applied sciences

MDPI

Review

COVID-19 Lung Injury: Unique and Familiar Aspects of Pathophysiology

Stefan Hall [1,2], Geraint Berger [2] and Christian Lehmann [1,2,3,4,*]

[1] Department of Physiology and Biophysics, Faculty of Medicine, Dalhousie University, Halifax, NS B3H 4R2, Canada; shall@dal.ca
[2] Department of Anesthesia, Pain Management, and Perioperative Medicine, Faculty of Medicine, Dalhousie University, Halifax, NS B3H 4R2, Canada; gcberger@dal.ca
[3] Department of Pharmacology, Faculty of Medicine, Dalhousie University, Halifax, NS B3H 4R2, Canada
[4] Department of Microbiology and Immunology, Faculty of Medicine, Dalhousie University, Halifax, NS B3H 4R2, Canada
* Correspondence: chlehmann@dal.ca

Abstract: Acute lung injury (ALI), diagnosed clinically as acute respiratory distress syndrome (ARDS), refers to a spectrum of acute inflammatory processes culminating in increased permeability of the pulmonary alveolar–capillary barrier and impaired gas exchange. The pandemic caused by the novel coronavirus, SARS-CoV-2, has raised questions as to the similarities and differences between COVID-19 lung injury and ALI of other etiologies. This review summarizes current knowledge regarding the pathophysiology of ALI and COVID-19 lung injury and draws comparisons between the latter and other infectious etiologies of ALI. Indeed, severe COVID-19 is characterized by a unique array of disease mechanisms including suppression of interferon responses, widespread inflammasome activation, altered leukocyte phenotypes, and hyperactive thrombotic activity. Moreover, these mechanisms manifest as a unique clinical progression, which further differentiates COVID-19 from other viral respiratory pathogens such as SARS, MERS, and influenza. These unique features of COVID-19 pathophysiology bear important implications for current and future therapeutic strategies.

Keywords: COVID-19; acute lung injury; ALI; acute respiratory distress syndrome; ARDS

Citation: Hall, S.; Berger, G.; Lehmann, C. COVID-19 Lung Injury: Unique and Familiar Aspects of Pathophysiology. *Appl. Sci.* **2024**, *14*, 11048. https://doi.org/10.3390/app142311048

Academic Editors: Francesca Silvagno and Vittorio Gentile

Received: 27 September 2024
Revised: 18 November 2024
Accepted: 22 November 2024
Published: 27 November 2024

1. Introduction

Acute lung injury (ALI) refers to a spectrum of acute inflammatory processes culminating in increased permeability of the pulmonary alveolar–capillary barrier and impaired gas exchange. Clinically, ALI is diagnosed as acute respiratory distress syndrome (ARDS), a life-threatening condition characterized by acute non-cardiogenic pulmonary edema and respiratory insufficiency [1]. The currently accepted Berlin definition classifies ARDS as mild, moderate, or severe based on the degree of hypoxemia measured at a defined positive end-expiratory pressure (Table 1) [2]. Despite significant advancements in ARDS management, mortality has remained unacceptably high and ranges from 34.9% to 46.1% depending on severity [3].

ARDS etiology is varied and complex. While pneumonia and non-pulmonary sepsis are the most common causes, ARDS may arise from numerous other inciting factors originating within the lungs (i.e., direct lung injury) or elsewhere in the body (i.e., indirect lung injury) [4]. These include fungal pneumonias, aspiration of gastric contents, water inhalation, pulmonary contusion, pulmonary embolism, trauma, hemorrhagic shock, transfusion-associated lung injury, and pancreatitis [5]. Ventilator-induced lung injury (VILI) is also a significant contributor to lung injury but is often secondary to an inciting cause of ARDS [6]. Additionally, it is estimated that up to 21% of ARDS patients have mixed etiologies of lung injury [7].

Table 1. The Berlin definition of acute respiratory distress syndrome.

	Mild	Moderate	Severe
Timing	Within 1 week of a known clinical indult, or new/worsening respiratory symptoms		
Degree of Hypoxemia	200 mmHg < PaO_2/FiO_2 ≤ 300 mmHg	100 mmHg < PaO_2/FiO_2 ≤ 200 mmHg	100 mmHg ≤ PaO_2/FiO_2
PEEP Requirement	PEEP or CPAP ≥ 5 cm H_2O	PEEP ≥ 5 cm H_2O	PEEP ≥ 5 cm H_2O
Edema	Respiratory failure not fully explained by cardiac failure or fluid overload. Require objective assessment to exclude hydrostatic edema if no risk factors present		
Chest Imaging	Bilateral opacities, not fully explained by pleural effusions, lobar/lung collapse, or nodules		

The COVID-19 pandemic introduced in 2020 a novel etiology and massive increase in ARDS morbidity and mortality. In the first year, COVID-19 was associated with an unprecedented five-fold rise in ARDS-related deaths in the United States alone (this figure may be underestimated, as suggested by autopsy studies) [8]. At the time of writing this manuscript, there have been over 775 million confirmed cases of COVID-19 and over 7 million deaths [9]. Considering the high prevalence of ARDS in COVID-19 decedents, questions have been raised as to whether COVID-19 lung injury differs from other etiologies of ALI [10]. Indeed, COVID-19 lung injury involves distinct pathophysiological mechanisms that require a comprehensive comparison with other forms of lung injury. Mechanistic understanding of the differences and/or similarities defining COVID-19 lung injury is therefore indispensable for developing novel therapeutics and providing optimal care to patients. Although traditional causes of ALI, such as pneumonia and non-pulmonary sepsis, are well understood, COVID-19 lung injury introduces distinct pathophysiological features that necessitate a detailed comparison with other forms of lung injury. Consequently, this review aims to describe generalized pathophysiology of ALI, summarize current knowledge regarding the pathogenesis of COVID-19 lung injury, and compare COVID-19 lung injury to specific etiologies of ALI, including pneumonia and sepsis.

2. Pathophysiology of Acute Lung Injury

ALI can be characterized by numerous pathophysiological processes involving disruption of the alveoli [11]. To address the pathophysiology of ALI, this section describes the alveolar–capillary microenvironment, etiology and epidemiology, mechanisms of epithelial and endothelial injury and repair, and how these mechanisms impact respiratory physiology in the short and long term.

2.1. Cellular and Molecular Mechanisms of Lung Injury

The alveoli, otherwise known as the lung's functional respiratory unit, is critically involved in ALI (Figure 1). The alveoli are thin-walled air sacs approximately 200 µm in diameter composed of ultra-thin alveolar type 1 epithelial cells and surfactant-producing alveolar type 2 epithelial cells [12]. To facilitate gas exchange, the alveoli are surrounded by dense networks of pulmonary capillaries lined with pulmonary microvascular endothelial cells. Under normal physiological circumstances, epithelial and endothelial cells form tight barriers that actively restrict and modulate fluid flux to mitigate formation of edema [13]. This function is complemented by resident immune cells, including alveolar macrophages which employ phagocytic and anti-microbial functions to maintain a clear epithelial surface for gas exchange. During ALI, however, epithelial and/or endothelial insults activate host inflammatory responses leading to a breakdown of the barrier function, formation of alveolar edema, and impairment of gas exchange [11].

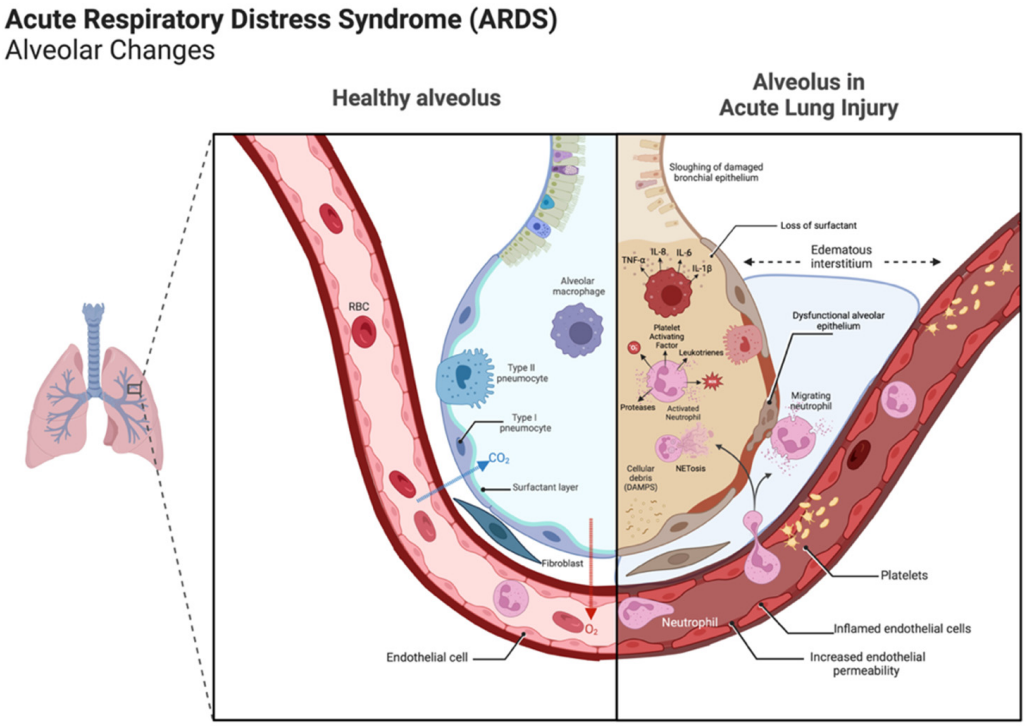

Figure 1. Alveolar changes during ALI. Under normal conditions (left), gas exchange is facilitated by a thin epithelial–endothelial barrier which is maintained by the collective functions of alveolar epithelial cells (pneumocytes), endothelial cells, and alveolar macrophages. During ALI (right), damage to the epithelial–endothelial barrier sets in motion a cascade of inflammatory processes that exacerbate tissue damage, accelerate edema formation, and critically impair gas exchange. Figure created with BioRender.com.

Primary damage to the alveolar–capillary barrier can occur from a wide variety of factors. For example, during pneumonia, the epithelium is initially damaged directly by pathogens through, e.g., bacterial pore-forming toxins or lytic viral replication [14,15]. Direct damage can also occur from hypercapnia or hyperoxia, which can impair the alveolar epithelium by inducing mitochondrial dysfunction and free radical formation. Moreover, mechanical stretch induced by positive-pressure ventilation can disrupt epithelial tight junctions and cause cellular detachment from the basement membrane. In parallel, the endothelium may be damaged initially by similar factors including pathogens, ventilator-induced mechanical stretch, and circulating inflammatory mediators [4]. Collectively, these and other insults directly impair the alveolar–capillary barrier function and initiate a cascade of inflammatory events, which favors the development of ALI.

Primary damage to the alveolar–capillary barrier, if significant, is followed by a wave of immune activation [11]. This is initiated by pattern recognition receptors (PRRs), which are activated by pathogen-associated molecular patterns (PAMPs, e.g., bacterial lipopolysaccharide) and damage-associated molecular patterns (DAMPs, e.g., extracellular DNA). Various PRRs are involved in ALI, including toll-like receptors (TLRs), retinoic acid-inducible gene-I-like receptors (RLRs), nucleotide-binding oligomerization domain-like receptors (NLRs), and C-type lectin receptors (CLRs), among others. Upon activation, PRRs initiate signaling cascades which drive release of pro-inflammatory mediators, production of anti-microbial agents, and induction of cell death pathways [1,16]. For example, numerous inputs stimulate NLRP3 inflammasome formation, which activates caspase-1, leading to cleavage of the cytokines interleukin (IL)-1β and IL-18 into their active forms [17]. Through binding IL-1R, IL-1β activates transcription of IL-6, IL-8, tumor necrosis factor (TNF), type 1 interferon (IFN-I), and other cytokines and chemokines. Caspase-1 also cleaves gasdermin D (GDSMD), leading to formation of plasma membrane pores and eventual pyroptosis.

Pyroptosis inherently causes release of DAMPs and other pro-inflammatory mediators, which further propagates the immune response [16]. These mechanisms signal through paracrine and autocrine mechanisms to augment the host immune response.

Elevated concentrations of pro-inflammatory mediators in the pulmonary milieu facilitates the recruitment of circulating leukocytes to participate in host defense. This process is initiated in pulmonary microvascular endothelial cells, wherein inflammatory cytokines induce destabilization of intercellular junctions, shedding of the endothelial glycocalyx, secretion of chemokines, and expression of leukocyte adhesion molecules such as intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, and dipeptidase 1 [18,19]. These changes facilitate the adhesion and diapedesis of circulating leukocytes such as neutrophils and monocytes, which migrate into the tissue along established C-X-C motif and/or C-C motif chemokine gradients [20]. The recruited leukocytes then employ a suite of antimicrobial tactics including phagocytosis, formation of extracellular traps (e.g., neutrophil extracellular traps, NETs), and secretion of proteases and reactive oxygen species (ROS) to attempt to neutralize the threat. While these functions may be beneficial or essential for host defense, they also consequently inflict significant damage to host tissues [21]. As tissue damage increases, pre-existing alveolar–capillary barrier dysfunction is exacerbated in an accelerating manner.

Breakdown of the alveolar–capillary barrier increases vascular permeability, leading to leakage of fluid and proteins into the alveolar space (i.e., edema). Alveolar edema is further exacerbated by damage to epithelial and endothelial cells which impair homeostatic alveolar and interstitial fluid clearance mechanisms [13,22]. Moreover, edema impairs the surfactant function, leading to increased surface tension and risk of atelectasis (alveolar collapse) [23]. In addition to impaired alveolar ventilation, ALI is often associated with impairment in pulmonary capillary perfusion due to coagulation and subsequent formation of physiologic dead space. In this process, activated endothelial cells initiate the extrinsic coagulation cascade via upregulation of tissue factor, leading to activation of thrombin and formation of fibrin clots [4]. Exposure of subendothelial collagen also leads to integrin- and glycoprotein receptor-mediated platelet binding [24]. Importantly, many coagulative mechanisms interact with the other pathomechanisms of ALI. For example, binding of thrombin to protease-activated receptor-1 (PAR_1) drives actomyosin shifts and increases in paracellular permeability. Moreover, neutrophils play a synergistic role in fibrin clot formation and stability through NETosis [19]. Thus, coagulation, while protective under normal conditions, can become an important contributor to the pathology of ALI [24].

2.2. Clinical Pathophysiology and Findings

Hypoxemia in ARDS fundamentally results from inadequate gas exchange between ventilated lung regions and perfused lung regions, and vice versa. A major driver of this failure is ventilation–perfusion (V/Q) mismatch, which occurs secondary to insufficient air or blood flow to a given lung region [1]. Insufficient ventilation results from alveolar edema or atelectasis, reducing the fraction of alveoli available to participate in gas exchange. These non-ventilated regions cause intrapulmonary shunts as unoxygenated blood bypasses the lungs and enters systemic circulation, contributing to an elevated V/Q ratio in that region [11]. Conversely, capillary microthrombi and pulmonary emboli reduce the fraction of perfused capillaries [4]. Since local alveoli are ventilated but unable to participate in gas exchange, increased pulmonary dead space decreases the V/Q ratio in the region. Overall, the presence of multiple regions of V/Q mismatch increases hypoxemia and hypercapnia resulting in respiratory acidosis and critically reducing the ability of supplemental oxygen to restore normal PaO_2 levels. Additionally, loss of compliance in edematous lung regions decreases total lung compliance and increases work of breathing (under non-invasive ventilation support) and regional overdistension (under mechanical ventilation), which can contribute to VILI. Consistent with this, increased pulmonary dead space and decreased compliance are predictive of mortality in ARDS [25].

Diffuse alveolar damage (DAD) is the prototypical histological finding associated with ALI [26]. The acute (exudative) phase of DAD is characterized by edema, formation of hyaline membranes, and infiltration of immune cells, and may last approximately 7 days. Following this, an organizing (proliferative) phase occurs which may last weeks to months in survivors [11]. Proliferation of alveolar type 2 epithelial cells is the defining feature of this phase. Importantly, while these two phases are sequential, they may display regional heterogeneity, with different tissue areas undergoing acute and organizing phases simultaneously as ALI progresses [11,26]. Furthermore, heterogeneity exists among ARDS patients. It has been reported that approximately half or less of autopsy and biopsy specimens from patients with ARDS fulfill criteria for DAD, while most others display histologic patterns of alveolar inflammation consistent with acute pneumonia [27,28]. The presence of DAD, however, was associated with higher mortality attributable to refractory hypoxemia [28].

Biomarker analyses of bronchoalveolar lavage fluid (BALF) and plasma in ARDS patients has provided insight into the mechanisms contributing to lung injury. Elevated plasma levels of surfactant protein D and RAGE are consistent with disruption and cell death, respectively, within the alveolar epithelial barrier [29,30]. Similarly, endothelial activation and coagulation are supported by plasma elevations in angiopoietin 2 and vWF and decreases in Protein C [31]. Most notably, elevated levels of the cytokines IL-1β, IL-6, IL-8, and TNF in plasma and BALF correlate with poorer outcomes, demonstrating the role of dysregulated inflammation in ARDS [32–35]. Cytokine analysis has played an important role in determining the role of low tidal volume lung-protective ventilation strategies in decreasing VILI-induced inflammation and improving outcomes [36]. The failure of any one pharmacotherapy to broadly improve outcomes in all ARDS patients has necessitated identification of subphenotypes that might respond differently to treatment. The most promising of these proposes a hyperinflammatory subphenotype, characterized by high levels of pro-inflammatory mediators and comprising approximately one-third of patients, and a hypoinflammatory subphenotype, with lower levels of pro-inflammatory mediators and comprising approximately two-thirds of patients. Consistent with this classification, analyses of multiple clinical trials have demonstrated that the two subphenotypes respond differently to fluid management, ventilation strategies, and anti-inflammatory treatment [34]. These findings are promising, although further research is warranted to establish mechanisms behind the different phenotypes and whether further subcategorization could be of therapeutic benefit.

It is imperative to consider that impairment and tissue injury associated with ARDS is not isolated to the respiratory system. While delineating directional causality between ALI and extrapulmonary organ dysfunction is challenging in critically ill patients with varying etiologies and comorbidities, the spectrum of pathophysiology in ARDS clearly bears harmful systemic effects. Most notably, patients with ARDS are at high risk of septic shock and multi-organ dysfunction [3]. This risk involves numerous factors including tissue hypoxia, translocation of respiratory pathogens, increased pro-inflammatory and pro-coagulative mediators, increased susceptibility to secondary infections, and perturbations in lung and gut microbiomes [37–40]. Undoubtedly, therapeutic strategies for ARDS will benefit from a greater understanding of protective and pathological crosstalk between organ systems involved in ALI.

Survivors of ARDS experience long-term sequelae characterized by deficits in quality of life related to physical and mental health [41]. Surprisingly, many survivors recover near-normal lung function by one-year post-discharge, a finding which is consistent with low percentages (<10%) of abnormal lung parenchyma upon radiological examination at this stage [42]. Nonetheless, survivors demonstrate reduced exercise capacity related to muscle wasting, weakness, and physical disabilities at both 1- and 5-year follow-up [41]. Furthermore, neuropsychological impairment is prevalent among ARDS survivors, with high incidence of post-traumatic stress disorder (28% at 5 years), depression (58% at 2 years), and executive dysfunction (55% at 1 year) [43–45]. Mechanistically, these impairments may

be driven by a number of factors related to critical illness, including hypoxemia, mechanical ventilation, profound deconditioning, and polypharmacy [41].

3. Pathogenesis of COVID-19-Induced Lung Injury

The mechanisms by which COVID-19 causes pulmonary and systemic disease have been an area of immense research in recent years. These efforts have contributed to both our understanding of COVID-19 and more broadly to our understanding of ALI. This section aims to summarize current knowledge regarding the pathogenesis of COVID-19 lung injury by focusing on key virus-mediated and host-mediated disruptions in immune activation, microvascular function, and respiratory physiology that drive progression to severe disease and death (summarized in Figure 2).

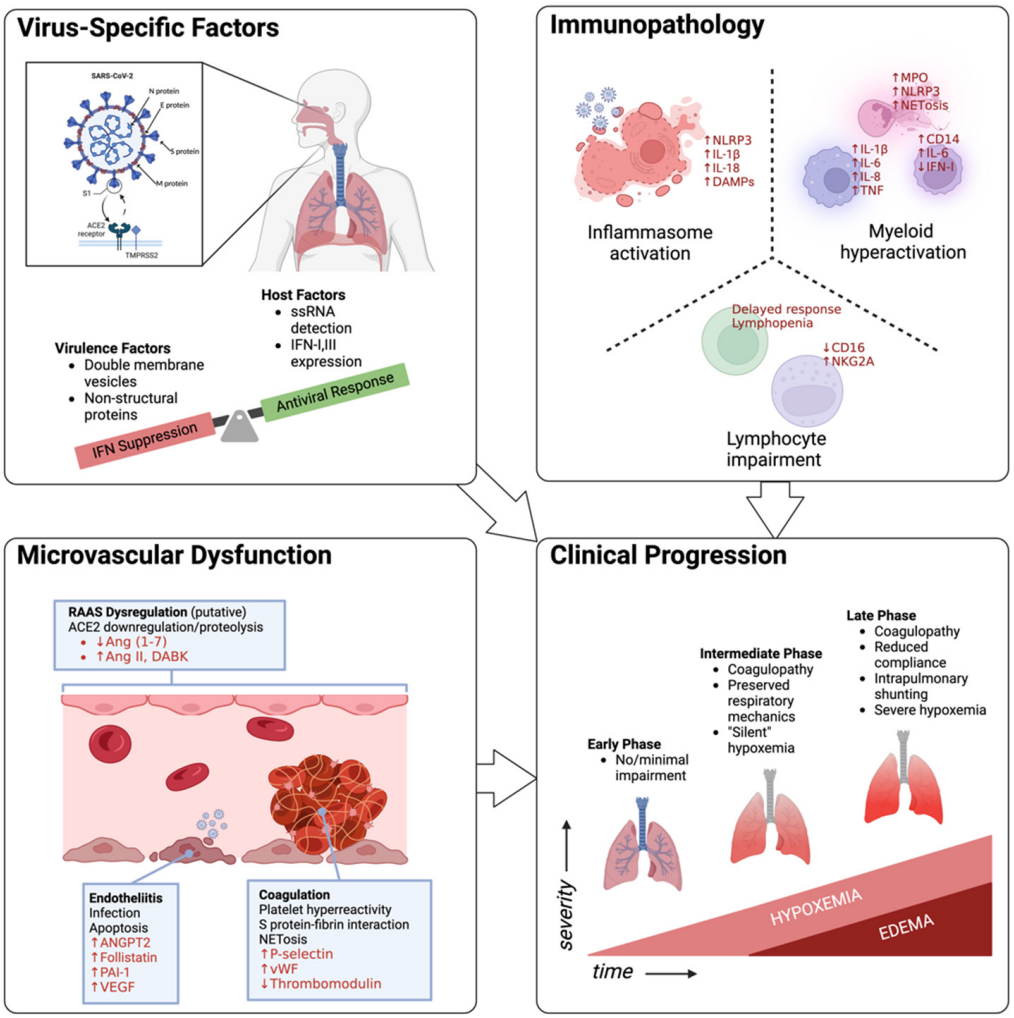

Figure 2. COVID-19 pathophysiology: a simplified representation. Upon gaining entry to host cells, SARS-CoV-2 (upper left) employs multiple strategies to suppress host antiviral responses, facilitating spread and infection of the lower respiratory tract. During severe infection, the host immune system (upper right) exhibits a deleterious hyperinflammatory innate phenotype combined with profound loss of function in cytotoxic/adaptive domains. Simultaneously, pulmonary and systemic microcirculation (bottom left) is impaired by dysregulated coagulation and aberrant endothelial inflammation. These pathological mechanisms contribute to a biphasic clinical progression characterized by early hypoxemia, which is exacerbated by accelerating alveolar edema. Figure created with BioRender.com.

3.1. Clinical Presentation and Epidemiology

Symptoms of COVID-19 infection range from asymptomatic to mild and moderate symptoms including cough and fever persisting for up to 14 days. However, some patients

develop severe disease characterized by lower respiratory tract infection and hypoxemia with associated lung pathology [46]. Patients in this stage can rapidly progress to critical condition including ARDS, septic shock, and multiple organ dysfunction [46]. While less common, COVID-19 can cause diverse extrapulmonary manifestations including anosmia, ageusia, gastrointestinal symptoms, myocardial dysfunction, and acute hepatic or kidney injury [47].

The epidemiology of COVID-19 lung injury is complex due to the dynamic nature of the pandemic. A retrospective cohort study of 201 patients with confirmed COVID-19 pneumonia in Wuhan, China, early in the pandemic found that 41.8% developed ARDS and 52.4% of those diagnosed with ARDS died [48]. More recent evidence suggests similar or lower mortality rates compared to non-COVID-19 ARDS, scaling with severity from 24% to 39%, which may reflect evolving care practices and the impact of vaccination [49]. Older age is a significant risk factor for severe disease and mortality, as are the presence of underlying comorbidities including hypertension, diabetes, cancer, and chronic kidney, heart, and/or lung disease [50]. Male individuals may also be at increased risk of severe disease and mortality [51].

3.2. Viral Structure, Tropism, Replication, and Evasion

SARS-CoV-2 is classified under the genus *Betacoronavirus* and exhibits the characteristic crown-like appearance attributed to viruses in the *Coronaviridae* family. Four canonical proteins—nucleocapsid (N), spike (S), membrane (M), and envelope (E)—form the structure of the virus. S protein, a transmembrane protein, contains the receptor-binding domain responsible for interaction with host cell receptors. M and E proteins also span the lipid bilayer viral envelope and have multiple functions including roles in viral assembly and budding. Inside the viral envelope, N protein interacts with and organizes the ~30 kb positive-sense single-stranded RNA genome and adopts important functions throughout the viral life cycle [52].

Coronavirus tropism is predominantly determined by the S protein structure, which in the case of SARS-CoV-2, displays a high affinity for the human angiotensin-converting enzyme 2 (ACE2) receptor. ACE2 is quite ubiquitous in the human body and is highly expressed in the upper respiratory tract, cardiac muscle, alveolar epithelium, vascular endothelium, liver, kidney, intestine, brain, testes, and immune cells [53]. As a result, SARS-CoV-2 displays a broad tropism and capability to impact numerous body systems, although initial infection typically targets the upper respiratory tract. Additionally, SARS-CoV-2 variants may differ in their tropism [54].

SARS-CoV-2 infection typically begins in multiciliated and sustentacular cells of the upper respiratory tract [55,56]. The viral replication cycle is initiated by binding of the S1 subunit to host ACE2. Next, host transmembrane protease serine 2 (TMPRSS2) cleaves the S protein, causing S2 subunit-mediated fusion of viral and host lipid bilayers and release of the viral RNA-N protein complex into the cytoplasm [52]. Notably, other cell entry routes including endocytosis and use of alternative co-receptors have been reported. Once inside the cell, SARS-CoV-2 exploits host ribosomes to synthesize a full suite of 16 non-structural proteins (NSPs). The NSPs form replication-transcription complexes (RTCs) and remodel the endoplasmic reticulum (ER) and Golgi apparatus to establish double-membrane vesicles (DMVs) that protect viral replication from innate immune detection. As new copies of structural proteins and RNA genomes are synthesized, fully formed SARS-CoV-2 virions are released via ER budding and exocytosis. The cytopathic replication cycle of SARS-CoV-2 can extend in this manner until cell homeostasis is sufficiently disrupted to trigger cell death pathways [57,58].

To induce severe illness, SARS-CoV-2 must infect the lower respiratory tract. In this environment, direct tissue damage mediated by viral replication largely determines the extent of tissue damage caused by activation of local and systemic inflammatory responses. Thus, the ability (or inability) to limit initial viral replication and propagation plays a critical role in determining disease severity [59]. Airway immune cells such as AMs and

plasmacytoid dendritic cells (DCs) play a key role in detecting endocytosed SARS-CoV-2 ssRNA. Infected epithelial cells can invoke cytosolic PRRs that identify non-self RNA PAMPs. The activated PRRs then induce IFN-I and IFN-III transcription [52]. These "early" IFNs signal through IFN-activated receptors (IFNARs) to induce transcription of IFN-stimulated genes (ISGs), promoting an antiviral cell-state which restrains infection through numerous mechanisms [59,60]. The importance of these signaling pathways in COVID-19 has been suggested by several studies. In vitro experiments have shown that SARS-CoV-2 is highly susceptible to IFN I treatment [61]. Consistent with this, patient samples from mild-to-moderate cases of COVID-19 show higher expression of ISGs than in patients with severe illness [62]. Thus, sufficient release of IFN-I and III early in infection may be an important determinant of COVID-19 severity [59].

Unsurprisingly, SARS-CoV-2 employs numerous tactics mediated by NSPs and accessory proteins to suppress the host's innate antiviral response. For example, through NSP–ribosome interactions, SARS-CoV-2 can selectively block translation of host mRNA while permitting translation of its own transcripts [63]. Other NSPs and accessory proteins collaborate to reduce IFN signal transduction at various steps by inducing JAK2 degradation, inhibiting STAT phosphorylation, and inhibiting phosphorylation and nuclear translocation of NF-κB and IRF3 [63,64]. Through these mechanisms (and others), SARS-CoV-2 is highly capable of suppressing the release of host IFN-I and III and facilitating replication. Severe COVID-19 has been associated with an impaired IFN-I response [65], and subsets of these patients have even been shown to express IFN-I autoantibodies [66,67]. Moreover, IFN-I autoantibodies have been shown to inhibit IFN signaling in monocytes and dendritic cells, suggesting that this process could impair the mounting of appropriate cellular immune responses [68].

3.3. COVID-19 Immunopathology

Efficient clearance of SARS-CoV-2 with minimal damage to the host requires a coordinated innate immune response to control infection and stimulate organization of a targeted adaptive immune response. In severe disease, however, numerous mechanisms cause dysregulation of the innate response, leading to significant immune-mediated damage affecting the lungs as well as other organ systems. Furthermore, the disturbed innate response leads to a late, ineffective adaptive immune response, setting the stage for critical illness [59].

Several studies point toward inflammasome activation as a key mechanism in COVID-19 immunopathogenesis [60,69,70]. This is supported by high association with disease severity in key mediators associated with inflammasome activation in serum and/or BALF. These include lactate dehydrogenase—an alarmin released during pyroptosis, IL1β and IL-18—cytokines cleaved by activated caspases, as well as a variety of cytokines strongly induced by IL-1β, including IL-6, IL8, and TNF-α [71,72]. By interrogating a combination of biomarkers, Tojo and colleagues identified increased alveolar epithelial necrosis in COVID-19 patients with vs. without ARDS. Using a 24 h experimental model of COVID-19 lung injury, the authors demonstrated significant involvement of pyroptosis and necroptosis—both of which are necrotic pathways activated by inflammasome formation [73]. The exact mechanisms of inflammasome activation in these contexts may be multifactorial, as evidence exists for both PRR-mediated DAMP detection and viral accessory protein mechanisms. These findings suggest that COVID-19 may induce extensive inflammasome activation early in the disease phase in both alveolar epithelial and endothelial cells. Moreover, viral suppression of IFN-I/III release likely exacerbates this phenomenon as unfettered viral replication would enhance inflammasome activation and alveolar epithelial necrosis [60].

Lung-resident macrophages are also subject to inflammasome activation. A recent study demonstrated a novel mechanism in lung macrophages induced by direct SARS-CoV-2 infection. Using isolated human lung macrophages and a humanized mouse model of COVID-19, Sefik and colleagues found that ACE2 and CD16-mediated infection led to

inflammasome activation, release of IL-1β and IL-18, and pyroptosis, driving significant lung inflammation [70]. Interestingly, inhibition of NLRP3 decreased lung pathology but led to the release of infectious virus, suggesting pyroptosis in infected macrophages is simultaneously virus-killing and immunopathologic [70]. These findings are consistent with depleted AMs in BALF of patients with critical COVID-19. Furthermore, the depleted AMs were replaced with large infiltrates of monocyte-derived macrophages which expressed inflammatory phenotypes characterized by expression of IL-1β, IL-6, IL-8, CXCL10, and TNF-α. Gene expression profiling of these macrophages was suggestive of hyperactivation due to similarity with the profiles of macrophage activation syndrome (MAS) and hemophagocytic lymphohistiocytosis (HLH) [74]. Thus, while AMs are vital in pulmonary immune homeostasis under normal conditions, SARS-CoV-2 infection appears to trigger inflammasome activation and pyroptosis of AMs, leading to lung pathology.

Circulating monocytes also play an important role in COVID-19 immunopathology. PBMCs isolated from patients with severe COVID-19 bear striking differences to those isolated from mild cases. Specifically, expression of surface markers in these PBMC populations skews towards $CD14^{high}$, $S100A^{high}$, $IL\text{-}6^{high}$, and $HLA\text{-}DR^{low}$, indicating high pro-inflammatory activity and low antigen-presenting capacity [74]. Furthermore, the hypoxemic milieu of severe COVID-19 can reduce PBMC antiviral activity via the transcriptional corepressor hypoxia-inducible factor-1α (HIF-1α). Under hypoxic conditions, HIF-1α was shown to attenuate HMGB1-induced synthesis of IFN-I but not IL-1β or TNF-α, suggesting that pro-inflammatory activity was not impacted [75]. To make matters worse, approximately 10% of PBMCs may be infected by SARS-CoV-2 via CD16-mediated uptake of antibody-opsonized virus, leading to abortive replication and pyroptosis [76]. These findings demonstrate that the circulating monocyte compartment is heavily shifted towards a pro-inflammatory phenotype in severe COVID-19 with reductions in virus-targeted activity.

Neutrophilia is a consistent finding in patients with severe COVID-19 and appears to be driven by the expansion of immature subpopulations. These immature neutrophils, identified via expression of CD11b/CD16/CD24/CD34/CD38, are suggestive of emergency myelopoiesis and display enhanced myeloperoxidase, inflammasome, HIF-1α, and NETosis activity [77]. NETosis appears to be a significant contributor to COVID-19 pathology and severity [78]. Functionally, NETosis has been experimentally induced in vitro using patient sera and has potential to induce widespread immunothrombosis and barrier disruption. The driving mechanism of this may be viral in nature, as S protein has been shown to induce NETosis in vivo, and it remains to be seen whether neutrophils, which express ACE2, can be directly infected by SARS-CoV-2 [79]. In addition to the immature subpopulation, multiple studies have isolated a myeloid-derived suppressor cell (MDSC)-like subpopulation shown to impede T cell proliferation and IFNγ production, suggesting a potential mechanism for the pathognomonic lymphopenia observed in severe COVID-19. Finally, while neutrophils (especially NETs) are prevalent in the pulmonary microcirculation in severe COVID-19, autopsy analysis suggests they may only be a potent infiltrator of alveolar spaces in a minority (25–50%) of cases [80]. Notably, there is a question whether the alveolar neutrophilia in some cases might have been attributable to secondary bacterial infection.

The function of other innate immune cells may also be compromised in severe COVID-19. Natural killer (NK) cells are depleted in the periphery and have been reported to display signs of functional exhaustion including increased expression of NK group 2 member A (NKG2A) and decreased expression of CD16, suggesting reductions in cytotoxicity and licensing activity, respectively [81]. Findings regarding pulmonary infiltration of NK cells are mixed and may be suggestive of recruitment late in disease course [82]. Plasmacytoid DCs are similarly depleted in the periphery and may increase in the lungs during later stages of disease. Of note, pro-apoptotic programming, reduced migration, and impaired IFN-I production may contribute to a reduced antiviral response [83]. Data regarding NK cells and DCs in severe COVID-19, however, appear to be consistent with reduced killing of infected cells and impaired activation of the adaptive immune response [59,64,74,82]. Additionally, recent single cell RNA sequencing data have suggested that monocyte-derived

soluble pro-inflammatory mediators could play a role in the development of a dysfunctional NK cell response [84].

The adaptive immune response plays a critical role in controlling infection and is typically activated within several days of symptom onset in COVID-19. Profound lymphopenia and exhaustion of CD4+ and CD8+ T cells have been frequently correlated with poor outcomes among patients with severe COVID-19 [59,67,85,86]. One possible mechanism behind this observation is migration to pulmonary tissues and resulting lung pathology. However, this concept conflicts with inverse association between T cell levels in BALF and mortality, suggesting a protective role of T cell responses within the lung parenchyma [52,71]. Alternatively, autopsies in COVID-19 fatalities have revealed extensive lymphocyte apoptosis in lymph nodes and in the spleen accompanied by hemophagocytic macrophages, which were proposed to induce apoptosis via high IL-6 expression [87]. In addition to cell-mediated immunity, the humoral response also plays a non-negligible role in COVID-19 given the high immunogenicity of SARS-CoV-2 proteins. However, low neutralizing antibody titers in a significant portion of recovered cases may suggest that cell-mediated adaptive responses are more critical for controlling infection [88,89]. Collectively, the data regarding adaptive immune responses in severe COVID-19 suggest impaired CD4+ and CD8+ responses contribute to poorer outcomes.

In summary, altered innate and adaptive immune responses are significant drivers of COVID-19 immunopathology. Severe COVID-19 is characterized by reduced IFN-I/III release and unfettered viral replication in the lung parenchyma, leading to widespread induction of inflammasome activation [60]. The effects of inflammasome activation are twofold: first, necroptosis and pyroptosis drive release of DAMPs which enhance inflammasome activation in a positive-feedback manner. Second, IL-1β release drives induction of an inflammasome-directed cytokine profile, including IL-6, IL-8, and TNF-α [69]. These factors coalesce to drive cell-mediated lung injury through infiltration of inflammatory monocyte-derived macrophages and widespread NETosis [76,90]. Finally, through a multitude of mechanisms including a blunted early IFN response, impaired stimulation by antigen-presenting cells, and induction of apoptosis, CD4+ and CD8+ lymphocytes are unable to mount a timely and effective response to infection [88]. These factors lead to a persistent infection coinciding with severe immunopathology, increasing the likelihood of critical disease and death [74].

3.4. Microvascular Dysfunction

Numerous studies point toward microvascular dysfunction in COVID-19 as a key contributor to hypoxemia and worse outcomes [91–99]. This phenomenon appears to involve endothelial dysfunction, coagulopathy, and dysregulation of ACE2.

Loss of barrier integrity and adoption of a pro-coagulative state in the vascular endothelium, termed endotheliitis, is proposed to be a major contributor to COVID-19 lung injury [100]. Plasma markers of endothelial injury (angiopoietin-2, follistatin, PAI-1) were elevated and demonstrated to have a strong mortality-predictive capacity in a study on hospitalized COVID-19 patients. VEGF was also shown to be increased and associated with intussusceptive capillary angiogenesis [101]. Mechanisms driving endotheliitis may be related to ACE2-mediated viral infection of endothelial cells, which has been observed in in vitro organoid models and on autopsy of lung and other organs [102]. Moreover, viral presence in autopsy samples colocalized with caspase-3 staining, indicating induction of endothelial apoptosis [103]. It is likely that host-mediated effects also drive the development of endotheliitis in severe COVID-19 via high levels of pro-inflammatory cytokines and DAMPs. Collectively, this shift in endothelial status has critical consequences for the host. In addition to impairing the alveolar–capillary barrier function, endotheliitis is suggested to cause the observed loss of hypoxic vasoconstriction in severe COVID-19, which exacerbates V/Q mismatch and hypoxemia [104].

The activated and disrupted endothelium acts synergistically with other processes to drive coagulopathy in COVID-19. Circulating levels of tissue factor-expressing extracellular

vesicles are associated with disease severity and incidence of venous thromboembolism (VTE) [105]. Possibly driven by the pro-inflammatory milieu or direct infection, platelets in COVID-19 are hyperreactive and display enhanced P-selectin expression and immune cell-aggregation capacity [106]. NETs also appear to be a massive contributor to coagulation due to high levels of tissue factor expression and findings of aggregated NETs occluding microvessels in autopsy studies [80]. Critically, upregulation of genes encoding pro-coagulative factors (e.g., vWF) were accompanied by downregulation of genes encoding anticoagulative factors (e.g., thrombomodulin) in COVID-19 patient BALF, signaling a profound shift to a procoagulative state [107]. These observed mechanisms of coagulation are consistent with autopsy findings of capillary microthrombi and high incidence of VTE (21–69%) in severe COVID-19 [108]. Furthermore, interactions among S protein, fibrin, and immune cells contribute to the formation of pro-inflammatory blood clots that exacerbate thrombotic inflammation and pathology [109,110].

Dysregulated ACE2 activity may also contribute to vascular dysfunction. ACE2 performs important hemostatic roles in the renin–angiotensin–aldosterone system (RAAS), by converting angiotensin II (ang II) to angiotensin (1-7) (ang (1-7)), and the kallikrein–kinin system (KKS), by inactivating des-Arg9-bradykinin (DABK). Consequently, ACE2 prevents build-up of both ang II and DABK, which could otherwise be detrimental to the host [53]. In the RAAS, Ang II exerts vasoconstrictive and pro-inflammatory effects via the angiotensin receptor 1 (AT1), whereas ang (1-7) exerts counterbalancing vasodilatory and anti-inflammatory effects via the MAS receptor. Meanwhile, in the KKS, DABK promotes vasodilation and vascular permeability via the bradykinin 2 receptor (B2R) [111]. Following SARS-CoV-2 binding, ACE2 is thought to be internalized and downregulated or proteolytically shed, leading to a soluble ACE2 (sACE2) [53,112]. These mechanisms reduce ACE2 activity and cause deleterious effects via ang II and DABK; however, clinical data have yet to show clear trends in COVID-19-induced changes in ACE2 expression or function [113]. Importantly, ACE2 appears to be protective based on in vivo experiments with SARS-CoV-1, and increased expression does not raise host susceptibility as demonstrated by a lack of risk in patients with medication (ACE inhibitors, angiotensin receptor blockers)-induced ACE2 upregulation [114,115]. Thus, available data suggest that dysregulated RAAS activity is an important contributor to microvascular dysfunction in COVID-19 [116].

Although these and other discoveries have significantly furthered our understanding of COVID-19-associated vasculopathies, there is still much that remains unknown. This was exemplified in a recent study using electric cell-substrate impedance sensing, in which the authors concluded that an unknown heat-labile component of COVID-19 patient plasma may drive endothelial permeability to a greater extent than known viral or host factors [117]. Further research may clarify this finding and provide greater insight into endothelial dysfunction in COVID-19 and other diseases.

3.5. Clinical Pathophysiology

Similar to the general pathophysiology of ARDS, hypoxemia in severe COVID-19 results from inadequacy in gas exchange between ventilated and perfused lung regions [1]. However, clinical observations have inspired the hypothesis that COVID-19 follows a distinct pattern of respiratory features that occur in chronological order. As proposed by Gattinoni and colleagues, early COVID-19 presents a type "L" phenotype characterized by low degrees of elastance (i.e., high compliance), V/Q ratio, lung weight, and recruitability, while deterioration leads to a type "H" phenotype characterized by a high degree of elastance, intrapulmonary shunting, lung weight, and recruitability [118]. As such, type H is typically consistent with a diagnosis of severe ARDS.

In the early stages of severe COVID-19, tissue injury appears to localize to the periphery of the lungs, consistent with coagulopathy and microvascular alterations observed in lung biopsies at this stage [119–122]. Conversely, a lack of hyaline membranes and preservation of lung weight, compliance, and recruitability at this stage is suggestive of a relative lack of alveolar edema [118]. Of note, alveolar type 2 epithelial hyperplasia has

been observed at this stage as well, likely replacing cytopathy within the alveolar epithelium [80]. Interestingly, patients in this stage may also present with profound hypoxemia but a notable lack of dyspnea, a paradoxical finding which has come to be termed "silent hypoxia" [123,124]. The mechanism for this phenomenon is proposed to involve impaired oxygen-sensing in the carotid body, and case reports of SARS-CoV-2 within the carotid body have emerged [124].

Progression of COVID-19 to critical stages may occur due to combined impacts of evolving pneumonia as well as patient self-inflicted lung injury (P-SILI) related to neurologically driven respiratory efforts during mechanical ventilation [125,126]. At this stage, increasing barrier dysfunction drives the development of alveolar edema, leading to reduced compliance while increasing lung weight and intrapulmonary shunting [118]. These features are consistent with findings on autopsy specimens which report DAD as the predominant histopathological finding of COVID-19 [80]. Notably, lymphocytes have been shown to be the primary inflammatory cell in lung specimens, and while neutrophils were observed in a percentage of cases, their presence may have been related to bacterial superinfection [80]. Microvascular dysfunction appears to be a key driver of respiratory failure at this stage as well. Functional respiratory imaging demonstrated that COVID-19 ARDS patients have markedly reduced blood volume in small caliber vessels relative to matched non-COVID-19 ARDS patients [127]. These factors contribute to the high mortality seen in the H-type phenotype.

Beyond lung injury, diverse extrapulmonary manifestations have been reported in COVID-19 patients. Myocardial dysfunction, including myocardial injury, acute coronary syndromes, arrhythmias, and other manifestations have been reported in 20–30% of hospitalized patients [47,97]. Renal injury is reported in up to 29% of cases and is often characterized by acute tubular injury and microvascular occlusions [80]. Neurological complications are among the most diverse and frequently reported manifestations, ranging from common mild symptoms, such as anosmia and fatigue, to rare and severe presentations, such as stroke and Guillain–Barre syndrome [47]. The mechanisms of these effects have been hypothesized to involve viral cytotoxicity, endotheliitis, immune dysregulation, and/or RAAS dysregulation [47]. COVID-19 is also associated with long-term complications which have been termed "long COVID" or post-acute sequelae of COVID-19 [128]. Long COVID encompasses a range of symptoms including gastrointestinal symptoms, memory loss, shortness of breath, and others. The mechanism of long COVID is likely related to autoimmunity and persisting viral particles and is thought to scale with acute disease severity [129]. Additionally, patients with long COVID were shown to have ongoing alterations in leukocyte populations and humoral responses relative to healthy controls [130]. While comparatively little is known at this stage, longitudinal studies will be critical in understanding the true long-term burden of this phenomenon.

4. Comparisons to Other Etiologies

Whether or not COVID-19 lung injury is similar or distinct from other ALI etiologies is a source of ongoing research and debate. COVID-19 displays broad similarities to the spectrum that is ARDS, including alveolar–capillary barrier dysfunction and the need for ventilatory support. However, variance in patient responses to certain therapies underscore the fact that COVID-19, and perhaps all causes of ALI, is not best treated using a "one size fits all" model. This chapter discusses differences in pathophysiology between COVID-19 lung injury and the three most historically frequent causes of ALI, namely, other viral respiratory pathogens, bacterial pneumonias, and non-pulmonary sepsis (summarized in Table 2).

4.1. Viral Respiratory Pathogens

Despite its unprecedented global impact, SARS-CoV-2 is a relative newcomer among viruses known to induce ALI. Influenza virus, respiratory syncytial virus (RSV), and other coronaviruses have historically been the most impactful [131]. Similar to SARS-CoV-2, the

ability of these pathogens to cause ALI is contingent upon infection of the lower respiratory tract, although as described below, resulting lung injury may differ in both mechanism and presentation [132].

COVID-19 is the third coronavirus of global significance to arise in little over two decades. SARS-CoV-1 and Middle East respiratory syndrome (MERS)-CoV emerged in 2002 and 2012, respectively, and combined have caused over 1500 deaths in the years since [133]. With 79.6% sequence homology to SARS-CoV-2, SARS-CoV-1 bears similarities including ACE2-mediated cell entry, which is similarly believed to induce RAAS derangement via the ang II-AT1 axis [134]. Indeed, many other features of SARS draw parallels to COVID-19 lung injury. For example, histological findings of DAD with monocytic and lymphocytic infiltrates, as well as systemic lymphopenia and thrombocytopenia, are consistent with COVID-19 pathogenesis [135]. Increased inflammatory cytokine release with reduced IFN-I production was associated with more severe ALI and may suggest a similar immunopathology, while high rates of pulmonary microthrombi (58%) and emboli (28%) suggest a similar degree of coagulopathy as in COVID-19 [136]. Notably, there is a higher mortality rate in SARS (10%), which may indicate more severe disease, although it is unclear what role evolving care practices may play in this [137]. MERS, on the other hand, is least similar among these three coronavirus diseases. MERS-CoV initiates cell entry via binding dipeptidyl-peptidase 4 (DPP4; a.k.a. CD26) [133]. Lung injury characterized by neutrophil and macrophage infiltrates is reported, and radiographic findings are consistent with viral pneumonia and ARDS. Additionally, MERS bears a high preponderance for renal injury, a feature which may be explained by direct infection, as kidney cells highly express DPP4 [137]. Similar to SARS and COVID-19, however, it is suggested severe disease involves a prolonged innate immune response and weaker adaptive response. The mortality rate for MERS has been reported at 40%, representing a massive increase relative to COVID-19 and SARS [137].

Influenza viruses are negative-sense single-stranded RNA viruses responsible for seasonal epidemics and occasional pandemics such as the 2009 H1N1 pandemic [132]. Influenza A viruses (IAV) are responsible for the latter and other pandemics and will be the focus here. The pathophysiology of influenza lung injury is similar to COVID-19 in some respects. IAV tropism, mediated by viral hemagglutinin and host sialic acid residues, has been demonstrated to include AECs, endothelial cells, and leukocytes [132,138]. In the early stage of infection, cell death (apoptosis, pyroptosis, and necroptosis have been observed) and IFN-I responses are induced in epithelial cells, while the virus employs several strategies to limit ISG activation and enhance replication [132,139]. As with COVID-19, host innate responses are a double-edged sword. Elevated production of inflammatory cytokines promotes inflammatory monocyte infiltration and contributes to disruption of the alveolar–capillary barrier [140]. In both COVID-19 and IAV, neutrophil activity is directed towards NETosis within the pulmonary microcirculation, whereas direct infiltration of the alveoli is less frequent. Indeed, microvascular dysfunction is similarly involved in the pathophysiology of IAV. Endothelial cells are suggested to be a primary contributor to cytokine production and leukocyte recruitment, and direct infection by several IAV strains has been observed [140,141]. Additionally, platelet activation and pulmonary thrombosis are a frequent finding in both experimental and clinical scenarios. However, several differences in clinical studies suggest IAV may exert considerably less pulmonary microvascular dysfunction relative to COVID-19. Autopsy analyses of lungs from COVID-19 patients revealed a 9-fold increase in prevalence of alveolar capillary microthrombi relative to lungs from IAV patients [92]. More recently, Kronibus et al. assessed respiratory parameters over a 16-day period in COVID-19 patients and matched IAV patients in ICU and observed declining and stable respiratory system compliance, respectively, in each group [132,142]. The temporal decline in compliance in COVID-19 patients in this study could result from widespread initial capillary microthrombi followed by increasing alveolar edema as the disease progresses. Conversely, comparatively stable compliance in IAV patients is not suggestive of major changes in alveolar edema. Thus, while COVID-19 and IAV share

similarities in tropism and immune response, available evidence supports the idea that COVID-19 lung injury is characterized by greater microvascular dysfunction and resultant pulmonary thrombosis.

RSV is an enveloped single-stranded RNA virus belonging to the family *paramyxoviridae* and constitutes a frequent cause of respiratory illness in pediatric and elderly populations [132]. The main target receptor of RSV is CX3CR1, which it uses to primarily infect respiratory epithelial cells from the trachea to the bronchioles, although it may also infect AECs, primary neurons, and immune cells [143]. Inside the host cell, RSV employs several pathogenic strategies to facilitate replication, including impairment of mitochondrial function and inhibition of IFN-I responses [144]. While these mechanisms bear similarity to SARS-CoV-2, RSV's method of inducing respiratory epithelial damage is markedly different. RSV causes fusion of epithelial membranes and development of syncytia, leading to sloughing of the respiratory epithelium and release of pro-inflammatory mediators [144]. While this may cause direct impairment of the alveolar-capillary barrier and edema, RSV is more classically characterized by bronchiolitis, with a "wheezing" phenotype [144]. Furthermore, unlike the mononuclear infiltrates frequently observed in COVID-19, neutrophils appear to be the primary responder in RSV, although eosinophils have been reported, resulting from previous G protein sensitization [143]. Endothelial involvement in RSV is not reported and contrasts sharply with the endotheliitis observed in COVID-19. Nonetheless, some degree of endothelial barrier dysfunction is evident considering observations of peribronchial thickening coinciding with ground-glass opacities and consolidation on chest radiography [145].

4.2. Bacterial Pneumonia

Compared to viral pathogens, bacterial pneumonias are typically characterized by more rapid disease onset. Bacterial pneumonia is classified as community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) and can be caused by diverse gram-negative or gram-positive species, each of which possess different virulence factors that drive infection and lung injury [146].

CAP is most often caused by *Streptococcus pneumoniae*, a gram-positive bacterium. *S. pneumoniae* is an extracellular pathogen and can induce damage to host cells through several mechanisms. Like many other bacteria, *S. pneumoniae* uses biofilm formation to modulate host inflammatory responses and evade phagocytosis [147]. Additionally, its pore-forming toxins such as pneumolysin and hemolysin compromise the epithelial barrier through induction of alveolar type 2 epithelial cell death and release of pro-inflammatory cytokines [15]. Similar to COVID-19, inflammasome activation appears to play an important role in pathogenesis, and NLRP3-deficient mice were shown to have better outcomes. IFN-I production has been shown to be beneficial to the host, although through an apparently different mechanism than COVID-19, involving protection of AEC2 cells [148,149].

Mycoplasma pneumoniae is an atypical bacteria and common cause of CAP, responsible for up to 40% of CAP in children over the age of 5 [149]. *M. pneumoniae* is predominantly an extracellular pathogen that binds to respiratory epithelial cells using a polarized attachment organelle [150]. This allows it to bind respiratory cilia, where it produces hydrogen peroxide and superoxide, promoting sloughing of epithelial cells injury. M. pneumonia also produces a unique exotoxin termed community-acquired respiratory distress syndrome (CARDS) toxin, which induces a potent inflammatory response, resulting in cell swelling, nuclear lysis, mucous proliferation, and cellular vacuolization [151].

Legionella pneumophila, a less common cause of CAP, is clinically distinct from other causes of bacterial pneumonia as well as COVID 19 ALI [152]. The presence of certain symptoms, mainly diarrhea and mental confusion, are much more common in *L. pneumophila* infection compared to other bacterial pneumonias [152]. *L. pneumophila* is a facultative intracellular bacterium that has a high propensity to invade alveolar macrophages. Its Dot/Icm type IV secretion system delivers effector proteins into the host, inhibiting phagosome–lysosomal fusion, therefore facilitating bacterial proliferation [153]. Interestingly, Legion-

naires disease produces distinctive histopathological findings. Erythroleukoplagocytosis is a hallmark finding, which reflects the intravascular hemolysis and leukopenia caused by infection [154]. Moreover, the scarcity of neutrophils in the alveolar exudate contrasts with the abundance of neutrophils that is commonly seen in other types of bacterial pneumonias [154].

HAP, which includes ventilator-associated pneumonia (VAP), can become a severe complication of pre-existing infections or illnesses in health care settings. The most common causative pathogens of HAP include *Pseudomonas aeruginosa* and *Staphylococcus aureus* [146]. *P. aeruginosa* is a gram-negative opportunistic bacterium that secretes several products that play a key role in its pathogenesis. These include exotoxins and exoenzymes that impair intercellular junctions in the epithelium and endothelium, as well as alkaline protease, which decreases the airway surface liquid through the activation of ENaC [147,155]. *S. aureus* is a gram-positive opportunistic aerobe which induces host epithelial damage through several mechanisms including hemolysin pore-forming toxins and a leukocytolytic exotoxin known as Panton–Valentine leukocidin (PVL). PVL is particularly insidious in the development of ALI and can induce epithelial necrosis of AEC1s as well as recruitment and degranulation of neutrophils [147].

Whereas COVID-19 is more often characterized by mononuclear infiltrates, neutrophils play a primary role in immune recruitment in early phases of most bacterial pneumonias [147]. Furthermore, the degree to which endothelial activation occurs in bacterial pneumonia appears to much less extensive than in COVID-19. While many patients present with a pro-coagulant phenotype, this may be complicated by the presence of other comorbidities and does not reflect the extensive endotheliitis and coagulopathy observed in COVID-19 [146]. Moreover, radiographic findings in COVID-19 point to a more diffuse pattern of ALI, whereas bacterial pneumonias commonly exhibit focal patterns of lung injury that may even be localized to individual lobes depending on the site of infection [146].

The contribution of bacterial pneumonias to super-infection in patients with viral pneumonia should also be mentioned. For example, it is well established that influenza, through modulation of the host immune system, increases the risk of bacterial co-infection [156,157]. Whether direct mechanisms occur in COVID-19 is not yet established, although indirect risks are suggested in patients treated with immunosuppressants [158]. Finally, while comorbidities confer increased susceptibility in COVID-19 and bacterial pneumonia, patients with impairments in muco-ciliary clearance (e.g., cystic fibrosis) have a long-established risk of bacterial pneumonia [147]. Conversely, mechanisms of these risks have not been fully elucidated in COVID-19, and this is an area of ongoing research.

4.3. Fungal Pneumonia

Respiratory fungal infections can also cause ALI and pose a significant clinical challenge, especially in immunocompromised patients. *Aspergillus*, *Cryptococcus*, *Pneumocystis*, *Candida* and endemic fungi are the most common sources of fungal infection in humans [159]. While these infections are rarely observed in healthy subjects, they can result in life-threatening illness in immunocompromised patients [159]. Innate myeloid cells, including macrophages, dendritic cells, and neutrophils are the initial responder to mycotic infection. NK cells also aid in controlling fungal expansion via direct and indirect killing of invading organisms, while Th1 and Th17 cells confer anti-fungal activity via the production of IFN-γ and IL-17 [159]. COVID-19 infection can induce significant lymphopenia, which in combination with immunosuppressant therapy, significantly increases the risk of opportunistic fungal infection [160]. COVID-19-associated fungal infections are associated with a 2-fold increase in ICU admission rates and a 4-fold increase in in-hospital death rates compared to non-COVID-associated fungal infection [161]. COVID-19-associated pulmonary aspergillosis (CAPA) and COVID-19-associated mucormycosis (CAM) are two well described fungal co-infections, with mortality rates reaching as high as 40–49% [162,163] In fungal infection, airway fibrinogenolysis and disruption of airway epithelial tight junctions by fungal proteases promote allergic inflammation, further sustaining lung pathol-

ogy [164]. This can result in airway obstruction due to the release of fibrinous material from damaged or dead cells, further reducing gas exchange and contributing to the hypoxic milieu [162,165].

4.4. Non-Pulmonary Sepsis

Sepsis is defined as life-threating organ dysfunction caused by a dysregulated host response to infection, and non-pulmonary sepsis is among the most common risk factors associated with development of ARDS [11,166]. Conceptually, sepsis-induced ALI differs from pneumonia-induced ALI in that the endothelial barrier is affected prior to the epithelium [167]. However, the severe endothelial disruption observed in COVID-19 lung injury raises questions as to whether its pathophysiology might closely resemble that of sepsis-induced ALI.

Both sepsis and severe COVID-19 demonstrate an exacerbated innate inflammatory response that contributes to the development of ALI. In sepsis, these responses are characterized by elevated plasma levels of an array of pro-inflammatory mediators including IL-1, IL-6, IL-8, and TNF-α, a similar profile reported in COVID-19 [10,69,167,168]. These cytokines and chemokines stimulate the activation of immune cells, especially neutrophils and monocytes which further contribute to inflammation through interacting with the endothelium, releasing antimicrobial agents and, in the case of neutrophils, undergoing NETosis [79,169]. In terms of immune cells infiltrating the lungs, unlike COVID-19, neutrophils are the predominant effector in sepsis, and alveolar neutrophil presence is associated with worse outcomes [167]. The acute hyper-inflammatory phase of sepsis is generally followed by a state of immune exhaustion characterized by severe lymphopenia with associated activation of programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) signaling [170]. Indeed, lymphopenia associated with elevated PD-1 is well reported in severe and critical COVID-19 [81]. Thus, there are important shared trends of innate and adaptive immune activation in sepsis and COVID-19. However, it should be emphasized that these trends have potential to be more heterogeneous in non-pulmonary sepsis due to multiple possible causative agents.

Endothelial activation is observed in both sepsis and COVID-19 but may be driven primarily by different mechanisms. Activation of TNF receptors and PAR-1, as well as decreased shear stress due to septic shock, are proposed to be key events in sepsis driving the shift to a pro-inflammatory and pro-coagulative state [171]. While these are also contributing factors in COVID-19, some reports suggest that direct infection by SARS-CoV-2 may be the most important factor. Nonetheless, ensuing barrier permeability and pro-inflammatory cytokine transcription in both cases point towards a similar phenotype of widespread endothelial activation. In keeping with this, both sepsis and severe COVID-19 are characterized by extensive coagulopathy [122]. Patients in both groups present with elevated D-dimer and PAI-1, the levels of which are correlated with poor outcomes [122,172,173]. In either case, NETosis plays a central role in coagulation through the exposure of histones, nucleic acids, and tissue factor, which promote platelet aggregation and clot formation [78,174]. Disseminated intravascular coagulation (DIC) is described as intravascular activation of coagulation with loss of localization and has been well reported in sepsis as a contributing factor to organ dysfunction and death [172]. DIC has been suggested to occur in COVID-19; however, some suggest that the latter represents a different phenotype due to significant contributions of intra-alveolar fibrin deposition [122]. Indeed, a novel definition for "COVID-19-associated coagulopathy" is a current area of focus. Differences aside, coagulation within the pulmonary microcirculation prompts the formation of capillary microthrombi and ensuing perfusion defects, worsening gas exchange.

Table 2. Comparison of COVID-19 to other etiologies of ALI.

Etiology	Virulence Profile	Immune Profile	Microvascular Profile	Clinical Profile
COVID-19 [46,52,60,80,89,142]	S protein ACE2-mediated entry Strong IFN-I inhibition	Inflammasome hyperactivation Hypercytokinemia (IL-1β, IL-6, IL-8, TNF) Lymphopenia	Thrombocytopenia NETosis/microthrombi RAAS dysregulation Reduced vasoreactivity	Viral pneumonia, DAD Main infiltrates: monocyte-derived macrophages, lymphocytes Biphasic progression
Severe Acute Respiratory Syndrome [132–134,136]	S protein ACE2-mediated entry IFN-I inhibition	Inflammasome hyperactivation Hypercytokinemia (IL-1β, IL-6, IL-8, TNF) Lymphopenia	Thrombocytopenia NETosis/microthrombi	Viral pneumonia, DAD Main infiltrates: monocyte-derived macrophages, lymphocytes
Middle East Respiratory Syndrome [132–134,137]	S protein DPP4-mediated cell entry IFN-I inhibition	Inflammasome hyperactivation Hypercytokinemia (IL-1β, IL-6, IL-8, TNF) Lymphopenia	Thrombocytopenia NETosis/microthrombi	Viral pneumonia, DAD Main infiltrates: monocyte-derived macrophages, neutrophils
Influenza A Virus [134,135,138,139]	Hemagglutinin Sialic acid-mediated cell entry IFN-I inhibition	Inflammasome hyperactivation Hypercytokinemia (IL-1β, IL-6, IL-8, TNF) Lymphopenia	Thrombocytopenia NETosis/microthrombi (lesser than COVID-19)	Viral pneumonia, DAD Main infiltrates: neutrophils, lymphocytes
Respiratory Syncytial Virus [143–145]	F/G glycoproteins CX3CR1-mediated cell entry IFN-I inhibition Syncytia formation	Varying cytokine responses	Not pathognomonic	Bronchiolitis, viral pneumonia Main infiltrates: neutrophils, eosinophils
Bacterial Pneumonia [146–148]	Biofilm formation Pore-forming toxins Exotoxins/exoenzymes	Inflammasome hyperactivation Varying cytokine responses	Not pathognomonic	Various phenotypes of lung injury Main infiltrates: neutrophils
Fungal Pneumonia [159,160,165]	Biofilm formation Tissue invasion by hyphae	Varying cytokine responses	Not pathognomonic	Various phenotypes of lung injury Main infiltrates: neutrophils
Non-Pulmonary Sepsis [38,39,166,167]	Various	Hypercytokinemia (IL-1β, IL-6, IL-8, TNF) Lymphopenia	Thrombocytopenia NETosis/microthrombi DIC Reduced shear stress (shock)	Diffuse lung injury Main infiltrates: neutrophils

5. Therapeutic and Supportive Strategies for COVID-19

The COVID-19 pandemic stimulated a concerted global effort to develop novel therapeutics, repurpose approved medications, define optimal supportive strategies, and create effective vaccines to reduce disease burden. Many drugs have shown promise either conceptually or pre-clinically, only to fall short in large-scale clinical trials. Other treatments have demonstrated success, with the caveat that ARDS has been and remains associated with extremely high mortality rates. Recently, our increasing understanding of COVID-19 has provided rationale for the outcomes of some of these trials and has emphasized the importance of timing and patient factors in selecting appropriate therapies. This section provides a brief overview of supportive measures and relevant drug therapies which have been recommended and trialed in COVID-19 patients.

5.1. Ventilatory Support

Since hypoxemic respiratory failure is the primary cause of death in COVID-19, ventilatory support is potentially the most vital aspect of patient care. Numerous factors such as timing, method, positioning, and respiratory mechanics may all play a role in determining outcomes, highlighting the need for high quality evidence to inform such decisions.

The goal of oxygen supplementation is to correct hypoxemia and consequently prevent hypoxia and damage to vital organs [123]. For patients with severe COVID-19, the WHO recommends maintaining SpO_2 > 90%, which may be achieved through the use of a high-flow nasal cannula (HFNC) or non-invasive ventilation (NIV) [175]. HFNCs and NIV are important intermediate measures as they reduce requirement of invasive mechanical ventilation (IMV), which is associated with risk of VILI [1]. Notably, NIV and HFNO were trialed in 1273 patients, and only the former reduced occurrence of tracheal intubation or mortality compared to conventional oxygen therapy (36% vs. 44%) [176]. Additionally, an important hazard to avoid when using a HFNC or NIV is hyperoxygenation, which is associated with toxic effects in the lungs and other tissues [123].

If non-invasive oxygen supplementation fails, IMV must be used to oxygenate the patient, which prompts consideration of a range of parameters. Research has identified the importance of lung-protective ventilation strategies characterized by low tidal volumes (4–8 mL/kg predicted body weight), low plateau pressures (<30 cmH_2O), and adequate positive end-expiratory pressure (PEEP; 5–20 cmH_2O). These factors help to limit VILI by reducing regional overdistension of alveoli and atelectasis [11]. Prone positioning is a simple but highly effective tool for correcting regional V/Q mismatch deficits and has been recommended for 12–16 h per day in patients with severe ARDS [177]. Additionally, conservative fluid management, neuromuscular blockade, and pulmonary vasodilators can be useful in managing ventilated patients [178]. Finally, if lung-protective IMV and associated measures are insufficient to maintain oxygenation, extracorporeal membrane oxygenation (ECMO) can be a life-saving therapy.

5.2. Pharmacotherapy Targeting SARS-CoV-2

Significant research in recent years has focused on identifying compounds with antiviral activity against SARS-CoV-2. However, translating this research to effective, well-tolerated antiviral effects in humans remains challenging. Remdesivir, nirmatrelvir, and molnupiravir have been among the most effective antivirals to date.

Remdesivir, a nucleoside analog prodrug, inhibits RNA viruses by competing with ATP, hindering viral RNA replication [179]. Three clinical trials (ACTT-1, PINETREE, Solidarity) have demonstrated benefit with remdesivir treatment compared to placebo and may point towards the importance of appropriate timing and patient criteria in treatment effectiveness. In these studies, remdesivir was shown to shorten the time to recovery in hospitalized patients (10 days vs. 15 days), reduce hospitalization or death in high-risk outpatients (1.6% vs. 8.3%), and reduce mortality in non-ventilated (at entry) hospitalized patients (11.9% vs. 13.5%) [180–182]. Interestingly, in the latter study, no benefit was observed in patients who were already ventilated at entry. This could suggest immunopathology, and not viral replication, as the main contributing factor to disease progression once mechanical ventilation is required. The 87% lower risk of hospitalization or death in the outpatient cohort is consistent with a more beneficial effect in early stages of COVID-19 [181].

Another oral prodrug, molnupiravir, incorporates into newly synthesized viral RNA as N4-hydroxycytidine and induces transcription errors [183]. These errors cause non-functional proteins which accumulate and worsen with each replication cycle, leading to non-functional virions. Molnupiravir was trialed in 1433 outpatients with mild-to-moderate COVID-19 and significantly reduced the primary outcome of hospitalization or death compared with placebo (6.8% vs. 9.7%) [184]. Notably, a point of concern has been raised regarding the mechanism of action of molnupiravir, since partially functional proteins could confer resistance over time. However, this has not been observed to date [178].

One of the most recently studied antivirals for COVID-19, nirmatrelvir, specifically inhibits the SARS-CoV-2 main protease (NSP5). NSP5 is responsible for the formation of other NSPs via cleavage of viral polyproteins; thus, loss of NSP5 function attenuates viral replication [185]. Most recently, nirmatrelvir was trialed as a twice-daily combination therapy with ritonavir, a repurposed viral protease inhibitor which improves the drug's pharmacokinetic profile, for 5 days in 2246 symptomatic unvaccinated outpatients. Nirmatrelvir–ritonavir was associated with a lower risk of hospitalization or death compared to placebo (0.77% vs. 7.01%) as well as reduced viral loads [186]. The effects of nirmatrelvir–ritonavir thus appear to mirror those in the outpatient remdesivir study, and its potential efficacy in hospitalized cohorts remains to be seen.

5.3. Pharmacotherapy Targeting Inflammation

Many anti-inflammatory and immunosuppressive therapies have targeted a proposed "hyper-active" immune response in COVID-19. Few have been successful, perhaps due to the complex immunopathology of the disease. Among these, dexamethasone, IL-6 antagonists, and baricitinib have shown notable results.

Dexamethasone is a corticosteroid which enacts anti-inflammatory and/or immunosuppressive effects via the glucocorticoid receptor [187]. The Randomized Evaluation of COVID-19 Therapy (RECOVERY) group assessed the effects of 6 mg of daily oral or intravenous (i.v.) dexamethasone for $\leq$10 days vs. standard care in 6425 hospitalized patients. Results showed a significant reduction in mortality in mechanically ventilated patients, while patients not receiving oxygen exhibited a non-significant increase in mortality [188]. These findings have since been recapitulated in other studies and appear to be consistent with knowledge of COVID-19 immunopathology [178]. Namely, suppression of innate responses in the early stage (i.e., patients not receiving oxygen) could facilitate viral proliferation and contribute to poor outcomes.

Tocilizumab, sarilumab, and siltuximab are recombinant monoclonal antibodies that function as IL-6 antagonists by binding membrane-bound and soluble forms of IL-6 receptor (e.g., tocilizumab, sarilumab) or by binding IL-6 directly (e.g., siltuximab) [189]. The World Health Organization (WHO) Rapid Evidence Appraisal for COVID-19 Therapies (REACT) group examined the efficacy of IL-6 antagonists compared to standard care or placebo and observed a slight reduction in all-cause 28-day mortality risk (22% vs. 25%). Of note, a higher percentage of secondary infections occurred among IL-6 antagonist-treated patients (21.9% vs. 17.6%) although the difference was not statistically significant [190].

Baricitinib is an oral disease-modifying antirheumatic drug (DMARD) that reduces transcription of pro-inflammatory cytokines by inhibiting Janus kinase (JAK) 1 and 2 [191]. Originally indicated in rheumatoid arthritis, baricitinib was trialed in patients receiving standard of care (systemic corticosteroids plus antivirals) at 4 mg daily for $\leq$14 days. While baricitinib did not significantly reduce progression to ventilatory support (primary endpoint), it was associated with reduced 28-day and 60-day mortality compared to standard care (8% vs. 13%, and 10% vs. 15%, respectively). Notably, incidence of thrombotic events was similar between the groups and could suggest baricitinib did not impact coagulation either mechanistically or by virtue of timing in disease stage [192].

5.4. Pharmacotherapy Targeting Coagulopathy

Coagulopathy and ensuing thrombotic events are a frequent and deadly aspect of COVID-19 pathophysiology. Empirical use of anti-coagulant and anti-platelet agents has thus become an important tool in patient care, although an optimal strategy has not yet been clearly defined [178]. Several studies have explored various antithrombotic agents in COVID-19, including anti-platelet agents, heparin-based anticoagulants, and direct oral anticoagulants.

Anti-platelet therapy reduces the activation and aggregation of platelets by antagonizing the $P2Y_{12}$ receptor (i.e., $P2Y_{12}$ inhibitors, e.g., clopidogrel) or inhibiting thromboxane A2 synthesis (i.e., aspirin) [193]. However, anti-platelet agents have generally been found

to be ineffective across all severities of disease and were associated with increased bleeding risk in critically ill patients [178]. Considering this, it may be possible that platelets play a simultaneously pathological and homeostatic role in COVID-19. On the one hand, platelet activation leading to aggregation with immune cells could contribute to the development of capillary microthrombi-reduced perfusion. On the other hand, platelet aggregation may be beneficial in preventing hemorrhage through the damaged endothelium in COVID-19. Experimental approaches aimed at selectively blocking the former pathway could therefore be of interest.

Anticoagulant use has demonstrated some benefits in the management of COVID-19 patients. Heparin-based anticoagulants (e.g., unfractionated heparin, dalteparin) reduce clot formation by indirectly inhibiting the formation of factor Xa and thrombin via antithrombin III, whereas direct oral anticoagulants (e.g., rivaroxaban) directly inhibit factor Xa [194]. Thromboprophylaxis with anticoagulants has been recommended for hospitalized patients with moderate or severe COVID-19, and specifically, heparin-based anticoagulants are recommended in the latter. In patients with moderate illness, therapeutic dosing has demonstrated benefits in two large-scale clinical trials. However, no benefit was shown in critically ill patients, and potential for harm was indicated due to increased bleeding rates [178]. Conceptually, these findings could suggest differences in microvascular dysfunction depending on disease severity or stage. Current evidence and guidelines suggest that antithrombotic therapy in COVID-19 patients should not diverge significantly from non-COVID-19 patients [175]. Furthermore, these data emphasize the importance of balancing the use of antithrombotic agents with limiting the risk of bleeding.

5.5. Emerging Pharmacotherapeutic Strategies

The ongoing impact of COVID-19 combined with a deeper understanding of its disease mechanisms continues to fuel exploration of novel therapeutic opportunities. Prominent among these is the discovery of druggable targets in the SARS-CoV-2 replication cycle. Inhibition of viral binding has been achieved in vitro and in vivo with various approaches including S protein-targeted nanobodies and inhibitors of serine proteases (i.e., TMPRSS2) required for S protein priming [195–198]. A range of inhibitors of viral enzymes including small molecules, bismuth-containing compounds, and small interfering RNAs have shown promising effects in vitro [199–201]. Additionally, blockade of virus-induced apoptotic signals was effective in reducing viral load and lung injury in a humanized mouse model of SARS-CoV-2 infection [202]. Which, if any, of these strategies will advance beyond the pre-clinical stage remains to be determined. While a significant portion of research in immunomodulatory therapy for COVID-19 has focused on suppressing inflammatory responses, promoting antiviral responses remains an interesting approach. Induction of IFN responses was efficacious in a humanized mouse model of COVID-19 [203]. Moreover, patients receiving nebulized IFN-I have shown improvements in viral clearance and speed of recovery [204,205]. Given the crucial role of the early IFN response against SARS-CoV-2, further research ought to elucidate the full therapeutic potential of IFN induction in COVID-19.

6. Conclusions and Future Perspectives

This comprehensive review sought to examine the degree to which COVID-19 lung injury differs from other etiologies. Several key themes were described with implications for therapeutic development. First, through complex interactions between SARS-CoV-2, IFN-I/III production, and inflammasome activation, the early innate immune response plays a highly crucial role in the outcome of COVID-19. Modulation of this phase through appropriate antiviral and immunomodulatory therapy is undoubtedly key to improving clinical outcomes. Second, COVID-19 is differentiated from other etiologies of ALI by a high degree of endothelial activation and coagulation in the pulmonary microvasculature, which impairs perfusion and contributes to profound hypoxemia. This hypercoagulable state further complicates clinical management and warrants investigation of more effective

and reliable anticoagulant therapies. Third, COVID-19 lung injury presents with significant hypoxemia and appears to evolve from high compliance to low compliance respiratory mechanics due to increasing alveolar edema. This unique clinical progression may necessitate careful monitoring of moderately-to-severely ill patients with COVID-19 to improve precision therapy.

Author Contributions: Conceptualization, S.H. and C.L.; writing—original draft preparation, S.H.; writing—review and editing, S.H. and G.B.; supervision, C.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Mowery, N.T.; Terzian, W.T.H.; Nelson, A.C. Acute Lung Injury. *Curr. Probl. Surg.* **2020**, *57*, 100777. [CrossRef] [PubMed]
2. Ranieri, V.M.; Rubenfeld, G.D.; Thompson, B.T.; Ferguson, N.D.; Caldwell, E.; Fan, E.; Camporota, L.; Slutsky, A.S. Acute Respiratory Distress Syndrome: The Berlin Definition. *JAMA* **2012**, *307*, 2526–2533. [CrossRef] [PubMed]
3. Bellani, G.; Laffey, J.G.; Pham, T.; Fan, E.; Brochard, L.; Esteban, A.; Gattinoni, L.; Van Haren, F.M.P.; Larsson, A.; McAuley, D.F.; et al. Epidemiology, Patterns of Care, and Mortality for Patients with Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. *JAMA* **2016**, *315*, 788–800. [CrossRef] [PubMed]
4. Bos, L.D.J.; Ware, L.B. Acute Respiratory Distress Syndrome: Causes, Pathophysiology, and Phenotypes. *Lancet* **2022**, *400*, 1145–1156. [CrossRef] [PubMed]
5. Shaver, C.M.; Bastarache, J.A. Clinical and Biological Heterogeneity in ARDS: Direct versus Indirect Lung Injury. *Clin. Chest Med.* **2014**, *35*, 639. [CrossRef] [PubMed]
6. Slutsky, A.S.; Ranieri, V.M. Ventilator-Induced Lung Injury. *N. Engl. J. Med.* **2013**, *22369*, 2126–2136. [CrossRef]
7. Brun-Buisson, C.; Minelli, C.; Bertolini, G.; Brazzi, L.; Pimentel, J.; Lewandowski, K.; Bion, J.; Romand, J.A.; Villar, J.; Thorsteinsson, A.; et al. Epidemiology and Outcome of Acute Lung Injury in European Intensive Care Units Results from the ALIVE Study. *Intensive Care Med.* **2004**, *30*, 51–61. [CrossRef]
8. Oud, L.; Garza, J. The Contribution of COVID-19 to Acute Respiratory Distress Syndrome-Related Mortality in the United States. *J. Clin. Med. Res.* **2023**, *15*, 279–281. [CrossRef]
9. World Health Organization. COVID-19 Cases | WHO COVID-19 Dashboard. Available online: https://data.who.int/dashboards/covid19/cases?n=o (accessed on 7 August 2024).
10. Morris, G.; Bortolasci, C.C.; Puri, B.K.; Marx, W.; O'Neil, A.; Athan, E.; Walder, K.; Berk, M.; Olive, L.; Carvalho, A.F.; et al. The Cytokine Storms of COVID-19, H1N1 Influenza, CRS and MAS Compared. Can One Sized Treatment Fit All? *Cytokine* **2021**, *144*, 155593. [CrossRef]
11. Matthay, M.A.; Zemans, R.L.; Zimmerman, G.A.; Arabi, Y.M.; Beitler, J.R.; Mercat, A.; Herridge, M.; Randolph, A.G.; Calfee, C.S. Acute Respiratory Distress Syndrome. *Nat. Rev. Dis. Primers* **2018**, *5*, 18. [CrossRef]
12. Ochs, M.; Nyengaard, J.R.; Jung, A.; Knudsen, L.; Voigt, M.; Wahlers, T.; Richter, J.; Gundersen, H.J.G. The Number of Alveoli in the Human Lung. *Am. J. Respir. Crit. Care Med.* **2012**, *169*, 120–124. [CrossRef]
13. Berthiaume, Y.; Matthay, M.A. Alveolar Edema Fluid Clearance and Acute Lung Injury. *Respir. Physiol. Neurobiol.* **2007**, *159*, 350. [CrossRef] [PubMed]
14. Peteranderl, C.; Herold, S.; Schmoldt, C. Human Influenza Virus Infections. *Semin. Respir. Crit. Care Med.* **2016**, *37*, 487–500. [CrossRef] [PubMed]
15. Nishimoto, A.T.; Rosch, J.W.; Tuomanen, E.I. Pneumolysin: Pathogenesis and Therapeutic Target. *Front. Microbiol.* **2020**, *11*, 1543. [CrossRef] [PubMed]
16. Xiang, M.; Fan, J. Pattern Recognition Receptor-Dependent Mechanisms of Acute Lung Injury. *Mol. Med.* **2010**, *16*, 69–82. [CrossRef]
17. Zhou, H.; Fan, E.K.; Fan, J. Cell-Cell Interaction Mechanisms in Acute Lung Injury. *Shock* **2021**, *55*, 167–176. [CrossRef]
18. Choudhury, S.R.; Babes, L.; Rahn, J.J.; Ahn, B.Y.; Goring, K.A.R.; King, J.C.; Lau, A.; Petri, B.; Hao, X.; Chojnacki, A.K.; et al. Dipeptidase-1 Is an Adhesion Receptor for Neutrophil Recruitment in Lungs and Liver. *Cell* **2019**, *178*, 1205–1221.e17. [CrossRef]
19. Kolaczkowska, E.; Kubes, P. Neutrophil Recruitment and Function in Health and Inflammation. *Nat. Rev. Immunol.* **2013**, *13*, 159–175. [CrossRef]

20. Bhatia, M.; Zemans, R.L.; Jeyaseelan, S. Role of Chemokines in the Pathogenesis of Acute Lung Injury. *Am. J. Respir. Cell Mol. Biol.* **2012**, *46*, 566–572. [CrossRef]
21. Potey, P.M.; Rossi, A.G.; Lucas, C.D.; Dorward, D.A. Neutrophils in the Initiation and Resolution of Acute Pulmonary Inflammation: Understanding Biological Function and Therapeutic Potential. *J. Pathol.* **2019**, *247*, 672–685. [CrossRef]
22. Guillot, L.; Nathan, N.; Tabary, O.; Thouvenin, G.; Le Rouzic, P.; Corvol, H.; Amselem, S.; Clement, A. Alveolar Epithelial Cells: Master Regulators of Lung Homeostasis. *Int. J. Biochem. Cell Biol.* **2013**, *45*, 2568–2573. [CrossRef] [PubMed]
23. Kollisch-Singule, M.; Satalin, J.; Blair, S.J.; Andrews, P.L.; Gatto, L.A.; Nieman, G.F.; Habashi, N.M. Mechanical Ventilation Lessons Learned From Alveolar Micromechanics. *Front. Physiol.* **2020**, *11*, 233. [CrossRef] [PubMed]
24. Finigan, J.H. The Coagulation System and Pulmonary Endothelial Function in Acute Lung Injury. *Microvasc. Res.* **2009**, *77*, 35–38. [CrossRef] [PubMed]
25. Nuckton, T.J.; Alonso, J.A.; Kallet, R.H.; Daniel, B.M.; Pittet, J.-F.; Eisner, M.D.; Matthay, M.A. Pulmonary Dead-Space Fraction as a Risk Factor for Death in the Acute Respiratory Distress Syndrome. *N. Engl. J. Med.* **2002**, *346*, 1281–1286. [CrossRef] [PubMed]
26. Butt, Y.; Kurdowska, A.; Allen, T.C. Acute Lung Injury: A Clinical and Molecular Review. *Arch. Pathol. Lab. Med.* **2016**, *140*, 345–350. [CrossRef]
27. Thille, A.W.; Esteban, A.; Fernández-Segoviano, P.; Rodriguez, J.M.; Aramburu, J.A.; Peñuelas, O.; Cortés-Puch, I.; Cardinal-Fernández, P.; Lorente, J.A.; Frutos-Vivar, F. Comparison of the Berlin Definition for Acute Respiratory Distress Syndrome with Autopsy. *Am. J. Respir. Crit. Care Med.* **2013**, *187*, 761–767. [CrossRef]
28. Cardinal-Fernandez, P.; Lorente, J.A.; Ballen-Barragan, A.; Matute-Bello, G. Acute Respiratory Distress Syndrome and Diffuse Alveolar Damage New Insights on a Complex Relationship. *Ann. Am. Thorac. Soc.* **2017**, *14*, 844–850. [CrossRef]
29. Uchida, T.; Shirasawa, M.; Ware, L.B.; Kojima, K.; Hata, Y.; Makita, K.; Mednick, G.; Matthay, Z.A.; Matthay, M.A. Receptor for Advanced Glycation End-Products Is a Marker of Type I Cell Injury in Acute Lung Injury. *Am. J. Respir. Crit. Care Med.* **2006**, *173*, 1008. [CrossRef]
30. Eisner, M.D.; Parsons, P.; Matthay, M.A.; Ware, L.; Greene, K. Plasma Surfactant Protein Levels and Clinical Outcomes in Patients with Acute Lung Injury. *Thorax* **2003**, *58*, 983. [CrossRef]
31. Calfee, C.S.; Janz, D.R.; Bernard, G.R.; May, A.K.; Kangelaris, K.N.; Matthay, M.A.; Ware, L.B. Distinct Molecular Phenotypes of Direct vs Indirect ARDS in Single-Center and Multicenter Studies. *Chest* **2015**, *147*, 1539–1548. [CrossRef]
32. Meduri, G.U.; Headley, S.; Kohler, G.; Stentz, F.; Tolley, E.; Umberger, R.; Leeper, K. Persistent Elevation of Inflammatory Cytokines Predicts a Poor Outcome in ARDS: Plasma IL-1β and IL-6 Levels Are Consistent and Efficient Predictors of Outcome over Time. *Chest* **1995**, *107*, 1062–1073. [CrossRef] [PubMed]
33. Meduri, G.U.; Kohler, G.; Headley, S.; Tolley, E.; Stentz, F.; Postlethwaite, A. Inflammatory Cytokines in the BAL of Patients with ARDS: Persistent Elevation over Time Predicts Poor Outcome. *Chest* **1995**, *108*, 1303–1314. [CrossRef] [PubMed]
34. Calfee, C.S.; Delucchi, K.; Parsons, P.E.; Thompson, B.T.; Ware, L.B.; Matthay, M.A. Subphenotypes in Acute Respiratory Distress Syndrome: Latent Class Analysis of Data from Two Randomised Controlled Trials. *Lancet Respir. Med.* **2014**, *2*, 611–620. [CrossRef] [PubMed]
35. Sinha, P.; Delucchi, K.L.; Thompson, B.T.; McAuley, D.F.; Matthay, M.A.; Calfee, C.S. Latent Class Analysis of ARDS Subphenotypes: A Secondary Analysis of the Statins for Acutely Injured Lungs from Sepsis (SAILS) Study. *Intensive Care Med.* **2018**, *44*, 1859–1869. [CrossRef] [PubMed]
36. Parsons, P.E.; Eisner, M.D.; Thompson, B.T.; Matthay, M.A.; Ancukiewicz, M.; Bernard, G.R.; Wheeler, A.P. Lower Tidal Volume Ventilation and Plasma Cytokine Markers of Inflammation in Patients with Acute Lung Injury. *Crit. Care Med.* **2005**, *33*, 1–6. [CrossRef]
37. Dickson, R.P.; Singer, B.H.; Newstead, M.W.; Falkowski, N.R.; Erb-Downward, J.R.; Standiford, T.J.; Huffnagle, G.B. Enrichment of the Lung Microbiome with Gut Bacteria in Sepsis and the Acute Respiratory Distress Syndrome. *Nat. Microbiol.* **2016**, *1*, 16113. [CrossRef]
38. Arora, J.; Mendelson, A.A.; Fox-Robichaud, A. Sepsis: Network Pathophysiology and Implications for Early Diagnosis. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2023**, *324*, R613–R624. [CrossRef]
39. Cecconi, M.; Evans, L.; Levy, M.; Rhodes, A. Sepsis and Septic Shock. *Lancet* **2018**, *392*, 75–87. [CrossRef]
40. Deng, J.C.; Standiford, T.J. The Systemic Response to Lung Infection. *Clin. Chest Med.* **2005**, *26*, 1–9. [CrossRef]
41. Chiumello, D.; Coppola, S.; Froio, S.; Gotti, M. What's next after ARDS: Long-Term Outcomes. *Respir. Care* **2016**, *61*, 689–699. [CrossRef]
42. Wilcox, M.E.; Patsios, D.; Murphy, G.; Kudlow, P.; Paul, N.; Tansey, C.M.; Chu, L.; Matte, A.; Tomlinson, G.; Herridge, M.S. Radiologic Outcomes at 5 Years after Severe ARDS. *Chest* **2013**, *143*, 920–926. [CrossRef] [PubMed]
43. Schelling, G.; Stoll, C.; Haller, M.; Briegel, J.; Manert, W.; Hummel, T.; Lenhart, A.; Heyduck, M.; Polasek, J.; Meier, M.; et al. Health-Related Quality of Life and Posttraumatic Stress Disorder in Survivors of the Acute Respiratory Distress Syndrome. *Crit. Care Med.* **1998**, *26*, 651–659. [CrossRef] [PubMed]
44. Chiumello, D.; Taccone, P.; Berto, V.; Marino, A.; Migliara, G.; Lazzerini, M.; Gattinoni, L. Long-Term Outcomes in Survivors of Acute Respiratory Distress Syndrome Ventilated in Supine or Prone Position. *Intensive Care Med.* **2012**, *38*, 221–229. [CrossRef] [PubMed]

45. Cheung, A.M.; Tansey, C.M.; Tomlinson, G.; Diaz-Granados, N.; Matté, A.; Barr, A.; Mehta, S.; Mazer, C.D.; Guest, C.B.; Stewart, T.E.; et al. Two-Year Outcomes, Health Care Use, and Costs of Survivors of Acute Respiratory Distress Syndrome. *Am. J. Respir. Crit. Care Med.* **2006**, *174*, 538–544. [CrossRef] [PubMed]
46. Osuchowski, M.F.; Winkler, M.S.; Skirecki, T.; Cajander, S.; Shankar-Hari, M.; Lachmann, G.; Monneret, G.; Venet, F.; Bauer, M.; Brunkhorst, F.M.; et al. The COVID-19 Puzzle: Deciphering Pathophysiology and Phenotypes of a New Disease Entity. *Lancet Respir. Med.* **2021**, *9*, 622–642. [CrossRef]
47. Gupta, A.; Madhavan, M.V.; Sehgal, K.; Nair, N.; Mahajan, S.; Sehrawat, T.S.; Bikdeli, B.; Ahluwalia, N.; Ausiello, J.C.; Wan, E.Y.; et al. Extrapulmonary Manifestations of COVID-19. *Nat. Med.* **2020**, *26*, 1017–1032. [CrossRef]
48. Wu, C.; Chen, X.; Cai, Y.; Xia, J.; Zhou, X.; Xu, S.; Huang, H.; Zhang, L.; Zhou, X.; Du, C.; et al. Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern. Med.* **2020**, *180*, 934–943. [CrossRef]
49. Ferrando, C.; Suarez-Sipmann, F.; Mellado-Artigas, R.; Hernández, M.; Gea, A.; Arruti, E.; Aldecoa, C.; Martínez-Pallí, G.; Martínez-González, M.A.; Slutsky, A.S.; et al. Clinical Features, Ventilatory Management, and Outcome of ARDS Caused by COVID-19 Are Similar to Other Causes of ARDS. *Intensive Care Med.* **2020**, *46*, 2200–2211. [CrossRef]
50. Li, J.; Huang, D.Q.; Zou, B.; Yang, H.; Hui, W.Z.; Rui, F.; Yee, N.T.S.; Liu, C.; Nerurkar, S.N.; Kai, J.C.Y.; et al. Epidemiology of COVID-19: A Systematic Review and Meta-Analysis of Clinical Characteristics, Risk Factors, and Outcomes. *J. Med. Virol.* **2021**, *93*, 1449–1458. [CrossRef]
51. Ho, J.Q.; Sepand, M.R.; Bigdelou, B.; Shekarian, T.; Esfandyarpour, R.; Chauhan, P.; Serpooshan, V.; Beura, L.K.; Hutter, G.; Zanganeh, S. The Immune Response to COVID-19: Does Sex Matter? *Immunology* **2022**, *166*, 429–443. [CrossRef]
52. Lamers, M.M.; Haagmans, B.L. SARS-CoV-2 Pathogenesis. *Nat. Rev. Microbiol.* **2022**, *20*, 270–284. [CrossRef] [PubMed]
53. Rezaei, M.; Ziai, S.A.; Fakhri, S.; Pouriran, R. ACE2: Its Potential Role and Regulation in Severe Acute Respiratory Syndrome and COVID-19. *J. Cell. Physiol.* **2021**, *236*, 2430–2442. [CrossRef]
54. Shafqat, A.; Shafqat, S.; Al Salameh, S.; Kashir, J.; Alkattan, K.; Yaqinuddin, A. Mechanistic Insights Into the Immune Pathophysiology of COVID-19; An In-Depth Review. *Front. Immunol.* **2022**, *13*, 835104. [CrossRef] [PubMed]
55. Ahn, J.H.; Kim, J.M.; Hong, S.P.; Choi, S.Y.; Yang, M.J.; Ju, Y.S.; Kim, Y.T.; Kim, H.M.; Rahman, T.; Chung, M.K.; et al. Nasal Ciliated Cells Are Primary Targets for SARS-CoV-2 Replication in the Early Stage of COVID-19. *J. Clin. Investig.* **2021**, *131*. [CrossRef]
56. Khan, M.; Yoo, S.J.; Clijsters, M.; Backaert, W.; Vanstapel, A.; Speleman, K.; Lietaer, C.; Choi, S.; Hether, T.D.; Marcelis, L.; et al. Visualizing in Deceased COVID-19 Patients How SARS-CoV-2 Attacks the Respiratory and Olfactory Mucosae but Spares the Olfactory Bulb. *Cell* **2021**, *184*, 5932. [CrossRef] [PubMed]
57. Lupu, L.; Palmer, A.; Huber-Lang, M. Inflammation, Thrombosis, and Destruction: The Three-Headed Cerberus of Trauma- and SARS-CoV-2-Induced ARDS. *Front. Immunol.* **2020**, *11*, 1. [CrossRef]
58. Lim, S.; Zhang, M.; Chang, T.L. ACE2-Independent Alternative Receptors for SARS-CoV-2. *Viruses* **2022**, *14*, 2535. [CrossRef] [PubMed]
59. Merad, M.; Blish, C.A.; Sallusto, F.; Iwasaki, A. The Immunology and Immunopathology of COVID-19. *Science* **2022**, *375*, 1122–1127. [CrossRef]
60. Vora, S.M.; Lieberman, J.; Wu, H. Inflammasome Activation at the Crux of Severe COVID-19. *Nat. Rev. Immunol.* **2021**, *21*, 694–703. [CrossRef]
61. Vanderheiden, A.; Ralfs, P.; Chirkova, T.; Upadhyay, A.A.; Zimmerman, M.G.; Bedoya, S.; Aoued, H.; Tharp, G.M.; Pellegrini, K.L.; Manfredi, C.; et al. Type I and Type III Interferons Restrict SARS-CoV-2 Infection of Human Airway Epithelial Cultures. *J. Virol.* **2020**, *94*, e00985-20. [CrossRef]
62. Sposito, B.; Broggi, A.; Pandolfi, L.; Crotta, S.; Clementi, N.; Ferrarese, R.; Sisti, S.; Criscuolo, E.; Spreafico, R.; Long, J.M.; et al. The Interferon Landscape along the Respiratory Tract Impacts the Severity of COVID-19. *Cell* **2021**, *184*, 4953–4968.e16. [CrossRef] [PubMed]
63. Madden, E.A.; Diamond, M.S. Host Cell-Intrinsic Innate Immune Recognition of SARS-CoV-2. *Curr. Opin. Virol.* **2022**, *52*, 30–38. [CrossRef] [PubMed]
64. Lebeau, G.; Vagner, D.; Frumence, É.; Ah-Pine, F.; Guillot, X.; Nobécourt, E.; Raffray, L.; Gasque, P. Deciphering SARS-CoV-2 Virologic and Immunologic Features. *Int. J. Mol. Sci.* **2020**, *21*, 5932. [CrossRef]
65. Hadjadj, J.; Yatim, N.; Barnabei, L.; Corneau, A.; Boussier, J.; Smith, N.; Péré, H.; Charbit, B.; Bondet, V.; Chenevier-Gobeaux, C.; et al. Impaired Type I Interferon Activity and Inflammatory Responses in Severe COVID-19 Patients. *Science* **2020**, *369*, 718–724. [CrossRef]
66. Koning, R.; Bastard, P.; Casanova, J.L.; Brouwer, M.C.; van de Beek, D.; van Agtmael, M.; Algera, A.G.; Appelman, B.; van Baarle, F.; Bax, D.; et al. Autoantibodies against Type I Interferons Are Associated with Multi-Organ Failure in COVID-19 Patients. *Intensive Care Med.* **2021**, *47*, 704. [CrossRef]
67. Bastard, P.; Rosen, L.B.; Zhang, Q.; Michailidis, E.; Hoffmann, H.H.; Zhang, Y.; Dorgham, K.; Philippot, Q.; Rosain, J.; Béziat, V.; et al. Autoantibodies against Type I IFNs in Patients with Life-Threatening COVID-19. *Science* **2020**, *370*, eabd4585. [CrossRef]
68. Aoki, A.; Iwamura, C.; Kiuchi, M.; Tsuji, K.; Sasaki, A.; Hishiya, T.; Hirasawa, R.; Kokubo, K.; Kuriyama, S.; Onodera, A.; et al. Suppression of Type I Interferon Signaling in Myeloid Cells by Autoantibodies in Severe COVID-19 Patients. *J. Clin. Immunol.* **2024**, *44*, 104. [CrossRef]

69. Sun, C.; Zhao, H.; Han, Y.; Wang, Y.; Sun, X. The Role of Inflammasomes in COVID-19: Potential Therapeutic Targets. *J. Interferon Cytokine Res.* **2022**, *42*, 406–420. [CrossRef] [PubMed]
70. Sefik, E.; Qu, R.; Junqueira, C.; Kaffe, E.; Mirza, H.; Zhao, J.; Brewer, J.R.; Han, A.; Steach, H.R.; Israelow, B.; et al. Inflammasome Activation in Infected Macrophages Drives COVID-19 Pathology. *Nature* **2022**, *606*, 585–593. [CrossRef]
71. Liao, M.; Liu, Y.; Yuan, J.; Wen, Y.; Xu, G.; Zhao, J.; Cheng, L.; Li, J.; Wang, X.; Wang, F.; et al. Single-Cell Landscape of Bronchoalveolar Immune Cells in Patients with COVID-19. *Nat. Med.* **2020**, *26*, 842–844. [CrossRef]
72. Wauters, E.; Van Mol, P.; Garg, A.D.; Jansen, S.; Van Herck, Y.; Vanderbeke, L.; Bassez, A.; Boeckx, B.; Malengier-Devlies, B.; Timmerman, A.; et al. Discriminating Mild from Critical COVID-19 by Innate and Adaptive Immune Single-Cell Profiling of Bronchoalveolar Lavages. *Cell Res.* **2021**, *31*, 272–290. [CrossRef] [PubMed]
73. Tojo, K.; Yamamoto, N.; Tamada, N.; Mihara, T.; Abe, M.; Nishii, M.; Takeuchi, I.; Goto, T. Early Alveolar Epithelial Cell Necrosis Is a Potential Driver of COVID-19-Induced Acute Respiratory Distress Syndrome. *iScience* **2023**, *26*, 105748. [CrossRef] [PubMed]
74. Paludan, S.R.; Mogensen, T.H. Innate Immunological Pathways in COVID-19 Pathogenesis. *Sci. Immunol.* **2022**, *7*, 5505. [CrossRef] [PubMed]
75. Peng, T.; Du, S.Y.; Son, M.; Diamond, B. HIF-1α Is a Negative Regulator of Interferon Regulatory Factors: Implications for Interferon Production by Hypoxic Monocytes. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2106017118. [CrossRef] [PubMed]
76. Junqueira, C.; Crespo, Â.; Ranjbar, S.; de Lacerda, L.B.; Lewandrowski, M.; Ingber, J.; Parry, B.; Ravid, S.; Clark, S.; Schrimpf, M.R.; et al. FcγR-Mediated SARS-CoV-2 Infection of Monocytes Activates Inflammation. *Nature* **2022**, *606*, 576–584. [CrossRef]
77. Reusch, N.; De Domenico, E.; Bonaguro, L.; Schulte-Schrepping, J.; Baßler, K.; Schultze, J.L.; Aschenbrenner, A.C. Neutrophils in COVID-19. *Front. Immunol.* **2021**, *12*, 652470. [CrossRef]
78. Middleton, E.A.; He, X.Y.; Denorme, F.; Campbell, R.A.; Ng, D.; Salvatore, S.P.; Mostyka, M.; Baxter-Stoltzfus, A.; Borczuk, A.C.; Loda, M.; et al. Neutrophil Extracellular Traps Contribute to Immunothrombosis in COVID-19 Acute Respiratory Distress Syndrome. *Blood* **2020**, *136*, 1169–1179. [CrossRef]
79. Ackermann, M.; Anders, H.J.; Bilyy, R.; Bowlin, G.L.; Daniel, C.; De Lorenzo, R.; Egeblad, M.; Henneck, T.; Hidalgo, A.; Hoffmann, M.; et al. Patients with COVID-19: In the Dark-NETs of Neutrophils. *Cell Death Differ.* **2021**, *28*, 3125–3139. [CrossRef]
80. Zarrilli, G.; Angerilli, V.; Businello, G.; Sbaraglia, M.; Traverso, G.; Fortarezza, F.; Rizzo, S.; De Gaspari, M.; Basso, C.; Calabrese, F.; et al. The Immunopathological and Histological Landscape of COVID-19-Mediated Lung Injury. *Int. J. Mol. Sci.* **2021**, *22*, 974. [CrossRef]
81. Zheng, M.; Gao, Y.; Wang, G.; Song, G.; Liu, S.; Sun, D.; Xu, Y.; Tian, Z. Functional Exhaustion of Antiviral Lymphocytes in COVID-19 Patients. *Cell. Mol. Immunol.* **2020**, *17*, 533–535. [CrossRef]
82. van Eijk, L.E.; Binkhorst, M.; Bourgonje, A.R.; Offringa, A.K.; Mulder, D.J.; Bos, E.M.; Kolundzic, N.; Abdulle, A.E.; van der Voort, P.H.J.; Olde Rikkert, M.G.M.; et al. COVID-19: Immunopathology, Pathophysiological Mechanisms, and Treatment Options. *J. Pathol.* **2021**, *254*, 307–331. [CrossRef] [PubMed]
83. Delorey, T.M.; Ziegler, C.G.K.; Heimberg, G.; Normand, R.; Yang, Y.; Segerstolpe, Å.; Abbondanza, D.; Fleming, S.J.; Subramanian, A.; Montoro, D.T.; et al. COVID-19 Tissue Atlases Reveal SARS-CoV-2 Pathology and Cellular Targets. *Nature* **2021**, *595*, 107–113. [CrossRef] [PubMed]
84. Lee, M.J.; de los Rios Kobara, I.; Barnard, T.R.; Vales Torres, X.; Tobin, N.H.; Ferbas, K.G.; Rimoin, A.W.; Yang, O.O.; Aldrovandi, G.M.; Wilk, A.J.; et al. NK Cell–Monocyte Cross-Talk Underlies NK Cell Activation in Severe COVID-19. *J. Immunol. Author Choice* **2024**, *212*, 1693. [CrossRef] [PubMed]
85. Zhou, R.; To, K.K.W.; Wong, Y.C.; Liu, L.; Zhou, B.; Li, X.; Huang, H.; Mo, Y.; Luk, T.Y.; Lau, T.T.K.; et al. Acute SARS-CoV-2 Infection Impairs Dendritic Cell and T Cell Responses. *Immunity* **2020**, *53*, 864. [CrossRef] [PubMed]
86. Mathew, D.; Giles, J.R.; Baxter, A.E.; Oldridge, D.A.; Greenplate, A.R.; Wu, J.E.; Alanio, C.; Kuri-Cervantes, L.; Pampena, M.B.; D'Andrea, K.; et al. Deep Immune Profiling of COVID-19 Patients Reveals Distinct Immunotypes with Therapeutic Implications. *Science* **2020**, *369*, eabc8511. [CrossRef]
87. Gustine, J.N.; Jones, D. Immunopathology of Hyperinflammation in COVID-19. *Am. J. Pathol.* **2021**, *191*, 4–17. [CrossRef]
88. Sette, A.; Crotty, S. Adaptive Immunity to SARS-CoV-2 and COVID-19. *Cell* **2021**, *184*, 861–880. [CrossRef]
89. Sette, A.; Sidney, J.; Crotty, S. T Cell Responses to SARS-CoV-2. *Annu. Rev. Immunol.* **2023**, *41*, 343–373. [CrossRef]
90. Garnier, Y.; Claude, L.; Hermand, P.; Sachou, E.; Claes, A.; Desplan, K.; Chahim, B.; Roger, P.M.; Martino, F.; Colin, Y.; et al. Plasma Microparticles of Intubated COVID-19 Patients Cause Endothelial Cell Death, Neutrophil Adhesion and Netosis, in a Phosphatidylserine-Dependent Manner. *Br. J. Haematol.* **2022**, *196*, 1159–1169. [CrossRef]
91. Siddiqi, H.K.; Libby, P.; Ridker, P.M. COVID-19—A Vascular Disease. *Trends Cardiovasc. Med.* **2021**, *31*, 1–5. [CrossRef]
92. Ackermann, M.; Verleden, S.E.; Kuehnel, M.; Haverich, A.; Welte, T.; Laenger, F.; Vanstapel, A.; Werlein, C.; Stark, H.; Tzankov, A.; et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in COVID-19. *N. Engl. J. Med.* **2020**, *383*, 120–128. [CrossRef] [PubMed]
93. Maincent, C.; Perrin, C.; Chironi, G.; Baqué-Juston, M.; Berthier, F.; Paulmier, B.; Hugonnet, F.; Dittlot, C.; Farhad, R.L.; Renvoise, J.; et al. Microvascular Injuries, Secondary Edema, and Inconsistencies in Lung Vascularization between Affected and Nonaffected Pulmonary Segments of Non-Critically Ill Hospitalized COVID-19 Patients Presenting with Clinical Deterioration. *Ther. Adv. Respir. Dis.* **2022**, *16*, 17534666221096040. [CrossRef] [PubMed]

94. Markovic, N.; McCaig, L.A.; Stephen, J.; Mizuguchi, S.; Veldhuizen, R.A.W.; Lewis, J.F.; Cepinskas, G. Mediators Released from LPS-Challenged Lungs Induce Inflammatory Responses in Liver Vascular Endothelial Cells and Neutrophilic Leukocytes. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2009**, *297*, 1066–1076. [CrossRef] [PubMed]
95. Varga, Z.; Flammer, A.J.; Steiger, P.; Haberecker, M.; Andermatt, R.; Zinkernagel, A.S.; Mehra, M.R.; Schuepbach, R.A.; Ruschitzka, F.; Moch, H. Endothelial Cell Infection and Endotheliitis in COVID-19. *Lancet* **2020**, *395*, 1417–1418. [CrossRef]
96. Calabretta, E.; Moraleda, J.M.; Iacobelli, M.; Jara, R.; Vlodavsky, I.; O'Gorman, P.; Pagliuca, A.; Mo, C.; Baron, R.M.; Aghemo, A.; et al. COVID-19-Induced Endotheliitis: Emerging Evidence and Possible Therapeutic Strategies. *Br. J. Haematol.* **2021**, *193*, 43–51. [CrossRef]
97. Vrints, C.J.M.; Krychtiuk, K.A.; Van Craenenbroeck, E.M.; Segers, V.F.; Price, S.; Heidbuchel, H. Endothelialitis Plays a Central Role in the Pathophysiology of Severe COVID-19 and Its Cardiovascular Complications. *Acta Cardiol.* **2021**, *76*, 109–124. [CrossRef]
98. Higashikuni, Y.; Liu, W.; Obana, T.; Sata, M. Pathogenic Basis of Thromboinflammation and Endothelial Injury in COVID-19: Current Findings and Therapeutic Implications. *Int. J. Mol. Sci.* **2021**, *22*, 12081. [CrossRef]
99. Li, K.; Yao, L.; Wang, J.; Song, H.; Zhang, Y.H.; Bai, X.; Zhang, K.; Zhou, D.M.; Ai, D.; Zhu, Y. SARS-CoV-2 Spike Protein Promotes VWF Secretion and Thrombosis via Endothelial Cytoskeleton-Associated Protein 4 (CKAP4). *Signal Transduct. Target. Ther.* **2022**, *7*, 332. [CrossRef]
100. Perico, L.; Benigni, A.; Casiraghi, F.; Ng, L.F.P.; Renia, L.; Remuzzi, G. Immunity, Endothelial Injury and Complement-Induced Coagulopathy in COVID-19. *Nat. Rev. Nephrol.* **2020**, *17*, 46. [CrossRef]
101. Pine, A.B.; Meizlish, M.L.; Goshua, G.; Chang, C.H.; Zhang, H.; Bishai, J.; Bahel, P.; Patel, A.; Gbyli, R.; Kwan, J.M.; et al. Circulating Markers of Angiogenesis and Endotheliopathy in COVID-19. *Pulm. Circ.* **2020**, *10*, 2045894020966547. [CrossRef]
102. Monteil, V.; Kwon, H.; Prado, P.; Hagelkrüys, A.; Wimmer, R.A.; Stahl, M.; Leopoldi, A.; Garreta, E.; Hurtado del Pozo, C.; Prosper, F.; et al. Inhibition of SARS-CoV-2 Infections in Engineered Human Tissues Using Clinical-Grade Soluble Human ACE2. *Cell* **2020**, *181*, 905–913.e7. [CrossRef] [PubMed]
103. Li, S.; Jiang, L.; Li, X.; Lin, F.; Wang, Y.; Li, B.; Jiang, T.; An, W.; Liu, S.; Liu, H.; et al. Clinical and Pathological Investigation of Patients with Severe COVID-19. *JCI Insight* **2020**, *5*, e138070. [CrossRef] [PubMed]
104. Habashi, N.M.; Camporota, L.; Gatto, L.A.; Nieman, G. Functional Pathophysiology of SARS-CoV-2-Induced Acute Lung Injury and Clinical Implications. *J. Appl. Physiol.* **2021**, *130*, 877–891. [CrossRef]
105. Caillon, A.; Trimaille, A.; Favre, J.; Jesel, L.; Morel, O.; Kauffenstein, G. Role of Neutrophils, Platelets, and Extracellular Vesicles and Their Interactions in COVID-19-Associated Thrombopathy. *J. Thromb. Haemost.* **2022**, *20*, 17–31. [CrossRef]
106. Hottz, E.D.; Azevedo-Quintanilha, I.G.; Palhinha, L.; Teixeira, L.; Barreto, E.A.; Pão, C.R.R.; Righy, C.; Franco, S.; Souza, T.M.L.; Kurtz, P.; et al. Platelet Activation and Platelet-Monocyte Aggregate Formation Trigger Tissue Factor Expression in Patients with Severe COVID-19. *Blood* **2020**, *136*, 1330–1341. [CrossRef]
107. Mast, A.E.; Wolberg, A.S.; Gailani, D.; Garvin, M.R.; Alvarez, C.; Izaak Miller, J.; Aronow, B.; Jacobson, D. SARS-CoV-2 Suppresses Anticoagulant and Fibrinolytic Gene Expression in the Lung. *Elife* **2021**, 10. [CrossRef] [PubMed]
108. Obi, A.T.; Barnes, G.D.; Napolitano, L.M.; Henke, P.K.; Wakefield, T.W. Venous Thrombosis Epidemiology, Pathophysiology, and Anticoagulant Therapies and Trials in Severe Acute Respiratory Syndrome Coronavirus 2 Infection. *J. Vasc. Surg. Venous Lymphat. Disord.* **2021**, *9*, 23. [CrossRef]
109. Ryu, J.K.; Yan, Z.; Montano, M.; Sozmen, E.G.; Dixit, K.; Suryawanshi, R.K.; Matsui, Y.; Helmy, E.; Kaushal, P.; Makanani, S.K.; et al. Fibrin Drives Thromboinflammation and Neuropathology in COVID-19. *Nature* **2024**, *633*, 905. [CrossRef]
110. Villacampa, A.; Alfaro, E.; Morales, C.; Díaz-García, E.; López-Fernández, C.; Bartha, J.L.; López-Sánchez, F.; Lorenzo, Ó.; Moncada, S.; Sánchez-Ferrer, C.F.; et al. SARS-CoV-2 S Protein Activates NLRP3 Inflammasome and Deregulates Coagulation Factors in Endothelial and Immune Cells. *Cell Commun. Signal.* **2024**, *22*, 38. [CrossRef]
111. Tabassum, A.; Iqbal, M.S.; Sultan, S.; Alhuthali, R.A.; Alshubaili, D.I.; Sayyam, R.S.; Abyad, L.M.; Qasem, A.H.; Arbaeen, A.F. Dysregulated Bradykinin: Mystery in the Pathogenesis of COVID-19. *Mediat. Inflamm.* **2022**, *2022*, 7423537. [CrossRef]
112. Wang, J.; Zhao, H.; An, Y. ACE2 Shedding and the Role in COVID-19. *Front. Cell. Infect. Microbiol.* **2022**, *11*, 1422. [CrossRef] [PubMed]
113. Yang, C.; Li, Y.; Xiao, S.Y. Do We Really Understand the Relationship Between Expression of ACE2 and Coronavirus Disease 2019 Lung Pathophysiology? *J. Thorac. Oncol.* **2021**, *16*, 1785–1787. [CrossRef] [PubMed]
114. Shukla, A.K.; Banerjee, M. Angiotensin-Converting-Enzyme 2 and Renin-Angiotensin System Inhibitors in COVID-19: An Update. *High Blood Press. Cardiovasc. Prev.* **2021**, *28*, 129–139. [CrossRef]
115. Kuba, K.; Imai, Y.; Rao, S.; Gao, H.; Guo, F.; Guan, B.; Huan, Y.; Yang, P.; Zhang, Y.; Deng, W.; et al. A Crucial Role of Angiotensin Converting Enzyme 2 (ACE2) in SARS Coronavirus-Induced Lung Injury. *Nat. Med.* **2005**, *11*, 875–879. [CrossRef]
116. Jasiczek, J.; Doroszko, A.; Trocha, T.; Trocha, M. Role of the RAAS in Mediating the Pathophysiology of COVID-19. *Pharmacol. Rep.* **2024**, *76*, 475. [CrossRef]
117. Kovacs-Kasa, A.; Zaied, A.A.; Leanhart, S.; Koseoglu, M.; Sridhar, S.; Lucas, R.; Fulton, D.J.; Vazquez, J.A.; Annex, B.H. Elevated Cytokine Levels in Plasma of Patients with SARS-CoV-2 Do Not Contribute to Pulmonary Microvascular Endothelial Permeability. *Microbiol. Spectr.* **2022**, *10*, e0167121. [CrossRef]
118. Gattinoni, L.; Chiumello, D.; Caironi, P.; Busana, M.; Romitti, F.; Brazzi, L.; Camporota, L. COVID-19 Pneumonia: Different Respiratory Treatments for Different Phenotypes? *Intensive Care Med.* **2020**, *46*, 1099–1102. [CrossRef] [PubMed]

119. Camporota, L.; Cronin, J.N.; Busana, M.; Gattinoni, L.; Formenti, F. Pathophysiology of Coronavirus-19 Disease Acute Lung Injury. *Curr. Opin. Crit. Care* **2022**, *28*, 9–16. [CrossRef] [PubMed]
120. Abou-Arab, O.; Beyls, C.; Khalipha, A.; Guilbart, M.; Huette, P.; Malaquin, S.; Lecat, B.; MacQ, P.Y.; Roger, P.A.; Haye, G.; et al. Microvascular Flow Alterations in Critically Ill COVID-19 Patients: A Prospective Study. *PLoS ONE* **2021**, *16*, e0246636. [CrossRef]
121. Panigrahi, S.; Goswami, T.; Ferrari, B.; Antonelli, C.J.; Bazdar, D.A.; Gilmore, H.; Freeman, M.L.; Lederman, M.M.; Sieg, S.F. SARS-CoV-2 Spike Protein Destabilizes Microvascular Homeostasis. *Microbiol. Spectr.* **2021**, *9*, e0073521. [CrossRef]
122. Kohansal Vajari, M.; Shirin, M.; Pourbagheri-Sigaroodi, A.; Akbari, M.E.; Abolghasemi, H.; Bashash, D. COVID-19-Related Coagulopathy: A Review of Pathophysiology and Pharmaceutical Management. *Cell Biol. Int.* **2021**, *45*, 1832–1850. [CrossRef] [PubMed]
123. Cajanding, R.J.M. Silent Hypoxia in COVID-19 Pneumonia: State of Knowledge, Pathophysiology, Mechanisms, and Management. *AACN Adv. Crit. Care* **2022**, *33*, 143–153. [CrossRef] [PubMed]
124. Porzionato, A.; Emmi, A.; Contran, M.; Stocco, E.; Riccetti, S.; Sinigaglia, A.; Macchi, V.; Barzon, L.; De Caro, R. Case Report: The Carotid Body in COVID-19: Histopathological and Virological Analyses of an Autopsy Case Series. *Front. Immunol.* **2021**, *12*, 4475. [CrossRef]
125. Gattinoni, L.; Marini, J.J.; Camporota, L. The Respiratory Drive: An Overlooked Tile of COVID-19 Pathophysiology. *Am. J. Respir. Crit. Care Med.* **2020**, *208*, 1079–1080. [CrossRef]
126. Spinelli, E.; Mauri, T.; Beitler, J.R.; Pesenti, A.; Brodie, D. Respiratory Drive in the Acute Respiratory Distress Syndrome: Pathophysiology, Monitoring, and Therapeutic Interventions. *Intensive Care Med.* **2020**, *46*, 606–618. [CrossRef] [PubMed]
127. Thillai, M.; Patvardhan, C.; Swietlik, E.M.; McLellan, T.; De Backer, J.; Lanclus, M.; De Backer, W.; Ruggiero, A. Functional Respiratory Imaging Identifies Redistribution of Pulmonary Blood Flow in Patients with COVID-19. *Thorax* **2021**, *76*, 182–184. [CrossRef]
128. Littlefield, K.M.; Watson, R.O.; Schneider, J.M.; Neff, C.P.; Yamada, E.; Zhang, M.; Campbell, T.B.; Falta, M.T.; Jolley, S.E.; Fontenot, A.P.; et al. SARS-CoV-2-Specific T Cells Associate with Inflammation and Reduced Lung Function in Pulmonary Post-Acute Sequalae of SARS-CoV-2. *PLoS Pathog.* **2022**, *18*, e1010359. [CrossRef]
129. Su, Y.; Yuan, D.; Chen, D.G.; Ng, R.H.; Wang, K.; Choi, J.; Li, S.; Hong, S.; Zhang, R.; Xie, J.; et al. Multiple Early Factors Anticipate Post-Acute COVID-19 Sequelae. *Cell* **2022**, *185*, 881–895.e20. [CrossRef]
130. Klein, J.; Wood, J.; Jaycox, J.R.; Dhodapkar, R.M.; Lu, P.; Gehlhausen, J.R.; Tabachnikova, A.; Greene, K.; Tabacof, L.; Malik, A.A.; et al. Distinguishing Features of Long COVID Identified through Immune Profiling. *Nature* **2023**, *623*, 139. [CrossRef]
131. Ruuskanen, O.; Lahti, E.; Jennings, L.C.; Murdoch, D.R. Viral Pneumonia. *Lancet* **2011**, *377*, 1264–1275. [CrossRef]
132. Clementi, N.; Ghosh, S.; De Santis, M.; Castelli, M.; Criscuolo, E.; Zanoni, I.; Clementi, M.; Mancini, N. Viral Respiratory Pathogens and Lung Injury. *Clin. Microbiol. Rev.* **2021**, *34*, e00103-20. [CrossRef] [PubMed]
133. Yin, Y.; Wunderink, R.G. MERS, SARS and Other Coronaviruses as Causes of Pneumonia. *Respirology* **2018**, *23*, 130–137. [CrossRef] [PubMed]
134. Abdelrahman, Z.; Li, M.; Wang, X. Comparative Review of SARS-CoV-2, SARS-CoV, MERS-CoV, and Influenza A Respiratory Viruses. *Front. Immunol.* **2020**, *11*, 552909. [CrossRef] [PubMed]
135. Hendrickson, C.M.; Matthay, M.A. Viral Pathogens and Acute Lung Injury: Investigations Inspired by the SARS Epidemic and the 2009 H1N1 Influenza Pandemic. *Semin. Respir. Crit. Care Med.* **2013**, *34*, 475–486. [CrossRef] [PubMed]
136. Chen, J.; Subbarao, K. The Immunobiology of SARS. *Annu. Rev. Immunol.* **2007**, *25*, 443–472. [CrossRef]
137. Zumla, A.; Hui, D.S.; Perlman, S. Middle East Respiratory Syndrome. *Lancet* **2015**, *386*, 995–1007. [CrossRef]
138. Latreille, E.; Lee, W.L. Interactions of Influenza and Sars-Cov-2 with the Lung Endothelium: Similarities, Differences, and Implications for Therapy. *Viruses* **2021**, *13*, 161. [CrossRef]
139. Gregory, D.J.; Kobzik, L. Influenza Lung Injury: Mechanisms and Therapeutic Opportunities. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2015**, *309*, L1041–L1046. [CrossRef]
140. Klomp, M.; Ghosh, S.; Mohammed, S.; Nadeem Khan, M. From Virus to Inflammation, How Influenza Promotes Lung Damage. *J. Leukoc. Biol.* **2021**, *110*, 115–122. [CrossRef]
141. Herold, S.; Becker, C.; Ridge, K.M.; Budinger, G.R.S. Influenza Virus-Induced Lung Injury: Pathogenesis and Implications for Treatment. *Eur. Respir. J.* **2015**, *45*, 1463–1478. [CrossRef]
142. Kronibus, N.; Seiler, F.; Danziger, G.; Muellenbach, R.M.; Reyher, C.; Becker, A.P.; Kamphorst, M.; Rixecker, T.M.; Metz, C.; Bals, R.; et al. Respiratory Physiology of COVID-19 and Influenza Associated Acute Respiratory Distress Syndrome. *J. Clin. Med.* **2022**, *11*, 6237. [CrossRef]
143. Bergeron, H.C.; Tripp, R.A. Immunopathology of Rsv: An Updated Review. *Viruses* **2021**, *13*, 2478. [CrossRef] [PubMed]
144. Shang, Z.; Tan, S.; Ma, D. Respiratory Syncytial Virus: From Pathogenesis to Potential Therapeutic Strategies. *Int. J. Biol. Sci.* **2021**, *17*, 4073–4091. [CrossRef] [PubMed]
145. Mammas, I.N.; Drysdale, S.B.; Rath, B.; Theodoridou, M.; Papaioannou, G.; Papatheodoropoulou, A.; Koutsounaki, E.; Koutsaftiki, C.; Kozanidou, E.; Achtsidis, V.; et al. Update on Current Views and Advances on RSV Infection (Review). *Int. J. Mol. Med.* **2020**, *46*, 509–520. [CrossRef]
146. Torres, A.; Cilloniz, C.; Niederman, M.S.; Menéndez, R.; Chalmers, J.D.; Wunderink, R.G.; van der Poll, T. Pneumonia. *Nat. Rev. Dis. Primers* **2021**, *7*, 25. [CrossRef] [PubMed]

147. Lucas, R.; Hadizamani, Y.; Gonzales, J.; Gorshkov, B.; Bodmer, T.; Berthiaume, Y.; Moehrlen, U.; Lode, H.; Huwer, H.; Hudel, M.; et al. Impact of Bacterial Toxins in the Lungs. *Toxins* **2020**, *12*, 223. [CrossRef]
148. Grousd, J.A.; Rich, H.E.; Alcorn, J.F. Host-Pathogen Interactions in Gram-Positive Bacterial Pneumonia. *Clin. Microbiol. Rev.* **2019**, *32*, e00107-18. [CrossRef]
149. Atkinson, T.P.; Waites, K.B. Mycoplasma Pneumoniae Infections in Childhood. *Pediatr. Infect. Dis. J.* **2014**, *33*, 92–94. [CrossRef]
150. Distelhorst, S.L.; Jurkovic, D.A.; Shi, J.; Jensen, G.J.; Balish, M.F. The Variable Internal Structure of the Mycoplasma Penetrans Attachment Organelle Revealed by Biochemical and Microscopic Analyses: Implications for Attachment Organelle Mechanism and Evolution. *J. Bacteriol.* **2017**, *199*, e00069-17. [CrossRef]
151. Su, X.; You, X.; Luo, H.; Liang, K.; Chen, L.; Tian, W.; Ye, Z.; He, J. Community-Acquired Respiratory Distress Syndrome Toxin: Unique Exotoxin for *M. pneumoniae*. *Front. Microbiol.* **2021**, *12*, 766591. [CrossRef]
152. Brady, M.F.; Awosika, A.O.; Nguyen, A.D.; Sundareshan, V. Legionnaires Disease. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2024.
153. Copenhaver, A.M.; Casson, C.N.; Nguyen, H.T.; Fung, T.C.; Duda, M.M.; Roy, C.R.; Shin, S. Alveolar Macrophages and Neutrophils Are the Primary Reservoirs for Legionella Pneumophila and Mediate Cytosolic Surveillance of Type IV Secretion. *Infect. Immun.* **2014**, *82*, 4325. [CrossRef] [PubMed]
154. Mittal, S.; Singh, A.P.; Gold, M.; Leung, A.N.; Haramati, L.B.; Katz, D.S. Thoracic Imaging Features of Legionnaire's Disease. *Infect. Dis. Clin. N. Am.* **2017**, *31*, 43–54. [CrossRef] [PubMed]
155. Sawa, T. The Molecular Mechanism of Acute Lung Injury Caused by *Pseudomonas aeruginosa*: From Bacterial Pathogenesis to Host Response. *J. Intensive Care* **2014**, *2*, 10. [CrossRef]
156. Wang, C.; Armstrong, S.M.; Sugiyama, M.G.; Tabuchi, A.; Krauszman, A.; Kuebler, W.M.; Mullen, B.; Advani, S.; Advani, A.; Lee, W.L. Influenza-Induced Priming and Leak of Human Lung Microvascular Endothelium upon Exposure to Staphylococcus Aureus. *Am. J. Respir. Cell Mol. Biol.* **2015**, *53*, 459–470. [CrossRef]
157. Shirey, K.A.; Perkins, D.J.; Lai, W.; Zhang, W.; Fernando, L.R.; Gusovsky, F.; Blanco, J.C.G.; Vogel, S.N. Influenza "Trains" the Host for Enhanced Susceptibility to Secondary Bacterial Infection. *mBio* **2019**, *10*, e00810–e00819. [CrossRef]
158. Sandhu, G.; Piraino, S.T.; Piticaru, J. Secondary Infection Risk in Patients with Severe COVID-19 Pneumonia Treated with Tocilizumab. *Am. J. Ther.* **2022**, *29*, E275–E278. [CrossRef] [PubMed]
159. Li, Z.; Lu, G.; Meng, G. Pathogenic Fungal Infection in the Lung. *Front. Immunol.* **2019**, *10*, 1524. [CrossRef]
160. Bhatt, K.; Agolli, A.; Patel, M.H.; Garimella, R.; Devi, M.; Garcia, E.; Amin, H.; Domingue, C.; Del Castillo, R.G.; Sanchez-Gonzalez, M. High Mortality Co-Infections of COVID-19 Patients: Mucormycosis and Other Fungal Infections. *Discoveries* **2021**, *9*, e126. [CrossRef]
161. Gold, J.A.W.; Adjei, S.; Gundlapalli, A.V.; Huang, Y.L.A.; Chiller, T.; Benedict, K.; Toda, M. Increased Hospitalizations Involving Fungal Infections during COVID-19 Pandemic, United States, January 2020–December 2021. *Emerg. Infect. Dis.* **2023**, *29*, 1433. [CrossRef]
162. Hoenigl, M.; Seidel, D.; Sprute, R.; Cunha, C.; Oliverio, M.; Goldman, G.H.; Ibrahim, A.S.; Carvalho, A. COVID-19-Associated Fungal Infections. *Nat. Microbiol.* **2022**, *7*, 1127. [CrossRef]
163. Hoenigl, M.; Seidel, D.; Carvalho, A.; Rudramurthy, S.M.; Arastehfar, A.; Gangneux, J.P.; Nasir, N.; Bonifaz, A.; Araiza, J.; Klimko, N.; et al. The Emergence of COVID-19 Associated Mucormycosis: A Review of Cases from 18 Countries. *Lancet Microbe* **2022**, *3*, e543. [CrossRef] [PubMed]
164. Wiesner, D.L.; Merkhofer, R.M.; Ober, C.; Kujoth, G.C.; Niu, M.; Keller, N.P.; Gern, J.E.; Brockman-Schneider, R.A.; Evans, M.D.; Jackson, D.J.; et al. Club Cell TRPV4 Serves as a Damage Sensor Driving Lung Allergic Inflammation. *Cell Host Microbe* **2020**, *27*, 614. [CrossRef] [PubMed]
165. Kowalski, C.H.; Kerkaert, J.D.; Liu, K.W.; Bond, M.C.; Hartmann, R.; Nadell, C.D.; Stajich, J.E.; Cramer, R.A. Fungal Biofilm Morphology Impacts Hypoxia Fitness and Disease Progression. *Nat. Microbiol.* **2019**, *4*, 2430. [CrossRef]
166. Jacobi, J. The Pathophysiology of Sepsis—2021 Update: Part 1, Immunology and Coagulopathy Leading to Endothelial Injury. *Am. J. Health-Syst. Pharm.* **2022**, *79*, 329–337. [CrossRef]
167. Kumar, V. Pulmonary Innate Immune Response Determines the Outcome of Inflammation During Pneumonia and Sepsis-Associated Acute Lung Injury. *Front. Immunol.* **2020**, *11*, 1722. [CrossRef]
168. Li, W.; Li, D.; Chen, Y.; Abudou, H.; Wang, H.; Cai, J.; Wang, Y.; Liu, Z.; Liu, Y.; Fan, H. Classic Signaling Pathways in Alveolar Injury and Repair Involved in Sepsis-Induced ALI/ARDS: New Research Progress and Prospect. *Dis. Markers* **2022**, *2022*, 6362344. [CrossRef] [PubMed]
169. Nishibori, M. Novel Aspects of Sepsis Pathophysiology: NETs, Plasma Glycoproteins, Endotheliopathy and COVID-19. *J. Pharmacol. Sci.* **2022**, *150*, 9–20. [CrossRef]
170. Chang, K.; Svabek, C.; Vazquez-Guillamet, C.; Sato, B.; Rasche, D.; Wilson, S.; Robbins, P.; Ulbrandt, N.; Suzich, J.A.; Green, J.; et al. Targeting the Programmed Cell Death 1: Programmed Cell Death Ligand 1 Pathway Reverses T Cell Exhaustion in Patients with Sepsis. *Crit. Care* **2014**, *18*, R3. [CrossRef] [PubMed]
171. López-Collazo, E.; Avendaño-Ortiz, J.; Martín-Quirós, A.; Aguirre, L.A. Immune Response and COVID-19: A Mirror Image of Sepsis. *Int. J. Biol. Sci.* **2020**, *16*, 2479–2489. [CrossRef]

172. Tuculeanu, G.; Barbu, E.C.; Lazar, M.; Chitu-Tisu, C.E.; Moisa, E.; Negoita, S.I.; Ion, D.A. Coagulation Disorders in Sepsis and COVID-19—Two Sides of the Same Coin? A Review of Inflammation–Coagulation Crosstalk in Bacterial Sepsis and COVID-19. *J. Clin. Med.* **2023**, *12*, 601. [CrossRef]
173. Conway, E.M.; Mackman, N.; Warren, R.Q.; Wolberg, A.S.; Mosnier, L.O.; Campbell, R.A.; Gralinski, L.E.; Rondina, M.T.; van de Veerdonk, F.L.; Hoffmeister, K.M.; et al. Understanding COVID-19-Associated Coagulopathy. *Nat. Rev. Immunol.* **2022**, *22*, 639–649. [CrossRef] [PubMed]
174. Park, I.; Kim, M.; Choe, K.; Song, E.; Seo, H.; Hwang, Y.; Ahn, J.; Lee, S.H.; Lee, J.H.; Jo, Y.H.; et al. Neutrophils Disturb Pulmonary Microcirculation in Sepsis-Induced Acute Lung Injury. *Eur. Respir. J.* **2019**, *53*, 1800786. [CrossRef]
175. Lamontagne, F.; Agoritsas, T.; MacDonald, H.; Leo, Y.S.; DIaz, J.; Agarwal, A.; Appiah, J.A.; Arabi, Y.; Blumberg, L.; Calfee, C.S.; et al. A Living WHO Guideline on Drugs for COVID-19. *BMJ* **2020**, *370*, m3379. [CrossRef]
176. Perkins, G.D.; Ji, C.; Connolly, B.A.; Couper, K.; Lall, R.; Baillie, J.K.; Bradley, J.M.; Dark, P.; Dave, C.; De Soyza, A.; et al. Effect of Noninvasive Respiratory Strategies on Intubation or Mortality among Patients with Acute Hypoxemic Respiratory Failure and COVID-19: The RECOVERY-RS Randomized Clinical Trial. *JAMA* **2022**, *327*, 546–558. [CrossRef] [PubMed]
177. Shelhamer, M.C.; Wesson, P.D.; Solari, I.L.; Jensen, D.L.; Steele, W.A.; Dimitrov, V.G.; Kelly, J.D.; Aziz, S.; Gutierrez, V.P.; Vittinghoff, E.; et al. Prone Positioning in Moderate to Severe Acute Respiratory Distress Syndrome Due to COVID-19: A Cohort Study and Analysis of Physiology. *J. Intensive Care Med.* **2021**, *36*, 241–252. [CrossRef]
178. Murakami, N.; Hayden, R.; Hills, T.; Al-Samkari, H.; Casey, J.; Del Sorbo, L.; Lawler, P.R.; Sise, M.E.; Leaf, D.E. Therapeutic Advances in COVID-19. *Nat. Rev. Nephrol.* **2023**, *19*, 38–52. [CrossRef]
179. Kokic, G.; Hillen, H.S.; Tegunov, D.; Dienemann, C.; Seitz, F.; Schmitzova, J.; Farnung, L.; Siewert, A.; Höbartner, C.; Cramer, P. Mechanism of SARS-CoV-2 Polymerase Stalling by Remdesivir. *Nat. Commun.* **2021**, *12*, 1–7. [CrossRef]
180. Henao-Restrepo, A.M.; Pan, H.; Peto, R.; Preziosi, M.P.; Sathiyamoorthy, V.; Abdool Karim, Q.; Alejandria, M.; Hernández García, C.; Marie-Paule, K.; Malekzadeh, R.; et al. Remdesivir and Three Other Drugs for Hospitalised Patients with COVID-19: Final Results of the WHO Solidarity Randomised Trial and Updated Meta-Analyses. *Lancet* **2022**, *399*, 1941–1953. [CrossRef]
181. Gottlieb, R.L.; Vaca, C.E.; Paredes, R.; Mera, J.; Webb, B.J.; Perez, G.; Oguchi, G.; Ryan, P.; Nielsen, B.U.; Brown, M.; et al. Early Remdesivir to Prevent Progression to Severe COVID-19 in Outpatients. *N. Engl. J. Med.* **2022**, *386*, 305–315. [CrossRef]
182. Beigel, J.H.; Tomashek, K.M.; Dodd, L.E.; Mehta, A.K.; Zingman, B.S.; Kalil, A.C.; Hohmann, E.; Chu, H.Y.; Luetkemeyer, A.; Kline, S.; et al. Remdesivir for the Treatment of COVID-19—Final Report. *N. Engl. J. Med.* **2020**, *383*, 1813–1826. [CrossRef]
183. Tian, L.; Pang, Z.; Li, M.; Lou, F.; An, X.; Zhu, S.; Song, L.; Tong, Y.; Fan, H.; Fan, J. Molnupiravir and Its Antiviral Activity Against COVID-19. *Front. Immunol.* **2022**, *13*, 855496. [CrossRef] [PubMed]
184. Jayk Bernal, A.; Gomes da Silva, M.M.; Musungaie, D.B.; Kovalchuk, E.; Gonzalez, A.; Delos Reyes, V.; Martín-Quirós, A.; Caraco, Y.; Williams-Diaz, A.; Brown, M.L.; et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. *N. Engl. J. Med.* **2022**, *386*, 509–520. [CrossRef]
185. Saravolatz, L.D.; Depcinski, S.; Sharma, M. Molnupiravir and Nirmatrelvir-Ritonavir: Oral Coronavirus Disease 2019 Antiviral Drugs. *Clin. Infect. Dis.* **2023**, *76*, 165–171. [CrossRef] [PubMed]
186. Dryden-Peterson, S.; Kim, A.; Kim, A.Y.; Caniglia, E.C.; Lennes, I.T.; Patel, R.; Gainer, L.; Dutton, L.; Donahue, E.; Gandhi, R.T.; et al. Nirmatrelvir Plus Ritonavir for Early COVID-19 in a Large U.S. Health System: A Population-Based Cohort Study. *Ann. Intern. Med.* **2023**, *176*, 77–84. [CrossRef]
187. Saklatvala, J. Glucocorticoids: Do We Know How They Work? *Arthritis Res.* **2002**, *4*, 146–150. [CrossRef] [PubMed]
188. RECOVERY Collaborative Group Dexamethasone in Hospitalized Patients with COVID-19. *N. Engl. J. Med.* **2021**, *384*, 693–704. [CrossRef] [PubMed]
189. Mohseni Afshar, Z.; Barary, M.; Babazadeh, A.; Tavakoli Pirzaman, A.; Hosseinzadeh, R.; Alijanpour, A.; Allahgholipour, A.; Miri, S.R.; Sio, T.T.; Sullman, M.J.M.; et al. The Role of Cytokines and Their Antagonists in the Treatment of COVID-19 Patients. *Rev. Med. Virol.* **2023**, *33*, e2372. [CrossRef]
190. Hermine, O.; Mariette, X.; Porcher, R.; Resche-Rigon, M.; Tharaux, P.L.; Ravaud, P. Effect of Interleukin-6 Receptor Antagonists in Critically Ill Adult Patients with COVID-19 Pneumonia: Two Randomized Controlled Trials of the CORIMUNO-19 Collaborative Group. *Eur. Respir. J.* **2022**, *60*, 2102523. [CrossRef]
191. Montero, P.; Milara, J.; Roger, I.; Cortijo, J. Role of Jak/Stat in Interstitial Lung Diseases; Molecular and Cellular Mechanisms. *Int. J. Mol. Sci.* **2021**, *22*, 6211. [CrossRef]
192. Abani, O.; Abbas, A.; Abbas, F.; Abbas, J.; Abbas, K.; Abbas, M.; Abbasi, S.; Abbass, H.; Abbott, A.; Abbott, A.; et al. Baricitinib in Patients Admitted to Hospital with COVID-19 (RECOVERY): A Randomised, Controlled, Open-Label, Platform Trial and Updated Meta-Analysis. *Lancet* **2022**, *400*, 359. [CrossRef]
193. Quatromoni, N.; Tuteja, S.; Kolanksy, D.M.; Matthai, W.H.; Giri, J. Novel Anti-Platelet Agents in Acute Coronary Syndrome: Mechanisms of Action and Opportunities to Tailor Therapy. *Curr. Atheroscler. Rep.* **2015**, *17*, 23. [CrossRef]
194. Heestermans, M.; Poenou, G.; Hamzeh-Cognasse, H.; Cognasse, F.; Bertoletti, L. Anticoagulants: A Short History, Their Mechanism of Action, Pharmacology, and Indications. *Cells* **2022**, *11*, 3214. [CrossRef]
195. Li, K.; Meyerholz, D.K.; Bartlett, J.A.; McCray, P.B. The Tmprss2 Inhibitor Nafamostat Reduces Sars-Cov-2 Pulmonary Infection in Mouse Models of COVID-19. *mBio* **2021**, *12*, e0097021. [CrossRef]
196. Chan, J.F.W.; Yuan, S.; Chu, H.; Sridhar, S.; Yuen, K.Y. COVID-19 Drug Discovery and Treatment Options. *Nat. Rev. Microbiol.* **2024**, *22*, 391–407. [CrossRef]

197. Chen, Y.; Zhao, X.; Zhou, H.; Zhu, H.; Jiang, S.; Wang, P. Broadly Neutralizing Antibodies to SARS-CoV-2 and Other Human Coronaviruses. *Nat. Rev. Immunol.* **2022**, *23*, 189. [CrossRef] [PubMed]
198. Hoffmann, M.; Hofmann-Winkler, H.; Smith, J.C.; Krüger, N.; Sørensen, L.K.; Søgaard, O.S.; Hasselstrøm, J.B.; Winkler, M.; Hempel, T.; Raich, L.; et al. Camostat Mesylate Inhibits SARS-CoV-2 Activation by TMPRSS2-Related Proteases and Its Metabolite GBPA Exerts Antiviral Activity. *bioRxiv* 2020, *preprint*. [CrossRef]
199. Wang, R.; Chan, J.F.W.; Wang, S.; Li, H.; Zhao, J.; Ip, T.K.Y.; Zuo, Z.; Yuen, K.Y.; Yuan, S.; Sun, H. Orally Administered Bismuth Drug Together with N-Acetyl Cysteine as a Broad-Spectrum Anti-Coronavirus Cocktail Therapy. *Chem. Sci.* **2022**, *13*, 2238–2248. [CrossRef] [PubMed]
200. Zeng, J.; Weissmann, F.; Bertolin, A.P.; Posse, V.; Canal, B.; Ulferts, R.; Wu, M.; Harvey, R.; Hussain, S.; Milligan, J.C.; et al. Identifying SARS-CoV-2 Antiviral Compounds by Screening for Small Molecule Inhibitors of Nsp13 Helicase. *Biochem. J.* **2021**, *478*, 2405–2423. [CrossRef] [PubMed]
201. Idris, A.; Davis, A.; Supramaniam, A.; Acharya, D.; Kelly, G.; Tayyar, Y.; West, N.; Zhang, P.; McMillan, C.L.D.; Soemardy, C.; et al. A SARS-CoV-2 Targeted SiRNA-Nanoparticle Therapy for COVID-19. *Mol. Ther.* **2021**, *29*, 2219. [CrossRef]
202. Chu, H.; Shuai, H.; Hou, Y.; Zhang, X.; Wen, L.; Huang, X.; Hu, B.; Yang, D.; Wang, Y.; Yoon, C.; et al. Targeting Highly Pathogenic Coronavirus-Induced Apoptosis Reduces Viral Pathogenesis and Disease Severity. *Sci. Adv.* **2021**, *7*, eabf8577. [CrossRef]
203. Tamir, H.; Melamed, S.; Erez, N.; Politi, B.; Yahalom-Ronen, Y.; Achdout, H.; Lazar, S.; Gutman, H.; Avraham, R.; Weiss, S.; et al. Induction of Innate Immune Response by TLR3 Agonist Protects Mice against SARS-CoV-2 Infection. *Viruses* **2022**, *14*, 189. [CrossRef] [PubMed]
204. Monk, P.D.; Marsden, R.J.; Tear, V.J.; Brookes, J.; Batten, T.N.; Mankowski, M.; Gabbay, F.J.; Davies, D.E.; Holgate, S.T.; Ho, L.P.; et al. Safety and Efficacy of Inhaled Nebulised Interferon Beta-1a (SNG001) for Treatment of SARS-CoV-2 Infection: A Randomised, Double-Blind, Placebo-Controlled, Phase 2 Trial. *Lancet Respir. Med.* **2021**, *9*, 196–206. [CrossRef] [PubMed]
205. Zheng, F.; Zhou, Y.; Zhou, Z.; Ye, F.; Huang, B.; Huang, Y.; Ma, J.; Zuo, Q.; Tan, X.; Xie, J.; et al. SARS-CoV-2 Clearance in COVID-19 Patients with Novaferon Treatment: A Randomized, Open-Label, Parallel-Group Trial. *Int. J. Infect. Dis.* **2020**, *99*, 84. [CrossRef] [PubMed]