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Review Article

Influenza infection, SARS, MERS and COVID-19: Cytokine storm – The common denominator and the lessons to be learned

Varvara A. Ryabkova^a, Leonid P. Churilov^a, Yehuda Shoenfeld^{a,b,*}

^a Laboratory of the Mosaics of Autoimmunity, Saint Petersburg State University, Saint-Petersburg, Russian Federation

^b Zabłudowicz Center for Autoimmune Diseases, Sheba Medical Center, Affiliated to Tel-Aviv University School of Medicine, Tel-Hashomer, Israel

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ABSTRACT

The outbreak of COVID-19 reminds us that the emerging and reemerging respiratory virus infections pose a continuing threat to human life. Cytokine storm syndromes of viral origin seem to have a common pathogenesis of the imbalanced immune response with the exaggerated inflammatory reaction combined with the reduction and functional exhaustion of T cells. Immunomodulatory therapy is gaining interest in COVID-19, but this strategy has received less attention in other respiratory viral infections than it deserved. In this review we suggest that based on the similarities of the immune dysfunction in the severe cases of different respiratory viral infections, some lessons from the immunomodulatory therapy of COVID-19 (particularly regarding the choice of an immunomodulatory drug, the selection of patients and optimal time window for this kind of therapy) could be applied for some cases of severe influenza infection and probably for some future outbreaks of novel severe respiratory viral infections.

1. Introduction

The emerging and reemerging respiratory virus infections pose a continuing threat to human life. Acute respiratory viral diseases claim over 4 million deaths and cause millions of hospitalizations worldwide every year [1]. In the last century, swine and avian influenza infection, severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) were the most damaging respiratory infections for human being all over the world [1]. However, even leaving aside outbreaks of the novel respiratory viral infections, 294, 000 to 518, 000 deaths annually are associated with seasonal influenza [2] and a significant number of deaths occur despite antivirals, especially in A (H1N1)pdm09 virus infection which continues to circulate as a seasonal flu [3]. While it is logical to look for a potential treatment for the new disease based on the previous experience with some other similar illnesses, the opposite approach (i.e. to implement some lessons from the new disease for the old one) might also give some interesting results. In this article we use this approach to discuss the lessons from the emerging immunomodulatory therapy of COVID-19 for the search of more

effective treatment for severe influenza infection. We also consider that the same lessons might be useful for some future outbreaks of diseases with novel respiratory viruses.

2. Cytokine storm and systemic inflammatory response syndrome

Comparing the infections with the emerging and re-emerging respiratory viruses, which achieved global impact in the 21st century (SARS, MERS, influenza A H1N1 2009, influenza A H5N1 and COVID-19), a significant prevalence of the common pattern of virus-induced hyperinflammation can be revealed [4]. Moreover, several studies have reported the association of this virus-induced hyperinflammatory syndrome with the disease severity for each of the mentioned infections [5,6]. An in-depth study of this hyperinflammatory state might lead to the more effective treatment of the diseases associated with it.

Proinflammatory cytokines play a major role in the up-regulation of inflammatory reaction, both of infectious and non-infectious origin. Inflammation is primarily a local process able to establish barriers

Abbreviations: ARDS, acute respiratory distress syndrome; COVID 19, coronavirus disease 2019; CRP, C-reactive protein; CSS, cytokine storm syndromes; HLH, hemophagocytic lymphohistiocytosis; HRS, Hamman-Rich syndrome; MERS, Middle East respiratory syndrome; MODS, Multi-Organ Dysfunction Syndrome; PD-1, programmed cell death protein-1; SARS, severe acute respiratory syndrome; SIRS, Systemic Inflammatory Response Syndrome; TIM-3, T-cell immunoglobulin domain and mucin domain protein-3.

* Corresponding author at: Zabłudowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer 52621, Israel.

E-mail address: shoenfel@post.tau.ac.il (Y. Shoenfeld).

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restricting the systemic spread of causing pathogens, but also limiting the systemic action of the bioregulators involved in focal events. It is well accepted that the loss of local control of this process leads to the excessive release of cytokines and other autacoids to systemic circulation with potentially deleterious consequences including the Systemic Inflammatory Response Syndrome (SIRS), circulatory shock, Multi-Organ Dysfunction Syndrome (MODS), and death [7]. The main pro-inflammatory cytokines are TNF α , IL-1, IL-6, IL-8 and macrophage inflammatory protein-1 α (MIP-1 α) [7]. They are produced by several cell types in response to activation of pattern recognition receptors or cell death and released in a cascade: initial cytokines include TNF α and IL-1 β ; these stimulate further production of other cytokines. Regarding their clinical significance in SIRS of various etiology, all major pro-inflammatory cytokines have consistently been shown to correlate with the mortality following severe injury, with TNF α and IL-6 levels also correlating with poor outcome from sepsis [7].

To describe this phenomenon, the term “cytokine storm” has been widely used both in scientific literature and in mass media in last 10 years [8,9]. The recent increased interest in this area is related to the new challenge for human beings – coronavirus disease 2019 (COVID-19). As cytokine storm is considered as the result of the disrupted immune response to the initial insult, the range of the clinical conditions, associated with this phenomenon, is very wide. For this reason, the term “cytokine storm syndromes” (CSS) has been proposed [10]. The most studied infectious triggers of CSS are avian influenza, SARS-related coronavirus (SARS-CoV), MERS-related coronavirus (MERS-CoV) and Ebola virus [4]. However, sepsis of various etiology is also directly associated with cytokine storm [11]. Non-infectious medical conditions, which are able to induce systemic cytokine response, include severe traumas and burns, acute pancreatitis, hemorrhage, ischemia-reperfusion syndrome, macrophage activating syndrome, secondary malignancy-related and primary hemophagocytic lymphohistiocytosis (HLH), graft-versus-host disease, chimeric antigen receptor T cell therapy etcetera [8,9,12]. For the clinical manifestations of dysregulated immune response to infectious or noninfectious stimuli the term SIRS was coined in 1991 [13]. The pathophysiology of SIRS was considered as a 3-stage model [14]:

- 1) Initiation of the essential inflammatory process at the primary injury site; pro-inflammatory cytokines are produced locally.
- 2) Release of small quantities of local cytokines into the systemic circulation, which improves the local response by the recruitment of macrophages and activate remote tissue-protective and repair-promoting systems, including hypothalamic-pituitary-adrenal axis. Via cytokine influences on liver and bone marrow change of plasma protein composition and leukocytosis are established. The examples of the plasma proteins whose levels reflect systemic effects of inflammation are C-reactive protein and ferritin. This *acute phase response* is typically well controlled by a decrease in the pro-inflammatory mediators and by the release of their endogenous antagonists; the goal is to maintain homeostasis. Clinically, some minimal malaise and low-grade fever may become manifest at this stage.
- 3) If the homeostasis between pro-inflammatory and anti-inflammatory reaction is lost or the immune response to the initial damaging factor is highly stimulated, but ineffective, severe excessive systemic reaction occur (i.e. systemic inflammatory response syndrome – SIRS) with overwhelming production of cytokines (“cytokine storm”). If SIRS continues, however, circulatory shock with MODS develops which may eventually lead to death. In the early phase of MODS, circulating cytokines cause universal endothelium injury. The endothelial cells have many mechanisms to prevent aberrant coagulation in the absence of systemic inflammation. However, pro-inflammatory cytokines, pathogen-associated molecular patterns such as bacterial endotoxins, or neutrophil extracellular traps increase the expression of tissue factor by the endothelial cell [15]. Tissue factor

activates the coagulation system by amplifying many-fold the enzymatic capacity of factors VII and X, triggering thrombin generation and clot formation. Upon activation, the endothelial cells can also release pre-formed von Willebrand factor that in higher molecular weight multimers provides a potent bridge for platelet aggregates and thrombus assembly, favouring formation of an organized clot [15]. In addition, there is a complex crosstalk between cytokines and the complement system and excessive complement activation also results in endothelial injury [16]. These mechanisms underlie capillary leak syndrome and coagulopathy, which often accompany cytokine storm [7,16]. Regarding clinical implications of widespread endothelial dysfunction, it should be mentioned that the vascular endothelium of the lung and kidneys are recognized as particularly vulnerable sites to complement-mediated injury [16].

3. Cytokine storm in influenza infection and COVID-19

The pathogenesis of the influenza virus infection implies inflammatory process in the respiratory system caused by direct viral infection of the respiratory epithelium and both innate and adaptive immune responses, which primarily aim to handle the spreading virus, but in fact sometimes contribute to the lung injury [17]. The mediators of inflammation can spread systemically and cause a multiorgan failure, but these consequences are generally downstream of the lung compromise and severe respiratory distress [18]. Besides MODS and death as a consequence of SIRS, the mechanisms of other non-pulmonary conditions associated with influenza virus disease (in particular, cardiac sequelae in the weeks following the infection) are also considered to be related to the general inflammatory profile [17]. Influenza virus, especially avian H5N1, is known for its systemic endothelial tropism and can cause damage of microvasculature not only via systemic action of cytokines but even directly [19].

Cytokine storm has been identified in association with seasonal influenza, avian flu (H5N1) and pandemic influenza (H1N1 2009) [20]. However, severe cytokine storm is rarely observed in seasonal mild influenza, indicating that high cytokine/chemokine levels correlate strongly with disease severity [5].

Severe COVID-19 represents viral pneumonia from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection leading to acute respiratory distress syndrome (ARDS) [21]. ARDS is a form of severe hypoxemic respiratory failure with a disorder of surfactant function that is characterized by inflammatory injury to the alveolar capillary barrier, with extravasation of protein-rich edema fluid into the airspace [22]. ARDS is a systemic inflammatory condition, rather than a local pulmonary process. The levels of inflammatory cytokines, such as IL-1 β , TNF- α , IL-6, and IL-8, are elevated both in bronchoalveolar lavage fluid and circulating plasma in ARDS subjects [22]. The cytokine storm, induced by COVID-19, is one of the major mechanisms contributing to the development of ARDS in this case. The cytokine storm is an important factor that causes COVID-19 exacerbation or even death, not only because of pulmonary injury, but also owing to extrapulmonary multiple-organ failure [23]. Interestingly, long before COVID-19 epidemic, since 1933 there were described several hundred of episodic and familial cases of so called Hamman-Rich syndrome (HRS), idiopathic acute interstitial pneumonia resulting in typical ARDS and acute *cor pulmonale* which in sub-acute period causes idiopathic diffuse pneumofibrosis [24]. Both manifestations and pathomorphology of HRS, as well as its complications - all strikingly resemble that of COVID-19. The last disease looks very much like acquired phenocopy of HRS, although HRS apparently never was considered to be a contagious disease, rather listed among the genetically based ones. Excessive content of few proinflammatory cytokines in HRS lungs has been revealed [25]. One may guess, either the sporadic cases of HRS were related to unrecognized type of coronavirus having very small contagiousness; or, which looks much more probable, both entities, having different (infectious and non-infectious, presumably, genetic) etiologies, address

similar or identical weak point of immune system, making its self-destructiveness caused by cytokine storm the crucial links of pathogenesis [26].

4. Comparing immunopathology in COVID-19 and severe influenza infection

Hyperproduction of the inflammatory cytokines in severe influenza infection and COVID-19 appears to represent one and the same typical pathological process, as is clear from the comparison of immunopathology in these two infectious diseases. The serum levels of C-reactive protein (CRP) have been associated with the severity of symptoms and poorer outcomes both in influenza infection and COVID-19 [27–30]. Notably, that regarding influenza the same association was revealed in the infection caused by pandemic H1N1 virus, avian H7N9 virus and seasonal human influenza viruses even though cytokine storm have been rarely described in seasonal influenza. The elevation of the serum ferritin levels also predicts poor outcome both in seasonal influenza and COVID-19 [28,31,32]. Higher levels of many cytokines and chemokines were found in both diseases. Although some differences have been observed in cytokine profiles even between influenza A and B, and the cytokine profiles in the peripheral blood are very dynamic in viral infections, the key mediators of cytokine storm are common to both influenza infection and COVID-19. These are IL-6, IL-1 β , TNF- α , IL-10, IP-10, and they were shown to correlate with the disease severity in both entities [28,33–35]. In influenza infection and COVID-19 cytokine storm is closely related to coagulopathy and disseminated intravascular coagulation [36,37].

Both influenza virus and SARS-CoV induce NLRP3 inflammasome activation [38], which is associated with pyroptosis - a highly inflammatory form of programmed cell death of immune cells. Inflammasome-activating properties of SARS-CoV-2 is still a subject to be studied.

Some might find it paradoxical that a hyperinflammatory state can go hand in hand with immunosuppression. But some findings suggest that this is right for the severe forms of both influenza infection and COVID-19 (Table 1). Lymphocytopenia is characteristic of both influenza infection and COVID-19 and associated with poorer outcome [39,40]. The continuous expression of inhibitory markers such as programmed cell death protein-1 (PD-1) and T-cell immunoglobulin domain and mucin domain protein-3 (TIM-3) by T-cells and NK cells as well as their overall reduced polyfunctionality and cytotoxicity argue in favor for their exhaustion during the infection course [41,42]. Kong et al. assessed levels of soluble forms of checkpoint molecules in patients with COVID-19 [43]. According to the current knowledge, soluble forms may reflect the degree of membrane expression of the corresponding checkpoint proteins [44]. Kong et al. found that levels of 13 out of 14 tested molecules were significantly higher in patients with severe COVID-19 than in those with mild, moderate, or asymptomatic infection [43]. Levels of 8 soluble checkpoint molecules including PD-1 and TIM-3 were negatively correlated with absolute counts of total, CD4, and CD8 T cells but not neutrophil counts, and TIM-3 was identified to have good

predictive value for COVID-19 progression. Ueland et al. confirmed the association between levels of soluble TIM-3 and COVID-19 severity [44]. These findings are interesting because recent data shows that TIM-3 play a dual role: it participates in the activation of infected macrophages and negatively regulates Th1 immune response [45]. This is consistent with the current understanding of cytokine storm in COVID-19 as primarily the hyperactivation of the innate immune system [23]. At the same time one study reported a protective role of Tim-3 in acute influenza infection in mice [46] and another research group showed that patients who survived after acute lung injury had higher level of T regs and higher levels of Tim-3 on Tregs at the time of recruitment than those who died [47]. There is also some data on PD-1/PD-L1 pathway in severe influenza infection. Histological sections of tissue collected from the lower airways of pediatric patients with severe H1N1 influenza A virus reveal increased expression of PD-1 and PD-L1 [48], and in the other study PD-L1 expression was identified on dendritic cells and T cells from the sera of patients with H1N1 influenza infection [49]. PD-L1 expression on CD8+ T cells correlated inversely with T cell proportions in these patients. It was shown in vitro cocultures of airway epithelial cells and T cells and in vivo models of influenza virus infection, that blockade of airway epithelial PDL-1 improves CD8 T cell function [50]. Rutigliano et al. showed that debilitated CD8+ T cells functionality observed in acute, high-pathological influenza A virus infection in mice (but not in infection with low-pathological strains of the virus) was associated with increased PD-1 expression on virus-specific CD8+ T cells [51]. Blockade of PD-L1 in vivo led to reduced virus titers and increased CD8+ T cell numbers but not their functionality in this study. At the same time PD-1-/- mice took longer to recover from influenza infection than wild type mice, as measured by weight loss [48]. These findings suggest dual role of PD-1/PD-L1 pathway, which negatively regulates CD8+ T cells: down-regulation of these cells may both cause impaired viral clearance and speed recovery by limiting adverse immune-mediated effects.

When the immune response is analyzed and compared between mild and severe cases, it can be noted that severe cases of influenza infection and COVID-19 share a similar phenotype: reduced number of circulating CD8+ and CD4+ T cells combined with increased amounts of a pro-inflammatory cytokines [28,52]. There are several possible explanations for such combination:

- 1) Lower numbers of peripheral immune cells during the acute phase in severe disease could be a consequence of aggressive trafficking into the airways and not a truly deficient immune response [52]. The diffuse infiltration of the lungs, along with focal infiltration of the kidney, liver, intestine, adrenals, pancreas and pericardium by lymphocytes, dominated by CD8+ T cells has been identified in autopsies from the deceased patients from COVID-19 [53]. These findings favor the hypothesis of the aggressive T cell trafficking responsible for their reduction in circulation - probably due to the general autoimmune processes during COVID-19 [53].
- 2) Cytokine storm could promote apoptosis or necrosis of T cells, and consequently reduce their number [54].

Table 1

Comparison of the immunopathology in COVID-19, SARS, MERS and influenza infection. + = has been reported; NS = not stated.

	Influenza infection	COVID-19	SARS	MERS	[Ref.]
Hyperinflammation					
Hypercytokinemia associated with poor prognosis	+	+	+	+	[34,78,80,119,120]
Increased CRP levels associated with poor prognosis	+	+	+	+	[27,29,30,41,121,122]
Hyperferritinemia associated with poor prognosis	+	+	+	NS	[28,31,123]
Immunosuppression					
Lymphopenia associated with the severe disease	+	+	+	NS ¹	[40,41]
Reduction of NK cell counts in the blood and/or NK cell dysfunction associated with the severe disease	+	+	+	NS	[41,124]
Reduction of both CD4 and CD8 T cell counts in the blood associated with severe disease	+	+	+	NS	[41,52]

¹ Lymphopenia is commonly observed in patients with MERS, however, its association with the disease severity has not been studied.

3) The immunodeficiency linked to abnormal T cell number or function could be the *primum mobile* of cytokine storms such as in hemophagocytic lymphohistiocytosis [28]. A vicious circle could occur in this case since the exposure to the high levels of proinflammatory cytokines induces a cytolytic dysfunction of NK cells and T lymphocytes and exaggerates activities of macrophages [55].

It is crucial to identify the right mechanism from those described above because effectiveness of treatment for the severe cases of influenza infection, COVID-19 or some other infectious diseases with the described immune phenotype will depend on the pathogenesis underlying the state of dysregulated immunity.

5. Targeting the cytokine storm in COVID-19

Several immunomodulatory drugs which blunt cytokine storm have been suggested as potential treatments for the selected cases of COVID-19 [56]. However, it is important to remember that immunosuppressive agents are double-edged swords in a viral infection. It is considered that those drugs which reduce inflammation and modulate the innate immune response without compromising the adaptive one could be more effective for the management of patients with the cytokine storm [57]. The adaptive arm of the immune system is generally considered to play a key role in the clearance of viruses and establishment of immunological memory to protect the host from a recall infection. A decrease in peripheral blood T cells is associated with disease severity and negatively correlated to the level of inflammation in COVID-19 [28]. According to the recent meta-analysis, both CD4 + T and CD8 + T counts significantly reduced in severe COVID-19 group compared with non-severe group [58]. Although T cells in severe COVID-19 seem to be more activated, it looks like their hyperactivation is secondary to the failure of the successful elimination of the virus. The evidence for the exhaustion of the T cells and NK cells are discussed above. Higher titers of IgG which have been observed in critically ill patients might also be secondary due to the same reason and by far it is unknown whether antibody responses somehow contribute to pulmonary pathology [41]. At the same time the host innate immune system appears to be the main driver of lung inflammation. Because of that, the search of highly tailored anti-inflammatory drugs for the selected cases of COVID-19 is urgently needed. To date, randomized control studies of both non-specific anti-inflammatory therapy (corticosteroids, chloroquine, hydroxychloroquine, Janus kinase inhibitors, colchicine, cyclosporin A) and specific anti-cytokine interventions (IL-6R antagonists (tocilizumab, sarilumab), IL-1R antagonist anakinra, TNF inhibitor adalimumab, complement inhibitor eculizumab, IFN- γ antagonist emapalumab) for the treatment of COVID-19 are ongoing [6,28,59]. Even when cytokine-specific drugs are used, the double-edged sword of the immunosuppression in viral infections should be kept in mind. For example, in spite of the documented efficacy of the IL-6 inhibitor tocilizumab in the treatment of COVID-19, IL-6 inhibitors may cause even more profound immunosuppression than steroids, increasing the risk of sepsis, bacterial pneumonia, gastrointestinal perforation, and hepatotoxicity [60]. This can be at least partly due to the pharmacokinetics of many monoclonal antibody drugs which have been initially designed to treat patients with chronic inflammatory conditions where optimal pharmacokinetics demand prolonged half-lives. But in the settings of acute viral infection long-lasting and indiscriminate suppression of inflammation raises concerns about impaired clearance of SARS-CoV-2 and increased risk for secondary infections. Probably, greater attention should be paid to the drugs which have a short half-life such as anakinra [28]. Although the matter of detrimental general immunosuppression is more pressing when it comes to non-specific anti-inflammatory therapy, old good glucocorticoids with their complex action on the balance between local and systemic defensive reactions may be no less useful in treatment of severe COVID-19 than new selective agents of immunobiotherapy. At least in severe SIRS and in any kind of shock potent adrenocortical

response is protective and establishes better survival chances because hormones of eustress downregulate both inflammation and systemic cytokine storm and stimulate the expression of surfactant in the lungs. It was suggested that some histological lesions in postmortem biopsies in COVID-19 positive patients might be the target for corticosteroid use in severe patients [61]. Severe COVID-19, in addition, causes lymphoid infiltration of adrenals, like in autoimmune adrenal failure [53]. The recent data on effectiveness of corticosteroids in COVID-19 are reviewed below.

6. The lessons from the immunomodulatory therapy of COVID-19 for severe influenza

The increased interest in the management of the cytokine storm caused by the COVID-19 outbreak led to the initiation of numerous clinical trials which assess the effectiveness of different immunomodulatory drugs in this disease. The results of these clinical investigation as well as the information from the published case series provide valuable information on the application of these remedies with immunosuppressive effects in the settings of viral infection. Based on the similarities between the immunopathology in COVID-19 and influenza infection, one might suggest the implementation of some lessons learned from the management of the cytokine storm in COVID-19 for the influenza infection (Fig. 1). The immunomodulatory agents proposed for the reduction of the exaggerated inflammatory response in influenza infection include peroxisome proliferator-activated receptors (PPARs) agonists, zirconia (ZrO₂) nanoparticles, sphingosine-1-phosphate receptor 1 agonists, cyclooxygenase inhibitors, anti-TNF therapy, CC chemokine receptor 5 (CCR5) inhibitor, suppressor of cytokine signaling 4 (SOCS4), tyrosine kinase inhibitor ponatinib, IP-10 antibody and IL-8 receptor (CXCR1/2) antagonist [62,63,64]. However, the majority of these drugs is still at the stage of experimental studies. Only COX inhibitors from the list above have been used for severe human influenza infection. In a phase III clinical trial of celecoxib in combination with oseltamivir (NCT02108366), it was shown that this treatment reduced mortality and serum levels of IL-6 and IL-10 without increased adverse effects in hospitalized patients with seasonal influenza [65]. The experience of immunomodulatory therapy targeting cytokine storm in human influenza infection is scarce (except for corticosteroids, which, however, have been reported to worsen patient outcomes in the majority of observational studies [3]), but the development of this area might be promoted by the rapid progress in the management of the cytokine storm in COVID-19.

6.1. Lesson 1: Who might benefit from the immunomodulatory therapy in severe respiratory viral infections including severe influenza infection?

Thorough selection of patients and an appropriate timing of the therapy initiation and seems to be key issues in the effective use of anti-inflammatory drugs in respiratory viral infections. It was stated that given the great frequency of non-severe presentations, immunomodulatory treatments should be kept for the certain group of patients [28]. Although the ideal candidate for the immunomodulatory therapy in COVID-19 remains unknown, it is reasonable to focus on the experience of the studies, in which the its effectiveness have been shown. For example, the COVID-19 Treatment Guidelines Panel recommend low-dose dexamethasone for severely ill patients who are on supplemental oxygen or ventilatory support based on a preliminary analysis of the data from the Randomized Evaluation of COVID-19 Therapy (RECOVERY) study, but it is also recommended that dexamethasone (or other glucocorticoids) should not be used for either prevention or treatment of mild to moderate COVID-19 cases (with patients not on oxygen therapy) [66]. This is because in the mentioned study a benefit was not seen among patients who did not require either oxygen or ventilatory support – instead, there was a non-significant trend towards higher mortality in this group [67]. This data is in line with the findings that patients with

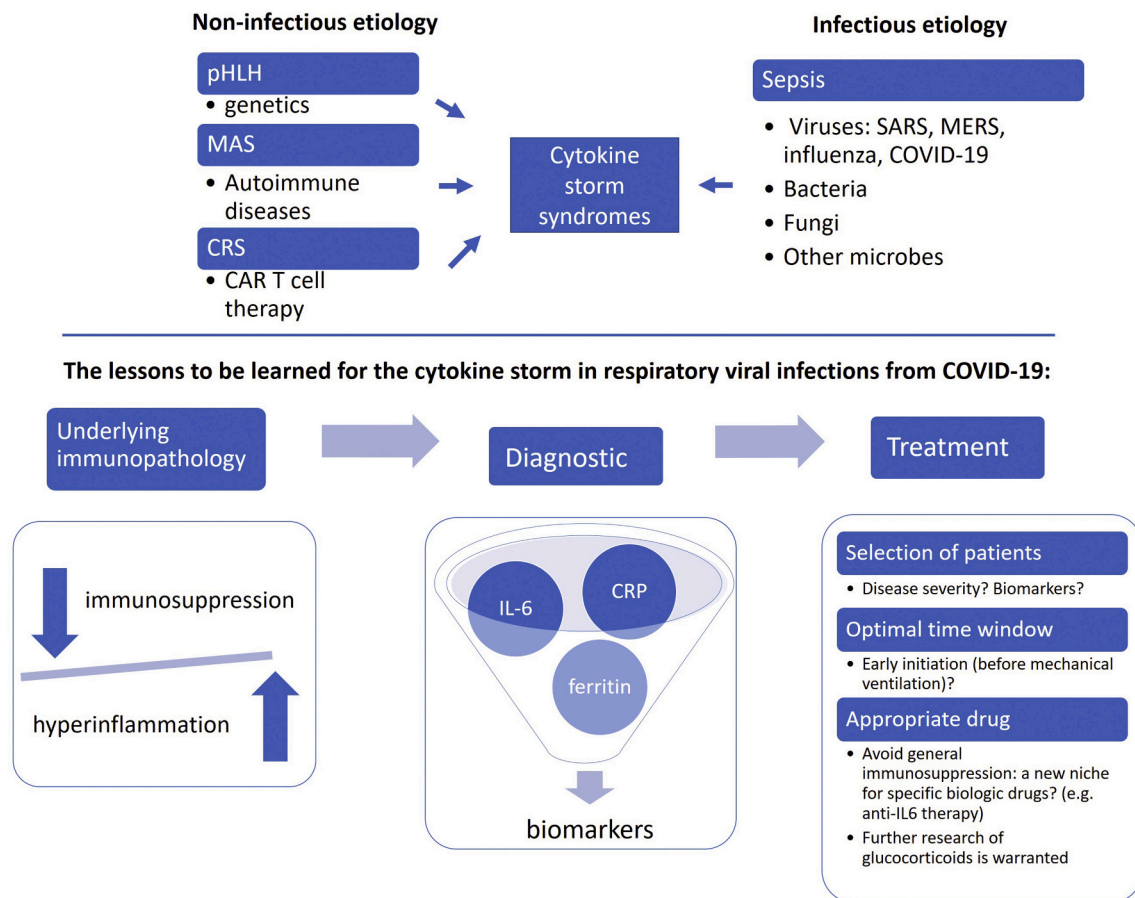


Fig. 1. The range of clinical conditions, associated with an excessive systemic action of the inflammatory autacoids termed “cytokine storm syndrome”, is very wide and includes both infectious and non-infectious diseases. While distinct etiology implies the important differences in the treatment strategies of these medical conditions, some lessons (both for diagnosis and therapy) have been recently learned from non-infectious cytokine storm syndromes for the similar hyper-inflammatory phenotype in COVID-19. Therefore, we suggest that some lessons from COVID-19 could be implemented for other respiratory viral infections, including widespread influenza infection and possible future outbreaks of novel respiratory viruses. These lessons concern taking into account the complex immunopathology underlying cytokine storm syndrome in this context, prompt diagnosis of this phenotype and judicious application of anti-inflammatory therapy (particularly regarding the selection of patients for this kind of therapy, optimal time window for this therapy and the choice of an immunomodulatory drug). CRP C-reactive protein; CRS cytokine release syndrome; MAS macrophage activation syndrome; MERS Middle East respiratory syndrome; pHLH primary hemophagocytic lymphohistiocytosis; SARS severe acute respiratory syndrome.

COVID-19 mount a marked and appropriate cortisol stress response in the acute settings [68], but 40% percent of survivors of SARS-CoV outbreak in 2003 had evidence of central hypocortisolism [69]. Regarding IL-6-directed therapy, the inclusion criteria in some earlier studies were severe and critical pneumonia and reflected mainly lung involvement (i.e. hypoxemia while breathing room air, ARDS requiring ventilatory support, tachypnea (respiratory rate > 30 breaths/min), or P_{aO_2}/F_{iO_2} ratio <300) [70–72]. Later, given the similarities of COVID-19 to CRS, several biomarkers related to the hyperinflammatory state itself have been proposed to aid in identifying appropriate candidates for immunosuppressive therapy [71,72]. However, cytokines themselves are not routine markers in clinical practice - in most medical centers, IL-6 measurement, for example, is a “send-out” test that entails a delay in obtaining the results [71]. Some more easily accessible potential biomarkers of CRS are remarkably high levels of C reactive protein, D-dimer and ferritin. Another valuable discriminator is the high H Score (a diagnostic score for HLH), which computes a value based on the following components: temperature, organomegaly, number of cytopenias, triglycerides, fibrinogen, ferritin, aspartate aminotransferase, haemophagocytosis on bone marrow aspirate and known immunosuppression [73]. There is a somewhat surprisingly little amount of data about immunomodulatory therapy in influenza infection [74]. One could suggest the use of the mentioned above biomarkers to identify the

group of patients with severe influenza infection who may benefit from the immunomodulatory therapy. It is worth noting that although IL-6 have been reported to be elevated above the normal range in COVID-19 (especially in severe disease), in most cases, however, its plasma level is lower than in previous cohorts of patients with ARDS and almost 1000-fold lower than in patients who developed CRS following treatment with chimeric antigen receptor T cells [75]. Ferritin levels in COVID-19 are also lower than in HLH and CRS [76,77]. These findings mean that the cut-off for the mentioned markers regarding the benefit from the immunomodulatory drugs in COVID-19 and probably also other respiratory viral infection could differ from those in other cytokine storm syndromes of non-infectious origin. Several authors have reported the cut-offs of IL-6 and CRP for the poor prognosis in COVID-19. IL6 predicted mortality at the cut-off value of 163.4 pg/mL, with a sensitivity of 91.7% and specificity of 57.6% in one study [78]. Grifoni et al. showed that IL-6 > 25 pg/mL is a better prognosticator for the negative outcome than D-dimer, lymphocyte count or age over 60 years [79]. Herold et al. reported the threshold levels for both biomarkers which predict the need in mechanical ventilation (IL-6: >35 pg/mL at presentation and maximal value >80 pg/mL; CRP: >32.5 mg/L at presentation and maximal value >97 mg/L) [80]. With a cut-off value of 41.4, admission CRP exhibited sensitivity 90.5% and specificity 77.6% for the adverse outcomes of COVID-19 in another study [81]. Wang et al.

showed that CRP was significantly associated with aggravation of non-severe COVID-19 patients, (sensitivity of 81.3% and specificity of 79.3% with a threshold value of 26.9 mg/L at admission). Regarding influenza infection, a study of 134 patients with avian-origin H7N9 influenza in 2013 showed that IL-6 plasma levels higher than 80 pg/mL were found in all patients with a lethal outcome compared to only 8.3% of surviving patients [82]. It was also reported that a cut-off value of 33 mg/L for CRP at admission to emergency department achieved 100% sensitivity but a specificity of only around 40% for ICU admission or mechanical ventilation in patients with pandemic H1N1 influenza infection [83]. By comparison, a slightly higher CRP cut-off of 64 mg/L achieved lower but acceptable sensitivities of 82% and 75% for ICU admission and mechanical ventilation with higher specificities of 68% and 65%, respectively in this group of patients. According to another research group, the cut-off value of CRP for ICU admission and mortality in seasonal influenza was indicated as 76.5 mg/L (sensitivity 82.1% and 90.9% and specificity 91.3% and 83.3% respectively) [84]. In summary, the listed cut-offs are generally lower than the median CRP level in ARDS [85]. IL-6 level and CRP level are considered as useful markers that predict poor outcome in COVID-19 with high accuracy and can help physicians correctly allocate patients who might benefit from early treatment escalation (e.g. initiation of anti-inflammatory therapy) [80]. But could these markers predict the benefit from this kind of therapy? This question requires further research but some data have already been published. In particular, glucocorticoid treatment of hospitalized patients with COVID-19 who had CRP ≥ 20 mg/dL at admission was associated with significantly reduced risk of mortality or mechanical ventilation (odds ratio, 0.23; 95% CI, 0.08–0.70), while glucocorticoid treatment of patients with CRP < 10 mg/dL was associated with significantly increased risk of mortality or mechanical ventilation (OR, 2.64; 95% CI, 1.39–5.03) [86]. Probably, similar cutoff for CRP at admission can be chosen for the trial of corticosteroids in other respiratory viral infections with presumptive cytokine storm syndrome.

6.2. Lesson 2: At what stage of the disease might patients with severe respiratory viral infections benefit most from the anti-inflammatory therapy?

It is generally accepted, that although pro-inflammatory mediators can exacerbate infectious disease through tissue damage, they are vital for resolution of infection. Therefore, the strategy of controlling the inflammatory response should be considered at later time points in infection when viral load is already limited but excessive host inflammatory response persists [74]. However, the experience with COVID-19 pandemic raised some questions regarding the best timing of initiation of the immunomodulatory therapy. Although that is the patients with severe COVID-19 who benefit most from IL6-directed agents, recent findings indicated that the therapy should not be postponed and used mainly for the treatment of those who require mechanical ventilation [87]. It is important to remember that the cytokine storm may start from the early course of disease to later stage and it may be rapidly progressive at any time [88]. It was suggested that probably the efforts should be made to prevent this process at an early course of disease [88]. Along these lines, monitoring of the cytokine storm biomarkers seems to be an essential part of the follow-up of the patients with COVID-19. Regarding the appropriate timing for the anti-IL6 therapy, tocilizumab use prior to ventilation in intensive care unit was considered optimal since 50% patients who start receiving this therapy after placing on mechanical ventilation remain ventilated and show serious superinfection [87]. The non-ventilated group generally had milder inflammation, which can discourage the clinicians from the use of tocilizumab. However, in a recent study it was shown that patients with COVID-19 on non-invasive ventilation treated with tocilizumab require invasive ventilation significantly less frequently than controls [89]. In another study early receipt of tocilizumab (within 12 days of symptom onset) in patients with severe COVID-19 was the only factor independently

associated with in-hospital survival at 28 days [90]. These findings further support the early anti-IL6 treatment in an appropriate group of patients with COVID-19. If this is also true for the patients with influenza infection who has the laboratory markers of the hyperinflammatory state associated with the risk of the poor disease outcome – is the question to be answered. At the same time there is a concern of potential detrimental effects of systemic corticosteroid therapy in mild cases of COVID-19 (in patients who did not require respiratory support) [67]. Furthermore, as we have mentioned, potential adrenal insufficiency is suspected to occur later in the course of the disease and absent in the early stages. However, according to the recent study, detrimental effects of systemic corticosteroids is related to the early initiation of this kind of therapy, but to the absence of severe inflammatory response (based on the serum level of CRP) [86].

6.3. Lesson 3: Which immunomodulatory drugs could be effective for the management of the cytokine storm in these patients?

The management of the infection-induced CSS is more complicated than the treatment of the other ones which relate to inflammation not caused by infection. General deep immunosuppression should be certainly avoided, and the careful selection of the appropriate immunomodulatory drug play an important role. As an example, certain immunosuppressive medications can either directly (e.g. lymphocyte-depleting antibodies) or indirectly (eg, antimetabolites) cause lymphopenia, which is a reported risk factor for severe COVID-19 illness and for pneumonia caused by influenza virus [91]. A caution should be taken also when considering systemic glucocorticoids therapy. According to the results of the mentioned above RECOVERY study, low-dose dexamethasone is beneficial for severely ill patients with COVID-19 who are on supplemental oxygen or ventilatory support [67]. However, adverse effects (including secondary infections) were not reported in this study. In some other studies corticosteroid use is associated with increased mortality in patients with SARS-CoV-2 pneumonia [92]. The efficacy of corticosteroids was suggested in SARS, MERS and H1N1 influenza, but later larger studies and systematic reviews showed either increase in viral load, no efficacy or harmfulness [93]. Regardless, if HLH, which is a specific type of CSS, develops, etoposide-based protocol including dexamethasone (which is the standard of care for secondary HLH) has been reported to be of value in severe influenza A/H1N1 [94]. In addition, currently, low-dose corticosteroids (e.g. hydrocortisone 50 mg q6h) is recommended for treatment of refractory septic shock in patients with severe influenza [3]. Despite the results of a recent meta-analysis of observational studies of corticosteroids in influenza which found an association with increased mortality, completed randomized trials on this issue are absent and urgently needed, because there were important concerns regarding the risk of bias in observational studies [95]. While the use of corticosteroids in viral pneumonia is controversial as they are known to cause prolonged viral shedding, prolonged shedding of influenza virus was observed in high-dose but not in low dose corticosteroid therapy [96]. In accordance with these findings, it was low-dose dexamethasone that reduced deaths in patients with COVID-19 in RECOVERY study [67]. It was also reported that low-dose corticosteroid therapy does not delay viral clearance in patients with COVID-19 [97]. Therefore, the role of low dose adjuvant corticosteroids for patients with severe influenza, which have already shown some promising results among patients with PaO₂/FiO₂ less than 300 mmHg, is of great interest [3]. Comparing with synthetic disease modifying antirheumatic drugs, biologic ones that target cytokines specifically block one element of the immune system (which is related to the hyperinflammatory state) while leaving remaining components unmanipulated [73] and therefore might be a better choice in severe respiratory viral infections. IL-6 inhibitor tocilizumab is approved by Food and Drug Administration (FDA) and European Medicines Agency (EMA) for patients with chimeric antigen receptor T cell treatment associated cytokine release syndrome. The results of observational studies of this drug in the patients with severe

COVID-19 are encouraging [70–72,87,98]. However, anti-IL6 therapy, to our knowledge, has not been studied in influenza infection-induced cytokine storm syndrome yet. One could suggest the efficacy of the IL6 inhibitor in these settings based on the positive experience of its application in COVID-19 and a small case series of 10 patients with juvenile idiopathic arthritis who experienced influenza, which showed that tocilizumab reduced inflammation associated with influenza and resulted in mild symptoms during the infection compared with the control group of patients treated with conventional immunosuppressive agents without biologics [99]. At the same time, it is important to remember even with specific immunomodulatory therapy targeting the innate immune response that it plays a key role in the early stages of viral infection. Lack of IL-6 or IL-6R signals, for example, leads to an impaired clearance of the influenza virus in vivo, emphysema-like destruction of the lung and, ultimately, death of the laboratory animals [100]. Regarding COVID-19, despite promising results of observational studies, recently published results of three two randomized control trials (RCT) as well as preliminary results of another two RCT are conflicting and overall discouraging [101–104]. Differences in mortality attributable to tocilizumab at day 28 or 30 were not observed across all randomized trials. But 2 of the 5 trials reported evidence of efficacy, particularly related to the risk of mechanical ventilation [102].

Another anti-cytokine agent which showed promising results in COVID-19 pneumonia in case series, retrospective and prospective studies is the IL-1 inhibitor anakinra [105–107]. The efficacy of inhibition of IL-1 in patients who received anakinra was reflected by the significant reduction in IL-6, CRP, LDH, and D-dimer levels in the anakinra group compared with the controls. While the majority of studies included patients with obvious hyperinflammatory state according to the laboratory parameters, the authors of the recently published prospective study emphasized, that the treatment effect of anakinra was likewise noted in patients with and without demonstrable hyperinflammation (CRP > 150 mg/L, or IL-6 > 60 pg/mL, or ferritin > 1500 µg/L) and was seen only in patients without advanced respiratory failure (i.e. who did not require non-invasive ventilation) [107]. Optimal timing of the therapy and optimal cutoffs of the laboratory markers which does not underrecognize early hyperinflammation are very important, as discussed above, and merit further study. Although there is also no data on the use of anakinra in influenza-induced cytokine storm syndrome, high concentrations of IL-1β in the lung and sera are associated with severe and fatal influenza A virus infections in humans [108]. Probably, anakinra, a recombinant IL-1 receptor antagonist, might help to neutralize the severe influenza-related hyperinflammatory state. Some other biologic drugs have been considered for the treatment of COVID-19 and are currently evaluated in the clinical trials. Several trials has been launched to determine the therapeutic effect of eculizumab, which is a complement inhibitor targeting C5 activation, in pneumonia associated with COVID-19 [6]. The blockage of complement components can prevent ARDS and reduce systemic inflammation [6]. It was shown in 2013 that inhibition of C5 activation in a murine model of influenza A infection results in a significant inhibition of neutrophil and macrophage infiltration in the airways, neutrophil extracellular traps formation, death of leukocytes, lung epithelial injury and overall lung damage induced by the infection [109]. The same decrease in systemic inflammatory response in the infected lungs have been observed in A (H7N9)-infected monkeys that received anti-C5a treatment [3]. These findings suggest that targeting C5 activation could be a promising approach to reduce excessive inflammatory reactions associated with severe forms of influenza A infection [109]. One more promising therapy for the cytokine storm syndrome in respiratory viral infections is therapeutic plasma exchange, which can remove harmful mediators from the bloodstream. There are some available data to suggest that this strategy can stabilize and promote recovery in patients with severe COVID-19 [110]. Regarding influenza infection, there are only a couple of clinical case reports of plasmapheresis in pediatric patients with severe influenza. All the clinical case reports showed that plasmapheresis

was effective, but because of the very small number of subjects, this evidence is insufficient and a large-scale prospective randomized controlled study is warranted [111]. Search for the COVID-19 drugs continues. Previous experience with influenza infection could provide some ideas for drug testing. One example is adamantane derivatives. In 1976, amantadine was developed for the treatment of influenza H1N1; however, this drug is not recommended for the treatment of influenza, because it mutates and loses sensitivity to the drug [112]. A small observational study of amantadine in COVID-19 gave some promising results [112]. The potential utility of memantine and other adamantane derivatives in COVID-19 has been recently discussed. Despite being known as a medication used to treat moderate-to-severe Alzheimer's disease, memantine decrease not only neuroinflammation but also pulmonary inflammation in rat models and has anti-inflammatory effects in the human microvascular endothelium [113]. Furthermore, it has been recently shown that memantine inhibits E protein of SARS-CoV2 – an ion channel and therefore the essential component of the virus [114]. Tanner et al. showed in 2005 that a class of other adamantane derivatives named bananins, inhibited the replication of SARS-CoV in cell culture by inhibiting the helicase ATPase activity [115]. However, it is increasingly recognized that antiviral monotherapy for moderately to severely ill patients admitted to hospital with COVID-19 is not enough and combination therapy with antivirals and immunomodulators for severe COVID-19 should be a priority for ongoing and future clinical trials [116].

7. Conclusion

CSS represent a heterogeneous group and the mechanisms behind its certain subtypes (macrophage activating syndrome, HLH, cytokine release syndrome) are still not fully understood [117]. CSS in severe respiratory viral infections seems to have a common pathogenesis of the imbalanced immune response with the exaggerated inflammatory reaction combined with the reduction and functional exhaustion of the key players of the adaptive immunity, namely T cells. Some of the recently approved biologic anti-rheumatic drugs may prove to be strong allies in the fight against COVID-19 as they can precisely target the key steps of the dysregulated immune response [118]. This strategy could not be applied to SARS with the outbreak in early 2000s, and we could have not identify any observational studies done so far or case series that described the use of biologic immunomodulatory drugs in severe cases of other respiratory viral infections, particularly in severe influenza infection and MERS. In this review we suggest that based on the similarities of the immune dysfunction in the severe cases of different respiratory viral infections (mainly influenza infection and COVID-19), some lessons from the immunomodulatory therapy of COVID-19 (particularly regarding the selection of patients for this kind of therapy, optimal time window for this therapy and the choice of an immunomodulatory drug) could be applied for some cases of severe influenza infection and probably for some future outbreaks of novel severe respiratory viral infections.

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References

- [1] İ. Çelik, E. Saatçi, F.Ö. Eyüboğlu, Emerging and reemerging respiratory viral infections up to covid-19, *Turkish J. Med. Sci.* 50 (2020) 557–562, <https://doi.org/10.3906/sag-2004-126>.
- [2] J. Paget, P. Spreewenber, V. Charu, R.J. Taylor, A.D. Iuliano, J. Bresee, L. Simonsen, C. Viboud, Global mortality associated with seasonal influenza epidemics: new burden estimates and predictors from the GLAMOR project, *J. Glob. Health* 9 (2019), <https://doi.org/10.7189/jogh.09.020421>.
- [3] D.S. Hui, N. Lee, P.K. Chan, J.H. Beigel, The role of adjuvant immunomodulatory agents for treatment of severe influenza, *Antivir. Res.* 150 (2018) 202–216, <https://doi.org/10.1016/j.antiviral.2018.01.002>.
- [4] J.R. Teijaro, Cytokine storms in infectious diseases, *Semin. Immunopathol.* 39 (2017) 501–503, <https://doi.org/10.1007/s00281-017-0640-2>.
- [5] Q. Liu, Y.H. Zhou, Z.Q. Yang, The cytokine storm of severe influenza and development of immunomodulatory therapy, *Cell. Mol. Immunol.* 13 (2016) 3–10, <https://doi.org/10.1038/cmi.2015.74>.
- [6] M. Cardone, M. Yano, A.S. Rosenberg, M. Puig, Lessons learned to date on COVID-19 Hyperinflammatory syndrome: considerations for interventions to mitigate SARS-CoV-2 viral infection and detrimental hyperinflammation, *Front. Immunol.* 11 (2020) 1131, <https://doi.org/10.3389/fimmu.2020.01131>.
- [7] U. Jaffer, R.G. Wade, T. Gourlay, Cytokines in the systemic inflammatory response syndrome: a review, *HSR Proc. Intensive Care Cardiovasc. Anesth.* 2 (2010) 161–175. <http://www.ncbi.nlm.nih.gov/pubmed/23441054> (accessed May 3, 2020).
- [8] J.R. Tisoncik, M.J. Korth, C.P. Simmons, J. Farrar, T.R. Martin, M.G. Katze, Into the eye of the cytokine storm, *Microbiol. Mol. Biol. Rev.* 76 (2012) 16–32, <https://doi.org/10.1128/mmb.05015-11>.
- [9] C. Rosário, G. Zandman-Goddard, E.G. Meyron-Holtz, D.P. D’Cruz, Y. Shoenfeld, The Hyperferritinemic syndrome: macrophage activation syndrome, Still’s disease, septic shock and catastrophic antiphospholipid syndrome, *BMC Med.* 11 (2013) 185, <https://doi.org/10.1186/1741-7015-11-185>.
- [10] S.W. Cannan, E.M. Behrens, Making sense of the cytokine storm: a conceptual framework for understanding, diagnosing, and treating Hemophagocytic syndromes, *Pediatr. Clin. N. Am.* 59 (2012) 329–344, <https://doi.org/10.1016/j.pcl.2012.03.002>.
- [11] B.G. Chousterman, F.K. Swirski, G.F. Weber, Cytokine storm and sepsis disease pathogenesis, *Semin. Immunopathol.* 39 (2017) 517–528, <https://doi.org/10.1007/s00281-017-0639-8>.
- [12] A. Cauwels, E. Rogge, B. Vandendriessche, S. Shiva, P. Brouckaert, Extracellular ATP drives systemic inflammation, tissue damage and mortality, *Cell Death Dis.* 5 (2014) e1102, <https://doi.org/10.1038/cddis.2014.70>.
- [13] R.C. Bone, R.A. Balk, F.B. Cerra, R.P. Dellinger, A.M. Fein, W.A. Knauer, R.M. H. Schein, W.J. Sibbald, Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis, *Chest.* 101 (1992) 1644–1655, <https://doi.org/10.1378/chest.101.6.1644>.
- [14] R.C. Bone, Immunologic dissonance: a continuing evolution in our understanding of the systemic inflammatory response syndrome (SIRS) and the multiple organ dysfunction syndrome (MODS), *Ann. Intern. Med.* 125 (1996) 680–687, <https://doi.org/10.7326/0003-4819-125-8-199610150-00009>.
- [15] P. Libby, T. Lüscher, COVID-19 is, in the end, an endothelial disease, *Eur. Heart J.* 41 (2020) 3038–3044, <https://doi.org/10.1093/eurheartj/ehaa623>.
- [16] N. Mangalmurti, C.A. Hunter, Cytokine storms: understanding COVID-19, *Immunity.* 53 (2020) 19–25, <https://doi.org/10.1016/j.immuni.2020.06.017>.
- [17] A.C. Kalil, P.G. Thomas, Influenza virus-related critical illness: pathophysiology and epidemiology, *Crit. Care* 23 (2019) 258, <https://doi.org/10.1186/s13054-019-2539-x>.
- [18] A. Zangrillo, G. Biondi-Zoccai, G. Landoni, G. Frati, N. Patroniti, A. Pesenti, F. Pappalardo, Extracorporeal membrane oxygenation (ECMO) in patients with H1N1 influenza infection: a systematic review and meta-analysis including 8 studies and 266 patients receiving ECMO, *Crit. Care* 17 (2013), <https://doi.org/10.1186/cc12512>.
- [19] K.R. Short, E.J.B. Veldhuis Kroeze, L.A. Reperant, M. Richard, T. Kuiken, Influenza virus and endothelial cells: a species specific relationship, *Front. Microbiol.* 5 (2014) 653, <https://doi.org/10.3389/fmicb.2014.00653>.
- [20] E.S. Sen, A.V. Ramanan, Cytokine storm syndrome associated with Hemorrhagic fever and other viruses, in: *Cytokine Storm Syndr*, Springer International Publishing, 2019, pp. 277–297, https://doi.org/10.1007/978-3-030-22094-5_16.
- [21] P. Gibson, L. Qin, S. Puah, COVID-19 acute respiratory distress syndrome (ARDS): clinical features and differences from typical pre-COVID-19 ARDS, *Med. J. Aust. preprint* 213 (2020) 54–56.e1, <https://doi.org/10.5694/mja2.50674>. <http://www.mja.com.au/journal/2020/213/2/covid-19-acute-respiratory-distress-syndrome-ards-clinical-features-and>.
- [22] S. Han, R.K. Mallampalli, The acute respiratory distress syndrome: from mechanism to translation, *J. Immunol.* 194 (2015) 855–860, <https://doi.org/10.4049/jimmunol.1402513>.
- [23] Q. Ye, B. Wang, J. Mao, The pathogenesis and treatment of the “cytokine storm” in COVID-19, *J. Inf. Secur.* (2020), <https://doi.org/10.1016/j.jinf.2020.03.037>.
- [24] S. Mukhopadhyay, J.G. Parambil, Acute interstitial pneumonia (AIP): relationship to hamman-rich syndrome, diffuse alveolar damage (DAD), and acute respiratory distress syndrome (ARDS), *Semin. Respir. Crit. Care Med.* 33 (2012) 476–485, <https://doi.org/10.1055/s-0032-1325158>.
- [25] E. Turillazzi, S. Di Donato, M. Neri, I. Riezzo, V. Fineschi, An immunohistochemical study in a fatal case of acute interstitial pneumonitis (Hamman-rich syndrome) in a 15-year-old boy presenting as sudden death, *Forensic Sci. Int.* 173 (2007) 73–77, <https://doi.org/10.1016/j.forsciint.2006.12.002>.
- [26] Y. Stroeve, L. Churilov, Diagnosis of the diseases of respiratory system and its pathophysiological basis. III. Cor pulmonale – pulmonary heart disease., *Rus. Biomed. Res.* 5 (2020) 4–16.
- [27] J.P. Haran, S. Suner, F. Gardiner, Correlation of C-reactive protein to severity of symptoms in acute influenza a infection, *J. Emerg. Trauma Shock.* 5 (2012) 149–152, <https://doi.org/10.4103/0974-2700.96484>.
- [28] Y. Jamilloux, T. Henry, A. Belot, S. Viel, M. Fauter, T. El Jammal, T. Walzer, B. François, P. Sève, Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions, *Autoimmun. Rev.* (2020), 102567, <https://doi.org/10.1016/j.autrev.2020.102567>.
- [29] W. Wu, D. Shi, D. Fang, F. Guo, J. Guo, F. Huang, Y. Chen, L. Lv, L. Li, A new perspective on C-reactive protein in H7N9 infections, *Int. J. Infect. Dis.* 44 (2016) 31–36, <https://doi.org/10.1016/j.ijid.2016.01.009>.
- [30] D. Vasileva, A. Badawi, C-reactive protein as a biomarker of severe H1N1 influenza, *Inflammation Research* 68 (2019) 39–46, <https://doi.org/10.1007/s00011-018-1188-x>.
- [31] A. Lalueza, B. Ayuso, E. Arrieta, H. Trujillo, D. Folgueira, C. Cueto, A. Serrano, J. Laureiro, C. Arévalo-Cañas, C. Castillo, C. Díaz-Pedroche, C. Lumbereras, Elevation of serum ferritin levels for predicting a poor outcome in hospitalized patients with influenza infection, *Clin. Microbiol. Infect.* (2020), <https://doi.org/10.1016/j.cmi.2020.02.018>.
- [32] Z. Lin, F. Long, Y. Yang, X. Chen, L. Xu, M. Yang, Serum ferritin as an independent risk factor for severity in COVID-19 patients, *J. Inf. Secur.* 0 (2020), <https://doi.org/10.1016/j.jinf.2020.06.053>.
- [33] A. Fiore-Gartland, A. Panoskaltis-Mortari, A.A. Agan, A.J. Mistry, P.G. Thomas, M.A. Matthay, T. Hertz, A.G. Randolph, Cytokine profiles of severe influenza virus-related complications in children, *Front. Immunol.* 8 (2017), <https://doi.org/10.3389/fimmu.2017.01423>.
- [34] X. zhi J. Guo, P.G. Thomas, New fronts emerge in the influenza cytokine storm, *Semin. Immunopathol.* 39 (2017) 541–550, <https://doi.org/10.1007/s00281-017-0636-y>.
- [35] J.-R. Bian, W. Nie, Y.-S. Zang, Z. Fang, Q.-Y. Xiu, X.-X. Xu, Clinical aspects and cytokine response in adults with seasonal influenza infection, *Int. J. Clin. Exp. Med.* 7 (2014) 5593.
- [36] R.J. Jose, A. Manuel, COVID-19 cytokine storm: the interplay between inflammation and coagulation, *Lancet Respir.* 2019 (2019) 2019–2020, [https://doi.org/10.1016/S2213-2600\(20\)30216-2](https://doi.org/10.1016/S2213-2600(20)30216-2).
- [37] Y. Yang, H. Tang, Aberrant coagulation causes a hyper-inflammatory response in severe influenza pneumonia, *Cell. Mol. Immunol.* 13 (2016) 432–442, <https://doi.org/10.1038/cmi.2016.1>.
- [38] I.Y. Chen, M. Moriyama, M.F. Chang, T. Ichinohe, Severe acute respiratory syndrome coronavirus viroporin 3a activates the NLRP3 inflammasome, *Front. Microbiol.* 10 (2019), <https://doi.org/10.3389/fmicb.2019.00050>.
- [39] L. Tan, Q. Wang, D. Zhang, J. Ding, Q. Huang, Y.Q. Tang, Q. Wang, H. Miao, Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study, *Signal Transduct. Target. Ther.* 5 (2020) 1–3, <https://doi.org/10.1038/s41392-020-0148-4>.
- [40] A. Lalueza, D. Folgueira, C. Díaz-Pedroche, P. Hernández-Jiménez, B. Ayuso, C. Castillo, J. Laureiro, H. Trujillo, M. Torres, C. Lumbereras, Severe lymphopenia in hospitalized patients with influenza virus infection as a marker of a poor outcome, *Infect. Dis. (Auckl.)* 51 (2019) 543–546, <https://doi.org/10.1080/23744235.2019.1598572>.
- [41] N. Vabret, G.J. Britton, C. Gruber, S. Hegde, J. Kim, M. Kuksin, R. Levantovsky, L. Malle, A. Moreira, M.D. Park, L. Pia, E. Risson, M. Saffern, B. Salomé, M. Esai Selvan, M.P. Spindler, J. Tan, V. van der Heide, J.K. Gregory, K. Alexandropoulos, N. Bhardwaj, B.D. Brown, B. Greenbaum, Z.H. Gümüş, D. Homann, A. Horowitz, A.O. Kamphorst, M.A. Curotto de Lafaille, S. Mehandru, M. Merad, R. M. Samstein, M. Agrawal, M. Aleyknik, M. Belabed, M. Brown, M. Casanova-Acebes, J. Catalan, M. Centa, A. Charap, A. Chan, S.T. Chen, J. Chung, C. C. Bozkus, E. Cody, F. Cossarini, E. Dalla, N. Fernandez, J. Grout, D.F. Ruan, P. Hamon, E. Humblin, D. Jha, J. Kodysh, A. Leader, M. Lin, K. Lindblad, D. Lozano-Ojalvo, G. Lubitz, A. Magen, Z. Mahmood, G. Martinez-Delgado, J. Mateus-Tique, E. Meritt, C. Moon, J. Noel, T. O’Donnell, M. Ota, T. Plitt, V. Pothula, J. Redes, I. Reyes Torres, M. Roberto, A.R. Sanchez-Paulete, J. Shang, A.S. Schanoski, M. Suprun, M. Tran, N. Vaninov, C.M. Wilk, J. Aguirre-Ghiso, D. Bogunovic, J. Cho, J. Faith, E. Grasset, P. Heeger, E. Kenigsberg, F. Krammer, U. Laserson, Immunology of COVID-19: current state of the science, *Immunity.* 52 (2020) 910–941, <https://doi.org/10.1016/j.immuni.2020.05.002>.
- [42] S. Varchetta, D. Mele, B. Oliviero, S. Mantovani, S. Ludovisi, A. Cerino, R. Bruno, A. Castelli, M. Mosconi, M. Vecchia, S. Roda, M. Sachs, C. Klersy, M.U. Mondelli, Unique immunological profile in patients with COVID-19, *Cell. Mol. Immunol.* (2020), <https://doi.org/10.1038/s41423-020-00557-9>.
- [43] Y. Kong, Y. Wang, X. Wu, J. Han, G. Li, M. Hua, K. Han, H. Zhang, A. Li, H. Zeng, Storm of soluble immune checkpoints associated with disease severity of COVID-19, *Signal Transduct. Target. Ther.* 5 (2020), <https://doi.org/10.1038/s41392-020-00308-2>.
- [44] T. Ueland, L. Heggelund, A. Lind, A.R. Holten, K. Tonby, A.E. Michelsen, S. Jenum, M.J. Jørgensen, A. Barratt-Due, L.G. Skeie, I. Nordøy, M.S. Aanensen Fraz, E. Quist-Paulsen, S.E. Pischke, S.K. Johal, L. Hestvedt, M. Bogen, B. Fevang, B. Halvorsen, F. Müller, G.K. Bekken, T.E. Mollnes, S. Dudman, P. Aukrust, A. M. Dyrhol-Riise, J.C. Holter, Elevated plasma sTIM-3 levels in patients with severe COVID-19, *J. Allergy Clin. Immunol.* 0 (2020), <https://doi.org/10.1016/j.jaci.2020.09.007>.

- [45] R. Ocaña-Guzman, L. Torre-Bouscoulet, I. Sada-Ovalle, TIM-3 regulates distinct functions in macrophages, *Front. Immunol.* 7 (2016) 229, <https://doi.org/10.3389/fimmu.2016.00229>.
- [46] J.L. Cho, M.I. Roche, B. Sandall, A.L. Brass, B. Seed, R.J. Xavier, B.D. Medoff, Enhanced Tim3 activity improves survival after influenza infection, *J. Immunol.* 189 (2012) 2879–2889, <https://doi.org/10.4049/jimmunol.1102483>.
- [47] H. Song, Y. Zhou, G. Li, J. Bai, Regulatory T cells contribute to the recovery of acute lung injury by upregulating Tim-3, *Inflammation.* 38 (2015) 1267–1272, <https://doi.org/10.1007/s10753-014-0096-7>.
- [48] J.J. Erickson, P. Gilchuk, A.K. Hastings, S.J. Tollefson, M. Johnson, M. B. Downing, K.L. Boyd, J.E. Johnson, A.S. Kim, S. Joyce, J.V. Williams, Viral acute lower respiratory infections impair CD8 + T cells through PD-1, *J. Clin. Invest.* 122 (2012) 2967–2982, <https://doi.org/10.1172/JCI62860>.
- [49] N. Valero-Pacheco, L. Arriaga-Pizano, E. Ferat-Osorio, L.M. Mora-Velandia, R. Pastelin-Palacios, M.A. Villasís-Keever, C. Alpuche-Aranda, L.E. Sánchez-Torres, A. Isibasi, L. Bonifaz, C. López-Macías, PD-L1 expression induced by the 2009 pandemic influenza A(H1N1) virus impairs the human T cell response, *Clin. Dev. Immunol.* 2013 (2013), <https://doi.org/10.1155/2013/989673>.
- [50] B. McNally, F. Ye, M. Willette, E. Flaño, Local blockade of epithelial PD-L1 in the airways enhances T cell function and viral clearance during influenza virus infection, *J. Virol.* 87 (2013) 12916–12924, <https://doi.org/10.1128/jvi.02423-13>.
- [51] J.A. Rutigliano, S. Sharma, M.Y. Morris, T.H. Oguin, J.L. McClaren, P.C. Doherty, P.G. Thomas, Highly pathological influenza A virus infection is associated with augmented expression of PD-1 by functionally compromised virus-specific CD8+ T cells, *J. Virol.* 88 (2014) 1636–1651, <https://doi.org/10.1128/jvi.02851-13>.
- [52] S. Wong, C. Oshansky, X. Guo, J. Ralston, T. Wood, Severe influenza is characterized by prolonged immune activation: results from the SHIVERS cohort study - PubMed, *J. Infect. Dis.* 217 (2018) 245–256, <https://doi.org/10.1093/infdis/jix571>.
- [53] M. Ehrenfeld, A. Tincani, L. Andreoli, M. Cattalini, A. Greenbaum, D. Kanduc, J. Alijotas-Reig, V. Zinserling, N. Semenova, H. Amital, Y. Shoenfeld, Covid-19 and autoimmunity, *Autoimmun. Rev.* 19 (2020), 102597, <https://doi.org/10.1016/j.autrev.2020.102597>.
- [54] B. Diao, C. Wang, Y. Tan, X. Chen, Y. Liu, L. Ning, L. Chen, M. Li, Y. Liu, G. Wang, Z. Yuan, Z. Feng, Y. Wu, Y. Chen, Reduction and functional exhaustion of T Cells in patients with coronavirus disease 2019 (COVID-19), *MedRxiv.* (2020), <https://doi.org/10.1101/2020.02.18.20024364>, 2020.02.18.20024364.
- [55] P. Ruscitti, O. Berardicurti, A. Iagnocco, R. Giacomelli, Cytokine storm syndrome in severe COVID-19, *Autoimmun. Rev.* 19 (2020), 102562, <https://doi.org/10.1016/j.autrev.2020.102562>.
- [56] J. Alijotas-Reig, E. Esteve-Valverde, C. Belizna, A. Selva-O'Callaghan, J. Pardos-Gea, A. Quintana, A. Mekiñian, A. Anunciacion-Llunell, F. Miró-Mur, Immunomodulatory therapy for the management of severe COVID-19. Beyond the anti-viral therapy: a comprehensive review, *Autoimmun. Rev.* 19 (2020) 102569, <https://doi.org/10.1016/j.autrev.2020.102569>.
- [57] R.H. Manjili, M. Zarei, M. Habibi, M.H. Manjili, COVID-19 as an acute inflammatory disease, *J. Immunol.* 205 (2020) 12–19, <https://doi.org/10.4049/jimmunol.2000413>.
- [58] H. Zhang, T. Wu, CD4+T, CD8+T counts and severe COVID-19: a meta-analysis, *J. Inf. Secur.* 81 (2020) e82–e84, <https://doi.org/10.1016/j.jinf.2020.06.036>.
- [59] B. Burt, Cyclosporine For The Treatment Of COVID-19(+) NLM identifier: NCT04492891 - ClinicalTrials.gov, (n.d.). <https://clinicaltrials.gov/ct2/show/NCT04492891> (accessed November 29, 2020).
- [60] L. Romani, C. Tomino, P. Puccetti, E. Garaci, Off-label therapy targeting pathogenic inflammation in COVID-19, *Cell Death Dis.* 6 (2020) 49, <https://doi.org/10.1038/s41420-020-0283-2>.
- [61] S. Goursaud, R. Descamps, C. Daubin, D. du Cheyron, X. Valette, Corticosteroid use in selected patients with severe acute respiratory distress syndrome related to COVID-19, *J. Inf. Secur.* 81 (2020) e89–e90, <https://doi.org/10.1016/j.jinf.2020.05.023>.
- [62] Irene Ramos, Ana Fernandez-Sesma, Modulating the innate immune response to influenza A virus: Potential therapeutic use of anti-inflammatory drugs, *Frontiers in Immunology* 6 (2015), 361, <https://doi.org/10.3389/fimmu.2015.00361>.
- [63] C. Huo, J. Xiao, K. Xiao, S. Zou, M. Wang, P. Qi, T. Liu, Y. Hu, Pre-treatment with zirconia nanoparticles reduces inflammation induced by the pathogenic H5N1 influenza virus, *Int. J. Nanomedicine* 15 (2020) 661–674, <https://doi.org/10.2147/IJN.S221667>.
- [64] S. Chen, G. Liu, J. Chen, A. Hu, L. Zhang, W. Sun, W. Tang, C. Liu, H. Zhang, C. Ke, J. Wu, X. Chen, Ponatinib protects mice from lethal influenza infection by suppressing cytokine storm, *Front. Immunol.* 10 (2019) 1393, <https://doi.org/10.3389/fimmu.2019.01393>.
- [65] I.F. Hung, K. Kai, W. To, J. Chan, K. Chan, K. Yuen, O0815 treatment of severe influenza A infection with celecoxib : a double-blind, randomised, controlled trial, in: *proc. 29th ECCMID 13-16 April 2019, Amsterdam* (2019) O0815.
- [66] US National Institute of Health, Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. <https://www.covid19treatmentguidelines.nih.gov/>, 2020 (accessed July 15, 2020).
- [67] P. Horby, W.S. Lim, J. Emberson, M. Mafham, J. Bell, L. Linsell, N. Staplin, C. Brightling, A. Ustianowski, E. Elmahi, B. Prudon, C. Green, T. Felton, D. Chadwick, K. Rege, C. Fegan, L.C. Chappell, S.N. Faust, T. Jaki, K. Jeffery, A. Montgomery, K. Rowan, E. Juszczak, J.K. Baillie, R. Haynes, M.J. Landray, R.C. Group, Effect of dexamethasone in hospitalized patients with COVID-19: preliminary report, *MedRxiv.Org the Prepr. Serv. Heal. Sci.* (2020), <https://doi.org/10.1101/2020.06.22.20137273>.
- [68] T. Tan, B. Khoo, E.G. Mills, M. Phylactou, B. Patel, P.C. Eng, L. Thurston, B. Muzi, K. Meeran, A.T. Prevost, A.N. Comminos, A. Abbara, W.S. Dhillon, Association between high serum total cortisol concentrations and mortality from COVID-19, *Lancet Diabetes Endocrinol.* 8 (2020) 659–660, [https://doi.org/10.1016/S2213-8587\(20\)30216-3](https://doi.org/10.1016/S2213-8587(20)30216-3).
- [69] M.K.S. Leow, D.S.K. Kwek, A.W.K. Ng, K.C. Ong, G.J.L. Kaw, L.S.U. Lee, Hypocortisolism in survivors of severe acute respiratory syndrome (SARS), *Clin. Endocrinol.* 63 (2005) 197–202, <https://doi.org/10.1111/j.1365-2265.2005.02325.x>.
- [70] G. Guaraldi, M. Meschiari, A. Cozzi-Lepri, J. Milic, R. Tonelli, M. Menozzi, E. Franceschini, G. Cuomo, G. Orlando, V. Borghi, A. Santoro, M. Di Gaetano, C. Puziolante, F. Carli, A. Bedini, L. Corradi, R. Fantini, I. Castaniere, L. Tabbi, M. Girardis, S. Tedeschi, M. Giannella, M. Bartoletti, R. Pascale, G. Dolci, L. Brugioni, A. Pietrangelo, A. Cossarizza, F. Pea, E. Clini, C. Salvarani, M. Massari, P.L. Viale, C. Mussini, Tocilizumab in patients with severe COVID-19: a retrospective cohort study, *Lancet Rheumatol.* (2020), [https://doi.org/10.1016/s2665-9913\(20\)30173-9](https://doi.org/10.1016/s2665-9913(20)30173-9).
- [71] C. Calabrese, P. Rajendram, G. Sacha, L. Calabrese, Practical aspects of targeting IL-6 in COVID-19 disease: Posted april 21, 2020, *Cleve. Clin. J. Med.* 87 (2020) 1–5, <https://doi.org/10.3949/CJIM.87A.CCC018>.
- [72] C.C. Price, F.L. Altice, Y. Shyr, A. Koff, L. Pischel, G. Goshua, M.M. Azar, D. Mcmanus, S.C. Chen, S.E. Gleeson, C.J. Britto, V. Azmy, K. Kaman, D. C. Gaston, M. Davis, T. Burrello, Z. Harris, M.S. Villanueva, L. Aoun-Barakat, I. Kang, S. Seropian, G. Chupp, R. Bucala, N. Kaminski, A.I. Lee, P.M. LoRusso, J. E. Topal, C. Dela Cruz, M. Malinis, Tocilizumab treatment for cytokine release syndrome in hospitalized COVID-19 patients: survival and clinical outcomes, *Chest.* 0 (2020), <https://doi.org/10.1016/j.chest.2020.06.006>.
- [73] R.B.M. Landewé, R.B.M. Landewé, P.M. MacHado, F. Kroon, H.W.J. Bijlsma, G. R. Burmester, L. Carmona, B. Combe, M. Galli, L. Gossec, L. Gossec, A. Iagnocco, J.D. Isaacs, X. Mariette, X. Mariette, I. McInnes, U. Mueller-Ladner, P. Openshaw, J.S. Smolen, T.A. Stamm, D. Wiek, H. Schulze-Koops, EULAR provisional recommendations for the management of rheumatic and musculoskeletal diseases in the context of SARS-CoV-2, *Ann. Rheum. Dis.* 79 (2020) 851–858, <https://doi.org/10.1136/annrheumdis-2020-217877>.
- [74] S. Davidson, Treating influenza infection, from now and into the future, *Front. Immunol.* 9 (2018) 1946, <https://doi.org/10.3389/fimmu.2018.01946>.
- [75] P. Sinha, M.A. Matthay, C.S. Calfee, Is a “cytokine storm” relevant to COVID-19? *JAMA Intern. Med.* (2020) <https://doi.org/10.1001/jamainternmed.2020.3313>.
- [76] Q. Ruan, K. Yang, W. Wang, L. Jiang, J. Song, Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China, *Intensive Care Med.* 46 (2020) 846–848, <https://doi.org/10.1007/s00134-020-05991-x>.
- [77] D.T. Teachey, S.F. Lacey, P.A. Shaw, J.J. Melenhorst, S.L. Maude, N. Frey, E. Pequignot, V.E. Gonzalez, F. Chen, J. Finklestein, D.M. Barrett, S.L. Weiss, J. C. Fitzgerald, R.A. Berg, R. Aplenc, C. Callahan, S.R. Rheingold, Z. Zheng, S. Rose-John, J.C. White, F. Nazimuddin, G. Wertheim, B.L. Levine, C.H. June, D. L. Porter, S.A. Grupp, Identification of predictive biomarkers for cytokine release syndrome after chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia, *Cancer Discov.* 6 (2016) 664–679, <https://doi.org/10.1158/2159-8290.CD-16-0040>.
- [78] M. Mandel, G. Harari, M. Gurevich, A. Achiron, Cytokine prediction of mortality in COVID19 patients, *Cytokine.* 134 (2020), 155190, <https://doi.org/10.1016/j.cyto.2020.155190>.
- [79] E. Grifoni, A. Valoriani, F. Cei, R. Lamanna, A.M.G. Gelli, B. Ciambotti, V. Vannucchi, F. Moroni, L. Pelagatti, R. Tarquini, G. Landini, S. Vanni, L. Masotti, Interleukin-6 as prognosticator in patients with COVID-19, *J. Inf. Secur.* 81 (2020) 452–482, <https://doi.org/10.1016/j.jinf.2020.06.008>.
- [80] T. Herold, V. Jurinovic, C. Amreich, B.J. Lipworth, J.C. Hellmuth, M. von Bergwelt-Baildon, M. Klein, T. Weinberger, Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19, *J. Allergy Clin. Immunol.* 146 (2020) 128–136.e4, <https://doi.org/10.1016/j.jaci.2020.05.008>.
- [81] X. Luo, W. Zhou, X. Yan, T. Guo, B. Wang, et al., Prognostic value of C-reactive protein in patients with COVID-19, *Clin. Infect. Dis.* (2020) ciaa641, <https://doi.org/10.1093/cid/ciaa641>.
- [82] Z. Wang, A. Zhang, Y. Wan, X. Liu, C. Qiu, X. Xi, Y. Ren, J. Wang, Y. Dong, M. Bao, L. Li, M. Zhou, S. Yuan, J. Sun, Z. Zhu, L. Chen, Q. Li, Z. Zhang, X. Zhang, S. Lu, P.C. Doherty, K. Kedzierska, J. Xu, Early hypercytokinemia is associated with interferon-induced transmembrane protein-3 dysfunction and predictive of fatal H7N9 infection, *Proc. Natl. Acad. Sci. U. S. A.* 111 (2014) 769–774, <https://doi.org/10.1073/pnas.1321748111>.
- [83] O. Zimmerman, O. Rogowski, G. Aviram, M. Mizrahi, D. Zeltser, D. Justo, E. Dahan, R. Arad, O. Touvia, L. Tau, J. Tarabeia, S. Berlinner, Y. Paran, C-reactive protein serum levels as an early predictor of outcome in patients with pandemic H1N1 influenza A virus infection, *BMC Infect. Dis.* 10 (2010) 288, <https://doi.org/10.1186/1471-2334-10-288>.
- [84] O. Karasahin, H.S. Özger, R. Harman, S.I. Yilmaz, Cut-off levels of CRP to predict outcomes in patients with influenza infection, *J. Clin. Diagn. Res.* 12 (2018) DC56–DC60, <https://doi.org/10.7860/JCDR/2018/35263.11695>.
- [85] K. Komiya, H. Ishii, S. Teramoto, O. Takahashi, N. Eshima, O. Yamaguchi, N. Ebi, J. Murakami, H. Yamamoto, J.I. Kadota, Diagnostic utility of C-reactive protein combined with brain natriuretic peptide in acute pulmonary edema: a cross sectional study, *Respir. Res.* 12 (2011), <https://doi.org/10.1186/1465-9921-12-83>.
- [86] M.J. Keller, E.A. Kitsis, S. Arora, J.-T. Chen, S. Agarwal, M.J. Ross, Y. Tomer, W. Southern, Effect of systemic glucocorticoids on mortality or mechanical

- ventilation in patients with COVID-19, *J. Hosp. Med.* 22 (2020), <https://doi.org/10.12788/jhm.3497>, 2020.
- [87] L. Quartuccio, A. Sonaglia, D. McGonagle, M. Fabris, M. Peghin, D. Pecori, A. De Monte, T. Bove, F. Curcio, F. Bassi, S. De Vita, C. Tascini, Profiling COVID-19 pneumonia progressing into the cytokine storm syndrome: results from a single Italian Centre study on tocilizumab versus standard of care, *J. Clin. Virol.* 129 (2020), 104444, <https://doi.org/10.1016/j.jcv.2020.104444>.
- [88] A. Kronbichler, M. Effenberger, M. Eisenhut, K.H. Lee, J. Il Shin, Seven recommendations to rescue the patients and reduce the mortality from COVID-19 infection: an immunological point of view, *Autoimmun. Rev.* 19 (2020), 102570, <https://doi.org/10.1016/j.autrev.2020.102570>.
- [89] L.M. Canziani, S. Trovati, E. Brunetta, A. Testa, M. De Santis, E. Bombardieri, G. Guidelli, G. Albano, M. Folci, M. Squadroni, G.D. Beretta, M. Ciccarelli, M. Castoldi, A. Lleo, A. Aghemo, L. Vernile, A. Malesci, P. Omodei, C. Angelini, S. Badalamenti, M. Ceconi, A. Cremonesi, C. Selmi, Interleukin-6 receptor blocking with intravenous tocilizumab in COVID-19 severe acute respiratory distress syndrome: A retrospective case-control survival analysis of 128 patients, *J. Autoimmun.* (2020) 102511, <https://doi.org/10.1016/j.jaut.2020.102511>.
- [90] A.R. Morrison, J.M. Johnson, K.M. Griebel, M.C. Jones, J.J. Stine, L.N. Hencken, L. To, M.L. Bianchini, A.T. Vahia, J. Swiderek, M.S. Ramesh, M.A. Peters, Z. R. Smith, Clinical characteristics and predictors of survival in adults with coronavirus disease 2019 receiving tocilizumab, *J. Autoimmun.* 102512 (2020), <https://doi.org/10.1016/j.jaut.2020.102512>.
- [91] Q. Zhao, M. Meng, R. Kumar, Y. Wu, J. Huang, Y. Deng, Z. Weng, L. Yang, Lymphopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a systemic review and meta-analysis, *Int. J. Infect. Dis.* 96 (2020) 131–135, <https://doi.org/10.1016/j.ijid.2020.04.086>.
- [92] Z. Ye, Y. Wang, L.E. Colunga-Lozano, M. Prasad, W. Tangamornsukan, B. Rochweg, L. Yao, S. Motaghi, R.J. Couban, M. Ghadimi, M.M. Bala, H. Gomaa, F. Fang, Y. Xiao, G.H. Guyatt, Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis, *Can. Med. Assoc. J.* 192 (2020), <https://doi.org/10.1503/cmaj.200645> cmaj.200645.
- [93] J.-W. Yang, L. Yang, R.-G. Luo, J.-F. Xu, Corticosteroid administration for viral pneumonia: COVID-19 and beyond, *Clin. Microbiol. Infect.* (2020) 1, <https://doi.org/10.1016/j.cmi.2020.06.020>.
- [94] J.I. Henter, K. Palmkvist-Kajiser, B. Holzgraefe, Y.T. Bryceson, K. Palmér, Cytotoxic therapy for severe swine flu A/H1N1, *Lancet.* 376 (2010) 2116, [https://doi.org/10.1016/S0140-6736\(10\)61345-1](https://doi.org/10.1016/S0140-6736(10)61345-1).
- [95] W.S. Lim, C. Brittain, L. Duley, S. Edwards, S. Gordon, A. Montgomery, J. Nguyen-Van-Tam, R. Read, D. Whitham, D. Whynes, M. Woodhead, D. Wootton, Blinded randomised controlled trial of low-dose adjuvant steroids in adults admitted to hospital with pandemic influenza (ASAP): a trial 'in hibernation', ready for rapid activation, *Health Technol. Assess. (Rockv.)* 19 (2015) 1, <https://doi.org/10.3310/hta19160>.
- [96] S. Li, Z. Hu, X. Song, High-dose but not low-dose corticosteroids potentially delay viral shedding of patients with COVID-19, *Clin. Infect. Dis.* (2020) ccaa829, <https://doi.org/10.1093/cid/ciaa829>.
- [97] X. Fang, Q. Mei, T. Yang, L. Li, Y. Wang, F. Tong, S. Geng, A. Pan, Low-dose corticosteroid therapy does not delay viral clearance in patients with COVID-19, *J. Inf. Secur.* 81 (2020) 147–178, <https://doi.org/10.1016/j.jinf.2020.03.039>.
- [98] T. Kewan, F. Covut, M.J. Al-Jaghbeer, L. Rose, K.V. Gopalakrishna, B. Akbik, Tocilizumab for treatment of patients with severe COVID-19: A retrospective cohort study, *EclinicalMedicine.* (2020) 100418, <https://doi.org/10.1016/j.eclinm.2020.100418>.
- [99] J.I. Kawada, Y. Kitagawa, N. Iwata, Y. Ito, Clinical characteristics of influenza virus infection in juvenile idiopathic arthritis patients treated with tocilizumab, *Mod. Rheumatol.* 23 (2013) 972–976, <https://doi.org/10.1007/s10165-012-0780-0>.
- [100] O. Dienz, J.G. Rud, S.M. Eaton, P.A. Lanthier, E. Burg, A. Drew, J. Bunn, B. T. Surat, L. Haynes, M. Rincon, Essential role of IL-6 in protection against H1N1 influenza virus by promoting neutrophil survival in the lung, *Mucosal Immunol.* 5 (2012) 258–266, <https://doi.org/10.1038/mi.2012.2>.
- [101] J.H. Stone, M.J. Frigault, N.J. Serling-Boyd, A.D. Fernandes, L. Harvey, A. S. Foulkes, N.K. Horick, B.C. Healy, R. Shah, A.M. Bensaci, A.E. Woolley, S. Nikiforow, N. Lin, M. Sagar, H. Schrager, D.S. Huckins, M. Axelrod, M. D. Pincus, J. Fleisher, C.A. Sacks, M. Dougan, C.M. North, Y.-D. Halvorsen, T. K. Thurber, Z. Dagher, A. Scherer, R.S. Wallwork, A.Y. Kim, S. Schoenfeld, P. Sen, T.G. Neilan, C.A. Perugino, S.H. Unizony, D.S. Collier, M.A. Matza, J.M. Yin, K. A. Bowman, E. Meyerowitz, A. Zafar, Z.D. Drobnik, M.B. Bolster, M. Kohler, K. M. D'Silva, J. Dau, M.M. Lockwood, C. Cubbison, B.N. Weber, M.K. Mansour, Efficacy of Tocilizumab in Patients Hospitalized with Covid-19, *N. Engl. J. Med.* (2020), <https://doi.org/10.1056/NEJMoa2028836>. NEJMoa2028836.
- [102] J.B. Parr, Time to reassess Tocilizumab's role in COVID-19 pneumonia, *JAMA Intern. Med.* (2020), <https://doi.org/10.1001/jamainternmed.2020.6557>.
- [103] O. Hermine, X. Mariette, P.-L. Tharaux, M. Resche-Rigon, R. Porcher, P. Ravaud, CORIMUNO-19 Collaborative Group, Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial, *JAMA Intern. Med.* (2020), <https://doi.org/10.1001/jamainternmed.2020.6820>.
- [104] C. Salvarani, G. Dolci, M. Massari, D.F. Merlo, S. Cavuto, L. Savoldi, P. Bruzzi, F. Boni, L. Braglia, C. Turrà, P.F. Ballerini, R. Sciascia, L. Zammarchi, O. Para, P. G. Scotton, W.O. Inojosa, V. Ravagnani, N.D. Salerno, P.P. Sainaghi, A. Brignone, M. Codeluppi, E. Teopompi, M. Milesi, P. Bertomoro, N. Claudio, M. Salio, M. Falcone, G. Cenderello, L. Donghi, V. Del Bono, P.L. Colombelli, A. Angehen, A. Passaro, G. Secondo, R. Pascale, I. Piazza, N. Facciolo, M. Costantini, RCT-TCZ-COVID-19 Study Group, Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial, *JAMA Intern. Med.* (2020), <https://doi.org/10.1001/jamainternmed.2020.6615>.
- [105] T. Huet, H. Beaussier, O. Voisin, S. Jouveshomme, G. Dauriat, I. Lazareth, E. Sacco, J.M. Naccache, Y. Bézie, S. Laplanche, A. Le Berre, J. Le Pavec, S. Salmeron, J. Emmerich, J.J. Mourad, G. Chatellier, G. Hayem, Anakinra for severe forms of COVID-19: a cohort study, *Lancet Rheumatol.* 2 (2020) e393–e400, [https://doi.org/10.1016/S2665-9913\(20\)30164-8](https://doi.org/10.1016/S2665-9913(20)30164-8).
- [106] G. Cavalli, G. De Luca, C. Campochiaro, E. Della-Torre, M. Ripa, D. Canetti, C. Oltolini, B. Castiglioni, C. Tassan Din, N. Boffini, A. Tomelleri, N. Farina, A. Ruggeri, P. Rovere-Querini, G. Di Luca, S. Martinenghi, R. Scotti, M. Tresoldi, F. Ciceri, G. Landoni, A. Zangrillo, P. Scarpellini, L. Dagna, Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study, *Lancet Rheumatol.* 2 (2020) e325–e331, [https://doi.org/10.1016/S2665-9913\(20\)30127-2](https://doi.org/10.1016/S2665-9913(20)30127-2).
- [107] A. Balkhair, I. Al-Zakwani, M. Al Busaidi, A. Al-Khribash, S. Al Mubaihsi, H. BaTaher, J. Al Aghbari, I. Al Busaidi, M. Al Kindi, S. Baawain, A. Al Alawi, A. Al Lawati, B. Al Rawahi, K. Al-Baimani, K. Al Zidi, N. Elfatih, B. Dawud, B. John, F. Rehman, F. Yousif, G. Al Khadouri, I. Saber, J. Lal, M. Gargouri, M. Al-Ward, N. AbuDraz, S. Al Ruqeishi, S. Kumar, W. Abdelmottaleb, Z. Al-Naamani, Z. Bin Nazar, O. Balkhair, Anakinra in hospitalized patients with severe COVID-19 pneumonia requiring oxygen therapy: results of a prospective, open-label, interventional study, *Int. J. Infect. Dis.* 0 (2020), <https://doi.org/10.1016/j.ijid.2020.11.149>.
- [108] J.D.H. Ong, A. Mansell, M.D. Tate, Hero turned villain: NLRP3 inflammasome-induced inflammation during influenza a virus infection, *J. Leukoc. Biol.* 101 (2017) 863–874, <https://doi.org/10.1189/jlb.4mr0616-288r>.
- [109] C.C. Garcia, W. Weston-Davies, R.C. Russo, L.P. Tavares, M.A. Rachid, J.C. Alves-Filho, A.V. Machado, B. Ryffel, M.A. Nunn, M.M. Teixeira, Complement C5 activation during influenza a infection in mice contributes to neutrophil recruitment and lung injury, *PLoS One* 8 (2013) 64443, <https://doi.org/10.1371/journal.pone.0064443>.
- [110] F. Khamis, I. Al-Zakwani, S. Al Hashmi, S. Al Dowaiqi, M. Al Bahrani, N. Pandak, H. Al Khalili, Z. Memish, Therapeutic plasma exchange in adults with severe COVID-19 infection, *Int. J. Infect. Dis.* 0 (2020), <https://doi.org/10.1016/j.ijid.2020.06.064>.
- [111] W.S. Choi, J.H. Baek, Y. Bin Seo, S.Y. Kee, H.W. Jeong, H.Y. Lee, B.W. Eun, E. J. Choo, J. Lee, Y.K. Kim, J.Y. Song, S.H. Wie, J.S. Lee, H.J. Cheong, W.J. Kim, Severe influenza treatment guideline, *Korean J. Intern. Med.* 29 (2014) 132–147, <https://doi.org/10.3904/kjim.2014.29.1.132>.
- [112] G.E. Aranda-Abreu, J.D. Aranda-Martínez, R. Araújo, M.E. Hernández-Aguilar, D. Herrera-Covarrubias, F. Rojas-Durán, Observational study of people infected with SARS-CoV-2, treated with amantadine, *Pharmacol. Rep.* 1 (2020) 3, <https://doi.org/10.1007/s43440-020-00168-1>.
- [113] F.J. Jiménez-Jiménez, H. Alonso-Navarro, E. García-Martín, J.A.G. Agúndez, Anti-inflammatory effects of amantadine and memantine: possible therapeutics for the treatment of Covid-19? *J. Pers. Med.* 10 (2020) 217, <https://doi.org/10.3390/jpm10040217>.
- [114] P.P. Singh Tomar, I.T. Arkin, SARS-CoV-2 E protein is a potential ion channel that can be inhibited by Gliclazide and Memantine, *Biochem. Biophys. Res. Commun.* 530 (2020) 10–14, <https://doi.org/10.1016/j.bbrc.2020.05.206>.
- [115] J.A. Tanner, B.J. Zheng, J. Zhou, R.M. Watt, J.Q. Jiang, K.L. Wong, Y.P. Lin, L. Y. Lu, M.L. He, H.F. Kung, A.J. Kesel, J.D. Huang, The adamantane-derived bananins are potent inhibitors of the helicase activities and replication of SARS coronavirus, *Chem. Biol.* 12 (2005) 303–311, <https://doi.org/10.1016/j.chembiol.2005.01.006>.
- [116] B. Cao, F.G. Hayden, Antiviral monotherapy for hospitalised patients with COVID-19 is not enough, *Lancet.* 396 (2020) 1310–1311, [https://doi.org/10.1016/S0140-6736\(20\)32078-X](https://doi.org/10.1016/S0140-6736(20)32078-X).
- [117] E.M. Behrens, G.A. Koretzky, Review: cytokine storm syndrome: looking toward the precision medicine era, *Arthritis Rheum.* 69 (2017) 1135–1143, <https://doi.org/10.1002/art.40071>.
- [118] P. Sarzi-Puttini, V. Giorgi, S. Sirotti, D. Marotto, S. Ardizzone, G. Rizzardini, S. Antinori, M. Galli, COVID-19, cytokines and immunosuppression: what can we learn from severe acute respiratory syndrome? *Clin. Exp. Rheumatol.* 38 (2020) 337–342.
- [119] T.O. First, Predictors of Mortality in Middle East Respiratory Syndrome (MERS), 2017, pp. 1–4.
- [120] Y. Zhang, J. Li, Y. Zhan, L. Wu, X. Yu, W. Zhang, L. Ye, S. Xu, R. Sun, Y. Wang, J. Lou, Analysis of serum cytokines in patients with severe acute respiratory syndrome, *Infect. Immun.* 72 (2004) 4410–4415, <https://doi.org/10.1128/IAI.72.8.4410-4415.2004>.
- [121] C.Y. Liu, L.J. Huang, C.H. Lai, H.P. Chen, T.L. Chen, C.P. Fung, C.Y. Liu, Clinical characteristics, management and prognostic factors in patients with probable severe acute respiratory syndrome (SARS) in a SARS Center in Taiwan, *J. Chin. Med. Assoc.* 68 (2005) 110–117, [https://doi.org/10.1016/S1726-4901\(09\)70231-X](https://doi.org/10.1016/S1726-4901(09)70231-X).
- [122] J.H. Ko, G.E. Park, J.Y. Lee, J.Y. Lee, S.Y. Cho, Y.E. Ha, C.I. Kang, J.M. Kang, Y. J. Kim, H.J. Huh, C.S. Ki, B.H. Jeong, J. Park, C.R. Chung, D.R. Chung, J.H. Song, K.R. Peck, Predictive factors for pneumonia development and progression to

- respiratory failure in MERS-CoV infected patients, *J. Inf. Secur.* 73 (2016) 468–475, <https://doi.org/10.1016/j.jinf.2016.08.005>.
- [123] P.R. Hsueh, P.J. Chen, C.H. Hsiao, S.H. Yeh, W.C. Cheng, J.L. Wang, B.L. Chiang, S.C. Chang, F.Y. Chang, W.W. Wong, C.L. Kao, P.C. Yang, D.S. Chen, Y.T. Lee, C. M. Teng, H.N. Ho, P.J. Chen, M.F. Chang, J.T. Wang, W.K. Wang, Patient data, early SARS epidemic, Taiwan, *Emerg. Infect. Dis.* 10 (2004) 489–493, <https://doi.org/10.3201/eid1003.030571>.
- [124] H. Mao, W. Tu, Y. Liu, G. Qin, J. Zheng, P.-L. Chan, K.-T. Lam, J.S.M. Peiris, Y.-L. Lau, Inhibition of human natural killer cell activity by influenza Virions and hemagglutinin, *J. Virol.* 84 (2010) 4148–4157, <https://doi.org/10.1128/jvi.02340-09>.