GRUPPO ITALIANO PER LA VALUTAZIONE DEGLI INTERVENTI IN TERAPIA INTENSIVA
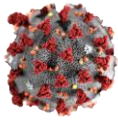
I dubbi della medicina senza evidenze

Pietro Caironi, MD

Anestesia e Rianimazione, AOU S. Luigi Gonzaga
Università degli Studi di Torino
pietro.caironi@unito.it
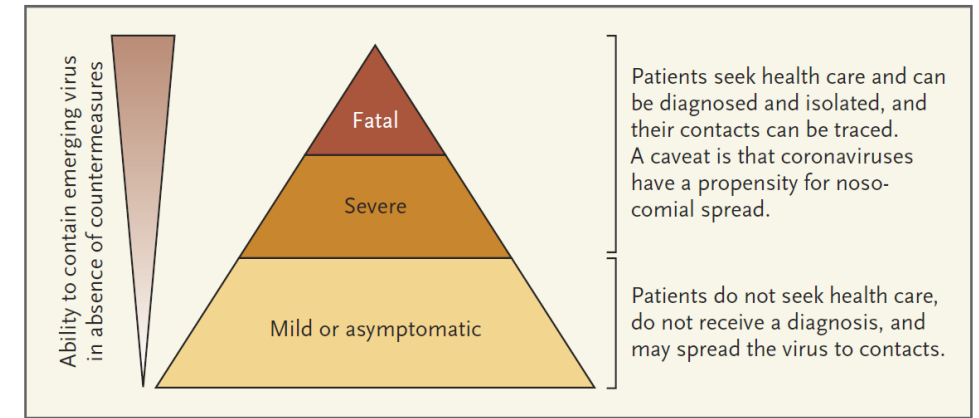
First report on NEJM

A Novel Coronavirus Emerging in China — Key Questions for Impact Assessment

Vincent J. Munster, Ph.D., Marion Koopmans, D.V.M., Neeltje van Doremalen, Ph.D., Debby van Riel, Ph.D., and Emmie de Wit, Ph.D.

Pathogenicity and Transmissibility Characteristics of Recently Emerged Viruses in Relation to Outbreak Containment.

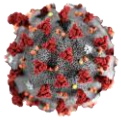| Virus	Case Fatality Rate (%)	Pandemic	Contained	Remarks
2019-nCoV	Unknown*	Unknown	No, efforts ongoing	
pH1N1	0.02–0.4	Yes	No, postpandemic circulation and establishment in human population	
H7N9	39	No	No, eradication efforts in poultry reservoir ongoing	
NL63	Unknown	Unknown	No, endemic in human population	
SARS-CoV	9.5	Yes	Yes, eradicated from intermediate animal reservoir	58% of cases result from nosocomial transmission
MERS-CoV	34.4	No	No, continuous circulation in animal reservoir and zoonotic spillover	70% of cases result from nosocomial transmission
Ebola virus (West Africa)	63	No	Yes	

* Number will most likely continue to change until all infected persons recover.

Ability to contain emerging virus in absence of countermeasures

Fatal

Severe

Mild or asymptomatic

Patients seek health care and can be diagnosed and isolated, and their contacts can be traced.
A caveat is that coronaviruses have a propensity for nosocomial spread.

Patients do not seek health care, do not receive a diagnosis, and may spread the virus to contacts.

Surveillance Pyramid and Its Relation to Outbreak Containment.

The proportion of mild and asymptomatic cases versus severe and fatal cases is currently unknown for 2019-nCoV — a knowledge gap that hampers realistic assessment of the virus's epidemic potential and complicates the outbreak response.

"A novel coronavirus (2019-nCoV) emerged in Wuhan, China, at the end of 2019.
As of January 2020, 830 cases had been diagnosed in 9 countries. Twenty-six fatalities occurred, mainly in patients who had serious underlying illness. (…)"

The situation in Italy: *first country struck after China (Wuhan)*

On February 20, 2020 first patient diagnosed in Italy

IL GIORNO

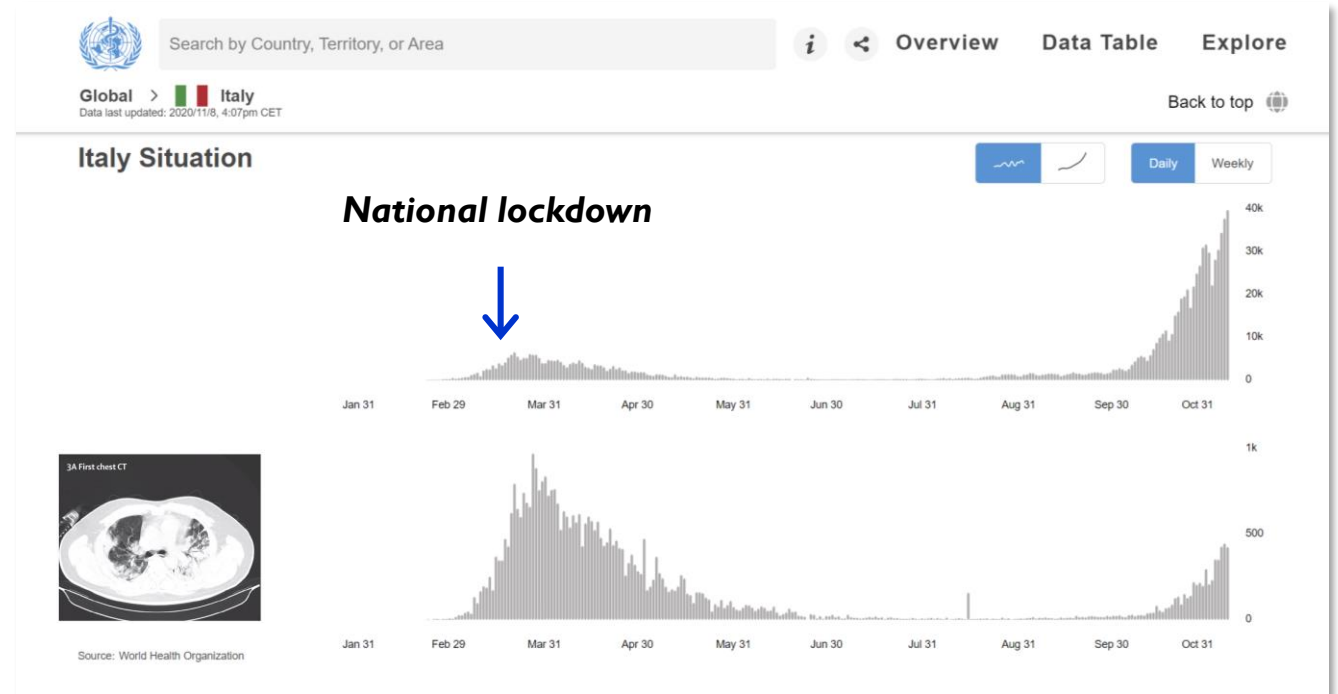**"Quel 20 febbraio alle prese con un virus sconosciuto": il racconto del medico lodigiano**

Stefano Paglia, responsabile del pronto soccorso di Lodi e Codogno, ripercorre attimo dopo attimo i primi momenti della lotta al Covid
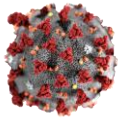
di PAOLA ARENSI

*An "**unknown**" disease*

*Extremely **high numbers** with an extremely **high severity***

TABLE 1 Some notable pandemic and epidemic diseases[a]

Yr(s)	Disease (agent)	No. of deaths	Comments
430 BCE	Plague of Athens	~100,000	First identified transregional pandemic
541	Plague of Justinian (Yersinia pestis)	30–50 million	Pandemic; killed half of the world's population
1340s	Black Death (Yersinia pestis)	~50 million	Pandemic; killed at least a quarter of the world's population
1494	Syphilis (Treponema pallidum)	>50,000	Pandemic brought to Europe from the Americas
ca. 1500	Tuberculosis	High millions	Ancient disease; became pandemic in Middle Ages
1520	Hueyzahuatl (Variola major)	3.5 million	Pandemic brought to the New World by Europeans
1793–1798	American plague	~25,000	Yellow fever, which terrorized colonial America
1832	2nd cholera pandemic in Paris	18,402	Spread from India to Europe/Western Hemisphere
1918	Spanish influenza	~50 million	Led to additional pandemics in 1957, 1968, 2009
1976–2020	Ebola	15,258	First recognized in 1976; 29 regional epidemics to date
1981	Acute hemorrhagic conjunctivitis	Few	First recognized in 1969; pandemic in 1981
1981	HIV/AIDS	~32 million	First recognized in 1981; ongoing pandemic
2002	SARS	813	Near pandemic
2009	H1N1 swine flu	284,000	5th influenza pandemic of the century
2014	Chikungunya	Few	Pandemic, mosquito borne
2015	Zika	~1,000?[b]	Pandemic, mosquito borne

[a]Refer to the pandemic and epidemic definitions in the text and cited references, particularly references 7 and 8. The table is not comprehensive but lists notable emergences of historical importance. Many of these diseases have emerged/reemerged on multiple occasions. For most historical pandemics, estimated numbers of deaths have varied widely, and figures cannot be considered accurate.
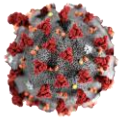[b]Zika deaths occur mostly in utero or in newborns; death in older children and adults is rare.

Largest pandemic so far…(modern era)

> 231,703,120 cases
(as for September 28, 2020)
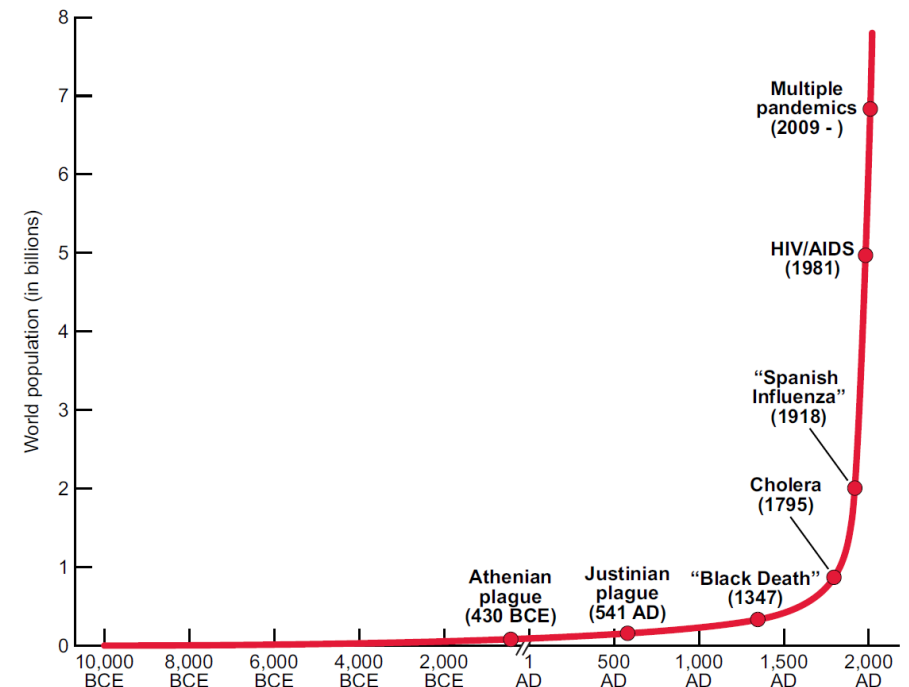
FIG 1 Estimated world population and selected known pandemics/widespread disease emergences, from 10,000 BCE to 2020 AD.

Morens DM et al., mBio 2020;11:e00812-20

General Context

Large and rapidly increasing numbers of severe patients

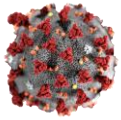Absence of knowledge (similar to other viral-related ARDS?)

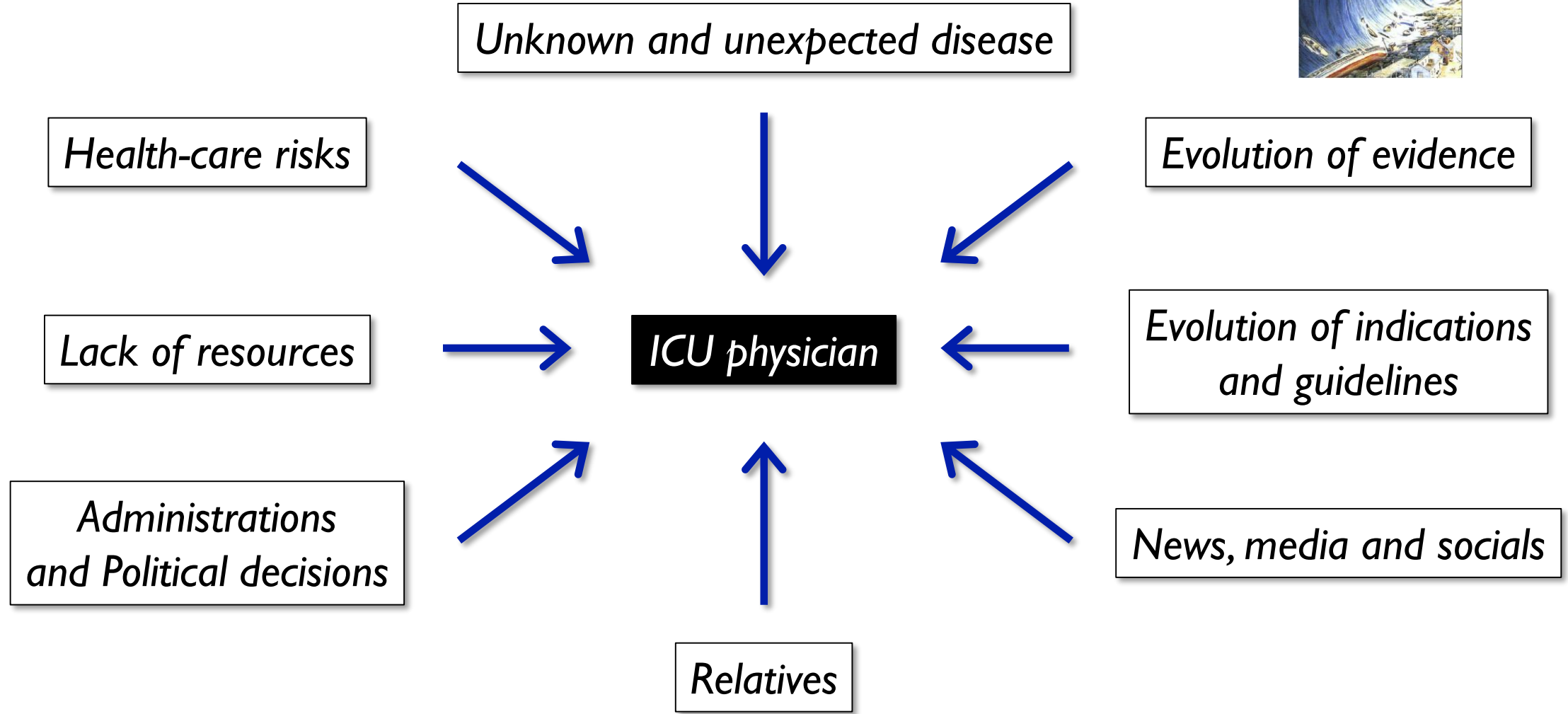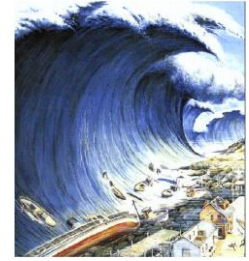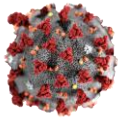High lethality

Lack of knowledge

What to do?

→ *General context (what's happened?)*

→ *Why has the system been distressed?*

→ *Few examples (use of tocilizumab / therapeutic anticoagulation)*

→ *Important aspects (positive and negative…)*

→ *Open questions*

ICU Physicians **Under Pressures** (…a tsunami…)

Unknown and unexpected disease

Health-care risks

Evolution of evidence

Lack of resources

ICU physician

Evolution of indications and guidelines

Administrations and Political decisions
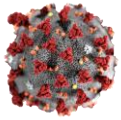
News, media and socials

Relatives

Dalla prima Video-Conferenza GiViTI (durante la 1° ondata pandemica) – in data 10/03/2020
Esperienze delle TI di Lodi, Pavia, Monza, Lecco (su organizzazione, diagnosi, e trattamento)

➤ *"(Sul paziente 1) – Tutto sarebbe partito lo stesso… una fiumana di persone…"*

➤ *"…90-100 malati al giorno, tutti stampini. È chiaro che abbiamo finito i ventilatori, maschere e CPAP il secondo giorno. (…) è una bell'onda…*

➤ *"Ci siamo organizzati subito con un nostro algoritmo (Paglia, PS Lodi)"*
"Subito coordinamento…"

➤ *"Pensavamo che 5 PL di subintensiva bastassero… e invece…"*
"Il PL singolo a pressione negative, in realtà ha poco senso, per la portata del fenomeno…"

➤ *"Personale di guardia, contagiato, per non aver indossato DPI adeguati"*

➤ *"Un paio di settimane fa… anche se sembra passato tantissimo tempo"*
"Poche settimane… sembra passato un anno e mezzo…"

Evolution of therapies…

Therapeutics and COVID-19

LIVING GUIDELINE
24 SEPTEMBER 2021

World Health Organization

the**bmj**   covid-19   Research ⌄   Education ⌄   News & Views ⌄   Campaigns ⌄   Jobs ⌄

Population

This recommendation applies only to people with these characteristics:

Patients with confirmed covid-19

Disease severity

Non-severe	Severe	Critical
Absence of signs of severe or critical disease	Oxygen saturation <90% on room air	Requires life sustaining treatment
	Signs of pneumonia	Acute respiratory distress syndrome
	Signs of severe respiratory distress ⓘ	Sepsis
		Septic shock

Interventions

Initially: chloroquine (hydroxychloroquine), anti-retrovirals, steroids (+/-), ab (+/-), etc…

21 Maggio 2020

In condizioni disperate per il coronavirus, salvato con l'ossigeno-ozono terapia

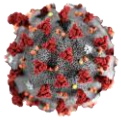La storia a lieto fine al ▮▮▮▮▮ di Torino

ALESSANDRO MONDO

PUBBLICATO IL
21 Maggio 2020

ULTIMA MODIFICA
21 Maggio 2020 12:05

TORINO. Dato per morto, trattato in extremis, curato e dimesso. Nei giorni scorsi è stato salvato un uomo di 76 anni, affetto da Covid-19, quando le sue condizioni erano ormai considerate disperate, con la terapia dell'ossigeno-ozono, presso ▮▮▮▮▮▮▮▮▮▮ di Torino.

18 Marzo 2020

SPECIALE CORONAVIRUS
COVID-19

AGGIORNAMENTO SCIENTIFICO

Tocilizumab, farmaco artrite contro Coronavirus/ A Napoli migliorano 2 pazienti gravi

Coronavirus, il medico di Napoli che per primo ha usato il farmaco anti-artrite: "Resto cauto, ma i dati sono incoraggianti"

L'Agenzia italiana del farmaco ha autorizzato uno studio per valutare l'efficacia del tocilizumab. L'oncologo Paolo Ascierto: "Non tutti i pazienti rispondono, la sperimentazione chiarirà su chi puntare"

Anche a Napoli state andando avanti?

«Sì, all'ospedale Cotugno a lunedì sono stati trattati 11 pazienti, tutti tra i cinquanta e i sessant'anni, di cui 7 in rianimazione e 4 in reparto. Dei 7 in rianimazione 5 hanno mostrato un miglioramento importante mentre uno è stazionario e un altro, che aveva patologie concomitanti, è purtroppo deceduto. Dei 4 che sono stati trattati in reparto con una grave insufficienza respiratoria, a distanza di 48 ore dall' infusione tutti avevano segni di miglioramento».

Sono stati fatti passi avanti in Italia nella ricerca contro il **Coronavirus**.

La risposta al **Covid-19** potrebbe arrivare dal **Tocilizumab**, un farmaco che solitamente viene usato nella cura dell'artrite reumatoide. Inoltre, è un medicinale di elezione nel trattamento della sindrome da rilascio citochimica dopo il trattamento con le cellule **Car-T**. Questo farmaco è stato usato in **Cina** su 21 pazienti, ma per la prima volta viene ora somministrato in Italia in casi di Coronavirus e comincia a dare risultati significativi.

*(…) But we all forget that **the time of science and research is not the time of media and news** (…)"*

Coccolini F et al., World J Emerg Surg 2021;16:46

Pietro Caironi

|	
From:	███████████████████████████
Sent:	Monday, October 12, 2020 9:15 PM
To:	pietro.caironi@unito.it
Subject:	Gentile Professore Pietro Caironi

Gentile Professor Caironi
mi scuso se mi permetto di disturbarLa, in veste di marito di una sua paziente, ███████████
ricoverata in terapia intensiva, da oggi anche mediante intubazione.
Le chiedo se fosse eventualmente consigliabile, in aggiunta al trattamento con eparina e steroide, una
sieroprofilassi tramite plasma iperimmune, compatibilmente allo situazione in essere.
La ringrazio per la disponibilità della sua attenzione Cordialmente ███████████████████
███████████

*Rapporti con i parenti in un contesto di assenza di evidenze certe,
ma circolazione di ipotesi / notizie / case reports, etc.*
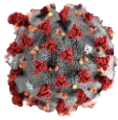
Sanità

Aprire le terapie intensive (anche Covid) è un dovere

di Sabina Pignataro | 22 aprile 2021

VITA
NEWSLETTER
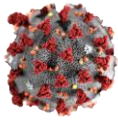Scopri la newsletter di Vita.it

Maschera, visiera, tre paia di guanti: da novembre l'ospedale Cisanello di Pisa i famigliari possono fare visita ai pazienti ricoverati nel reparto di terapie intensiva Covid. «Anche in piena pandemia non c'è nessun motivo per vietare l'ingresso ai parenti», spiega il primario Paolo Malacarne, che da anni sostiene le terapie intensive aperte. «Dovevamo avere un "sussulto organizzativo" e modificare il dogma della restrizione vigente e rendere fruibile l'accesso. Era un nostro dovere»

"Umanizzazione delle cure"

Terapie Covid, via libera dal Consiglio di Stato all'idrossiclorochina

Data notizia: 11 Dicembre 2020

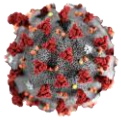> L'Assessore alla Sanità del ████████ e coordinatore nazionale della Commissione, Salute ████████ "Si apre un nuovo della lotta al virus"

E' un grande giorno per il riconoscimento delle cure al Covid-19. **L'utilizzo dell'idrossiclorochina è stato sperimentato nella prima ondata pandemica in Piemonte con risultati molto incoraggianti**, non riuscivamo a capire perché i nostri medici dovessero rinunciarvi, quando anche l'Organizzazione mondiale della Sanità aveva sciolto le riserve emerse sulla base di pubblicazioni rivelatesi del tutto inconsistenti. Finalmente torniamo a disporre di un'arma che può essere utilmente impiegata nella lotta al covid-19, soprattutto sul fronte del trattamento precoce della malattia, attraverso i

████████ aveva portato ad esempio l'esperienza del Distretto ████████████ ████████ che dal 18 marzo al 30 aprile aveva preso in carico e seguito a casa, precocemente, attraverso il **protocollo "Covid a casa" della dott.ssa** ████████ **che prevedeva l'utilizzo dell'idrossiclorochina, 340 pazienti, con una drastica riduzione dei ricoveri**, **in controtendenza con i dati della stessa provincia**, tra le più colpite del ████████ Su 340 pazienti, infatti, si sono avuti 22 ricoveri e 9 decessi, numeri dolorosi, ma nettamente inferiori a quelli attesi in base ai dati epidemiologici.

On 15 June, 2020, FDA revoked EUA (safety reasons and absence of efficacy) On 20 June, 2020, ORCHID trial (NIH) discontinued for futility

LACKS

Total patients by 7 May 2020
- 95 COVID-ICUs in 72 hospitals
- Total patients: 4585
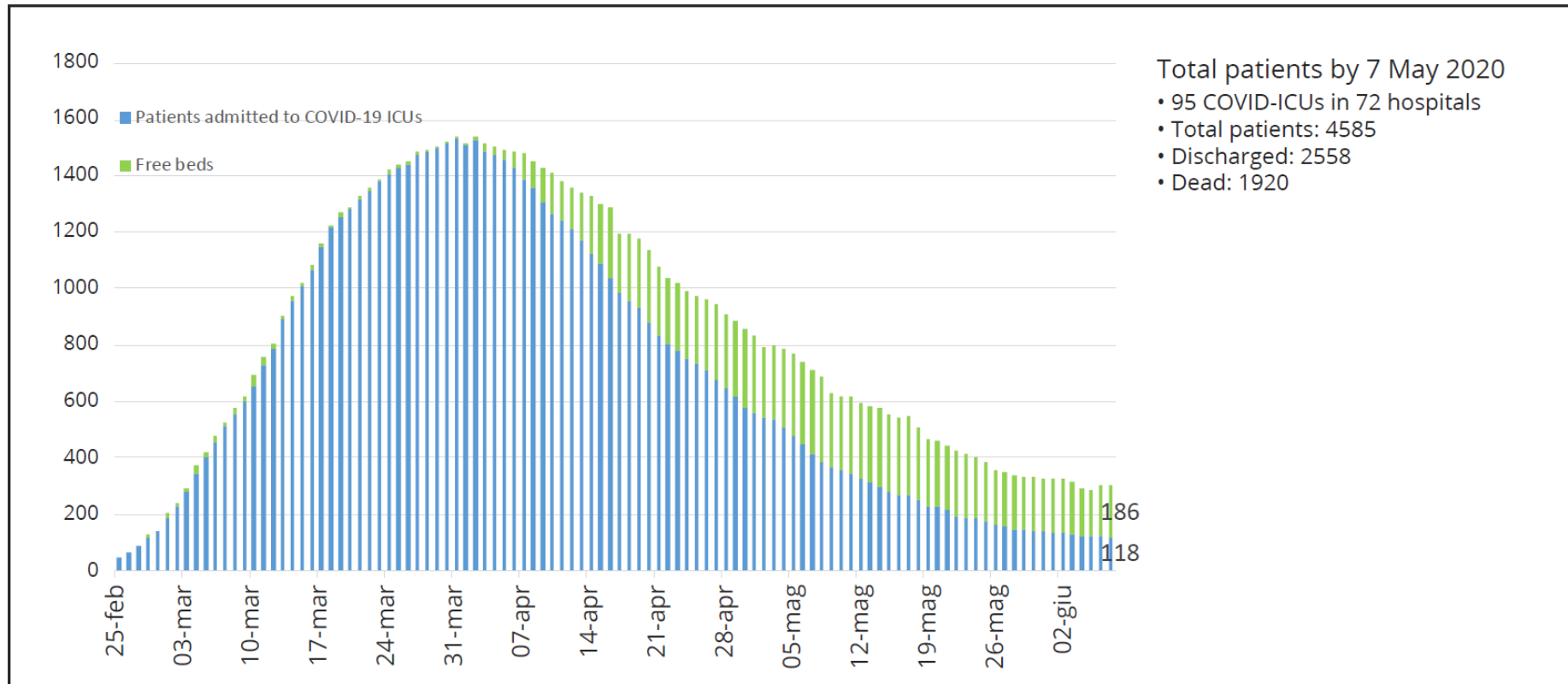- Discharged: 2558
- Dead: 1920

Figure 1.—Trend of patients admitted to the ICUs of the COVID-19 Lombardy Network from 25 February 2020.
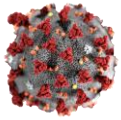
Lack of ICU beds   Lack of materials   Lack of PPE   Lack of diagnostic testing

Foti G et al., Minerva Anestesiologica 2020;86:1234-45

→ General context (what's happened?)

→ **Why has the system been distressed?**

→ Few examples (use of tocilizumab / therapeutic anticoagulation)

→ Important aspects (positive and negative…)

→ Open questions
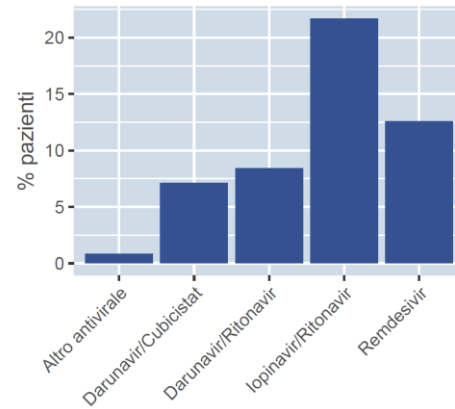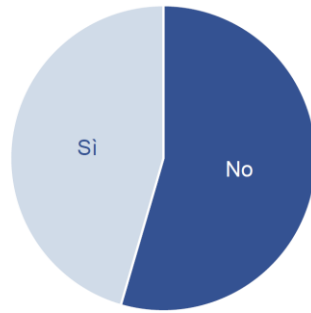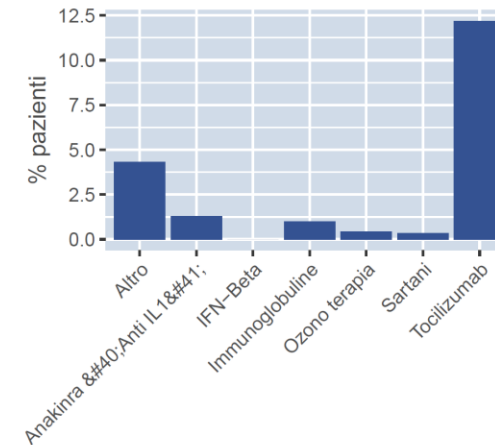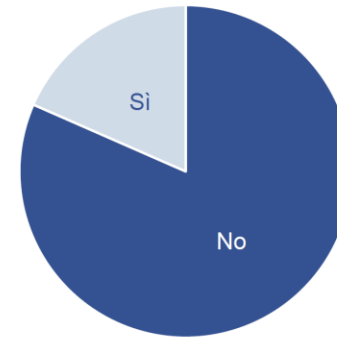
Cosa ha messo in crisi il sistema e ci ha messo in crisi? (almeno in parte…)

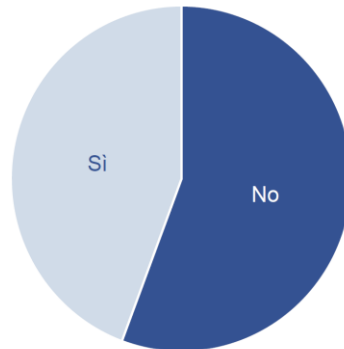*Noi, comunque abituati (abbastanza) a seguire linee-guida / raccomandazioni / evidenze?*
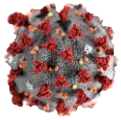

Antivirali

Farmaci Sperimentali

Idrossiclorochina

*Elevata variabilità delle terapie applicate
e delle opinioni (e considerazioni) ad esse associate*

Cosa ha messo in crisi il sistema e _ci_ ha messo in crisi? (almeno in parte...)

Something unknown

Inizialmente simile ad altre cause di ARDS da polmonite interstiziale (o virale), come H1N1, etc. Poi, evidenza clinica di differenze (manifestazione e gravità dell'ipossia, rischio trombotico, etc.)

Big numbers

Vs. malattie rare (dove siamo più abituati a non avere evidenze o linee-guida)
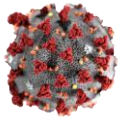
Severity

Si fosse trattato di qualche cosa di meno grave, avremmo "accettato" più facilmente l'assenza di evidenze

Organizational issues

Problematiche logistiche e mancanza di materiale (poco spazio per ragionare o raccogliere evidenze)

Timing

No tempo per "metabolizzare" i cambiamenti e le evidenze...

PERSPECTIVE

THE COVID-19 INFODEMIC

The Covid-19 Infodemic — Applying the Epidemiologic Model to Counter Misinformation

David Scales, M.D., Ph.D., Jack Gorman, M.D., and Kathleen H. Jamieson, Ph.D.

NIH National Library of Medicine
National Center for Biotechnology Information

Log in

Pub**Med**.gov

covid 19 ✕ **Search**
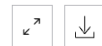
Advanced   Create alert   Create RSS   User Guide

Save   Email   Send to   Sorted by: Best match   Display options

MY NCBI FILTERS

182,127 results

RESULTS BY YEAR

Use COVID-19 filters from PubMed Clinical Queries to refine your search ✕

Treatment   Mechanism   Transmission   More filters

See more SARS-CoV-2 literature, sequence, and clinical content from NCBI
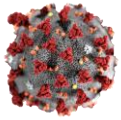
1981   2022

TEXT AVAILABILITY

☐ False-positive **COVID**-19 results: hidden problems and costs.
1   Surkova E, Nikolayevskyy V, Drobniewski F.
Cite   Lancet Respir Med. 2020 Dec;8(12):1167-1168. doi: 10.1016/S2213-2600(20)30453-7. Epub 2020 Sep 29.
PMID: 33007240   **Free PMC article.**   No abstract available.

☐ Abstract   Share
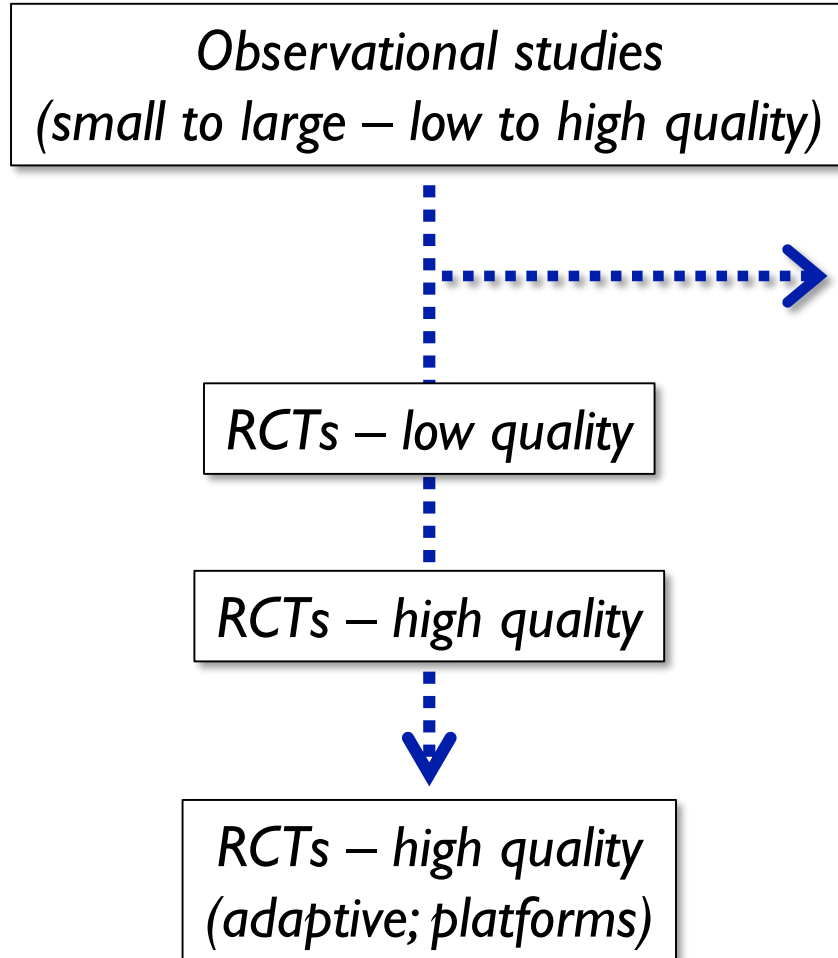
From absence of Information To a Pandemic of Information

Evolution of types of evidence among the COVID-19 infodemic

Large bulk of "evidence"

Evidence rapidly changing
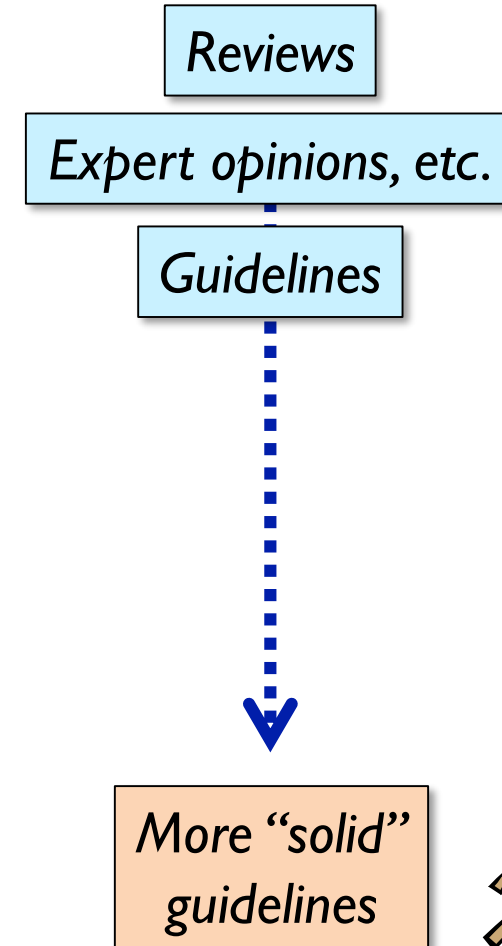
Observational studies
(small to large – low to high quality)

RCTs – low quality

RCTs – high quality

RCTs – high quality
(adaptive; platforms)

Clinical cases,
Case series,
Research letters

Reviews

Expert opinions, etc.

Guidelines

More "solid"
guidelines

General context (what's happened?)

Why has the system been distressed?

Few examples (use of tocilizumab / therapeutic anticoagulation)

Important aspects (positive and negative…)

Open questions

First observations from Wuhan, China

9 March, 2020

Effective treatment of severe COVID-19 patients with tocilizumab

Xiaoling Xu[a,1,2], Mingfeng Han[b,1], Tiantian Li[a], Wei Sun[b], Dongsheng Wang[a], Binqing Fu[c,d], Yonggang Zhou[c,d], Xiaohu Zheng[c,d], Yun Yang[e], Xiuyong Li[f], Xiaohua Zhang[b], Aijun Pan[e], and Haiming Wei[c,d,2]
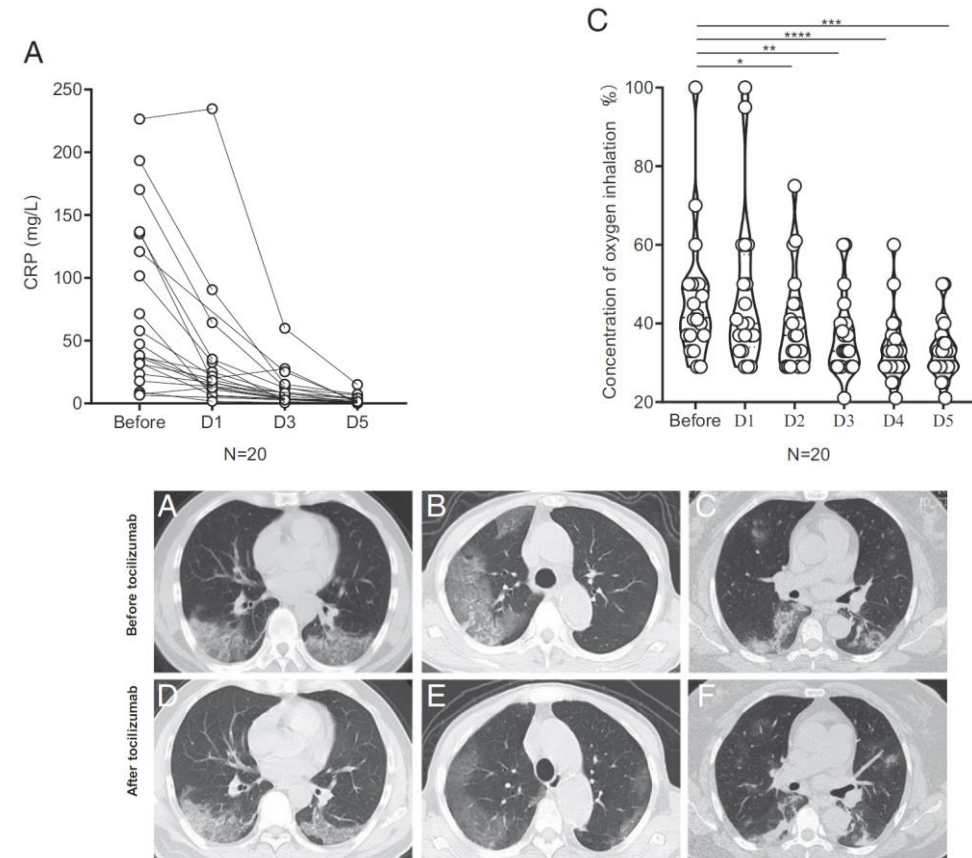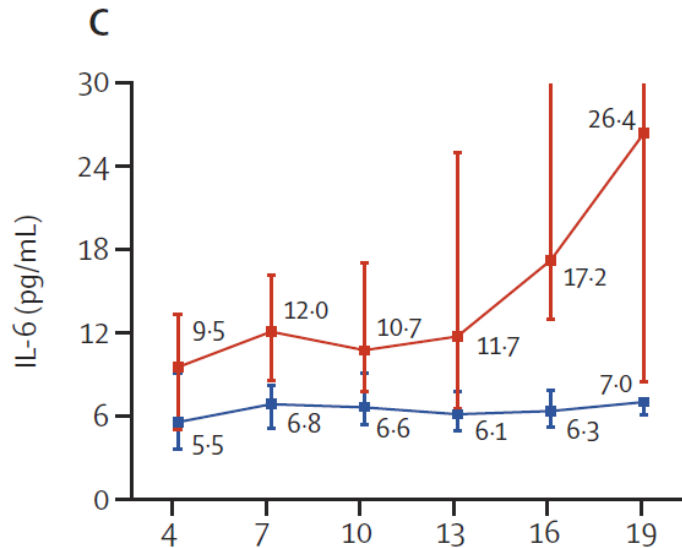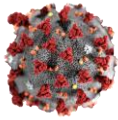
20 April, 2020

I **IL-6 Receptor Blockers (Tocilizumab and Sarilumab)**

CRONACA

Usciti dalla terapia intensiva i due pazienti curati col Tocilizumab a Napoli

I due fanno parte dei 16 contagiati da Covid-19 in terapia intensiva all'ospedale Cotugno e dei 5 trattati con il farmaco prodotto da Roche sulla base dell'intuizione dell'equipe dell'Istituto tumori Pascale guidata da Paolo Ascierto

30/03/2020
Roche (e AIFA) –
approvato uso compassionevole
del farmaco

DRUG INFORMATION

Pts treated with tocilizumab are at **increased risk for developing serious infections** that may lead to hospitalization and death.
The **risk and benefits** of treatment with tocilizumab should be carefully considered prior to initiating therapy

(AIFA) Approvazione di numerosi RCTs

Half-life of 16 days

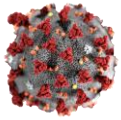**Risk / Benefit Ratio** (without solid evidence of efficacy)…?
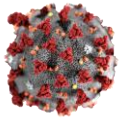
Tocilizumab in patients with severe COVID-19: a retrospective cohort study

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Methods This retrospective, observational cohort study included adults (≥18 years) with severe COVID-19 pneumonia who were admitted to tertiary care centres in Bologna and Reggio Emilia, Italy, between Feb 21 and March 24, 2020, and a tertiary care centre in Modena, Italy, between Feb 21 and April 30, 2020. All patients were treated with the

Findings Of 1351 patients admitted, 544 (40%) had severe COVID-19 pneumonia and were included in the study. 57 (16%) of 365 patients in the standard care group needed mechanical ventilation, compared with 33 (18%) of 179 patients treated with tocilizumab (p=0·41; 16 [18%] of 88 patients treated intravenously and 17 [19%] of 91 patients treated subcutaneously). 73 (20%) patients in the standard care group died, compared with 13 (7%; p<0·0001) patients treated with tocilizumab (six [7%] treated intravenously and seven [8%] treated subcutaneously). After adjustment for sex, age, recruiting centre, duration of symptoms, and SOFA score, tocilizumab treatment was associated with a reduced risk of invasive mechanical ventilation or death (adjusted hazard ratio 0·61, 95% CI 0·40–0·92; p=0·020). 24 (13%) of 179 patients treated with tocilizumab were diagnosed with new infections, versus 14 (4%) of 365 patients treated with standard of care alone (p<0·0001).

First RCT

ORIGINAL ARTICLE

Efficacy of Tocilizumab in Patients Hospitalized with Covid-19

- Randomized, double-blind, placebo-controlled trial in pts with severe ARDS SARS-CoV-2 Infection (N=243 pts)

- Randomization 2:1 to receive either tocilizumab (8 mg/kg) or standard of care

- Primary outcome was intubation or death (time-to-event analysis)

A — Mechanical Ventilation or Death

No. at Risk				
Tocilizumab	161	148	145	144	144
Placebo	81	72	71	70	69

Tocilizumab was not effective for preventing intubation or death in moderately ill hospitalized pts (wide IC for efficacy)

Stone JH et al., N Engl J Med 2020;383:2333-44
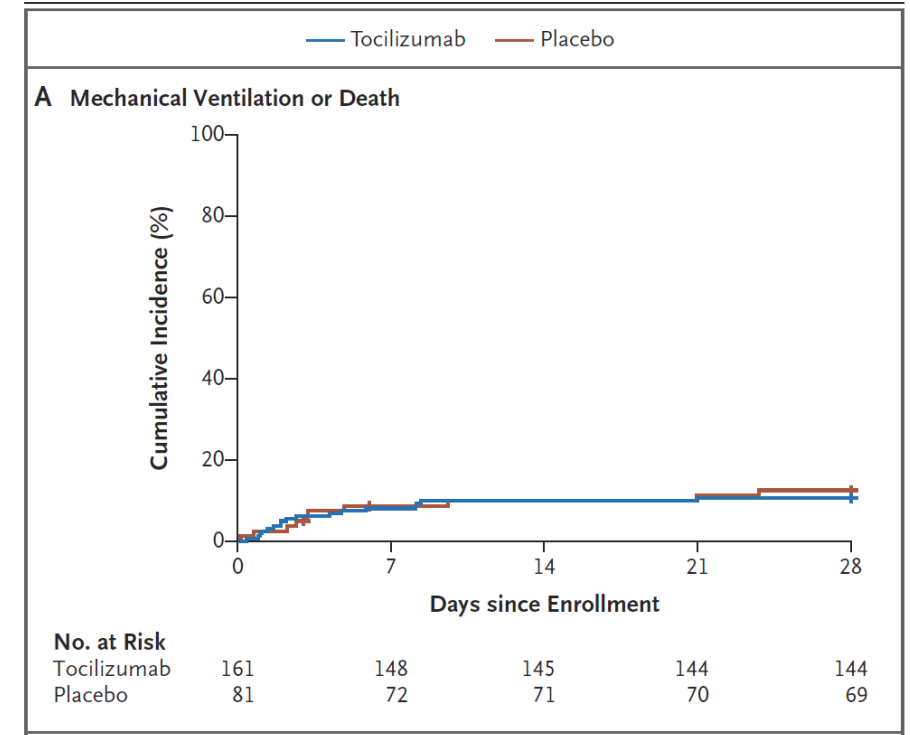
22 April, 2021

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

The REMAP-CAP Investigators*

Adult pts within 24h after starting organ support in ICU
N=353 pts (tocilizumab); N=48 (sarilumab); N=402 (control) – Bayesian statistical model
Both treatments met pre-defined criteria for efficacy
(organ support-free days 10 vs. 11 vs 0 – 90-day survival HR 1.61, 1.25-2.08)

1 May, 2021

Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

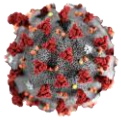RECOVERY Collaborative Group*

Adult with hypoxia (SpO2 <92% or O2) and PCR ≥ 75 mg/L
N=4116 (from 21550 included in the RECOVERY trial)
28-day mortality (31%, tocilizumab vs. 35%, standard of care, P=0.0028)

I *IL-6 Receptor Blockers (Tocilizumab and Sarilumab)*

WHO Living Guideline – (6th edition)

Therapeutics and COVID-19

LIVING GUIDELINE
24 SEPTEMBER 2021

World Health Organization

Il-6 blockers reduce mortality and need for mechanical ventilation based on high certainty of evidence

the bmj covid-19 Research ∨ Education ∨ News & Views ∨ Campaigns ∨ Jobs ∨

Population
This recommendation applies only to people with these characteristics:

Patients with confirmed covid-19

Disease severity

Non-severe	Severe	Critical
Absence of signs of severe or critical disease	Oxygen saturation <90% on room air	Requires life sustaining treatment
	Signs of pneumonia	Acute respiratory distress syndrome
	Signs of severe respiratory distress	Sepsis
		Septic shock

Interventions

IL-6 receptor blockers
Interleukin-6 receptor blockers

Recommendation in favour (strong)

The evidence regarding the risk of SAEs (risk of infection) is uncertain (short follow-up, etc.).

Risks and benefits of therapy should be considered carefully in pts with any active, severe infection other than COVID-19 – history of recurrent or chronic infection or with underlying conditions which may predispose them to infections
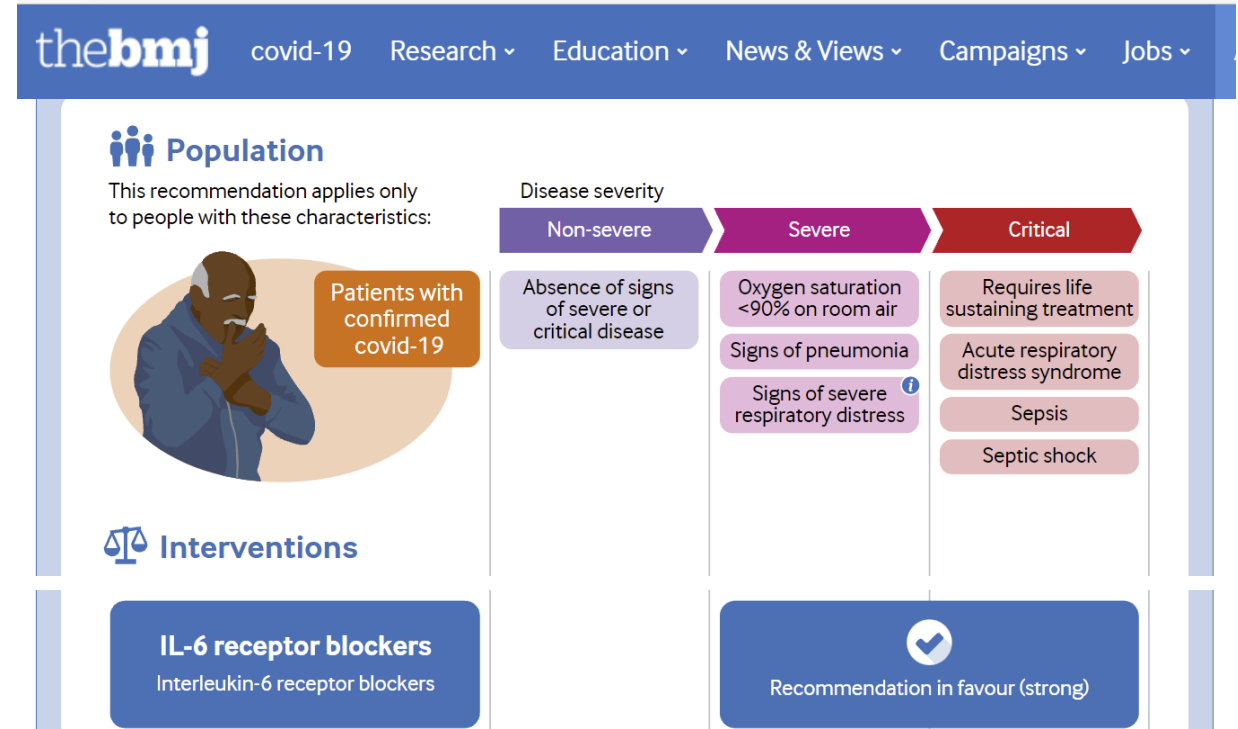
Increased risk of Arterial and Venous TE with COVID-19

Fig. 1. Incidence rates of thromboembolic events, by the type of thromboembolic event and COVID-19 status. TE; thrombo-embolic events.
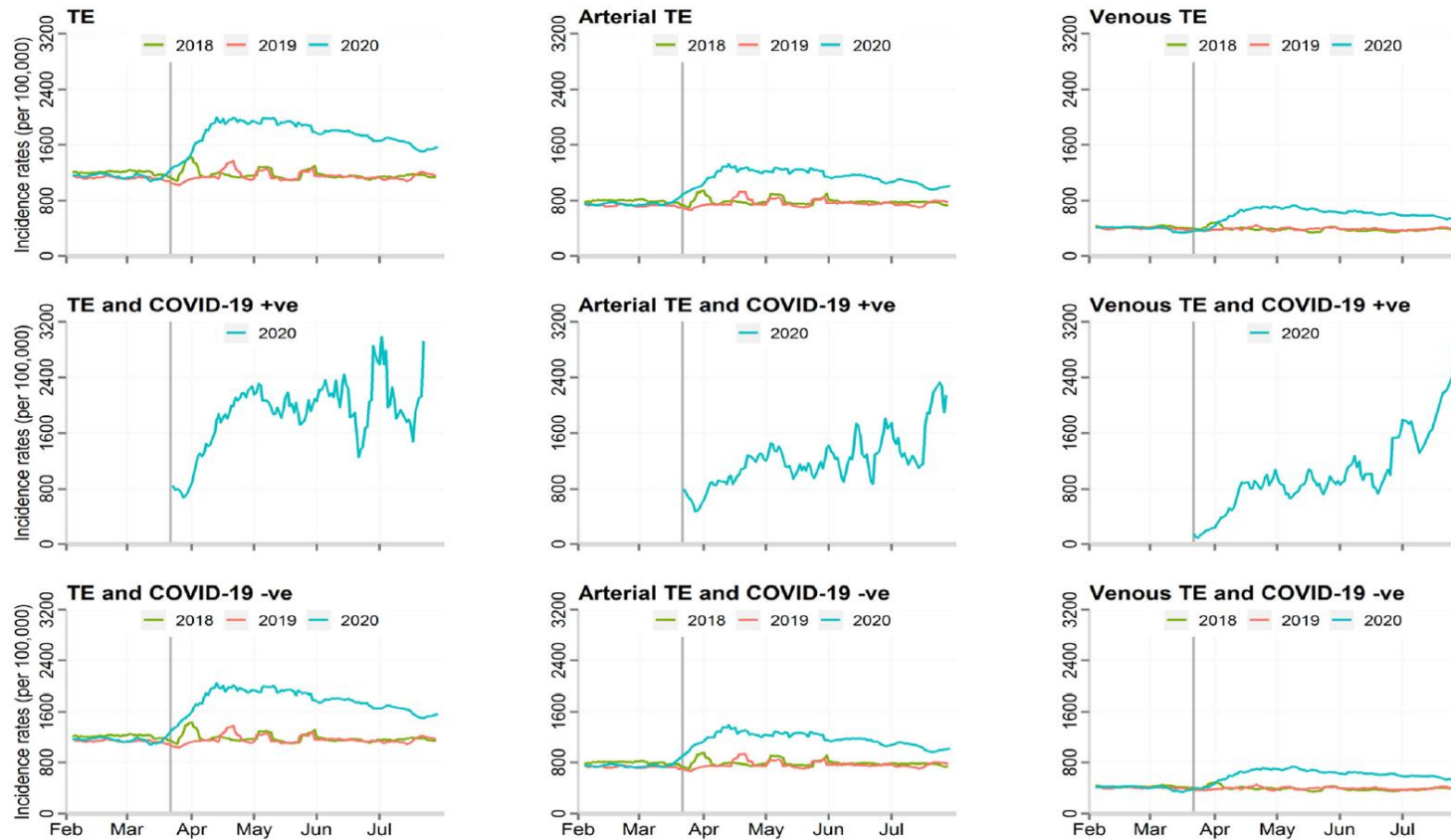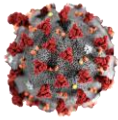
Immediate several Expert Consensus or Indications for Anti-coagulation (absence of evidence)

Aktaa s et al., Thrombosis Research 2021;202:17-23

ORIGINAL ARTICLE

jth

Anticoagulant interventions in hospitalized patients with COVID-19: A scoping review of randomized controlled trials and call for international collaboration

Abstract

Introduction: Coronavirus disease (COVID-19) is associated with a high incidence of thrombosis and mortality despite standard anticoagulant thromboprophylaxis. There is equipoise regarding the optimal dose of anticoagulant intervention in hospitalized patients with COVID-19 and consequently, immediate answers from high-quality randomized trials are needed.

Methods: The World Health Organization's International Clinical Trials Registry Platform was searched on June 17, 2020 for randomized controlled trials comparing increased dose to standard dose anticoagulant interventions in hospitalized COVID-19 patients. Two authors independently screened the full records for eligibility and extracted data in duplicate.

Results: A total of 20 trials were included in the review. All trials are open label, 5 trials use an adaptive design, 1 trial uses a factorial design, 2 trials combine multi-arm parallel group and factorial designs in flexible platform trials, and at least 15 trials have multiple study sites. With individual target sample sizes ranging from 30 to 3000 participants, the pooled sample size of all included trials is 12 568 participants. Two trials include only intensive care unit patients, and 10 trials base patient eligibility on elevated D-dimer levels. Therapeutic intensity anticoagulation is evaluated in 14 trials. All-cause mortality is part of the primary outcome in 14 trials.

Discussion: Several trials evaluate different dose regimens of anticoagulant interventions in hospitalized patients with COVID-19. Because these trials compete for sites and study participants, a collaborative effort is needed to complete trials faster, conduct pooled analyses and bring effective interventions to patients more quickly.

*A **collaborative effort** is needed…*
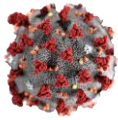
Therapeutic Anticoagulation

Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19

The ATTACC, ACTIV-4a, and REMAP-CAP Investigators*

*Open-label, adaptive, multiplatform, controlled trial – hospitalized COVID-19 pts not critically ill: therapeutic-dose anticoagulation with heparin vs. usual-care pharmacological thromboprophylaxis. Trial stopped as pre-specified criteria for **efficacy** were met – Bayesian statistical model (N=2219 pts) (increased organ support-free days adjusted OR 1.27, 1.03-1.58).*

Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19

The REMAP-CAP, ACTIV-4a, and ATTACC Investigators*

*Open-label, adaptive, multiplatform, controlled trial – hospitalized COVID-19 pts not critically ill: therapeutic-dose anticoagulation with heparin vs. usual-care pharmacological thromboprophylaxis. Trial stopped as pre-specified criteria for **futility** were met – Bayesian statistical model (N=1098 pts) (increased organ support-free days adjusted OR 0.83, 0.67-1.03).*

E noi cosa facciamo…?? (dati GiViTI…)

→ *General context (what's happened?)*

→ *Why has the system been distressed?*

→ *Few examples (use of tocilizumab / therapeutic anticoagulation)*

→ *Important aspects (positive and negative...)*

→ *Open questions*

Video-conferenze *(durante la 1° ondata pandemica)*

- ✓ *6 incontri, di circa 2h ciascuano*
- ✓ *> 30 relatori*
- ✓ *Visualizzazioni totali: ~160.000*
- ✓ *Picco connesioni simulatanee 1° incontro: 5278*

10/03/2020   *Esperienze clinico / organizzative da TI di Lodi, Pavia, Monza e Lecco (diagnosi e trattamento)*

17/03/2020   *Aspetti organizzativi e gestionali*

24/03/2020   *Aspetti psicologici correlati allo stress del personale e alla comunicazione con i parenti dei pazienti*

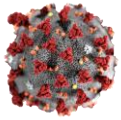*31/03/2020*   *Con SIAARTI – gestione delle vie aeree, decisione di intubare, svezzamento*

07/04/2020   *Meccanismi patogenetici della malattia*

14/04/2020   *Multi-disciplinarietà nell'emergenza*

Medical Journals and the 2019-nCoV Outbreak

Eric J. Rubin, M.D., Ph.D., Lindsey R. Baden, M.D., Stephen Morrissey, Ph.D.,
and Edward W. Campion, M.D.

✓ *Sharing important information
with public health authorities (WHO), with authors approval*

✓ *Expedite review process (on 2019-nCoV data)*

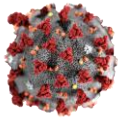✓ *Article freely available*

Observational studies

Research letters

Review article (formulating hypothesis)

Pre-print publications

Risk of retractions…

*N Engl J Med 2020;382:9 – **January 27, 2020** (online)*

RECOVERY
Randomised Evaluation of COVID-19 Therapy

1.2 Treatment Options

There are currently no approved anti-viral or host-directed treatments for COVID-19. This protocol allows reliable assessment of the effects of multiple different treatments (including re-purposed and novel drugs) on major outcomes in COVID-19. All patients will receive usual care for the participating hospital.

1.3 Design Considerations

The RECOVERY Protocol describes an overarching trial design to provide reliable evidence on the efficacy of candidate therapies for confirmed COVID-19 infection in hospitalised adult patients receiving usual standard of care.

There are no known treatments for COVID-19. The anticipated scale of the epidemic is such that hospitals, and particularly intensive care facilities, may be massively overstretched. Under some models of pandemic spread, up to 50% of the adult population may fall sick over a period of 8-12 weeks, of whom around 10% may require hospitalisation. This would involve about 2 million hospital admissions. In this situation, even treatments with only a moderate impact on survival or on hospital resources could be worthwhile. Therefore, the focus of the COVID-19 Core Protocol is the impact of candidate treatments on mortality and on the need for hospitalisation or ventilation.
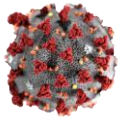
The protocol is deliberately flexible so that it is suitable for a wide range of settings, allowing:
- a broad range of patients to be enrolled in large numbers;
- randomisation between only those treatment arms that are *both* available at the hospital *and* not believed by the enrolling doctor to be contraindicated (e.g. by particular co-morbid conditions or concomitant medications);
- treatment arms to be added or removed according to the emerging evidence; and
- additional sub-studies may be added to provide more detailed information on side effects or sub-categorisation of patient types but these are not the primary objective and are not required for participation.

In a cohort of 191 hospitalised COVID-19 patients with a completed outcome, the median time from illness onset to discharge was 22·0 days (IQR 18·0–25·0) and the median time to death was 18·5 days (15·0–22·0). Thirty-two patients (17%) required invasive mechanical ventilation and the median time from onset to mechanical ventilation was 14.5 days. Therefore, early endpoint assessment, such as 28 days after admission, is likely to provide largely complete outcome data and will permit early assessment of treatment efficacy and safety.[5]

**Adaptive design
(interim analysis / DMC)**

Eligibility criteria simple

Trial processes minimized (CRF and endpoint)

www.recoverytrial.net

RECOVERY

Randomised Evaluation of COVID-19 Therapy

2.4 Randomisation

Eligible patients will be randomised using a central web-based randomisation service (without stratification or minimization) in a 2:1:1:1 ratio to one of the following treatment arms (in addition to usual care):
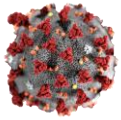
Arm 1: No additional treatment

Arm 2: Lopinavir 400mg-Ritonavir 100mg by mouth (or nasogastric tube) every 12 hours for 10 days or until discharge.

Arm 3: Interferon-β-1a . Nebulized solution of IFN-β1a 6MIU (0.5ml of a solution containing 12MIU/ml) once-daily for 10 days or until discharge.

Arm 4: Corticosteroid in the form of dexamethasone administered as an oral liquid or intravenous preparation 6 mg once daily for 10 days or until discharge (Note: It is permitted to switch between the two routes of administration according to clinical circumstances).

If one or more of the active drug treatments is not available at the hospital or is believed, by the attending clinician, to be contraindicated (or definitely indicated) for the specific patient, then this fact will be recorded via the web-based form prior to randomisation; random allocation will then be between the remaining arms (in a 2:1:1 or 2:1 ratio).

Role of Regulatory Authorities

28 March, 2020

*FDA approved chloroquine and hydroxychloroquine
for emergency use to treat COVID-19*

24 April, 2020

*FDA issued a cautioning statement against use of
chloroquine and hydroxychloroquine for COVID-19 outside hospital setting
Or clinical trial (risk for arrhythmias)*

15 June, 2020

*FDA revoked the emergency authorization (EUA) use of
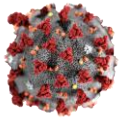chloroquine and hydroxychloroquine as a potential COVID-19 treatment*

20 June, 2020

*NIH announced discontinuation of the ORCHID trial
(safety issues and futility)*

→ *General context (what's happened?)*

→ *Why has the system been distressed?*

→ *Few examples (use of tocilizumab / therapeutic coagulation)*

→ *Important aspects (positive and negative…)*

→ *Open questions*

How to facilitate research process (gathering information and evidence)
in the context of a pandemic? And emergency situations, dealing with severe patients?

How to improve the creation of collaborative networks (more solid and more rapid data)
in this context?

How to ease the transfer from clinical evidence to clinical indications
(rigorous guidelines and statement)?

How to speed up the spread of information, and how to deal in a "proper" manner
with media and socials?

How should regulatory authorities deal in a rigorous but effective manner
with research (evidence) and decisions (indications)?
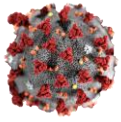
Anyway, we have run a long way...

"(...) I follow in the tradition of my predecessors, who have all been men in the avant-garde of science, men of fighting spirit.
I am fighting for physiology because it is the future of medicine."

"From Bernard's letters to Mme. Raffalovich" 1873, Paris