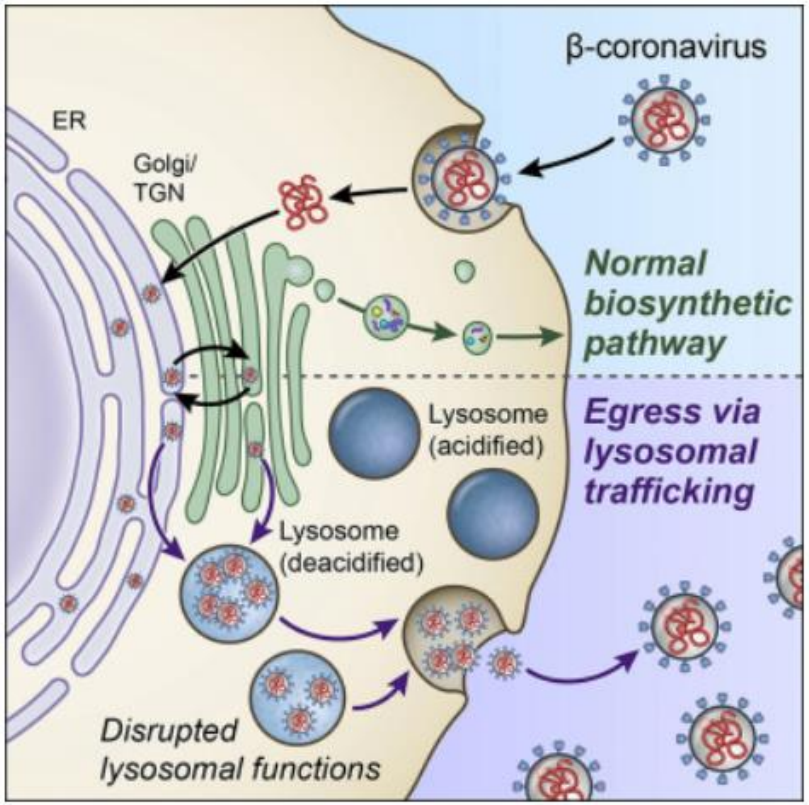
RICERCA BIBLIOGRAFICA COVID 19 SETTIMANA 14-20.12.2020 FONDAZIONE POLICLINICO UNIVERSITARIO A. GEMELLI IRCCS, UOC MALATTIE INFETTIVE DOTT.SSA ELEONORA TADDEI			
AUTORE/RIVISTA	**TITOLO**	**OUTCOME PRINCIPALE**	**ABSTRACT**
Pairo-Castineira E et al Nature https://doi.org/10.1038/s41586-020-03065-y	Genetic mechanisms of critical illness in Covid-19	Risultati di uno studio genome-wide su 2244 pazienti critici con COVID-19, alla ricerca di target molecolari implicati nella patogenesi dell'infezione grave, possibile bersaglio di farmaci già esistenti.	Host-mediated lung inflammation is present, and drives mortality, in critical illness caused by Covid-19. Host genetic variants associated with critical illness may identify mechanistic targets for therapeutic development. Here we report the results of the GenOMICC (Genetics Of Mortality In Critical Care) genome-wide association study(GWAS) in 2244 critically ill Covid-19 patients from 208 UK intensive care units (ICUs). We identify and replicate novel genome-wide significant associations, on chr12q24.13 (rs10735079, p=1.65 × 10-8) in a gene cluster encoding antiviral restriction enzyme activators (OAS1, OAS2, OAS3), on chr19p13.2 (rs2109069, p=2.3 × 10-12) near the gene encoding tyrosine kinase 2 (TYK2), on chr19p13.3 (rs2109069, p=3.98 × 10-12) within the gene encoding dipeptidyl peptidase 9 (DPP9), and on chr21q22.1 (rs2236757, p=4.99 × 10-8) in the interferon receptor gene IFNAR2. We identify potential targets for repurposing of licensed medications: using Mendelian randomisation we found evidence in support of a causal

			link from low expression of IFNAR2, and high expression of TYK2, to life-threatening disease; transcriptome-wide association in lung tissue revealed that high expression of the monocyte/macrophage chemotactic receptor CCR2 is associated with severe Covid-19. Our results identify robust genetic signals relating to key host antiviral defence mechanisms, and mediators of inflammatory organ damage in Covid-19. Both mechanisms may be amenable to targeted treatment with existing drugs. Large-scale randomised clinical trials will be essential before any change to clinical practice.
Ghosh S et al Cell https://www.cell.com/cell/fulltext/S0092-8674(20)31446-X	β-Coronaviruses Use Lysosomes for Egress Instead of the Biosynthetic Secretory Pathway	Dimostrazione che i beta-Coronavirus, tra cui SARS-CoV-2, utilizzano i lisosomi – la cui funzione viene alterata - come via d'uscita dalle cellule infettate.	β-Coronaviruses are a family of positive-strand enveloped RNA viruses that includes the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Much is known regarding their cellular entry and replication pathways, but their mode of egress remains uncertain. Using imaging methodologies and virus-specific reporters, we demonstrate that β-coronaviruses utilize lysosomal trafficking for egress rather than the biosynthetic secretory pathway more commonly used by other enveloped viruses. This unconventional egress is regulated by the Arf-like small GTPase Arl8b and can be blocked by the Rab7 GTPase competitive inhibitor CID1067700. Such non-lytic release of β-coronaviruses results in lysosome deacidification, inactivation of lysosomal degradation enzymes, and disruption of antigen presentation pathways. β-Coronavirus-induced exploitation of lysosomal organelles for egress provides insights into the cellular and immunological abnormalities observed in patients and suggests new therapeutic modalities.

			
Selhorst P et al Clinical Infectious Diseases https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1850/6033730?searchresult=1	Symptomatic SARS-CoV-2 reinfection of a health care worker in a Belgian nosocomial outbreak despite primary neutralizing antibody response	Caso di reinfezione sintmatica ma lieve da SARS-CoV-2 in una giovane operatrice sanitaria immunocompetente, dopo 185 giorni dalla prima infezione e dopo sviluppo di una risposta anticorpale efficace.	Background : It is currently unclear whether SARS-CoV-2 reinfection will remain a rare event, only occurring in individuals who fail to mount an effective immune response, or whether it will occur more frequently when humoral immunity wanes following primary infection. Methods : A case of reinfection was observed in a Belgian nosocomial outbreak involving 3 patients and 2 health care workers. To distinguish reinfection from persistent infection and detect potential transmission clusters, whole genome sequencing was performed on nasopharyngeal swabs of all individuals including the

			reinfection case's first episode. IgA, IgM, and IgG and neutralizing antibody responses were quantified in serum of all individuals, and viral infectiousness was measured in the swabs of the reinfection case. Results : Reinfection was confirmed in a young, immunocompetent health care worker as viral genomes derived from the first and second episode belonged to different SARS-CoV-2 clades. The symptomatic reinfection occurred after an interval of 185 days, despite the development of an effective humoral immune response following symptomatic primary infection. The second episode, however, was milder and characterized by a fast rise in serum IgG and neutralizing antibodies. Although contact tracing and virus culture remained inconclusive, the health care worker formed a transmission cluster with 3 patients and showed evidence of virus replication but not of neutralizing antibodies in her nasopharyngeal swabs. Conclusion : If this case is representative of most Covid-19 patients, long-lived protective immunity against SARS-CoV-2 after primary infection might not be likely.
Abu-Raddad LJ et al Clinical Infectious Diseases https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1846/6033728?searchresult=1	Assessment of the risk of SARS-CoV-2 reinfection in an intense re-exposure setting	Studio retrospettivo di 243 casi di nuova positività del tampone nasofaringeo per SARS-CoV-2 a >45 giorni di distanza dal primo tampone positivo; si sospettano 54 casi di vera reinfezione, con un tasso di 0.36 per 10.000 settimane-persona e un ruschio di reinfezione dello 0.02%.	Background : Risk of reinfection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is unknown. We assessed risk and incidence rate of documented SARS-CoV-2 reinfection in a cohort of laboratory-confirmed cases in Qatar. Methods : All SARS-CoV-2 laboratory-confirmed cases with at least one PCR positive swab that is ≥45 days after a first-positive swab were individually investigated for evidence of reinfection, and classified as showing strong, good, some, or weak/no evidence for reinfection. Viral genome sequencing of the paired first-positive and reinfection viral specimens was conducted to confirm reinfection. Risk and incidence rate of reinfection were estimated.

			Results : Out of 133,266 laboratory-confirmed SARS-CoV-2 cases, 243 persons (0.18%) had at least one subsequent positive swab ≥45 days after the first-positive swab. Of these, 54 cases (22.2%) had strong or good evidence for reinfection. Median time between first and reinfection swab was 64.5 days (range: 45-129). Twenty-three of the 54 cases (42.6%) were diagnosed at a health facility suggesting presence of symptoms, while 31 (57.4%) were identified incidentally through random testing campaigns/surveys or contact tracing. Only one person was hospitalized at time of reinfection, but was discharged the next day. No deaths were recorded. Viral genome sequencing confirmed four reinfections out of 12 cases with available genetic evidence. Reinfection risk was estimated at 0.02% (95% CI: 0.01-0.02%) and reinfection incidence rate at 0.36 (95% CI: 0.28-0.47) per 10,000 person-weeks. Conclusions : SARS-CoV-2 reinfection can occur but is a rare phenomenon suggestive of protective immunity against reinfection that lasts for at least a few months post primary infection.
Pettit NN et al Clinical Infectious Diseases https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1851/6033734?searchresult=1	Remdesivir Use in the Setting of Severe Renal Impairment: A Theoretical Concern or Real Risk?	Studio retrospettivo su 135 pazienti trattati con remdesivir per COVID-19, fra cui 20 con insufficienza renale grave (CrCl < 30 ml/min): gli effetti avversi da farmaco non sono significativamente più numerosi in caso di insufficienza renale grave.	Introduction : Remdesivir (RDV) is FDA approved for COVID-19, but not recommended for patients with severe renal impairment (SRI, i.e. creatinine clearance < 30ml/min). Few studies have evaluated RDV in patients with SRI due to theoretical toxicity concerns. Methods : Hospitalized patients receiving RDV for COVID-19 between 5/1/2020-10/31/2020 were analyzed in a retrospective chart review. We compared incident adverse events (AEs) following RDV in patients with and without SRI, including hepatotoxicity, nephrotoxicity, any reported AE, mortality and length of stay. Results : A total of 135 patients received RDV, 20 patients had SRI. Patients with SRI were significantly older (70 vs. 54 years, p=0.0001). The incidence of possible AEs following RDV was 20% among those with SRI versus 11% without (p=0.26). LFT elevations

occurred in 10% vs. 4% (p=0.28), and SCr elevations occurred in 20% vs. 6% (p=0.06) of patients with SRI versus those without, respectively. The LFT and SCr elevations were not attributed to RDV in either group. Mortality and length of stay were comparable and consistent with historical controls.

Conclusion : RDV AEs occurred infrequently with low severity and were not significantly different between those with and without SRI. While a higher percentage of patients with SRI experienced SCr elevations, 3 (75%) patients were in AKI prior to RDV. Overall, the use of RDV in this small series of patients with SRI appeared to be relatively safe, and the potential benefit outweighed the theoretical risk of liver or renal toxicity; however, additional studies are needed to confirm this finding.

Table 2: Adverse Events and Clinical Outcomes

	SRI (N=20)	No SRI (N=115)	p-value
Any adverse drug event	6 (30)	13 (11)	0.26
Transaminitis	2 (10)	5 (4)	0.28
Hearing loss	0 (0)	1 (0.9)*	>0.99
Serum Creatinine (SCr) elevation†	4 (27)‡	7 (6)	0.02
Length of stay, median (IQR)	8.5 (8, 13)	7 (5, 10)	0.01
Mortality (%)	5 (25)	4 (3.5)	0.004

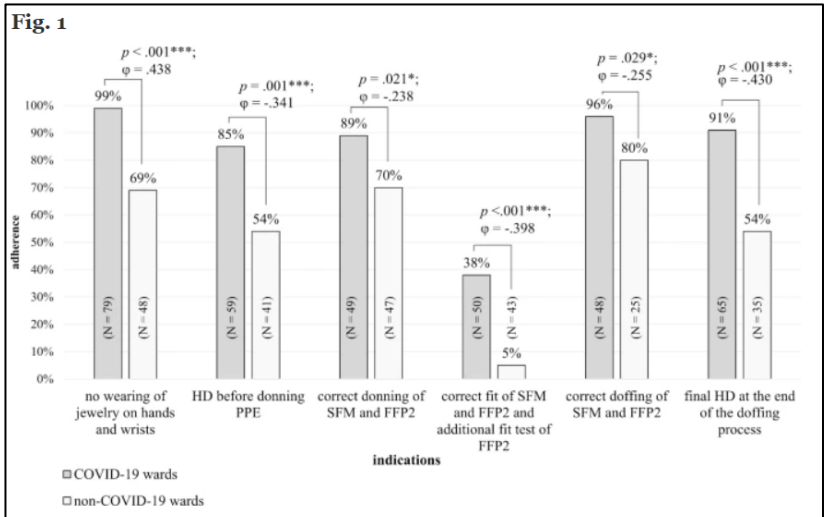
* One patient had both LFT elevation and hearing loss

† SCr elevation of >/=1.5 times baseline

‡ 3 of 4 patients in AKI prior to starting RDV, the remaining 1 patient had AKI secondary to clinical decompensation resulting in vasopressor administration, excluding patients on RRT at baseline, n=15

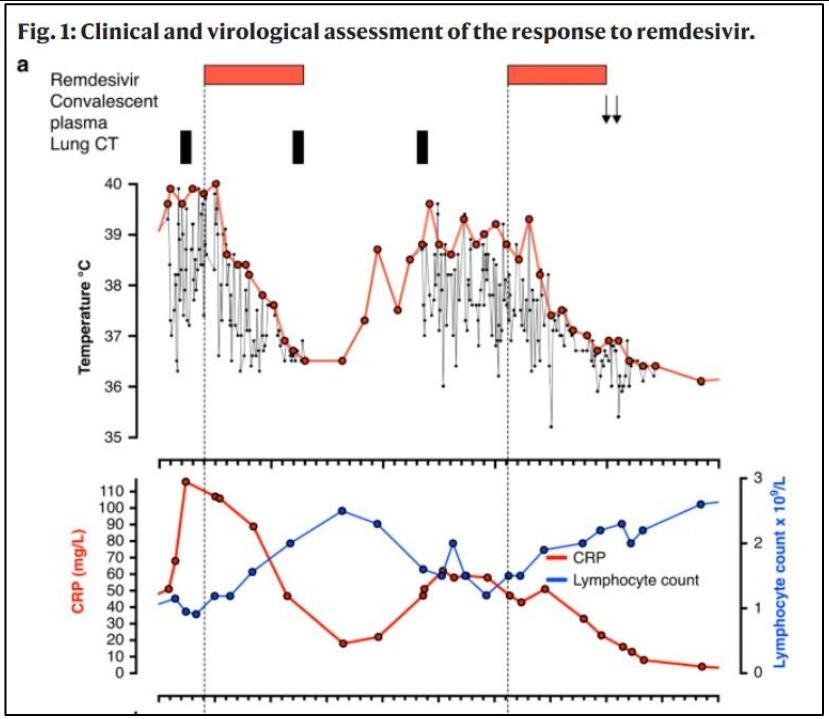
Leet SC et al Scientific Reports https://www.nature.com/articles/s41598-020-77791-8	Impact of comorbid asthma on severity of coronavirus disease (COVID-19)	Studio retrospettivo che confronta 686 pazienti con infezione da SARS-CoV-2 e storia di asma con 6586 pazienti privi di tale comorbidità: una storia di riacutizzazione recente, ma non di asma in genere, è un fattore di rischio per insufficienza respiratoria e morte.	The severity of the coronavirus disease (COVID-19) is associated with various comorbidities. However, no studies have yet demonstrated the potential risk of respiratory failure and mortality in COVID-19 patients with pre-existing asthma. We selected 7272 adult COVID-19 patients from the Korean Health Insurance Review and Assessment COVID-19 database for this nationwide retrospective cohort study. Among these, 686 patients with asthma were assessed by their severities and evaluated by the clinical outcome of COVID-19 compared to patients without asthma. Of 7272 adult COVID-19 patients, 686 with asthma and 6586 without asthma were compared. Asthma was not a significant risk factor for respiratory failure or mortality among all COVID-19 patients (odds ratio [OR] = 0.99, P = 0.997 and OR = 1.06, P = 0.759) after adjusting for age, sex, and the Charlson comorbidity score. However, a history of acute exacerbation (OR = 2.63, P = 0.043) was significant risk factors for death among COVID-19 patients with asthma. Asthma is not a risk factor for poor prognosis of COVID-19. However, asthma patients who had any experience of acute exacerbation in the previous year before COVID-19 showed higher COVID-19-related mortality, especially in case of old age and male sex. **Table 4.** Multivariate analyses of risk factors associated mortality in patients with asthma. OR, odds ratio; CI, confidence interval; MPR, medication possession ratio.

Variable	Respiratory failure risk		Mortality	
	Adjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Age	1.05 (1.02–1.08)	< 0.001	1.10 (1.07–1.14)	< 0.001
Sex, male	1.00 (0.38–2.62)	0.985	2.26 (1.12–4.54)	0.021
Severity				
Mild	1 (Reference)		1 (Reference)	
Moderate-severe	0.81 (0.17–3.76)	0.795	1.33 (0.54–3.30)	0.526
Number of acute exacerbation(s)				
0	1 (Reference)		1 (Reference)	
≥ 1	0.42 (0.05–3.58)	0.432	2.63 (1.02–6.72)	0.043

Neuwirth M et al Antimicrobial Resistance & Infection Control https://aricjournal.biomedcentral.com/articles/10.1186/s13756-020-00864-w	Adherence to personal protective equipment use among healthcare workers caring for confirmed COVID-19 and alleged non-COVID-19 patients.	In questo studio osservazionale condotto in Germania, il personale dei reparti "COVID" è maggiormente aderente alle corrette procedure di utilizzo di dispositivi di protezione individuale rispetto agli operatori che lavorano con pazienti considerati non infetti.	Adherence observations of health care workers (HCW) revealed deficiencies in the use of recommended personal protective equipment (PPE) among HCW caring in COVID-19 and non-COVID-19 wards during the first period of the SARS-CoV-2 pandemic in a university hospital in Germany. The adherence to wearing surgical face or FFP2-masks and disinfecting hands prior to donning and after doffing the PPE was significantly higher in COVID-19 wards However, there was no total adherence of 100% in COVID-19 wards. **Fig. 1**  Differences in adherence regarding PPE use in COVID-19 and non-COVID-19 wards
Donnelly JP et al JAMA https://jamanetwork.com/journals/jama/fullarticle/2774380?resultClick=1	Readmission and Death After Initial Hospital Discharge Among Patients With COVID-19 in a Large Multihospital System	In questo studio retrospettivo, i pazienti dimessi dopo ricovero per COVID-19 hanno un tasso di riospedalizzazione a 60 giorni del 19.9% e di morte o riospedalizzazione del 27%. Tali tassi sono inferiori	Although more patients are surviving severe coronavirus disease 2019 (COVID-19), there are limited data on outcomes after initial hospitalization. We therefore measured the rate of readmission, reasons for readmission, and rate of death after hospital discharge among patients with COVID-19 in the nationwide Veterans Affairs (VA) health care system.

		a quelli di una coorte di controllo ospedalizzata per polmonite non-COVID relata o scompenso cardiaco, salvo che nei primi 10 giorni dopo la dimissione, periodo di apparente fragilità dei pazienti con storia di COVID-19.	
CDC - Advisory Committee on Immunization Practices Morbidity and Mortality Weekly Report https://www.cdc.gov/mmwr/volumes/69/wr/mm6950e2.htm?s_cid=mm6950e2_w	The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine — United States, December 2020	L'Advisory Committee on Immunization Practices (ACIP) ha rilasciato delle line guida ad interim sull'utilizzo del vaccino Pfizer contro SARS-CoV-2 per soggetti di età superiore a 16 anni. In base ai dati attuali, il livello di evidenza a supporto di un effetto preventivo di COVID-19 è 1 (elevata sicurezza), per la prevenzione dell'ospedalizzazione è livello 3 (bassa), per la prevenzione della mortalità livello 4 (molto bassa). Per quanto riguarda gli effetti avversi, si attribuisce alle evidenze attuali un livello 2 (moderata sicurezza) e per gli effetti avversi gravi livello 1 (elevata sicurezza). Non ci	What is already known about this topic? On December 11, 2020, the Food and Drug Administration issued an Emergency Use Authorization for the Pfizer-BioNTech COVID-19 vaccine. What is added by this report? On December 12, 2020, after an explicit, evidence-based review of all available data, the Advisory Committee on Immunization Practices (ACIP) issued an interim recommendation for use of the Pfizer-BioNTech COVID-19 vaccine in persons aged ≥16 years for the prevention of COVID-19. What are the implications for public health practice? The recommendation for the Pfizer-BioNTech COVID-19 vaccine should be implemented in conjunction with ACIP's interim recommendation for allocating initial supplies of COVID-19 vaccines.

		sono dati in merito alla prevenzione dell'infezione asintomatica.	
Buckland MS et al Nature communications https://www.nature.com/articles/s41467-020-19761-2	Treatment of COVID-19 with remdesivir in the absence of humoral immunity: a case report	Paziente con agammaglobulinemia X-linked trattato con remdesivir per polmonite persistente da SARS-CoV-2 con beneficio.	The response to the coronavirus disease 2019 (COVID-19) pandemic has been hampered by lack of an effective severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antiviral therapy. Here we report the use of remdesivir in a patient with COVID-19 and the prototypic genetic antibody deficiency X-linked agammaglobulinaemia (XLA). Despite evidence of complement activation and a robust T cell response, the patient developed persistent SARS-CoV-2 pneumonitis, without progressing to multi-organ involvement. This unusual clinical course is consistent with a contribution of antibodies to both viral clearance and progression to severe disease. In the absence of these confounders, we take an experimental medicine approach to examine the in vivo utility of remdesivir. Over two independent courses of treatment, we observe a temporally correlated clinical and virological response, leading to clinical resolution and viral clearance, with no evidence of acquired drug resistance. We therefore provide evidence for the antiviral efficacy of remdesivir in vivo, and its potential benefit in selected patients.

			
Keddie S et al Brain https://academic.oup.com/brain/advance-article/doi/10.1093/brain/awaa433/6031905	Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome	L'incidenza di casi di sindrome di Guillain-Barré si è ridotta nel corso della pandemia da COVID-19 rispetto agli anni precedenti, probabilmente per effetto della minore circolazione di agenti infettivi che la scatenano. La sindrome non appare associata a SARS-CoV-2.	Reports of Guillain-Barré syndrome (GBS) have emerged during the Coronavirus disease 2019 (COVID-19) pandemic. This epidemiological and cohort study sought to investigate any causative association between COVID-19 infection and GBS. The epidemiology of GBS cases reported to the UK National Immunoglobulin Database was studied from 2016 to 2019 and compared to cases reported during the COVID-19 pandemic. Data were stratified by hospital trust and region, with numbers of reported cases per month. UK population data for COVID-19 infection were collated from UK public health bodies. In parallel, but separately, members of the British Peripheral Nerve Society prospectively reported incident cases of GBS during the pandemic

			at their hospitals to a central register. The clinical features, investigation findings and outcomes of COVID-19 (definite or probable) and non-COVID-19 associated GBS cases in his cohort were compared. The incidence of GBS treated in UK hospitals from 2016 to 2019 was 1.65–1.88 per 100 000 individuals per year. In 2020, GBS and COVID-19 incidences varied between regions and did not correlate with one another (r = 0.06, 95% confidence interval: −0.56 to 0.63, P = 0.86). GBS incidence fell between March and May 2020 compared to the same months of 2016–19. In an independent cohort study, 47 GBS cases were reported (COVID-19 status: 13 definite, 12 probable, 22 non-COVID-19). There were no significant differences in the pattern of weakness, time to nadir, neurophysiology, CSF findings or outcome between these groups. Intubation was more frequent in the COVID-19 affected cohort (7/13, 54% versus 5/22, 23% in COVID-19-negative) likely related to COVID-19 pulmonary involvement. Although it is not possible to entirely rule out the possibility of a link this study finds no epidemiological or phenotypic clues of SARS-CoV-2 being causative of GBS. GBS incidence has fallen during the pandemic, which may be the influence of lockdown measures reducing transmission of GBS inducing pathogens such as Campylobacter jejuni and respiratory viruses.
Madewell ZJ et al JAMA https://doi.org/10.1001/jamanetworkopen.2020.31756	Household Transmission of SARS-CoV-2: A Systematic Review and Meta-analysis.	Revisione sistematica delle conoscenze attuali sulla trasmissione domestica di SARS-CoV-2: il tasso di trasmissione che emerge dagli studi è 16.6%, si è più a rischio se il caso indice è	Importance: Crowded indoor environments, such as households, are high-risk settings for the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Objectives: To examine evidence for household transmission of SARS-CoV-2, disaggregated by several covariates, and to compare it with other coronaviruses. Data Source: PubMed, searched through October 19, 2020. Search terms included SARS-CoV-2 or COVID-19 with secondary attack rate, household, close contacts, contact

		sintomatico, adulto e partner del contatto.	transmission, contact attack rate, or family transmission. Study Selection: All articles with original data for estimating household secondary attack rate were included. Case reports focusing on individual households and studies of close contacts that did not report secondary attack rates for household members were excluded. Data Extraction and Synthesis: Meta-analyses were done using a restricted maximum-likelihood estimator model to yield a point estimate and 95% CI for secondary attack rate for each subgroup analyzed, with a random effect for each study. To make comparisons across exposure types, study was treated as a random effect, and exposure type was a fixed moderator. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline was followed. Main Outcomes and Measures: Secondary attack rate for SARS-CoV-2, disaggregated by covariates (ie, household or family contact, index case symptom status, adult or child contacts, contact sex, relationship to index case, adult or child index cases, index case sex, number of contacts in household) and for other coronaviruses. Results: A total of 54 relevant studies with 77758 participants reporting household secondary transmission were identified. Estimated household secondary attack rate was 16.6% (95% CI, 14.0%-19.3%), higher than secondary attack rates for SARS-CoV (7.5%; 95% CI, 4.8%-10.7%) and MERS-CoV (4.7%; 95% CI, 0.9%-10.7%). Household secondary attack rates were increased from symptomatic index cases (18.0%; 95% CI, 14.2%-22.1%) than from asymptomatic index cases (0.7%; 95% CI, 0%-4.9%), to adult contacts (28.3%; 95% CI, 20.2%-37.1%) than to child contacts (16.8%; 95% CI, 12.3%-21.7%), to spouses (37.8%; 95% CI, 25.8%-50.5%) than to other family contacts (17.8%; 95% CI, 11.7%-24.8%), and in households with 1 contact (41.5%; 95% CI, 31.7%-51.7%) than in households with 3 or

			more contacts (22.8%; 95% CI, 13.6%-33.5%). Conclusions and Relevance: The findings of this study suggest that given that individuals with suspected or confirmed infections are being referred to isolate at home, households will continue to be a significant venue for transmission of SARS-CoV-2.
Ledford H et al Nature https://www.nature.com/articles/d41586-020-03542-4	US authorization of first COVID vaccine marks new phase in safety monitoring	L'approvazione del vaccino Pfizer contro SARS-CoV-2 negli USA da parte della FDA apre la fase della sorveglianza post-marketing, che amplierà le conoscenze sugli effetti avversi, apparentemente limitati al momento.	The FDA has issued an emergency-use authorization for the Pfizer–BioNTech vaccine. Regulators are gearing up to look for side effects.
Maykin M et al Vaccine https://www.sciencedirect.com/science/article/pii/S0264410X20315723?via%3Dihub	Pregnant people deserve the protection offered by SARS-CoV-2 vaccines	Le donne in gravidanza dovrebbero essere incluse nella sperimentazione dei vaccini contro SARS-CoV-2 per assicurare loro un accesso ampio al vaccino, basato su solida evidenza di efficacia e sicurezza.	It is imperative that vaccine development and deployment include pregnant individuals because they are at equal, if not greater, risk of severe COVID-19 illness than nonpregnant patients. Vertical transmission of SARS-CoV-2 to the fetus has been documented. Placental injury from SARS-CoV-2 may lead to stillbirth and poor neonatal outcome.
Faust JS et al JAMA https://jamanetwork.com/journals/jama/fullarticle/2774445	All-Cause Excess Mortality and COVID-19–Related Mortality Among US Adults Aged 25-44 Years, March-July 2020	Mortalità in eccesso per ogni causa e per COVID-19 nella fascia d'età 25-44 anni negli Stati Uniti, periodo marzo-ulgio 2020: si registra un aumento, ma solo il 38% dei casi è attribuibile con sicurezza a COVID-19.	Coronavirus disease 2019 (COVID-19) has caused a marked increase in all-cause deaths in the US, mostly among older adults. Although the burden of COVID-19 among hospitalized younger adults has been described, fewer data focus on mortality in this demographic, owing to lower case-fatality rates.

		Secondo gli autori il dato relativo a COVID-19 è sottoriportato nella popolazione giovane.	Excess mortality reflects the full burden of the pandemic that may go uncaptured due to uncoded COVID-19 and other pandemic-related deaths. Accordingly, we examined all-cause excess mortality and COVID-19–related mortality during the early pandemic period among adults aged 25 to 44 years. Because unintentional drug overdoses are the usual leading cause of death in this demographic, COVID-19 deaths were compared with unintentional opioid deaths.
Joffe S et al JAMA https://jamanetwork.com/journals/jama/fullarticle/2774383	Evaluating SARS-CoV-2 Vaccines After Emergency Use Authorization or Licensing of Initial Candidate Vaccines	Una volta che i vaccini contro SARS-CoV-2 saranno ampiamente disponibili, condurre trial clinici controllati con placebo, per quanto rigoroso, apparirà poco etico: una soluzione potrebbe essere confrontare vaccini già approvati con altri non autorizzati tramite "platform-trial".	The US Food and Drug Administration (FDA) will likely issue emergency use authorizations for 2 vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), one developed jointly by Pfizer and BioNTech and the other by Moderna. According to company press releases and data made available by the FDA, both vaccines have shown approximately 95% efficacy in preventing symptomatic COVID-19 infections in phase 3 trials, without significant safety concerns that might hinder authorization by the FDA. Additional phase 3 trials of vaccines manufactured by Janssen and AstraZeneca are underway; with rapidly rising case counts in the US, initial results from those trials may not be far behind. All of these trials compare the incidence of symptomatic infection among vaccine recipients with that among a placebo control group. However, once authorized vaccines become widely available, conducting placebo-controlled trials of subsequent vaccine candidates may become challenging. Alternative strategies to evaluate those vaccines, and to compare their safety and efficacy with those of authorized products, are needed.
Lindan CE et al The Lancet	Neuroimaging manifestations in children with SARS-CoV-2 infection: a multinational, multicentre collaborative study	Revisione di 38 casi internazionali di infezione da SARS-CoV-2 con interessamento del sistema nervoso centrale in bambini.	Background: The CNS manifestations of COVID-19 in children have primarily been described in case reports, which limit the ability to appreciate the full spectrum of the disease in paediatric patients. We aimed to identify enough cases that could be evaluated in

https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(20)30362-X/fulltext		Il neuroimaging mostra più comunemente caratteristiche di encefalomielite acuta disseminata post-infettiva.	aggregate to better understand the neuroimaging manifestations of COVID-19 in the paediatric population. Methods: An international call for cases of children with encephalopathy related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and abnormal neuroimaging findings was made. Clinical history and associated plasma and cerebrospinal fluid data were requested. These data were reviewed by a central neuroradiology panel, a child neurologist, and a paediatric infectious diseases expert. The children were categorised on the basis of their time of probable exposure to SARS-CoV-2. In addition, cases were excluded when a direct link to SARS-CoV-2 infection could not be established or an established alternate diagnostic cause could be hypothesised. The accepted referral centre imaging data, from ten countries, were remotely reviewed by a central panel of five paediatric neuroradiologists and a consensus opinion obtained on the imaging findings. Findings: 38 children with neurological disease related to SARS-CoV-2 infection were identified from France (n=13), the UK (n=8), the USA (n=5), Brazil (n=4), Argentina (n=4), India (n=2), Peru (n=1), and Saudi Arabia (n=1). Recurring patterns of disease were identified, with neuroimaging abnormalities ranging from mild to severe. The most common imaging patterns were postinfectious immune-mediated acute disseminated encephalomyelitis-like changes of the brain (16 patients), myelitis (eight patients), and neural enhancement (13 patients). Cranial nerve enhancement could occur in the absence of corresponding neurological symptoms. Splenial lesions (seven patients) and myositis (four patients) were predominantly observed in children with multisystem inflammatory syndrome. Cerebrovascular complications in children were less common than in adults. Significant pre-existing conditions were

			absent and most children had favourable outcomes. However, fatal atypical CNS co-infections developed in four previously healthy children infected with SARS-CoV-2. Interpretation: Acute-phase and delayed-phase SARS-CoV-2-related CNS abnormalities are seen in children. Recurring patterns of disease and atypical neuroimaging manifestations can be found and should be recognised being as potentially due to SARS-CoV-2 infection as an underlying aetiological factor. Studies of paediatric specific cohorts are needed to better understand the effects of SARS-CoV-2 infection on the CNS at presentation and on long-term follow-up in children.

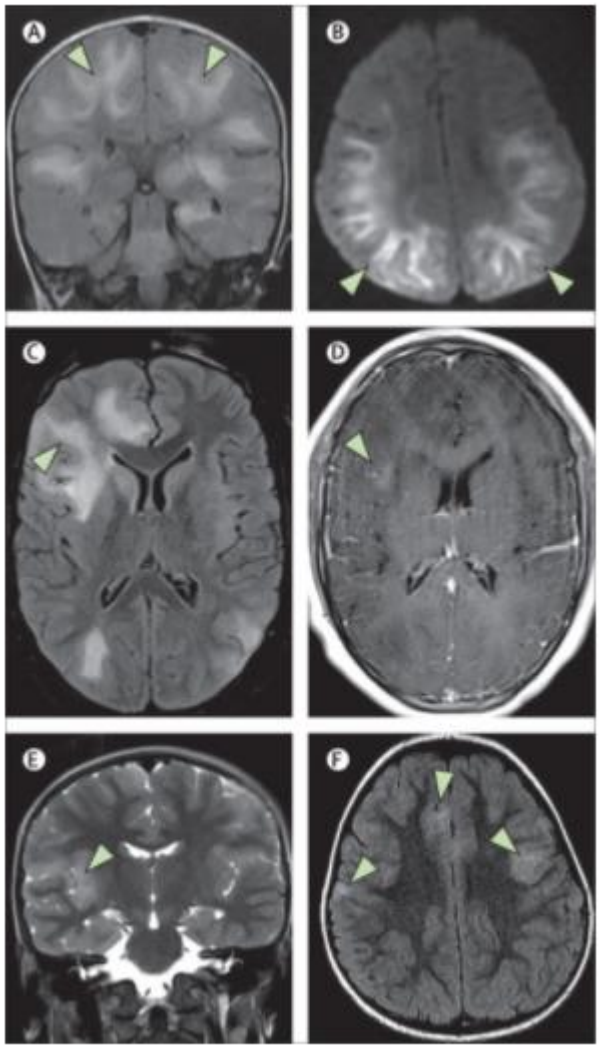
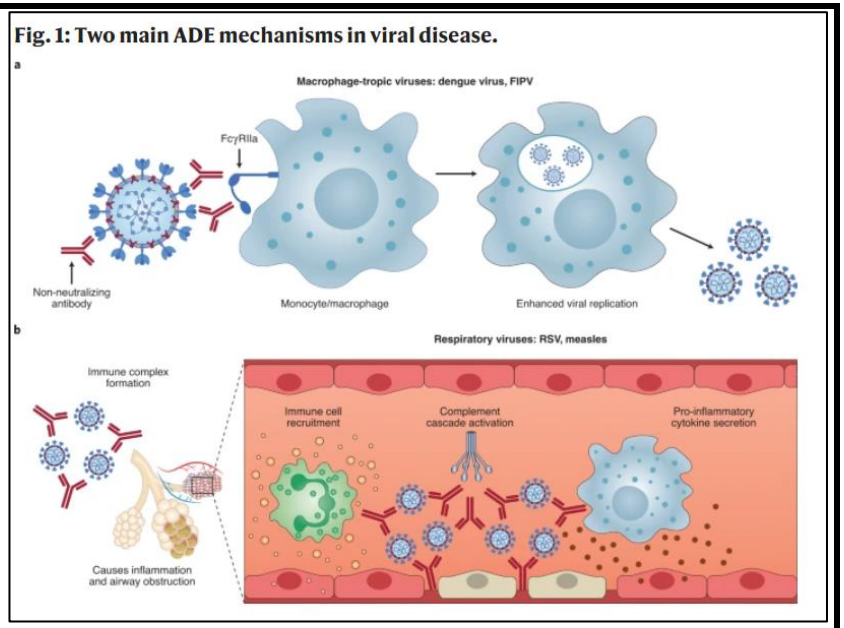
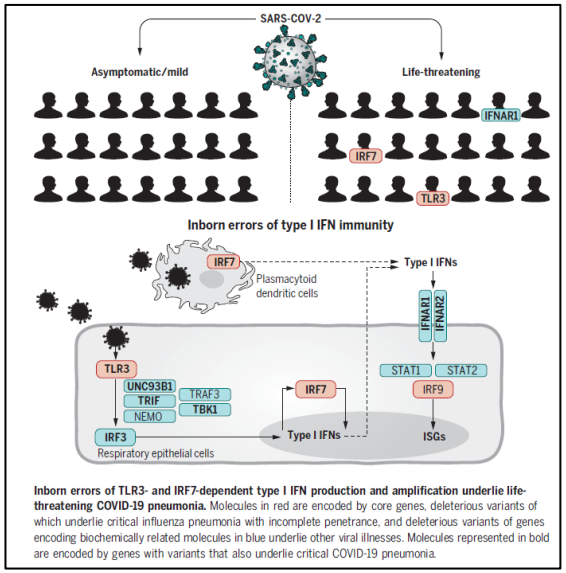


Figure 1 ADEM-like brain changes

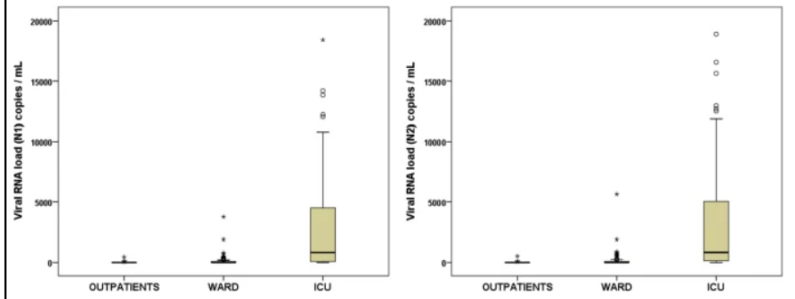
Jalali MS et al Journal of the American Medical Informatics Association https://academic.oup.com/jamia/advance-article/doi/10.1093/jamia/ocaa310/6039104?searchresult=1	Telemedicine, privacy, and information security in the age of COVID-19	La pandemia da COVID-19 ha comportato una accelerazione nella messa in pratica della telemedicina, con le relative importanti questioni di sicurezza e privacy che devono essere regolamentate.	The spread of COVID-19 has resulted in unprecedented circumstances that have necessitated a shift toward adopting infrastructure for telemedicine, due in large part to the inaccessibility of traditional care services and high exposure risks of in-person healthcare visits. With the increased strain and demand on traditional medical resources, telemedicine has emerged as an essential component of clinical care delivery and many healthcare organizations are reporting substantial increases in telemedicine use. For example, 1 medical center in New York City saw an increase in urgent care virtual visits from a pre-COVID-19 average of 102 daily to 802 post-COVID-19 expansion (March 2, 2020–April 14, 2020).
Shi Lee W et al Nature https://www.nature.com/articles/s41564-020-00789-5	Antibody-dependent enhancement and SARS-CoV-2 vaccines and therapies	L'enhancement anticorpo-mediato in una infezione è un fenomeno per cui questa si presenta in forma più grave in soggetti già dotati di anticorpi contro il patogeno specifico. Non è ancora chiaro se tale fenomeno possa verificarsi con l'infezione da SARS-CoV-2.	Antibody-based drugs and vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are being expedited through preclinical and clinical development. Data from the study of SARS-CoV and other respiratory viruses suggest that anti-SARS-CoV-2 antibodies could exacerbate COVID-19 through antibody-dependent enhancement (ADE). Previous respiratory syncytial virus and dengue virus vaccine studies revealed human clinical safety risks related to ADE, resulting in failed vaccine trials. Here, we describe key ADE mechanisms and discuss mitigation strategies for SARS-CoV-2 vaccines and therapies in development. We also outline recently published data to evaluate the risks and opportunities for antibody-based protection against SARS-CoV-2.

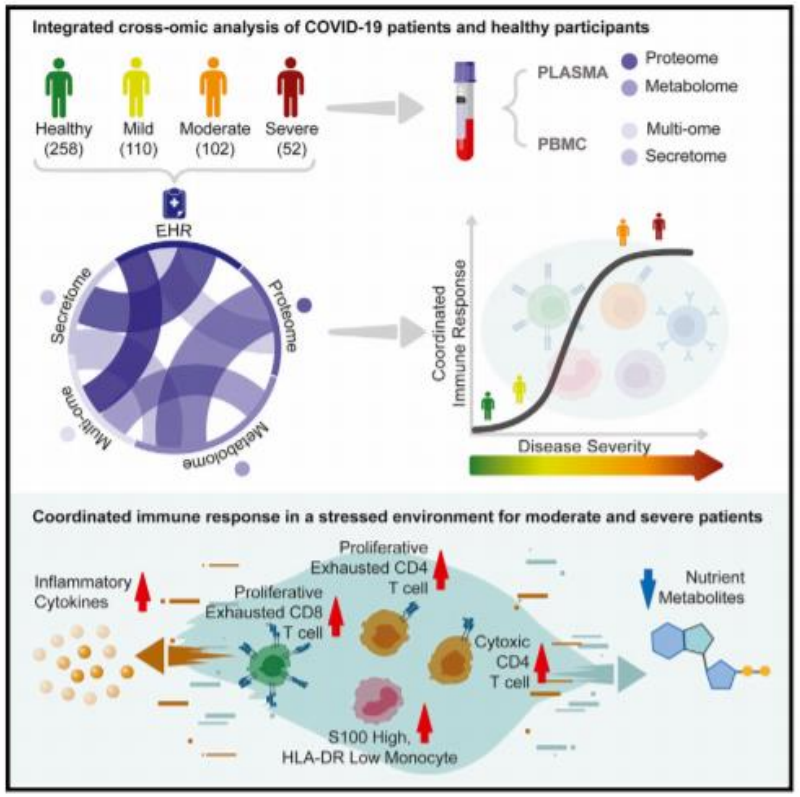
			
Zhang Q et al Science https://science.sciencemag.org/content/370/6515/eabd4570.long	Inborn errors of type I IFN immunity in patients with life-threatening COVID-19	La gravità dell'infezione da SARS-CoV-2 è ampiamente variabile fra individui. In analogia con la polmonite influenzale, un fattore determinante tale differenza protrebbero essere delle varianti "loss-of-function" in geni codificanti per proteine della via dell'interferone I e III, come dimostrato in questo studio che confronta il genoma di 659 persone con storia di COVID-19 grave	INTRODUCTION: Clinical outcomes of human severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection range from silent infection to lethal coronavirus disease 2019 (COVID-19). Epidemiological studies have identified three risk factors for severe disease: being male, being elderly, and having other medical conditions. However, interindividual clinical variability remains huge in each demographic category. Discovering the root cause and detailed molecular, cellular, and tissue- and body-level mechanisms underlying life-threatening COVID-19 is of the utmost biological and medical importance. RATIONALE: We established the COVID Human Genetic Effort (www.covidhge.com) to test the general hypothesis that life-threatening COVID-19 in some or most patients may be caused by monogenic inborn errors of immunity to SARS-CoV-2 with incomplete or complete penetrance. We sequenced the exome or

		con quello di 534 dal decorso benigno.	genome of 659 patients of various ancestries with life-threatening COVID-19 pneumonia and 534 subjects with asymptomatic or benign infection. We tested the specific hypothesis that inborn errors of Toll-like receptor 3 (TLR3)– and interferon regulatory factor 7 (IRF7)–dependent type I interferon (IFN) immunity that underlie life-threatening influenza pneumonia also underlie life-threatening COVID-19 pneumonia. We considered three loci identified as mutated in patients with life-threatening influenza: TLR3, IRF7, and IRF9. We also considered 10 loci mutated in patients with other viral illnesses but directly connected to the three core genes conferring influenza susceptibility: TICAM1/TRIF, UNC93B1, TRAF3, TBK1, IRF3, and NEMO/IKBKG from the TLR3-dependent type I IFN induction pathway, and IFNAR1, IFNAR2, STAT1, and STAT2 from the IRF7- and IRF9-dependent type I IFN amplification pathway. Finally, we considered various modes of inheritance at these 13 loci. RESULTS: We found an enrichment in variants predicted to be loss-of-function (pLOF), with a minor allele frequency <0.001, at the 13 candidate loci in the 659 patients with life-threatening COVID-19 pneumonia relative to the 534 subjects with asymptomatic or benign infection (P = 0.01). Experimental tests for all 118 rare nonsynonymous variants (including both pLOF and other variants) of these 13 genes found in patients with critical disease identified 23 patients (3.5%), aged 17 to 77 years, carrying 24 deleterious variants of eight genes. These variants underlie autosomal-recessive (AR) deficiencies (IRF7 and IFNAR1) and autosomal-dominant (AD) deficiencies (TLR3, UNC93B1, TICAM1, TBK1, IRF3, IRF7, IFNAR1, and IFNAR2) in four and 19 patients, respectively. These patients had never been hospitalized for other life-threatening viral illness. Plasmacytoid dendritic cells from IRF7-deficient patients produced

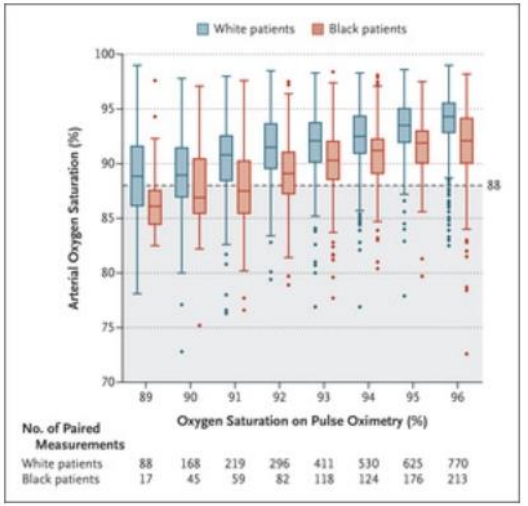
			no type I IFN on infection with SARS-CoV-2, and TLR3−/−, TLR3+/−, IRF7−/−, and IFNAR1−/− fibroblasts were susceptible to SARS-CoV-2 infection in vitro. CONCLUSION: At least 3.5% of patients with life-threatening COVID-19 pneumonia had known (AR IRF7 and IFNAR1 deficiencies or AD TLR3, TICAM1, TBK1, and IRF3 deficiencies) or new (AD UNC93B1, IRF7, IFNAR1, and IFNAR2 deficiencies) genetic defects at eight of the 13 candidate loci involved in the TLR3- and IRF7-dependent induction and amplification of type I IFNs. This discovery reveals essential roles for both the double-stranded RNA sensor TLR3 and type I IFN cell-intrinsic immunity in the control of SARS-CoV-2 infection. Type I IFN administration may be of therapeutic benefit in selected patients, at least early in the course of SARS-CoV-2 infection.  **Inborn errors of TLR3- and IRF7-dependent type I IFN production and amplification underlie life-threatening COVID-19 pneumonia.** Molecules in red are encoded by core genes, deleterious variants of which underlie critical influenza pneumonia with incomplete penetrance, and deleterious variants of genes encoding biochemically related molecules in blue underlie other viral illnesses. Molecules represented in bold are encoded by genes with variants that also underlie critical COVID-19 pneumonia.

Bermejo-Martin JF et al Critical Care Medicine	Viral RNA load in plasma is associated with critical illness and a dysregulated host response in COVID-19.	La presenza di viremia da SARS-CoV-2 e i relativi livelli sono associati alla gravità dell'infezione da SARS-CoV-2, come emerge in questo studio su 250 pazienti fra ambulatoriali, lievi e critici con COVID-19.	BACKGROUND: COVID-19 can course with respiratory and extrapulmonary disease. SARS-CoV-2 RNA is detected in respiratory samples but also in blood, stool and urine. Severe COVID-19 is characterized by a dysregulated host response to this virus. We studied whether viral RNAemia or viral RNA load in plasma is associated with severe COVID-19 and also to this dysregulated response. METHODS: A total of 250 patients with COVID-19 were recruited (50 outpatients, 100 hospitalized ward patients and 100 critically ill). Viral RNA detection and quantification in plasma was performed using droplet digital PCR, targeting the N1 and N2 regions of the SARS-CoV-2 nucleoprotein gene. The association between SARS-CoV-2 RNAemia and viral RNA load in plasma with severity was evaluated by multivariate logistic regression. Correlations between viral RNA load and biomarkers evidencing dysregulation of host response were evaluated by calculating the Spearman correlation coefficients. RESULTS: The frequency of viral RNAemia was higher in the critically ill patients (78%) compared to ward patients (27%) and outpatients (2%) ($p < 0.001$). Critical patients had higher viral RNA loads in plasma than non-critically ill patients, with non-survivors showing the highest values. When outpatients and ward patients were compared, viral RNAemia did not show significant associations in the multivariate analysis. In contrast, when ward patients were compared with ICU patients, both viral RNAemia and viral RNA load in plasma were associated with critical illness (OR [CI 95%], p): RNAemia (3.92 [1.183-12.968], 0.025), viral RNA load (N1) (1.962 [1.244-3.096], 0.004); viral RNA load (N2) (2.229 [1.382-3.595], 0.001). Viral RNA load in plasma correlated with higher levels of chemokines (CXCL10, CCL2), biomarkers indicative of a systemic inflammatory response (IL-6, CRP, ferritin), activation of NK cells (IL-15), endothelial dysfunction

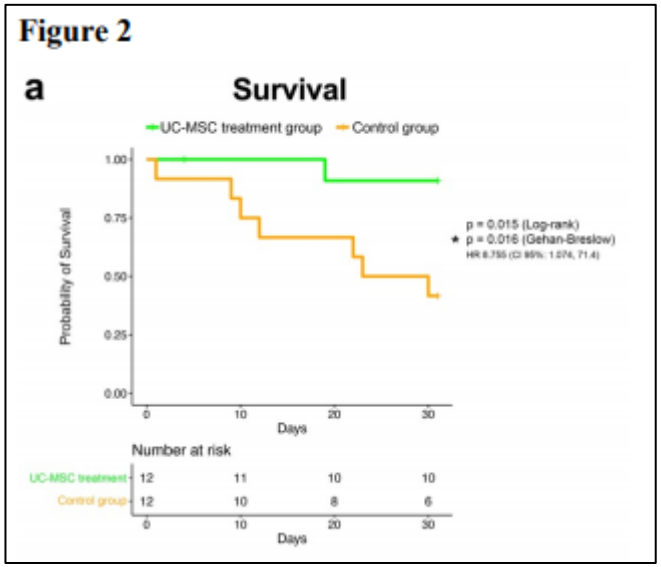
			(VCAM-1, angiopoietin-2, ICAM-1), coagulation activation (D-Dimer and INR), tissue damage (LDH, GPT), neutrophil response (neutrophils counts, myeloperoxidase, GM-CSF) and immunodepression (PD-L1, IL-10, lymphopenia and monocytopenia). CONCLUSIONS: SARS-CoV-2 RNAemia and viral RNA load in plasma are associated with critical illness in COVID-19. Viral RNA load in plasma correlates with key signatures of dysregulated host responses, suggesting a major role of uncontrolled viral replication in the pathogenesis of this disease. **Fig. 1**  Viral RNA load in plasma, targeting the N1 region (left) and the N2 region (right), in the three groups of patients. Results are provided as copies of cDNA per mL of plasma
Yapeng S et al Cell https://www.cell.com/action/showPdf?pii=S0092-8674%2820%2931444-6	Multi-Omics Resolves a Sharp Disease-State Shift between Mild and Moderate COVID-19	Caratteristiche cliniche, immunologiche e genomiche di 139 pazienti con COVID-19 studiati nella prima settimana di malattia: i pazienti dalla gravità “moderata” (in base al WHO ordinal score comunemente usato in molti trial) mostrano una differenza rilevante di metaboliti plasmatici e attivazione	We present an integrated analysis of the clinical measurements, immune cells, and plasma multi-omics of 139 COVID-19 patients representing all levels of disease severity, from serial blood draws collected during the first week of infection following diagnosis. We identify a major shift between mild and moderate disease, at which point elevated inflammatory signaling is accompanied by the loss of specific classes of metabolites and metabolic processes. Within this stressed plasma environment at moderate disease, multiple unusual immune cell phenotypes emerge and amplify with increasing disease severity. We condensed over 120,000 immune features into a single axis to capture how different immune cell classes

		della risposta immunitaria rispetto a quelli con malattia lieve.	coordinate in response to SARS-CoV2. This immune-response axis independently aligns with the major plasma composition changes, with clinical metrics of blood clotting, and with the sharp transition between mild and moderate disease. This study suggests that moderate disease may provide the most effective setting for therapeutic intervention. **Graphical Abstract** 

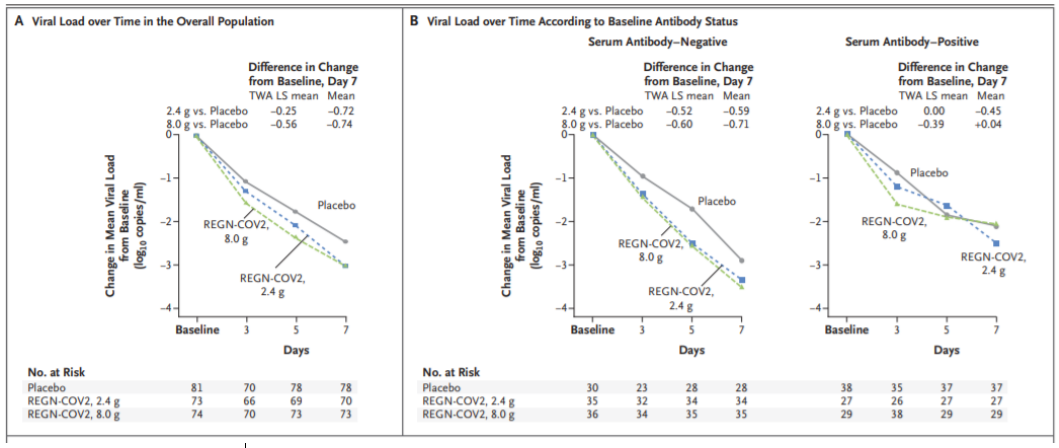
Martinez-Portilla, R J et al Ultrasounds in Obstetrics and Gynecology https://doi.org/10.1002/uog.23575	Pregnant women with SARS-CoV-2 infection are at higher risk of death and severe pneumonia: propensity score-matched analysis of a nationwide prospective cohort study (COV19Mx)	Dati prospettici raccolti in Messico su donne in età fertile, fra cui 5183 gravide, in merito al rischio di outcome avversi per COVID-19: maggior rischio per le gravide di sviluppare polmonite, essere ricoverate in terapia intensiva e di morire.	BACKGROUND: Limited, unmatched data reported low complication rates in pregnant women with COVID-19. This study compared COVID-19-related outcomes in pregnant women versus non-pregnant women after adjusting for potential risk factors for severe outcomes. METHODS: Data were obtained from the COVID-19 National Data Registry of Mexico, which is an ongoing prospective cohort of people of any age with clinically suspected SARS-CoV-2 infection and admitted to 475 monitoring hospitals. This study included pregnant and non-pregnant women of reproductive age (15-49 y) with COVID-19 confirmed by reverse transcription polymerase chain reaction. To adjust for underlying risk factors, propensity score matching was conducted for chronic obstructive pulmonary disease, asthma, smoking, hypertension, cardiovascular disease, obesity, diabetes, and age. The primary outcome was death. Secondary outcomes were pneumonia, intubation, and intensive care unit (ICU) admission. RESULTS: The initial sample comprised of 5183 pregnant and 175,908 non-pregnant COVID-19 patients. The crude (unmatched) rates of death, pneumonia, intubation, and ICU admission in pregnant and non-pregnant women were 1.5% vs. 1.5%, 9.9% vs. 6.5%, 8.1% vs. 9.9%, 13.0% vs. 6.9%, respectively. After propensity score matching (5183 pregnant- and 5183 non-pregnant matched women), pregnant women had higher odds of death (odds ratio [OR] 1.65, 95% CI 1.30-2.09), pneumonia (OR 1.99, 95% CI 1.81-2.19) and ICU admission (OR 2.25, 95% CI 1.86-2.71) than non-pregnant women, but similar odds of intubation (OR 0.93, 95% CI 0.70-1.25). CONCLUSIONS: After adjusting for background demographic and medical factors, pregnancy is a risk factor for death, intubation and ICU admission in SARS-CoV-2-infected women of reproductive age.

Sjoding MW et al NEJM https://www.nejm.org/doi/full/10.1056/NEJMc2029240?query=featured_home	Racial Bias in Pulse Oximetry Measurement	La pulsossimetria potrebbe non essere affidabile per la valutazione della saturazione periferica nelle persone di colore: analizzando complessivamente 10789 misurazioni di saturazione periferica e arteriosa, nell'11% dei casi circa una saturazione <88% non viene rilevata dal saturimetro nelle persone di colore.	Oxygen is among the most frequently administered medical therapies, with a level that is commonly adjusted according to the reading on a pulse oximeter that measures patients' oxygen saturation. Questions about pulse oximeter technology have been raised, given its original development in populations that were not racially diverse. The clinical significance of potential racial bias in pulse oximetry measurement is unknown. **Figure 1.**  Accuracy of Pulse Oximetry in Measuring Arterial Oxygen Saturation, According to Race.
Lanzoni G et al Accepted - Stem Cell Translational Medicine	Umbilical Cord Mesenchymal Stem Cells for COVID-19 ARDS: a Double Blind, Phase 1/2a, Randomized Controlled Trial	Trial clinico che esplora sicurezza ed efficacia delle cellule staminali mesenchimali da cordone, dal noto effetto immunomodulatore, per pazienti con ARSD da	Background: Acute Respiratory Distress Syndrome (ARDS) in COVID-19 is associated with high mortality. Mesenchymal Stem Cells (MSC) are potent immunomodulatory cells. The aim of this study was to determine safety and explore efficacy of Umbilical Cord (UC)-MSC infusions in COVID-19 ARDS.

file:///C:/Users/ingresso/Downloads/Lanzonietal.2020.pdf		COVID-19: dei 12 pazienti trattati con le staminali il 91% è sopravvissuto a 28 giorni, contro il 42% del braccio di controllo, senza eventi avversi gravi. Una interessante prospettiva per il futuro della terapia di COVID-19.	Methods: A double-blind, phase 1/2a, randomized, controlled trial was performed in subjects with ARDS secondary to COVID-19, at a single institution in Miami, Florida, USA. Randomization and stratification by ARDS severity was used to foster balance among groups. Participants received two intravenous infusions of 100x106 UC-MSC, or vehicle, at day 0 and 3. The primary endpoint was safety, defined by occurrence of prespecified infusion associated adverse events, along with adverse events during 28 day follow-up. All subjects were analyzed under an intention to treat design. Exploratory efficacy endpoints included survival at 28 days and time to recovery (ClinicalTrials.gov NCT04355728). Findings: 24 subjects (12 per group) were recruited between April 25 and July 21 2020. At 28 days post last infusion, patient survival was 91% and 42% in the UC-MSC and Control groups, respectively (p=0.015). No serious adverse events (SAEs) were observed related to UC-MSC infusions. There was no observed difference in number of subjects experiencing infusion-associated adverse events. Treatment unrelated SAEs were reported in 2 and 8 patients in the UC-MSC and Control groups, respectively (p=0.04). UC-MSC treatment was associated with increased SAE-free survival (p=0.008) and decreased time to recovery (p=0.03) compared to controls. Interpretation: UC-MSC infusions in COVID-19 subjects with ARDS were safe and associated with fewer SAEs, compared to control. Further, exploratory efficacy analyses provide preliminary evidence of reduction in mortality and time to recovery. Notwithstanding sample size limitations of this trial, the observed findings strongly support further investigation in a larger trial designed to estimate and test for efficacy.

			Funding: The Cure Alliance, Barilla, NABTU, DRIF. **Figure 2** 
Weinreich DM et al NEJM https://www.nejm.org/doi/full/10.1056/NEJMoa2035002	REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19	Analisi ad interim dei risultati di un trial clinico condotto su pazienti non ricoverati con infezione da SARS-CoV-2 per valutare sicurezza ed efficacia di due anticorpi monoclonali utilizzati in combinazione nell'abbattere la carica virale su tampone nasale: dopo una settimana dall'infusione, i pazienti trattati hanno una riduzione significativa rispetto al	BACKGROUND: Recent data suggest that complications and death from coronavirus disease 2019 (Covid-19) may be related to high viral loads. METHODS: In this ongoing, double-blind, phase 1–3 trial involving nonhospitalized patients with Covid-19, we investigated two fully human, neutralizing monoclonal antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein, used in a combined cocktail (REGN-COV2) to reduce the risk of the emergence of treatment-resistant mutant virus. Patients were randomly assigned (1:1:1) to receive placebo, 2.4 g of REGN-COV2, or 8.0 g of REGN-COV2 and were prospectively characterized at baseline for endogenous immune response against SARS-CoV-2 (serum antibody–positive or serum antibody–negative). Key end

		placebo, più evidente se all'inizio del trattamento erano sieronegativi.	points included the time-weighted average change from baseline in viral load from day 1 through day 7 and the percentage of patients with at least one Covid-19–related medically attended visit through day 29. Safety was assessed in all patients. RESULTS: Data from 275 patients are reported. The least-squares mean difference (combined REGN-COV2 dose groups vs. placebo group) in the time-weighted average change in viral load from day 1 through day 7 was −0.56 log10 copies per milliliter (95% confidence interval [CI], −1.02 to −0.11) among patients who were serum antibody–negative at baseline and −0.41 log10 copies per milliliter (95% CI, −0.71 to −0.10) in the overall trial population. In the overall trial population, 6% of the patients in the placebo group and 3% of the patients in the combined REGN-COV2 dose groups reported at least one medically attended visit; among patients who were serum antibody–negative at baseline, the corresponding percentages were 15% and 6% (difference, −9 percentage points; 95% CI, −29 to 11). The percentages of patients with hypersensitivity reactions, infusion-related reactions, and other adverse events were similar in the combined REGN-COV2 dose groups and the placebo group. CONCLUSIONS: In this interim analysis, the REGN-COV2 antibody cocktail reduced viral load, with a greater effect in patients whose immune response had not yet been initiated or who had a high viral load at baseline. Safety outcomes were similar in the combined REGN-COV2 dose groups and the placebo group.

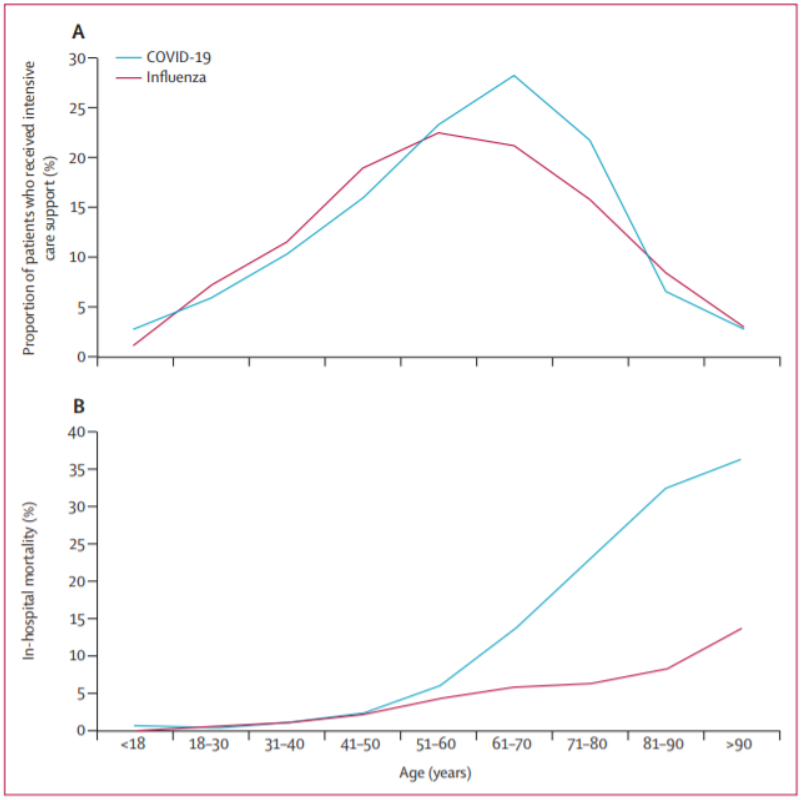
		
Baric RS et al NEJM https://www.nejm.org/doi/pdf/10.1056/NEJMcibr2032888?articleTools=true	Emergence of a Highly Fit SARS-CoV-2 Variant	La nota mutazione D614G emersa a Febbraio 2020 nel genoma di SARS-CoV-2 ha comportato un vantaggio di fitness per il virus (in termini di legame al recettore ACE2 e di replicazione nelle cellule delle alte vie respiratorie, ma non di virulenza) e si è rapidamente imposta a livello mondiale; apparentemente, i vaccini basati sulla “vecchia” variante D614 saranno efficaci anche per la nuova G614.	Sarbecoviruses have emerged twice in the 21st century, causing a worldwide epidemic and pandemic. The ongoing pandemic of coronavirus disease 2019 (Covid-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARSCoV-2), has caused unprecedented disruption of human society. Since its emergence in December 2019, SARS-CoV-2 has spread worldwide, infecting more than 70 million persons and causing more than 1.6 million deaths as of early December 2020. Previous studies have clearly shown that epidemic and pandemic RNA virus spread may select for mutations that alter RNA virus pathogenesis, virulence, transmissibility, or a combination of these, yet this process remains poorly studied among emerging coronaviruses in animals and humans.

Morales DR et al The Lancet https://www.thelancet.com/journals/landig/article/PIIS2589-7500(20)30289-2/fulltext	Renin–angiotensin system blockers and susceptibility to COVID-19: an international, open science, cohort analysis	Studio di coorte internazionale che ha valutato i data clinici di 1 355 349 pazienti in terapia con ACE-inibitori, sartani tiazidici o calcio-antagonisti: nessuna associazione fra utilizzo di ACE-I o sartani con il rischio di contrarre l'infezione da SARS-CoV-2, di essere ricoverati o di avere complicanze quali polmonite, insufficienza respiratoria e sepsi. Per questi motivi, l'interruzione o la modifica di terapie antipertensive in relazione a COVID-19 non appare giustificata.	Background: Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been postulated to affect susceptibility to COVID-19. Observational studies so far have lacked rigorous ascertainment adjustment and international generalisability. We aimed to determine whether use of ACEIs or ARBs is associated with an increased susceptibility to COVID-19 in patients with hypertension. Methods: In this international, open science, cohort analysis, we used electronic health records from Spain (Information Systems for Research in Primary Care [SIDIAP]) and the USA (Columbia University Irving Medical Center data warehouse [CUIMC] and Department of Veterans Affairs Observational Medical Outcomes Partnership [VA-OMOP]) to identify patients aged 18 years or older with at least one prescription for ACEIs and ARBs (target cohort) or calcium channel blockers (CCBs) and thiazide or thiazide-like diuretics (THZs; comparator cohort) between Nov 1, 2019, and Jan 31, 2020. Users were defined separately as receiving either monotherapy with these four drug classes, or monotherapy or combination therapy (combination use) with other antihypertensive medications. We assessed four outcomes: COVID-19 diagnosis; hospital admission with COVID-19; hospital admission with pneumonia; and hospital admission with pneumonia, acute respiratory distress syndrome, acute kidney injury, or sepsis. We built large-scale propensity score methods derived through a data-driven approach and negative control experiments across ten pairwise comparisons, with results meta-analysed to generate 1280 study effects. For each study effect, we did negative control outcome experiments using a possible 123 controls identified through a data-rich algorithm. This process used a set of predefined baseline patient characteristics to provide the most accurate

			prediction of treatment and balance among patient cohorts across characteristics. The study is registered with the EU Post-Authorisation Studies register, EUPAS35296. Findings: Among 1 355 349 antihypertensive users (363 785 ACEI or ARB monotherapy users, 248 915 CCB or THZ monotherapy users, 711 799 ACEI or ARB combination users, and 473 076 CCB or THZ combination users) included in analyses, no association was observed between COVID-19 diagnosis and exposure to ACEI or ARB monotherapy versus CCB or THZ monotherapy (calibrated hazard ratio [HR] 0·98, 95% CI 0·84–1·14) or combination use exposure (1·01, 0·90–1·15). ACEIs alone similarly showed no relative risk difference when compared with CCB or THZ monotherapy (HR 0·91, 95% CI 0·68–1·21; with heterogeneity of >40%) or combination use (0·95, 0·83–1·07). Directly comparing ACEIs with ARBs demonstrated a moderately lower risk with ACEIs, which was significant with combination use (HR 0·88, 95% CI 0·79–0·99) and non-significant for monotherapy (0·85, 0·69–1·05). We observed no significant difference between drug classes for risk of hospital admission with COVID-19, hospital admission with pneumonia, or hospital admission with pneumonia, acute respiratory distress syndrome, acute kidney injury, or sepsis across all comparisons. Interpretation: No clinically significant increased risk of COVID-19 diagnosis or hospital admission-related outcomes associated with ACEI or ARB use was observed, suggesting users should not discontinue or change their treatment to decrease their risk of COVID-19.
Piroth L et al The Lancet	Comparison of the characteristics, morbidity, and mortality of COVID-19 and seasonal influenza: a	Studio di coorte retrospettivo condotto in Francia per confrontare fattori di rischio, caratteristiche cliniche ed	Background: To date, influenza epidemics have been considered suitable for use as a model for the COVID-19 epidemic, given that they are respiratory diseases with similar modes of transmission. However, data directly comparing the two diseases are scarce.

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30527-0/fulltext	nationwide, population-based retrospective cohort study	outcome di pazienti ricoverati per COVID-19 nel periodo marzo-aprile 2020 con ricoverati per influenza nel periodo dicembre-febbraio 2019: si dimostrano differenze notevoli in tutti gli aspetti, in particolare i tassi di insufficienza respiratoria acuta e mortalità sono più significativi per COVID-19.	Methods: We did a nationwide retrospective cohort study using the French national administrative database (PMSI), which includes discharge summaries for all hospital admissions in France. All patients hospitalised for COVID-19 from March 1 to April 30, 2020, and all patients hospitalised for influenza between Dec 1, 2018, and Feb 28, 2019, were included. The diagnosis of COVID-19 (International Classification of Diseases [10th edition] codes U07.10, U07.11, U07.12, U07.14, or U07.15) or influenza (J09, J10, or J11) comprised primary, related, or associated diagnosis. Comparisons of risk factors, clinical characteristics, and outcomes between patients hospitalised for COVID-19 and influenza were done, with data also stratified by age group. Findings: 89 530 patients with COVID-19 and 45 819 patients with influenza were hospitalised in France during the respective study periods. The median age of patients was 68 years (IQR 52–82) for COVID-19 and 71 years (34–84) for influenza. Patients with COVID-19 were more frequently obese or overweight, and more frequently had diabetes, hypertension, and dyslipidaemia than patients with influenza, whereas those with influenza more frequently had heart failure, chronic respiratory disease, cirrhosis, and deficiency anaemia. Patients admitted to hospital with COVID-19 more frequently developed acute respiratory failure, pulmonary embolism, septic shock, or haemorrhagic stroke than patients with influenza, but less frequently developed myocardial infarction or atrial fibrillation. In-hospital mortality was higher in patients with COVID-19 than in patients with influenza (15 104 [16·9%] of 89 530 vs 2640 [5·8%] of 45 819), with a relative risk of death of 2·9 (95% CI 2·8–3·0) and an age-standardised mortality ratio of 2·82. Of the patients hospitalised, the proportion of paediatric patients (<18 years) was smaller for COVID-19 than for influenza (1227 [1·4%] vs

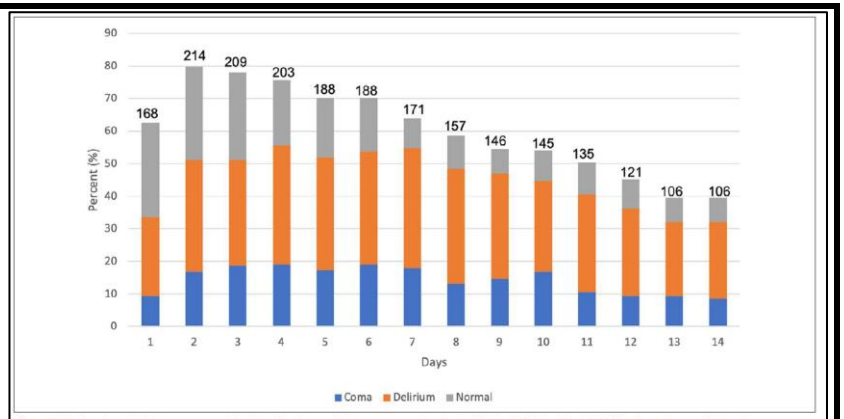
			8942 [19·5%]), but a larger proportion of patients younger than 5 years needed intensive care support for COVID-19 than for influenza (14 [2·3%] of 613 vs 65 [0·9%] of 6973). In adolescents (11–17 years), the in-hospital mortality was ten-times higher for COVID-19 than for influenza (five [1·1% of 458 vs one [0·1%] of 804), and patients with COVID-19 were more frequently obese or overweight. Interpretation: The presentation of patients with COVID-19 and seasonal influenza requiring hospitalisation differs considerably. Severe acute respiratory syndrome coronavirus 2 is likely to have a higher potential for respiratory pathogenicity, leading to more respiratory complications and to higher mortality. In children, although the rate of hospitalisation for COVID-19 appears to be lower than for influenza, in-hospital mortality is higher; however, low patient numbers limit this finding. These findings highlight the importance of appropriate preventive measures for COVID-19, as well as the need for a specific vaccine and treatment.

			 ***Figure 1:*** **Intensive care support and mortality of patients hospitalised in France for COVID-19 or seasonal influenza, by age at admission** Date are for patients who were hospitalised for COVID-19 between March 1 and April 30, 2020, and for patients who were hospitalised for seasonal influenza between Dec 1, 2018, and Feb 28, 2019.
Bharat A et al Science https://stm.sciencemag.org/content/12/574/eabe4282	Lung transplantation for patients with severe COVID-19	Il trapianto di polmone, soluzione estrema all'insufficienza respiratoria causata da SARS-CoV-2, è stato eseguito con successo sui 3 pazienti di questa case-series trattati con ossigenazione	Lung transplantation can potentially be a life-saving treatment for patients with nonresolving COVID-19–associated respiratory failure. Concerns limiting lung transplantation include recurrence of SARS-CoV-2 infection in the allograft, technical challenges imposed by viral-mediated injury to the native lung, and the potential risk for allograft infection by pathogens causing ventilator-associated pneumonia in the native lung. Additionally, the native lung might recover, resulting in long-term outcomes preferable to those of

		extracorporea (ECMO) e il cui recupero della funzione respiratoria era giudicato non verosimile. In tutti i casi si era sviluppata fibrosi polmonare istologicamente dimostrata.	transplant. Here, we report the results of lung transplantation in three patients with nonresolving COVID-19–associated respiratory failure. We performed single-molecule fluorescence in situ hybridization (smFISH) to detect both positive and negative strands of SARS-CoV-2 RNA in explanted lung tissue from the three patients and in additional control lung tissue samples. We conducted extracellular matrix imaging and single-cell RNA sequencing on explanted lung tissue from the three patients who underwent transplantation and on warm postmortem lung biopsies from two patients who had died from COVID-19–associated pneumonia. Lungs from these five patients with prolonged COVID-19 disease were free of SARS-CoV-2 as detected by smFISH, but pathology showed extensive evidence of injury and fibrosis that resembled end-stage pulmonary fibrosis. Using machine learning, we compared single-cell RNA sequencing data from the lungs of patients with late-stage COVID-19 to that from the lungs of patients with pulmonary fibrosis and identified similarities in gene expression across cell lineages. Our findings suggest that some patients with severe COVID-19 develop fibrotic lung disease for which lung transplantation is their only option for survival.

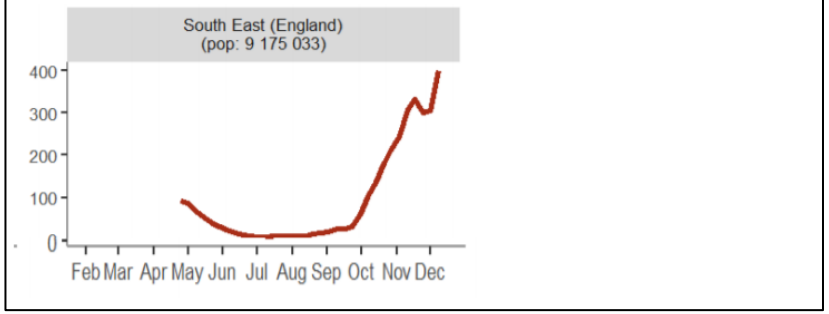
			Table 1. Clinical characteristics of lung transplant recipients. Variable / COVID-19 patients (3) Age, years: 44.3 ± 13.9 Female: 1 (33.3%) BMI, kg/m2: 25.2 ± 4.5 Operating time (hours): 9.5 ± 1.0 Intraoperative blood transfusion pRBC: 10.6 ± 4.1 FFP: 5.3 ± 2.4 Plt: 2.6 ± 1.2 Intraoperative VA ECMO use: 3 (100%) Intraoperative VA ECMO time (hours): 2.8 ± 0.3 Ischemic time (hours): 5.1 ± 0.1 ICU stay (days): 13.3 ± 7.0 Post transplant ventilator (days): 12.6 ± 8.3 Pleural drainage (days): 20.3 ± 4.4 Continuous data are shown as means ± standard deviation (SD). BMI, Body Mass Index; VV ECMO, Veno-Venous ExtraCorporeal Membrane Oxygenation; ICU, Intensive Care Unit
Khan S et al Critical Care Medicine https://journals.lww.com/ccejournal/Fulltext/2020/12000/Delirium_Incidence,_Duration,_and_Severity_in.9.aspx	Delirium Incidence, Duration, and Severity in Critically Ill Patients With Coronavirus Disease 2019	Studio retrospettivo sull'incidenza di delirium nei pazienti critici con COVID-19: Su 268 ricoverati in rianimazione, il fenomeno si verifica nel 29.1% dei casi con persistenza mediana di 5 giorni ed è associato alla ventilazione meccanica.	Objectives: To determine delirium occurrence rate, duration, and severity in patients admitted to the ICU with coronavirus disease 2019. Design: Retrospective data extraction study from March 1, 2020, to June 7, 2020. Delirium outcomes were assessed for up to the first 14 days in ICU. Setting: Two large, academic centers serving the state of Indiana. Patients: Consecutive patients admitted to the ICU with positive severe acute respiratory syndrome coronavirus 2 nasopharyngeal swab polymerase chain reaction test from March 1, 2020, to June 7, 2020, were included. Individuals younger than 18 years of age, without any delirium assessments, or without discharge disposition were excluded. Measurements and Main Results: Primary outcomes were delirium rates and duration, and the secondary outcome was delirium severity. Two-hundred sixty-eight consecutive patients were included in the analysis with a mean age of 58.4 years (sd, 15.6 yr), 40.3% were female, 44.4% African American, 20.7% Hispanic, and a

			median Acute Physiology and Chronic Health Evaluation II score of 18 (interquartile range, 13–25). Delirium without coma occurred in 29.1% of patients, delirium prior to coma in 27.9%, and delirium after coma in 23.1%. The first Confusion Assessment Method for the ICU assessment was positive for delirium in 61.9%. Hypoactive delirium was the most common subtype (87.4%). By day 14, the median number of delirium/coma-free were 5 days (interquartile range, 4–11 d), and median Confusion Assessment Method for the ICU-7 score was 6.5 (interquartile range, 5–7) indicating severe delirium. Benzodiazepines were ordered for 78.4% of patients in the cohort. Mechanical ventilation was associated with greater odds of developing delirium (odds ratio, 5.0; 95% CI, 1.1–22.2; p = 0.033) even after adjusting for sedative medications. There were no between-group differences in mortality. Conclusions: Delirium without coma occurred in 29.1% of patients admitted to the ICU. Delirium persisted for a median of 5 days and was severe. Mechanical ventilation was significantly associated with odds of delirium even after adjustment for sedatives. Clinical attention to manage delirium duration and severity, and deeper understanding of the virus' neurologic effects is needed for patients with coronavirus disease 2019.

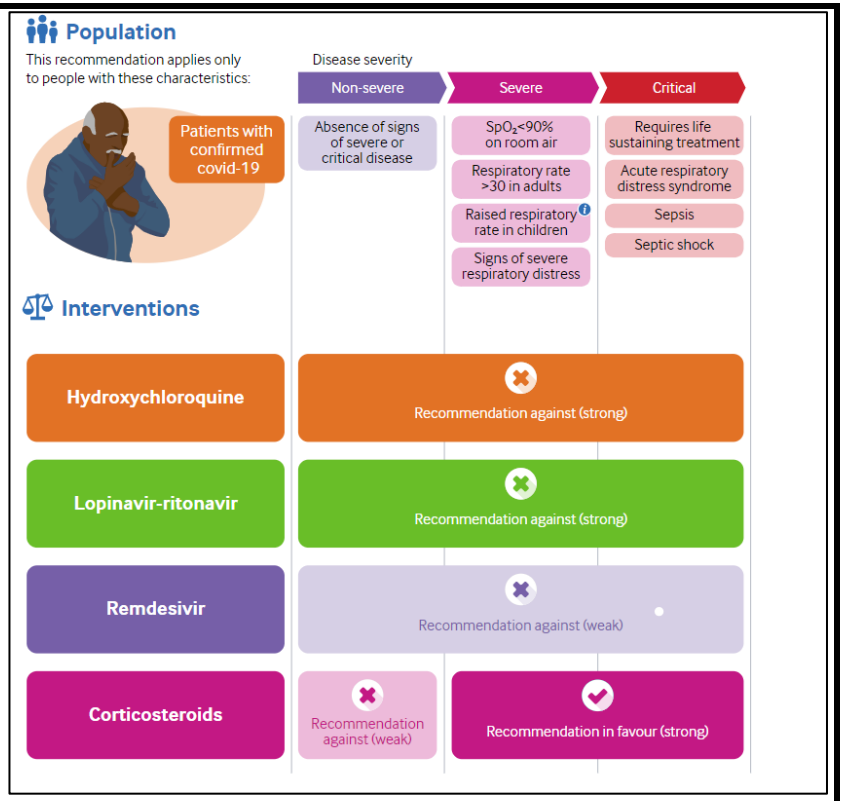
			 **Figure 1.** Daily rates of delirium, coma, or without delirium/coma status as assessed up to first 14 d of ICU stay ($n = 268$). Number above each bar column indicates number of patients assessed per day. Daily percentages do not equal 100% due to incomplete assessments, death, or discharge from ICU. Delirium was defined as a positive Confusion Assessment Method for the ICU (CAM-ICU) assessment on either morning or afternoon assessment. Coma was defined by Richmond Agitation-Sedation Scale (RASS) score of −4 or −5. Without delirium or coma was defined by RASS greater than −4 and a negative CAM-ICU on either morning or afternoon assessment.
Guaraldi G et al Clinical Infectious Diseases https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1864/6041857?searchresult=1	HIV care models during the COVID-19 era	Come può cambiare la cura del paziente HIV positivo in conseguenza della pandemia di COVID-19.	The COVID-19 pandemic is an unprecedented global challenge that substantially risks reversing the progress in ending HIV. At the same time, it may offer the opportunity for a new era of HIV management. This viewpoint presents the impact of COVID-19 on HIV care, including the Joint United Nations Programme on HIV/AIDS (UNAIDS) “three 90s” targets. It outlines how to enhance a patient-centered care approach, now known as the "fourth 90,” by integrating face-to-face patient–physician and telemedicine encounters. It suggests a framework for prevention and treatment of multimorbidity and frailty, to achieve a good health-related quality of life and preserve intrinsic capacity in all people living with HIV.
Jones JM et al Emerging Infectious Diseases	SARS-CoV-2 infections among recent organ recipients, March–May 2020, United States.	Ricostruzione di 8 casi di infezione da SARS-CoV-2 in trapiantati d’organo in cui la causa verosimile del contagio è una esposizione comunitaria e non la trasmissione con il	We conducted public health investigations of 8 organ transplant recipients who tested positive for severe acute respiratory syndrome coronavirus 2 infection. Findings suggest the most likely source of transmission was community or healthcare exposure, not the organ donor. Transplant centers should educate transplant

https://wwwnc.cdc.gov/eid/article/27/2/20-4046_article		trapianto, come era stato ipotizzato.	candidates and recipients about infection prevention recommendations.
Dal-Ré R et al The Lancet https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30568-3/fulltext	Remdesivir for COVID-19 in Europe: will it provide value for money?	Considerando le evidenze deboli a sostegno di un reale beneficio del remdesivir, il prezzo imposto da Gilead negli usa dovrebbe essere sostanzialmente ridotto in Europa secondo gli autori di questo articolo.	Remdesivir is the first antiviral drug fully licensed for the treatment of patients with COVID-19. The use of remdesivir in 2020, can be summarised in five stages. First, between May and July, several regulatory agencies issued the authorisation—under emergency or conditional schemes—to treat selected patients hospitalised with COVID-19. Second, the manufacturer, Gilead, set a price of US$2340 for a 5-day treatment course in late June. Third, in October, the US Food and Drug Administration (FDA) granted full approval for use of remdesivir in adults and adolescent patients (aged 12 years or older; >40 kg) with COVID-19; it should be given intravenously for 5 days (six vials) to patients who do not need invasive mechanical ventilation or extracorporeal membrane oxygenation, or both, and 10 days (11 vials) in those who require this type of support. Fourth, the European Commission signed a joint procurement contract in October for $1·2 billion of remdesivir vials to treat 500 000 patients in 36 European countries, although the full marketing authorisation has not been granted yet. And fifth, the negative interim results on mortality from the largest randomised controlled trial (RCT), WHO Solidarity, were reported.
Priesemann V et al The Lancet https://www.thelancet.com/journals/lancet/article/	Calling for pan-European commitment for rapid and sustained reduction in SARS-CoV-2 infections	Più di 200 ricercatori hanno firmato questo appello su Lancet chiedendo all'Europa di stabilire obiettivi comuni fra stati per la lotta alla pandemia da SARS-CoV-2.	Across Europe, the COVID-19 pandemic is causing excess deaths, placing a burden on societies and health systems and harming the economy. European governments have yet to develop a common vision to guide the management of the pandemic. Overwhelming evidence shows that not only public health, but also society and the economy benefit greatly from reducing cases of severe acute

PIIS0140-6736(20)32625-8/fulltext			respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Vaccines will help control the virus, but not until late 2021.
European Centre for Disease Prevention and Control https://www.ecdc.europa.eu/en/publications-data/threat-assessment-brief-rapid-increase-sars-cov-2-variant-united-kingdom	Threat Assessment Brief: Rapid increase of a SARS-CoV-2 variant with multiple spike protein mutations observed in the United Kingdom	Indicazioni degli ECDC in relazione all'emergere a partire dal Sud-Est del Regno Unito di una variante di SARS-CoV-2 caratterizzata da mutazioni che ne aumenterebbero la trasmissibilità – ma non apparentemente la virulenza. Attualmente è fondamentale il tracciamento dei casi.	Over the last few weeks, the United Kingdom (UK) has faced a rapid increase in COVID-19 cases in South East England, leading to enhanced epidemiological and virological investigations. Analysis of viral genome sequence data identified a large proportion of cases belonged to a new single phylogenetic cluster. The new variant is defined by multiple spike protein mutations (deletion 69-70, deletion 144, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H) present as well as mutations in other genomic regions. While it is known and expected that viruses constantly change through mutation leading to the emergence of new variants, preliminary analysis in the UK suggests that this variant is significantly more transmissible than previously circulating variants, with an estimated potential to increase the reproductive number (R) by 0.4 or greater with an estimated increased transmissibility of up to 70%. This new variant has emerged at a time of the year when there has traditionally been increased family and social mixing. There is no indication at this point of increased infection severity associated with the new variant. A few cases with the new variant have to date been reported by Denmark and the Netherlands and, according to media reports, in Belgium.

			Figure 1. Fourteen-day COVID-19 case notification rates per 100 000 population in South East England, UK, by reporting date as of 16 December 2020 
Rambaut A et al Virological.org https://virological.org/t/preliminary-genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-the-uk-defined-by-a-novel-set-of-spike-mutations/563	Preliminary genomic characterisation of an emergent SARS-CoV-2 lineage in the UK defined by a novel set of spike mutations	Caratterizzazione del lineage B1.1.7 di SARS-CoV-2 che si sta diffondendo a partire da alcune regioni del Regno Unito, ove è stato isolato per la prima volta in settembre 2020. Le mutazioni definenti questo lineage hanno dei prevedibili effetti biologici e necessitano di ulteriore definizione e monitoraggio.	Recently a distinct phylogenetic cluster (named lineage B.1.1.7) was detected within the COG-UK surveillance dataset. This cluster has been growing rapidly over the past 4 weeks and since been observed in other UK locations, indicating further spread. Several aspects of this cluster are noteworthy for epidemiological and biological reasons and we report preliminary findings below. In summary: The B.1.1.7 lineage accounts for an increasing proportion of cases in parts of England. The number of B.1.1.7 cases, and the number of regions reporting B.1.1.7 infections, are growing. B.1.1.7 has an unusually large number of genetic changes, particularly in the spike protein. Three of these mutations have potential biological effects that have been described previously to varying extents: Mutation N501Y is one of six key contact residues within the receptor-binding domain (RBD) and has been identified as increasing binding affinity to human and murine ACE2. The spike deletion 69-70del has been described in the context of evasion to the human immune response but has also occurred a number of times in association with other RBD changes.

			Mutation P681H is immediately adjacent to the furin cleavage site, a known location of biological significance. The rapid growth of this lineage indicates the need for enhanced genomic and epidemiological surveillance worldwide and laboratory investigations of antigenicity and infectivity.
Siemieniuk R et al BMJ https://www.bmj.com/content/370/bmj.m3379	A living WHO guideline on drugs for covid-19	Aggiornamento delle indicazioni del WHO sull'utilizzo di farmaci per COVID-19 rispetto ai dati disponibili da trial clinici.	This living guideline responds to emerging evidence from randomised controlled trials (RCTs) on existing and new drug treatments for covid-19. More than 2800 trials on covid-19 interventions have been registered or are ongoing (see section on emerging evidence). Among these are large national and international platform trials (such as RECOVERY, WHO SOLIDARITY, and DISCOVERY) that recruit large numbers of patients, with a pragmatic and adaptive design. These platform trials are currently investigating and reporting on drugs such as antiviral monoclonal antibodies and immunomodulators. This rapidly evolving evidence landscape requires trustworthy interpretation and expeditious clinical practice guidelines to inform clinicians, patients, governments, ministries, and health administrators.

			
Aschele C et al JAMA https://jamanetwork.com/journals/jamaoncology/fullarticle/2773836	Incidence of SARS-CoV-2 Infection Among Patients Undergoing Active Antitumor Treatment in Italy	Studio retro-prospettico su 59989 pazienti in trattamento attivo per neoplasie in Italia, in cui si registra una incidenza di infezione da SARS-CoV-2 di 0.68%: bassa, e certamente non tale da scoraggiare il prosieguo delle cure oncologiche per timore del contagio.	The interactions between cancer and susceptibility to coronavirus disease 2019 (COVID-19) are poorly understood. Early reports suggested a higher COVID-19 risk in patients with cancer not specifically selected for recent anticancer treatment, but data on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission among patients undergoing antitumor treatment are lacking.

Iversen K et al The Lancet https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30589-2/fulltext	Risk of COVID-19 in health-care workers in Denmark: an observational cohort study	Studio di coorte osservazionale che riporta i risultati di test di screening eseguiti su 29295 membri delpersonale sanitario della regione di Copenhagen tramite ricerca point-of-care di IgM e IgG: sieroprevalenza 4.04%, maggiore nel personale in prima linea nei reparti COVID.	Background: Health-care workers are thought to be highly exposed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. We aimed to investigate the prevalence of antibodies against SARS-CoV-2 in health-care workers and the proportion of seroconverted health-care workers with previous symptoms of COVID-19. Methods: In this observational cohort study, screening was offered to health-care workers in the Capital Region of Denmark, including medical, nursing, and other students who were associated with hospitals in the region. Screening included point-of-care tests for IgM and IgG antibodies against SARS-CoV-2. Test results and participant characteristics were recorded. Results were compared with findings in blood donors in the Capital Region in the study period. Findings: Between April 15 and April 23, 2020, we screened 29 295 health-care workers, of whom 28 792 (98·28%) provided their test results. We identified 1163 (4·04% [95% CI 3·82–4·27]) seropositive health-care workers. Seroprevalence was higher in health-care workers than in blood donors (142 [3·04%] of 4672; risk ratio [RR] 1·33 [95% CI 1·12–1·58]; p<0·001). Seroprevalence was higher in male health-care workers (331 [5·45%] of 6077) than in female health-care workers (832 [3·66%] of 22 715; RR 1·49 [1·31–1·68]; p<0·001). Frontline health-care workers working in hospitals had a significantly higher seroprevalence (779 [4·55%] of 16 356) than health-care workers in other settings (384 [3·29%] of 11 657; RR 1·38 [1·22–1·56]; p<0·001). Health-care workers working on dedicated COVID-19 wards (95 [7·19%] of 1321) had a significantly higher seroprevalence than other frontline health-care workers working in hospitals (696 [4·35%] of 15 983; RR 1·65 [1·34–2·03]; p<0·001). 622 [53·5%] of 1163 seropositive participants reported

			symptoms attributable to SARS-CoV-2. Loss of taste or smell was the symptom that was most strongly associated with seropositivity (377 [32·39%] of 1164 participants with this symptom were seropositive vs 786 [2·84%] of 27 628 without this symptom; RR 11·38 [10·22–12·68]). The study is registered at ClinicalTrials.gov, NCT04346186.
Dan-Yu L et al Clinical Infectious Diseases https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1863/6042236	Evaluating the Efficacy of COVID-19 Vaccines	Oltre all'infezione virologicamente confermata e alla malattia sintomatica da SARS-CoV-2, i trial che studiano i nuovi vaccini contro il virus dovrebbero includere come endpoint anche la malattia grave. Gli stessi endpoint possono essere utilizzati per il monitoraggio dell'efficacia nel tempo.	A large number of studies are being conducted to evaluate the efficacy and safety of candidate vaccines against novel coronavirus disease-2019 (COVID-19). Most Phase 3 tri- als have adopted virologically confirmed symptomatic COVID-19 disease as the primary efficacy endpoint, although laboratory-confirmed SARS-CoV-2 is also of interest. In addi- tion, it is important to evaluate the effect of vaccination on disease severity. To provide a full picture of vaccine efficacy and make efficient use of available data, we propose using SARS-CoV-2 infection, symptomatic COVID-19, and severe COVID-19 as dual or triple pri- mary endpoints. We demonstrate the advantages of this strategy through realistic simulation studies. Finally, we show how this approach can provide rigorous interim monitoring of the trials and efficient assessment of the durability of vaccine efficacy.