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Commentary
Life-Threatening COVID-19: Defective Interferons Unleash Excessive Inflammation

Qian Zhang,1,8 Paul Bastard,1,2,3,8 Alexandre Bolze,4,8 Emmanuelle Jouanguy,1,2,3,8 Shen-Ying Zhang,1,2,3,8 COVID Human Genetic Effort, Aurélie Cobat,2,3,8 Luigi D. Notarangelo,5,8 Helen C. Su,5,8 Laurent Abel,1,2,3,8 and Jean-Laurent Casanova1,2,3,6,7,8,*

The risk of life-threatening COVID-19 pneumonia increases sharply after 65 years of age, but other epidemiological risk factors, genetic or otherwise, are modest. Various rare monogenic inborn errors of type I interferons (IFNs) underlie critical disease, and neutralizing autoantibodies against type I IFNs account for at least 10% of critical cases.

Introduction
Inter-individual clinical variability after respiratory infection with SARS-CoV-2 is immense. Most infected individuals (>98%) remain asymptomatic or develop mild, ambulatory disease. About a month after infection, a very small minority (<0.01%) develop a severe systemic inflammatory syndrome closely resembling Kawasaki disease (KD). A much larger minority of infected subjects develop pneumonia 1 to 2 weeks post infection, requiring hospitalization (<2%), and sometimes intensive care, because of acute respiratory distress syndrome and/or the failure of other organs (<0.5%).1 Enormous efforts have understandably been invested in descriptive studies, while fewer correlative studies have been performed, and even fewer studies have tried to discover the causal mechanisms underlying life-threatening COVID-19. Here, we discuss the epidemiological, genetic, and immunological studies that have tried to decipher the basis of life-threatening COVID-19 pneumonia. Population-based epidemiological studies try to correlate pre-existing demographic and medical information, or candidate or genome-wide genotypic information, with disease at population level. Conversely, patient-based genetic and immunological studies aim to discover the mechanisms by which germ-line genetic variants or pre-existing immunological abnormalities cause life-threatening disease in individual patients.

Increasing Risk of Life-Threatening COVID-19 Pneumonia with Age
Age is the major known risk factor for life-threatening COVID-19 pneumonia, as both mortality and critical disease (defined as hospitalization in intensive care unit and/or mechanical ventilation) are frequently reported in subjects >65 years of age but rarely in those <20 years of age. In two studies of >5,000 COVID-19 cases each, the risk for critical disease was about 3.5 times higher in patients >75 years of age than in those <45 years of age2 after adjustment for pre-existing comorbidities (Table 1). The adjusted effect of age was stronger for mortality than critical disease, increasing the risk for death by >10-fold in patients ≥80 years old with respect to those <50 years old.3,4 Maleness is also a risk factor. In a study of 5,279 hospitalized patients, the risks for critical illness and mortality were estimated to be 1.5 times and 1.3 times higher, respectively, for men than for women, after adjustment for other pre-existing risk factors.2 The impact of ancestry is less clear. In a study of 10,301 US veterans infected with SARS-CoV-2, the adjusted risk of critical disease was 1.5 times higher in black subjects, with no significant difference for mortality.3 However, some potentially important socioeconomic characteristics were not taken into account.

Pre-existing Comorbidities Modestly Increase the Risk of Severe COVID-19
Individuals with certain pre-existing comorbidities seem to be at higher risk of critical COVID-19 pneumonia. There are probably ascertainment biases, for example, in patients with known immunodeficiencies, who often take measures to avoid SARS-CoV-2. Meta-analyses suggest that the most common comorbidities associated with critical disease, and, to a lesser extent, mortality, are hypertension, diabetes, chronic cardiac disease, chronic pulmonary disease, and obesity. In a large study of SARS-CoV-2-infected US veterans, the adjusted hazard ratios for these comorbidities...
ranged from 1.2 to 1.4 for critical disease (Table 1) and were less significant for mortality. \(^3\) The adjusted risk for mortality was slightly increased by obesity, chronic cardiac, and chronic pulmonary conditions in at least one of three other large studies involving thousands of COVID-19 cases, but was not significantly increased by diabetes or hypertension. \(^2,4\) Overall, age is, by far, the strongest epidemiological factor influencing the severity and mortality of COVID-19 pneumonia, whereas sex and pre-existing comorbidities, when significant, make only a modest contribution, increasing the adjusted risk for critical disease (or to an even less significant extent for mortality) by a factor of \(<2\), and, generally \(<1.5\).

### Table 1. Epidemiological, Genetic, and Immunological Risk Factors for Critical COVID-19

| Risk Factor | Risk Estimates | Frequency | References |
|-------------|----------------|-----------|------------|
| **Epidemiological Studies (Non-genetic)** | | | |
| Age in years (study 1 / study 2) | 19–44 / 18–49 (reference group) | 1 / 1 | 0.35 / 0.19 | study 1, Petrilli et al. \(^2\) / study 2, Ioannou et al. \(^3\) |
| | 45–54 / – | NS / – | 0.17 / – |
| | 55–64 / 50–64 | 2.04 / 2.72 | 0.19 / 0.29 |
| | 65–74 / 65–79 | 2.88 / 4.32 | 0.15 / 0.37 |
| | \(\geq 75 / \geq 80\) | 3.46 / 3.98 | 0.14 / 0.15 |
| Male | 1.54 / 2.07 | 0.50 / 0.91 |
| Obesity: BMI \(\geq 40 / \text{BMI} \geq 35\) | 1.52 / 1.22 | 0.06 / 0.19 |
| Diabetes | 1.24 / 1.40 | 0.25 / 0.38 |
| Hypertension | NS / 1.30 | 0.43 / 0.62 |
| Chronic pulmonary disease | NS / NS | 0.18 / 0.19 |
| Coronary artery disease | NS / NS | 0.13 / 0.22 |
| **Population-Based Genetic Epidemiological Studies (Common Variants)** | | | |
| ABO group | | | |
| Group A | NS / 1.23\(^c\) | 0.34/0.26–0.42\(^d\) | Latz et al. \(^7\) / Golinelli et al. \(^6\) |
| Group O | NS / 0.77\(^e\) | 0.45/0.30–0.57\(^f\) | |
| rs73064425 (chr3p21.31):\(^e\) intronic variant of LZTFL1 | 2.11 / 2.14 | 0.08 (0.001–0.28) | Ellinghaus et al. \(^5\) / Paio-Castineira et al. \(^8\) |
| rs10735079 (chr 12q24.13):\(^e\) intronic variant of OAS3 | 1.29 | 0.64 (0.50–0.78) | Paio-Castineira et al. \(^8\) |
| rs2109069 (chr19p13.3):\(^e\) intronic variant of DPP9 | 1.36 | 0.33 (0.13–0.41) | |
| rs2236757 (chr 21q22.1):\(^e\) intronic variant of IFNAR2 | 1.28 | 0.71 (0.40–0.78) | |
| **Patient-Based Genetic Studies (Rare Variants)** | | | |
| TLR3, UNC93B1, TICAM1, TBK1, IRF3, IRF7, IFNAR1, IFNAR2 (autosomal-dominant model) | 9 | &lt;0.001 | Zhang et al. \(^9\) |
| IRF7, IFNAR1 (autosomal-recessive model) | &gt;50 | &lt;0.001 | |
| **Patient-Based Immunological Studies** | | | |
| Neutralizing type I IFN autoantibodies | &gt;50 | 0.0033 | Bastard et al. \(^10\) |

All studies compared patients presenting critical disease with patients presenting mild or asymptomatic SARS-CoV-2 infection as controls, except for the meta-analysis of Golinelli et al. \(^6\) and the GWASs of Ellinghaus et al. \(^5\) and Paio-Castineira et al. \(^8\), which used controls from the general population. NS, non-significant.

\(^a\)Data for epidemiological risk factors are taken from two large studies of COVID-19 cases, including 5,279 subjects from New York city (Petrilli et al. \(^2\)) and 10,131 US veterans (Ioannou et al. \(^3\)). The risks are odds ratios (Petrilli et al. \(^2\)) or hazard ratios (Ioannou et al. \(^3\)) adjusted for pre-existing risk factors. The frequency is that of the corresponding risk factor in the total sample of infected patients.

\(^b\)For genetic factors other than ABO group, risks are odds ratios for the risk allele under an additive model, unless otherwise specified.

\(^c\)Pooled odds ratio obtained in the meta-analysis of Golinelli et al. \(^6\) comparing the corresponding blood group with all other blood groups, and considering hospitalized COVID-19 patients as cases, and subjects from various cohorts (blood donors, general population, and patients hospitalized for conditions other than COVID-19) as controls.

\(^d\)Range of frequencies of the corresponding blood group observed in the control group of the studies contributing to the meta-analysis of Golinelli et al. \(^6\).

\(^e\)The GWAS results are those displaying genome-wide significance in the study of Paio-Castineira et al. \(^8\) replicated in the analyses of the COVID-19 human genetic initiative.

\(^f\)The frequency is that of the risk allele observed in Paio-Castineira et al. \(^8\). The range of allele frequencies observed across nine populations of gnomAD v3 is also provided in parentheses.
Candidate Gene Association Studies and ABO Blood Group
In population-based, genetic epidemiological studies, most association studies of candidate genes have been inconclusive, or their findings not confirmed by genome-wide association studies (GWASs). ABO blood group, which was suggested to influence SARS-CoV2 infection outcomes early in the pandemic, is a notable exception, also being reported in several GWASs.5 In a meta-analysis of 13 cohorts from 7 studies of a total of 7,503 COVID-19 cases and 2,962,160 controls from various cohorts (blood donors, general population, and patients hospitalized for conditions other than COVID-19), patients hospitalized for COVID-19 were more likely to belong to blood group A (pooled OR 1.23) and less likely to belong to blood group O (pooled OR = 0.77) than controls.6 By contrast, studies of severe outcomes in patients hospitalized for COVID-19 have detected no significant association with ABO group.7 These studies suggest that ABO blood group plays only a modest role, if any, in the development of severe COVID-19, instead influencing the likelihood of SARS-CoV-2 infection.

Genome-wide Association Studies of Severe COVID-19
In addition to the ABO locus, GWASs have identified four chromosomal regions associated with severe COVID-19 (oxygen supplementation or mechanical ventilation) relative to the general population in an additive model (Table 1). The first region encompasses a gene cluster on chr3p21.31, with an odds ratio (OR) between 1.6 and 2.1 for heterozygosity for the susceptibility haplotype.5,8 The distribution of the risk haplotype varies considerably around the world, from 28% in South Asia to less than 1% in East Asia and Africa (Table 1). It encompasses six genes, the possible contributions of which to COVID-19 remain unknown. Three other regions identified in a GWAS analyzing 2,244 critically ill patients in the UK were replicated in an international GWAS comparing hospitalized COVID-19 patients with the rest of the population.9 The ORs for the heterozygous susceptibility alleles are modest, between 1.2 and 1.4 (Table 1). However, two of these three regions encompass genes involved in antiviral immunity. The first, a region on chr12q24.13, includes a cluster of OAS1, OAS2, and OAS3 genes, interferon-stimulated genes (ISGs) required for the activation of RNase L, an antiviral enzyme. The second, a region on chr21q22.1, includes IFNAR2, encoding the second chain of the interferon receptor. These population-based, genetic epidemiological studies have yielded modest ORs, similar to those for the most contributive comorbidities.

Monogenic Inborn Errors of Type I IFN Immunity Underlie Critical COVID-19 Pneumonia
Deleterious variants at 13 loci encoding biochemically and immunologically connected proteins underlie life-threatening influenza pneumonia (IRF7, IRF9, and TLR3 genes), adverse reactions to live attenuated viral vaccines (IFNAR1, IFNAR2, STAT2, and herpes simplex encephalitis (HSE) (TLR3, UNC93B1, TICAM1, TRAF3, TBK1, IKBKGG, IFR3, IFNAR1, STAT1). These inborn errors disrupt TLR3- and IRF7-dependent intrinsic (in many cell types other than leukocytes, including pulmonary epithelial cells) and innate type I IFN immunity (in leukocytes, particularly in plasmacytoid dendritic cells [pDCs], which express IRF7 constitutively). We showed, in an international cohort,1 that about 3% of patients with critical COVID-19 carried loss-of-function variants at these loci, that TLR3-, IRF7-, or IFNAR1-deficient fibroblasts were highly vulnerable to SARS-CoV-2, and that IRF7-deficient pDCs did not produce type I IFNs in response to the virus.9 These genotypes were causal for the severe COVID-19 phenotype, with ORs probably ranging from about 5–10 for autosomal-dominant (AD) defects to about 50–100 for autosomal-recessive (AR) defects. The penetrance of the AR deficiencies is probably higher than that of the AD deficiencies. Notably, we identified two patients with AR IRF7 deficiency aged 49 and 50 years, and two patients with AR IFNAR1 deficiency aged 26 and 38 years. Before hospitalization for COVID-19 pneumonia, none of these four patients had been hospitalized for other viral infections, attesting to a lower-than-expected penetrance of these AR disorders for severe diseases caused by viruses less virulent than SARS-CoV-2, including seasonal influenza viruses.

Clinical and Biological Implications of Inborn Errors of Type I IFNs
Clinically, these findings pave the way for diagnosis and treatment in selected individuals. Subjects with a personal or familial history of adverse reactions to live viral vaccines, HSE, severe influenza, and other severe viral illnesses (including severe COVID-19) should be screened for genetic defects of the type I IFN circuit. The nebulized or subcutaneous administration of type I IFN (IFN-z2 or -β) may be beneficial in patients with such defects (other than those impairing type I IFN responses, e.g., IFNAR1 deficiency), if given early after infection. Biologically, the discovery that AR IRF7 or IFNAR1 deficiency can account for life-threatening COVID-19 in previously healthy adults revealed an unsuspected level of redundancy. Who would have thought that IRF7- or IFNAR1-deficient patients would reach the age of 30–50 years without hospitalization for severe viral illnesses? The discovery that rare coding variants of 8 of 13 candidate loci account for about 3% of critical cases suggests that more patients may carry inborn errors of the >400 known type I IFN-related genes, upstream or downstream of the 17 IFN loci. More importantly, the discovery that AR IRF7 and IFNAR1 deficiencies underlie life-threatening COVID-19 in adults provides a key piece of information: type I IFNs are essential for protective
immunity against SARS-CoV-2. This naturally led to the hypothesis that other disruptions of this mechanism might be involved in severe disease.

Autoantibodies against Type I IFNs Are Present in At Least 10% of Patients with Life-Threatening COVID-19

Autoantibodies against type I IFNs were first identified in the 1980s, in patients treated with IFN-α2 or IFN-β and in patients with systemic lupus erythematosus. In 2006, they were reported to be present in almost all autoimmune polyendocrinopathy type 1 (APS-1) patients. These autoantibodies seemed to be clinically silent. However, an elderly patient with severe varicella and neutralizing autoantibodies against type I IFN was reported in 1984. Strikingly, we identified three patients with APS-1 and autoantibodies against type I IFNs who became critically ill with COVID-19. We then found that at least 10% of patients with critical COVID-19 pneumonia, but none of the subjects with asymptomatic infection tested, had circulating autoantibodies capable of neutralizing large amounts of at least one, and typically most of the 17 individual type I IFNs, including their protective effect against SARS-CoV-2 in *vitro* and *in vivo*. These autoantibodies were pre-existing and were a cause of severe disease rather than a consequence of infection. They acted as a clinical phenocopy of AR-IFNAR1 deficiency in severe COVID-19, a situation reminiscent of the autoantibodies against IFN-γ, IL-6, and IL-17A/F mimicking inborn errors of IFN-γ, IL-6, and IL-17A/F, or their receptors, as causes of mycobacterial, staphylococcal, and fungal disease. Remarkably, 94% of the patients with autoantibodies were men, half over the age of 65 years, and more than a third died from COVID-19. Overall, a B cell auto-immune phenocopy of inborn errors of type I IFN immunity underlies life-threatening COVID-19 in at least 3.5% of women and 12.5% of men.

Clinical and Biological Implications of Autoantibodies against Type I IFNs

Testing for these autoantibodies is simpler and quicker than exome sequencing. Their early detection facilitates closer monitoring, making it possible to initiate specific treatment as early as possible during, or even perhaps before infection. Plasmapheresis could be used, although this treatment is logistically challenging and not free of complications. Alternatively, plasmocytes and/or B cells could be depleted, although this would have the disadvantage of also blocking the production of anti-SARS-CoV-2 antibodies. Early IFN-β administration might be more promising, particularly as only about 2% of individuals with autoantibodies against type I IFN have autoantibodies against IFN-β. Another important implication is that donors of convalescent plasma or the plasma samples themselves should be tested to exclude those positive for autoantibodies against type I IFN. The prevalence of these autoantibodies in the general population should also be determined as a function of age, sex, and ancestry, paving the way for studies of their pathogenesis. Why are they more common in men, particularly after the age of 65 years, at least in patients with critical COVID-19? This finding has other biological implications. Ironically, life-threatening COVID-19 may be seen as an adaptive, auto-immune attack on innate and intrinsic immunity in these patients. Why are autoantibodies against the 13 IFN-α and IFN-ω pathogenic, despite the lack of targeting of IFN-β, -κ, and -ε in most patients? Many important biological and clinical questions arise from this discovery of autoantibodies against type I IFNs in patients with critical COVID-19 pneumonia.

Type I IFN in the Pathogenesis of Severe Coronavirus Pneumonia in Mice

Mice are not naturally permissive to SARS-CoV-2 infection, but they can be experimentally infected after transduction with ACE2, which acts as a receptor for virus entry. Ifnar1-deficient mice developed in this way have more severe disease, with a greater weight loss and viral load, but lower levels of cellular infiltration in the lung.\(^1\) By contrast, other studies have reported lower levels of cellular infiltration in the lungs of Ifnar1-deficient mice with no effect on viral load,\(^2\) or greater cellular infiltration in the lung with no effect on viral load in wild-type mice treated with anti-Ifnar1 antibodies.\(^3\) These discrepant results may reflect different experimental routes of infection, inoculum levels, and background strains. Importantly, downstream type I IFN pathway effects may differ between mice and humans, as exemplified by the lack of a key interferon-stimulated gene (Mx1) in most laboratory mouse strains, conferring high susceptibility to influenza virus. Caution is therefore required when extrapolating these results to humans with SARS-CoV-2 infection. Nevertheless, experimental infections in inbred mice may suggest that type I IFNs exert not only beneficial, antiviral effects, but perhaps also detrimental, immunomodulatory effects in the course of infection with coronaviruses. Careful follow-up of patients with type I interferonopathies, who naturally produce excessive amounts of type I IFNs, during the course of natural infection with SARS-CoV-2 will make it possible to test this hypothesis in humans.

A Two-Step Model for the Pathogenesis of Life-Threatening COVID-19 Pneumonia

Patients with critical COVID-19 disease typically display a hyperinflammatory response characterized by increased myeloid cell infiltration into the lung, with increased production of numerous chemokines and cytokines, after about 10 days of infection. This results in the development of acute respiratory distress syndrome (ARDS). The discovery of inborn errors of TLR3- and IRF7-dependent type I IFN in 3% of
patients and neutralizing autoantibodies against type I IFN in 10% of patients with critical COVID-19 pneumonia unambiguously suggests a pathogenic role for inadequate type I IFN activity in life-threatening COVID-19.9,10 The deficiency of type I IFNs in the respiratory tract, in the first days or even hours of infection, accounts for severe pneumonia and disseminated disease in these patients (Figure 1). Type I IFN levels were not measured in the respiratory tract of these patients; both groups had low serum concentrations of the 13 types of IFN-α at disease onset. The pathogenesis of severe pneumonia in patients with detectable or large amounts of type I IFN in the blood may involve the disruption of proteins encoded by ISGs. Overall, a hypothetical two-step general model of the pathogenesis of life-threatening COVID-19 is emerging, with insufficient type I IFN immunity during the first few days of infection leading to viral growth and spread, resulting in damaging secondary, pulmonary, and systemic inflammation.

Implications of the Two-Step Pathogenesis Model for Clinical Trials of Type I IFN

The notion that COVID-19 may follow a biphasic pattern, with an early viral replication phase due to insufficient type I IFN immunity, followed by a hyper-inflammatory phase involving cytokine release, has important implications for the design of clinical trials of IFN-β or IFN-α2. The administration of these molecules should be considered in the first few days of SARS-CoV-2 infection. The observation that as many as 10% of patients with life-threatening COVID-19 pneumonia have neutralizing autoantibodies against type I IFNs, but that only 2% of these patients have autoantibodies against IFN-β, suggests that IFN-β treatment may be particularly useful. However, any such intervention should be initiated early in the course of disease, because peak viral load coincides with the onset of
symptoms in patients with COVID-19. Moreover, the administration of IFN-β later in the course of disease may aggravate inflammation, as suggested later in the course of disease may due, in many, or even most, patients, to inadequate type I IFN immunity during the first few days of SARS-CoV-2 infection. Interestingly, the discovery of patients with rare inborn errors of immunity, such as ARIFNAR1 deficiency, has led to that of a common cause of critical COVID-19, with autoantibodies against type I IFNs accounting for at least 10% of critical cases. As in other fields of internal medicine, the discovery of monogenic inborn errors, even in single patients, can serve as a compass, pointing the way toward life-saving interventions.

SUPPLEMENTAL INFORMATION
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CONSORTIA
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DECLARATION OF INTERESTS
The authors declare no competing interests.

WEB RESOURCES
COVID Human Genetic Effort, https://www.covidhge.com/

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