4S for YOUNG

SECONDO CONGRESSO NAZIONALE GIOVANI MEDICI

29-30 SETTEMBRE
1 OTTOBRE
2021

ROMA FIUMICINO
HILTON ROME AIRPORT

La trasformazione della Medicina Generale in era Covid tra riorganizzazione territoriale, telemedicina e nuove emergenze

SECONDO CONGRESSO NAZIONALE GIOVANI MEDICI

VENERDÌ | 1 OTTOBRE

9° SESSIONE	**Area pneumologica** Moderazione: ***V. Di Pietro***
11.15 - 11.45	Terapia nella polmonite da Covid-19 e nel paziente long Covid: l'uso dei nuovi inalatori ***R. Trevisan***

ASUGI
Azienda Sanitaria Universitaria Giuliano Isontina
REGIONE AUTONOMA FRIULI VENEZIA GIULIA

Ospedale Gorizia - Monfalcone
Dipartimento medico
S.S.D. Pneumologia

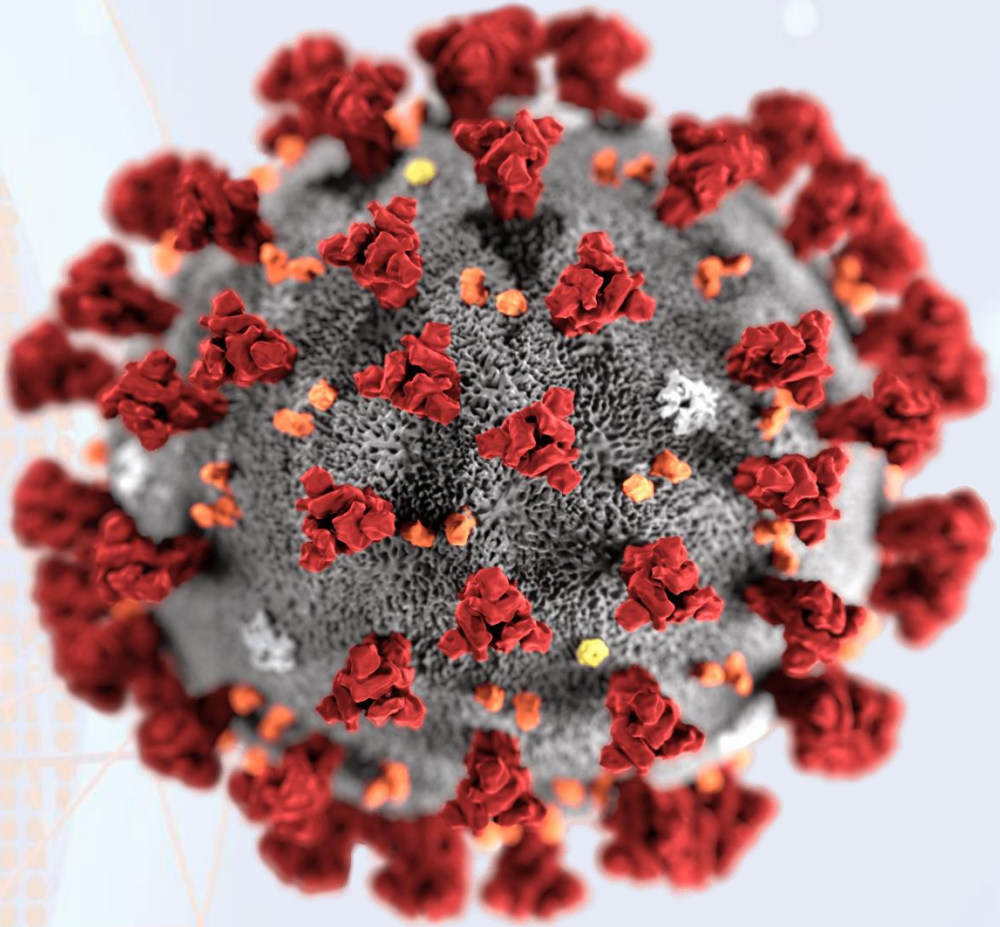
ITS ITALIAN THORACIC SOCIETY
AIPO ASSOCIAZIONE ITALIANA PNEUMOLOGI OSPEDALIERI
SEZIONE: FRIULI VENEZIA GIULIA

Disease

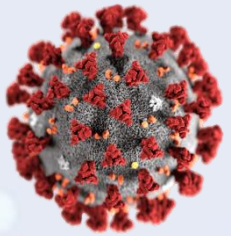
COVID-19

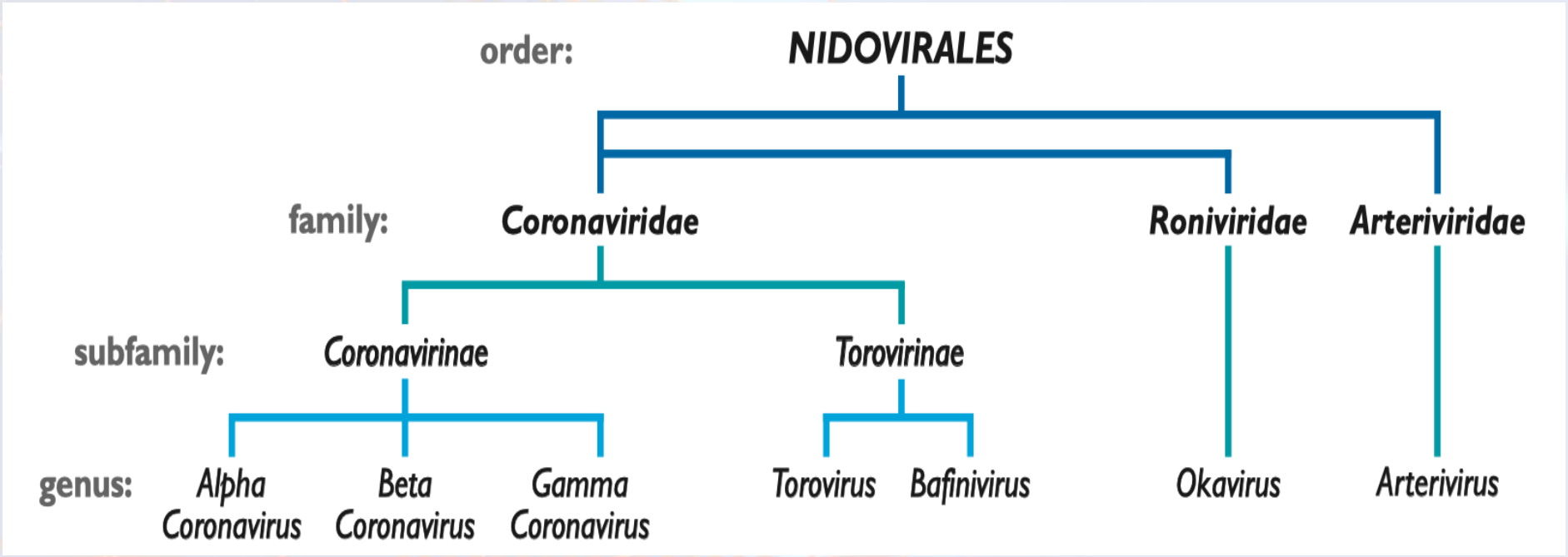
SARS-CoV-2
2019-nCov
HCoV-19

Virus Name



7 Human Coronaviruses: 4 normal; 3 “novel”

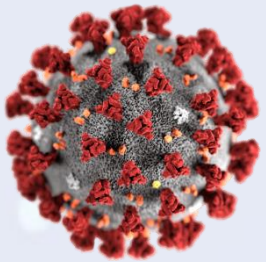




Alpha: HCoV-229E
HCoV-NL63

Beta: HCoV-HKU1, HCoV-OC43, MERS-CoV, SARS-CoV, SARS-CoV-2

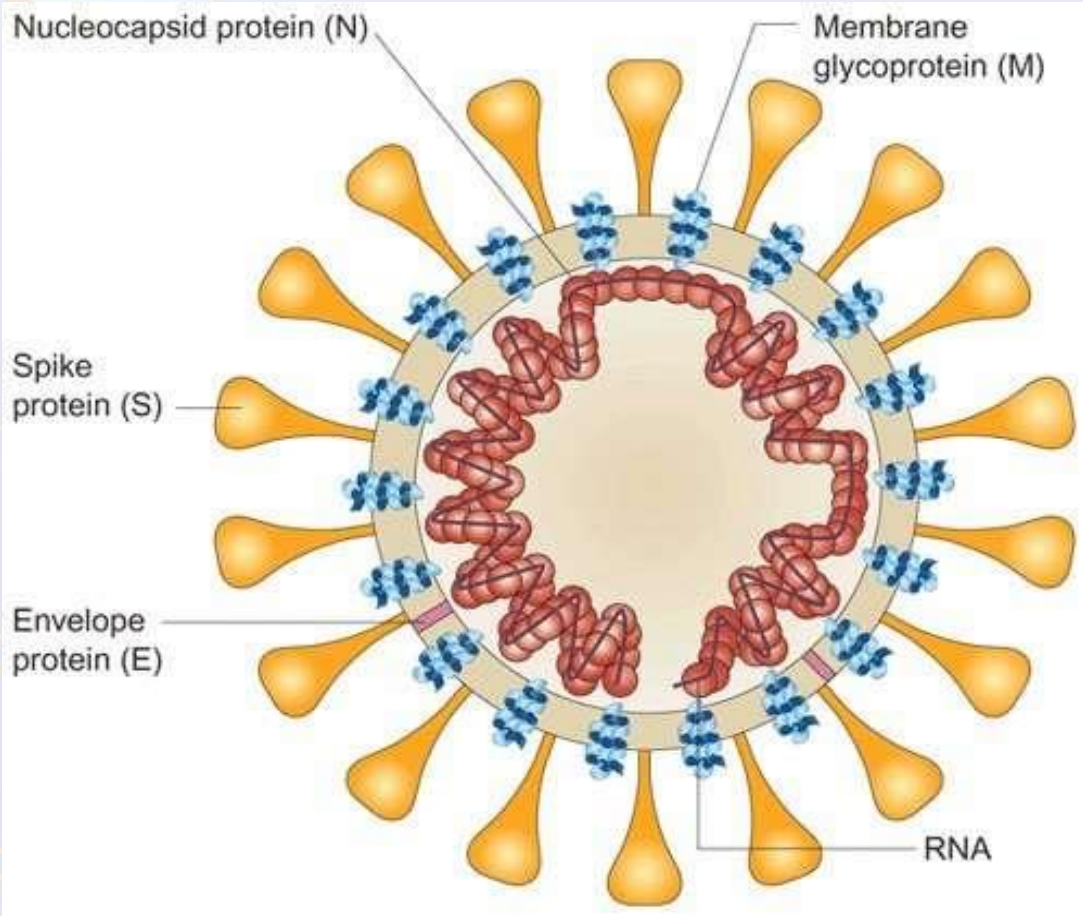
Coronavirus Structure



- Medium-sized virus size, but largest mRNA genome
- Enveloped +ve stranded RNA
- mRNA encased in nucleocapsid
- Lipid Bilayer – Soap works to disrupt this!

Corona = Crowns for Spikes

- Glycoprotein Spike (S) Peptomer
- Spikes allow it to attach to human cell receptors in upper or lower airway



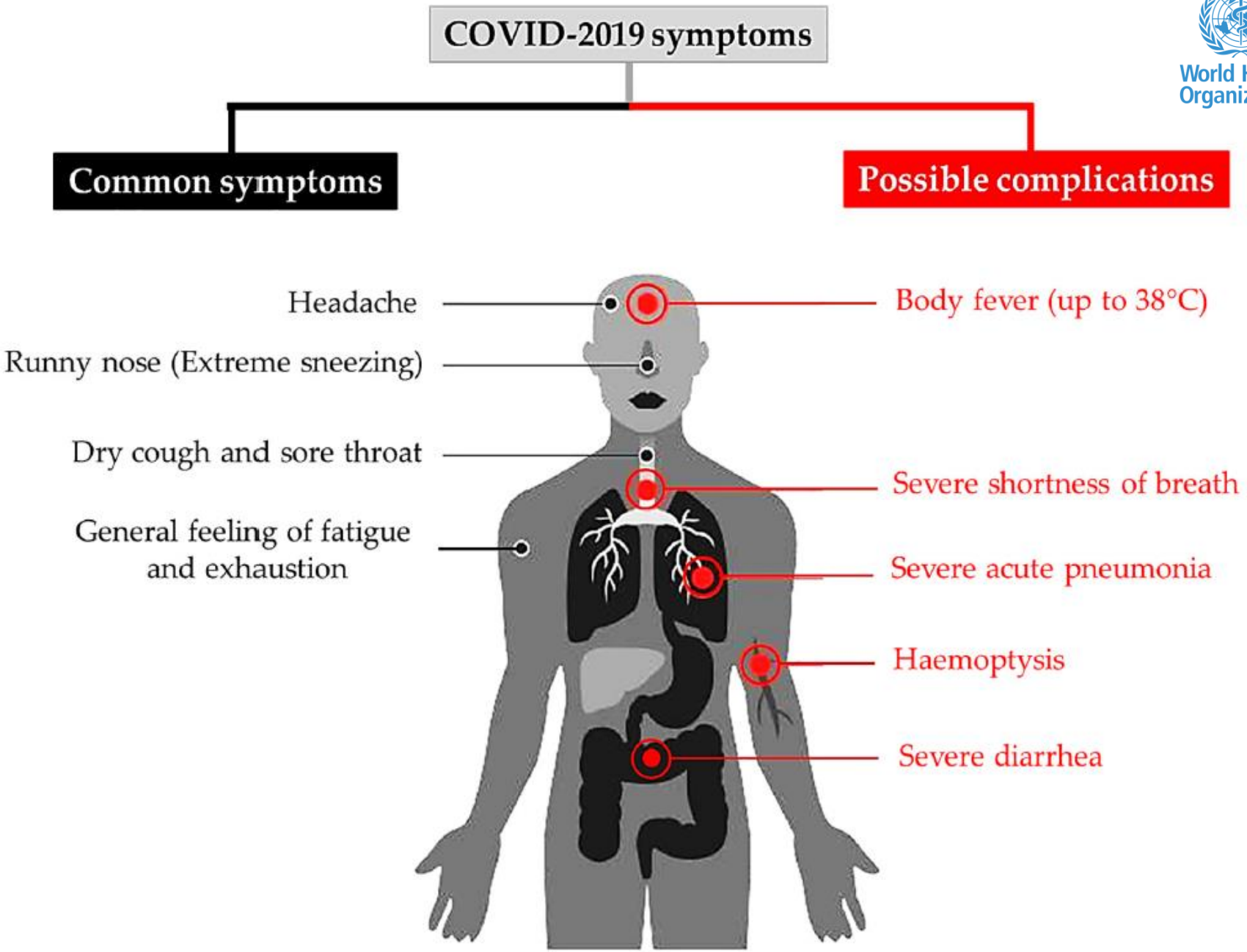


Fig. 4. The most common symptoms of COVID-19 according to the WHO.

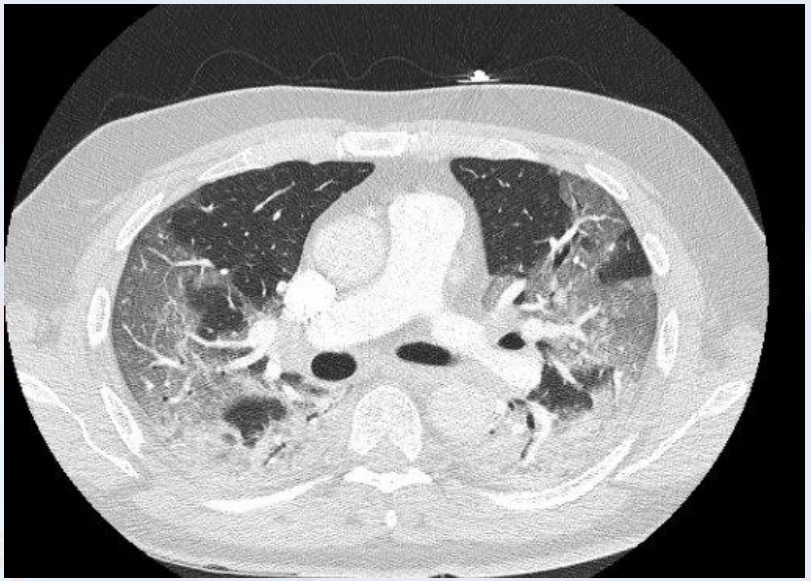
Histopathological findings and clinicopathologic correlation in COVID-19: a systematic review

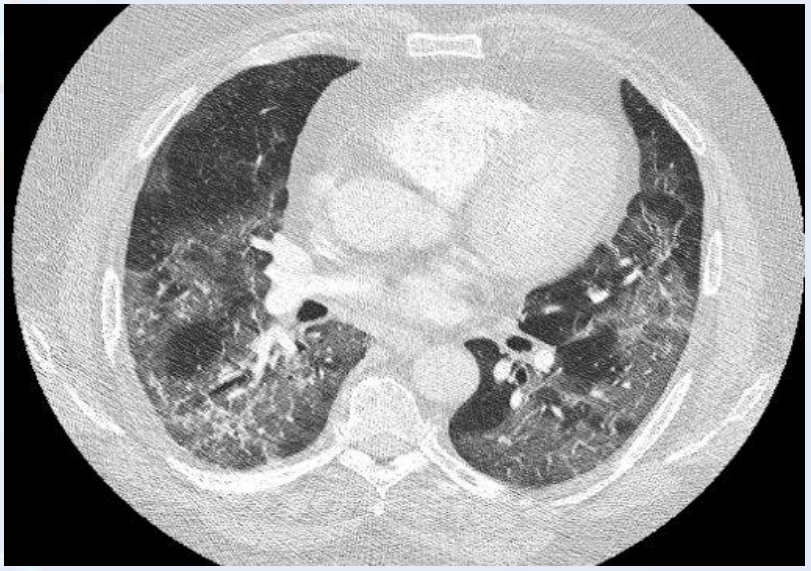
Modern Pathology (2021) 34:1614–1633

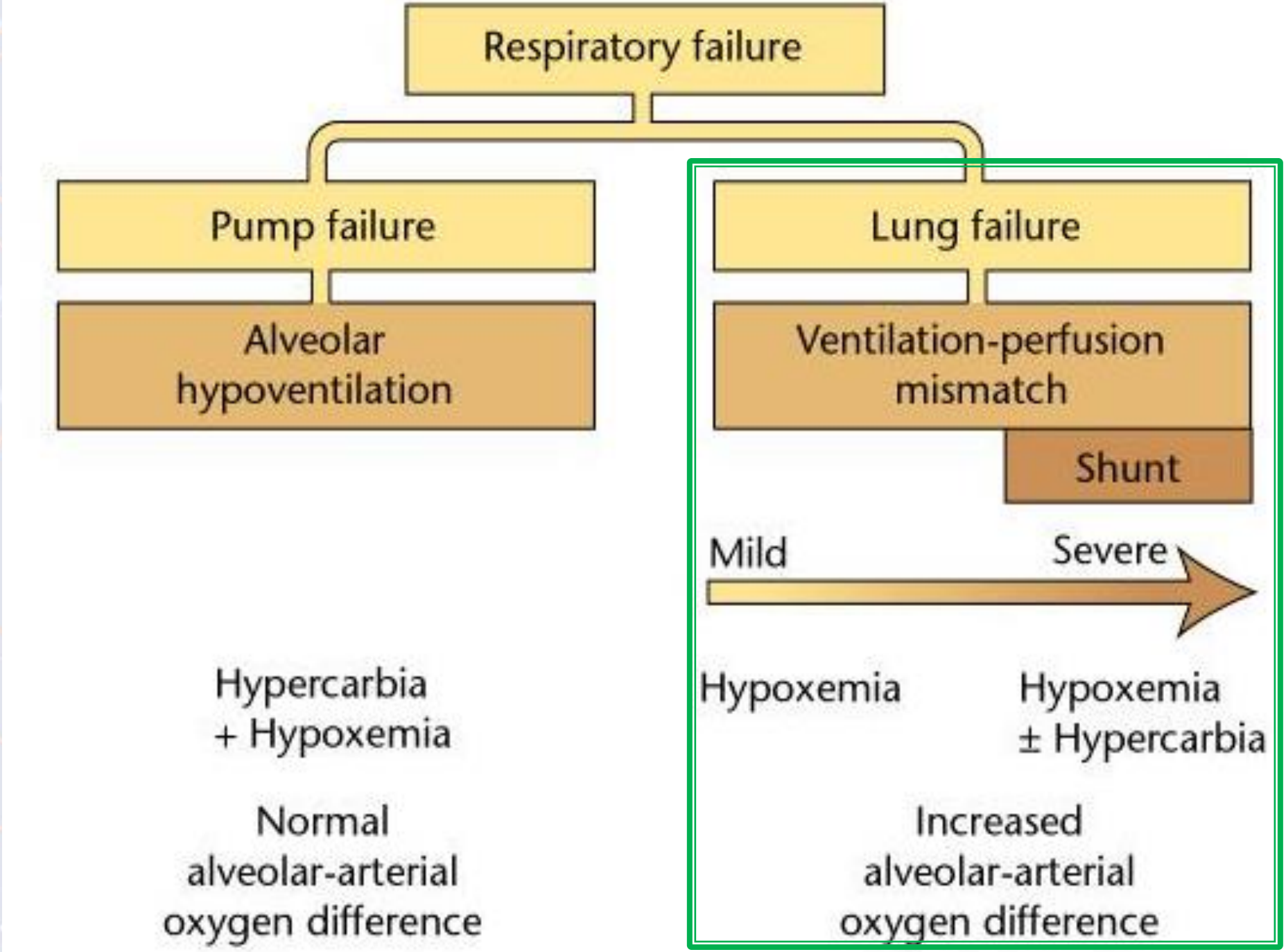
Stefania Caramaschi[1] · Meghan E. Kapp[2] · Sara E. Miller[3] · Rosana Eisenberg[2] · Joyce Johnson[2] · Garretson Epperly[4] · Antonino Maiorana[1] · Guido Silvestri[5,6] · Giovanna A. Giannico[2]

Table 2 Summary of main histopathologic findings in COVID-19.

Organ	Histopathologic findings	
Lung		
	DAD	Acute
		Acute-Proliferative
		Proliferative
		Proliferative-Fibrotic
		Fibrotic
	Interstitial/alveolar edema	
	Interstitial lymphocytic infiltrate	
	Pneumocyte reactive hyperplasia	
	Multinucleated giant cells	
	Alveolar/capillary megakaryocytes	
	Arteriolar vascular microthrombi	
	Alveolar/interstitial thickening	
	Pulmonary/alveolar hemorrhage	
	Vasculitis necrotizing/non-necrotizing	
	Bronchial/bronchiolar inflammation	
	Tracheobronchial inflammation	
	Acute bronchopneumonia (aspiration or secondary infection)	
	Acute pneumonia/bronchopneumonia NOS[a]	
	Organizing pneumonia	





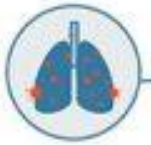

Respiratory failure
Pump failure
Lung failure
Alveolar hypoventilation
Ventilation-perfusion mismatch
Shunt
Mild
Severe
Hypercarbia + Hypoxemia
Hypoxemia
Hypoxemia ± Hypercarbia
Normal alveolar-arterial oxygen difference
Increased alveolar-arterial oxygen difference

COVID-19: Lasting impact

Even those survivors with mild initial cases can have wide-ranging health issues for six months or more.

WashU researchers link many diseases with COVID-19, signaling long-term complications for patients and a massive health burden for years to come.

Cardiovascular
acute coronary disease, heart failure, palpitations, arrythmias

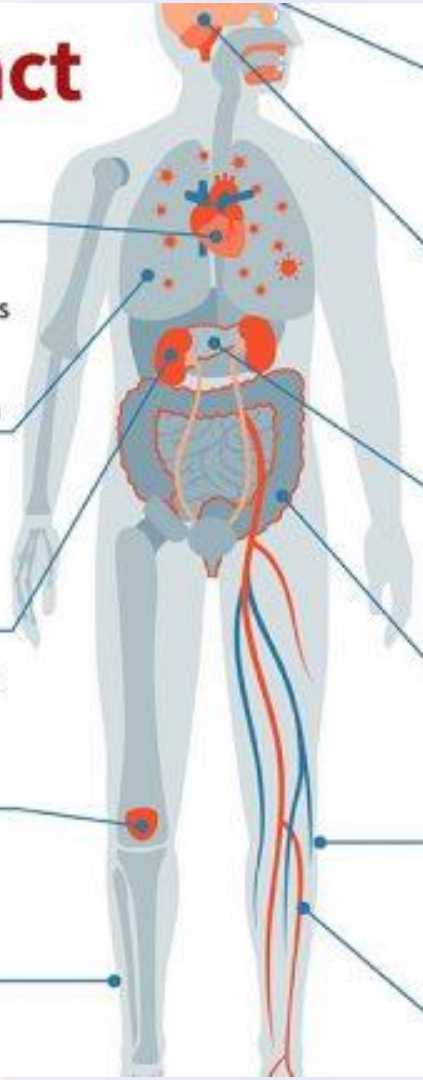


Respiratory system
cough, shortness of breath, low blood oxygen

Kidney
acute kidney injury, chronic kidney disease

Musculoskeletal
joint pain, muscle weakness

General
malaise, fatigue, anemia

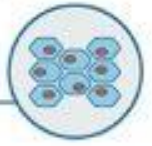


Mental health
anxiety, depression, sleep problems, substance abuse

Nervous system
stroke, headaches, memory problems, smell problems

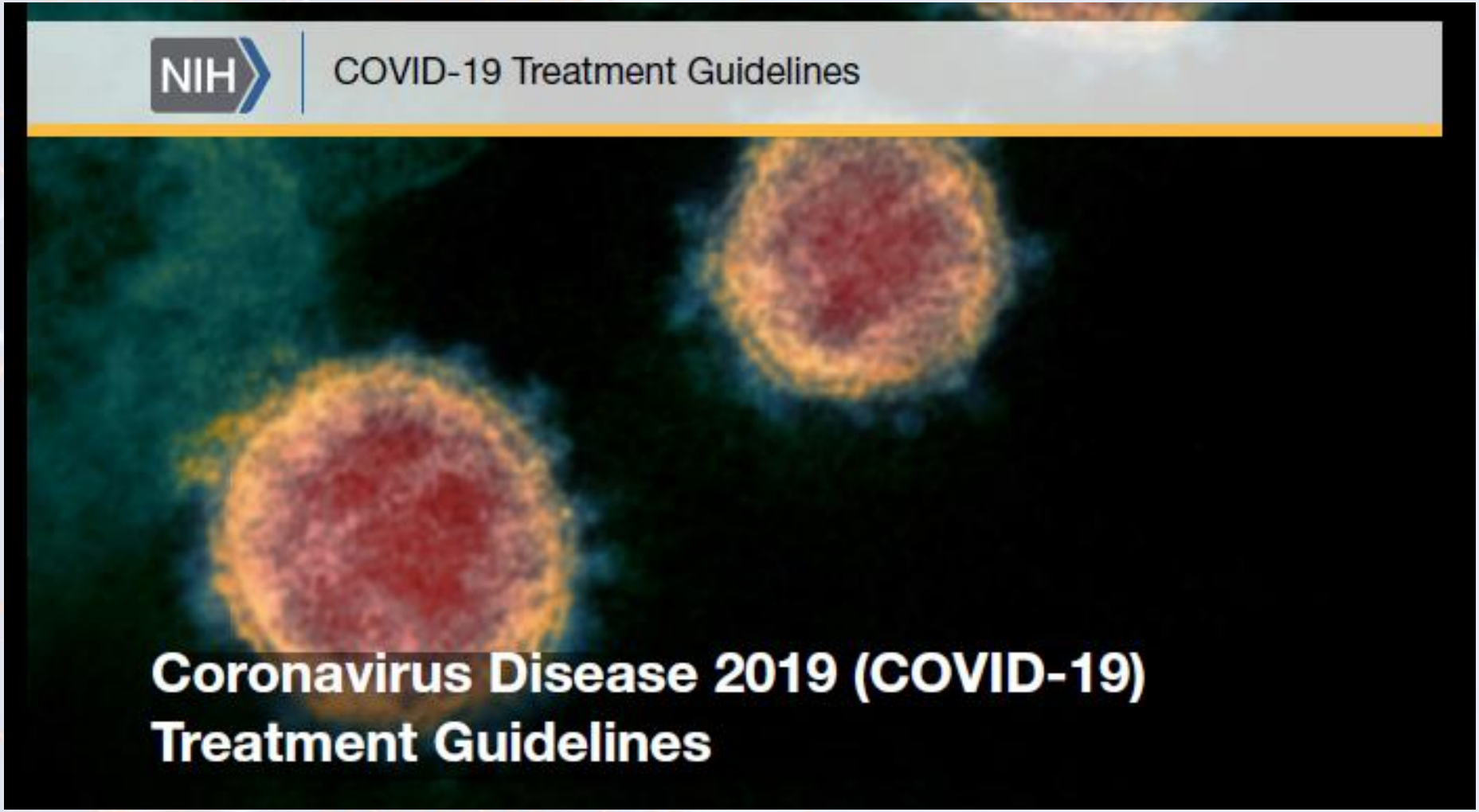
Metabolic/ endocrine
obesity, diabetes, high cholesterol

Gastrointestinal
constipation, diarrhea, acid reflux



Skin disorders
hair loss, rash

Coagulation disorders
blood clots


NIH
COVID-19 Treatment Guidelines
Coronavirus Disease 2019 (COVID-19)
Treatment Guidelines

Antiviral Drugs That Are Approved or Under Evaluation for the Treatment of COVID-19

Last Updated: July 8, 2021

Remdesivir is the only Food and Drug Administration-approved drug for the treatment of COVID-19. In this section, the COVID-19 Treatment Guidelines Panel (the Panel) provides recommendations for using antiviral drugs to treat COVID-19 based on the available data. **As in the management of any disease, treatment decisions ultimately reside with the patient and their health care provider.** For more information on these antiviral agents, see Table 2e.

Anti-SARS-CoV-2 Antibody Products

Anti-SARS-CoV-2 Monoclonal Antibodies for the Treatment of COVID-19

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using one of the following anti-SARS-CoV-2 monoclonal antibodies, listed in alphabetical order, to treat nonhospitalized patients with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by the Emergency Use Authorization (EUA) criteria:
  - **Casirivimab plus imdevimab**; *or*
  - **Sotrovimab**

At this time, the Panel **recommends against** the use of **bamlanivimab plus etesevimab** for the treatment of COVID-19 **(AIII)** because the Gamma (P.1) and Beta (B.1.351) variants of concern, which have reduced susceptibility to both agents, are circulating in the United States. See the Centers for Disease Control and Prevention COVID Data Tracker for the latest information on variant proportions by region in the United States.

Immunomodulators Under Evaluation for the Treatment of COVID-19

Last Updated: August 4, 2021

See Therapeutic Management of Hospitalized Adults with COVID-19 for the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations on the use of the following immunomodulators for patients according to their disease severity:

- Baricitinib with dexamethasone
- Dexamethasone
- Tocilizumab with dexamethasone

Additional Recommendations

There is insufficient evidence for the Panel to recommend either for or against the use of the following immunomodulators for the treatment of COVID-19:

- Colchicine for nonhospitalized patients
- Fluvoxamine
- Granulocyte-macrophage colony-stimulating factor inhibitors for hospitalized patients
- Inhaled budesonide
- Interleukin (IL)-1 inhibitors (e.g., anakinra)
- Interferon beta for the treatment of early (i.e., <7 days from symptom onset) mild to moderate COVID-19
- Sarilumab for patients who are within 24 hours of admission to the intensive care unit (ICU) and who require invasive mechanical ventilation, noninvasive ventilation, or high-flow oxygen (>0.4 FiO_2/30 L/min of oxygen flow)

Table 4b. Inhaled Corticosteroids: Selected Clinical Data

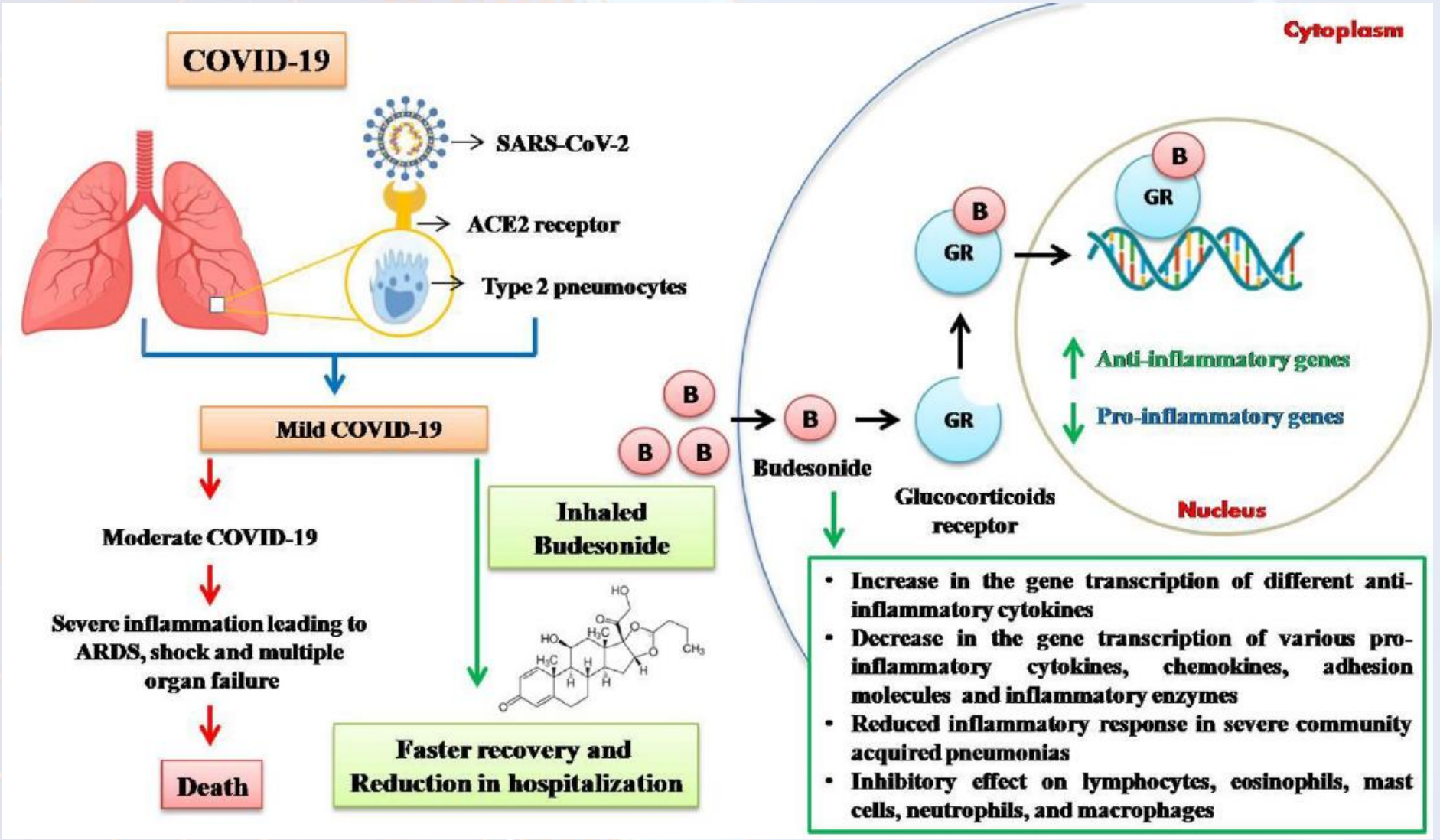
Last Updated: August 4, 2021

The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for inhaled corticosteroids. The studies summarized below are those that have had the greatest impact on the Panel's recommendations.

Study Design	Methods	Results	Limitations and Interpretation
STOIC: Inhaled Budesonide for the Treatment of Early COVID-19[1]			
Open-label, Phase 2, RCT in the United Kingdom (n = 146)	**Key Inclusion Criteria:** • Outpatients aged ≥18 years • Duration of symptoms ≤7 days **Key Exclusion Criteria:** • Use of inhaled or systemic glucocorticoids within the past 7 days • Known allergy or contraindication to budesonide **Interventions** *1:1 Randomization:* • Usual care (supportive therapy) • Usual care plus budesonide 800 mcg inhaled twice daily until symptom resolution **Primary Endpoint:** • COVID-19-related urgent care visit, including ED visit, or hospitalization	**Number of Participants:** • ITT analysis: Budesonide (n = 73) and usual care (n = 73) • Per-protocol analysis: Budesonide (n = 70) and usual care (n = 69) **Participant Characteristics:** • Mean age: 45 years • 58% women • Median number of comorbidities: 1; 9% had CVD, 5% had diabetes • 95% with positive SARS-CoV-2 RT-PCR • Median duration of symptoms prior to randomization: 3 days **Outcomes:** • Median duration of budesonide use: 7 days. • COVID-19-related urgent care visits or hospitalizations occurred in 1 participant (1%) in the budesonide arm and 10 participants (14%) in the usual care arm (difference in proportions 13%; 95% CI, 4–22; P = 0.004). Relative risk reduction of 91% for budesonide, NNT of 8.	**Key Limitations:** • Open-label study • Small sample size • Completed in a single UK region • The study was halted early after an independent statistical analysis determined that having additional participants would not alter the trial outcome. **Interpretation:** • In adult outpatients with mild COVID-19, inhaled budesonide may reduce the need for urgent medical care defined by urgent care or ED assessment and/or hospitalization. These findings should be interpreted with caution given the above limitations.

Commentary

Budesonide: A promising candidate therapeutic for early COVID-19



Commentary

Budesonide: A promising candidate therapeutic for early COVID-19

In conclusion, the fate of budesonide depend on the results of ongoing clinical trials but till date it appears as a promising candidate therapeutic for mild COVID-19 cases and may prove crucial in halting the disease in early form by shortening the recovery time and reducing the need of hospitalization.

Table 1
Clinical trials evaluating the efficacy of budesonide in COVID-19 patients (www.clinicaltrials.gov).

S. No.	NCT Number	Title	Phase	Interventions	Populations
1	NCT04331470	Evaluation of Efficacy of Levamisole and Formoterol +Budesonide in Treatment of COVID-19	Phase 2 Phase 3	•Drug: Levamisole Pill + Budesonide +Formoterol inhaler •Drug: Lopinavir/Ritonavir + hydoxychloroquine	Enrollment:30 Age: 15-100 Years (Child, Adult, Older Adult) Sex: All
2	NCT04361474	Trial Evaluating the Efficacy of Local Budesonide Therapy in the Management of Hyposmia in COVID-19 Patients Without Signs of Severity (COVIDORL)	Phase 3	•Drug: Budesonide Nasal •Other: Physiological serum	Enrollment:120 Age: 18 Years and older (Adult, Older Adult) Sex: All
3	NCT04416399	STerOids in COVID-19 Study (STOIC)	Phase 2	•Drug: Budesonide dry powder inhaler	Enrollment:146 Age: 18 Years and older (Adult, Older Adult) Sex: All
4	NCT04355637	Inhaled Corticosteroid Treatment of COVID19 Patients With Pneumonia	Phase 4	•Drug: Inhaled budesonide	Enrollment:300 Age:18 Years to 79 Years (Adult, Older Adult) Sex: All
5	NCT04331054	Protective Role of Inhaled Steroids for Covid-19 Infection (INHASCO)	Phase 3	•Drug: 2: Usual practice + SYMBICORT RAPIHALER •Other: 1: Usual practice	Enrollment:436 Age: 18 to 75 Years (Adult, Older Adult) Sex: All

Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial

Ly-Mee Yu, Mona Bafadhel*, Jienchi Dorward*, Gail Hayward, Benjamin R Saville, Oghenekome Gbinigie, Oliver Van Hecke, Emma Ogburn, Philip H Evans, Nicholas P B Thomas, Mahendra G Patel, Duncan Richards, Nicholas Berry, Michelle A Detry, Christina Saunders, Mark Fitzgerald, Victoria Harris, Milensu Shanyinde, Simon de Lusignan, Monique I Andersson, Peter J Barnes, Richard E K Russell, Dan V Nicolau Jr, Sanjay Ramakrishnan, F D Richard Hobbs†, Christopher C Butler†, on behalf of the PRINCIPLE Trial Collaborative Group‡*

Summary

Background A previous efficacy trial found benefit from inhaled budesonide for COVID-19 in patients not admitted to hospital, but effectiveness in high-risk individuals is unknown. We aimed to establish whether inhaled budesonide reduces time to recovery and COVID-19-related hospital admissions or deaths among people at high risk of complications in the community.

Methods PRINCIPLE is a multicentre, open-label, multi-arm, randomised, controlled, adaptive platform trial done remotely from a central trial site and at primary care centres in the UK. Eligible participants were aged 65 years or older or 50 years or older with comorbidities, and unwell for up to 14 days with suspected COVID-19 but not admitted to hospital. Participants were randomly assigned to usual care, usual care plus inhaled budesonide (800 µg twice daily for 14 days), or usual care plus other interventions, and followed up for 28 days. Participants were aware of group assignment. The coprimary endpoints are time to first self-reported recovery and hospital admission or death related to COVID-19, within 28 days, analysed using Bayesian models. The primary analysis population included all eligible SARS-CoV-2-positive participants randomly assigned to budesonide, usual care, and other interventions, from the start of the platform trial until the budesonide group was closed. This trial is registered at the ISRCTN registry (ISRCTN86534580) and is ongoing.

Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial

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Participants

People in the community were eligible if they were aged at least 65 years, or at least 50 years with comorbidities, and had ongoing symptoms from PCR-confirmed or suspected COVID-19 (in accordance with the UK National Health Service definition of high temperature, new, continuous cough, or change in sense of smell or taste),[17,18] which had started within the previous 14 days. Comorbidities required for eligibility in those aged 50–65 years were heart disease, hypertension, asthma or lung disease, diabetes, hepatic impairment, stroke or neurological problems, weakened immune system (eg, receiving chemotherapy), and self-reported obesity or body-mass index of at least 35 kg/m^2.

Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial

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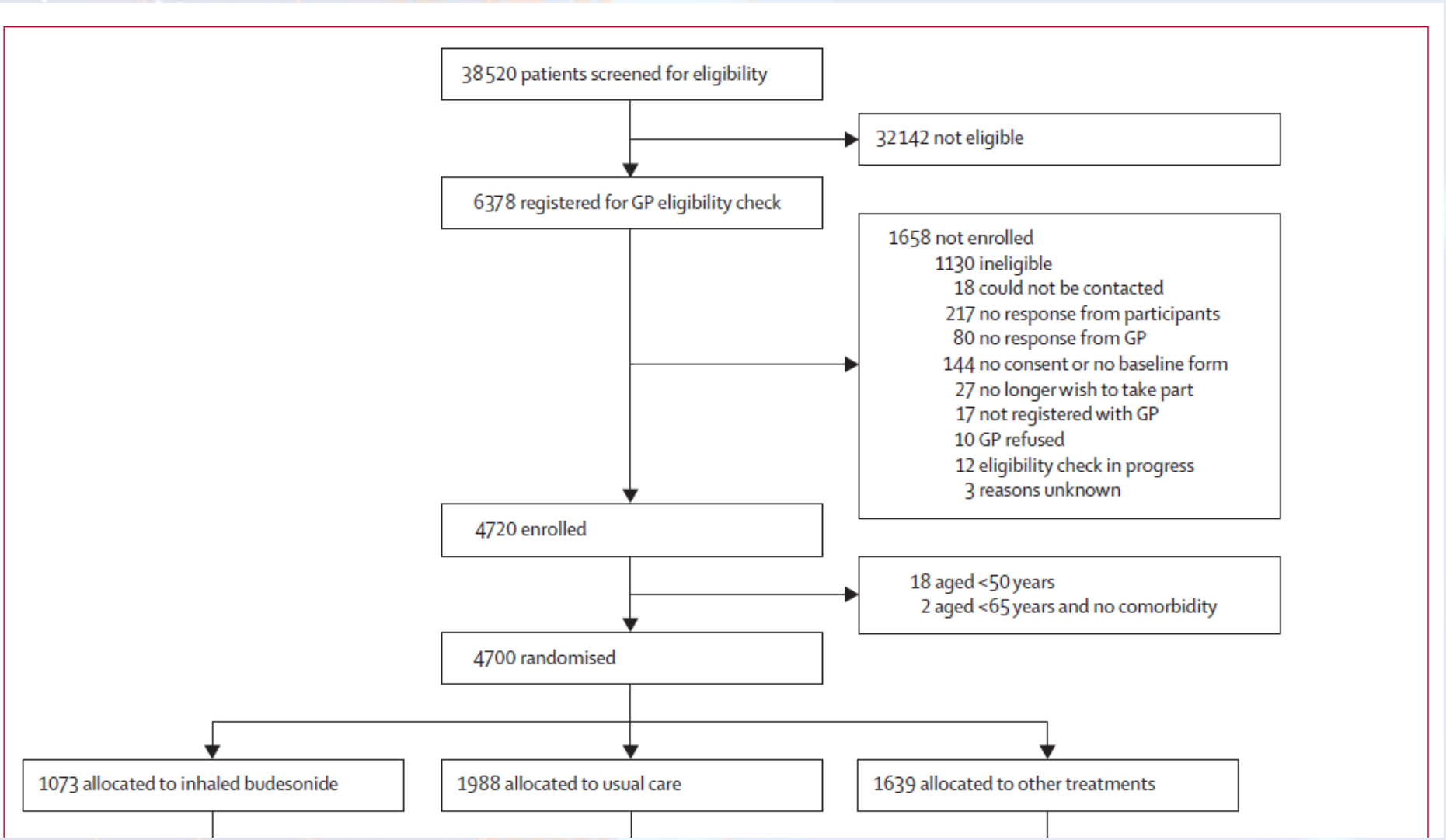

Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial

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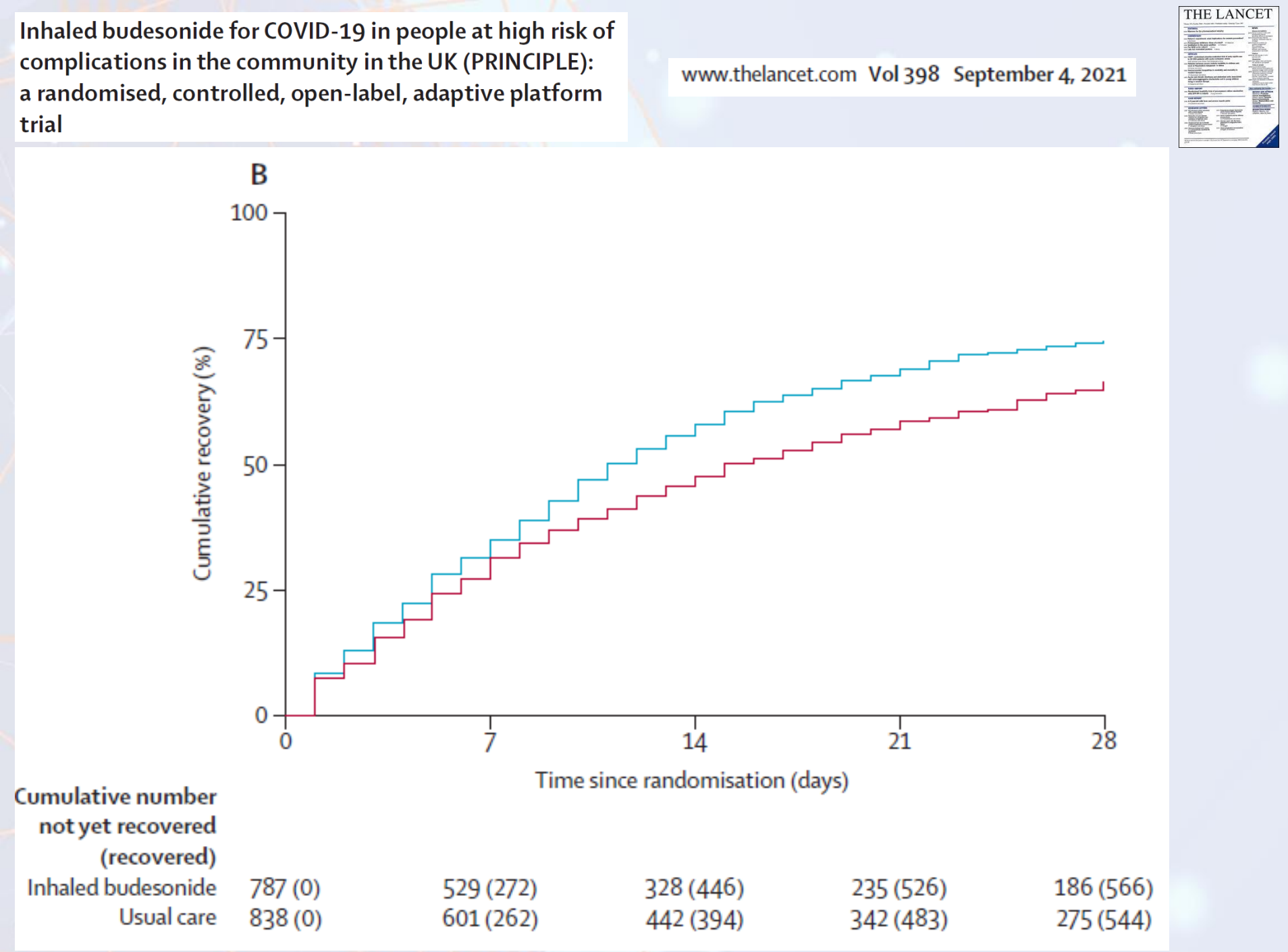

Cumulative number not yet recovered (recovered)					
Inhaled budesonide	787 (0)	529 (272)	328 (446)	235 (526)	186 (566)
Usual care	838 (0)	601 (262)	442 (394)	342 (483)	275 (544)

Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial

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Interpretation Inhaled budesonide improves time to recovery, with a chance of also reducing hospital admissions or deaths (although our results did not meet the superiority threshold), in people with COVID-19 in the community who are at higher risk of complications.

Added value of this study

To our knowledge, PRINCIPLE is the first pragmatic randomised trial to report the effectiveness of an inhaled corticosteroid for people with COVID-19 in the community. We found that inhaled budesonide reduced time to recovery by 3 days, with a high probability of also reducing COVID-19-related hospital admissions or deaths by an absolute difference of 2%.

Implications of all the available evidence

PRINCIPLE is the first randomised trial to demonstrate effectiveness of inhaled budesonide to treat COVID-19 in the community, and builds on earlier evidence from the phase 2 STOIC trial. Reducing time to recovery is an important outcome for patients, whereas potential prevention of hospital admissions or deaths would lessen the burden on hospitals during COVID-19 surges. There was no evidence in the STOIC trial of a negative effect of budesonide on SARS-CoV-2 viral loads, and in PRINCIPLE there were no concerning safety signals for inhaled budesonide. Inhaled budesonide should be considered for patients with COVID-19 who are at higher risk of complications in the community.

Article

Ciclesonide Inhaler Treatment for Mild-to-Moderate COVID-19: A Randomized, Open-Label, Phase 2 Trial

Journal of *Clinical Medicine*

Joon-Young Song [1], Jin-Gu Yoon [1], Yu-Bin Seo [2], Jacob Lee [2], Joong-Sik Eom [3], Jin-Soo Lee [4], Won-Suk Choi [5], Eun-Young Lee [6], Young-Ah Choi [7], Hak-Jun Hyun [1], Hye Seong [1], Ji-Yun Noh [1], Hee-Jin Cheong [1] and Woo-Joo Kim [1,*]

2. Materials and Methods

2.1. Study Design

This randomized, open-label, multicenter clinical trial was conducted in six hospitals in South Korea from 8 May 2020 to 31 March 2021 (Clinical Trial Number—NCT04330586). Clade GH SARS-CoV-2 circulated dominantly (>90%) in South Korea during study periods. Patients (aged ≥19 years) with mild-to-moderate COVID-19, confirmed by quantitative reverse transcription polymerase chain reaction (qRT-PCR), were enrolled in the study within 3 days of diagnosis or within 7 days from symptom onset.

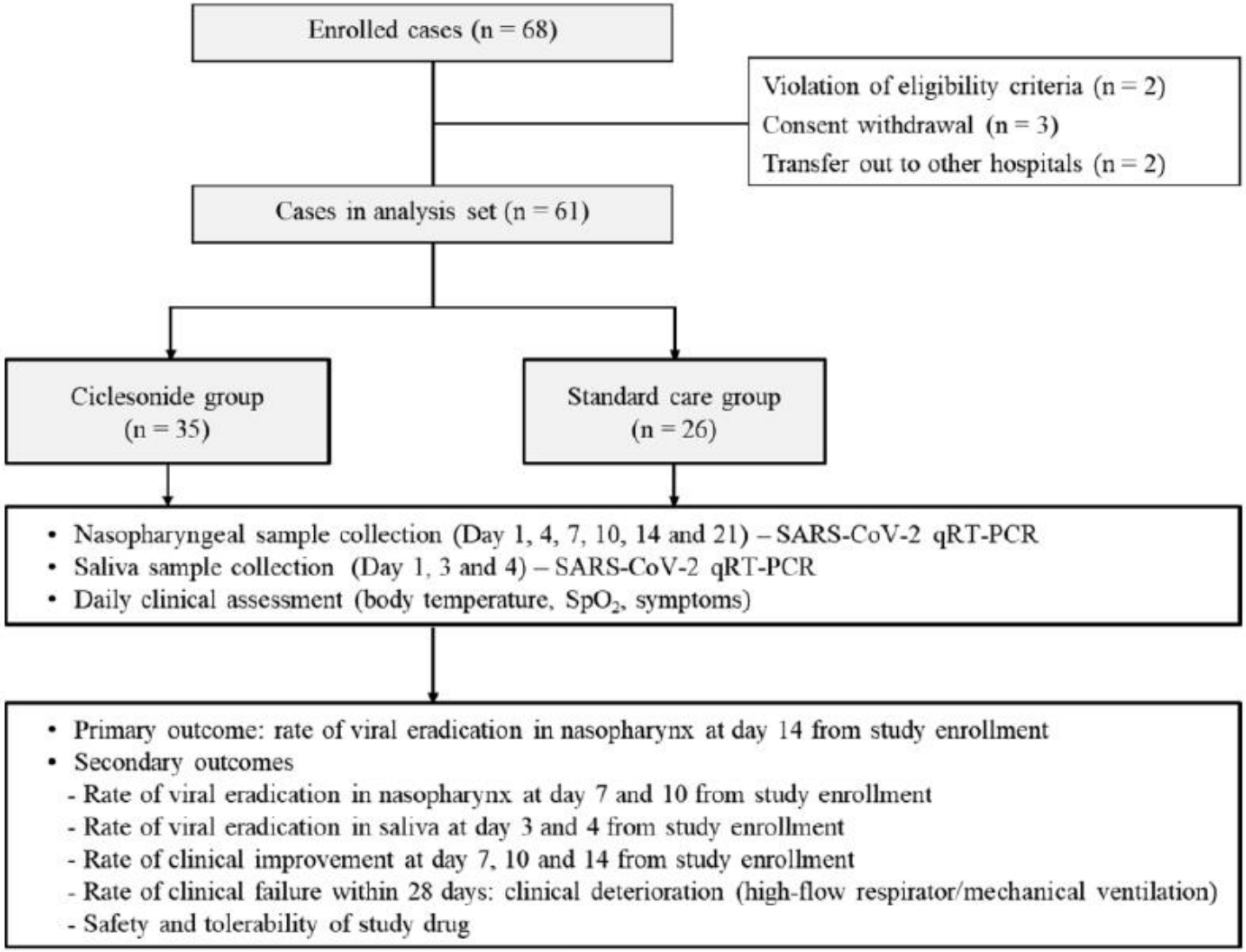
Eligible patients were randomly assigned in a 1:1:1 ratio to receive ciclesonide (320 μg inhalation twice per day for 14 days), ciclesonide-HCQ (320 μg inhalation twice per day for 14 days/400 mg daily for 10 days), or standard care. Expecting the synergistic or additive effect of ciclesonide and HCQ, the ciclesonide-HCQ combination was included in the comparison group. However, as data indicating that HCQ is not effective were published, the study design was altered to randomly assign patients to either ciclesonide or standard care groups.

J. Clin. Med. **2021**, *10*, 3545. https://doi.org/10.3390/jcm10163545

Article

Ciclesonide Inhaler Treatment for Mild-to-Moderate COVID-19: A Randomized, Open-Label, Phase 2 Trial

Journal of *Clinical Medicine*



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Article

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Journal of *Clinical Medicine*

Table 2. Comparison of clinical outcomes between ciclesonide and standard care groups.

	Ciclesonide Group (n = 35)	Standard Care Group (n = 26)	p-Value	Adjusted OR (95% CI) of Ciclesonide Treatment
Clinical failure rate, No. (%)	1 (2.9)	5 (19.2)	0.034	0.026 (0.001–0.845)
Clinical improvement rate at day 7, No. (%)	19 (54.3)	15 (57.7)	0.793	-
Clinical improvement rate at day 10, No. (%)	21 (60.0)	14 (53.8)	0.794	-
Clinical improvement rate at day 14, No. (%)	26 (74.3)	14 (53.8)	0.111	-
Virologic eradication rate at day 7, No. (%)	2/34 (5.9) [a]	0/22 (0) [b]	0.247	-
Virologic eradication rate at day 10, No. (%)	4/33 (12.1) [a]	0/22 (0) [b]	0.090	-
Virologic eradication rate at day 14, No. (%)	10/31 (32.3) [a]	1/20 (5.0) [b]	0.021	12.194 (1.187–125.240)
Duration of hospitalization, mean days ± SD	19.1 ± 7.7	19.5 ± 7.4	0.839	-

SD, standard deviation; OR, odds ratio; CI, confidence interval. [a] One patient was excluded at days 7, 10, and 14 because of clinical failure. In addition, one patient was excluded at day 10, and two more patients were excluded at day 14 because of early discharge with clinical improvement; respiratory specimens were not available. [b] Four patients were excluded at days 7 and 10, while five patients were excluded at day 14 because of clinical failure. In addition, one more patient was excluded at day 14 because of early discharge with clinical improvement; respiratory specimens were not available.

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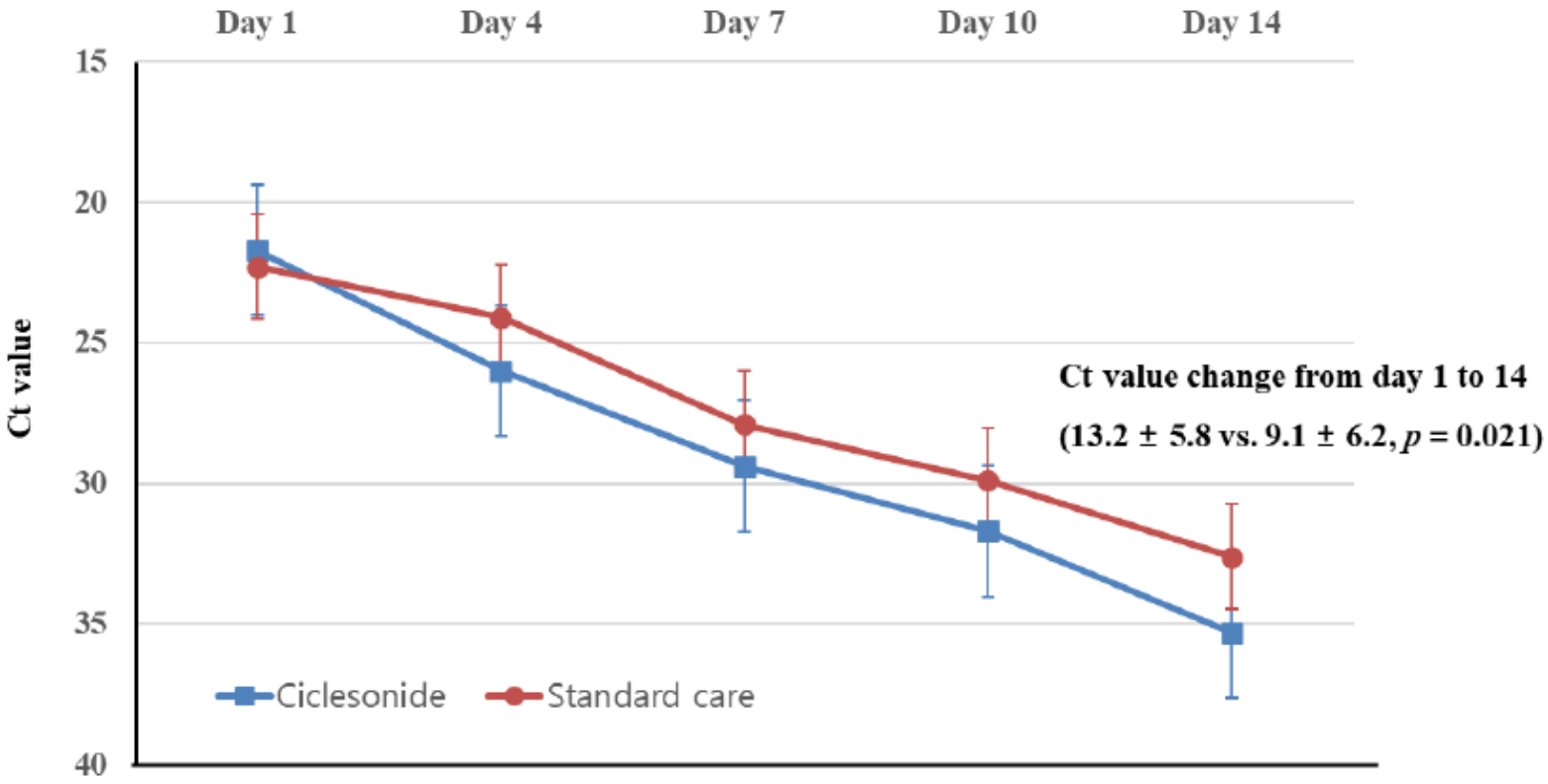

Figure 2. Comparison of serial cyclic threshold (Ct) values based on quantitative reverse transcription polymerase chain reaction targeting RdRp gene between ciclesonide and standard care groups. Four patients of ciclesonide group and six patients of standard care group were excluded in the analysis because of clinical failure or early discharge with clinical improvement, respectively.

J. Clin. Med. **2021**, *10*, 3545. https://doi.org/10.3390/jcm10163545

Article

Ciclesonide Inhaler Treatment for Mild-to-Moderate COVID-19: A Randomized, Open-Label, Phase 2 Trial

Journal of *Clinical Medicine*

This prospective, multicenter, randomized, open-label, phase 2 trial demonstrated that ciclesonide eradicated SARS-CoV-2 earlier and prevented the progression to severe COVID-19 among patients with mild-to-moderate COVID-19. Ciclesonide treatment increased the probability of SARS-CoV-2 negative conversion within 14 days by more than 12 times compared with standard care. Additionally, reduced risk of clinical failure (progression to hypoxia requiring respiratory management) by 97.4% was observed among patients who received ciclesonide compared with those who received standard care. However, in this study, we could not observe a significant shortening of symptom duration in the ciclesonide treatment group compared to the standard care group. The discrepancy may be due to the limitation of this study conducted in mild patients. Most mild symptoms other than fever are subjective, and self-limiting. Furthermore, because of individual variation, it

In conclusion, our results indicate that ciclesonide shortened SARS-CoV-2 viral shedding duration. Ciclesonide may inhibit the progression to acute respiratory failure in patients with mild-to-moderate COVID-19. Ciclesonide inhalation could be a useful therapeutic option for mild-to-moderate COVID-19 in an outpatient setting.

J. Clin. Med. **2021**, *10*, 3545. https://doi.org/10.3390/jcm10163545

That's all Folks!

Review

Inhalation Delivery for the Treatment and Prevention of COVID-19 Infection

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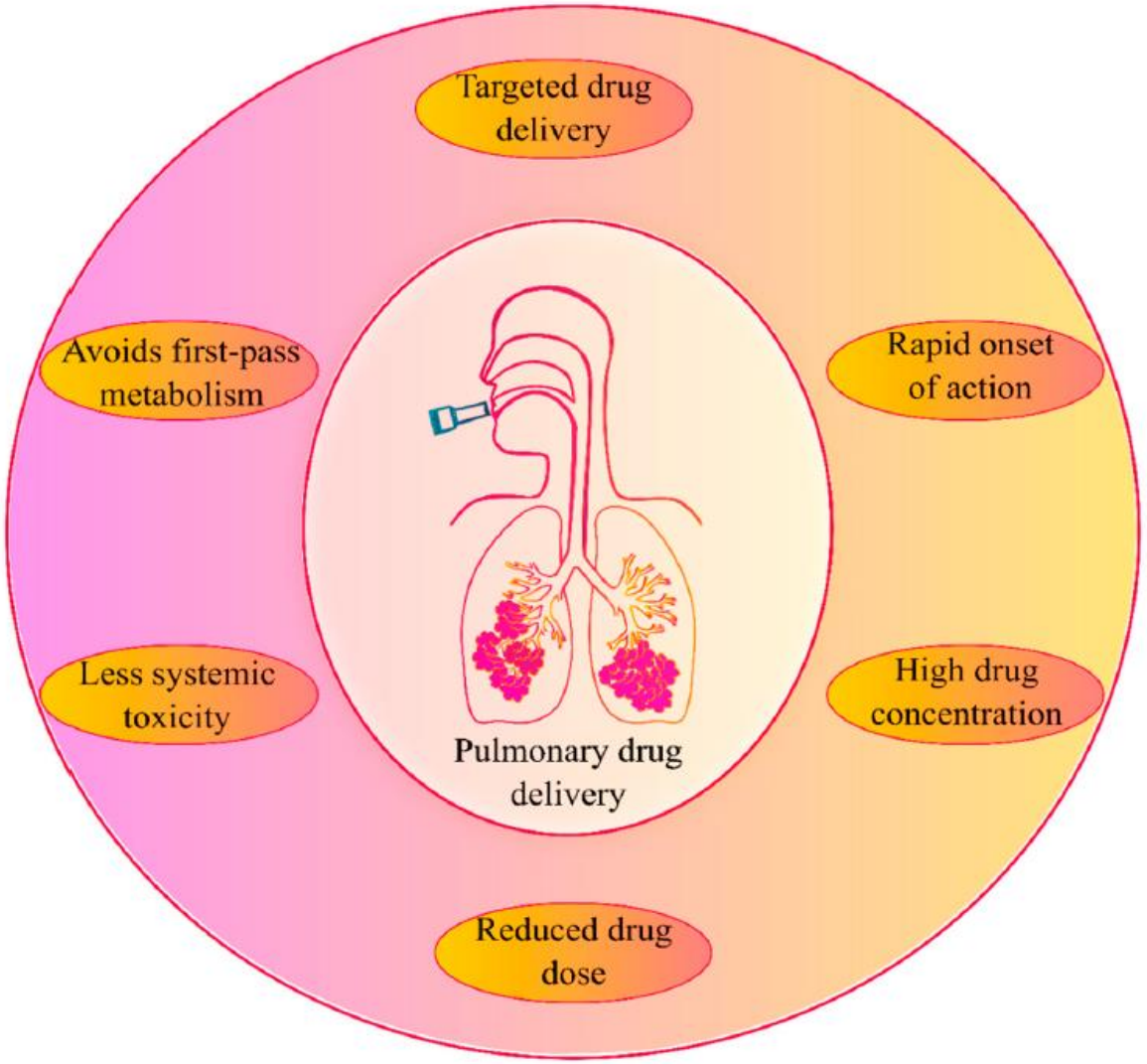
Inhalational Drug Administration—An Overview



Pharmaceutics **2021**, *13*, 1077

Inhalation Delivery for the Treatment and Prevention of COVID-19 Infection

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Inhaled COVID-19 Therapeutics

Drug	Category	Chemical Nature	Mode of Action	Inhaled Dose and Formulation/Device
Remdesivir	Antiviral	Nucleoside analogue	RNA polymerase inhibitor	31 mg and 62 mg (nebulizer)
Ciclesonide	Anti-inflammatory	Corticosteroid	Anti-inflammatory action	800 µg/day (MDI, Alvesco)
Budesonide	Anti-inflammatory	Corticosteroid	Anti-inflammatory action	800 µg twice daily for 14 days (DPI, Pulmicort Turbohaler)
Furosemide	Loop diuretic	Chlorobenzoic acid	Sodium-potassium-2 chloride (Na+-K+-2 Cl−) cotransporter inhibitor	40 mg (nebulizer)
Nitric Oxide	Pulmonary vasodilator	Oxides of nitrogen	Increases intracellular cGMP	250 µg/kg IBW/h (INOpulse®)
Epoprostenol	Pulmonary vasodilator	Prostaglandins I	Increases intracellular cAMP levels and antagonist of thromboxane A2	VentaProst (inhaled epoprostenol delivered via a dedicated delivery system)
Hydroxychloroquine	Antimalarial	Derivative of chloroquine	Inhibits lysosomal function	4, 8, 12 mg (nebulized) Up to 50 mg (nebulized) 20 mg (dry powder)
Plasminogen	Anticoagulant	Inert protein precursor	Thrombolytic	10 mg in 2 mL sterile water, twice daily (nebulized)

Review

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Inhaled COVID-19 Therapeutics

Modified Angiotensin-Converting Enzyme 2	Antiviral	Metallopeptidase	Regulates renin–angiotensin system and binds the viral spike protein and, thereby, neutralizes SARS-CoV-2	Not available
Interferon-β	Antiviral agent	Signaling proteins	Protease inhibitor	6 mIU of IFN-β
Anti-Microbial Colloidal Silver Formulations	Antimicrobial	Nano sized clusters of silver atoms	Destabilizes the cell membrane	10 µg/mL (ultrasonic mesh nebulizer)
Unfractionated heparin (UFH)	Anticoagulant	Sulfur-rich glycosaminoglycan	Inhibit factor Xa and factor IIa	25,000 IU/kg (Aeroneb Pro Nebulizer)
Salinomycin	Antibacterial agents	Polyketide	Inhibits endosomal acidification	Not available
Ivermectin	Antiparasitic drug	Macrocyclic lactone	Nuclear transport inhibitor	380 mg/m^3 (nebulized, dose in rats, no studies in humans)
Niclosamide	Antiparasitic agents	Benzamide	SKP2 inhibitor	Not yet released

Drugs that inhibit TMEM16 proteins block SARS-CoV-2 spike-induced syncytia

Luca Braga[1,9], Hashim Ali[1,9], Ilaria Secco[1], Elena Chiavacci[1], Guilherme Neves[2,3], Daniel Goldhill[4], Rebecca Penn[4], Jose M. Jimenez-Guardeño[5], Ana M. Ortega-Prieto[5], Rossana Bussani[6], Antonio Cannatà[1], Giorgia Rizzari[1], Chiara Collesi[6,7], Edoardo Schneider[1,7], Daniele Arosio[8], Ajay M. Shah[1], Wendy S. Barclay[4], Michael H. Malim[5], Juan Burrone[2,3] & Mauro Giacca[1,6,7] ✉

COVID-19 is a disease with unique characteristics that include lung thrombosis[1], frequent diarrhoea[2], abnormal activation of the inflammatory response[3] and rapid deterioration of lung function consistent with alveolar oedema[4]. The pathological substrate for these findings remains unknown. Here we show that the lungs of patients with COVID-19 contain infected pneumocytes with abnormal morphology and frequent multinucleation. The generation of these syncytia results from activation of the SARS-CoV-2 spike protein at the cell plasma membrane level.

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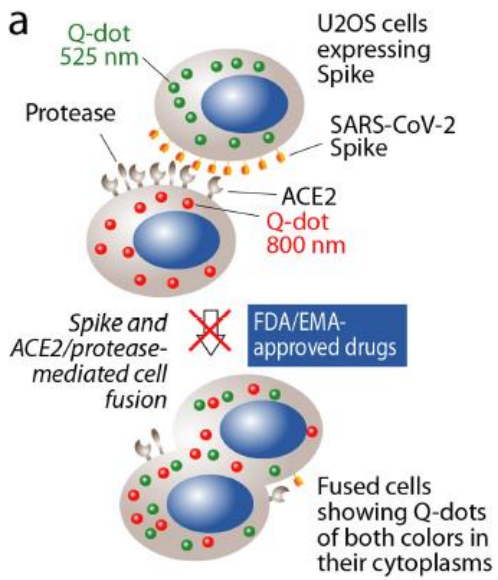
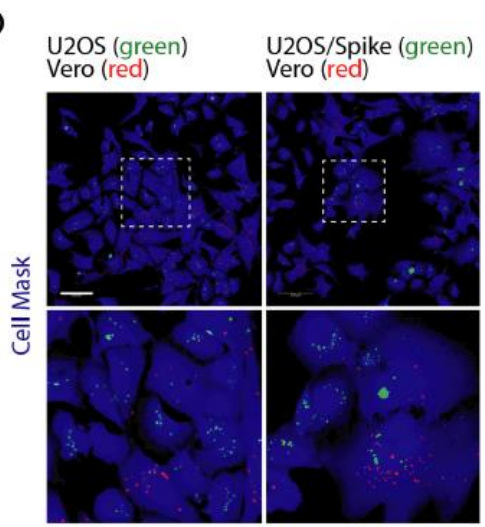
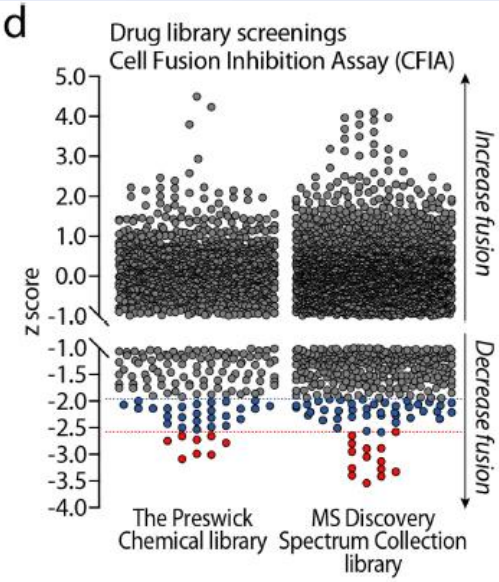
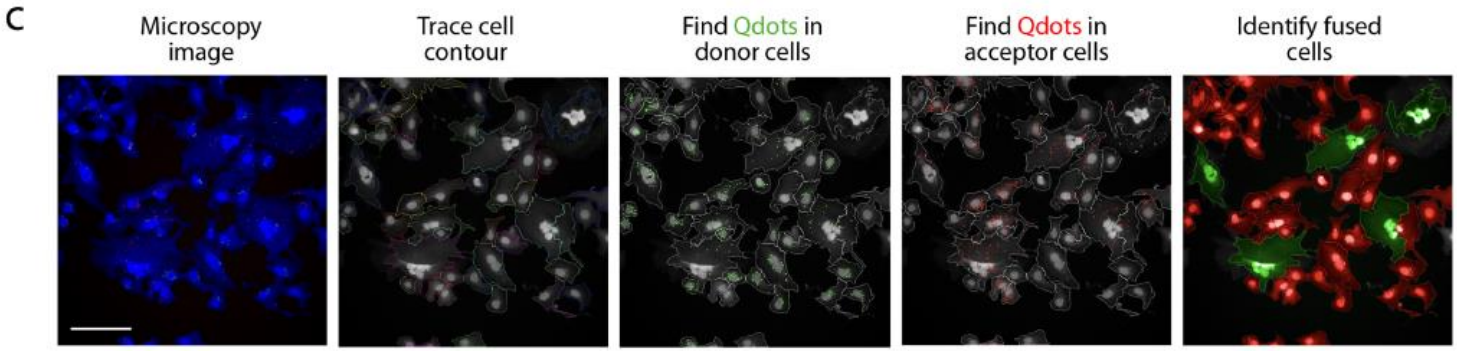
we performed two high-content microscopy-based screenings with more than 3,000 approved drugs to search for inhibitors of spike-driven syncytia. We converged on the identification of 83 drugs that inhibited spike-mediated cell fusion, several of which belonged to defined pharmacological classes. We focused our attention on effective drugs that also protected against virus replication and associated cytopathicity. One of the most effective molecules was the antihelminthic drug niclosamide, which markedly blunted calcium oscillations and membrane conductance in spike-expressing cells by suppressing the activity of TMEM16F (also known as anoctamin 6), a calcium-activated ion channel and scramblase that is responsible for exposure of phosphatidylserine on the cell surface. These findings suggest a potential mechanism for COVID-19 disease pathogenesis and support the repurposing of niclosamide for therapy.

Drugs that inhibit TMEM16 proteins block SARS-CoV-2 spike-induced syncytia









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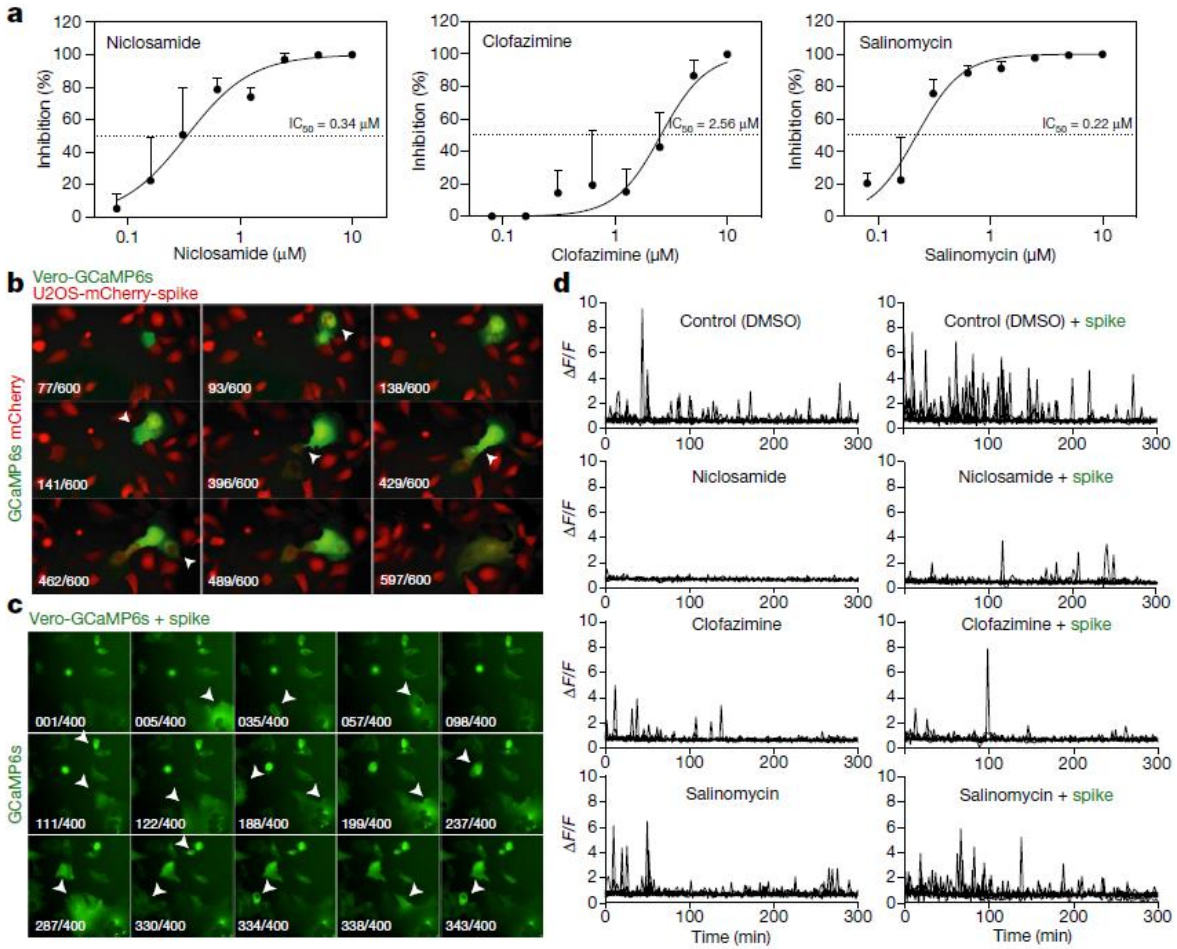

A randomized, double-blind, placebo-controlled phase 1 trial of inhaled and intranasal niclosamide: A broad spectrum antiviral candidate for treatment of COVID-19

Vibeke Backer[a,b,*], Ulf Sjöbring[c], Jesper Sonne[d], Anne Weiss[e,f], Morten Hostrup[g], Helle Krogh Johansen[e,h,i], Victoria Becker[b], David P. Sonne[d], Torben Balchen[j], Mads Jellingsø[c], Morten Otto Alexander Sommer[c,e,**]

Methods: We conducted a randomized, placebo-controlled, double-blind, single-centre, dose-ascending Phase 1 trial to assess the safety of UNI91104 in Denmark (NCT04576312). Healthy volunteers were randomly assigned to a ascending single dose in cohort 1–4 and five doses over 2.5 days in cohort 5. Inclusion criteria included a minimum 80% of predicted lung function. Exclusion criteria included severe, clinically significant allergies and current acute or chronic condition especially airway diseases. Safety was evaluated through adverse events (AEs) and pulmonary function tests including forced expiratory volume in one second (FEV1) and fractional exhaled nitric oxide (FeNO) tests. The primary endpoints were defined as the frequency of reported AEs and the change of safety variables relative to pre-dose. Data from all enroled healthy volunteers receiving any amount of IMP was included in the primary analyses. The pharmacokinetics of UNI91104 was determined.

The Lancet Regional Health - Europe 4 (2021) 100084

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Added value of the study

We conducted a single-centre, double-blinded, dose-ascending Phase 1 trial to assess the safety of five doses of UNI91104 (concentrated solution of niclosamide for inhalation and intranasal application) in healthy volunteers. We showed that UNI91104 is well-tolerated in all dose groups tested, with mild and transient irritation in the upper respiratory tract being the most frequent AE. Nasal application did not result in any AE findings.

Implications of all available evidence

Data from this study supports the testing of UNI91104, a promising candidate for viral respiratory infections such as COVID19, in patient trials.

Interpretation: UNI91104, a promising candidate for inhalation and intranasal therapy against COVID-19 and other viral respiratory tract infections is well-tolerated in healthy volunteers and warrants further testing in patient trials.

The Lancet Regional Health - Europe 4 (2021) 100084

Inhalation monoclonal antibody therapy: a new way to treat and manage respiratory infections

Hilal Ahmad Parray[1] · Shivangi Shukla[1] · Reshma Perween[1] · Ritika Khatri[1] · Tripti Shrivastava[1] · Vanshika Singh[1] · Praveenkumar Murugavelu[1] · Shubbir Ahmed[1] · Sweety Samal[1] · Chandresh Sharma[1] · Subrata Sinha[2] · Kalpana Luthra[2] · Rajesh Kumar[1]

Abstract

The route of administration of a therapeutic agent has a substantial impact on its success. Therapeutic antibodies are usually administered systemically, either directly by intravenous route, or indirectly by intramuscular or subcutaneous injection. However, treatment of diseases contained within a specific tissue necessitates a better alternate route of administration for targeting localised infections. Inhalation is a promising non-invasive strategy for antibody delivery to treat respiratory maladies because it provides higher concentrations of antibody in the respiratory airways overcoming the constraints of entry through systemic circulation and uncertainity in the amount reaching the target tissue. The nasal drug delivery route is one of the extensively researched modes of administration, and nasal sprays for molecular drugs are deemed successful and are presently commercially marketed.

Applied Microbiology and Biotechnology
https://doi.org/10.1007/s00253-021-11488-4

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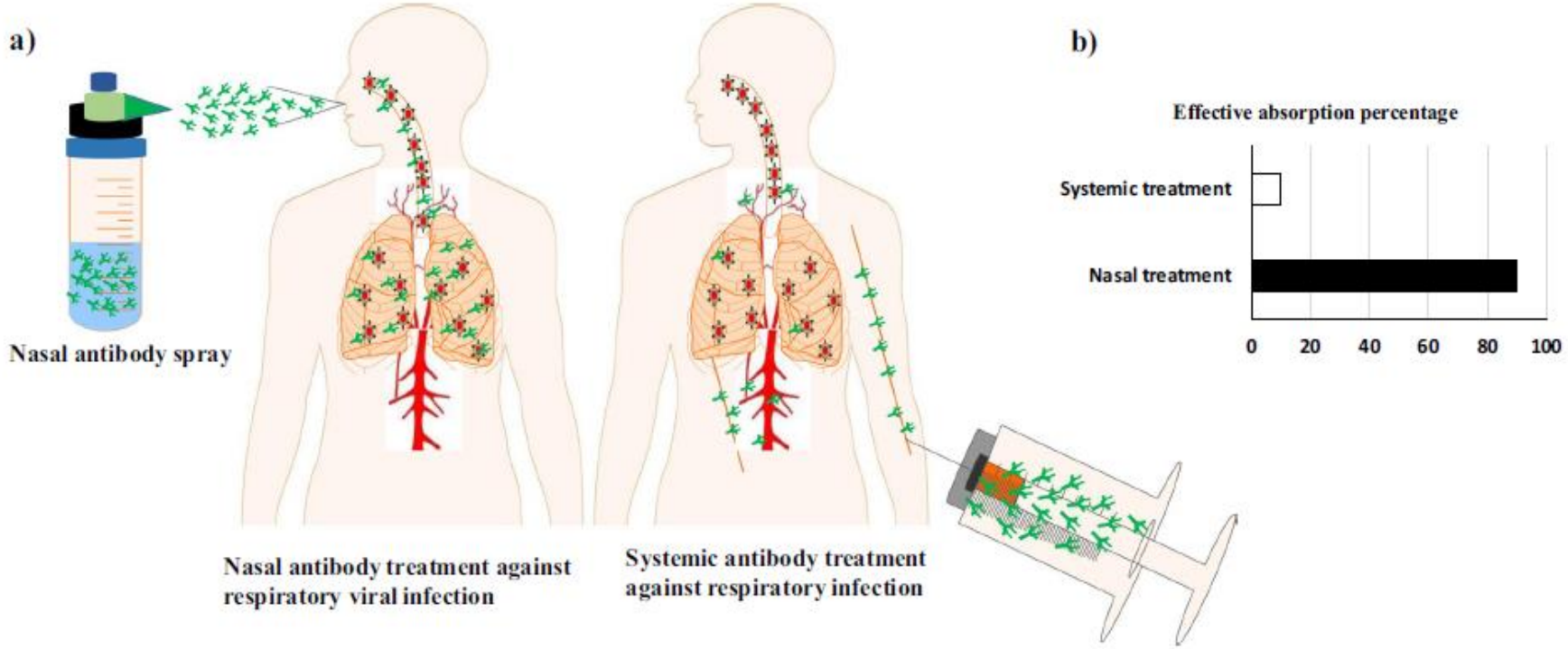
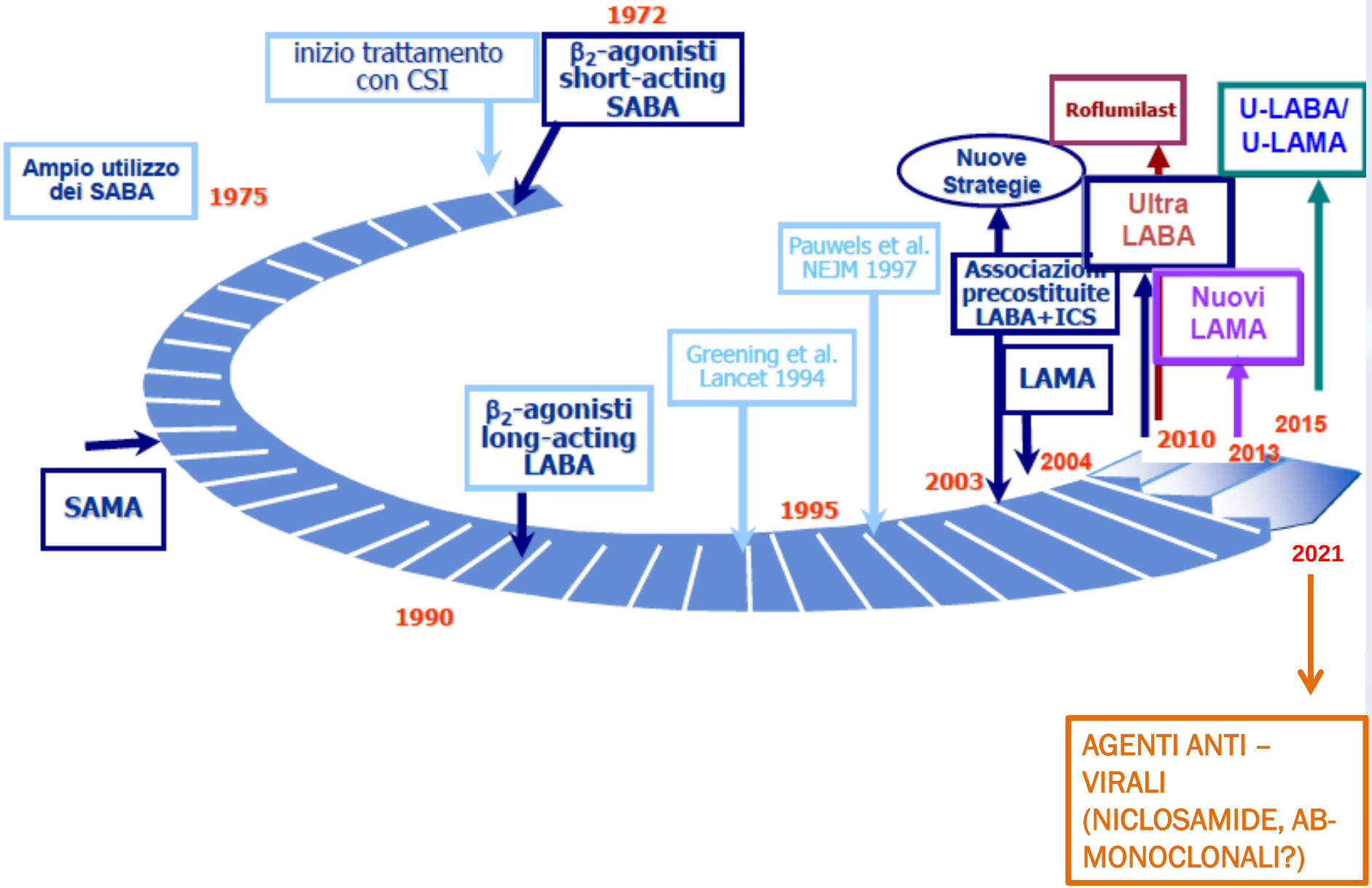


Fig. 2 Schematic representation of the antibody-based prevention strategies for respiratory infections. **a** The delivery of antibody-based therapeutics by mucosal route. The inhaled antibody route provides an attractive, local, and non-invasive way. It increases the therapeutic benefits and allows self-administration to patients that in turn reduces the overall dose and cost required. The mAbs in lungs by systemic route results in very low concentrations of the mAbs in the lungs, and exposing the rest of the body to potential adverse effects such as, toxicity, thickening of serum, and cytokine release syndrome. Delivering mAbs by inhaled route will not only neutralise virulence of respiratory virus outbreak as well as will provide protection and a unique preventive strategy. **b** The dose of mAbs needed at mucosal surfaces is substantially low to treat an established proliferating infection as compared to systematic or intravenous route (Bodier-Montagutelli et al. 2017; Zhang et al. 2020). The delivery of mAbs in lungs by systemic route results in very low absorption concentrations of the mAbs in the lungs (~ 10%) as compared to mucosal route (~ 90%)


1972
inizio trattamento con CSI
β2-agonisti short-acting SABA
Ampio utilizzo dei SABA
1975
Roflumilast
U-LABA/ U-LAMA
Nuove Strategie
Ultra LABA
Pauwels et al. NEJM 1997
Associazioni precostituite LABA+ICS
Nuovi LAMA
Greening et al. Lancet 1994
LAMA
β2-agonisti long-acting LABA
SAMA
2003
2004
2010
2013
2015
1995
2021
1990
AGENTI ANTI – VIRALI (NICLOSAMIDE, AB-MONOCLONALI?)

Il miglior modo per predire il futuro è crearlo.

ABRAHAM LINCOLN