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UNIVERSITÀ DI PISA

# Il ruolo degli antinfiammatori, del cortisone e degli immunomodulanti nel COVID-19 oggi

**Giusy Tiseo**

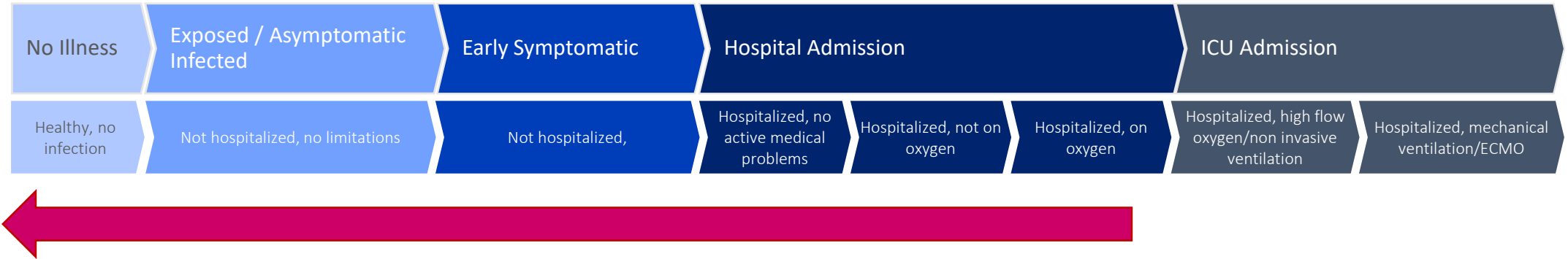
Division of Infectious Diseases, Department of Clinical and Experimental  
Medicine, University Hospital of Pisa, Italy



# Disclosures

Shionogi, MSD, Gilead

# Natural history of COVID-19



❖ **Vaccination**

❖ **Natural immunization**

❖ **New variants**



# Natural history of COVID-19



**Anti-inflammatory drugs**

**Steroids**

**Immunomodulant agents**



\* Not recommended in Italy

Adapted from NIH guidelines, October 10, 2023

# Clinical scenarios and supporting evidences



# First clinical scenario... one of the most common today



## Case vignette

A 73-year-old man with hypertension (losartan) and chronic obstructive pulmonary disease reports that he has had fever and cough for 2 days.

Vaccine SARS-CoV-2: 4 doses

Nasopharyngeal swab positive for SARS-CoV-2

No dyspnea, SaO<sub>2</sub> 95%

# COVID-19 therapy according to disease stage



Tixagevimab/cilgavimab prophylaxis

**Prophylactic Heparin**

- Monoclonal Antibodies
  - Bamlanivimab + etesevimab
  - Casirivimab + imdevimab
  - Sotrovimab
  - Tixagevimab/cilgavimab

**Symptoms management**

**Nirmatrelvir/ritonavir**  
**Early remdesivir**  
 Molnupiravir\*

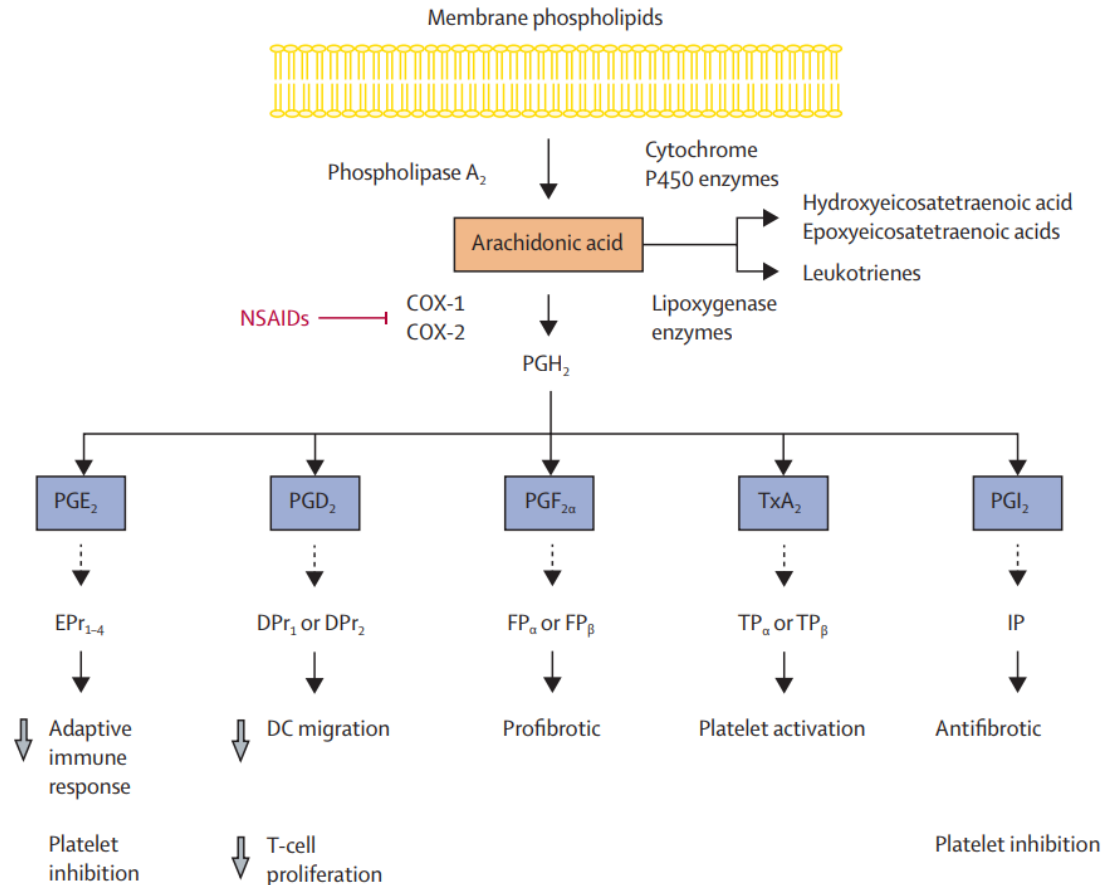


\* Not recommended in Italy

# Home as the new frontier for the treatment of COVID-19: the case for anti-inflammatory agents

Norberto Perico\*, Monica Cortinovia\*, Fredy Suter\*, Giuseppe Remuzzi

**Initial outpatient stage of COVID-19**





# What about NSAIDs?



ELSEVIER

Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Clinical Microbiology and Infection

journal homepage: [www.clinicalmicrobiologyandinfection.com](http://www.clinicalmicrobiologyandinfection.com)

**CMI**  
CLINICAL  
MICROBIOLOGY  
AND INFECTION

## Research note

### Ibuprofen use and clinical outcomes in COVID-19 patients

E. Rinott<sup>1</sup>, E. Kozer<sup>2,3</sup>, Y. Shapira<sup>3,4</sup>, A. Bar-Haim<sup>5</sup>, I. Youngster<sup>3,6,\*</sup>

## Impact of domiciliary administration of NSAIDs on COVID-19 hospital outcomes: an unCoVer analysis

Elena Salvador<sup>1\*†</sup>, Cristina Mazzi<sup>2†</sup>, Nicoletta De Santis<sup>1</sup>, Giulia Bertoli<sup>1</sup>, Antonija Jonjić<sup>3</sup>, Miran Coklo<sup>3</sup>, Marek Majdan<sup>4</sup>, José L. Peñalvo<sup>5,6</sup> and Dora Buonfrate<sup>1</sup>

**Table 1** Summary of in vitro and in vivo studies

Reference	Study type	Study objective	Key findings
Chen et al. (2020)	In vitro (Calu-3 and Huh7.5 cell lines)	Relevance of COX-2/PGE2 signalling and inhibition by ibuprofen and meloxicam in vitro (maximum non-toxic dose)	SARS-CoV-2 infection induced COX-2 upregulation in human cells and mice Suppression of COX-2/PGE2 signalling by NSAIDs did not affect ACE2 expression, and therefore susceptibility to infection, in human cells and mice
	In vivo (C57BL/6 J mice)	Relevance of COX-2/PGE2 signalling and inhibition by ibuprofen and meloxicam in vivo (ibuprofen: 30 mg/kg daily for 4 days; meloxicam: 1 mg/kg daily for 4 days)	NSAID treatment did not affect SARS-CoV-2 entry or replication in human cells and mice
Valenzuela et al. (2021)	In vitro (human alveolar type-II pneumocyte cells)	Effect of ibuprofen on ACE2 levels, levels of spike protein internalisation, and ADAM17 and TMPRSS2 activities	Ibuprofen upregulated ACE2 expression 24 and 48 h after treatment Upregulation of ACE2 counteracted by ibuprofen-induced mechanisms that reduced SARS-CoV-2 spike protein internalisation, particularly by inhibition of ADAM17 and TMPRSS2 activities
	In vivo (healthy adult rats and rat model of metabolic syndrome [MetS: rats with obesity, hypertension, hyperglycaemia])	Effect of ibuprofen (40 mg/kg) on lung levels of ACE2 and ADAM17 and TMPRSS2 in healthy and MetS rats	In healthy and MetS rats, treatment with ibuprofen increased lung ACE2 expression and RAS activity
de Bruin et al. (2022)	In vitro (Caco-2 cell line)	Influence of ibuprofen, flurbiprofen, etoricoxib and paracetamol (increasing concentrations in the range of c <sub>max</sub> plasma levels in humans) on the level of ACE2 mRNA/protein expression and activity, and influence on SARS-CoV-2 infection levels	All NSAIDs and paracetamol had no effect on ACE2 mRNA/protein expression and activity in the Caco-2 cell line Higher concentrations of ibuprofen and flurbiprofen reduced SARS-CoV-2 replication
	In vivo (C57BL/6 J mice)	ACE2 mRNA/protein levels and activity in the lung, heart and aorta of ibuprofen-treated mice (ibuprofen doses: 0 mg/kg, 50 mg/kg, 100 mg/kg and 200 mg/kg)	No upregulation of ACE2 mRNA/protein expression and activity in ibuprofen-treated mice compared with untreated mice Ibuprofen did not alter ACE2 activity

## Review

### Early Multi-Target Treatment of Mild-to-Moderate COVID-19, Particularly in Terms of Non-Steroidal Anti-Inflammatory Drugs and Indomethacin

Serafino Fazio<sup>1,\*</sup> and Paolo Bellavite<sup>2,\*</sup>



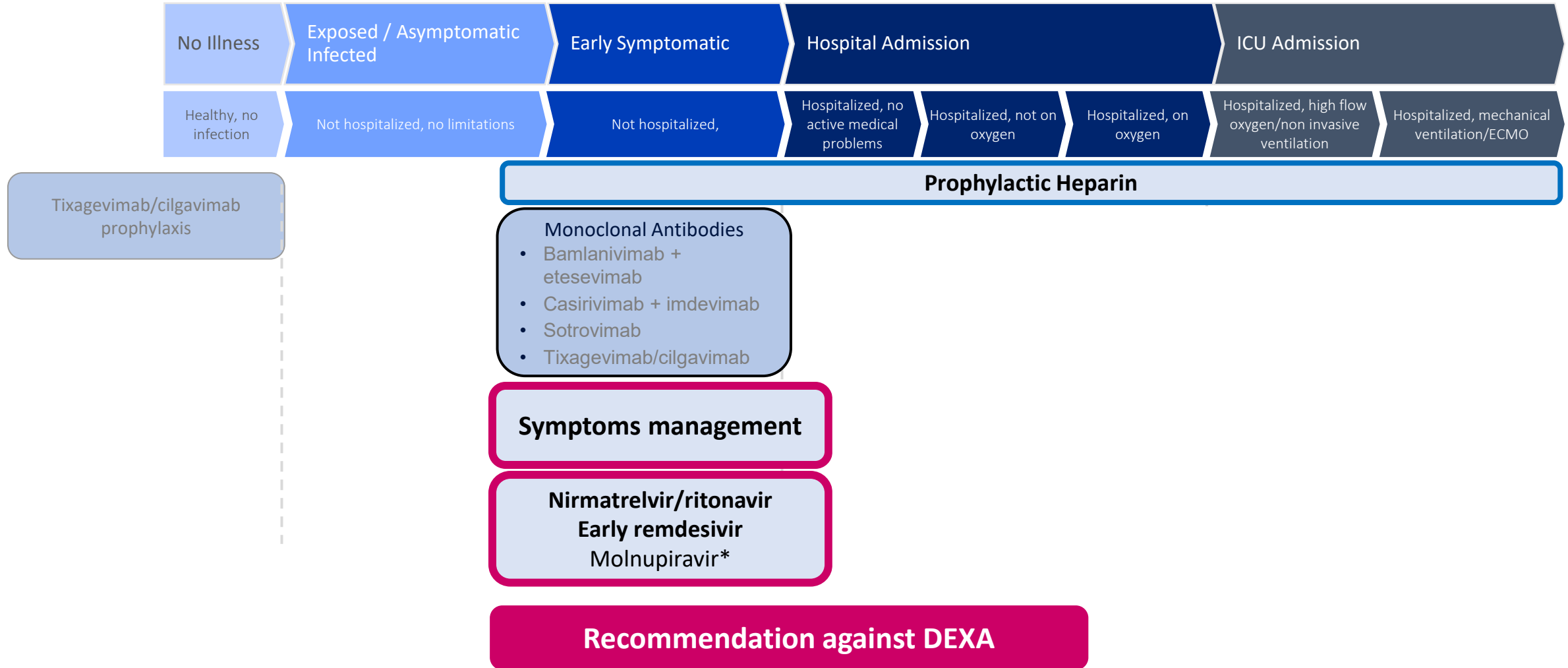
# What about NSAIDs?

Initial outpatient stage of COVID-19

- ❖ Ibuprofen
- ❖ Ketoprofen
- ❖ Ketoprofen lysine salt
- ❖ Nimesulide
- ❖ Celecoxib
- ❖ Aspirin
- ❖ and others...

According to patients comorbidities,  
indications, risk factors

# COVID-19 therapy according to disease stage



\* Not recommended in Italy

# First clinical scenario... one of the most common today



## Case vignette

- ❖ Nirmatrelvir/ritonavir 300/100 mg q12 h
- ❖ NSAIDs (symptom management)
- ❖ No steroids

**Successfull outpatient management**

# Clinical scenarios and supporting evidences



# Second clinical scenario

## Case vignette

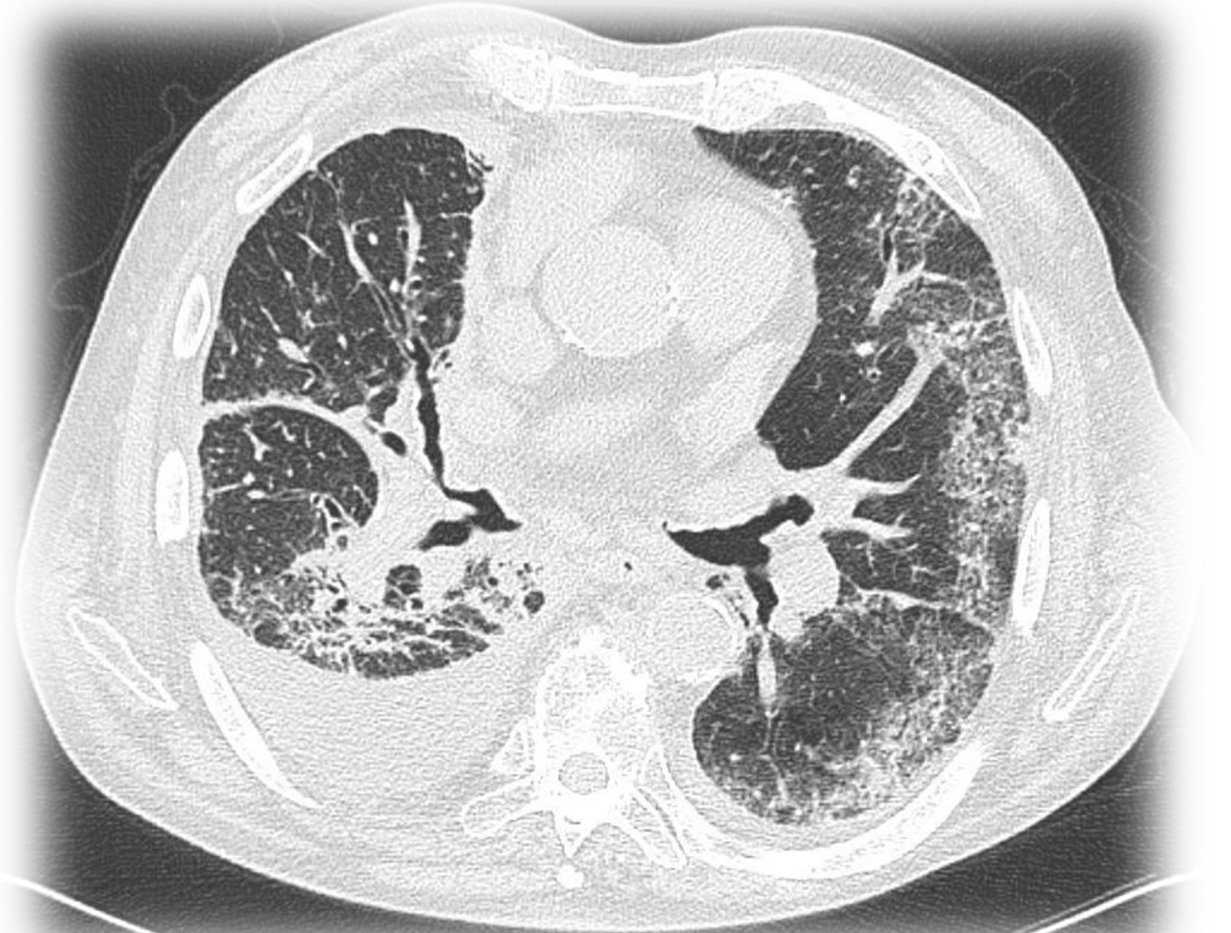
❖ A 70-year-old man with hypertension, ischemic cardiomyopathy reports that he has had fever and cough for 4 days.

ACE-I, statin, beta-blocker, cardioaspirin

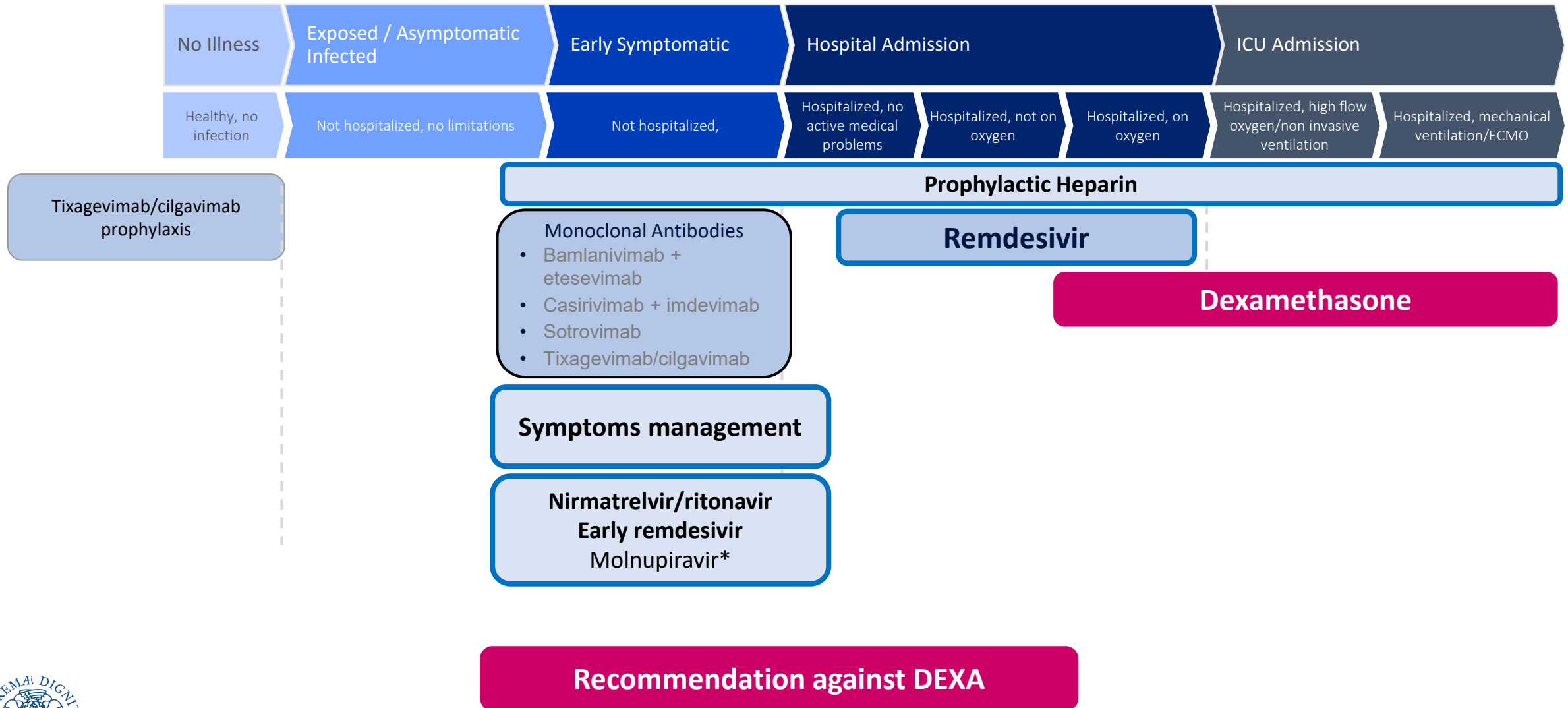
Vaccination: 3 doses

Nasopharyngeal swab positive for SARS-CoV-2

Need for oxygen delivery



# COVID-19 therapy according to disease stage

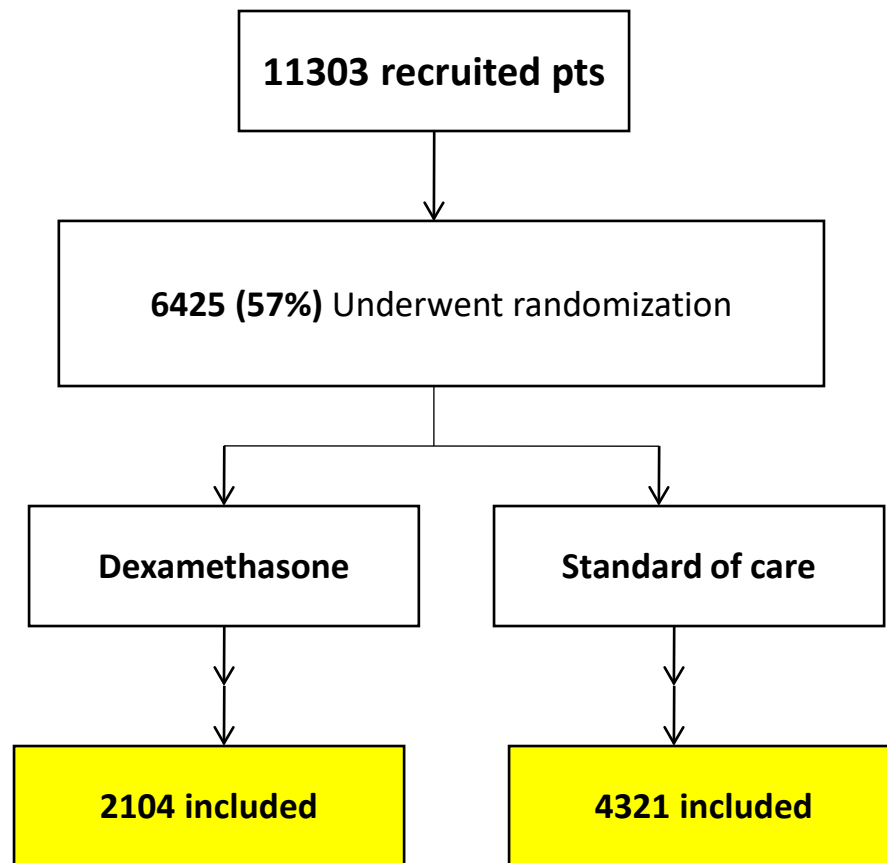


\* Not recommended in Italy

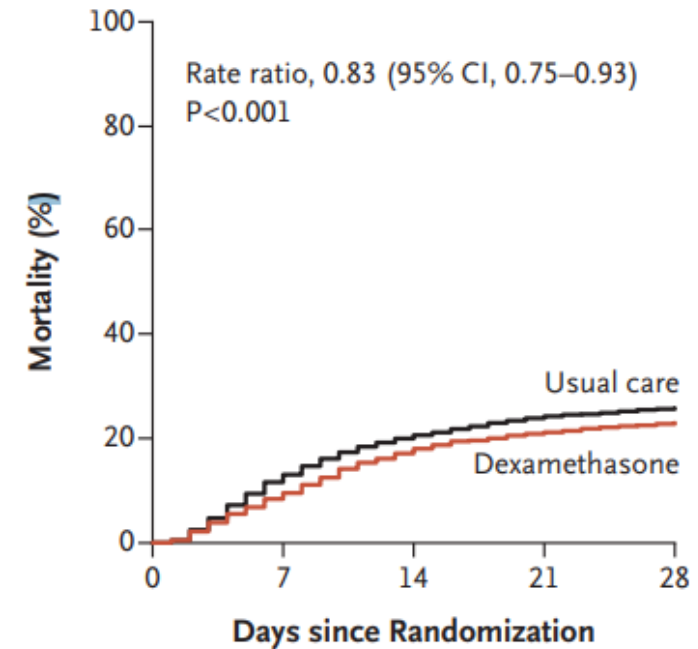
DEXA dexamethasone

Dexamethasone in Hospitalized Patients with Covid-19

The RECOVERY Collaborative Group\*



A All Participants (N=6425)



No. at Risk

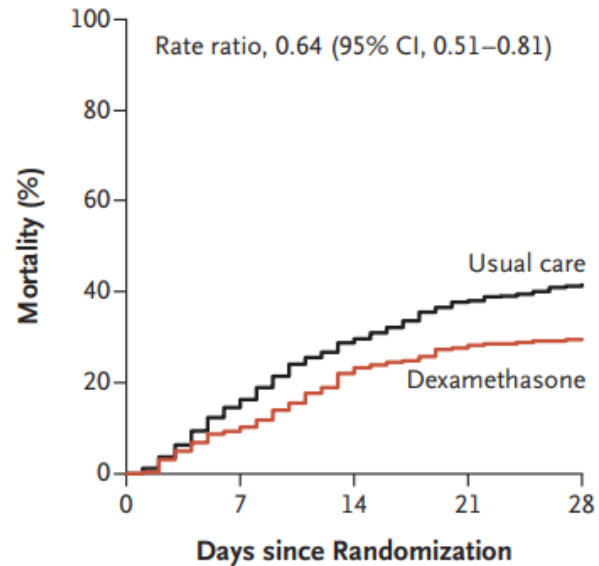
Usual care	4321	3754	3427	3271	3205
Dexamethasone	2104	1902	1724	1658	1620



Dexamethasone in Hospitalized Patients with Covid-19

The RECOVERY Collaborative Group\*

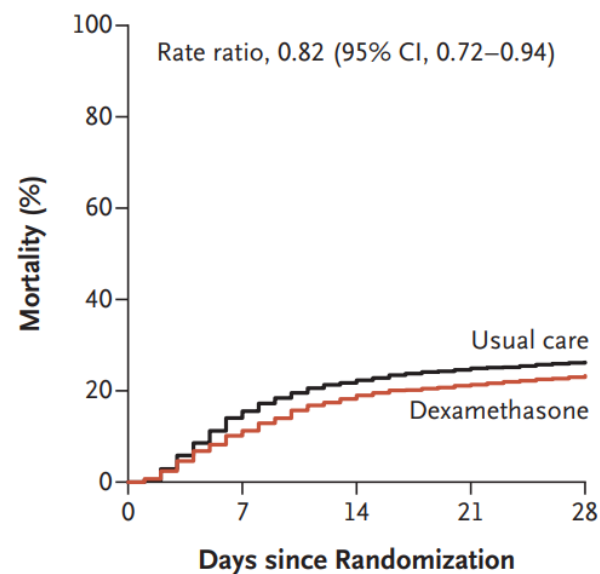
**B Invasive Mechanical Ventilation (N=1007)**



**No. at Risk**

Usual care	683	572	481	424	400
Dexamethasone	324	290	248	232	228

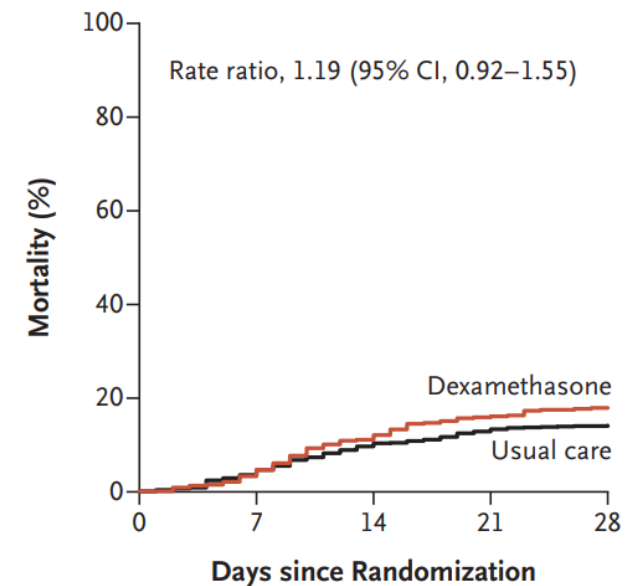
**C Oxygen Only (N=3883)**



**No. at Risk**

Usual care	2604	2195	2018	1950	1916
Dexamethasone	1279	1135	1036	1006	981

**D No Oxygen Received (N=1535)**



**No. at Risk**

Usual care	1034	987	928	897	889
Dexamethasone	501	477	440	420	411

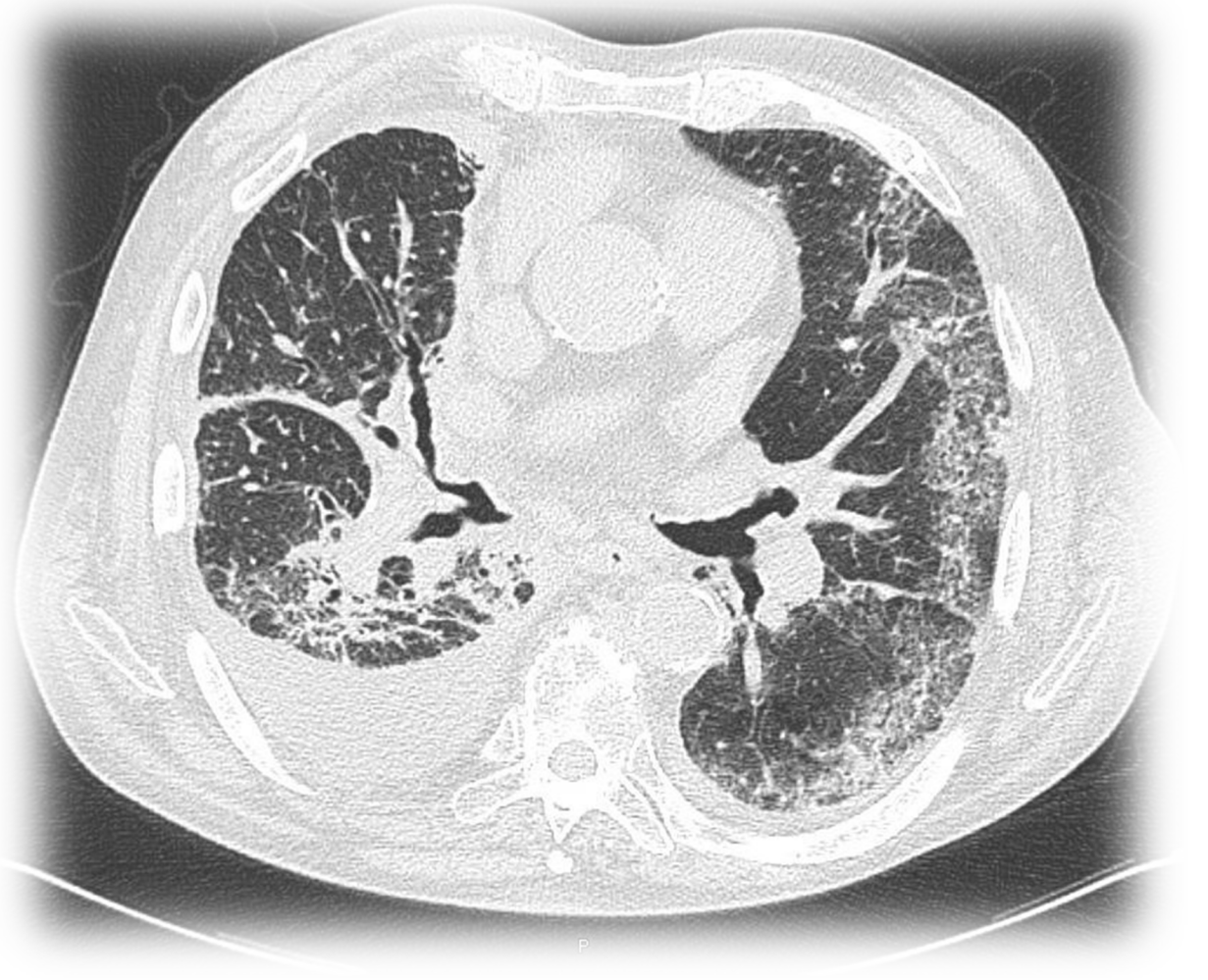
# Second clinical scenario

## Case vignette

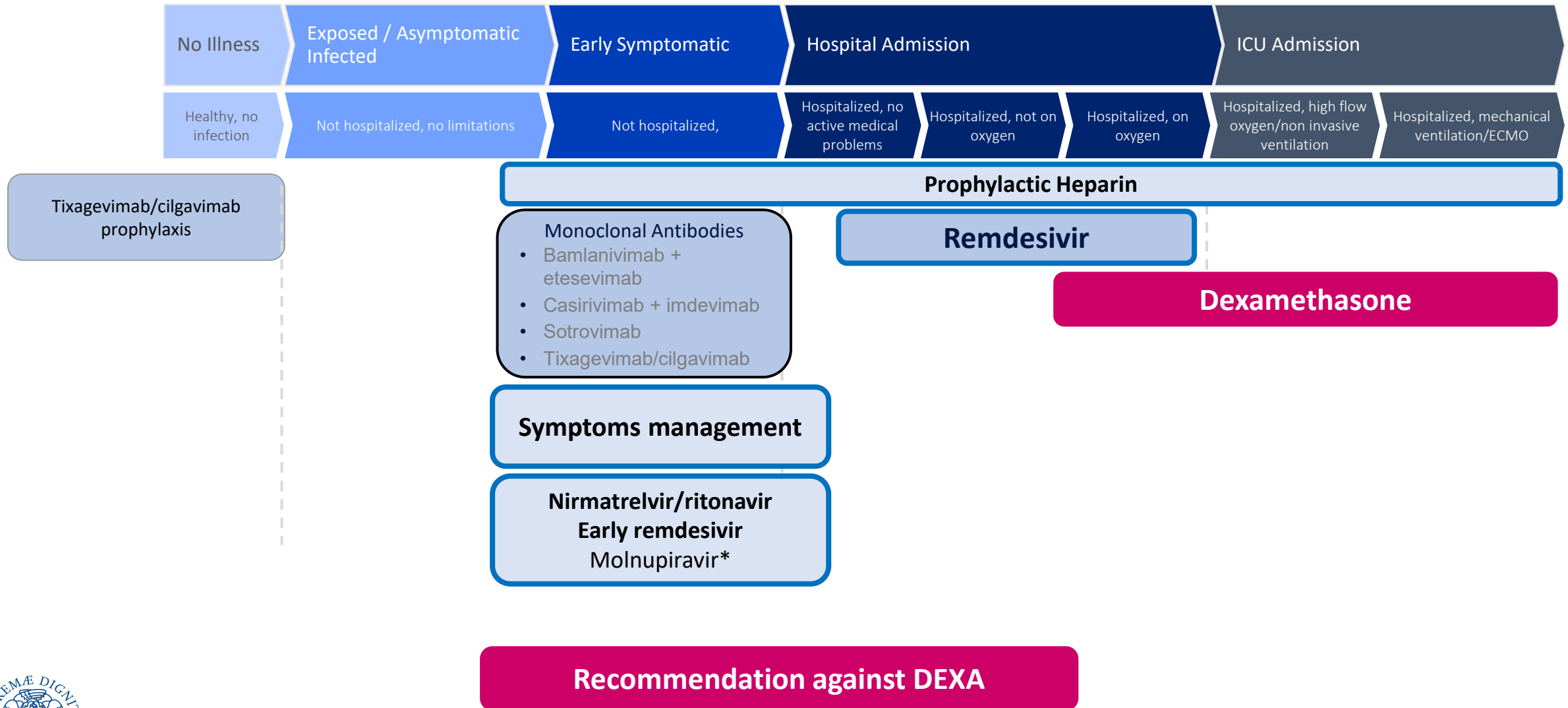
Remdesivir for 5 days

Dexamethasone 6 mg daily

Successful inpatient management



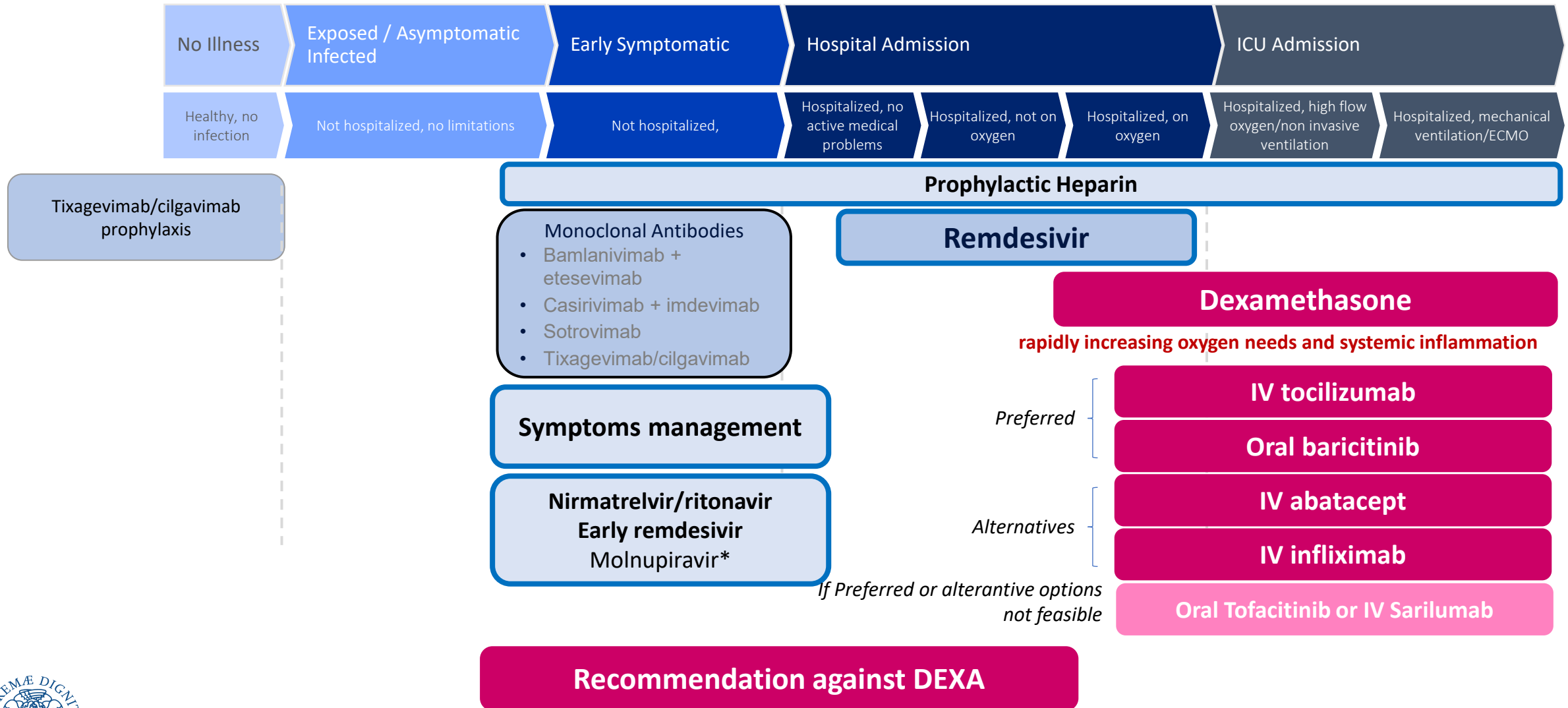
# COVID-19 therapy according to disease stage



\* Not recommended in Italy

DEXA dexamethasone

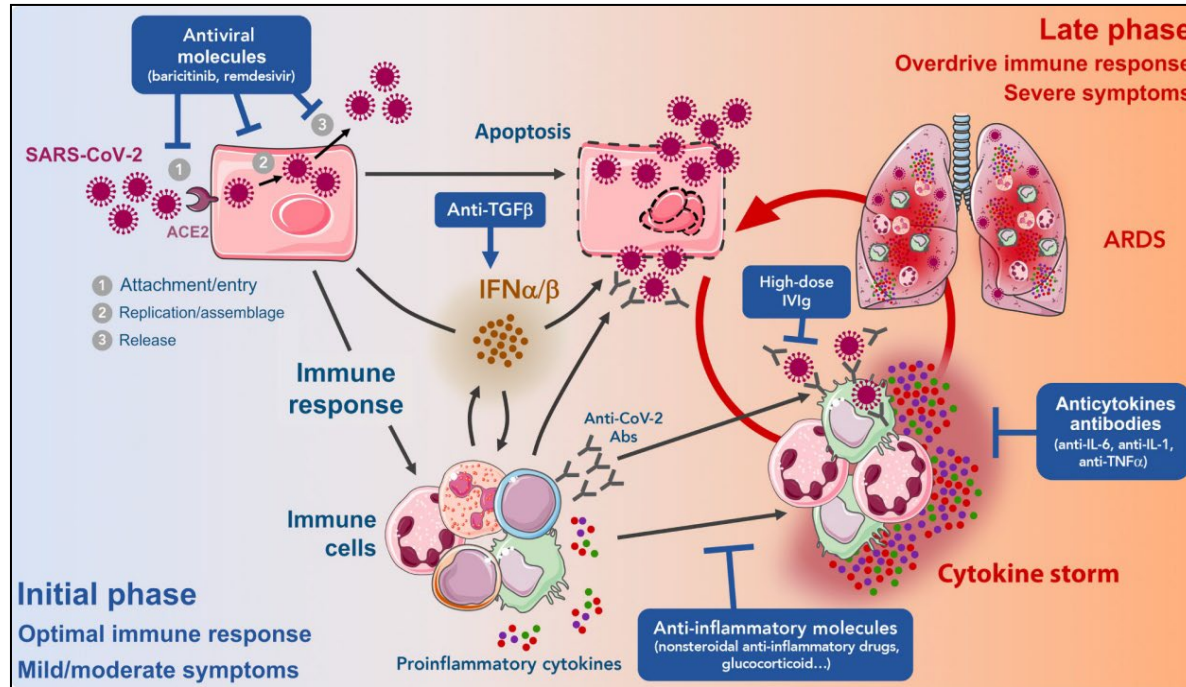
# COVID-19 therapy according to disease stage



\* Not recommended in Italy

DEXA dexamethasone

# Patients eligible for immunomodulants



## MARKERS OF INFLAMMATORY PHENOTYPE

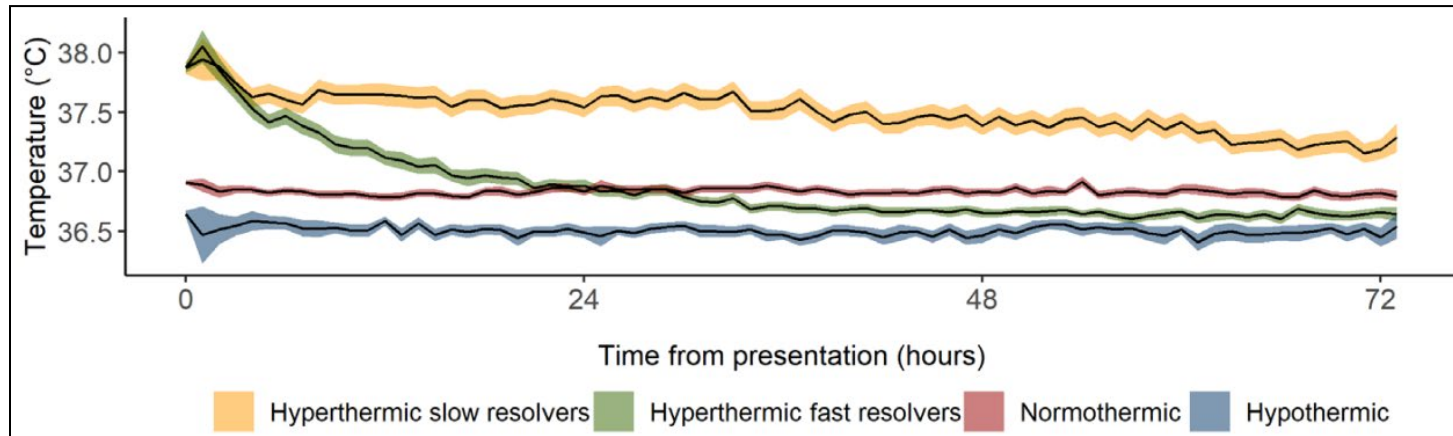
- 1) C-reactive protein
- 2) Ferritin values
- 3) Platelets
- 4) Fibrinogen
- 5) D-dimer
- 6) IL-6
- 7) suPAR (soluble urokinase plasminogen activator receptor)
- 8) ...

Inflammation

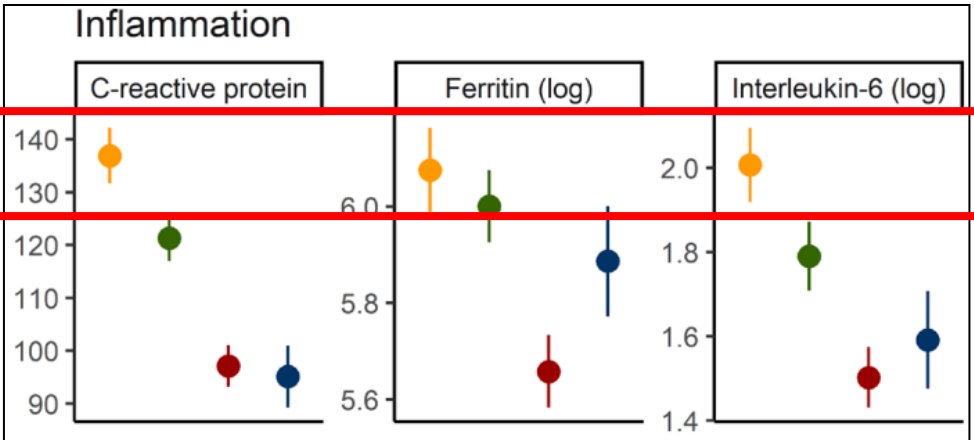
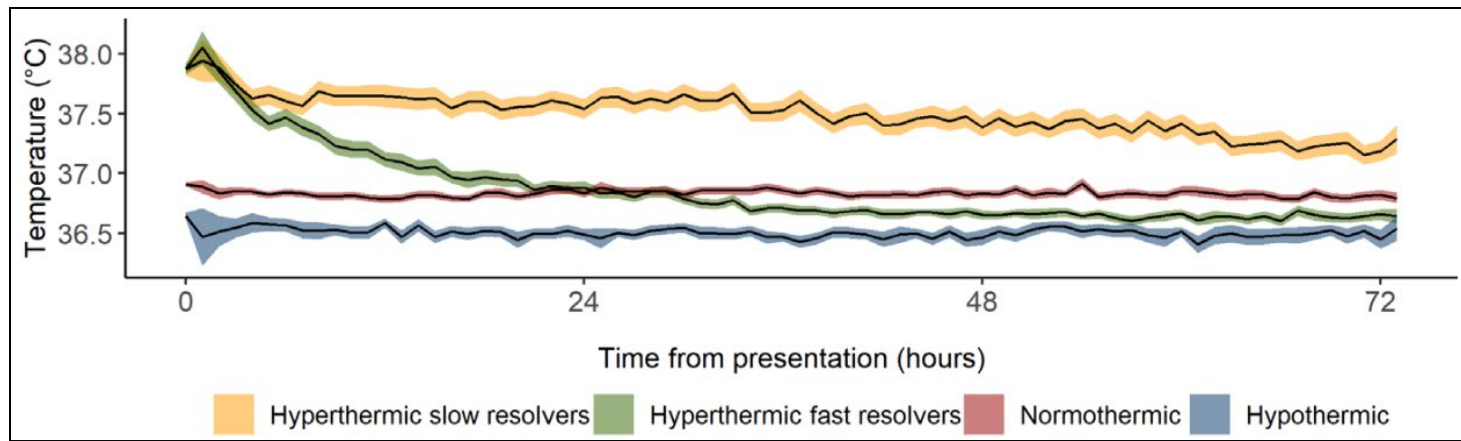
# Coronavirus Disease 2019 Temperature Trajectories Correlate With Hyperinflammatory and Hypercoagulable Subphenotypes

Temperature measurements from the first 72 hours of hospitalization

5903 hospitalized patients with COVID-19



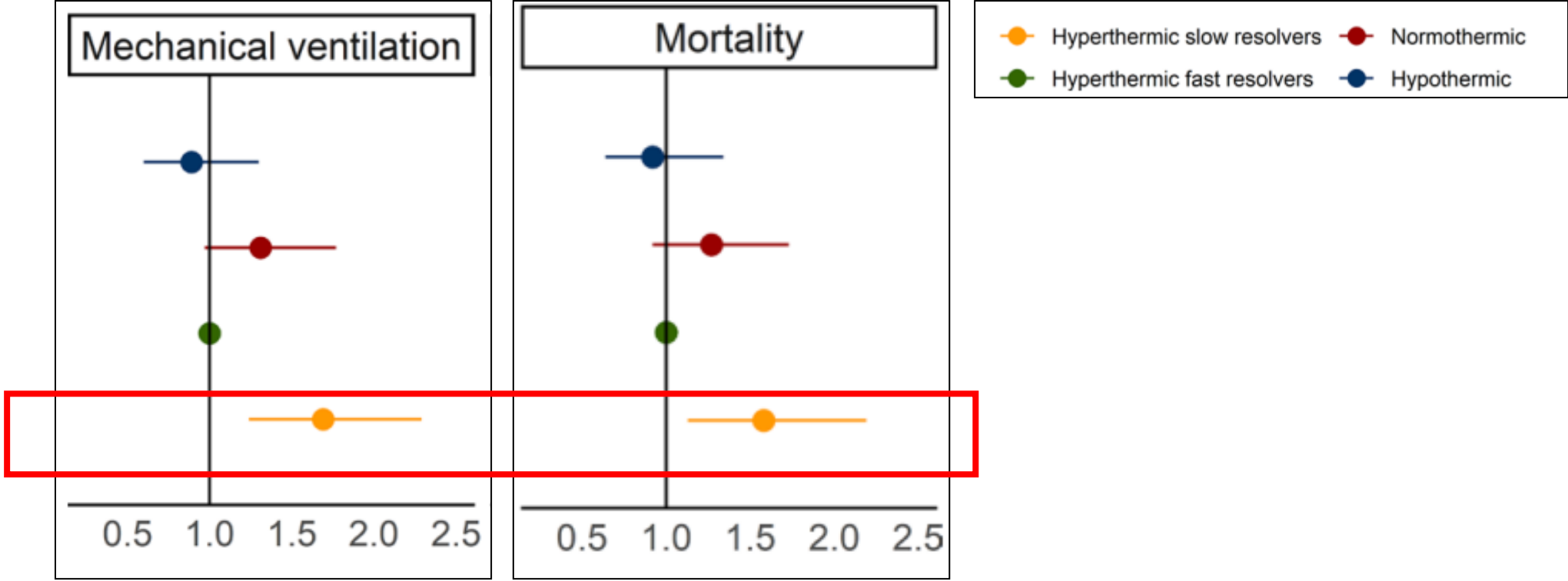
# Coronavirus Disease 2019 Temperature Trajectories Correlate With Hyperinflammatory and Hypercoagulable Subphenotypes



**Hyperthermic slow resolvers demonstrated several abnormalities consistent with a hyperinflammatory state**



# Coronavirus Disease 2019 Temperature Trajectories Correlate With Hyperinflammatory and Hypercoagulable Subphenotypes





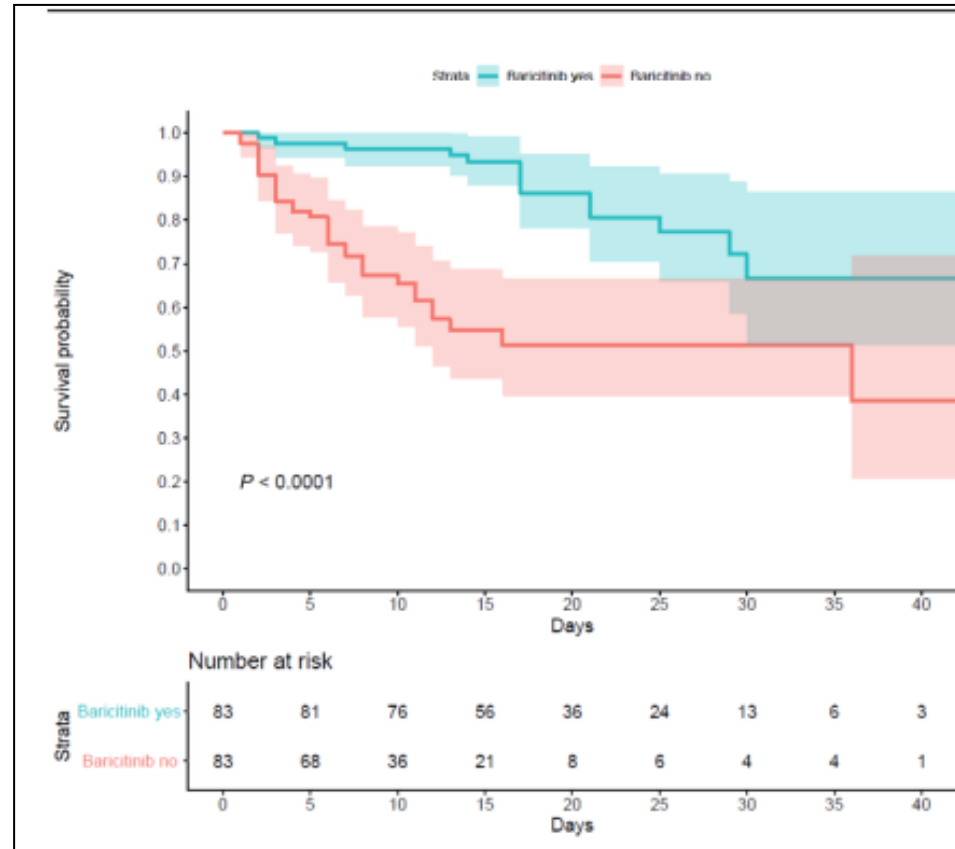
CORONAVIRUS

# JAK inhibition reduces SARS-CoV-2 liver infectivity and modulates inflammatory responses to reduce morbidity and mortality

Pisa, Italy

Albacete, Spain

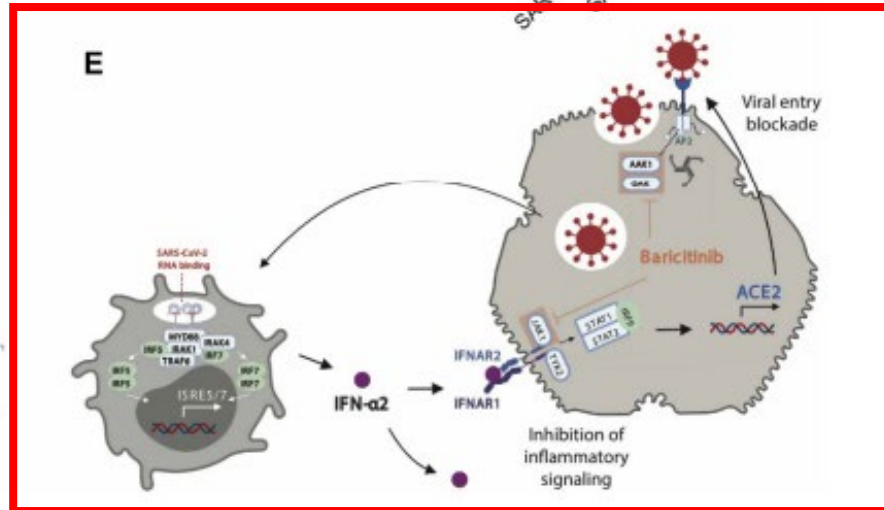
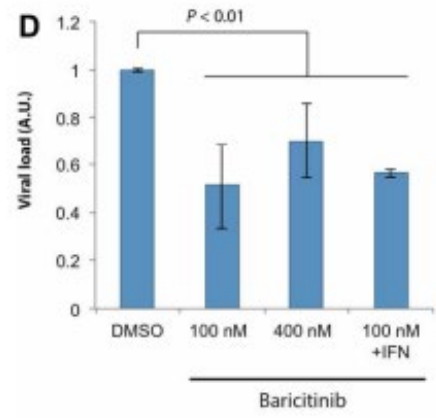
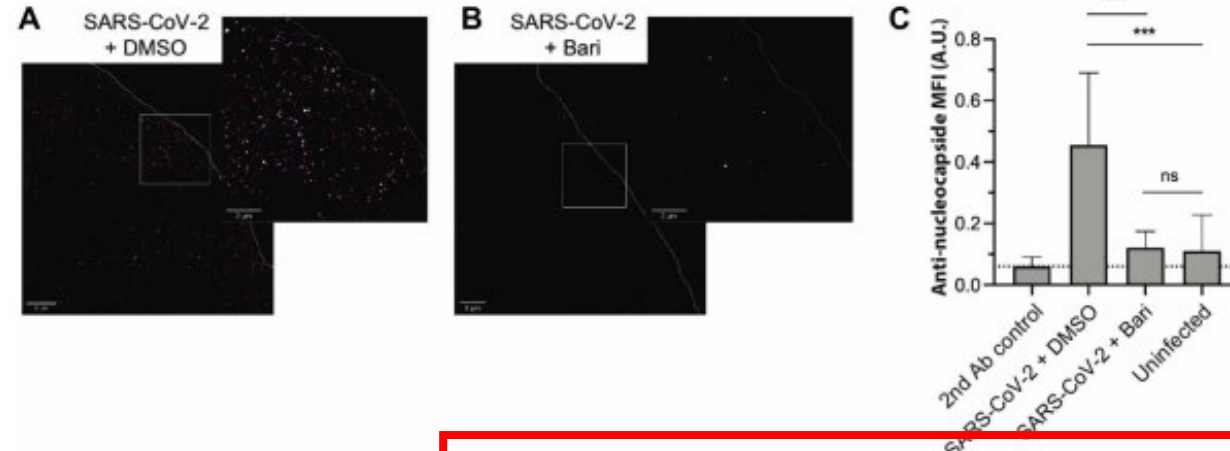
Imperial College, London, UK



CORONAVIRUS

**JAK inhibition reduces SARS-CoV-2 liver infectivity and modulates inflammatory responses to reduce morbidity and mortality**

**Baricitinib blocks viral entry of SARS-CoV-2**

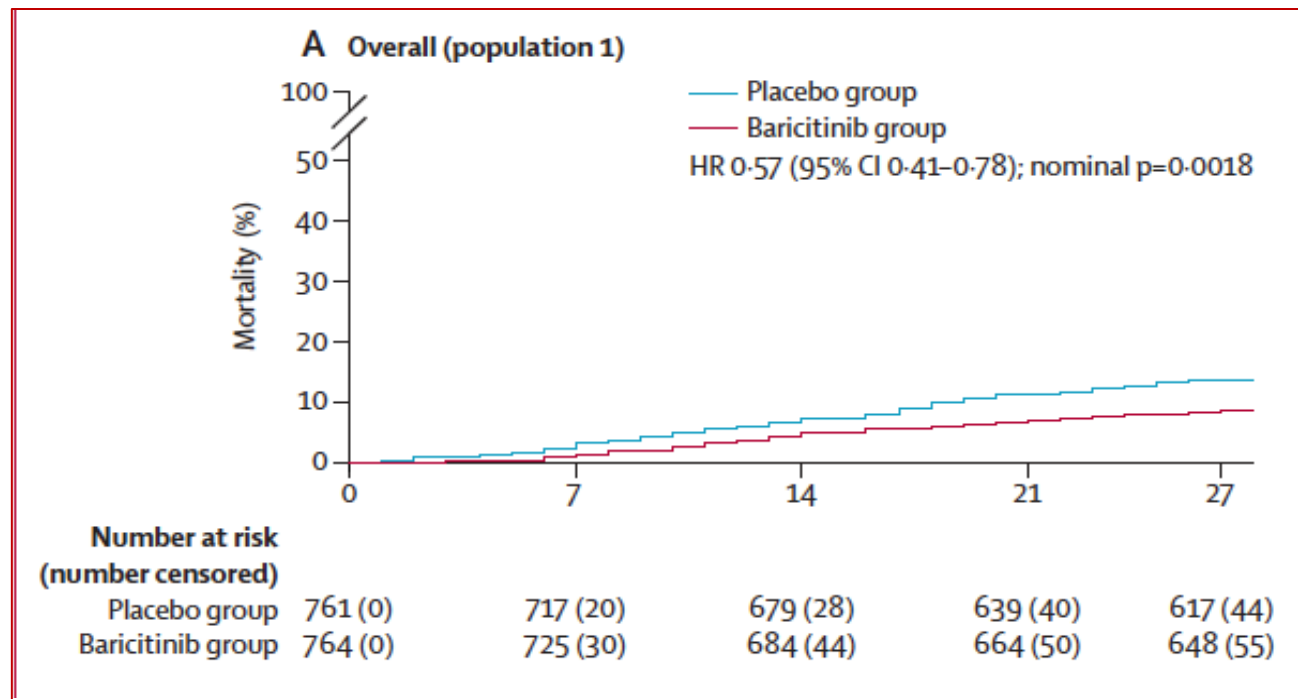


Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial



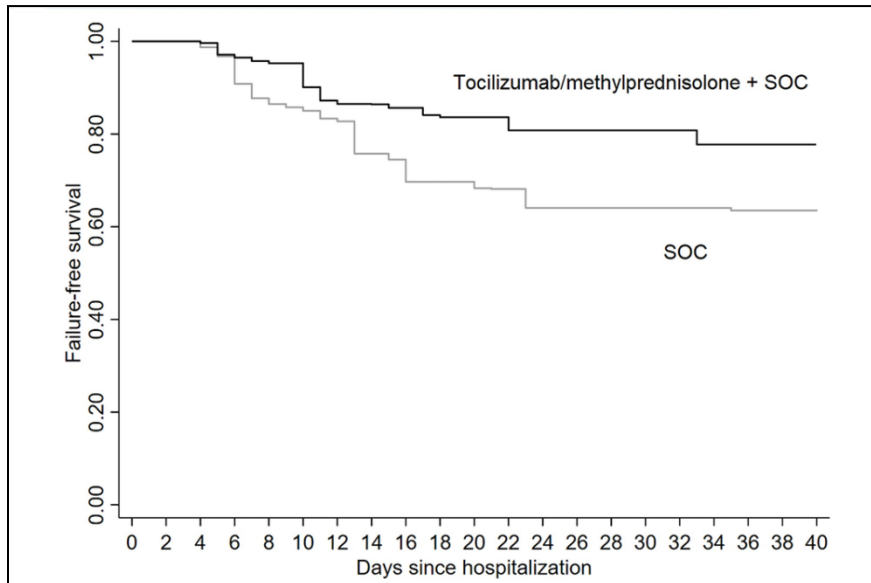
Phase 3, multicenter, double-blind, RCT including hospitalised adults with COVID-19 receiving standard of care were randomly assigned (1:1) to receive once-daily baricitinib (4 mg) or matched placebo for up to 14 days.

**28-day all-cause mortality**



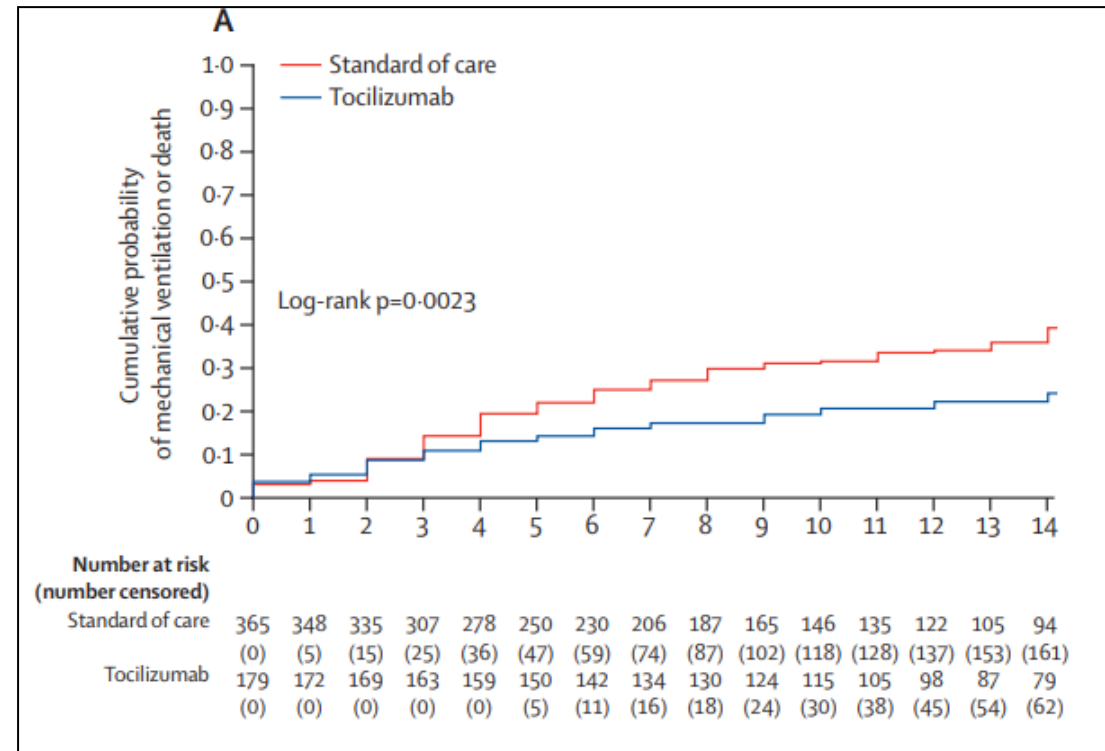
# Tocilizumab and steroid treatment in patients with COVID-19 pneumonia

Malgorzata Mikulska<sup>1,2\*</sup>, Laura Ambra Nicolini<sup>2</sup>, Alessio Signori<sup>3</sup>, Antonio Di Biagio<sup>1,2</sup>, Chiara Sepulcri<sup>1</sup>, Chiara Russo<sup>1</sup>, Silvia Dettori<sup>1</sup>, Marco Berruti<sup>1</sup>, Maria Pia Sormani<sup>3</sup>, Daniele Roberto Giacobbe<sup>1,2</sup>, Antonio Vena<sup>2</sup>, Andrea De Maria<sup>1,2</sup>, Chiara Dentone<sup>2</sup>, Lucia Taramasso<sup>2</sup>, Michele Mirabella<sup>1,2</sup>, Laura Magnasco<sup>1,2</sup>, Sara Mora<sup>4</sup>, Emanuele Delfino<sup>2</sup>, Federica Toscanini<sup>2</sup>, Elisa Balletto<sup>1,2</sup>, Anna Ida Alessandrini<sup>2</sup>, Federico Baldi<sup>1</sup>, Federica Briano<sup>1</sup>, Marco Camera<sup>2</sup>, Ferdinando Dodi<sup>2</sup>, Antonio Ferrazin<sup>2</sup>, Laura Labate<sup>1</sup>, Giovanni Mazzaello<sup>2</sup>, Rachele Pincino<sup>1</sup>, Federica Portunato<sup>2,5</sup>, Stefania Tutino<sup>1</sup>, Emanuela Barisione<sup>6</sup>, Bianca Bruzzone<sup>7</sup>, Andrea Orsi<sup>7,8</sup>, Eva Schenone<sup>2</sup>, Nirmala Rossetti<sup>2</sup>, Elisabetta Sasso<sup>9</sup>, Giorgio Da Rin<sup>10</sup>, Paolo Pelosi<sup>11,12</sup>, Sabrina Beltramini<sup>9</sup>, Mauro Giacomini<sup>4</sup>, Giancarlo Icardi<sup>7,8</sup>, Angelo Gratarola<sup>13</sup>, Matteo Bassetti<sup>1,2</sup>



## Tocilizumab in patients with severe COVID-19: a retrospective cohort study

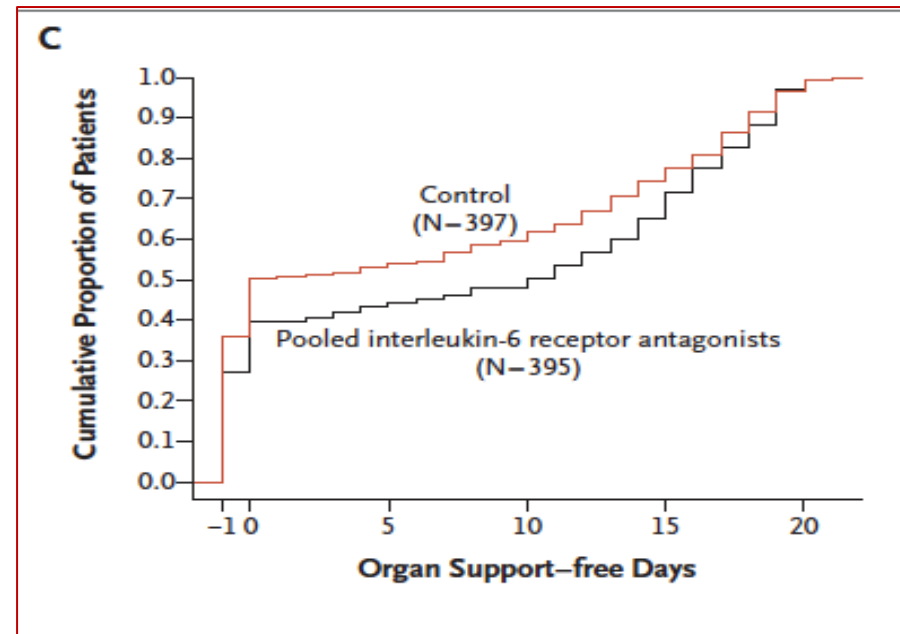
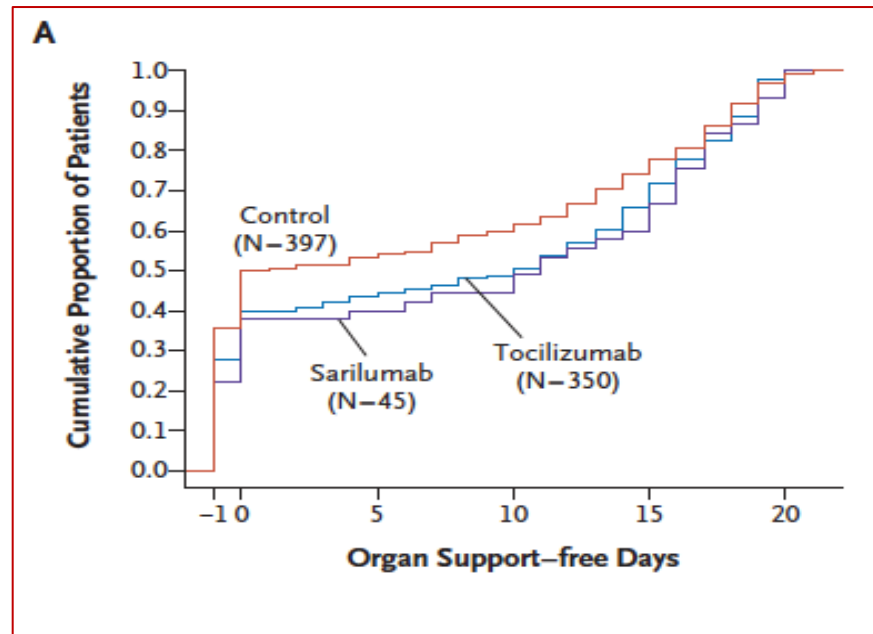
Giovanni Guaraldi\*, Marianna Meschiari\*, Alessandro Cozzi-Lepri, Jovana Milic, Roberto Tonelli, Marianna Menozzi, Erica Franceschini, Gianluca Cuomo, Gabriella Orlando, Vanni Borghi, Antonella Santoro, Margherita Di Gaetano, Cinzia Puzzolante, Federica Carli, Andrea Bedini, Luca Corradi, Riccardo Fantini, Ivana Castaniere, Luca Tabbi, Massimo Girardis, Sara Tedeschi, Maddalena Giannella, Michele Bartoletti, Renato Pascale, Giovanni Dolci, Lucio Brugioni, Antonello Pietrangelo, Andrea Cossarizza, Federico Pea, Enrico Clini, Carlo Salvarani, Marco Massari, Pier Luigi Viale, Cristina Mussini



Interleukin-6 Receptor Antagonists in Critically Ill Patients  
with Covid-19

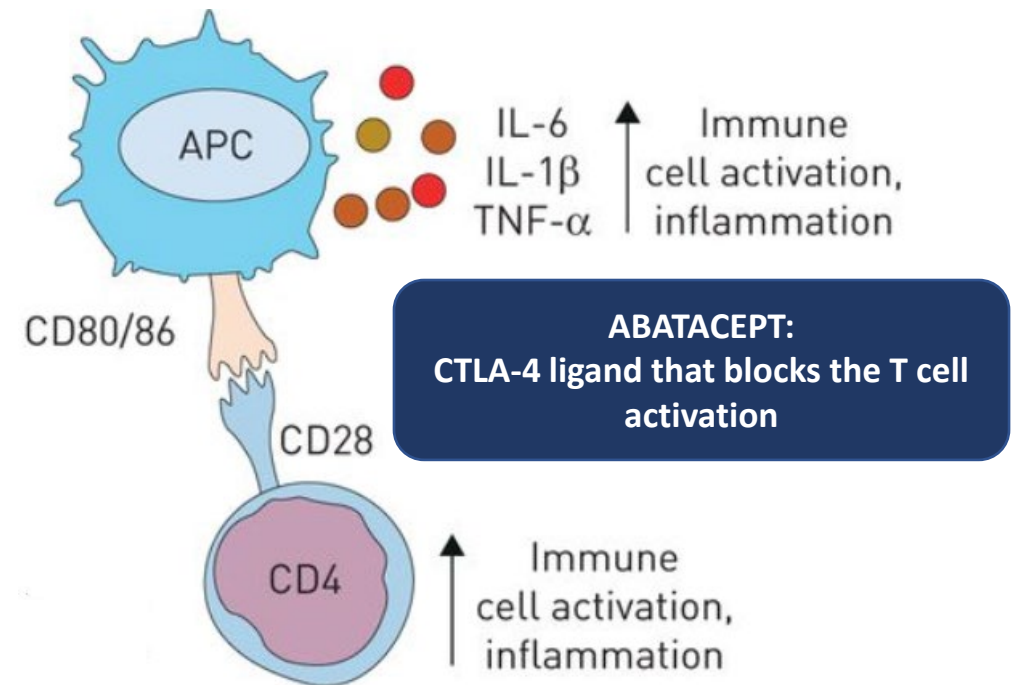
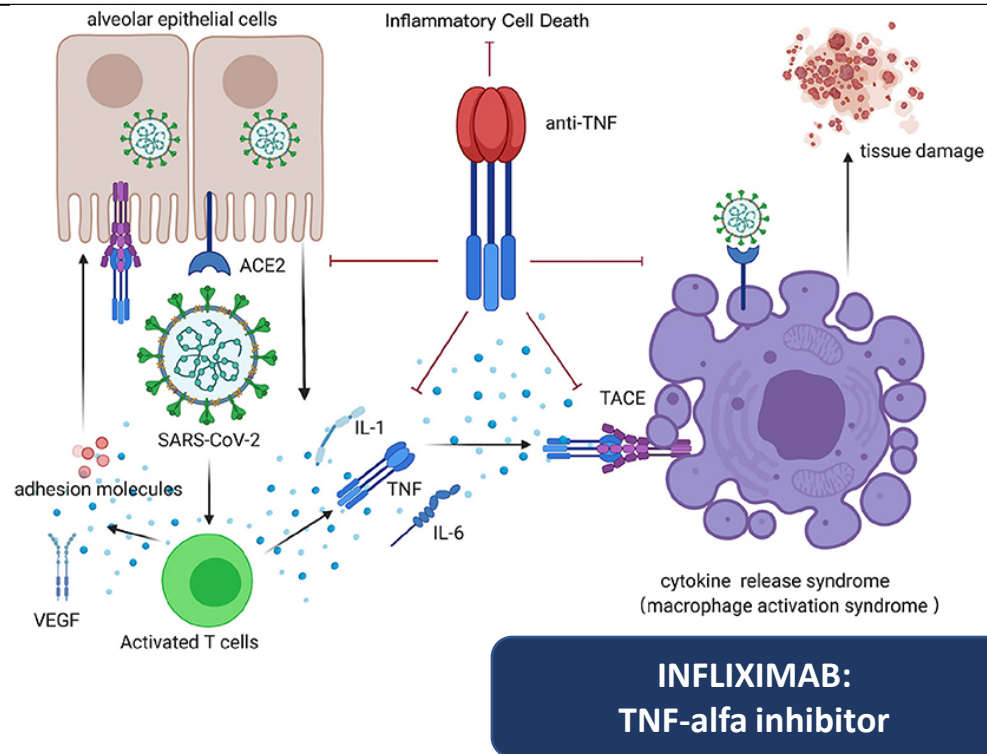
The REMAP-CAP Investigators\*

Patients with Covid-19, within 24 hours after starting organ support in the ICU, were randomly assigned to receive tocilizumab (8 mg per kilogram of body weight), sarilumab (400 mg), or standard care (control).



## Which Immunomodulator for Severe COVID-19?

Hana M. El Sahly, MD, reviewing O'Halloran JA et al. JAMA 2023 Jul 25 Kalil AC et al. JAMA 2023 Jul 25



# Abatacept, Cenicriviroc, or Infliximab for Treatment of Adults Hospitalized With COVID-19 Pneumonia

## A Randomized Clinical Trial

Patients received background standard of care:  
**remdesivir and steroids**

ITT population	Infliximab vs placebo	Abatacept vs placebo	Cenicriviroc vs placebo
Recovery from COVID-19 pneumonia at day 28*	79.3% vs 76.4% (p=ns)	79% vs 75.6% (p=ns)	75.8% vs 79.1% (p=ns)
14-day mortality	5.7% vs 8.3% (p<0.05)	4.9% vs 8% (p<0.05)	8.9% vs 7.2% (p=ns)
28-day mortality	10% vs 14.2% (p<0.05)	10.7% vs 14.7% (p<0.05)	13.6% vs 11.6% (p=ns)

\*Number of participants who have recovered by day 28

# Clinical scenarios and supporting evidences





# Third clinical scenario

## Case vignette

- ❖ A 35 years old man with no medical history
- ❖ Fever from 7 days (COVID-19)
- ❖ **Cardiac arrest**

Vaccination: 3 doses

Nasopharyngeal swab positive for SARS-CoV-2

Echocardiography: severe myocarditis with new-onset left ventricular dysfunction (LVEF 35%)



# Third clinical scenario

## Case vignette



Lab exams		
C-reactive protein, vn <0.5	↑	14 mg/dl
PCT		0.06 ng/dl
Ferritin, vn <300	↑	5470 ng/mL
PLT	↓	102000/mcL

## Multisystem Inflammatory Syndrome in Adults

# Third clinical scenario

## CDC GUIDELINES FOR MIS

### 1) Initial Immunomodulatory Therapy

- Intravenous **immunoglobulin** (IVIG) 2 g/kg IBW (up to a maximum total dose of 100 g) plus low to moderate dose **methylprednisolone**
- **Glucocorticoid** monotherapy, only if IVIG is unavailable or contraindicated

### 2) Intensification Immunomodulatory Therapy: in patients who do not improve within 24 hours

- High-dose **anakinra** 5–10 mg/kg IV or SUBQ once daily
- High-dose **glucocorticoid**
- **Infliximab** 5–10 mg/kg IV for 1 dose

### 3) Antithrombotic therapy



**Death**

# Take home messages

- ❖ NSAIDs can be used in outpatients for symptoms management
- ❖ Dexamethasone is indicated in patients with SARS CoV-2 pneumonia and need for oxygen therapy
- ❖ Immunomodulants in patients with inflammatory state (identify in the first 72 hours from admission)

**Treat early to avoid disease progression**