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Review Article

Pulmonary Thrombosis in Acute Respiratory Distress Syndrome: Theory, Evidence, and Clinical Relevance to Resource-Limited Settings

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ABSTRACT

Thrombosis is often seen in acute respiratory distress syndrome (ARDS) patients, increasing morbidity and mortality. This review highlights the pathophysiology of ARDS and how it links to pulmonary thrombosis. Understanding this link is furthermore critical as pulmonary thrombosis a serious issue in coronavirus diseases, such as COVID-19. There is a clear link between ARDS pathophysiology and pulmonary thrombosis as defined by the "two-path unifying theory" and "two-activation theory of the endothelium". Interestingly, ARDS in influenza versus COVID-19 patients have a slightly different pathophysiology, the latter having more compact fibrin clots that are more difficult to dissolve; this will impact the treatment of COVID-19 ARDS patients. We therefore also reviewed the current treatment options, underlining that potentially life-saving thrombosis-screening procedures could be lacking in resource-limited settings, therefore needing redress.

Background and Definition of Acute Respiratory Distress Syndrome

Acute respiratory distress in adults was first described by Ashbaugh *et al.* in 1967, where they studied a case series of twelve patients admitted to intensive care units [1]. They found that patients presented with similar clinical, physiological, pathological, and microscopic features; consisting of tachypnoea, hypoxaemia, decreased lung compliance, and diffuse alveolar infiltration. These features were like those of infantile respiratory distress syndrome (hyaline membrane disease) but failed to respond to the standard treatment strategies [2]. On closer inspection, the patients had different insults, varying from trauma and pancreatitis to viral disease; nevertheless, all showed an improvement in their oxygenation and atelectasis with raised positive end-expiratory pressure (PEEP). The benefit of PEEP was highlighted, whereas in others, the role of corticosteroids was advocated; however, the authors stressed that the underlying condition should still be addressed.

From the study by Ashbaugh, an acute lung injury score, the Murray Score, was developed, assessing the chest X-ray features, level of hypoxaemia, level of PEEP, and respiratory compliance [3]. The Murray score was shown to be flawed particularly on issues of validity and correlation between patients. Importantly, it did not account for timing of the insult nor the aetiology of pulmonary oedema [2].

In the two decades that followed, definitions of acute respiratory distress syndrome (ARDS) were inconsistent and unclear, and this affected the outcomes of the patients negatively. Fioretto and de Carvalho discussed the evolution of ARDS definitions and highlighted the importance of having a precise definition, especially regarding the initiation of treatment modalities and estimating the prognosis [2].

Eventually, in 2012, the currently used Berlin definition of ARDS was put forward: "ARDS is an acute diffuse, inflammatory lung injury, leading to increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue…[with] hypoxemia and bilateral radiographic opacities, associated with increased venous admixture, increased physiological dead space and decreased lung compliance" [4].

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ARDS, being a syndrome, has variable aetiologies, and is linked to mortality and multi-organ dysfunction. One such organ dysfunction, resulting in great mortality, is that of coagulopathy, specifically thrombosis. In this review, the aim is to specifically highlight the pathophysiology of ARDS and how it links to pulmonary thrombosis, a topic highly relevant given the current coronavirus pandemic. For example, the incidence of thrombosis was recorded to be as high as 46.1% in one cohort of SARS-CoV-2 infected individuals [5]. Similarly, the incidence of pulmonary emboli ranged between 16.7% and 35% in severely ill COVID-19 patients [5]. Further to this point, we synthesise the current treatment options and propose why in resource-limited settings screening limitations will affect early intervention.

Pathophysiology of ARDS

I Causes of ARDS

ARDS is not a disease, but rather a consequence of a disease process and forms part of the multi-organ dysfunction syndrome (MODS) [6]. The causes can be either pulmonary or extra-pulmonary in origin (see Table 1).

Table 1: Pulmonary or extra-pulmonary causes of ARDS (compiled from) [7-9].

Direct (Pulmonary) Causes	Indirect (Extra-pulmonary) Causes
Pneumonia (bacterial, viral, fungal, and parasitic)	Severe sepsis/septic shock (± pneumonia) (as part of MODS)
Gastric aspiration	Transfusion-associated lung injury (TRALI)
Drowning/submersion	Severe acute pancreatitis
Severe thoracic trauma/pulmonary contusion	Drug overdose (opiates, paraldehyde, paraquat) or toxins/chemicals/venom exposure
Fat emboli	Shock
Smoke/toxic gas inhalation	Severe non-thoracic trauma
Reperfusion pulmonary oedema (after lung transplant)	Disseminated intravascular coagulation
Pulmonary vasculitis	Pregnancy
Non-protective ventilation (VILI)	Severe burns
Thoracic surgery	Cardiopulmonary bypass (pump lung)

II The Three Phases of ARDS

i Inflammatory/Exudative Phase

This phase occurs during the first week after symptom onset and is marked by diffuse alveolar damage, presence of neutrophils, hyaline membranes, and interstitial and alveolar oedema. Areas of necrosis develop in the epithelial lining, while the endothelial lesions are less and may have areas of necrosis and fibrin clots. Macroscopically the lung appears heavy, rigid, and dark. Local thrombi occur. Pulmonary oedema leads to a ventilation-perfusion mismatch [10].

ii Proliferative Phase

This phase occurs during the second two weeks after respiratory failure. The alveoli become filled with leucocytes, red cells, fibrin, and cell debris, and later fibroblasts. This forms an organized matrix of exudates and fibrosis. The alveolar type II cells proliferate to cover the areas of necrosis in the epithelial basement membrane. There is loss of capillaries and pulmonary hypertension occurs. The lung becomes grey. Injury to the type II pneumocytes decreases surfactant and causes decreased compliance [10].

iii Fibrotic Phase

This phase begins after ten days, characterised by a marked decrease in neutrophils but where macrophages and lymphocytes accumulate. Collagen deposits in the lung. Fibrosis increases the work of breathing and can predict outcome. The scarring gives the lungs a cobblestone appearance. There is intimal thickening and tortuous veins. Scarring decreases diffusion capacity and leads to further hypoxia and decreased compliance [10].

III Key Agents in the Pathogenesis of ARDS

i Complement

The complement system is key in shaping adaptive immune responses. When an insult or pathogen initiates the host's innate immune system, to build an immune response, complement gets activated and exerts its protective function by opsonization of foreign surfaces by C3b. C3b phagocytoses the pathogen, amplifies complement activation, and assembles C5 convertase, which cleaves C5 and forms C5b-9 (membrane attack complex), lysing the pathogen [11].

ii Macrophages

Macrophages exist in two polarization states: the classically activated phenotype (M1) and alternatively activated phenotype (M2). There are two types of macrophages in the lung: resident alveolar macrophages and recruited macrophages. The resident macrophages are situated at the air–tissue interface (mainly M2 type) and release cytokines to recruit neutrophils and monocytes to promote or sustain inflammation. Recruited macrophages differentiate into the M1 phenotype macrophages and clear pathogens and limit the inflammatory response [12]. Interestingly, macrophages and monocytes are pro-inflammatory in the early stages of ARDS and anti-inflammatory in the later repair stages. Thus, depletion of macrophages is protective in the early stages but worsens lung injury in the later stages [12]. Macrophages also attract neutrophils to the site of inflammation through release of chemokines (macrophage inflammatory protein-2 and interleukin-8), where the neutrophils cause tissue damage.

As comprehensively reviewed by Huang *et al.* in 2018, macrophages are involved in all three phases of ARDS [12]:

a. Exudative phase*:* Toll-like receptors cause a shift to the M1 predominant phenotype macrophage, which releases pro-inflammatory cytokines (IL-1b, IL-6, IL-8) and attracts neutrophils into the alveolar space. If excessive amounts accumulate, tissue damage ensues.
b. Rehabilitation phase*:* Resident and recruited macrophages shift from the M1 to the anti-inflammatory M2 phenotype, which repairs lung tissue and release anti-inflammatory cytokines (IL-10, IL-1 receptor antagonist, and Th2). These anti-inflammatory cytokines clear neutrophils. M2 macrophages phagocytose necrotic cells and debris and apoptotic cells by a process called efferocytosis. This increases the IL-10 levels, and this further combats the inflammation and together with IL-4 and IL-3 further enhances the efferocytosis.
c. Fibrotic phase: The M2 macrophage phenotype promotes collagen deposition through IL-4 and IL-13 expression and causes excessive fibroblast proliferation and deposition on the extracellular matrix, causing the lungs to become stiff and fibrotic. There are, however, studies reporting that the IL-4-polarised M2 macrophages might limit fibrosis; this paradoxical generation and healing of fibrosis still needs to be clarified.

iii Neutrophils

Neutrophils are usually abundant but are not essential. They cause tissue damage through reactive oxygen species and release of inflammatory mediators and cytokines [10]. They can cause neutrophil extracellular traps (NETs) with traumatic tissue injury and cause vascular occlusion and increased vascular permeability [13, 14]. The role of neutrophils in thrombosis, although in need of further clarification, is thus highlighted [15, 16]. Indeed, more recently, evidence emerged of a relationship between NETs and thrombosis in COVID-19 patients [17].

iv Endothelium

The endothelium plays an important role in the pathophysiology of sepsis, ARDS, and multi-organ dysfunction syndrome [11, 18, 19]. The host response determines the eventual outcome in patients [18]. The interaction between the host cells and the pathogen leads to an inflammatory response causing a rise in cytokines like IL-1β, IL-3, IL-5, IL-6, IL-8, IL-11, IL-15, and TNF-alpha, and a coagulation response with increased D-dimer and decreased protein C levels [18, 20]. Monocytes, macrophages, and endothelial cells play a central role in the innate immune response [18, 20].

The endothelium has various functions, depending on the state of the host. Under normal conditions it provides homeostasis of metabolism and the vascular tone, permeability, and coagulation, while it balances vasodilating (nitric oxide and prostacyclin) and vasoconstricting factors (endothelin) [18, 20]. The endothelium is the first to recognize pathogens and acts towards the foreign material [18, 20]. They then warn the rest of the body of the invasion by producing pro-inflammatory cytokines and chemokines, which recruit even more immune cells [20]. Endothelial cells also promote the production of cytokines and can serve as antigen-presenting cells themselves [20]. Endothelial cell plasticity causes the endothelium to play a pivotal role in the immune response by adapting to its environment [20]. The host might try to contain the sepsis, thus causing collateral tissue damage [18]. The control of the innate immune response can decrease this collateral damage and prevent a dysregulated response, leading to SIRS or MODS [18]. Inflammatory mediators (IL-1, TNF-alpha, IFN, and oxygen free radicals) and hypoxia induce endothelial cell apoptosis, which is also pro-inflammatory [18].

The activation of the coagulation cascade leads to fibrin formation, which immobilises pathogens on the leukocyte surface [18]. Thrombin signalling leads to changes in cell shape, permeability, and release of the adhesion molecules E-Selectin, P-Selectin, intracellular-adhesion molecule (ICAM-1), and vascular cell adhesion molecule (VCAM-1), as well as von Willebrand factor (vWF) and platelet-activating factor (PAF) [18]. These adhesion molecules ensure strong adherence and transmigration of leukocytes [18]. Platelets are also recruited by the endothelial cells. Low flow states due to low cardiac output, vasoconstriction, and occlusion of vessels decrease clearance of activated serine proteases, thereby increasing clotting [18]. The above mentioned two pathways are integrated and are responsible for the profound host response leading to MODS, as depicted in (Figure 1) [18].

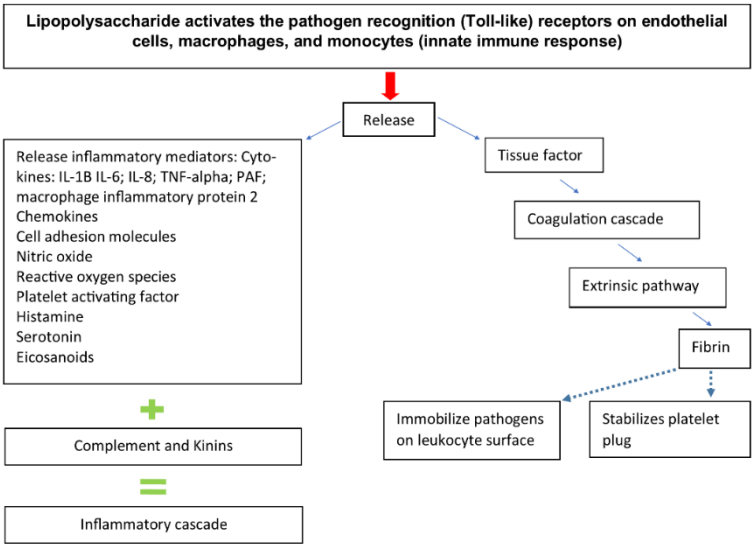

Figure 1: The role of the endothelium in mediating the host response to infection. Adapted from Aird [18].

Endotheliopathy of acute critical illness also might be due to a sympathetic-adrenal hyperactivation, as a means to perfuse the organs [21]. Excessive complement activation in critical illness leads to TTP-like syndrome and an endotheliopathy [19].

v Platelets

Platelets' primary role is to bring about homeostasis and support the immune response and haemostasis [22]. Platelet cell surface proteins contain immunomodulatory proteins that are either pro- or anti-inflammatory (Table 2).

Table 2: The immunomodulatory proteins of platelet cell surface proteins, which are either pro- or anti-inflammatory [22].

Pro-inflammatory	**Anti-inflammatory**
Selectin family: P-Selectin recruits neutrophils	Transforming growth factor-beta: immunosuppressive mediator
CD4 and CD154(CD40L) – interactions between lymphocytes and antigen presenting cells (dendritic cells/macrophages) – upregulate pro-inflammatory mediators (VCAM) – CD154 release IL-6 and tissue factor and upregulate E-selectin and P-selectin	
Toll-like receptors recognize pathogens and release pro-inflammatory mediators (chemokines; IL-1; TNF-alpha)	

Dysregulated coagulation and excessive inflammation form part of the pathogenesis of ARDS, and the platelets' contribution to this highlights its non-homeostatic features. As reviewed by Yadav and Kor, the platelet–neutrophil interaction increases Thromboxane A2, P-selectin, neutrophil activation, and expression of intracellular adhesion molecule (ICAM), which leads to neutrophil adhesion and migration [22]. Platelets also express alpha granules, which facilitate leucocyte migration and recruitment. These alpha granules and proteins have been found in the bronchoalveolar lavage fluid of ARDS patients and an increased concentration thereof has been linked to an increase in the severity of ARDS [23].

Platelets modulate the immune response by generating microparticles (PMPs). These break off from intact cells and trigger mechanical and shear injury and inflammation. They also promote cytokine and inflammatory mediator production from the endothelium. Platelets also activate neutrophil extracellular traps, which are web-like structures of DNA and condensed chromatin that have an intrinsic proteolytic activity against microbes. They need neutrophil apoptosis in order to form, but this can lead to excessive inflammation [22].

Platelets are also involved in the resolution of the immune response. By apoptosis of neutrophils, it decreases the neutrophils in the blood stream and decreases migration. They also produce pro-resolving mediators, such as Lipoxin, which are derived from arachidonic acid, as well as inhibit inflammatory processes, such as chemotaxis, reactive oxygen species, and neutrophil proliferation [22].

vi Other Factors in ARDS Pathophysiology

Herwig *et al*. confirmed previous studies that vascular endothelial cadherin, a cell adhesion molecule at the endothelial cell junctions, maintains endothelial cell integrity and that decreased expression thereof (caused by the cytokines TNF-alpha, IFN, and lipopolysaccharide) should be considered as a mechanism for increased vascular permeability in ARDS [24]. In turn, soluble vascular cell adhesion molecule-1 (sVCAM-1) is increased in ARDS bronchoalveolar lavage fluid and more increased in moderate and severe ARDS compared to milder forms [25]. This supports the endothelial activation role in ARDS pathogenesis; however, the study had some limitations in that the sample size was small, the study was not adequately powered, and only patients with suspected ventilator-associated pneumonia were included, which leads to bias. Lastly, surfactant is decreased in ARDS due to injured type II pneumocytes, and hypoxic pulmonary vasoconstriction is lost due to hypoxia, leading to mild pulmonary hypertension.

Pulmonary Thrombosis and ARDS

The Link between Pulmonary Thrombosis and ARDS

The balance between pro-coagulant and anticoagulant states is crucial in the homeostasis of coagulation in the host. The pro-coagulant factors are tissue factor, forming part of the extrinsic pathway, and the contact system, consisting of factor XII, pre-Kallikrein, and high-molecular-weight kininogen (HMWK), as part of the intrinsic pathway. The anticoagulant factors are the tissue factor pathway inhibitor (TFPI); antithrombin III (heparan), which neutralizes serine proteases and inhibits factors Xa and IIa; thrombomodulin and activated protein C and S, which inactivates factor Va and VIIIa; and plasmin, which degrades fibrin. Coagulation is important in trapping infections by forming a fibrin network, limiting dissemination. This inflammatory and coagulation response leads to pulmonary thrombosis [26].

Chang reviewed the endothelial molecular pathogenesis associated with vascular microthrombotic disease and ARDS as an organ phenotype of vascular microthrombotic disease [6]. He concluded that ARDS is a consequence of endotheliopathy, which activates two different pathways, explained by his "two-activation theory of the endothelium". The pathogen or insult injures the endothelium that then activates the inflammatory pathway and the microthrombotic pathway. The inflammatory pathway leads to systemic inflammatory response syndrome (SIRS) and a "cytokine storm", while the microthrombotic pathway activates platelets and causes exocytosis of unusually large von Willebrand factor multimers (ULVWF). These form microthrombi strings that attach to the endothelium if ADAMTS13 is deficient or insufficient. ADAMTS13 is synthesized in the liver and cleaves von Willebrand factor (vWF) [27]. A congenital (gene mutation) or acquired (auto-immune) deficiency causes thrombotic thrombocytopaenia purpura (TTP). Other disease states, such as infection, disseminated

malignancy, and haemolytic uraemic syndrome (HUS), can also cause a modest deficiency.

It is observed that, in ARDS, disseminated intravascular coagulation (DIC) is not mentioned, but rather disseminated intravascular thrombosis (DIT) and endotheliopathy-associated vascular microthrombotic disease (EA-VMTD). This is because the endotheliopathy causes microthrombi, while true DIC, as what occurs in acute promyelocytic leukemia (APL), is characterized by disseminated fibrin clots that occur without vascular injury, as seen in (Table 3) the "DIC" associated with ARDS and sepsis should thus be renamed as endotheliopathy-associated vascular microthrombotic disease (EA-VMTD) or disseminated intravascular thrombosis (DIT), which is a TTP-like syndrome, due to the oversupply of ULVWF secondary to endothelial exocytosis.

Table 3: A comparison of the changes in characteristics between EA-VMTD/DIT in ARDS and true DIC in APL.

EA-VMTD/DIT	True DIC in APL
Increased Factor VIII	Decreased FVIII
Decreased Factor VII	Normal FVII

EA-VMTD: Endotheliopathy-Associated Vascular Microthrombotic Disease; DIT: Disseminated Intravascular Thrombosis; DIC: Disseminated Intravascular Coagulation; APL: Acute Promyelocytic Leukemia.

The difference between TTP and TTP-like syndrome is that TTP causes a microvascular thrombosis in the microcirculation and activates an "aberrant" ULVWF path without intravascular injury, while TTP-like syndrome causes a vascular microthrombosis in the small and large vasculature, which activates the "normal" ULVWF path due to endothelial injury.

The "two-path unifying theory" by Chang explains that, depending on which structures in the vessel wall gets injured, three different types of blood clots can be formed [6]. If only the endothelium gets injured, then only the ULVWF path gets activated and not the tissue factor (TF) path, which leads to microthrombosis only. If there is subendothelial (SET) or extravascular tissue (EVT) injury, then the TF path and Factor VII gets activated, which causes fibrinogenesis. If both the endothelium and SET/EVT gets injured, then the microthrombi strings and fibrin mesh will cause blood clots (macrothrombogenesis). In summary, the clear link between ARDS and pulmonary thrombosis underlines the role of anticoagulant and antithrombotic therapy in treating ARDS patients.

How Does COVID-19 Contribute to Pulmonary Thrombosis in ARDS?

Batah and Fabro reviewed the pulmonary pathophysiology of ARDS in COVID-19, which stated that SARS-COV-2 binds to angiotensin converting enzyme-2 and toll-like receptors in pneumocytes and induce an inflammatory response [28]. The diffuse alveolar damage, leakage of protein-rich fluid, hyaline membrane formation, and intracapillary thrombosis of ARDS pathophysiology corresponds with ARDS in COVID-19 patients [28]. However, worth noting is that the ARDS lung mechanics in COVID-19 patients is atypical to classic ARDS patients due to the relatively well-preserved lung compliance in the former [29]. For example, one study found 28% higher median static lung compliance in COVID-19 ARDS versus classic ARDS [30]. Nonetheless, in a study done by Wu *et al*., 21.9% of COVID-19 patients developed ARDS [31]. In fact, ARDS is an often-seen complication after severe infection by SARS-CoV-2 [32].

COVID-19 patients are at increased risk for pulmonary vascular thrombosis. A recent systematic review concluded that 12.6% of 2928 COVID-19 patients managed in an ICU developed pulmonary embolism despite anticoagulant thromboprophylaxis. They reviewed 24 studies with a total thromboembolic incidence of 34%, with deep vein thrombosis comprising 16.1% [33]. In a French study, 17% of COVID-19 patients admitted to ICU were diagnosed with pulmonary embolism [34]. In Austria, autopsies on 11 deceased COVID-19 individuals were performed. In this cohort, 10 autopsies revealed thrombotic material in the pulmonary branches [35]. In a German study, 6 out of 16 COVID-19 patients had pulmonary thrombosis [36]. Other viral diseases, such as EBOLA and CMV, are also prone to DIC due to the activation of IL-6 and TNF, which activate the endothelial cells and tissue factor [37-39]. Indeed, coagulation is important in trapping viral infections by forming a fibrin network, limiting dissemination. This inflammatory and coagulation response lead to pulmonary thrombosis [26]. Patients who have died from COVID-19 have shown a higher D-dimer level and fibrin degradation products [40]. High D-dimer levels combined with low static lung compliance led to higher 28-day mortality in COVID-19 patients [30]. Thus, pulmonary thrombosis could cause prothrombotic endothelial dysfunction, causing complement and cytokine release and consumption coagulopathy [41].

A recent study compared the pathophysiology of COVID-19 pneumonia and Influenza-ARDS and found that there was an increased activation of the contact system pathway and factor XII with COVID-19 patients and that they had defective fibrinolytic ability [42]. The lag phase in fibrin formation was not prolonged in COVID-19 compared to Influenza. The fibrin clots in the COVID-19 group had thinner fibers and smaller pores, making it more compact. COVID-19 plasma contains factor XII autoactivation factors and the activated FXII alters the structure of the fibrin clot, which leads to a decrease in the FXII plasma levels. Clot lysis was only present in 30% of COVID patients compared to 84% in the ARDS-influenza group and normal clot dissolution in normal subjects. Fibrin deposits were found widespread in the vascular and alveolar tissue of COVID-19 patients and were more homogenous compared to ARDS-influenza patients who had fibrin predominantly in the alveolar spaces and displayed areas of high and low fiber density. Increased plasma levels of thrombin activatable fibrinolysis inhibitor (TAFI) and plasminogen-activator inhibitor (PAI-1) contributes to the thrombosis in COVID-19, despite an increase in tissue plasminogen activator (tPA).

Evidence emerged of a relationship between the presence of neutrophil extracellular traps and thrombosis in COVID-19 patients, which is an important finding, as it means that finding ways to neutralize the NETs may in the future help curb thrombus formation in coronavirus-induced ARDS patients [17].

Previously identified coronaviruses, such as the Middle Eastern Respiratory Syndrome (MERS) and severe acute respiratory syndrome (SARS), can also induce severe ARDS, suggesting that the outbreak of such coronaviruses is highly consistent with severe ARDS symptoms, including pulmonary thrombosis [43, 44]. Thus, for future SARS coronavirus pandemics, one should anticipate increased ARDS cases, and thus a high likelihood of pulmonary thrombosis, suggesting critical care health workers should be made aware of this impact of SARS coronaviruses in ARDS, to prepare a comprehensive toolbox of possible treatments.

Treatment Options

The first principle for treating ARDS would be to diagnose the cause (*sensu* Beale) [45]. Upon finding pulmonary thrombosis in ARDS as a cause, the following are possible treatments. A recent meta-analysis and systematic review highlighted the relevance of systematic screening of COVID-19 patients for venous thromboembolism [33, 46]. Duplex ultrasound was more diagnostic than clinical suspicion.

A French monocenter, retrospective study showed a high incidence of pulmonary embolism in critically ill COVID-19 patients and suggested venous thromboprophylaxis with unfractionated or low-molecular-weight heparins as a vital treatment to consider [34]. Apart from its anticoagulant effect, it also has anti-inflammatory and antiviral and protective effects on the pulmonary endothelium [46]. Heparin has been shown to decrease mortality [47]. Ball *et al*. commented in *The Lancet* showing that there were several studies that demonstrated benefit in administering nebulized heparin to help decrease the onset and progression of lung injury [48]. However, one meta-analysis by Glas *et al*. did not show any benefit [49]. The CHARLI study reviewed self-reported clinical outcomes in patients who received nebulized heparin but had limitations due to patients who failed to undergo follow-up or demised. It did, however, show that patients that received nebulized heparin had an earlier discharge out of hospital compared to those who only received standard therapy [48]. Ball *et al*. concluded that it is safe to use 25,000 IU of nebulized heparin six-hourly, combined with systemic low-molecular weight heparin or unfractionated heparin, provided that it gets stopped once sputum became blood-tinged or there is an excessive rise in activated partial thromboplastin time [48].

The precise therapeutic dosage of heparin is yet to be determined as patients with severe COVID-19 can also bleed with therapeutic dosages [50]. Dutt *et al*. (2020) looked at the relevance of anti-FXa levels in these patients and concluded that 95% of ICU patients did not achieve targeted anti-FXa activity compared to only 27% in ward patients [47]. They suggested to use a prophylactic dose of 40 mg enoxaparin twice daily instead of 40 mg once daily. Ward patients can still benefit from anti-FXa guided dosing as 30% of these patients have suboptimal levels. Pregnancy, renal impairment and obesity can lead to suboptimal thromboprophylaxis. Patients can also develop resistance to heparin, especially patients with ARDS. The review by Jenner *et al*. (2021) suggests using higher dosing regimens of heparin in ICU patients due to their higher incidence of thrombosis, and thus higher mortality risk, despite thromboprophylaxis [33].

As reviewed by O'Donnell *et al*. (2021) the thrombi in the pulmonary vasculature are predominantly composed of fibrin and platelets [50]. Antiplatelet therapy has also been proposed as a potential preventative therapy. Platelet inhibition with aspirin or glycoprotein IIb/IIIa inhibitors can decrease NET production and tissue injury in ARDS [22]. Aspirin triggers lipoxins to promote macrophage phagocytosis of apoptotic inflammatory cells and increase the concentration of resolvins, which can be a potential preventative therapy for ARDS [22]. The review by Yadav and Kor supports antiplatelet therapy in prevention of ARDS, as antiplatelet therapy decreased the incidence trend in ARDS, although it did not significantly decrease the risk [22]. In one prospective observational study, prehospital aspirin improved outcomes in decreasing overall ICU mortality [22]. However, the other studies, in that review, showed no significant association [22]. A multicenter, randomized control trial of aspirin prevention in acute lung injury (LIPS-A) by Kor *et al*. randomized at-risk patients in the emergency center into aspirin and placebo groups. They found that aspirin did not decrease ARDS risk at 7 days and did not support continuation to larger Phase 3 trials [51]. Treatment with anticoagulants, such as low molecular weight heparin (LMWH) and fondaparinux, can limit the inflammation–coagulation cycle and improve gas exchange [41]. Early prophylactic anticoagulation treatment could be considered where pulmonary thrombosis or embolism is suspected, although more data is needed to guide therapy [35].

Other experimental treatment modalities have also been trialled, some demonstrating great promise. Therapeutic plasma exchange (TPE) is utilized in conditions such as TTP-like syndrome, microangiopathic haemolytic anaemia (MAHA), and thrombotic microangiopathy. As the pathophysiology of ARDS, as reviewed by Chang, is due to an endotheliopathy and a TTP-like syndrome, TPE is advised and should be initiated early in the disease process [6]. Normal donor plasma with adequate amounts of ADAMTS13 cleaves excess unusually large vWF multimers (ULVWF). Antimicrothrombotic agents, such as recombinant ADAMTS13, has been effective *in vitro*, and is advocated for *in vivo*, but studies are still in Phase I trials and more trials are needed in septic patients [11]. Capalacizumab, an anti-vWF nanobody, showed clinical benefits in a study on acquired TTP, as reviewed by Chang [11]. Anti-complement therapy (Eculizumab) is also speculated to have a potential benefit in non-pathogen-related endotheliopathy-associated vascular microthrombotic disease (EA-VMTD) [11]. Limiting excessive pro-inflammatory response in the exudative phase and fibroblast proliferation in the repair phase may be a novel therapeutic target for ALI/ARDS [12].

Modification of macrophage activity in each stage can be used as a therapeutic strategy in the management of ARDS/ALI, but further studies and investigations are needed [12]. A potential treatment target in TRALI is neutrophil extracellular traps (NETs) [13]. Angiotensin I receptor increases vasoconstriction and blood pressure, thereby increasing pulmonary oedema – the aim is to block this receptor. Finally, a recent systematic review of COVID- and non-COVID-related ARDS found that corticosteroids are likely to reduce mortality and the duration of mechanical ventilation, a finding consistent in both COVID and non-COVID ARDS; thus, corticosteroids should be considered in most patients with ARDS, regardless of aetiology [52]. Other treatments to hamper the endotheliopathy like statins and prostacyclin are still under

investigation [50]. Immunomodulatory therapy like dexamethasone is being studied. Crizanlizumab can inhibit interaction of P-selectin with leucocytes and platelets [50].

Clinical Relevance to Resource-Limited Settings

At some tertiary hospitals in South Africa, the anti-factor Xa levels are measured to optimise the dosage of LMWH. The blood specimen must be obtained on the second day of therapy, three hours after the last dosage, and taken to the laboratory and processed within an hour. Thus, even though well-resourced hospitals might be able to execute this potentially life-saving screening of the therapeutic effectivity of heparin in clot lysis, it is unfeasible for smaller hospitals and healthcare facilities in resource-limited settings, who might have delayed specimen transportation to measure these levels. Resource-limited settings would thus have less guidance in treatment. Further studies are needed to guide dosing in these resource-limited areas.

Conclusion

It is clear that there is strong link between thrombosis and ARDS due to the dual activation of the two pathways involved. It is thus imperative that focus be placed on the prevention, early recognition, and treatment of pulmonary thrombosis as part of endotheliopathy-associated vascular microthrombotic disease. These findings are especially relevant given the current COVID-19 pandemic, which increased the cases of ARDS and thus pulmonary thrombosis. The authors advocate for the use of nebulised and systemic thromboprophylaxis. Therapies such as corticosteroid use may be of benefit to the COVID and non-COVID ARDS patient. Other potential therapies, such as prophylactic antiplatelet therapy, showed mixed results and warrant further investigation. Excitingly, several novel therapies are on the horizon. The safety and efficacy of these novel therapies are yet to be seen. Further investigation into these and other therapies may aid clinicians in managing and curing patients with ARDS and the concomitant pulmonary thrombosis. This is particularly critical in resource-limited settings, as coronavirus-disease patients would not be limited to tertiary institutions in South Africa.

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Conflicts of Interest

None.

Author Contributions

Both authors conceived the idea, and N.G. wrote the first draft. Both authors contributed to revising the manuscript.

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