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Annual Update in Intensive Care and Emergency Medicine 2021

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Abbreviations

AKI	Acute kidney injury
APACHE	Acute Physiology And Chronic Health Evaluation
ARDS	Acute respiratory distress syndrome
COVID	Coronavirus disease
CRP	C-reactive protein
CRRT	Continuous renal replacement therapy
CSF	Cerebrospinal fluid
DO_2	Oxygen delivery
ECMO	Extracorporeal membrane oxygenation
GCS	Glasgow Coma Scale
ICU	Intensive care unit
IFN	Interferon
IL	Interleukin
LV	Left ventricular
MAP	Mean arterial pressure
NO	Nitric oxide
NOS	Nitric oxide synthase
PEEP	Positive end-expiratory pressure
RBC	Red blood cell
RCT	Randomized controlled trial
RRT	Renal replacement therapy
RV	Right ventricular
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOFA	Sequential organ failure assessment
TBI	Traumatic brain injury
TNF	Tumor necrosis factor
VAP	Ventilator-associated pneumonia

Part I

Sepsis

Effect of Sex and Gender in Sepsis and Septic Shock: A Narrative Review

1

A. Lopez, I. Lakbar, and M. Leone

1.1 Introduction

Most diseases are expressed differently in men and women. While nearly 80% of cases of autoimmune disease occur in women, cancer is more frequent in men. This sexual dimorphism effect is also present in infectious diseases [1], which are one of the leading causes of mortality in the world.

In the intensive care unit (ICU), sepsis and septic shock are frequent and still have high mortality rates, reaching 45% for patients with septic shock [2]. Patient outcomes seem to rely on different phenotypes [3]. Sexual dimorphism could be approached as a first step in the personalized management of septic patients.

In this narrative review, we describe sex differences in infectious diseases in patients admitted to the ICU.

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1.2 Epidemiology

Men are more likely to develop infectious disease than women, with a mean annual relative risk (RR) of 1.28 (95% confidence interval [CI] 1.24–1.32) [4]. Over the last decade, large-scale studies have reported a higher incidence of sepsis in men than in women [4]. To understand the extent of this challenge, one should know that the number of men admitted to the ICU for sepsis and septic shock is higher than the number of men admitted to the ICU for other medical reasons [5]. Despite this finding, a multicenter study did not find any differences in patient sex on the decision to admit to the ICU [6].

1.2.1 Source of Infection

Epidemiological studies suggest different susceptibility to infectious diseases according to sex (Fig. 1.1). Men are more likely to have lower respiratory tract infections than women [7], whereas sinusitis and tonsillitis occur more frequently in women than in men because of differences in respiratory tract anatomy [8]. Men are overrepresented among patients with severe bloodstream infections, with a relative risk of 1.3 (95% CI 1.1–1.6, $P < 0.05$) [9], and among patients

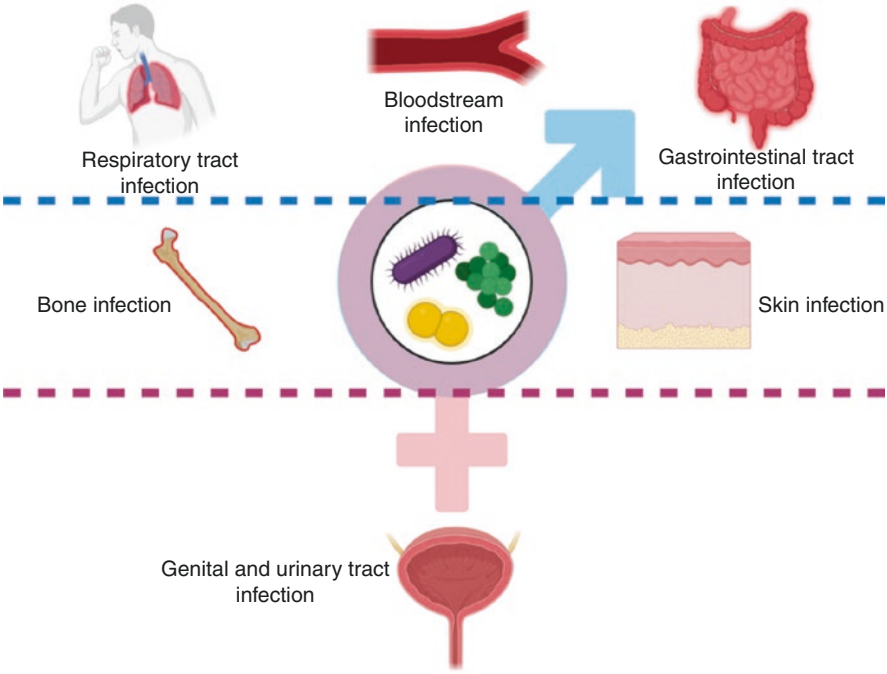

Fig. 1.1 Differences in source of infection according to sex

Table 1.1 Differences in sex distribution according to source of infection

Source of infection	Common causative bacteria	More frequent in
Respiratory tract	*Streptococcus pneumonia*	Men
	Chlamydophila pneumoniae	
	Legionella spp.	
	Mycoplasma pneumoniae	
	Mycobacterium tuberculosis	
	Pseudomonas aeruginosa	
	Acinetobacter baumanii	
Bloodstream	*Escherichia coli*	Men
	Staphylococcus aureus	
	Coagulase-negative staphylococci	
	Streptococcus pneumonia	
	Klebsiella spp	
Gastrointestinal tract	*Salmonella typhi*	Men
	Helicobacter pylori	
	Yersina enterocolitica	
	Escherichia coli	
	Enterobacteria	
	Enterococcus faecalis, Enterococcus faecium	
Urinary tract	*Escherichia coli*	Women
	Enterococcus spp.	
	Staphylococcus saprophyticus	
	Klebsiella pneumonia	

with digestive infections [10], probably in relation to differences in dietary and hygiene behavior between men and women. However, an animal study showed that the female intestinal mucosa was more resistant to hypoxia and acidosis than that of males and that the production of pro-inflammatory markers was increased in males. This production was decreased after administration of flutamide, a testosterone antagonist [11].

In contrast, women are more likely to develop urinary and genital tract infections than men. Differences in anatomy, physiology, and cell biology of the lower urinary tract may explain this finding. Moreover, the urinary microbiome and hormonal regulation may amplify the rate of urinary and genital tract infections in the female population [12]. Table 1.1 summarizes this sexual dimorphism in source of infection.

1.2.2 Sepsis and Septic Shock

Population-based cohort studies have identified an increase in the incidence of sepsis over time, probably due to an improvement in clinical diagnosis after the new Sepsis 3 definitions, but also to an increasing proportion of frail patients in the population [13]. In a recent review [14] of large multicenter studies, 54–61% of patients admitted to the ICU for sepsis or septic shock were men. Offner et al. identified male sex as an independent risk-factor for severe infections after trauma (odds ratio [OR] 1.58 [95% CI 1.01–2.48], $P = 0.04$) [15].

As the production of sex hormones evolves with aging, age interferes with the relationship between sex hormones and infectious diseases. In children, most studies show that sepsis distribution is similar in boys and girls. In adults, the widest difference in sepsis incidence between the sexes occurs between 25 and 30 years of age [16]. However, a small difference between male and female patients is still observed at extreme ages [16]. In elderly patients, sepsis tends to affect women at older ages than men [4].

1.2.3 Sepsis and Shock Septic Outcomes

Sepsis and septic shock are a worldwide public health problem. Sepsis involves life-threatening organ dysfunction, and has a global incidence of almost 50 million cases per year worldwide, with a mortality rate of nearly 20% [16]. In a meta-analysis, the frequency of septic shock was estimated at 10.4% for patients diagnosed at ICU admission and 8.4% for patients diagnosed at any time during an ICU stay [17]. In general, women seem to have better clinical outcomes than men, who have longer ICU and in-hospital lengths of stay [18]. A retrospective analysis of a large clinical database reported that male patients with sepsis were more likely to require mechanical ventilation ($P = 0.012$) and vasoactive agents (dopamine [$P = 0.113$], norepinephrine [$P = 0.016$], and epinephrine [$P = 0.093$]) during an ICU stay than women [18]. Men are also more likely to develop acute kidney injury than women [19].

All-cause ICU mortality and in-hospital mortality rates for septic shock are 37% and 39%, respectively [17]. In terms of differences according to sex, contrasting evidence is reported. Most epidemiological studies do not show sex differences in terms of sepsis-related deaths [20]. In a retrospective analysis of patients admitted to a polyvalent ICU, a higher mortality rate was found in older women with sepsis than in men [21]. However, age confounds the relationship between sex and mortality. In European countries, the median age at death in men in 2015 was 78 years, compared with 83 years in women [22]. Men are at higher risk of dying from major trauma, cancer, and cardiovascular diseases than women [1]. This can affect the findings associated with sepsis mortality.

1.2.4 Coronavirus Disease 2019 (COVID-19)

Another sexual dimorphism has recently been illustrated in ICUs around the world, with men developing more severe forms of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection than women. Men have been reported to be almost three times more likely to be admitted to the ICU with SARS-CoV-2 infection than women (OR = 2.84; 95% CI 2.06–3.92) [23], although this study was unable to adjust the data for sex differences in comorbidities. In a cohort of 1522 ICU patients, Moiseev et al. reported higher mortality rates in men over 50 years of

age than in women of the same age, although women had a higher occurrence of chronic diseases and comorbidities [24]. Therefore, sex disparities in disease severity may be explained by immune, hormonal, and chromosomal differences rather than by differences in comorbidities. Women exhibit higher CD4 T-cell counts and higher type I interferon (IFN-I) serum concentrations than men during viral disease [25]. IFN-I is believed to play a critical role in the immune response to SARS-CoV-2 infection [26]. On the other hand, estradiol reportedly stimulates humoral-mediated immune responses and increases the production of antibodies [26]. With respect to chromosome-bias differences, SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE-2), a protein encoded by X chromosome genes. Since ACE-2 is expressed differently in men and women, this may partly explain the lack of protection against SARS-CoV-2 in men [27].

1.3 Mechanisms Underlying Sex Differences

1.3.1 Animal Models

The effect of sexual dimorphism on infection has been determined by comparing males and females before and after castration. Males are less resistant to the development of endotoxic shock than females. The castration of males prevents this sexual dimorphism, but ovariectomy has no effect. The survival rate of females is higher than that of males and ovariectomized females in cecal ligation and puncture models [28]. In murine models, pro-inflammatory cytokines are higher in male than in female mice. In a murine model of intra-abdominal sepsis caused by injection of endotoxin, exogenous estradiol prevented organ oxidative damage [29].

Hence, sexual dimorphism reported in epidemiological studies is confirmed in experimental models of infection. A similar pattern has been found for most intracellular bacteria. Leone et al. showed that male and ovariectomized mice infected by *Coxiella burnetii* exhibited higher rates of tissue infection than female mice [30]. The susceptibility of male and ovariectomized female mice to *Mycobacterium avium-intracellulare* infection and resultant mortality were higher than those of females [31].

1.3.2 Sex Hormones

Merkel et al. showed excess mortality after induction of sepsis in ovariectomized female rats, which was corrected by the administration of estradiol; treatment with estradiol reduced mortality from 80% to 50% [32]. Female sex hormones seem to have a protective role and androgens an immunosuppressive action [1]. In animal models of infection, an immunosuppressive effect of androgens has been observed, resulting in worse outcomes in males [1].

Unfortunately, the picture at the bedside is more complex, with dual effects of sex hormones according to their concentrations. In the ICU, a high serum estradiol concentration is associated with increased mortality [33]. In elderly patients with infections, mortality is associated with elevated estradiol concentrations in both sexes [34]. At variance with previous studies, elevated testosterone concentrations were found in women who did not survive [34].

1.3.3 Chromosomes

The X chromosome supports not only many genes that affect sex hormone levels but also genes involved in the immune response. The X chromosome, X-linked genes, and X chromosome inactivation mechanisms contribute to male susceptibility to infectious diseases [35]. This observation arises from studies in autoimmune diseases. For example, an autoimmune female predisposition is found in systemic lupus erythematosus; indeed, the interleukin receptor-associated kinase 1 enzyme (IRAK-1), encoded by the X chromosome, is a risk factor for the occurrence of the disease [36]. In genetic chromosomal pathologies, there is a decrease in circulating T and B lymphocytes in Turner syndrome (45, X), but the opposite is noted in Klinefelter syndrome (47, XXY). Men with lowered serum testosterone concentrations exhibit immunoglobin levels close to those of healthy women [37]. In an experimental study on *Drosophila melanogaster*, X chromosome genes involved in the immune response were found to have a role in regulating bacterial load [38]. This can be a selective advantage for the female sex in the immune response to infection. The inactivation of the X chromosome during embryonic development in women is not complete, because 10% of the genes are not inactivated. Thus, this genetic dimorphism may give women a natural advantage over men in fighting infections.

1.3.4 Immune Response

Immune functions are affected by a specific sex response. Male and female lymphocyte cells possess sexual hormone receptors on their surface, which work as nuclear transcription factors [39]. Estrogens directly stimulate B-lymphocyte cells and antibody production. This explains the greater humoral immune response with higher levels of immunoglobins in women than in men [40]. Androgen receptors have also been described on the surface of immune cells. Testosterone reduces natural killer (NK)-lymphocyte cell activity and the production of pro-inflammatory cytokines by inhibiting the nuclear factor-kappa B (NF-κB) pathway. Testosterone has a negative control on Th1 differentiation, decreasing the production of IFNγ and tumor necrosis factor (TNF)-α, and increasing susceptibility to bacterial infection. Animal studies have observed a negative effect of testosterone also on the development of B-lymphocyte cells and thus on the development of antibody production [41].

1.3.5 Behavioral Factors and Gender Dimorphism

Exposure to pathogens and different social behaviors may interfere with the effect of sex in explaining differences between men and women. For a long time, smoking was more prevalent in men than in women [42] and was associated with an increased risk of respiratory diseases and infection [43]. Observational data may not discriminate between male groups and smoker groups among patients at high risk of infection; thus, the increased rate of infected men may be due to a higher prevalence of smokers among men than in women. This underlines the need for experimental investigations looking at the role of sex hormones in the process of infectious diseases.

Lifestyle is also influenced by gender. In a population of 761 adolescents, young girls did less physical exercise and had lower physical and psychological well-being but higher vegetable consumption and greater satisfaction from an educational context [44]. Such stereotypes may influence behavior and affect susceptibility to infection.

Gender inequalities also exist regarding access to healthcare. The prevalence of perceived unmet health care is significantly higher in women than in men. In 2019, the #LancetWomen movement was created to promote sex equality worldwide and highlight the inequalities in science, medicine, and global health between men and women [45].

In summary, the term 'sex' concerns biological features, chromosomes and hormone expression, whereas 'gender' refers more to social roles and human behavior (Fig. 1.2); both can influence the susceptibility and response to sepsis.

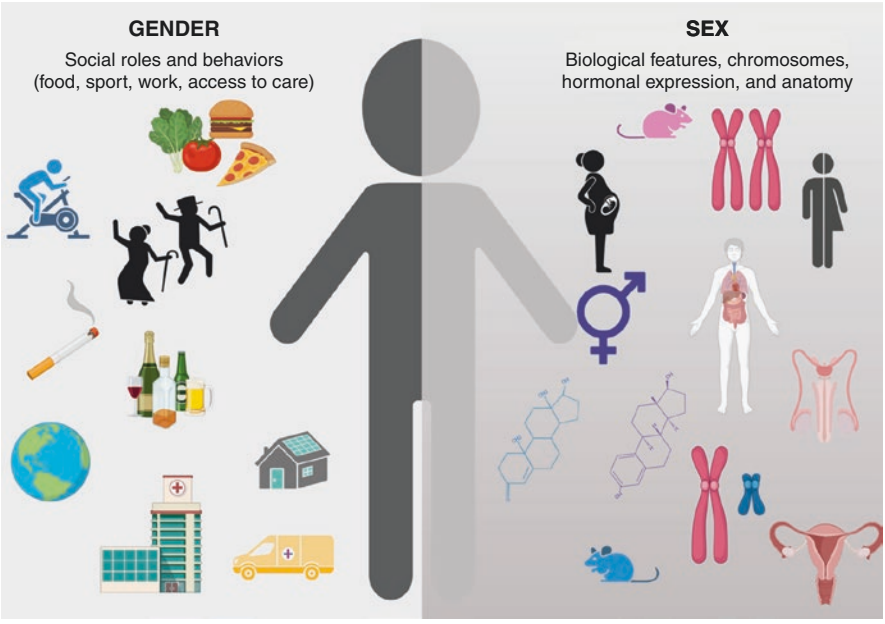

Fig. 1.2 Differences between gender and sex

1.4 Therapeutic Strategies and Sex Inequalities

Physicians should consider sex differences as the first step toward personalized management patient in sepsis. In an observational study on tuberculosis, women had a significantly longer delay before diagnosis and introduction of specific treatment [46]. In contrast, men had worse outcomes because of lower sputum culture conversion and higher mortality rates despite specific treatment [47]. These findings reflect a sexual dimorphism in patient management. In patients with septic shock, intravenous antimicrobials should be introduced as soon as possible after diagnosis [2]. However, the DISPARITY-II study found a delay of 31 min before antimicrobial onset in septic women compared with men after recognition of infectious sources [48]. This finding is in line with a nationwide cohort study, in which swifter diagnosis and shorter time to antibiotics were noted for men, without a significant difference in ICU nursing workload [49]. These findings justify the implementation of preventive protocols to reduce sex inequalities in health and wellbeing from an early age [45]. Finally, pharmacokinetics differs in men and women. In healthy volunteers, the median elimination half-life of Ringer's acetate was shorter in women than in men [50]. In animal studies, cardiac dysfunction during sepsis has been described in both sexes, but was more marked in male mice. Mathieu et al. compared the performance of landiolol, a short-acting beta-blocker, to prevent deleterious cardiac damage in male and female septic mice [51]. There were significant differences, with a dual effect being highlighted in males and females: whereas cardiac performance was improved in the male rats treated with landiolol, the treatment was deleterious in females. A sexual dimorphism of beta-receptors was described on tissue analysis [52]. This was related to sex hormones, because ovariectomy corrected this deleterious effect (personal data).

Regarding the effect of adjunctive corticosteroids during septic shock, hydrocortisone decreased the ICU length of stay and duration of mechanical ventilation in men compared to women, but no significant differences were found for outcomes, support therapy, or health-related quality of life [53]. It is still too early to direct therapy based on these findings; further multicenter studies are necessary.

1.5 Conclusion

Male sex predisposes to developing sepsis and septic shock. This difference between men and women seems to get worse until the onset of menopause in females, supporting a strong role for sex hormones. By contrast, the mortality of patients with sepsis is not affected by sex, probably because age confounds this outcome. Knowledge of sexual dimorphism mechanisms may offer an opportunity to personalize the management of patients with sepsis according to their age and sex.

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Complex Immune Dysregulation in COVID-19 and Implications for Treatment

2

M. Mouktaroudi and E. J. Giamarellos-Bourboulis

2.1 Introduction

The rise of the pandemic by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) generated a state of urgency within the medical community. This urgency was further aggravated by the accumulating number of critically ill patients admitted with acute respiratory distress syndrome (ARDS) and the considerable mortality. Early publications suggesting that the ARDS was associated with a storm of cytokines led to the administration of various anti-cytokine drugs for treatment. After several months of pandemic, data now suggest that complex immune phenomena exist in the host and they mandate a personalized approach for management. The purpose of this review is to focus on the change in the function of monocytes in severe coronavirus disease 2019 (COVID-19) and to propose therapeutic interventions for restoration of the immune function.

2.2 What Does Cytokine Storm Signify in COVID-19?

The dawn of the SARS-CoV-2 pandemic was followed by several publications describing increased concentrations of pro-inflammatory cytokines in the circulation of patients [1, 2], giving birth to the idea that hospitalized patients with severe or critical illness were suffering from cytokine storm syndrome. The real question is whether excess cytokine production is a unique feature for all patients with COVID-19 or whether the cytokine patterns in COVID-19 resemble what is seen in bacterial sepsis. Existing publications comparing the kinetics of cytokines in sepsis

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with those in COVID-19 are limited. In one, the distribution of pro-inflammatory cytokines, namely interleukin (IL)-1β, IL-6, IL-8, IL-18 and tumor necrosis factor-alpha (TNF-α) was compared in nine patients with severe COVID-19, 12 patients with ARDS due to SARS-CoV-2, and 16 patients with bacterial sepsis; no differences were found [3]. In another publication, IL-1β, IL-6 and IL-10 were measured in the plasma of critically ill patients; 20 patients had pneumonia due to SARS-CoV-2 and 20 patients had bacterial community-acquired pneumonia (CAP). Concentrations of IL-1β and IL-6 were greater in patients with critical COVID-19 than in those with bacterial CAP, whereas patients with bacterial CAP had significantly greater concentrations of IL-10. These findings suggest that one main feature of severe COVID-19 is a shift in the pro-inflammatory/anti-inflammatory balance of the host towards the pro-inflammatory spectrum [4].

It seems that, contrary to ARDS due to other causes, ARDS of COVID-19 origin is dominated by two main clusters of cytokines. The first is the cluster of C-X-C motif chemokine ligand 10 (CXCL10), granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-10 which drives progression to ARDS; the second is the cluster of IL-6, IL-1 receptor antagonist (IL-1ra), chemokine (C-C motif) ligand 20/macrophage inflammatory protein-3a (CCL20/MIP-3a), C-X3-C motif chemokine ligand 1 (CX3CL1) and IL-15, which drives organ dysfunction [5]. Cytokine concentrations increase when the disease is worsening but their comparative distribution in different patients is linear and is statistically better expressed in box plots showing individualized patterns. The increase in circulating cytokines follows the increase in circulating viral load and is accompanied by a decrease in monocytes and lymphocytes [6]. These findings suggest that COVID-19 is dominated by complex immune dysregulations that do not follow a unique pattern and in which individualization may play a major role. This individualization may arise from the different pattern of stimulation of monocytes that starts the inflammatory response of the host to an infectious trigger.

2.3 The Role of Monocytes

Circulating monocytes and tissue macrophages are the first line of host defence against the offending pathogens. The traditional paradigm from bacterial sepsis is that the interaction of pathogen-associated molecular patterns (PAMPs) of bacteria with pattern recognition receptors (PRRs) of monocytes and macrophages leads to the over-production of pro-inflammatory cytokines and to subsequent organ dysfunction. The detection of increased circulating levels of pro-inflammatory cytokines, namely of IL-6, at the start of the COVID-19 pandemic led to the assumption that these cytokines resulted from the excess stimulation of monocytes and macrophages by PAMPs of SARS-CoV-2. The described increase in the monocyte distribution width further corroborated this hypothesis [7].

Surprisingly, the addition of the spike S glycoprotein or of the entire viral particle of SARS-CoV-2 to the growth medium of monocytes does not stimulate high cytokine production. When cells are primed with one PRR ligand, the production of

IL-1β becomes marked. This is also accompanied by increased formation of caspase-1 [6], which is greater among patients who are receiving mechanical ventilation than among patients not on mechanical ventilation and which is also positively associated with the circulating levels of C-reactive protein (CRP) and IL-6. These findings suggest that early during the course of COVID-19 pneumonia, SARS-CoV-2 is able to act as a ligand for the NLRP3 inflammasome and this leads to over-production of caspase-1 and to the subsequent cleavage of pro-IL-1β to IL-1β [8]. The exaggerated production of IL-1β is also indirectly evidenced by the increased serum concentrations of ferritin in patients. High ferritin concentration is characteristic of the macrophage activation syndrome present in critically ill patients with sepsis [9] and is produced following the excess production of IL-1β by liver Kupffer cells. The hyperferritinemia of patients with COVID-19 led us to hypothesize that the macrophage activation syndrome may be a major element in the pathogenesis of the ARDS of COVID-19 caused by excess production of IL-1β.

Early during the course of the pandemic, we hypothesized that the progression of a patient with pneumonia from SARS-CoV-2 to ARDS was driven by two pathways: macrophage activation syndrome and complex immune dysregulation [10]. To classify patients, we used serum ferritin measured by an enzyme immunoassay and the expression of HLA-DR on circulating CD14-monocytes measured by flow cytometry. Macrophage activation syndrome was defined as serum ferritin >4420 ng/ml, as suggested in the past for sepsis [9]. Complex immune dysregulation was defined as an absolute number of HLA-DR molecules on CD14-monocytes of <5000 when ferritin was ≤4420 ng/ml. We compared patients with ARDS due to COVID-19 to patients with ARDS developing after bacterial CAP and found that contrary to bacterial CAP where most of the patients remain unclassified, all patients with COVID-19 ARDS could be classified into either macrophage activation syndrome or complex immune dysregulation. Macrophage activation syndrome was found in 25% of cases with COVID-19 ARDS and these patients also had increased hemophagocytosis scores (HScores). When monocytes with low HLA-DR expression in patients with complex immune dysregulation were stimulated for cytokine production, they retained their capacity to produce TNF-α and IL-6. The decrease in HLA-DR with maintenance of cytokine production is a unique immunological pattern that is different from the pattern of sepsis-induced immunosuppression in which monocytes defective for HLA-DR expression are unable to produce cytokines. This led us to name this new immune pattern, complex immune dysregulation. The decreased HLA-DR expression of complex immune dysregulation also drives the CD4-lymphopenia, CD8-lymphopenia, B-lymphopenia and hypoglobulinemia of ARDS COVID-19 [10].

Our findings have been corroborated by recent publications by other groups that described increased monocytes and decreased lymphocytes in the circulation of severe patients [11], increased monocytes in the alveolar space [12] and decreased CD4-lymphocytes in the alveoli [13]. These investigators described compartmentalized pro-inflammatory responses that were much more pronounced in the alveolar space than in the circulation. Inflammation in the alveoli is propagated over the time course of the disease as alveolar macrophages are replaced by monocytes migrating

from the circulation [12]. Using single-cell RNA sequencing, distinct clusters of monocyte activation were found in eight patients with mild COVID-19 and in 10 patients with severe COVID-19. Monocytes from patients with mild disease had aberrant expression of HLA-DR and remained potent for the production of antiviral cytokines. Monocytes from patients with severe disease had low HLA-DR expression and abnormal expression of alarmins [14].

2.4 From Pathogenesis to Treatment: Suggestion for an Individualized Approach

The dispersion within the ICU community of the idea that the pathogenesis of COVID-19 ARDS was driven by a storm of cytokines led to the clinical use of anakinra and tocilizumab for management. Anakinra is the recombinant human receptor antagonist of IL-1 and it blocks the action of both IL-1α and IL-1β. Tocilizumab blocks the receptor of IL-6. Mimicking the approach that was followed almost 30 years ago with sepsis, both agents were studied for *all* patients with critical COVID-19 without any selective approach.

A search in the PubMed database as of 15 February 2021, using the key-words "tocilizumab" and "COVID-19" and "clinical trials", retrieved 15 studies. We selected six of these studies because they reported clinical efficacy of tocilizumab in patients with severe or critical COVID-19 compared to controls. The six studies were either double-blind randomized clinical trials (RCTs), open-label RCTs or cohorts of patients using matched comparators [15–20]. Clinical benefit was reported in three of the studies. A summary of these studies is provided in Table 2.1. At the time this chapter was written, the results of the RECOVERY arm for patients receiving tocilizumab had not been published. According to the pre-print publication of the RECOVERY results [21], 2022 patients with COVID-19 receiving mechanical ventilation received one or two doses of tocilizumab and standard-of-care treatment, which included glucocorticoids; 2094 patients received standard-of-care treatment alone. The 28-day mortality rates were 29% and 33%, respectively (P = 0.007), showing a survival benefit from the addition of tocilizumab to glucocorticoids.

A search in the PubMed database as of 15 February 2021, using the key-words "anakinra" and "COVID-19", retrieved 150 studies. Six studies were selected because they reported on the clinical efficacy of anakinra using comparators [22–27]. Only one of these studies was an open-label RCT and the remaining were cohort studies with matched comparators. Clinical benefit was reported in five of the studies. A synopsis of these studies is provided in Table 2.2.

We believe that the selection of anakinra or tocilizumab as immunomodulatory treatment should be guided by biomarkers reflecting the mechanism of pathophysiology and the degree of severity. We have recently treated seven patients with ARDS COVID-19 and macrophage activation syndrome with intravenous

Table 2.1 Summary of the six published clinical trials of patients with COVID-19 treated with tocilizumab using parallel comparators

Reference	Design	Severity	Groups (n)	Primary endpoint	Efficacy (treatment vs. control)	Serious adverse events
[15]	RCT, open-label	Severe or critical	Standard-of-care (64) Standard-of-care + TCZ (65)	Death by day 15	3% vs. 17%	Study prematurely stopped for safety
[16]	RCT, double-blind	Hospitalized, without MV	Placebo (128) TCZ (249)	MV or death by day 28	19.4% vs. 12.0% (P = 0.04)	7.1% vs. 5.2%
[17]	RCT, double-blind	Hospitalized in need of oxygen	Standard-of-care (82) Standard-of-care + TCZ (161)	MV or death in time analysis	• Day 14: 10.0% vs. 9.9% • Day 28: 12.5% vs. 10.6%	• Neutropenia: 1.2% vs. 13.7% (P = 0.002) • Infections: 17.3% vs. 8.1% (P = 0.03)
[18]	RCT, open-label	Hospitalized, without MV	Usual care (67) Usual care + TCZ (63)	• Death, MV, NIV or HFO by day 14 • Death by day 28	• 35.8% vs. 23.8% (HR: 0.58; 95% CI: 0.30–1.11) • 25.3% vs. 26.9%	All reported: 43% vs. 32% (P = 0.210)
[19]	RCT, open-label	Hospitalized, without MV	Standard-of-care (66) Standard-of-care + TCZ (60)	Worsening into death or need for invasive ventilation	27.0% vs. 28.3%; prematurely stopped for futility	• All reported: 11.1% vs. 23.3% • Infections: 6.3% vs. 1.7%
[20]	Cohort using matched comparators	Patients with ≥2 of CRP >100 mg/l; ferritin >900 µg/l; D-dimer >1500 µg/l	Controls (86) Methylprednisolone for 5 days + TCZ if no response (86)	• Clinical improvement in WHO score by at least 2 points • Hospital mortality	• 51.2% vs. 74.4% (P = 0.0025) • 48.5% vs. 16.8% (P = 0.0004)	Bacterial infection: 8% vs. 9% (P = 0.787)

CRP C-reactive protein; *HFO* high-flow oxygen; *NIV* non-invasive ventilation; *MV* mechanical ventilation; *n* number of patients; *RCT* randomized clinical trial; *TCZ* tocilizumab; *vs.* versus; *WHO* World Health Organization

Table 2.2 Summary of the six published cohorts of patients with COVID-19 treated with anakinra using parallel comparators

Reference	Design	Severity	Groups (n)	Primary endpoint	Efficacy (treatment vs. controls)	Serious adverse events
[22]	Retrospective cohort with matching	Severe + CRP >100 mg/l or ferritin >900 ng/ml	Controls (56) ANA (56)	28-day survival	48.2% vs. 75.0% ($P = 0.007$)	Infections: 16.1% vs. 26.8% ($P = 0.260$)
[23]	RCT, open-label	Moderate or severe with no need for ICU	Usual care (57) ANA (59)	• Death or need of MV/NIV by day 4 • Survival without MV/NIV by day 14	• 38% vs. 36% • 54.5% vs. 51%	38% vs. 46% ($P = 0.450$)
[24]	Prospective, cohort	Severe + CRP >100 mg/l or ferritin >1000 ng/ml	Controls (55) Glucocorticoid + ANA (65)	28-day mortality	23% vs. 13.9% ($P = 0.004$)	Bloodstream infections: 7.3% vs. 13.8% ($P = 0.230$)
[25]	Retrospective cohort	Severe	Controls (24) ANA (45)	• Need for MV • In-hospital death	• 75% vs. 31% ($P < 0.0001$) • 46% vs. 29% ($P = 0.159$)	Bloodstream infections: 18% vs. 11% ($P = 0.461$)
[26]	Open-label, single arm with historical comparators	Severe	Controls (44) ANA (52)	MV and/or death	73% vs. 25% ($P < 0.0001$)	Increase of liver aminotransferases: 9% vs. 13%
[27]	Retrospective	Severe + CRP >100 mg/l or ferritin >900 ng/ml	Controls 16) ANA (29)	21-day mortality	44% vs. 10% ($P = 0.009$)	Bacteremia: 13% vs. 14%

ANA anakinra; *CRP* C-reactive protein; *ICU* intensive care unit; *NIV* non-invasive ventilation; *MV* mechanical ventilation; *n* number of patients; *RCT* randomized clinical trial; *vs.* versus

anakinra for 7 days; five patients improved by the end of treatment as demonstrated by increased baseline respiratory ratio and resolution of lung radiological opacities [28]. In the ESCAPE (Efficiency in management of organ dysfunction associated with infection by the novel SARS-Cov-2 virus through A PErsonalized immunotherapy approach) open-label trial, critically ill patients with COVID-19 received intravenous treatment with either anakinra or tocilizumab, based on their immune classification into macrophage activation syndrome or complex immune dysregulation. More precisely, 60 patients with macrophage activation syndrome or complex immune dysregulation and increased liver enzymes were treated with anakinra and 42 patients with complex immune dysregulation and normal liver enzymes were treated with tocilizumab. The primary study endpoint was either at least a 25% decrease in the baseline sequential organ failure assessment (SOFA) score or at least a 50% increase in the respiratory ratio by day 8. This endpoint was achieved in 58.3% of the patients treated with anakinra and 33.3% of the patients treated with tocilizumab ($P = 0.016$) [29].

The recent findings of monocytes highly expressing alarmins in severe COVID-19 [14] corroborates our hypothesis that progression into ARDS is a process of serial monocyte cell stimulation by alarmins produced by the bronchial tree upon invasion by SARS-CoV-2. These alarmins may be necessary for the priming of pro-IL-1β in monocytes and the subsequent cleavage to excess IL-1β through the SARS-CoV-2-stimulated NLRP3 inflammasome. We believe that concentrations of the biomarker soluble urokinase plasminogen activator receptor (suPAR) ≥6 ng/ml may indicate early which patients are likely to develop ARDS through exposure to alarmins. As a consequence, early treatment with anakinra driven by suPAR may block alarmins and prevent deterioration of these patients. We called this strategy SAVE (Suparguided Anakinra treatment for Validation of the risk and Early management of severe respiratory failure by COVID-19) and conducted a single-arm, open-label trial to demonstrate the safety and efficacy of anakinra administered as 100 mg once daily subcutaneously for 10 days to prevent progression into ARDS and need for mechanical ventilation (ClinicalTrials.gov Identifier: NCT04357366). As our comparators, we used parallel patients managed using standard-of-care in other departments of academic hospitals in whom the inclusion and exclusion criteria of the SAVE trial applied and who were propensity-score matched for age, comorbidities, admission severity scores (Acute Physiology and Chronic Health Evaluation [APACHE] II, SOFA, pneumonia severity index, WHO scale) and for treatment with azithromycin, hydroxychloroquine and dexamethasone. The incidence of ARDS after 14 days was 22.3% (95% confidence intervals [CI] 16.0–30.2%) among anakinra-treated patients and 59.2% (95% CI 50.6–67.3%) in the control group [30]. Following advice from the Emergency Task Force for COVID-19 of the European Medicine Agency, the pivotal, confirmatory phase III RCT with the acronym SAVE-MORE has been designed which is currently ongoing in 40 study sites; 32 sites in Greece and 8 sites in Italy (ClinicalTrials.gov Identifier: NCT04680949).

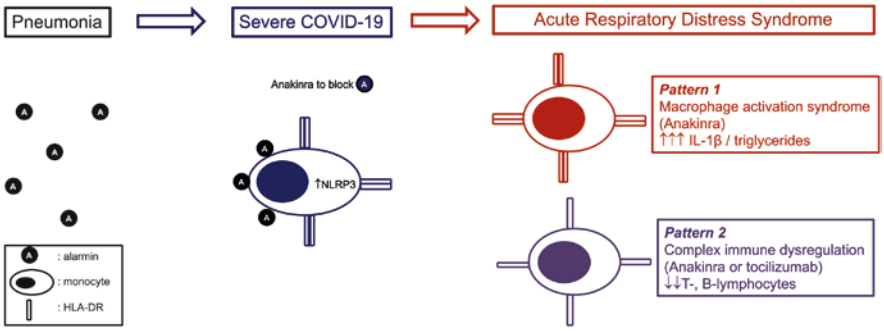

Fig. 2.1 Proposed mechanism of individualized pathogenesis in COVID-19
Pneumonia by SARS-CoV-2 stimulates the release of body alarmins. When severe disease emerges, alarmins stimulate monocytes and this is associated with activation of the NLRP3 inflammasome. The continuous alarmin stimulation leads to acute respiratory distress syndrome (ARDS) with the immune features either of macrophage activation syndrome or of complex immune dysregulation. Complex immune dysregulation is dominated by decreased expression of human leukocyte antigen (HLA)-DR on monocytes. Suggested immunomodulatory treatment directed on each target is given. *IL* interleukin

2.5 Conclusion

The above discussion suggests that there is heterogeneity in the pathogenesis of COVID-19 regarding the functional state of monocytes and their implications for the host. Different patterns seem to predominate upon transition from severe illness to ARDS and with different patterns of ARDS. The distinction of these different states of immune activation can only be done with the use of biomarkers and may help guide personalized immunotherapy (Fig. 2.1).

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