What we know and still ignore on COVID-19 immune pathogenesis and a proposal based on experience of allergic disorders.

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic started over one year ago and produced almost 3.5 million deaths worldwide. We have been recently overwhelmed by a wide literature on how the immune system recognizes Severe Acute Respiratory Syndrome Coronavirus 2 and contributes to COVID-19 pathogenesis. Although originally considered a respiratory viral disease, COVID-19 is recognized as a far more complex, multi-organ-, immuno-mediated-, and mostly heterogeneous disorder. Though efficient innate and adaptive immunity may control infection, when the patient fails to mount an adequate immune response, a high innate-induced inflammation can lead to different clinical outcomes through heterogeneous compensatory mechanisms. The variability of viral load and persistence, the genetic alterations of virus-driven receptors/signaling pathways and the plasticity of innate and adaptive responses may all account for the extreme heterogeneity of pathogenesis and clinical patterns. As recently done for some inflammatory disorders as asthma, rhinosinusitis with polyposis and atopic dermatitis, herein we suggest to define different endo-types and the related phenotypes along COVID-19. Patients should be stratified for evolving symptoms and tightly monitored for surrogate biomarkers of innate and adaptive immunity. This would allow to preventively identify each endo-type (and its related phenotype) and to treat patients precisely with agents targeting pathogenic mechanisms.

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Abstract The coronavirus disease 2019 (COVID-19) pandemic started over one year ago and produced almost 3.5 million deaths worldwide. We have been recently overwhelmed by a wide literature on how the immune system recognizes Severe Acute Respiratory Syndrome Coronavirus 2 and contributes to COVID-19 pathogenesis. Although originally considered a respiratory viral disease, COVID-19 is recognized as a far more complex, multi-organ-, immuno-mediated-, and mostly heterogeneous disorder. Though efficient innate and adaptive immunity may control infection, when the patient fails to mount an adequate immune response, a high innate-induced inflammation can lead to different clinical outcomes through heterogeneous compensatory mechanisms. The variability of viral load and persistence, the genetic alterations of virus-driven receptors/signaling pathways and the plasticity of innate and adaptive responses may all account for the extreme heterogeneity of pathogenesis and clinical patterns. As recently done for some inflammatory disorders as asthma, rhinosinusitis with polyposis and atopic dermatitis, herein we suggest to define different endo-types and the related phenotypes along COVID-19. Patients should be stratified for evolving symptoms and tightly monitored for surrogate biomarkers of innate and adaptive immunity. This would allow to preventively identify each endo-type (and its related phenotype) and to treat patients precisely with agents targeting pathogenic mechanisms. .*Introduction* The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) started in late 2019 in Wuhan (China) and caused already almost 3.5 million deaths. In a paper published last year, we underscored the unknowns about virus receptors and signaling, host immune response, disease pathogenesis and therapeutic tools able to control virus entry, replication and spread and harmful effects [1]. After over one year of pandemic, we have been overwhelmed by an enormous number of reports on SARS-CoV-2 infection and COVID-19 pathogenesis. Although originally defined as a respiratory viral infection, COVID-19 is now clearly recognized as a far more complex, multistep, multi-organ, immuno-mediated and mostly heterogeneous disease. The angiotensin-converting enzyme-2 (ACE2) is the SARS-CoV2 receptor and in ACE2-bearing cells (as monocytes/macrophages and epithelial cells), the virus triggers pattern recognition receptors as Toll-like receptors (TLRs) and cytosolic sensors. Their signaling essentially follows three pathways leading to the type I/III Interferon (IFN) secretion, the expression of costimulatory molecules for T-cell activation, and production of pro-inflammatory cytokines and chemokines [1]. This contributes to activation of innate immune responses, virus-specific cytotoxic CD8+ T cells and T follicular helper (Tfh) cells cooperating with B cells to mount a protective humoral response. Both innate and adaptive immunity can control the viral infection and determine clinical recovery: however, when an infected patient fails to produce the adequate immune responses, an ongoing innate-induced inflammation can lead to cytokine storm, interstitial pneumonia, diffuse organ involvement and failure. Today the main unanswered question is why the viral immune evasion predominates on the host immunity leading to hyper activation of macrophages and neutrophils with cytokine storm only in a proportion of patients. Even though many hypotheses have been proposed, the causes inducing variable responses of the immune system along such a multistep disease are only partially known [2, 3]. We will discuss such pathogenic hypotheses, underscoring the role of defective or excessive immune responses and the high degree of heterogeneity of the clinical patterns.*Immuno-pathogenesis of COVID-19*Some hypotheses attempting to unify immuno-pathogenesis of COVID19 have been proposed recently. They will be summarized, taking into account that the described mechanisms are not mutually exclusive.**Altered coordination between innate and adaptive Immunity.** When innate response lasts too long due to viral immune-evasion or impaired innate cell function, SARS-CoV-2 further replicates and compromises the adaptive immune responses [3]. The virus may develop mechanisms which impair components of type I/III IFN signaling pathway in infected cells as plasmacytoid dendritic cells (pDCs). The low levels of type I IFN detected in COVID-19 patients, suggest a potential defect in viral defense, which is negatively associated to disease severity [4]. Even though SARS-CoV-2 is highly sensitive to IFN, however, it interferes with downstream signaling at several levels, or inhibits IFN-stimulated gene products [5]. Remarkably, ACE2 expression on epithelial cells is upregulated by type I IFN itself, thus the virus can even exploit the most effective anti-viral molecule, when present [6]. In addition, pDCs (the main source of type I IFN) decrease in COVID-19 due

to recruitment into tissues and apoptosis and their number is negatively related to disease severity [7]. Low numbers of pDCs can be responsible for the reduced presentation of viral epitopes to T cells and for defective activation of natural killer (NK) cells [8]. NK cells may be impaired early due to: i. the over production of cytokines (mainly IL-6) by infected APC [9], ii. the excess of cytokines inducing metabolic changes and signs of exhaustion [10], iii. the spike subunit 1 (S1)-driven HLA-E expression on lung epithelium which binds S1 peptides and is recognized by the inhibitory receptor NKG2A [11], iv. the KLRC2 gene (encoding the activating receptor NKG2C) deletion or HLA-E*0101/0103 variants (poorly recognized by NKG2C) with consequent reduction of the NKG2C+ "memory" NK cells [10]; v. the impaired release from the bone marrow of "inflammatory precursors" which rapidly differentiate into mature NK progenies [12]. The factors delaying adaptive immunity are mostly due to early impaired innate responses. Endogenous corticosteroids and IL-10 might condition the timing of adaptive cellular response. IL-10 is elevated in COVID-19, mainly in critical/non-survivors, and mimics systemic sepsis [3, 13]. Factors compromising the adaptive response can be amplified by the age, since elderly patients show few naive T cells and a limited TCR repertoire, leading to delayed specific T cell responses which, in turn, cause the impaired B cells activation and production of neutralizing antibodies (Abs) [14]. It is likely that the innate immunity, in an attempt to compensate the defective T cells, mounts excessive responses leading to lung immunopathology and damages of other organs. Notably, the virus can directly (via TLR2) or indirectly (via FcRγ-induced trigger by virus/anti-virus Abs immune complexes) activate the NLRP3 inflammasome (NI), perpetrating the production of inflammatory mediators which favor severe outcomes [13-15]. This agrees with reports in which innate cytokine/chemokine signatures of immunopathology [7] have been associated with end-stage COVID-19 disease [16]. The lack of temporal coordination between innate and adaptive responses allows the persistence of a high viral load, which can trigger a second wave of inflammation, occurring during the third week from infection, which is crucial for the worst clinical outcomes [8].**Pre-existing immunity to the virus in unexposed individuals.**SARS-CoV-2-specific T cells have been detected in about 50% of unexposed individuals, suggesting T cell cross-reactivity between SARS-CoV-2 and common cold coronaviruses (CCC), which affect >75% of general young population [17]. High level of pre-existing memory CD4+ and CD8+ T cells could allow to favor a faster and stronger adaptive immune response upon exposure to SARS-CoV-2, limiting disease severity. Such a secondary-like response could associate with increased memory Tfh cells which cooperate with B cells and favor a more rapid humoral response [3]. This might look like what happens in recovered patients at six months from primary infection where a robust SARS-CoV-2-specific T cell response is maintained and prevents reinfection [18]. The pre-existing memory T cells induced by CCC previous infections might, however, be harmful, through an antibody-mediated disease enhancement mechanism [19]. High pre-existing T cell response may be detrimental if associated to a parallel dysfunction of naive- and induced-T regulatory (Treg) cells [20]. Since Treg cells limit antiviral responses and tissue immunopathology [21], their reduction may favor a vigorous amplification of any (specific or non-specific) T cell response including autoreactive T cells triggering autoimmunity. The direct interaction of CD147 (mainly expressed on Treg cells) and Spike 1 (S1) protein of SARS-CoV-2, which mediates infection of host cells, has been suggested to be responsible for Treg cell dysfunction observed in severe COVID-19 [8, 15, 21]. Indeed, CD147, also called Basigin (an inducer of matrix metalloproteases), is highly expressed by the early activated memory Foxp3+ Treg cells displaying the strongest suppressive activity [22].**Super-antigen hypothesis.** The similarity between severe COVID-19 and sepsis suggests that SARS-CoV-2 could contain super-antigenic sequences. Super-antigens (SAtgs) may enroll a large (even if variable) proportion of polyclonal T cells, which become chronically activated till exhaustion. Some HLA haplotypes are more permissive in binding SAtgs and account for the heterogeneity of immune responses and clinical outcomes [23]. Several SARS-CoV-2 SAtgs have been discovered: i. a polybasic sequence of S protein with a high homology to the SARS-Cov1 18-mer S protein peptide with SAtgs activity, ii. the homology of the previous sequence with SEB: notably, an anti-SEB monoclonal Ab inhibits SARS-CoV-2 infection by blocking the access of TMPRSS2 to the cleavage site [23], iii. the homology of the SAtg motif with a neurotoxin-like sequences binding TCR [24]. The analysis of TCR repertoire from patients with severe disease indicates a TCR skewing with extensive junctional diversity, enrichment of Vβ genes and increased J diversity, all consistent with SAtgs-induced activation [25]. Since SAtgs bind the non-polymorphic sequences of TCR and MHC class II, these molecules may activate T and B cells in non-

specific way and contribute to the dysfunction of humoral and cellular responses [23].**Unmasking latent auto-inflammatory/autoimmune mechanisms.**Viruses are considered the major trigger of autoimmune diseases in susceptible individuals. The hyper activation of the immune response against SARS-CoV2 may result, in some cases, in unpredictable symptoms of autoimmune/auto-inflammatory disorders (AAD), as observed in other infections. Even though they may often represent transient post-infectious epiphenomena, some COVID-19-related manifestations fulfill the diagnostic criteria of specific AAD. Several symptoms, related to autoimmune hematological diseases, autoimmune neuropathies, autoimmune coagulopathies and Kawasaki Disease-like vasculitis have been documented during COVID-19 [26, 27]. Histological patterns, as alveolar damage and fibro-myxoid proliferation observed in lung of COVID-19, are identical to those of Systemic Lupus Erythematosus (SLE), Dermatomyositis (DM), and Progressive Systemic Sclerosis [28]. Anti-nuclear-, centromere-, PM-Scl, SS-B/La, Jo-1, and Scl-70 auto-Abs have been described in a proportion of severe patients [29], while inconsistent results have been reported on anti-phospholipid Abs [29-31]. Circulating anti-PF4 auto-Abs are likely responsible for the very rare post-vaccination thromboses with thrombocytopenia. The anti-IFN-? auto-Abs, which may contribute to further impairment of anti-viral response, have been frequently detected in patients with life-threatening COVID-19 [32]. The repertoire of auto-Abs examined in MIS-C patients identified 189 peptide candidates for IgG- and 108 for IgA autoantigens. In this library the peptides expressed in cells of the immune system, La and Jo-1 autoantigens (present in SLE and autoimmune Myopathies), and those of tissues involved in the MIS-C are particularly abundant [33]. Furthermore, by using a high-throughput auto-Abs discovery technique analyzing the specificities towards more than 2,500 extracellular and secreted proteins, it was recently reported that a large panel of COVID-19 patients exhibited a dramatic increase of auto-Abs compared to uninfected people. Importantly, the majority of auto-Abs recognized immunomodulatory proteins including cytokines, chemokines, complement (C') components, and cell surface proteins, thus contributing to perturb immune function and viral load control in a very heterogeneous manner [34]. Such auto-Abs could also exacerbate disease severity in a mouse model of SARS-CoV-2 infection and were pathogenic, since their recognition of tissue antigens correlated with specific clinical patterns and severity [34]. Apparently, in odds with the ability of SARS-CoV2 to elicit autoimmunity, many reports indicate that patients, already affected by AAD and clinically stabilized with immunosuppressive drugs, display, when infected with SARS-CoV-2, similar morbidity rates of general population [35]. It has been suggested that the treatment with such drugs likely allows also to prevent the severity of infection, indirectly confirming that COVID-19 and AAD share common pathogenic pathways. Such explanation seems to be true also in asthmatic patients, controlled with inhaled corticosteroids (ICS), who display similar morbidity of infection of general population [36]. Indeed, budesonide (an ICS), largely employed in asthma, if administered at the initial phase of infection, has been recently shown to markedly reduce viral load and persistence, duration and severity of symptoms and timing of recovery in infected non-asthmatic patients [37]. Indeed, ICS are able to impair ACE2 expression on respiratory mucosa through the inhibition of type I IFN [38, 39]. If confirmed, this may be a real important breakthrough in the treatment of COVID-19. Besides Treg cells defect, several virus-related mechanisms impair peripheral tolerance and each mechanism, by itself or in association with others, may contribute to COVID-19 pathogenesis.*Molecular mimicry.* S1 protein shares sequence homology with an extraordinary number of tissue proteins that, if altered, mutated, deficient or improperly functioning by cross-reacting Abs, may associate with a wide range of AAD [40]. An epitope mapping analysis has identified linear immunogenic epitopes from DM patients matching with the SARS-CoV-2 peptides. HLA-B*15:03 which associates to Sjogren Syndrome, is able to present highly conserved SARS-CoV-2 peptides. Lastly, SARS-CoV-2 shares sequences with three proteins of the brainstem respiratory nucleus and with pulmonary surfactant, just offering a further possible explanation to neurological and pulmonary damages [41].*Neutrophils extracellular traps and epitope spreading.* The Neutrophil extracellular traps (NETs) have been observed in COVID-19 patients with elevated serum levels of cell-free DNA, myeloperoxidase-DNA complexes, and citrullinated histone H3 [16, 42]. NETs are a way to control microbial infections and this unique cell death program is called "NETosis". In this process, citrullinated chromatin and bactericidal proteins are released and produce a network structure, which immobilizes and kills invading pathogens in the environment. NETs can be activated through disease-related stimuli (as pathogens, Abs, etc.) and mediate tissue damage. Excessive spread of self-antigens, as dsDNA,

granule proteins, and histones, associated with increased NETosis and/or defects of mechanisms for their elimination leads to AAD and clotting activation [42].*Bystander Damage (BD).* It starts when the virus-specific CD8+ T cells are recruited into the infected tissues where they exert cytotoxic activity. Dead cells activate macrophages to release reactive oxygen species and nitric oxide resulting in bystander killing of uninfected cells [43]. CD4+T cells may also contribute to the BD through the release of pro-inflammatory cytokines [43]. Impaired clearance of killed cells induces spreading of autoantigens with the activation of bystander autoreactive T and B cells. BD is one of the mechanisms responsible for ARDS, myocarditis, and neurological involvement of COVID-19.*Trained immunity and hyper-activation of T cells*.When the virus persists, it may activate a dysregulated NI in infected cells favoring an excessive immune reaction through the combination of "trained innate immunity" effect and bystander T cells activation. The former process leads to increased response of previously activated innate cells, mostly myeloid and NK cells, to subsequent triggers, defined as 'innate immune memory', responsible for the persistence of inflammation in some disorders [44]. "Trained memory" NK cells have been described as a rapid protective mechanism in secondary infections, while their activation/proliferation upon SARS-CoV-2 (primary) infection would contribute to increase the late inflammation. No data are at present available regarding "memory" NKG2C+ NK cells in response to viral peptides in recovered or vaccinated people. The bystander activation of CD44+ T cells, including autoreactive T cells, is favored by the excess of environment signals facilitated by the early dysfunction of Treg cells. Bystander T cell activation contributes to not effective virus clearance and stimulates long-lived autoreactive B cells and auto-Abs. Autoreactive T cells prevalently display a Th17 profile as such development is favored by cytokines (IL-1β, IL-23) overproduced by NI-activated macrophages. Notably, autoreactive Th17 cells have been associated to the majority of AAD. Since Th17 cells are very plastic the environmental IL-12 and TNF-α usually induce their shift to a more aggressive profile (cytotoxic non-classical Th1 – ncTh1- cells) exerting further tissue injury in AAD and, likely, in COVID-19 [45]. The overproduction of IFN-γ from ncTh1 and NK cells (favored by the IL-18 excess) improves macrophage activation, thus starting a vicious circle leading to a clinical pattern known as macrophages activating syndrome (MAS) [46]. The environmental conditions with the chronic stimulation can shift memory Th17 cells to the production of IL-21 and TGF-β, but not IFN-γ, which in severely affected COVID-19 patients, may contribute to suppress T effector cells and, in parallel, favoring IgA2 production (absent in the moderate COVID-19) and the egress of circulating plasmablasts [47]**Prevalence of memory vs naïve T and B cells conditioning severe outcomes**. Age, male-gender, and pre-existing comorbidities are risk factors for a high morbidity and mortality of SARS-CoV-2 infection. They display a higher basal pro-inflammatory condition coupled with a progressive inability of the immune system to mount protective responses [48] This complex status called immune-senescence, often associated to the age, is characterized by: i. reduction in the CD4+/CD8+ T cell ratio, ii. impaired development of Tfh cells and, in turn, of memory B cells and humoral response, iii. reduction of the TCR repertoire and clonal expansion under the stimulation with novel antigens, iv. decreased cytotoxicity of CD8+ T and NKT cells favoring not effective response to new viruses, vi. improved trained immunity coupled with pro-inflammatory cytokines [48]. Since the immuno-senescence is associated with higher memory- and lower naive T cells, it has been speculated that such unbalance may contribute to the more severity observed in adult patients compared with children [49]. In adults the improved trained immunity is associated with bystander T cell activation, poor clonal T cell expansion and low viral clearance, while, in children, the predominant naive T cells develop a valid antiviral response with efficient clonal T cell expansion, viral clearance, and less tissue damage [48]. Besides naïve T cells, children exert higher levels of pre-existing innate or cross-reactive IgM+ memory B (mB) cells [50]. They produce natural antibodies and generate most IgA+ and IgG+ switched mB cells, leading to protective Abs at mucosal level during early infection [50]. Natural Abs do not undergo any modification by the antigen, exert few somatic mutations and broad reactivity, giving early protection in absence of previous encounter with antigen. Neutralizing IgG mB cells in COVID-19 display none or very few somatic mutations, thus suggesting that the innate mB cells repertoire may contain some SARS-CoV-2 specificities [49]. The excess of naïve T and mB cells in children might explain why most pediatric cases display no or mild symptoms and recovery within few days [51]. Table 1 summarizes the topics of the previously examined pathogenic mechanisms which are partially supported and that must to be further thoroughly investigated.*Multiple endotypes may explain the variability of*

*COVID-19*Despite the extraordinary amounts of reports, we are aware that many unknowns on the immune response to the virus and COVID-19 pathogenesis have to be clarified. Although the described pathogenic hypotheses contribute to shed light on multiple aspects of COVID-19, actually none of them is sufficient to fully explain the variability of the disease. Indeed, the major problem of this infection is its heterogeneity. The heterogeneity concerns the viral load (varying more than 10^5 times among different patients) which conditions the degree and the efficacy of the immune response [3]. Heterogeneity has been observed on viral replication and persistence (from some days to more than 3 months) or tissue distribution [3, 7, 14, 16]. The clinical course of infection exhibits heterogenic features (poor or no symptoms, mild disease with recovery, severe and critical illness with Acute Respiratory Distress Syndrome -ARDS-, multi organ failure, death). Different biological features are prevalent in patients with severe/critical disease: i. the reduction of class I and II expression on infected APC with dysregulated response of NK and T cells, ii. the NI activation in macrophages associated to high levels of IL-1β, IL-18, IL-23; iii. poor specific T cells with a prevalence of Th2/Th17 profiles; iv. high levels of Abs with activation of C' and clotting; v. pathogenic auto-Abs that affect immune responses and/or damage tissues. Such a variability of endotypes translates into different clinical outcomes of severe COVID-19 (Sepsis-like syndrome, Cytokine Released Syndrome -CRS -, ARDS, MAS, Secondary Haemophagocytic Lympho-histiocytosis -HLH -, Disseminated Intravascular Coagulation -DIC-, Multi-organ failure), and the variable symptoms of so-called "long COVID-19" of recovered patients. Heterogeneity of adverse events to new COVID-19 vaccines (from frequent minimal- to rare severe reactions, including anaphylaxis and thrombosis) have been documented. Heterogeneous response to therapies addressed to pathogenic mechanisms as those antagonizing TLR signaling (hydroxychloroquine), or cytokines as TNFα, IL-1β, or IL-6 has been shown [9, 52]. This has been likely the cause of failure of many clinical trials using these drugs in patients not stratified for endotypes. Heterogeneity has been observed also in the timing of onset and intensity of innate and adaptive immune responses [53]. The size of Abs responses to SARS-CoV-2 ranges of more than 1000 times, and the proportion of virus-specific T cells or NK cells is highly variable [14, 15, 17]. Single-cell transcriptomic analysis of virus-reactive CD4+ T cells provided evidence of heterogeneity across individual patients with different disease severity. The current problem is, therefore, to establish the causes of this heterogeneity. Some other viral infections, as, HBV, show variable clinical outcomes (recovery, chronicity or fatality) owing to the different balance between viral load and efficacy of antiviral immune response [54]. Three variable components can contribute to the different outcomes also in SARS-CoV2 infection: the viral load, the preexisting genetic factors conditioning the early immune response and the plasticity and/or redundancy of innate and adaptive responses to the virus along the disease. The variability and persistence of viral load along the disease is of the utmost importance. The virus triggers a lot of co-receptors able to start signals, which, in turn, activate a series of immunological mechanisms: genetics, epigenetics, pre-existing immunity, polymorphisms of signals/receptors of immune system, actually may contribute to the heterogeneity of the final response. Figure 1 summarizes the receptors and the antigenic activity of S1, the cells involved and their impact on immune response. In addition, the immune system is diverse in different people and one individual rarely responds to an infection in similar way to another person. Genetic variations as TLR7 in men [55], HLA haplotype allowing valid adaptive immunity or recognizing cross-reactive autoantigens or SAtgs of SARS-CoV2 sequence, molecules involved in signaling of type I IFN [55], predisposition to mount auto-Abs, ease to induce NI activation [33], all are important to explain the heterogeneity of antiviral response [8]. Elderly and related co-morbidities, showing a pro-inflammatory not completely controlled condition, introduce further elements of variability. Some pre-existing factors conditioning the heterogeneity of immune response to SARS-CoV2 infection are listed in Table 2. Whatever the duration and the pathways used by the immune system to counteract the virus and potentiate or regulate the inflammatory process, the peculiar timing of this multistep disease suggests a parallel underlying scenario of multistep pathogenic mechanisms. Even though variable, it is likely that different phases of infection and timing-related clinical outcomes (phenotypes), can be the expression of a progressive failure of some immunological processes (detrimental endotypes) with sometimes the reset (harnessing the redundancy and plasticity of immune response) of a novel setting. This latter, however, can recover in each clinical phase through the re-expansion of crucial anti-viral immune components (as Abs, NK- and CD8+ T cells) modulated by appropriate number of Treg cells or other regulatory mechanisms

(protective endotypes). If unstable, the novel setting can be short-circuited by mechanisms of the virus and immune system itself, that can induce newly uncontrolled hyper activation of innate and adaptive immunity leading to a next worse phase, which, later on, may lead to recovery or worsening. The virus, acting on several cellular targets, activates and/or inhibits multiple mechanisms of the immune system which tends to compensate, more or less validly, the produced alterations and damages. Protective endotypes are those that facilitate functional recovery (as IFN-γ-producing NK and memory T cells, clonally expanded CD8+T cells, high levels of Tfh, plasmablasts and neutralizing Abs, IgG and IgA1 prevalence, etc), while detrimental ones are unable to cope with damage and favor clinical worsening (as NI overactivation, hypersecretion of inflammatory cytokines/chemokines by macrophages and neutrophils, expansion of polyclonal activated T cells, prevalence of Th17 cells producing IL-21/TGF-β, early inhibition of memory Treg cells, NK impairment, IFN defect, 'C consumption, loss of circulating plasmablasts, IgA2 prevalence, etc.). An attempt to explain this concept, including different phenotypes and the corresponding protective or detrimental endotypes, is reported in Figure 2. The multiple phenotypes that characterize the critical phase of the disease may recognize different evolving endo-types, which likely can overlap or intersect in a variable way in each patient. An attempt to depict the major evolving endo-types which, through several immune mechanisms, may lead to more than one clinical pattern in severely affected COVID-19 is reported in Table 3. *Conclusion* In our opinion, in order to better explain the heterogeneity of the immune response in SARS-CoV-2 infection at molecular level, we need to establish precise endotypes and the corresponding phenotypes of COVID-19, similar to what has been made for asthma and other chronic inflammatory diseases (Rhinosinusitis with nasal polyps, Atopic dermatitis, Food allergy and eosinophilic esophagitis), through which the personalized therapy, targeting different pathogenic mechanisms, is successful today [56-60]. Recently, some sepsis endotypes and clinical and biochemical phenotypes of ARDS have been reported in COVID-19 [61-63]. Attempts to preventively identify endo-types during symptom onset or at the hospital admission of patients at high risks for a further clinical deterioration have been proposed [64, 65]. Therefore, it is important to stratify infected patients for evolving symptoms and recovery along infection and, in parallel, to monitor them tightly by detecting surrogate biomarkers of cells of innate and adaptive immunity (as cytokines/chemokines signatures and serum levels, proportion of circulating cells and function, neutralizing Abs, etc.) in association with essential parameters of inflammation, coagulation, organs' function, etc. [66]. It will allow to establish a detailed guideline able to preventively identify immunological (frequent and unfrequent) alterations correlated to changes of symptoms and, according to precision medicine dictates, to exploit this tool for the most suitable diagnostic and therapeutic strategy in each patient. Besides investigating the fine pathogenic mechanisms during SARS-CoV-2 infection, this strategy can also provide an outline of how we may approach emerging infections/pandemic in the future.***References***

1. Maggi E, Canonica WG, Moretta L. COVID-19: unanswered questions on immune response and pathogenesis. *J Allergy Clin Immunol.* 2020; 146(1):18-22. doi.org/10.1016/j.jaci.2020.05.001.
2. Yang L, Liu S, Liu J, et al. COVID-19: immune pathogenesis and Immune therapeutics. *Signal Transduct Target Ther* . 2020; 5:128.; https://doi.org/10.1038/s41392-020-00243-2.
3. Sette A, Crotty S. Adaptive immunity to SARS-CoV-2 and COVID-19. *Cell* 2021; 184 (4):861-880. doi: https://doi.org/10.1016/j.cell.2021.01.007.
4. Hadjadj J, Yatim N, Barnabei L, et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science* . 2020; 369:718–724.
5. Totura AL, Baric R. SARS coronavirus pathogenesis: host innate immune responses and viral antagonism of interferon. *Curr Opin Virol* . 2012; 2: 264-275.
6. Ziegler CGK, Allon SJ, Nyquist SK, et al. HCA Lung Biological Network. SARS-CoV-2 Receptor ACE2 Is an Interferon-Stimulated Gene in Human Airway Epithelial Cells and Is Detected in Specific Cell Subsets across Tissues. *Cell* . 2020; 181(5):1016-1035. e19. doi: 10.1016/j.cell.2020.04.035.
7. Kuri-Cervantes L, Pampena MB, Meng W, et al. Comprehensive mapping of immune perturbations associated with severe COVID-19. *Sci Immunol.* 2020; 5(49): eabd7114. doi: 10.1126/sciimmunol.abd7114.
8. Liu C, Martins AJ, Lau WW, et al. Time-resolved systems immunology reveals a late juncture linked to fatal COVID-19. *Cell* . 2021¸184(7):1836-1857. doi: 10.1016/j.cell.2021.02.018.

9. Mazzoni A, Salvati L, Maggi L, Capone M, Vanni A, Spinicci M, et al. Impaired immune cell cytotoxicity in severe COVID-19 is IL-6 dependent. *J Clin Invest* . 2020;130(9):4694-4703. doi: 10.1172/JCI138554.
10. Vietzen H, Zoufaly A, Traugott M, et al. Deletion of the NKG2C receptor encoding KLRC2 gene and HLA-E variants are risk factors for severe COVID-19. *Genet Med* . 2021 May;23(5):963-967. doi: 10.1038/s41436-020-01077-7.
11. Bortolotti D, Gentili V, Rizzo S, et al. SARS-CoV-2 Spike 1 Protein Controls Natural Killer Cell Activation via the HLA-E/NKG2A Pathway. *Cells* 2020 Aug 26;9(9):1975. doi: 10.3390/cells9091975.
12. Bozzano F, Della Chiesa M, Pelosi A, et al. HCMV-controlling NKG2C+ NK cells originate from novel circulating inflammatory precursors.*J Allergy Clin Immunol.* 2021 Jan 23: S0091-6749(21)00087-7. doi: 10.1016/j.jaci.2020.12.648.
13. Lucas C, Wong P, Klein J, et al. Yale IMPACT Team. Longitudinal analyses reveal immunological misfiring in severe COVID-19. *Nature.* 2020; 584:463-469.
14. Moderbacher CR, Ramirez SI, Dan JM, et al. Antigen-specific adaptive immunity to SARS-CoV-2 in acute COVID-19 and associations with age and disease severity. *Cell.* 2020; 183:996-1012.e19.
15. Vabret N, Britton GJ, Gruber C, et al. Sinai Immunology Review Immunology of COVID-19: current state of the science. *Immunity* . 2020; 52(6):910–941.
16. Radermecker C, Detrembleur N, Guiot J, et al. Neutrophil extracellular traps infiltrate the lung airway, interstitial, and vascular compartments in severe COVID-19. *J Exp Med* 2020; Dec 7;217(12): e20201012. doi: 10.1084/jem.20201012
17. Grifoni, A. Weiskopf D, Ramirez SI, et al. Targets of T cell responses to SARS- CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. *Cell.* 2020; 181, 1489–1501.
18. Zuo J, Dowell AC, Pearce H, et al. Robust SARS-CoV-2-specific T cell immunity is maintained at 6 months following primary infection.*Nat Immunol* . 2021 May;22(5):620-626. doi:10.1038/s41590-021-00902-8
19. Ricke DO. Two different antibody-dependent enhancement (ADE) risks for SARS-CoV-2 antibodies. *Front Immunol* . 2021; 12:640093. doi: 10.3389/fimmu.2021.640093.
20. Le Bert N, Tan AT, Kunasegaran K, et al. SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls.*Nature* . 2020; 584(7821):457-462. doi: 10.1038/s41586-020-2550-z.
21. Wang K, Chen W, Zhang Z, et al. CD147-spike protein is a novel route for SARS-CoV-2 infection to host cells. *Signal Transduct Target Ther.* 2020 Dec 4;5(1):283. doi: 10.1038/s41392-020-00426-x.
22. Solstad T, Bains SJ, Landskron J, et al. CD147 (Basigin/Emmprin) identifies FoxP3+CD45RO+CTLA4+- activated human regulatory T cells,*Blood* . 2011; 118:5141–5151. doi: 10.1182/blood-2011-02-339242
23. Noval Rivas M, Porritt RA, Cheng MH, et al. COVID-19-associated multisystem inflammatory syndrome in children (MIS-C): a novel disease that mimics toxic shock syndrome- the superantigen hypothesis *J Allergy Clin Immunol.* 2021; 147:57-59.
24. Cheng MH, Zhang S, Porritt RA, et al. Superantigenic character of an insert unique to SARS-CoV-2 spike supported by skewed TCR repertoire in patients with hyperinflammation. *Proc Natl Acad Sci.* USA 2020; 117:25254-25262.
25. Porritt RA, Paschold L, Rivas MN, et al. Identification of a unique TCR repertoire, consistent with a superantigen selection process in Children with Multi-system Inflammatory Syndrome. bioRxiv. 2020; Nov 9:2020.11.09.372169. doi: 10.1101/2020.11.09.372169.
26. Talotta R, Robertson E. Autoimmunity as the comet tail pf COVID-19 pandemic. *World J Clin Cases* . 2020; 8(17):3621-3644. doi:10.112998/wjcc.v8.i17.3621.
27. Belhadjer Z, Meot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. *Circulation* . 2020; 142(23):2282-2284. doi: 10.1161/circulationaha.120.050147.
28. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med.* 2020; 383(2):120–128. doi: 10.1056/NEJMoa2015432.
29. Zhou Y, Han T, Chen J, et al. Clinical and Autoimmune Characteristics of Severe and Critical Cases of COVID-19. *Clin Transl Sci.*2020; 13(6):1077-1086.vdoi: 10.1111/cts.12805

30. Borghi MO, Beltagy A, Garrafa E, et al. Anti-Phospholipid Antibodies in COVID-19 Are Different from Those Detectable in the Anti-Phospholipid Syndrome. *Front Immunol.* 2020 Oct 15; 11:584241. doi: 10.3389/fimmu.2020.584241
31. Zuo Y, Estes SK, Ali RA, Gandhi AA, et al. Prothrombotic autoantibodies in serum from patients hospitalized with COVID-19. *Sci Transl Med.* 2020 Nov 18;12(570): eabd3876. doi: 10.1126/scitranslmed.abd3876.
32. Bastard P, Rosen, LB, Zhang Q, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science* . 2020; Oct 23; 370(6515): eabd4585. doi: 10.1126/science.abd4585.
33. Gruber CN, Patel RS, Trachtman R, et al. Mapping Systemic Inflammation and Antibody Responses in Multisystem Inflammatory Syndrome in Children (MIS-C). *Cell.* 2020 Nov 12; 183(4):982-995.e14. doi: 10.1016/j.cell.2020.09.034.
34. Wang EY, Mao T, Klein J, et al. Diverse Functional Autoantibodies in Patients with COVID-19. *Nature.* 2021 May 19. doi: 10.1038/s41586-021-03631-y
35. Michelena X, Borrell H, Lopez-Corbeto M, et al. Incidence of COVID-19 in a cohort of adult and paediatric patients with rheumatic diseases treated with targeted biologic and synthetic disease-modifying anti-rheumatic drugs. *Semin Arthritis Rheum* . 2020; 50: 564-570. doi: 10.1016/j.semarthrit.2020.05.001.
36. Chhiba KD, Patel GB, Vu THT, et al. Prevalence and characterization of asthma in hospitalized and nonhospitalized patients with COVID-19. *J Allergy Clin Immunol.*2020;146(2):307-314.e4. doi: 10.1016/j.jaci.2020.06.010.
37. Ramakrishnan S, Nicolau DV Jr, Langford B, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomized controlled trial. *Lancet Respir Med* . 2021 Apr 9:S2213-2600(21)00160-0. doi: 10.1016/S2213-2600(21)00160-0
38. Zhang Y, Hu S, Wang J, et al. Dexamethasone inhibits SARS-CoV-2 spike pseudotyped virus viropexis by binding to ACE2. *Virology.* 2021 Feb; 554:83-88. doi: 10.1016/j.virol.2020.12.001
39. Finney LJ, Glanville N, Farne H, et al. Inhaled corticosteroids downregulate the SARS-CoV-2 receptor ACE2 in COPD through suppression of type I interferon. *J Allergy Clin Immunol.* 2021 Feb;147(2):510-519.e5. doi: 10.1016/j.jaci.2020.09.034
40. Vojdani A, Kharrazian D. Potential antigenic cross-reactivity between SARS-CoV- 2 and human tissue with a possible link to an increase in autoimmune diseases. *Clin Immunol.* 2020; 217:108480. doi.org/10.1016/j.clim.2020.108480.
41. Kanduc D, Shoenfeld Y, On the molecular determinants of the SARS-CoV-2 attack, *Clin. Immunol.* 2020; 215:108426. doi.org/10.1016/j.clim.2020.108426.
42. Zuo Y, Yalavarthi S, Shi H, et al. Neutrophil extracellular traps in COVID-19. *medRxiv* . 2020 Apr 14:2020.04.09.20059626. doi: 10.1101/2020.04.09.20059626.
43. Lee HG, Lee JU, Kim DH, et al. Pathogenic function of bystander-activated memory-like CD4(+) T cells in autoimmune encephalomyelitis. *Nat Commun* . 2019; 10(1): 709. doi: 10.1038/s41467-019-08482-w
44. Netea MG, van der Meer JW. Trained immunity: an ancient way of remembering. *Cell Host Microbe.* 2017; 21:297–300. doi: 10.1016/j.chom.2017.02.003
45. Maggi L, Cosmi L, Simonini G, et al. T cell subpopulations in juvenile idiopathic arthritis and their modifications after biotherapies. *Autoimmun Rev.* 2016;15(12):1141-1144. doi: 10.1016/j.autrev.2016.09.012.
46. Gerfaud-Valentin M, Jamilloux Y, Iwaz J, Seve P. Adult-onset Still's disease. *Autoimmun. Rev.* 2014; 13:708-722. doi.org/10.1016/j.autrev.2014.01. 058.
47. Ferreira-Gomes M, Kruglov A, Durek P, et al. SARS-CoV-2 in severe COVID-19 induces a TGF-β-dominated chronic immune response that does not target itself.*Nat Comm.* 2021; 12:1961. https://doi.org/10.1038/s41467-021-22210-3
48. Fulop T, Herbein G, Cossarizza A, Witkowski JM, Frost E, Dupuis G, et al. Immunosenescence and inflammatory aging as two sides of the same coin: friends or foes? *Front Immunol.* 2017; 42:28-46. doi: 10.1159/000448542.

49. de Candia P, Prattichizzo F, Garavelli S, Matarese G. T Cells: Warriors of SARS-CoV-2 Infection. *Trends Immunol.* 2021 Jan; 42(1):18-30. doi: 10.1016/j.it.2020.11.002.
50. Carsetti R, Di Sabatino A, Rosado MM, et al. Lack of Gut Secretory Immunoglobulin A in Memory B-Cell Dysfunction-Associated Disorders: A Possible Gut-Spleen Axis. *Front Immunol* . 2020; 10:2937. doi: 10.3389/fimmu.2019.02937.
51. Guo L, Ren L, Yang S, et al. Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19). *Clin Infect Dis* . 2020; 71(15):778–785. doi: 10.1093/cid/ciaa310.
52. Moutsopoulos HM. Anti-inflammatory therapy may ameliorate the clinical pic- ture of COVID-19. *Ann Rheum Dis.* 2020;79(9):1253-1254. doi: 10.1136/annrheumdis-2020-217562.
53. Mathew D, Giles JR, Baxter AE, et al. COVID Processing Unit Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications. *Science.* 2020; 4;369(6508): eabc8511. doi: 10.1126/science.abc8511.
54. Liaw YF. Clinical utility of HBV surface antigen quantification in HBV e antigen-negative chronic HBV infection. *Nat Rev Gastroenterol Hepatol.*2019;16(10):631-641. doi: 10.1038/s41575-019-0197-8.
55. Pairo-Castineira E, Clohisey S, Klaric L, et al. Genetic mechanisms of critical illness in Covid-19. *Nature.* 2021 Mar; 591(7848):92-98. doi: 10.1038/s41586-020-03065-y.
56. McDowell PJ, Heaney LG. Different endotypes and phenotypes drive the heterogeneity in severe asthma.*Allergy* . 2020; 75(2):302-310. doi: 10.1111/all.13966.
57. Baker MG & Samson HA. Phenotypes and endotypes of food allergy: A path to better understanding the pathogenesis and prognosis of food allergy. Ann Allergy Asthma Immunol. 2018 Mar;120(3):245-253. doi: 10.1016/j.anai.2018.01.027
58. Dunn JLM, Shoda T, Caldwll JM, et al. Esophageal type 2 cytokine expression heterogeneity in eosinophilic esophagitis in a multisite cohort. *J Allergy Clin Immunol* . 2020 Jun;145(6):1629-1640.e4. doi: 10.1016/j.jaci.2020.01.051.
59. Czamowicki T, He H, Krueger JG, Guttman-Yassky E. Atopic dermatitis endotypes and implications for targeted therapeutics. *J Allergy Clin Immunol* . 2019 Jan;143(1):1-11. doi: 10.1016/j.jaci.2018.10.032.
60. Staudacher AG Peters AT, Kato A, Stevens WW. Use of endotypes, phenotypes, and inflammatory markers to guide treatment decisions in chronic rhinosinusitis.*Ann Allergy Asthma Immunol* . 2020 Apr;124(4):318-325. doi: 10.1016/j.anai.2020.01.013.
61. DeMerle KM, Angus DC, Baillie JK, et al. Sepsis Subclasses: A Framework for Development and Interpretation. *Crit Care Med* . 2021 May 1;49(5):748-759. doi: 10.1097/CCM.0000000000004842.
62. Sweeney TE, Liesenfeld O, Wacker J et al, Validation of Inflammopathic, Adaptive, and Coagulopathic Sepsis Endotypes in Coronavirus Disease 2019. *Crit Care Med* . 2021 Feb 1;49(2): e170-e178. doi: 10.1097/CCM.0000000000004786,
63. Ranjeva S, Pinciroli R, Hodell E, et al, Identifying clinical and biochemical phenotypes in acute respiratory distress syndrome secondary to coronavirus disease-2019. *EClinicalMedicine.* 2021 Apr;3 4:100829. doi: 10.1016/j.eclinm.2021.100829
64. Vultaggio A, Vivarelli E, Virgili G, et al. Prompt Predicting of Early Clinical Deterioration of Moderate-to-Severe COVID-19 Patients: Usefulness of a Combined Score Using IL-6 in a Preliminary Study.*J Allergy Clin Immunol Pract* . 2020; 8(8):2575-2581.e2. doi: 10.1016/j.jaip.2020.06.013.
65. Ye CH, Hsu WL, Peng GR, et al. Role of the Immune Microenvironment in SARS-CoV-2 Infection. *Cell Transplant.*2021 Jan-Dec 30:9636897211010632. doi:10.1177/09636897211010632
66. Janssen NAF, Grondman I, de Nooijer AH, et al. Dysregulated Innate and Adaptive Immune Responses Discriminate Disease Severity in COVID-19. *J Infect Dis.* 2021 Apr 23; 223(8):1322-1333. doi: 10.1093/infdis/jiab

*Legend to the Figures*Figure 1. Multiple functions of SARS-CoV-2 S1 protein. S1 protein interacts with some active receptors/molecules expressed on many cell types, by directly or indirectly interfering with innate and adaptive immune responses. S1 protein induces also HLA-E expression on epithelial cells mediated by GATA3 activation which may negatively affect NKG2A+ NK cells in the lung. Finally S1 protein display

epitopes with super antigenic activity and/or cross reacting with self-antigens: they may amplify polyclonal activation of not specific T cells or bystander autoreactive T and B cells. Figure 2. Timing of clinical outcomes and related pathogenetic mechanisms of impairment or recovery in COVID-19. Detrimental or protective endo-types may condition the progression of symptoms or recovery in each phase of disease.

Table 1. Topics to be investigated for fully explaining the proposed pathogenic mechanisms of COVID-19

Pathogenic Hypothesis	Topics to be investigated
Altered coordination between innate and adaptive Immunity [3]	➢ Early alterations in asymptomatic, mild and severe diseases ➢ The timing and entity of IFN impairment, ➢ Mechanisms of altered NK function and exhaustion, ➢ Induction of trained NK response in asymptomatic, convalescent and vaccinated people, ➢ Impact of defeated innate response on the onset and entity of adaptive immunity, The circulating proportion of memory versus naïve T and B cells in adults compared with children, ➢ Reduction of CD4+/CD8+ T cell ratio and functional Th subsets, ➢ Impaired development of Tfh cells, mB cells and humoral response, ➢ Decrease of the TCR repertoire and clonal expansion to novel antigens, ➢ Impaired cytotoxicity of CD8+ T and NKT cells favoring not effective response to new viruses, ➢ Improved trained immunity coupled with pro-inflammatory cytokines. ➢ Factors/mechanisms delaying adaptive immunity.
Pre-existing immunity to the virus in unexposed individuals [17]	➢ Degree of protection given by preexisting immunity (memory T and B cells) towards reinfection, ➢ The permissive HLA haplotypes favoring a quick secondary-like response, ➢ Spectrum of T cell repertoire to CCC epitopes cross reacting with SARS-CoV-2 ones, ➢ The mechanism and the timing of memory Treg cells impairment
Super-antigenic hypothesis [24]	➢ The timing and the degree of SAtg stimulation on T (and B cells) ➢ The permissive HLA-haplotypes favoring polyclonal T cell activation till exhaustion, ➢ The interactions between chronically infected cells and polyclonal T cells activated by SAtgs.
Unmasking latent autoimmune/auto-inflammatory mechanisms [26]	➢ Mechanism(s) and timing of Treg cells dysfunction, ➢ Degree of Inflammasome activation of infected cells leading to a prevalent type 3 (Th17, Tc17, ILC3) response, ➢ Levels of NETosis by activated/infected macrophages favoring epitope spreading, ➢ Bystander activation of autoreactive T cells, ➢ Phenotype and function of autoreactive T and B cells and their expansion during infection, ➢ Molecular mimicry between SARS-CoV2 epitopes and self-antigens, ➢ Fine specificities and pathogenic role of autoantibodies observed in COVID-19.
Prevalence of memory vs naïve T and B cells [48, 50]	➢ The circulating proportion of memory versus naïve T and B cells in adults compared with children, ➢ Reduction of CD4+/CD8+ T cell ratio and functional Th subsets, ➢ Impaired development of Tfh cells, mB cells and humoral response, ➢ Decrease of the TCR repertoire and clonal expansion to novel antigens, ➢ Impaired cytotoxicity of CD8+ T and NKT cells favoring not effective response to new viruses, ➢ Improved trained immunity coupled with pro-inflammatory cytokines.

Table 2. Pre-existing factors conditioning innate and adaptive responses to SARS-CoV-2 infection

- Genetic (or epigenetic) polymorphisms of TLRs, TLR signaling, type I/III IFN and IFNR and their signaling, 'C factors, Inflammasome components
- HLA-E haplotypes and expression of KLRC gene (encoding NKG2C) conditioning trained memory NK cells
- HLA haplotypes binding the viral superantigens
- HLA haplotypes presenting viral epitopes, including those cross-reacting with self-antigens
- Degree of pre-existing immunity to cross-reacting epitopes of common cold coronaviruses
- Naïve T/memory T cells ratio (children vs elderly people)
- Proportion of Innate memory IgM+ B cells producing natural Abs cross reacting with SARS-CoV-2
- Susceptibility genes for autoimmunity conditioning the derangement of peripheral tolerance, the proportion of autoreactive bystander T and B cells, Treg cell function and ease to produce pathogenic autoantibodies
- Bone-marrow reservoir of inflammatory precursors (mobilized by inflammatory molecules) able to develop rapid NK and T cell progenies
- Bone marrow reservoir of neutrophil precursors with immunosuppressive function
- Not stabilized co-morbidities displaying uncontrolled inflammation

Table 3. Relationship between pathogenic mechanisms and clinical outcomes in severe/critical COVID-19

Evolving Endotypes*				**Phenotypes**
Viral Superantigens	⇒ Not specific T cell activation	⇒ Superinfection with other pathogens		**Sepsis-like Syndrome**
MBL and angiotensin II signaling bound to virus Hyperactivation of B cells	⇒ Pathogenic auto-Abs anti-platelets auto-Abs High anti-virus Abs	⇒ C' activation, Endothelium damage	⇒ Chronic clotting activation	**Disseminated Intravascular Coagulation**
Susceptibility to AD Molecular Mimicry Self antigen spreading Activation of inflammosome	⇒ Impairment of Treg cells High trained immunity Bystander activaction of autoreactive T and B cells	⇒ Expansion of Th17 ncTh1 and Tfh cells Activation of B cells	⇒ Pathogenic auto-Abs Tissue damage Immune alterations	**Autoimmune/auto-inflammatory –like syndrome, MIS-C**
Genetic impairment of trained immunity and of Inflammosome	⇒ IFN I/III Inhibition by the virus, pDC loss, Macrophages and neutrophils activation	⇒ Reduced function of NK and T cells with exhaustion	⇒ NK cells inhibition by HLA-E+ lung epithelia Alveolitis induced by Th17 cells/neutrophils	**Acute Respiratory Distress Syndrome**
Genetic polymorphysm of TLRs, type I/III IFN and their signaling	⇒ Virus-driven IFN I/III Inhibition, uneffective Innate immunity	⇒ High viral load Delayed and poor T cell response	⇒ Hyperactivation of Macrophages and neutrophils	**Cytokine Release Syndrome**
Activation of infected Macrophages, Increased free O2 radicals	⇒ Neutrophils activation increased NETs/NETosis	⇒ Increased DMSC-like cells Altered apoptotic cell clearance		**Secondary Haemophagocytic Lymphohistiocytosis**
Genetic polymorphisms of inflammasome complex	⇒ Altered innate and Adaptive immunity	⇒ Compensatory Increased cytokines and chemokines by Macrophages		**Macrophage Activating Syndrome**
Hyperactivation of B cells with high titers of specific Abs and auto-Abs	⇒ Activation of C' And Clotting	⇒ Immuno Complexes formation Tissue damage		**Multiorgan Failure**

*Each pathway should not be considered one way, since conditions favoring multiple mechanisms can coexist or intersect each other