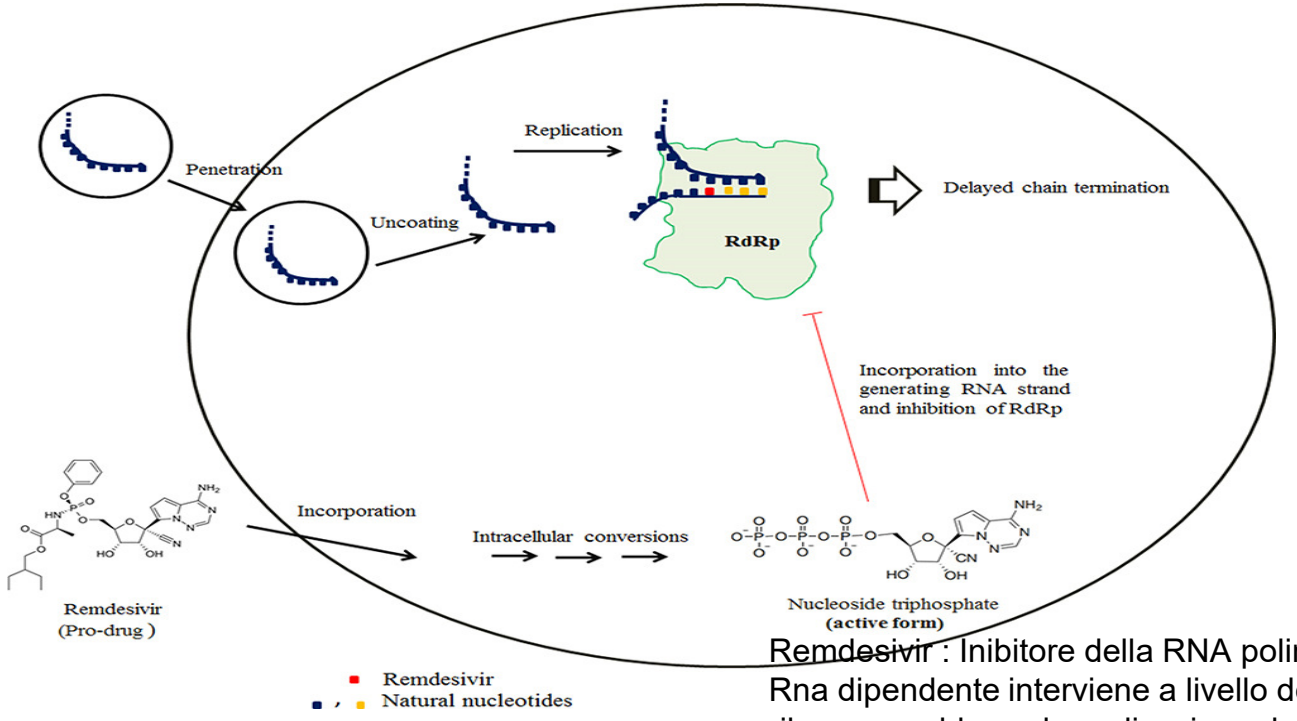
COVID-19 Principles of Treatment

Remdesivir



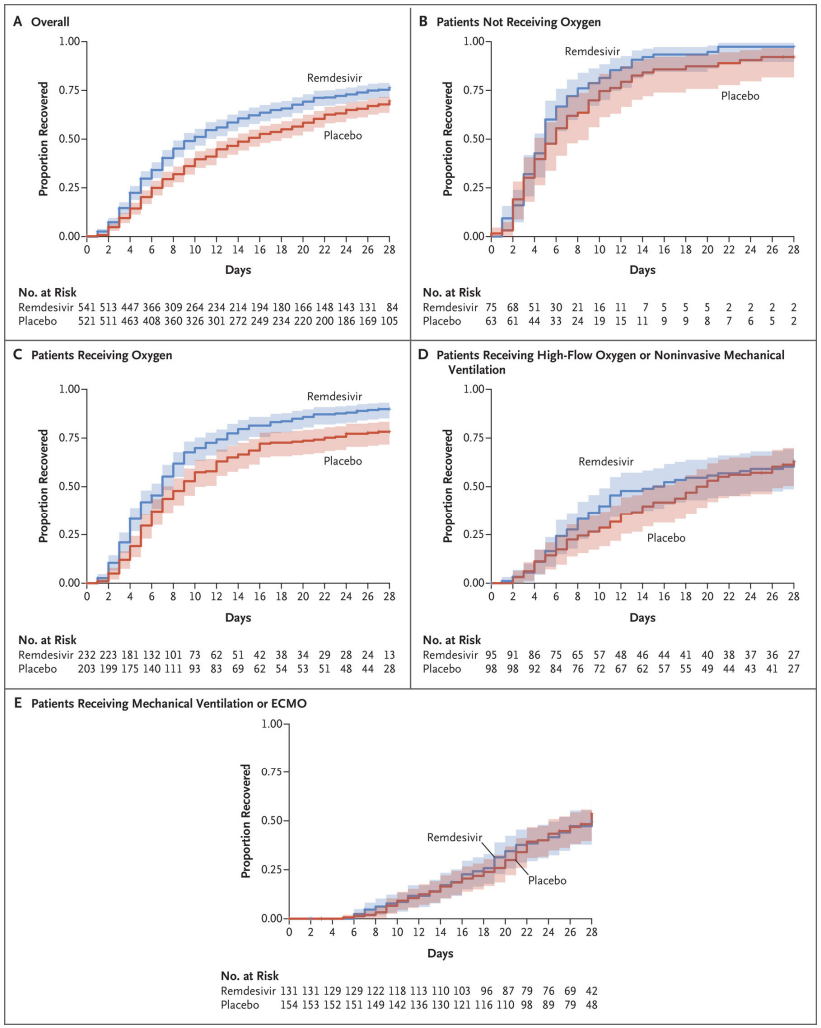
Remdesivir is a prodrug that is intended to allow intracellular delivery of GS-441524 monophosphate and subsequent biotransformation into GS-441524 triphosphate, a ribonucleotide analogue **inhibitor of viral RNA polymerase**



Remdesivir : Inibitore della RNA polimerasi Rna dipendente interviene a livello del ribosoma e blocca la replicazione del virus

chain terminator=terminatore di catena

IRC-19 Italian response to COVID-19

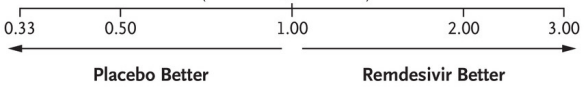


ORIGINAL ARTICLE

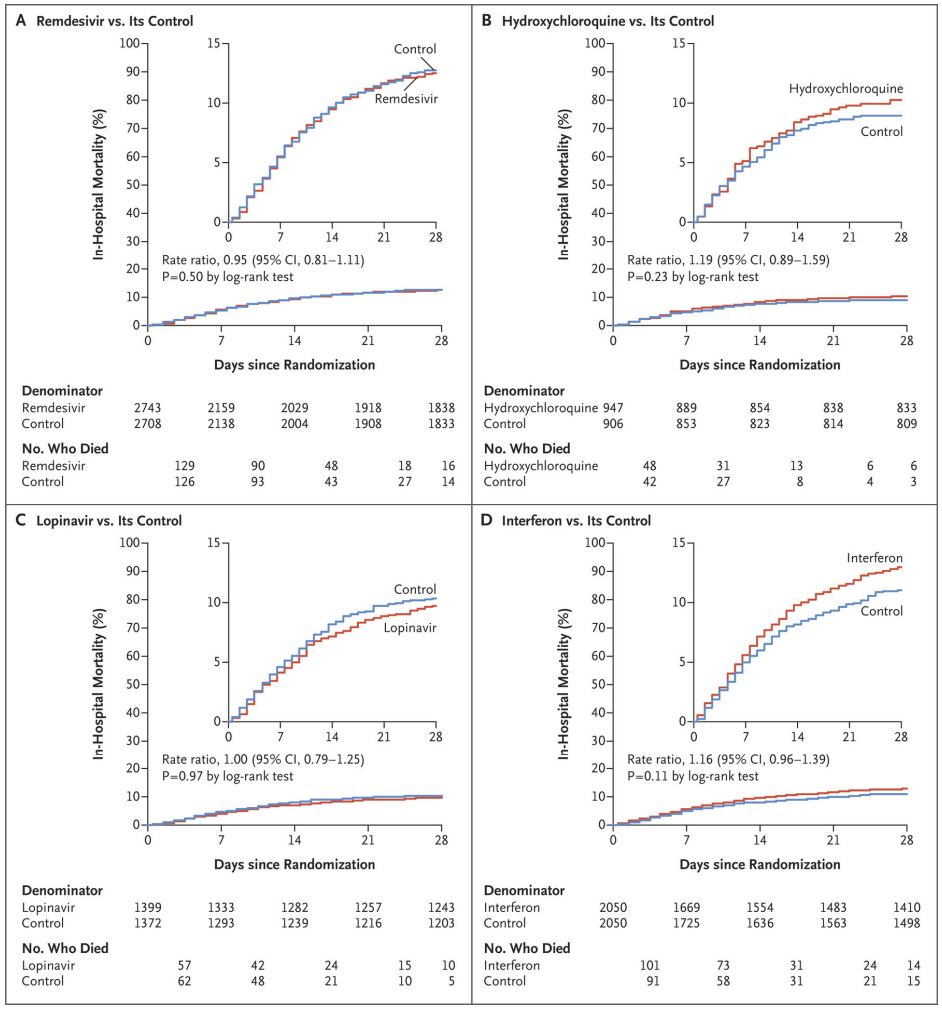
Beigel, NEJM 2020

Remdesivir for the Treatment of Covid-19 — Final Report

Subgroup	No. of Patients	Recovery Rate Ratio (95% CI)
All patients	1062	1.29 (1.12–1.49)
Geographic region		
North America	847	1.30 (1.10–1.53)
Europe	163	1.30 (0.91–1.87)
Asia	52	1.36 (0.74–2.47)
Race		
White	566	1.29 (1.06–1.57)
Black	226	1.25 (0.91–1.72)
Asian	135	1.07 (0.73–1.58)
Other	135	1.68 (1.10–2.58)
Ethnic group		
Hispanic or Latino	250	1.28 (0.94–1.73)
Not Hispanic or Latino	755	1.31 (1.10–1.55)
Age		
18 to <40 yr	119	1.95 (1.28–2.97)
40 to <65 yr	559	1.19 (0.98–1.44)
≥65 yr	384	1.29 (1.00–1.67)
Sex		
Male	684	1.30 (1.09–1.56)
Female	278	1.31 (1.03–1.66)
Symptoms duration		
≤10 days	676	1.37 (1.14–1.64)
>10 days	383	1.20 (0.94–1.52)
Baseline ordinal score		
4 (not receiving oxygen)	138	1.29 (0.91–1.83)
5 (receiving oxygen)	435	1.45 (1.18–1.79)
6 (receiving high-flow oxygen or noninvasive mechanical ventilation)	193	1.09 (0.76–1.57)
7 (receiving mechanical ventilation or ECMO)	285	0.98 (0.70–1.36)



IRC-19 Italian response to COVID-19



Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results

WHO Solidarity trial consortium*

*A complete list of SOLIDARITY Trial investigators is provided in the Supplementary Appendix.

CONCLUSIONS

These Remdesivir, Hydroxychloroquine, Lopinavir and Interferon regimens **appeared to have little or no effect on hospitalized COVID-19**, as indicated by overall mortality, initiation of ventilation and duration of hospital stay. The mortality findings contain most of the randomized evidence on Remdesivir and Interferon, and are consistent with meta-analyses of mortality in all major trials. (Funding: WHO. Registration: ISRCTN83971151, NCT04315948)

COVID-19 Principles of Treatment

- Antiviral therapy
- Oxygen therapy
- Anti-inflammatory therapy
- Anti-thrombotic therapy
- Antimicrobial therapy
- Plasma/monoclonal antibodies therapy

Cenni di Terapia (1) - Ossigenoterapia

SpO2 target > 92%. Se BPCO 88-94%

- O2 terapia con cannule nasale 1-6 litri massimo
- Maschera di Venturi fino al 60%
- Maschera Reservoir 10-15 litri/min

Valvola		FiO2
Celeste	2 l/min	24%
Gialla	4 l/min	28%
Bianca	6 l/min	31%
Verde	8 l/min	35%
Blu	10 l/min	40%
Arancio	12 l/min	50%
Rosa	15 l/min	60%

Se la SpO2 non è a target o peggiora iniziare

1. **CPAP**
   - Iniziale setting a 7,5 cmH2O, incrementabile fino a massimo 10 cm H2O
   - FiO2 60-100% da titolare in base all'andamento
2. **NIV** con PEEP 5 setting iniziale come per CPAP e PSV con setting iniziale 6 cmH2O, valutando il Volume Corrente FiO2 35-80% da titolare in base alla SpO2. Questa modalità è preferibile nei BPCO o dove la CPAP non funziona o provoca ipercapnia.

- Se non controindicato e fattibile tecnicamente considerare la **pronazione a paziente sveglio per 8-12 ore al giorno**. Se difficile, modificare il decubito del paziente da un fianco all'altro ogni 2-3 ore.

CAVE!

In caso di **improvvisa desaturazione**! pensare a embolia polmonare!!

Proning in Non-Intubated (PINI) in Times of COVID-19: Case Series and a Review

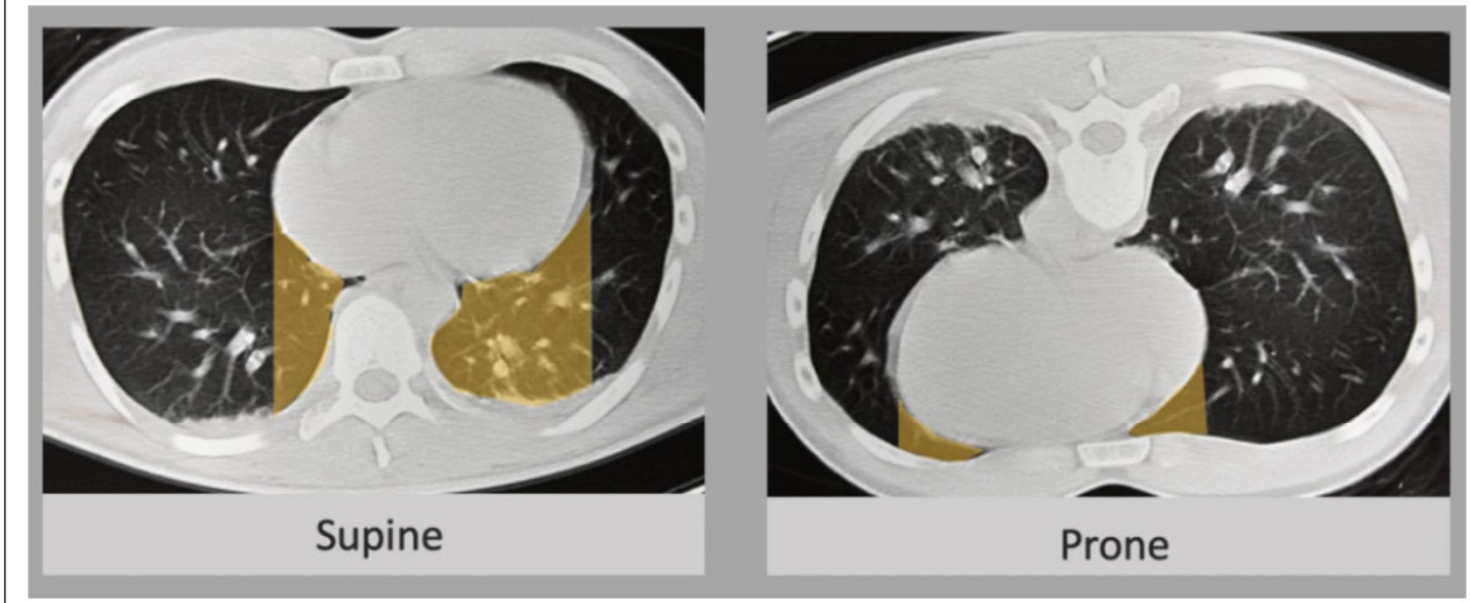


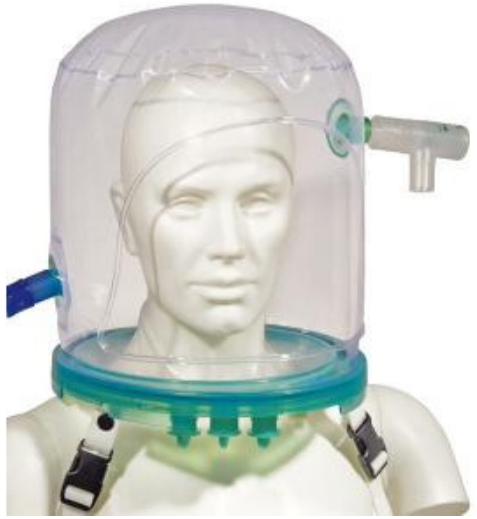
Figure 5. Comparison of lung compression by the heart in supine and prone positions (Adapted from the efficacy of prone position in acute respiratory distress syndrome patients: a pathophysiology-based review. V Koulouras, World J Crit Care Med. 2016;5(2): Page 126).

Ossigenoterapia

Se necessario, ventilazione non invasiva (NIV), cPAP (continuous positive airway pressure), HFNO (high-flow nasal oxygen)

Idratazione endovenosa

Terapia antibiotica empirica o mirata



COVID-19 Principles of Treatment

- Antiviral therapy
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- Plasma/monoclonal antibodies therapy

Corticosteroids for COVID-19

LIVING GUIDANCE
2 SEPTEMBER 2020

World Health Organization

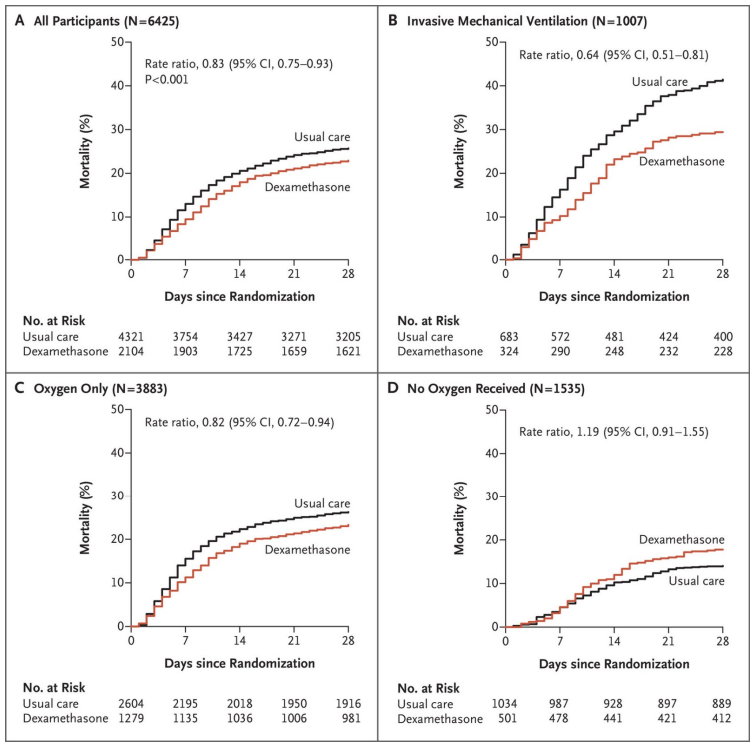
Recommendations: The panel made two recommendations: a strong recommendation for systemic (i.e. intravenous or oral) corticosteroid therapy (e.g. 6 mg of dexamethasone orally or intravenously daily or 50 mg of hydrocortisone intravenously every 8 hours) for 7 to 10 days in patients with severe and critical COVID-19, and a conditional recommendation not to use corticosteroid therapy in patients with non-severe COVID-19.

ORIGINAL ARTICLE

NEJM, 2020

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*



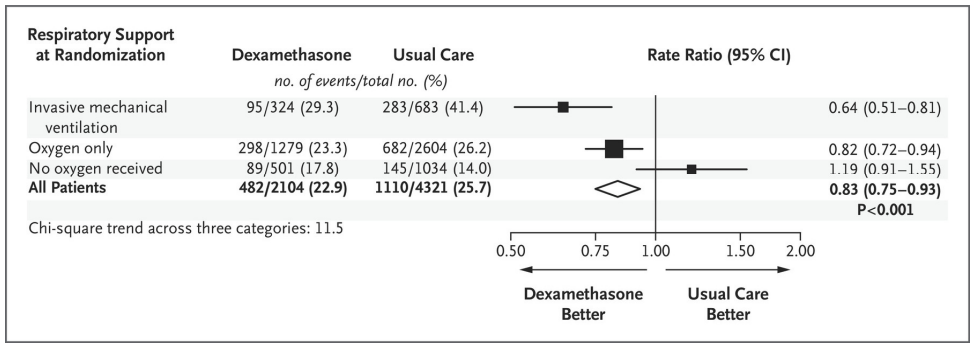


Table 2. Primary and Secondary Outcomes.

Outcome	Dexamethasone (N=2104)	Usual Care (N=4321)	Rate or Risk Ratio (95% CI)*
	no./total no. of patients (%)		
Primary outcome			
Mortality at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75–0.93)
Secondary outcomes			
Discharged from hospital within 28 days	1413/2104 (67.2)	2745/4321 (63.5)	1.10 (1.03–1.17)
Invasive mechanical ventilation or death†	456/1780 (25.6)	994/3638 (27.3)	0.92 (0.84–1.01)
Invasive mechanical ventilation	102/1780 (5.7)	285/3638 (7.8)	0.77 (0.62–0.95)
Death	387/1780 (21.7)	827/3638 (22.7)	0.93 (0.84–1.03)

Internal and Emergency Medicine
https://doi.org/10.1007/s11739-021-02655-6

IM - ORIGINAL

Timing of corticosteroids impacts mortality in hospitalized COVID-19 patients

Amit Bahl[1] · Steven Johnson[1] · Nai-Wei Chen[2]

[a]Propensity score matching analysis was Cox regression in the matched cohort

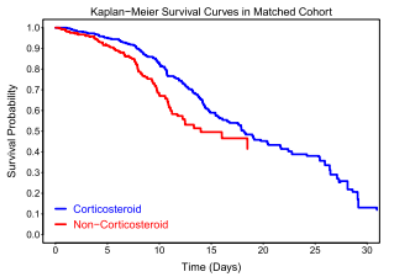


Figure 1. Kaplan-Meier survival curve for corticosteroids treatment. Figure shows overall survival for propensity score-matched patients treated with or without corticosteroids. The estimated survival curves were pooled from 20 imputed datasets

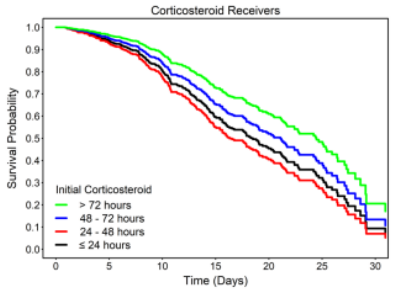


Figure 2. Survival curve for the timing of corticosteroids treatment. Figure shows overall survival of study patients associated with the initial receipt of corticosteroids treatment during the hospitalization. The direct adjusted survival curves were estimated based on a multivariable analysis and pooled from 20 imputed datasets

Patients receiving first dose of corticosteroids>72 h into hospitalization had a lower risk of death compared to patients with frst dose at earlier time intervals (HR 0.56, 95% CI 0.38–0.82; p=0.003).

There was a mortality beneft in patients with>7 days of symptom onset to initiation of corticosteroids (HR 0.56, 95% CI 0.33–0.95; p=0.03).

In patients receiving oxygen therapy, corticosteroids reduced risk of death in mechanically ventilated patients (HR 0.38, 95% CI 0.24–0.60; p7 days should trigger initiation of corticosteroids.

In the absence of invasive mechanical ventilation, corticosteroids should be initiated if the patient remains hospitalized at 72 h

IRC-19 Italian response to COVID-19

SYSTEMATIC REVIEW | ARTICLES IN PRESS

Efficacy and safety of tocilizumab in COVID-19 patients: a living systematic review and meta-analysis

Imad M. Tleyjeh • Zakariya Kashour • Moussab Damlaj • ... Rana Tleyjeh • Leslie Hassett • Tarek Kashour • Show all authors

Published: November 05, 2020 • DOI: https://doi.org/10.1016/j.cmi.2020.10.036

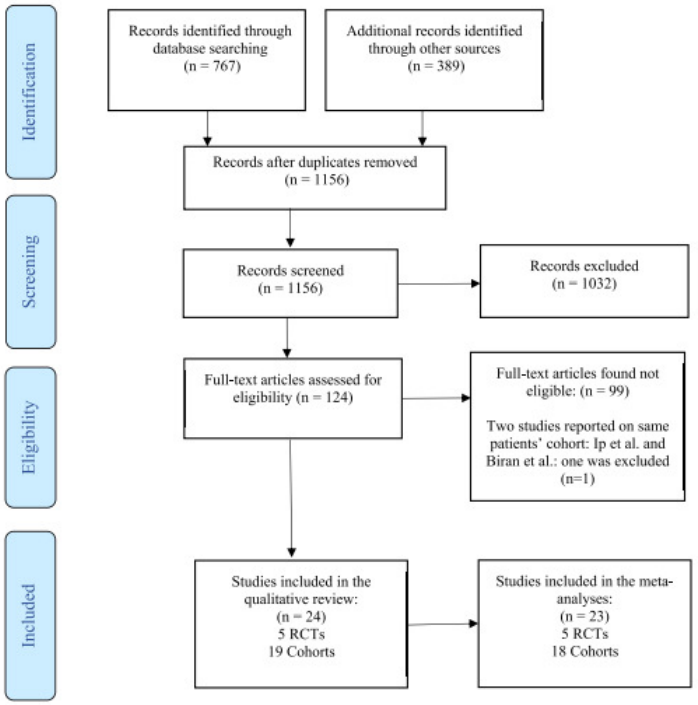
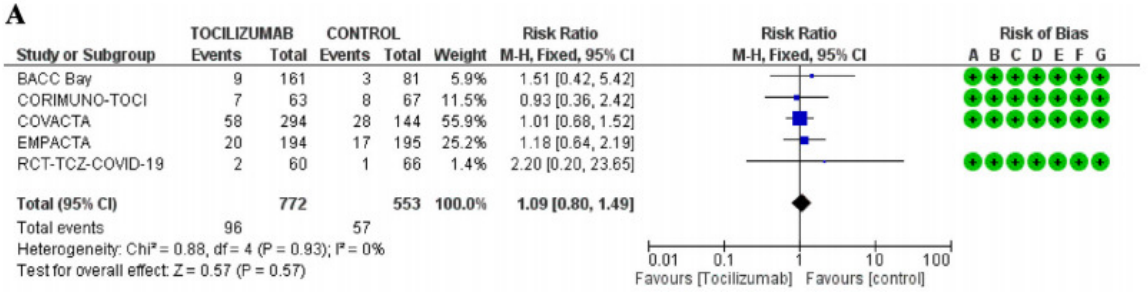


Fig. 1. Flow diagram of the assessment of studies identified in the systematic review.

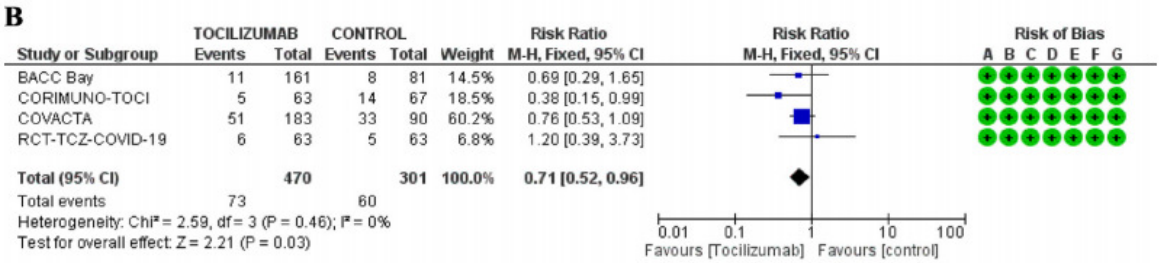
A



Study or Subgroup	TOCILIZUMAB Events	Total	CONTROL Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BACC Bay	9	161	3	81	5.9%	1.51 [0.42, 5.42]
CORIMUNO-TOCI	7	63	8	67	11.5%	0.93 [0.36, 2.42]
COVACTA	58	294	28	144	55.9%	1.01 [0.68, 1.52]
EMPACTA	20	194	17	195	25.2%	1.18 [0.64, 2.19]
RCT-TCZ-COVID-19	2	60	1	66	1.4%	2.20 [0.20, 23.65]
Total (95% CI)		**772**		**553**	**100.0%**	**1.09 [0.80, 1.49]**
Total events	96		57			

Heterogeneity: Chi² = 0.88, df = 4 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.57 (P = 0.57)

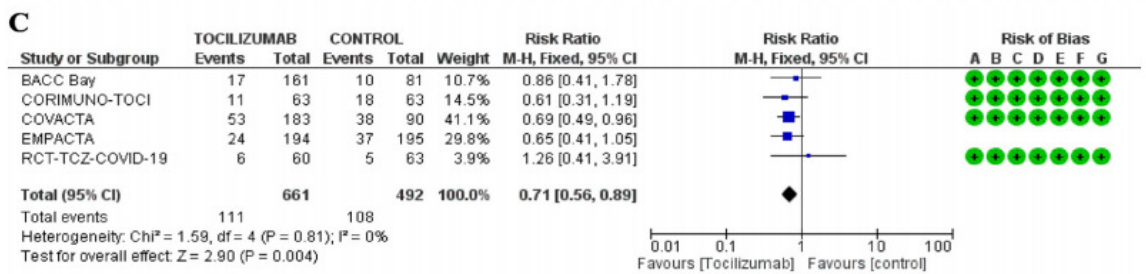
B



Study or Subgroup	TOCILIZUMAB Events	Total	CONTROL Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BACC Bay	11	161	8	81	14.5%	0.69 [0.29, 1.65]
CORIMUNO-TOCI	5	63	14	67	18.5%	0.38 [0.15, 0.99]
COVACTA	51	183	33	90	60.2%	0.76 [0.53, 1.09]
RCT-TCZ-COVID-19	6	63	5	63	6.8%	1.20 [0.39, 3.73]
Total (95% CI)		**470**		**301**	**100.0%**	**0.71 [0.52, 0.96]**
Total events	73		60			

Heterogeneity: Chi² = 2.59, df = 3 (P = 0.46); I² = 0%
Test for overall effect: Z = 2.21 (P = 0.03)

C

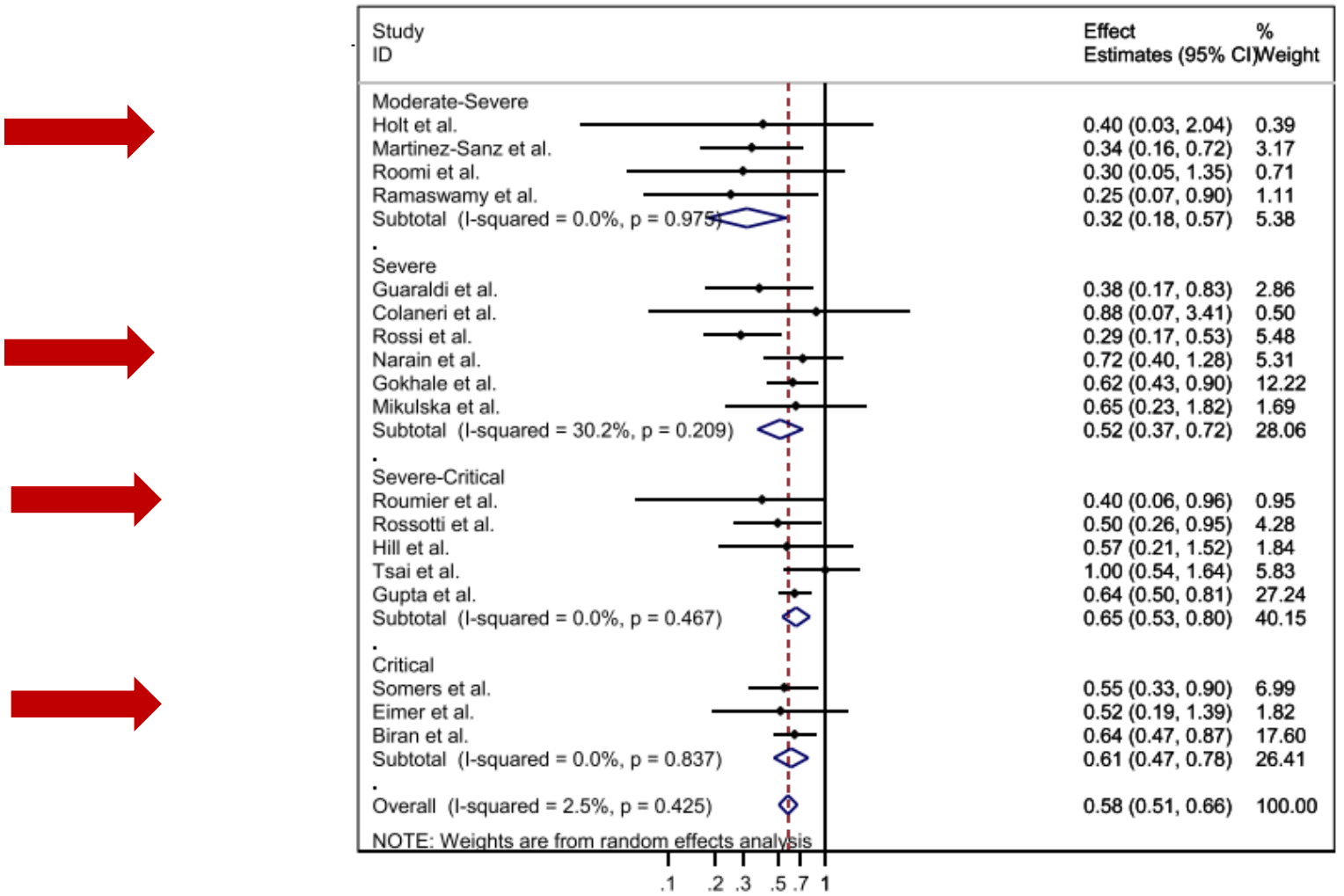


Study or Subgroup	TOCILIZUMAB Events	Total	CONTROL Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BACC Bay	17	161	10	81	10.7%	0.86 [0.41, 1.78]
CORIMUNO-TOCI	11	63	18	63	14.5%	0.61 [0.31, 1.19]
COVACTA	53	183	38	90	41.1%	0.69 [0.49, 0.96]
EMPACTA	24	194	37	195	29.8%	0.65 [0.41, 1.05]
RCT-TCZ-COVID-19	6	60	5	63	3.9%	1.26 [0.41, 3.91]
Total (95% CI)		**661**		**492**	**100.0%**	**0.71 [0.56, 0.89]**
Total events	111		108			

Heterogeneity: Chi² = 1.59, df = 4 (P = 0.81); I² = 0%
Test for overall effect: Z = 2.90 (P = 0.004)

A: Forest plot for the effect of tocilizumab on 28-30 days mortality in randomized controlled trials with corresponding risk of bias. **B:** Forest plot for the effect of tocilizumab on risk for mechanical ventilation in randomized controlled trials with corresponding risk of bias. **C:** Forest plot for the effect of tocilizumab on 28-30 days composite outcome in randomized controlled trials with corresponding risk of bias

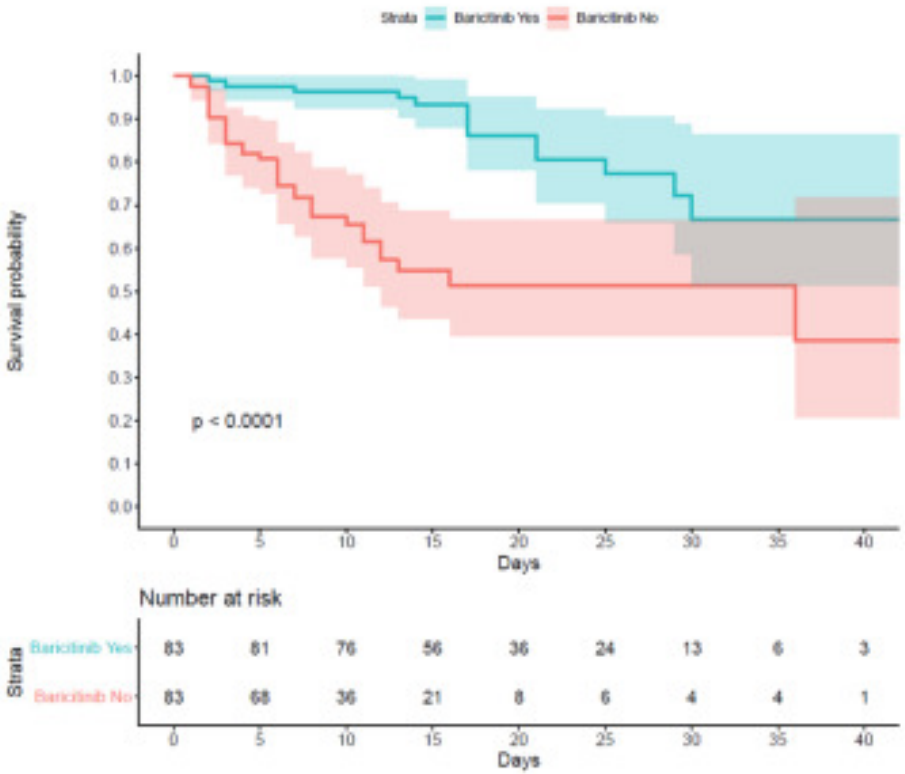
Forest plot of the association between tocilizumab use and short-term mortality in COVID-19 patients from cohorts at moderate risk of bias: stratified by disease severity



IRC-19 Italian response to COVID-19

Table 4. Multivariate Cox-regression analyses for the primary outcome in the propensity score matched populations from the University of Pisa and the Albacete Hospital. Selection bias was addressed by propensity score analysis. Briefly, this is a two-phase technique used to estimate a treatment effect in comparative groups selected by non-random means. In the first phase of a propensity score analysis, variables that influence selection to group assignment are used to model the probability of receiving treatment (or of being in the reference group, in this case, the baricitinib group). The resulting probability is the propensity score. In the second phase, the propensity score is used to adjust for pre-existing group differences in the analysis of the relevant outcomes. There are several ways to use propensity scores such as stratification variables, matching patients based on their propensity score or their use as a weighting or adjustment variable during multivariate analysis. In the current study, each baricitinib patient was matched to a control patients based on comparable propensity scores. Assuming that all relevant covariates are included in the propensity score model, the group effect observed in a propensity score analysis represents an unbiased estimate of the true treatment effect.

	HR (95% CI)	*p*
Baricitinib	0.29 (0.15-0.58)	0.0001
Age	1.01 (0.98-1.04)	0.470
Male sex	1.13 (0.54-2.34)	0.750
Hypertension	1.31 (0.52-3.32)	0.572
Diabetes	0.51 (0.23-1.17)	0.113
Chronic Obstructive Lung Disease	0.51 (0.17-1.54)	0.230
Cardiovascular disease	1.41 (0.68-2.92)	0.351
Cronic kidney disease	1.45 (0.51-4.15)	0.491
Solid cancer	1.18 (0.49-2.87)	0.709
Charlson Comorbidity Index	1.03 (0.90-1.17)	0.680
Baseline PaO_2/FiO_2	1.00 (1.00-1.00)	0.823
Lymphocyte count (/mcL)	1.00 (1.00-1.00)	0.657
Alanine aminotransferase	1.01 (1.00-1.03)	0.026
Hydroxychloroquine	2.77 (0.28-27.41)	0.384
Lopinavir/Ritonavir	1.18 (0.38-3.61)	0.776
Glucocorticoids	1.79 (0.60-5.34)	0.299
Low Molecular Weight Heparin	0.10 (0.01-1.33)	0.081
Antibiotics	2.34 (0.29-18.90)	0.427



COVID-19 Principles of Treatment

- Antiviral therapy
- Oxygen therapy
- Anti-inflammatory therapy
- Anti-thrombotic therapy
- Antimicrobial therapy
- Plasma/monoclonal antibodies therapy

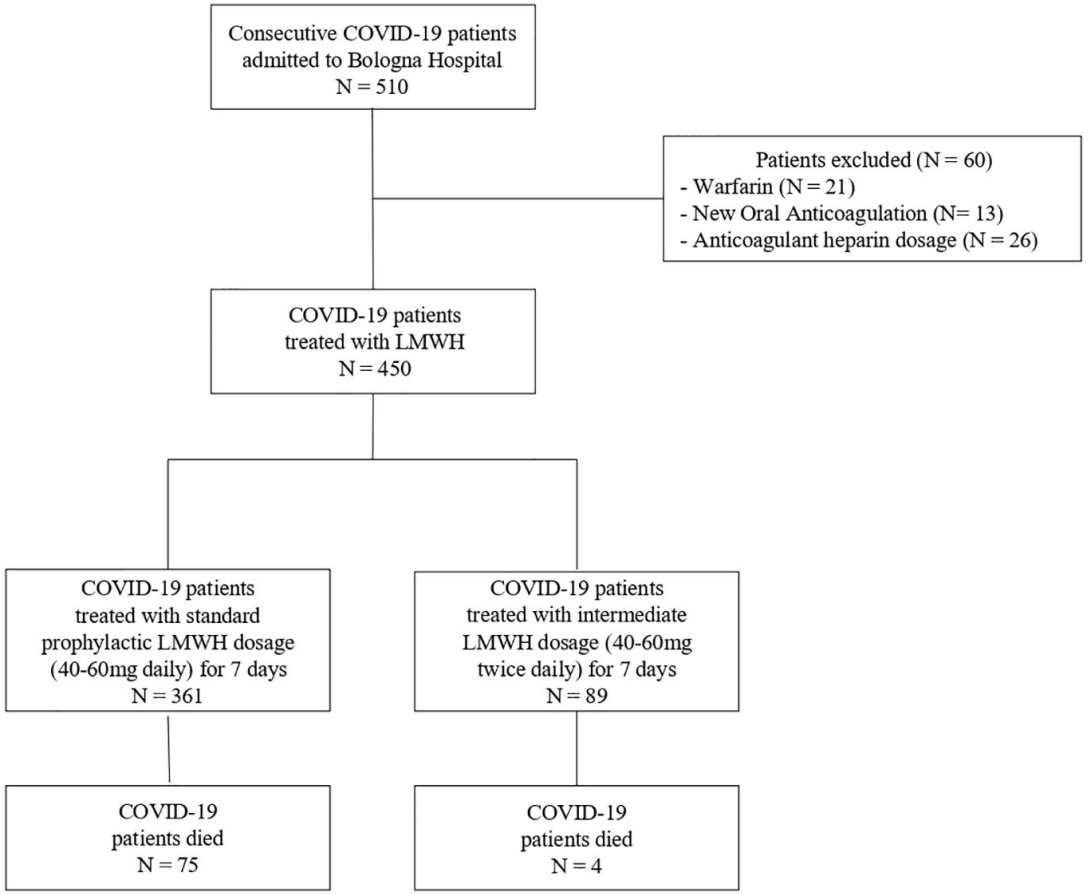
BRIEF RESEARCH REPORT ARTICLE
Front. Pharmacol., 06 August 2020 | https://doi.org/10.3389/fphar.2020.01124

Preliminary Experience With Low Molecular Weight Heparin Strategy in COVID-19 Patients

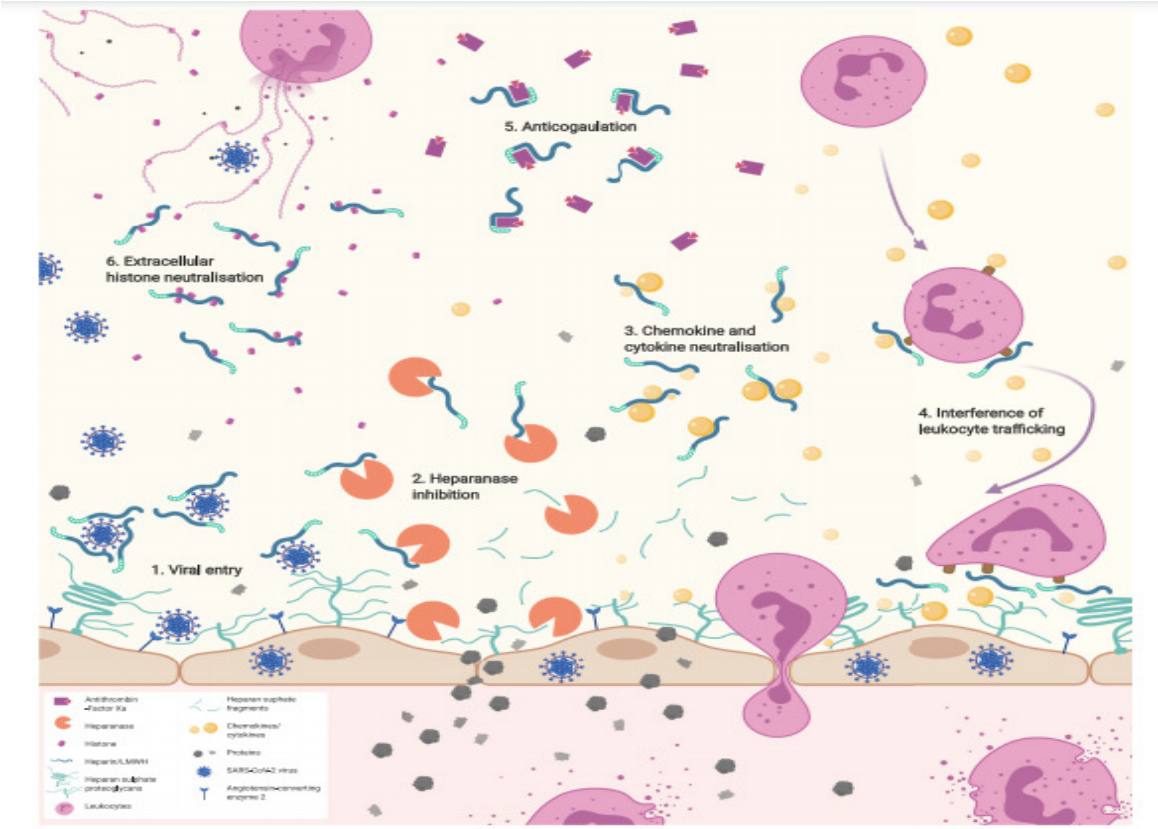
Out of 450 patients, 361 received standard deep vein thrombosis (DVT) prophylaxis enoxaparin treatment (40-60mg daily) and 89 patients received intermediate enoxaparin dosage (40–60 mg twice daily) for 7 days.

No significant differences in the main demographic characteristics and laboratory testings at admission were observed in the two heparin regimen subgroups, except for older age and prevalence of hypertension in the group treated with “standard” prophylaxis LMWH dosage.

The intermediate LMWH administration was associated with a lower in-hospital all-cause mortality compared to the “standard” prophylactic LMWH dosage (18.8% vs. 5.8%, p = 0.02). This difference remained significant after adjustment with the propensity score for variables that differed significantly between the dosage groups (OR= 0.260, 95% CI 0.089–0.758, p=0.014).



Beneficial non-anticoagulant mechanisms underlying heparin treatment of COVID-19 patients



Potential beneficial, non-anticoagulant mechanisms underlying treatment of COVID-19 patients with heparin/LMWH, which include:

(i) Inhibition of heparanase activity, responsible for endothelial leakage;
(ii) Neutralisation of chemokines, and cytokines;
(iii) Interference with leukocyte trafficking;
(iv) Reducing viral cellular entry, and
(v) Neutralisation of extracellular cytotoxic histones.

Baranca Buijsers et al. EBIO Medicine, SEPTEMBER 01, 2020

Le proprietà dell'eparina consentirebbero in pazienti affetti da Sars-CoV-2:

– a livello polmonare, **l'inibizione dell'infiammazione**, della formazione di trombi e dello sviluppo di ARDS (in quanto l'attivazione del sistema di coagulazione risulta rilevante nella patogenesi di quest'ultima grave complicazione respiratoria)

– a livello cardiaco, una **riduzione della formazione di trombi coronarici ed intrac**ardiaci, potenziali effetti benefici inibendo lo sviluppo di miocarditi e cardiomiopatie

– a livello vascolare, una potenziale **riduzione dei processi di ischemia microvascolare** e potenziali effetti benefici sulla disfunzione multiorgano

COVID-19 Principles of Treatment

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- Oxygen therapy
- Anti-inflammatory therapy
- Anti-thrombotic therapy
- Antimicrobial therapy
- Plasma/monoclonal antibodies therapy

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Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Guidelines

Recommendations for antibacterial therapy in adults with COVID-19 — an evidence based guideline

Table 2
Summary of recommendations

Recommendation	Strength	Quality of evidence
1. We generally suggest restrictive use of antibacterial drugs in patients with proven or a high likelihood of COVID-19. This especially applies for patients upon admission who are mild to moderately ill	Weak	Very low
2. We suggest that exceptions for the restrictive use of antibacterial drugs can be made for patients with proven or a high likelihood of COVID-19 who present with radiological findings and/or inflammatory markers compatible with bacterial co-infection. Other exceptions are patients who are severely ill or immunocompromised*	Weak	GPS
3. We recommend maximum efforts to obtain sputum and blood for culture as well as pneumococcal urinary antigen testing before start of empirical antibiotic therapy in patients with proven or high likelihood of COVID-19 upon admission	Strong	GPS
4. In case of suspected bacterial co-infection, we suggest against empirical antibiotic treatment covering atypical pathogens in patients with proven or high likelihood of COVID-19 hospitalized at the general ward. *Legionella* urinary antigen testing should be performed according to local and/or national guidelines for CAP	Weak	Very low
5. We recommend that the empirical antibiotic regimens in case of suspected bacterial co-infection depends on the severity of disease and according to local and/or national guidelines. For those fulfilling criteria of mild and moderate-severe CAP, we recommend to follow local and/or national guideline recommendations on antibacterial treatment in CAP	Weak	Very low
6. We recommend to follow local and/or national guideline recommendations on antibacterial treatment for patients with COVID-19 and suspected bacterial secondary infection	Strong	GPS
7. We suggest to stop antibiotics when representative sputum and blood culture as well as urinary antigen tests taken before start of empirical antibiotic therapy in patients with proven or high likelihood of COVID-19 show no bacterial pathogens after 48 hours of incubation	Weak	GPS
8. We suggest an antibiotic treatment duration of five days in patients with COVID-19 and suspected bacterial infection upon improvement of signs, symptoms and inflammatory markers	Weak	GPS

* immunocompromised is defined as the use of chemotherapy for cancer, bone marrow or organ transplantation, immune deficiencies, poorly controlled HIV or AIDS, or prolonged use of corticosteroids or other immunosuppressive medications; GPS: good practice statement.

COVID-19 Principles of Treatment

- Antiviral therapy
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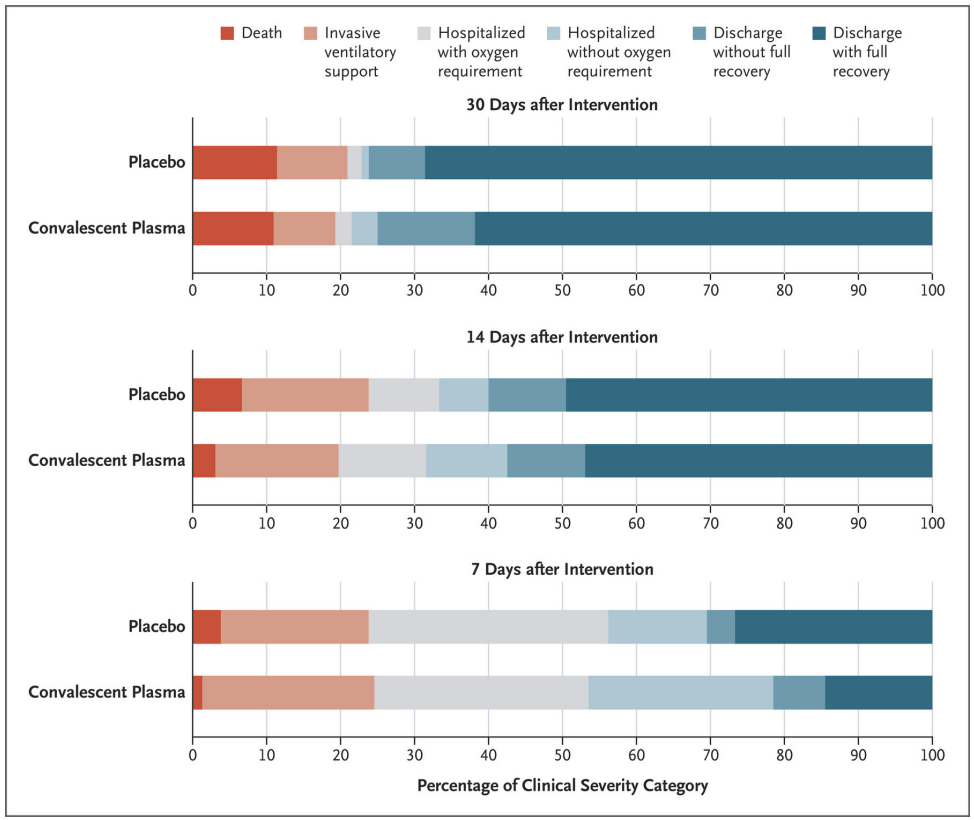
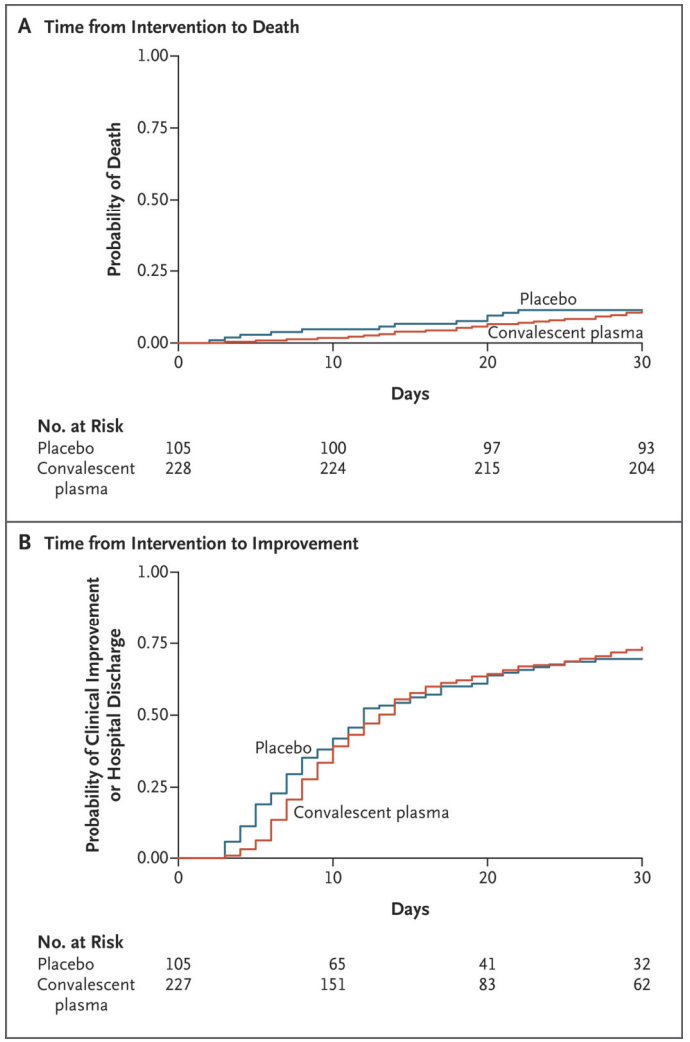
- Plasma/monoclonal antibodies therapy

ORIGINAL ARTICLE

A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia

Ventura A. Simonovich, M.D., Leandro D. Burgos Pratx, M.D., Paula Scibona, M.D., María V. Beruto, M.D., Marcelo G. Vallone, M.D., Carolina Vázquez, M.D., Nadia Savoy, M.D., Diego H. Giunta, M.D., M.P.H., Ph.D., Lucía G. Pérez, M.D., Marisa del L. Sánchez, M.D., Andrea Vanesa Gamarnik, Ph.D., Diego S. Ojeda, Ph.D., et al., for the PlasmAr Study Group*



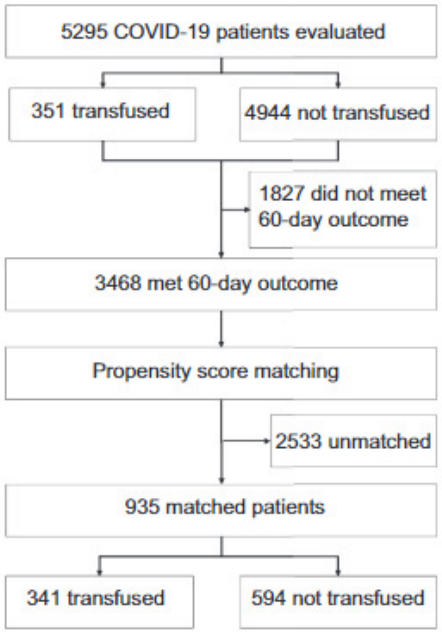


IRC-19 Italian response to COVID-19

The American Journal of Pathology
Available online 4 November 2020
In Press, Uncorrected Proof

Regular article

Significantly Decreased Mortality in a Large Cohort of Coronavirus Disease 2019 (COVID-19) Patients Transfused Early with Convalescent Plasma Containing High-Titer Anti–Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Spike Protein IgG



With respect to altering mortality, **our analysis identified an optimal window of 44 hours after hospitalization for transfusing COVID-19 patients with high-titer convalescent plasma**. In the aggregate, the analysis confirms and extends our previous preliminary finding that transfusion of COVID-19 patients soon after hospitalization with **high-titer anti-spike protein RBD IgG present in convalescent plasma significantly reduces mortality**.

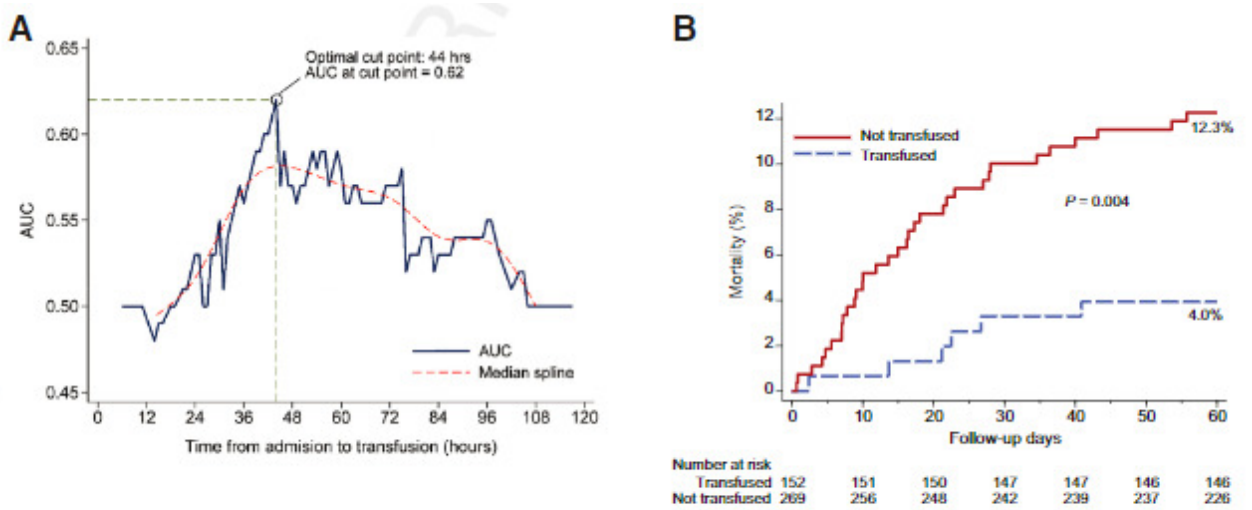


Figure 5 **A:** Receiver operating characteristic curve with Youden index analysis for mortality within 60 days shown for all patients transfused with coronavirus disease 2019 convalescent plasma. Optimal cut point identified as 44 hours with an area under the curve (AUC) of 0.62. Youden index was 0.23 with SEM of 0.0926. Sensitivity at cut point was 0.75 with a specificity of 0.48. **B:** Kaplan-Meier curves for mortality within 60 days after day 0 for patients transfused with plasma with an anti- receptor binding domain IgG titer ≥1:1350 within 44 hours after admission (blue) propensity score matched to control patients (red).

Clinical studies evaluating anti-SARS-CoV-2 monoclonal antibodies

Sponsors					
Junshi Biosciences / Eli Lilly and Company	JS016, LY3832479, LY-CoV016	Phase 2	NCT04441918; NCT04441931; NCT04427501	6/5/2020; 6/19/2020; 6/17/2020	Dec 2020; 10/2/2020; 3/11/2021
Brii Biosciences	BRII-196	Phase 1	NCT04479631	7/12/2020	Mar 2021
Brii Biosciences	BRII-198	Phase 1	NCT04479644	7/13/2020	Mar 2021
AbbVie	ABBV-47D11	Phase 1 pending	NCT04644120	11/27/2020	May 2021
Sorrento Therapeutics, Inc.	COVI-GUARD (STI-1499)	Phase 1	NCT04454398	9/17/2020	Feb 2021
Mabwell (Shanghai) Bioscience Co., Ltd.	MW33	Phase 1	NCT04533048	8/7/2020	Dec 2020
HiFiBiO Therapeutics	HFB30132A	Phase 1	NCT04590430	Oct 2020	July 2021
Ology Bioservices	ADM03820	Phase 1 pending	NCT04592549	11/16/2020	Aug 2021
Hengenix Biotech Inc	HLX70	Phase 1 pending	NCT04561076	12/9/2020	Sep 2021
U. Cologne / Boehringer Ingelheim	DZIF-10c	Phase 1 /2 pending	NCT04631705; NCT04631666	11/23/2020; 11/23/2020	6/30/2021; 6/30/2021
Sorrento Therapeutics, Inc.	COVI-AMG (STI-2020)	Phase 1 /2 pending	NCT04584697	Dec 2020	April 2021
Beigene	BGB DXP593	Phase 1; Phase 2 pending	NCT04532294; (NCT04551898	8/31/2020; 10/30/2020	10/15/2020; 2/28/2021
Sinocelltech Ltd.	SCTA01	Phase 1; Phase 2/3	NCT04483375; NCT04644185	7/24/2020; 2/10/2021	Nov 2020; 5/10/2021
Tychan Pte. Ltd.	TY027	Phase 3 pending	NCT04429529; NCT04649515	6/9/2020; 12/4/2020	Oct 2020; 8/31/2020
AstraZeneca	AZD7442 (AZD8895 + AZD1061)	Phase 1; Phase 3 pending	NCT04507256; NCT04625725; NCT04625972	8/17/2020; 11/17/2020; 11/16/2020	Sep 2021; 7/31/2021; 6/16/2021
Celltrion	CT-P59	Phase 1; Phase 2/3	NCT04525079; NCT04593641; NCT04602000	7/18/2020; 9/4/2020; 9/25/2020	Nov 2020; 12/23/2020; Dec 2020
Vir Biotechnol./GlaxoSmithKline	VIR-7831/ GSK4182136	Phase 2/3	NCT04545060	8/27/2020	Jan 2021
AbCellera / Eli Lilly and Company	LY-CoV555 (LY3819253); combination of LY-CoV555 with LY-CoV016 (LY3832479)	**EUA***	NCT04411628 (Phase 1); NCT04427501 (Phase 2); NCT04497987(Phase 3);NCT04501978 (Phase 3); NCT04518410 (Phase 2/3)	5/28/2020; 6/13/2020; 8/2/2020; 8/4/2020; Aug 2020	8/23/2020; 9/15/2020; 3/8/2021; July 2021; Nov 2020
Regeneron	REGN-COV2 (REGN10933 + REGN10987)	**EUA***	NCT04425629 (Phase 1/2); NCT04426695 (Phase	6/16/2020; 6/19/2020; 7/13/2020	12/19/2020; 1/25/2021; 6/15/2021

IRC-19 Italian response to COVID-19

APPROCCIO E GESTIONE	MALATTIA COVID-19				
	Modesta *rischio basso*	**Modesta** *rischio medio*	**Moderata**	**Severa**	**Critica**
Sintomi e segni	Tosse Febbre Rinorrea Mialgie Diarrea Disgeusia o disosmia		Dispnea persistente	Emottisi	Coscienza alterata
Parametri vitali	FC < 100 FR < 20 SaO2 ≥ 93% SaO2 dopo stress > 90% e calo < 5%	FC 101-120 FR 21-25 SaO2 dopo stress < 90% o calo ≥ 5%	FC > 120 FR ≥ 26 SaO2 89-92%	SaO2 ≤ 88%	PA sistolica < 90 mmHg
EGA - P/F		pO2 > 65 pCO2 > 30	pO2 55-65 P/F 250-300	pO2 < 55 P/F < 250	
Fattori rischio	Nessuno o uno	Due o più	Residenza RSA		
Comorbidità	Assenti	Presenti con indicazioni a osservazione	Presenti con indicazione a ricovero		
Diagnostica per immagini	Eventuale Eco e/o RxT	Eco e/o RxT normali o con alterazioni modeste (p.es.: Eco score < 9, RxT score 1)	Eco e/o RxT con alterazioni moderate (p.es.: Eco score 9-18, RxT score 2) Eventuale TAC	Eco e/o RxT con alterazioni gravi (p.es.: Eco score > 18 RxT score ≥ 3) EcoC con VD dilatato Eventuale TAC	
Test diagnostici	Ag o RT-PCR	Ag o RT-PCR	Ag o RT-PCR	Ag o RT-PCR	Ag o RT-PCR
Laboratorio	Eventuale	Assenza di alterazioni significative	Presenza di alterazioni significative	Lattato 2-4	Lattato > 4
Terapia	Sintomatici	O2 eventuale Eparina BPM eventuale Antibiotici eventuali	O2 / O2 HF Eparina BPM Desametasone Remdesivir Antibiotici eventuali	O2 HF / CPAP Eparina BPM Desametasone Antibiotici eventuali	O2 HF / CPAP / IOT Eparina BPM Desametasone Antibiotici eventuali
Destinazione del paziente	Dimissione	Osservazione Dimissione eventuale	Ricovero	Ricovero (da considerare TSI)	Ricovero (da considerare TI o TSI)

Classificazione stadi clinici:

- Malattia modesta o lieve
  - Basso rischio
  - Rischio medio
- Malattia moderata
- Malattia severa
- Malattia critica

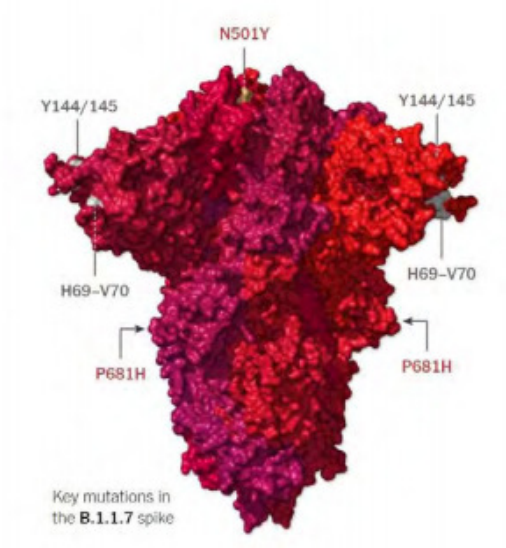
DOCTORS WITH AFRICA CUAMM | USAID FROM THE AMERICAN PEOPLE | UPO UNIVERSITÀ DEL PIEMONTE ORIENTALE RESEARCH CENTER IN EMERGENCY AND DISASTER MEDICINE CRIMEDIM

WHO Living Guidance: Corticosteroids for COVID-19

Categories of Illness	Definition	Recommendation
Critical COVID-19	▪ ARDS, sepsis, septic shock ▪ Other conditions that would normally require life-sustaining therapies (mechanical ventilation) or vasopressor therapy	▪ Recommend systemic corticosteroids rather than no systemic corticosteroids
Severe COVID-19	Any of the following: ▪ 0_2 < 90% on room air* ▪ RR > 30 breaths/min in adults and children aged > 5 yrs; RR ≥ 40 in children aged 1-5 yrs; RR ≥ 50 in children aged 2-11 mos ▪ Signs of respiratory distress (accessory muscle use, inability to complete full sentences; in children very severe chest wall indrawing, grunting, central cyanosis, etc)	▪ Recommend systemic corticosteroids rather than no systemic corticosteroids
Non-severe COVID-19	▪ Absence of any signs of severe or critical COVID-19	▪ Suggest no corticosteroids

B.1.1.7, 20I/501Y.V1, VOC202012/01

First detected by	United Kingdom
First appearance	20 September 2020
Key mutations	H69/V70 deletion; Y144 deletion; N501Y; A570D; D614G; P681H; S106/G107/F108 deletion in NSP6
Transmissibility*	Increased (43%-82%), increased secondary attack rate (10% to 13%)
Severity*	Likely associated with an increased risk of hospitalisation and death compared to infection with non-VOC viruses.
Neutralization capacity*	Slight reduction but overall neutralizing titers remained above the levels expected to confer protection
Potential impacts on vaccines*	No significant impact on Moderna, Pfizer-BioNTech, and Oxford-AstraZeneca
Potential impacts on diagnostics*	S gene target failure. No impact on Ag RDTs observed
Countries reporting cases (community transmission) as of 23 Feb	101 (45)



https://www.nytimes.com/interactive/2021/health/coronavirus-variant-tracker.html

nature

Article | Published: 15 March 2021

Increased mortality in community-tested cases of SARS-CoV-2 lineage B.1.1.7

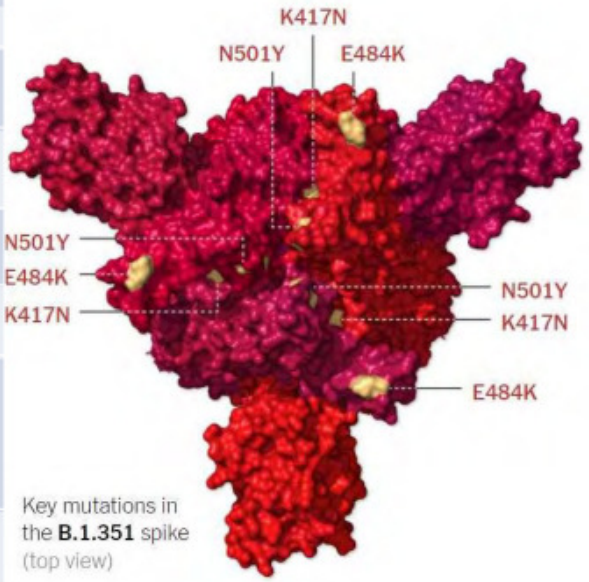
Nicholas G. Davies ✉, Christopher I. Jarvis, CMMID COVID-19 Working Group, W. John Edmunds, Nicholas P. Jewell, Karla Diaz-Ordaz & Ruth H. Keogh

B.1.1.7 infections **are associated with higher viral concentrations** on nasopharyngeal swabs, as measured by Ct values from PCR testing

Higher viral load could therefore be partly responsible for the observed increase in mortality; this could be assessed using a mediation analysis.

B.1.351, 20H/501Y.V2, VOC202012/02

First detected by	South Africa
First appearance	Early August 2020
Key mutations	L242/A243/L244 deletion; N501Y; D614G; E484K; K417N; S106/G107/F108 deletion in NSP6
Transmissibility*	Increased [1.50 (95% CI: 1.20-2.13) times more transmissible than previously circulating variants]
Severity*	No impact reported to date, no significant change in-hospital mortality
Neutralization capacity*	Decreased, suggesting potential increased risk of reinfection
Potential impacts on vaccines*	Reduction in the neutralizing activity, but impact on protection against disease or relative importance of other immune response mechanisms (e.g., T/B-cells), not fully known. Potentially decreased based on small, prelim studies.
Potential impacts on diagnostics*	None reported to date.
Countries reporting cases (community transmissions)	51 (13)

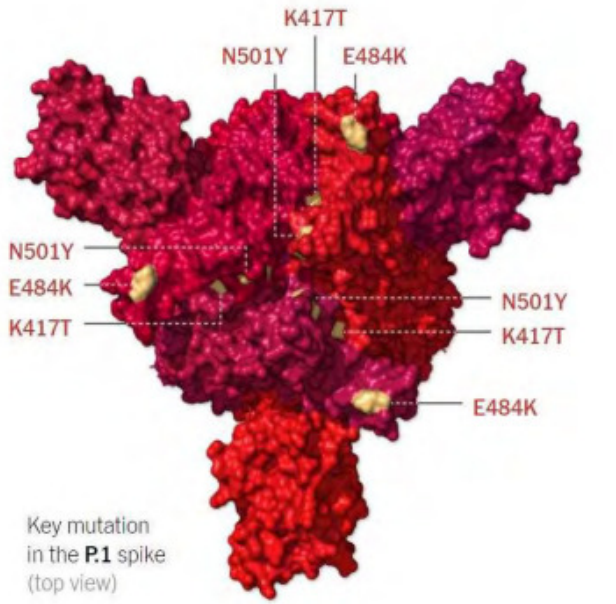


Key mutations in the **B.1.351** spike (top view)

https://www.nytimes.com/interactive/2021/health/coronavirus-variant-tracker.html

B.1.128.P.1, 20J/501Y.V3

First detected by	Brazil / Japan
First appearance	December 2020
Key mutations	N501Y; D614G; E484K; K417N; S106/G107/F108 deletion in NSP6
Transmissibility*	Suggested to be increased
Severity*	Under investigation, no impact reported to date
Neutralization capacity*	Potential decrease, small number of reinfections reported
Potential impacts on vaccines*	Under investigation
Potential impacts on diagnostics*	None reported to date
Countries reporting cases (Community transmission) as of 23 Feb	29 (3)



https://www.nytimes.com/interactive/2021/health/coronavirus-variant-tracker.html

A.23.1 2021-03-25

Description

International lineage with variants of biological significance F157L, V367F, Q613H and P681R, described fully in the preprint: Bugembe et al 2021. Q613H is predicted to be functionally equivalent to the D614G mutation that arose early in 2020.

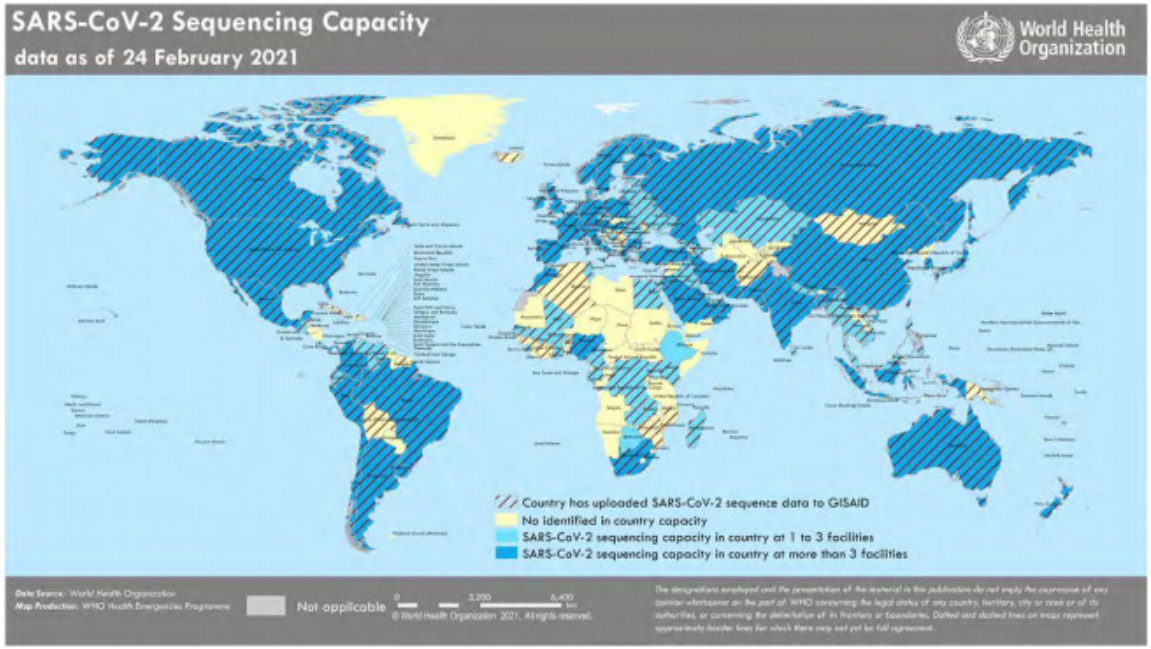
This webpage is generated using publically available sequence data from GISAID, shared by international sequencing efforts.

Table 1 | Summary of A.23.1 data

Statistic	Information
Countries reported	2
Countries with sequences	28
Sequence count	449
Countries	United Kingdom 163, Rwanda 88, Uganda 48, Canada 44, Belgium 21, United States of America 19, Cambodia 14, Latvia 8, Sweden 8, Denmark 6, Indonesia 5, Switzerland 3, Netherlands 3, Kenya 2, Zimbabwe 2, India 2, Germany 2, South Africa 1, United Arab Emirates 1, Italy 1, New Zealand 1, Norway 1, Australia 1, Mauritius 1, Vietnam 1, Israel 1, Ghana 1, Botswana 1
First detected	Uganda
Earliest sample date	2020-10-21
Defining SNPs	aa:S:F157L aa:S:V367F aa:S:Q613H aa:S:P681R

Global SARS-CoV-2 Sequencing Capacities

- **Globally:**
  - **523,778** WGS in GISAID
  - **134/194 (69%)** countries submitted WGS
  - **5%** of sequences with metadata
- **GISRS:**
  - At least **61% GISRS labs** submitted WGS to GISAID
    - **95 labs from 78 countries**
  - **32 GISRS labs** support sequencing for other GISRS and non-GISRS labs



IRC-19 Italian response to COVID-19

Per combattere il COVID → immunità di gregge → Vaccinazione

I vaccini SARS-CoV-2 approvati per l'uso nell'Unione europea nella fase attuale sono: Pfizer- BioNTech, Moderna e AstraZeneca. E' in fase di approvazione anche Sputnik, il vaccino russo. L'Agenzia italiana del farmaco (AIFA) autorizza il 22 dicembre 2020 l'immissione in commercio del vaccino anti COVID-19 , sviluppato da PFIZER, basato sull'antigene della glicoproteina spike (S) di SARS-CoV-2 codificato dall'RNA, formulato in nanoparticelle lipidiche (LNP).

VACCINO PFIZER (USA):

soggetti di età pari o superiore a 16 anni
2 iniezioni, a distanza di almeno 21 giorni l'una dall'altra.

MODERNA (USA) E ASTRAZANECA (OXFORD):

Soggetti a partire dai 18 anni d'età e fino ai 65 anni (coorte 1956)
in due dosi a distanza di 4-12 settimane .

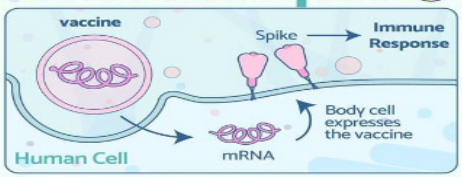
Il vaccino messo a punto da **AstraZeneca** è un **vaccino a vettore virale ed è stato realizzato utilizzando l'adenovirus degli scimpanzè**, un virus responsabile del raffreddore comune in questi animali. Una versione indebolita dell'adenovirus degli scimpanzè (incapace di replicarsi e innocua per l'organismo umano) nella quale è stato inserito il materiale genetico della proteina Spike, viene utilizzata come vettore ovvero come tramite per introdurre nelle cellule umane il materiale genetico della proteina Spike, quella che permette al virus SARS-CoV-2 di innescare l'infezione responsabile di COVID-19.

Il vaccino COVID-19 **Moderna mRNA** -1273 contiene le molecole di **RNA messaggero (mRNA)** con le indicazioni per costruire le proteine Spike del virus SARS-CoV-2. All'interno del vaccino, le molecole di mRNA sono protette da una microscopica vescicola lipidica: una "bollicina" che impedisce il rapido degradamento dell'RNA (come solitamente accade) e la sua distruzione da parte del sistema immunitario in quanto componente estraneo all'organismo, così che possa entrare nelle cellule.

IRC-19 Italian response to COVID-19

BNT162b2 $$

BioNTech/Pfizer



Encapsulated mRNA Vaccine

mRNA encoding for the Spike protein is protected in a lipid nanoparticles (like soap bubbles). Once absorbed, the cell expresses the Spike protein resulting in an immune response.

Efficacy : 95% (US/UK strain)
--% (B1.351 "SA" strain)

Dosing : 0.3mL - 2 doses - 21 days apart

Storage : -70°C - 6 months
+2-8°C - 5 days

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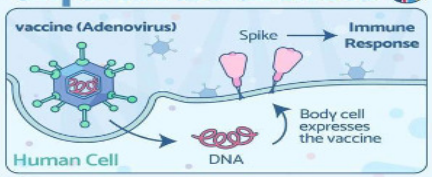
Last updated on 14/02/21

ChAdOx1 / AZD1222 (Covidshield) $

Oxford/Astrazeneca



Viral Vector Vaccine

dsDNA encoding for the Spike protein is protected in a safe virus. The infected cell expresses the Spike protein which leads to an immune response.

Efficacy : 82% (US/UK strain)
10% (B1.351 "SA" strain)

Dosing : 2 doses - 12 days apart

Storage : +2-8°C

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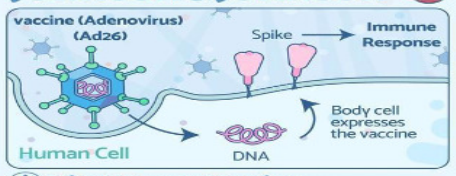
JNJ-78436735 / Ad26.COV2.S $

Johnson&Johnson



Viral Vector Vaccine

dsDNA encoding for the Spike protein is protected in a safe virus. The infected cell expresses the Spike protein which leads to an immune response.

Efficacy : 72% (US/UK strain)
57% (B1.351 "SA" strain)

Dosing : 1 dose

Storage : +2-8°C for 3 months
-20°C for 2 years

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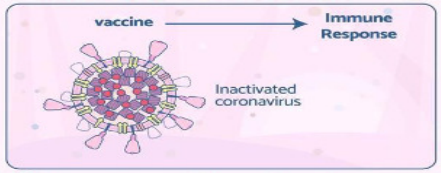
Last updated on 14/02/21

Covaxin

Bharat Biotech



Inactivated Virus Vaccine

SARS-CoV2 is chemically inactivated (with a chemical called beta-propiolactone•) so it cannot replicate but all the proteins remain intact.

Efficacy : --% (US/UK strain)
--% (B1.351 "SA" strain)

Dosing : 2 doses - 21 days apart

Storage : +2-8°C

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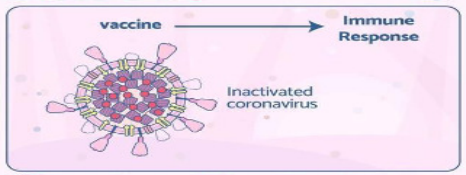
Last updated on 14/02/21

CoronaVac $$$

SinoVac



Inactivated Virus Vaccine

SARS-CoV2 is chemically inactivated (with a chemical called beta-propiolactone•) so it cannot replicate but all the proteins remain intact.

Efficacy : 50% (US/UK strain)
--% (B1.351 "SA" strain)

Dosing : 2 doses - 3 weeks apart

Storage : +2-8°C

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Last updated on 14/02/21

NVX-CoV2373 $

Novavax

Virus-like Particle Vaccine

Nanoparticles are coated with synthetic spike proteins. An additional element called adjuvant is added which allows to boost the immune reaction.

Efficacy : 89% (US/UK strain)
49% (B1.351 "SA" strain)

Dosing : 2 doses - 21 days apart

Storage : +2-8°C for 3 months
-20°C for 2 years

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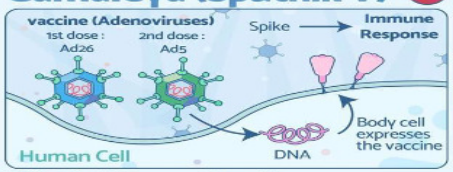
Sputnik V /Gam-Covid-Vac $

Gamaleya (Sputnik V)



Viral Vector Vaccine

dsDNA encoding for the Spike protein is protected in a safe virus. The infected cell expresses the Spike protein which leads to an immune response.

Efficacy : 91% (US/UK strain)
--% (B1.351 "SA" strain)

Dosing : 0.5mL - 2 doses - 28 days apart

Storage : +2-8°C for 3 months
-20°C for 2 years

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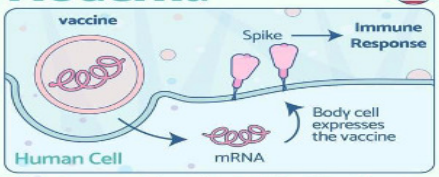
Last updated on 14/02/21

mRNA-1273 $$$

Moderna



Encapsulated mRNA Vaccine

mRNA encoding for the Spike protein is protected in a lipid nanoparticles (like soap bubbles). Once absorbed, the cell expresses the Spike protein resulting in an immune response.

Efficacy : 94.1% (US/UK strain)
--% (B1.351 "SA" strain)

Dosing : 0.5mL - 2 doses - 28 days apart

Storage : -20°C - 6 months
+2-8°C - 30 days

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IRC-19 Italian response to COVID-19

Report aggiornato al: 28-04-2021 06:10

18.502.829

Totale somministrazioni

Totale persone vaccinate | 5.430.357

(persone che hanno completato il ciclo vaccinale)

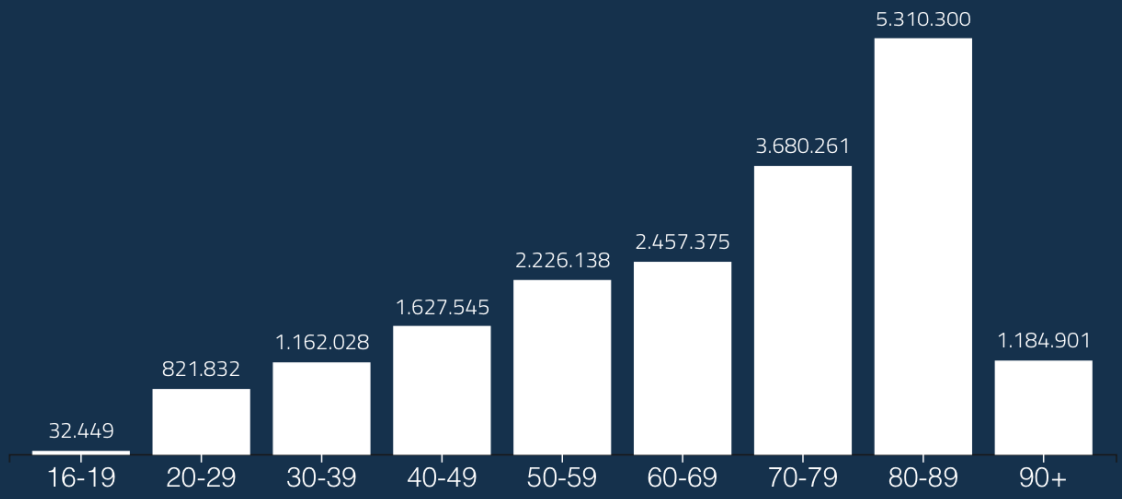
IRC-19 Italian response to COVID-19

Totale	**18.502.829**	**20.263.020**	**91.3%**

Somministrazioni per fasce di età

10.610.471

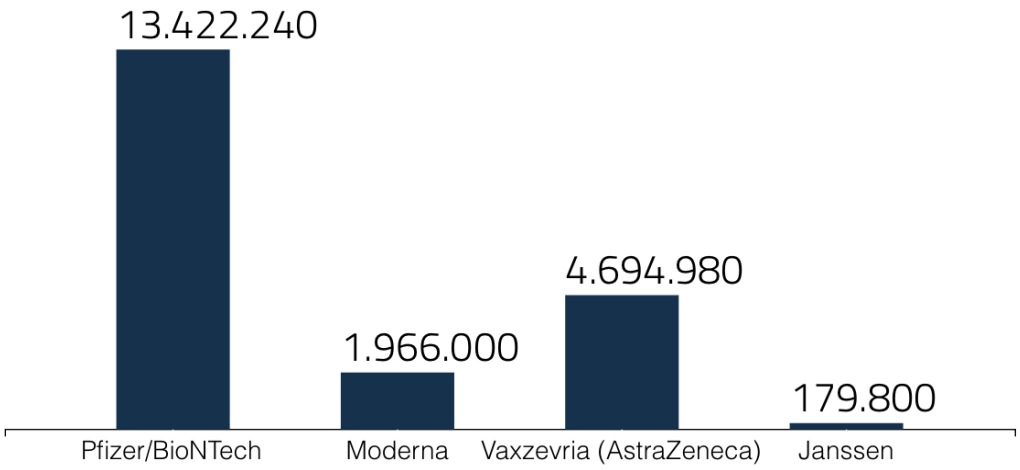
7.892.358



Distribuzione vaccini per fornitore

Totale
vaccini distribuiti

20.263.020

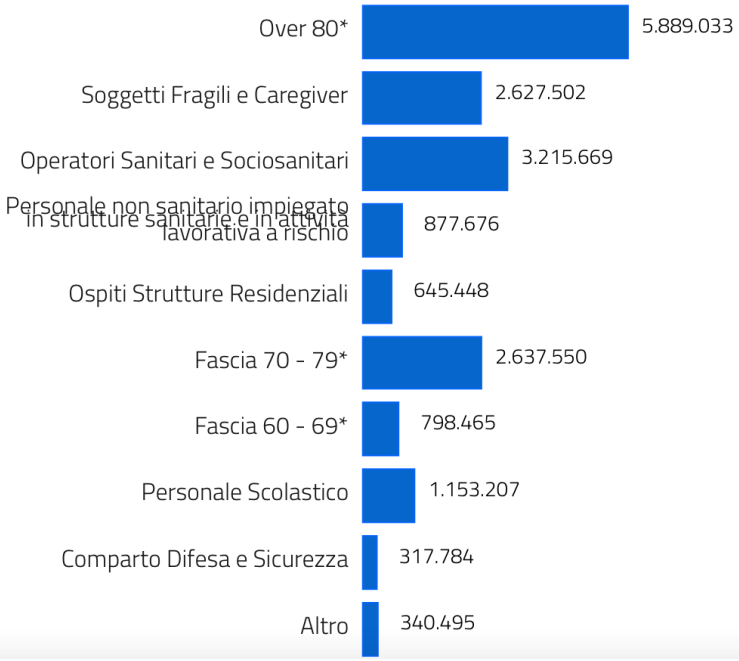


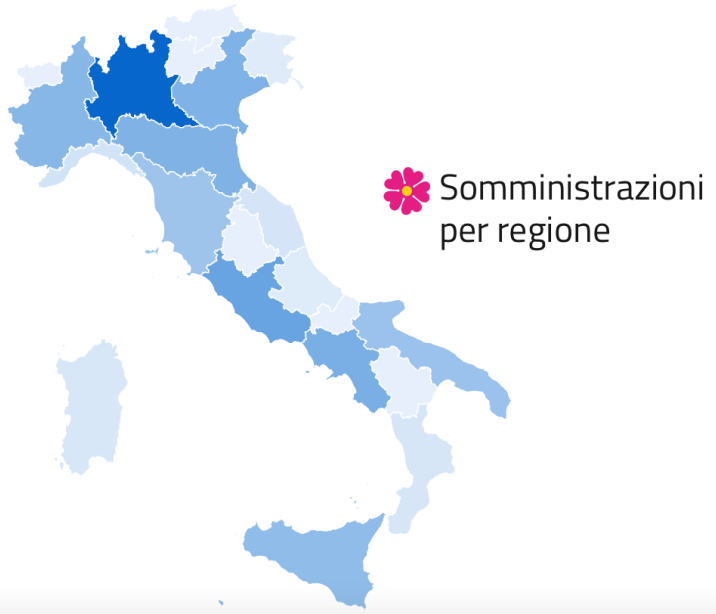
IRC-19 Italian response to COVID-19

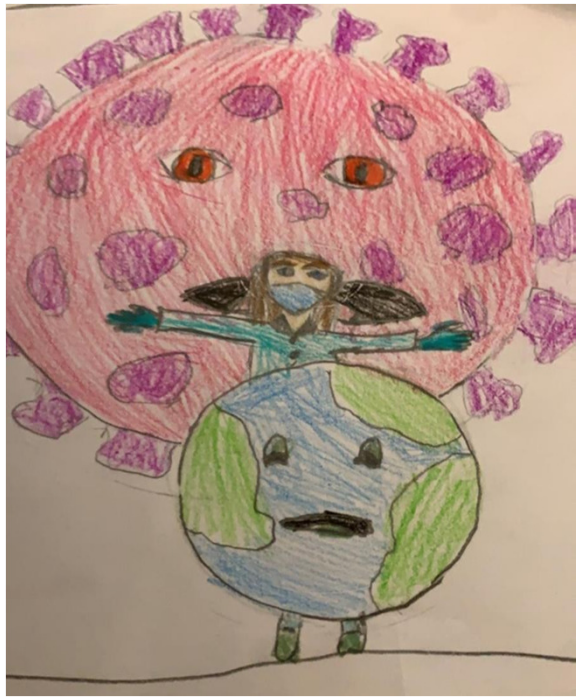
Somministrazioni per categoria

Totale somministrazioni

18.502.829







Grazie per l'attenzione!

francesco.digennaro@inmi.it