History of Medicine Studies
ISSN:1300-669
Volume 20 Issue 2 Aug 2024

Heparin, Heparan Sulphate, and Sepsis: Possible Novel Therapeutic Approaches

1. **A. Sai Saranya***, Asso. Professor, DEPT OF Pharmaceutical Analysis

2. D. Mahidhar Reddy, Asso. Professor, DEPT OF PHARMACEUTICS

3. Sk. Karimunnisa, Asst. Professor, DEPT OF PHARMACEUTICS

4. J. Surya Prakash, Asst. Professor, DEPT OF Pharmacy Practice

5.**Dr. M. SREENIVASULU**, PRINCIPAL, NARAYANA PHARMACY COLLEGE

[1,2,3,4,5] NARAYANA PHARMACY COLLEGE, CHINTHA REDDY PALEM, NELLORE

Abstract: Sepsis is a potentially fatal overreaction to an infection in which the host's tissues and organs are damaged by an overabundance of inflammation and immunological response. One of the main components of the cell surface glycocalyx is the glycosaminoglycanheparan sulphate (HS).Cell surface HS is a target for the pro-inflammatory enzyme heparanase and controls a number of sepsis pathways, including neutrophil recruitment and pathogen interactions with the host cell. A close structural cousin of HS, heparin is a potent anticoagulant and antithrombotic used in medicine.Numerous studies have shown that heparin, which has a significant negative charge and structural similarities to HS, might affect how sepsis-related events develop. Heparin's anticoagulant action, however, restricts its ability to treat inflammatory disorders by increasing the risk of bleeding and other unfavourable side effects.Heparin derivatives and mimetic compounds with decreased anticoagulant action have been developed since the anticoagulant potency of heparin is mostly governed by a single well-defined structural characteristic. In the case of sepsis, such heparin mimics may be useful as therapeutic medicines.

Keywords: heparin; heparinmimetics; heparansulphate; sepsis;neutrophils;heparanase

1. Introduction

According to Sepsis (who.int)URL (accessed on 24 November 2022), sepsis is a multi-organ failure disease brought on by a dysregulated host defence against infection. According to a 2017 research on the global burden of illnesses, injuries, and risk factors, 49 million individuals are thought to have sepsis, which results in 11 million fatalities annually worldwide [1].Antimicrobials may effectively treat sepsis, particularly when detected and treated early. It is difficult to make a conclusive diagnosis of sepsis, however. Although the global harmonisation of clinical diagnosis was improved by the 2016 update of the international consensus on the definition of sepsis [2] and the availability of guidelines on the diagnosis and treatment of pathological diseases associated with sepsis, such as disseminated intravascular coagulation (DIC) [3–6], sepsis-related mortality and morbidity continue to be a major public health concern.

It is well acknowledged that the two main causes of sepsis-related disease are abnormal coagulation and inflammation.Although Jarczak et al. [7] described the role of complement and coagulation pathways in the development of sepsis and the available treatments, they

came to the conclusion that the effectiveness of medications like steroids and immunoglobulins has not been shown and is still debatable.Numerous cell types, including monocytes and endothelial cells, are activated by microbes and associated endotoxins to produce procoagulant tissue factor.The contact phase of the coagulation cascade, which further supports the consumption of coagulation factors and inhibitors and, if left unchecked, results in thrombin production and DIC, is also triggered by concurrent activation of the proinflammatory complement pathways [8]. Additionally, studies have shown that heparin's binding to SARS-CoV-2 spike proteins may reduce the virus's ability to infect others [9, 10].Clinical trials using nebulised heparin are, in fact, investigating Heparin's antiviral and anti-inflammatory effects are still present [11–14].According to recent developments in heparin research, heparin influences the innate immune responses to infection by interacting not only with the coagulation cascades but also with blood cells and several complement system components [15]. Several recent studies of heparin's non-anticoagulant characteristics have addressed the problem of sepsis [16,17], and the relevant topic of potential roles for heparin mimics in the treatment of SARS-CoV-2 has garnered attention [18,19].Recent research has also examined the function of heparin in regulating the "thrombo-inflammatory" interaction between coagulation and inflammation in sepsis [8].The purpose of this paper is to provide a brief overview of the non-anticoagulant functions of heparin and its mimetics, which may affect the development of sepsis and sepsis-related pathologies by interfering with pathways that rely on matrix and cell surface heparan sulphate (HS). Figure 1 summarises the HS-dependent mechanisms in sepsis and functions as a "graphical table of contents."Despite the differences scientists make between coagulation, inflammation, and immunity, none of the processes shown are independent of one another; rather, they interact in a complicated network.

History of Medicine Studies
ISSN:1300-669
Volume 20 Issue 2 Aug 2024

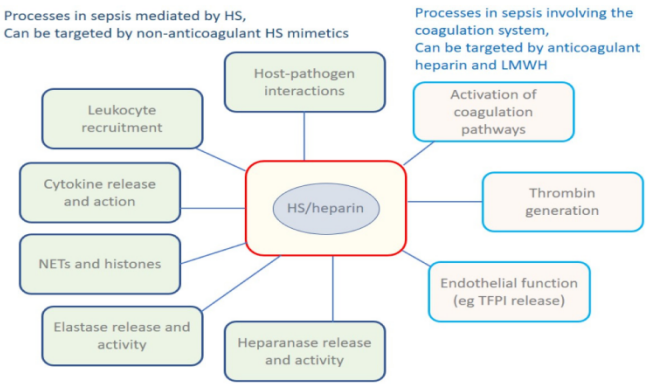

Figure1.
Theaspectsofsepsisthatmaybemodifiedbytheadministrationof heparin-basedtherapeu-tics can be divided into two categories, those for which the anticoagulant/antithrombotic propertiesofheparinarecriticalontheonehand, andthosethatarenotdependentonanticoagulantaction,but are based on disrupting HS-dependent processes. These processes are not independent of eachother,andperturbationofoneprocesswillbereflectedinallth eothers.Heparinanditsrelativesare well placed for development of treatment options in which anticoagulant and anti-inflammatoryproperties are combined to control the combination of excessive inflammatory and coagulationresponses to infection that give rise to sepsis.Abbreviations; HS: heparan sulphate; LMWH: lowmolecular weight heparin; NETs: neutrophil extracellular traps; TFPI: tissue factor pathway inhibitor.

2. AnticoagulantActionof HeparininSepsis

The haemostasis system is always altered by sepsis, necessitating therapeutic treatments [20], and some patients manifest with DIC [21]. Up to more than half of all sepsis patients will have thrombocytopenia [22, 23], and the severity of the condition is correlated with the platelet count [24]. In addition to decreased production [25], decreased consumption and activation also contribute to decreased platelet counts. Platelet activation and thrombin production are caused by the development of pro-inflammatory markers in the early stages of sepsis [26]. Additionally, platelets are consumed via the platelet–neutrophil interaction, which is discussed below and occurs in the setting of thrombo-inflammation [27].Due to their antithrombotic properties [28,29], heparin and similar mimetics may reduce the development of thrombus by inhibiting activated coagulation factors [30].Attenuation would be advantageous since thrombin is known to have targets outside of coagulation, such as the complement pathway [31]. Although the potential effect of parin in the later stages of sepsis may be restricted owing to sepsis disruption of this pathway, the release of cell surface HS anchored tissue factor pathway inhibitor (TFPI) [32] may have benefits early or pre-sepsis to prevent coagulation. Therefore, the timing of the use of parin or mimics in the treatment or prevention of sepsis may be crucial for their antithrombotic effects. Heparin and low molecular weight heparins have been advised because of the procoagulant and prothrombotic character of the early stages of sepsis [34]. Additionally, for the prevention and treatment of sepsis-associated thrombosis and DIC, see https://b-s-h.org.uk/guidelines/guidelines/diagnosis-and-management-of-disseminated-intravascular-coagulation-1URL (accessed on November 24, 2022). By reducing the consumption of plasmatic coagulation factors (and inhibitors), heparin is being utilised as an anticoagulant and antithrombotic in this situation. Numerous clinical studies have examined the safety and effectiveness of heparin's usage as an antithrombotic in preventing thrombosis in COVID-19 patients [34–44]. According to recent meta-analyses of clinical studies involving adult septic patients, heparin and low molecular weight heparin (LMWH) decreased multiple organ failure occurrences and 28-day mortality [45,46].Additionally, in the LMWH trials, There was also a decrease in inflammatory markers such IL-6 and tumour necrosis factor-α [46].Other heparinoids and mimics, including pentosan and daproid,Because of its possible antiviral and anti-inflammatory qualities, sulphate is also being studied as a therapy option to combat the prothrombotic character of infection. Danaparoid is an approved antithrombotic that is not indicated for heparin-induced thrombocytopenia. It is a combination of heparan, dermatan, and chondroitin sulphate.Experimental models of sepsis have shown that danaparoid may prevent multiple organ failure and reduce systemic inflammation [47, 48]. It has also been found to be more effective than heparin when combined with antithrombin [49]. In documented instances of vaccine-induced immunological thrombocytopenia, danaparoid has also been administered with effectiveness; this may have been facilitated by a decrease in the proinflammatory C-reactive protein [50]. Once employed as an antithrombotic and antilipemic drug, pentosan polysulphate is a semi-synthetic sulphated xylan that is now approved to treat osteoarthritis in animals and interstitial cystitis in humans. Pentosan polysulphate has been shown by Bertini et al. [51] to prevent SARS-CoV-2 entrance in overocells, suggesting that it may have antiviral properties.

Non-AnticoagulantActionofHeparinandSepsis

A prominent component of the glycocalyx, a thick layer rich in carbohydrates on the surface of cells, is heparan sulphate (HS), a member of the glycosaminoglycan family of linear sulphated polysaccharides. Heparin is a particularly highly sulphated form of HS that is present in mast cell granules. A particular pentasaccharide sequence in heparin that has a strong affinity for the serine protease inhibitor antithrombin is the structural characteristic that gives it its strong anticoagulant action; this motif is uncommon in HS. Heparin and HS structural details and their connection to biological characteristics have been examined [15,52,53].
Pathogen-HostRelationships
A significant component of virulence, adherence of microbial pathogens to the host cells and matrix mediates colonisation and infection [55]. Many microbial pathogens, including bacteria, viruses, and parasites, use cell-surface HS as a host attachment factor [16,54]. This includes both Gram+ve and Gram−ve bacteria, which are

the most common infections that cause sepsis. Furthermore, the phagocytosis of bacteria may be preceded by adhesion to the host phagocytic cell surface [56]. A decoy mechanism that reduces direct microbial contact with cell surface HS via competition may be used to suggest treatment with exogenous heparin or its mimetics. Sepsis caused by bacteria

Two of the most frequent causes of bacterial sepsis are Staphylococcus aureus (Gramme +ve) and Pseudomonas aeruginosa (Gramme −ve). Both of these organisms have the ability to connect with a number of cell surface attachment receptors, including HS.

Pseudomonas aeruginosa: It has been shown that prolonged, chronic P. aeruginosa lung colonisation causes a change in the structure of lung HS. It is hypothesised that parin-like HS rivals In addition to lowering the bacterial load, tors with little or no anticoagulant action decreased neutrophil recruitment and cytokine production in mice with acute and chronic P. aeruginosa lung infections [57].

The apical and basolateral surfaces of epithelial cells, for instance, vary because the glycocalyx of at least some cell types is not homogeneous over the whole surface. At the basolateral surface, interactions between bacterial flagella and host HS serve the same purpose as P. aeruginosa's use of interactions between its pili and host N-glycans to adhere to and infiltrate the apical surface of completely polarised epithelial cells [58,59].

When the heparina set that P.aeruginosa produces is altered, the bacteria cannot move systemically to the liver and spleen and mortality in thermally wounded and infected mice is significantly decreased [60].

The virulence factor protein A of Staphylococcus aureus (NCTC8325) is a heparin binding protein, and its mutation or deletion decreases the bacterium's ability to bind heparin [61]. S. aureus is known to bind to heparin and may stick to heparin-coated medical devices. S. aureus may attach to and be internalised by enterocytes in addition to mediating interactions with heparin and host cellular component proteins such fibronectin and thrombospondin [62].

the gut without regard to its most well-described form of attachment (via fibronectin and integrins). Heparin and exogenous HS may prevent this, which strongly suggests that HSPGs function as receptors or co-receptors [63].

There have been reports of S. aureus being successfully extracted from the blood of

An extracorporeal blood filter was used to immobilise heparin on top of polyethylene beads in an infected haemodialysis patient. More recently, a small experiment was conducted [64,65]. Delivering a high concentration of heparin to the site of the infection is necessary for its efficient usage as a direct competitor with HS in antibacterial treatment; in this instance, the infection was transported to the therapy by extracorporeal circulation. Similar therapy has also been studied for Streptococcus pneumoniae pneumonia in a baboon model [67] and for lowering the viral load in liver failure linked to HSV-2 [66].

Sepsis caused by viruses

Although a significant minority of sepsis cases were culture negative, indicating a non-bacterial cause, a 2018 review considered a diagnosis of viral sepsis to be extremely rare [68]. Severe dengue and severe malaria are two examples of non-bacterial infections that can result in conditions similar to hyper-inflammatory sepsis [69], and both of them bind to cell surface HS. Origami shells made of HS-derivatized DNA have been developed to encapsulate and sequester viruses, including dengue [70]. It has been demonstrated that the low-anticoagulant LMWH, sevuparin, inhibits rosetting, blocks merozoite invasion, and de-sequesters infected erythrocytes in humans with P. falciparum malaria [73,74]. In the case of malaria, both the BAEBL and circumsporozoite proteins of P. falciparum bind to HS on the surface of host cells [71,72].

The SARS-CoV-2, the infectious agent of the current COVID-19 pandemic, is the most extensively studied of the many viruses that bind cell surface heparan sulphate. The most severe stage of this condition involves a hyperinflammatory state that is sufficiently similar to bacterial sepsis to serve as an example of viral sepsis [75]. The viral invasion of host cells involves HS as an initial attachment factor, before the binding and internalisation occurs on interaction with the angiotensinconverting enzyme (ACE-2) viral receptor. The SARS-CoV-2 spikeprotein interaction with cell surface HS has been thoroughly studied, as summarised in a recent review [76]. Heparin was quickly found to be capable of preventing SARS-CoV-2 infection of cells by competing with HS for binding to the spike protein [10]. There is no proof that any HS structural motif is selective [77], and it has been demonstrated that a variety of sulphated polymers, such as marine sulphated glycans [78,79], pentosan polysulphate (asemi-synthetic sulphated xylan) [51], and others [80], compete with HS binding to the SARS-CoV-2 spike protein.

By competing with cell surface HS, direct nebuliser delivery of heparin to the airway has been demonstrated to improve lung function in patients with chronic obstructive pulmonary disease (COPD) [81], making it an appealing option for COVID-19 treatment or prevention [82]. Nebulised LMWH was shown to be efficacious in preventing SARS-CoV-2 infection of human nasal cells, indicating its potential for preventive usage [83]. Several nations are now conducting clinical studies for nebulised heparin in COVID-19 therapy [11–13,84].

"Cytokine Storm" during sepsis

The "cytokine storm" (CS), which is the most prevalent cause of sepsis, is a key event in the development of sepsis. It is characterised by high circulating cytokine levels, early systemic inflammatory symptoms, and severe secondary organ failure [85,86]. The involvement of both pro- and anti-inflammatory cytokines creates a complicated scenario that may lead to immune suppression on the one hand and hyperinflammation on the other at various points throughout the course of the illness [87].

Exogenous heparin can act by disrupting the leukocyte-directing cytokine gradients so created. It can also either enhance (as for IL-12 [89]) or inhibit (as for IL-6 [90]) the functional interaction between cytokine and receptor [91]. Heparin and HS can interact with a variety of cytokines, including chemokines, interleukins, and growth factors. The anti-inflammatory activity of heparin has been attributed, at least in part, to the neutralisation of cytokine activity [88].

Even though research on CSoften focusses on a few

number of pro-inflammatory cytokines (such IL-1β, IL-6, and TNF-α), transcriptome investigations have found many more and have also tracked how the profile of cytokine expression changes over time during sepsis/endotoxemia [92].
Because of this, it is difficult to anticipate how therapy with parin or one of its mimetics may affect the many cytokines generated in CS, and there is little research on this kind of intervention. A retrospective investigation, however, revealed substantially lower levels of IL-6 in patients treated with LMWH in cases of severe COVID-19, raising the possibility that this therapy might somewhat mitigate COVID-19-induced CS [93].
The role of neutrophils and related leukocytes in the pathophysiology of sepsis
Neutrophils, the most prevalent granulocytes [95] in the bloodstream, can respond in three main ways to stimuli: phagocytosis of the foreign agent, degranulation that releases antimicrobial proteins, and programmed cell death to form neutrophil extracellular traps (NETs) via a process known as NETosis (see below). These NETs "trap" and destroy microbes [96]. The triggering of NETosis is thought to be highly likely in patients with sepsis given the link between coagulation and inflammation (see below) and the occurrence of DIC in sepsis [97]. The term "immuno-thrombosis" may be used to describe an inflammatory response in conjunction with altered or decreased coagulation factors; this feature of sepsis has recently been addressed [98–100]. Organ failure and injury may result from the combination of unchecked coagulation and inflammatory reactions. Therefore, by reducing their release and activity, neutrophils make sense targets for the treatment and maybe prevention of sepsis. According to the findings of the HETRASE experiment [101], the lack of mortality benefit seen with the unfractionated heparin therapy may have been caused in part by the decrease in leukocyte activity. Therefore, there should be some care since lowering neutrophil/leukocyte activity may lead the immune response to stop targeting the underlying cause of sepsis. Nevertheless, despite this finding with heparin, there is a lot of interest in non-anticoagulant forms of the medication that preserve effectiveness in focussing on the neutrophil response. Heparin and related mimetics have been used to attenuate neutrophils, which has generated a lot of interest in inflammatory pulmonary conditions [102,103] and the treatment of COVID [14]. Heparin has demonstrated positive effects in reducing degranulation, disrupting NETs, and cell-cell interactions; these roles have a potential therapeutic application in sepsis, as briefly described below.
Platelet interaction, adhesion, and aggregation
Heparin has been demonstrated to affect neutrophil aggregation [104–107] and interactions/aggregation with platelets [104,108]. Heparin interference with platelet P-selectin [109] and leukocyte L-selectin [110] appears to be the mechanism by which aggregation is disrupted, and it would lower inflammatory activity by lowering platelet-mediated leukocyte inflammatory responses [111]. These interactions are also involved in neutrophil activation [112] and the release of NETs [113,114]. Additionally, heparin inhibited leukocyte adhesion, recruitment, and invasion in inflammatory models in vivo (see below for a discussion of the function of heparanase in invasion [110,115]). Once again, this is probably due to decreased L-selectin binding to heparan sulphate on endothelial cells during leukocyte attachment and rolling [116] and disruption of P-selectin interactions on endothelial cells [117,118]. Remarkably, endothelial cell E-selectin [110], which is produced after stimulation, is very weakly affected by heparin.
The 6-O-sulphate on glucosamine in heparin and a generally high degree of sulphation [119] appear to play a role in the activity of heparin to prevent selectin-mediated cell interactions. Modified non-anticoagulant heparin derivatives can also retain their effectiveness [120,121], suggesting that there may be additional structural features that enhance the disruption of platelet–leukocyte interactions. For instance, parnaparin, an LMWH, is more effective than unfractionated heparin [122].
Degranulation of Neutrophils and Elastase Release
Heparin can affect the later activation of neutrophils, but prevention of adhesion and cell-cell interaction act as limiters on the initial steps in neutrophil recruitment [123,124]. Heparin binds to the surface of neutrophils, which limits degranulation [125], the production of superoxide anions and the activity of lysosomal enzymes [104], and the release of felastase [126]. In experimental models, direct inhibition of flalastase was also found to be effective with LMWH and O-desulphated heparin [105,127], with a decasaccharide being optimal; however, this monodisperse fraction did not prevent cell adhesion, unlike heparin [125]. Plant-derived heparin mimetics, such as fucoidan and xyloglucan, can also neutralise elastase activity and have the added benefit of limited anticoagulant activity [128]. Finally, the low anticoagulant LMWHsevuparin has been determined to be neutralizationic proteins, such as thepsin G, elastase, and the appropriately named heparin binding protein (HBP), all of which may be released from neutrophils and increase vascular permeability [131]. Circulating levels of HBP correlate well as a predictive marker for sepsis [132].
NETs, or neutrophil extracellular traps
Neutrophils have been demonstrated to generate NETs as an immune response at the sites of bacterial and viral infections [133–135]. These traps are made up of decondensed chromatin (DNA and histones) released from the nucleus and granular components (elastase, cathepsin G, Myeloperoxidase) that form fibrous networks to trap and destroy pathogens [135]. A pathological nature of NETs has been proposed in a number of diseases, including systemic lupus erythematosus [136], preeclampsia [137], and small vessel vasculitis [138]. Such an uncontrolled inflammatory response occurs in sepsis and probably leads to excessive NET formation [139]. have been shown to be higher in septic patients [140]. Moreover, histone levels and cell-free DNA [142,143] are correlated with the severity of sepsis [141].
A prothrombotic and anti-fibrinolytic effect has been demonstrated by NETs [146,147], which can be disrupted by heparin, reducing localised thrombosis [148,149]. Heparin can also break down the formation of NETs [144], which sequesters shistones from NETs and exposes the DNA to degradation by DNAses in circulation [145]. Modified non-anticoagulant heparins often maintain these

inhibitory properties [150–152]. Histones have several detrimental effects, including activating platelets [144], promoting tissue factor expression in endothelial cells and monocytes [153,154], and binding to capillary glycocalyx, which can cause cell and organ damage [155]. The amount of unbound histones in NETs in septic patients can be 200 times or more than in healthy volunteers [141]. Heparinase-III therapy or the addition of exogenous heparin or heparan sulphate may block the interaction between histones and cell surface heparan sulphate, as shown in an experimental acute lung damage model [156]. In a histone-infused rat model, heparin and a non-anticoagulant heparin showed a protective effect by blocking circulating histones [152]. Zhu et al. [157] claimed that the attenuation effect of heparin was mediated through inhibition of calcium influx. Heparin or modified heparins limit cellular response to histones by acting as a heparan phosphate mimetic [53]. Heparin sequestration of histones by heparin appears to be a charge-based interaction [158,159]. Stopping histone stimulation prevents endothelial cells from releasing cytokines like IL6 [160] and complement activation [150]. Activated platelets may cause neutrophils to undergo NETosis [113,161–164]. Since heparin, non-anticoagulant derivatives, and mimetics can prevent platelets from activating and from binding to neutrophils, they may be considered broad inhibitors of NETosis and NETs and should be further studied for their potential use in treating sepsis.

Sepsis and Heparanase The endoglucuronidase heparanase-1 (HPase) has garnered a lot of attention lately. While previous research has focused mostly on identifying HPase as a target for anti-cancer treatment development (see, for instance, [165]), a number of recent reviews have highlighted its function in the breakdown of endothelial glycocalyx, especially in sepsis [166–170]. Heparin/HS is exclusively broken down by the mammalian enzyme HPase1; although being a protein identical to HPase, Heparanase-2 functions as an inhibitor of HPase and, as a result, protects the glycocalyx by halting the shedding of HS fragments [171]. These HPase products are purified and used in medicine; they are relatively (though not entirely) resistant to further HPase degradation and can bind and competitively inhibit the enzyme [174]. HPase cleaves the heparin/HS chain at the reducing side of GlcA between two N-sulphated, preferably also 6-O-sulphated glucosamine residues [165]. This results in moderately large oligosaccharides consisting of approximately 10–20 monosaccharides [172,173]. In mast cells, heparin is broken down from its macromolecular format attached to the PG serglycin [174].

Platelets are a cellular source of heparanase, and sepsis increases HPase expression and activity [172–177]. HPase is not abundant in most tissues under normal conditions, but it is expressed and activated more in tumours and inflamed tissues; see ref [176] (and papers cited therein). Highly sulphated, heparin-like HS oligosaccharides are released into the plasma when endothelial heparanase breaks down HS from the endothelium glycocalyx, causing local vascular damage [166]. During this process, HPase also releases cytokines, chemokines, and HS-bound growth factors that are sequestered by heparansulphate in the extracellular matrix and glycocalyx [178]. HPase-produced HS oligosaccharides have the ability to activate TLR-4, which in turn triggers the release of pro-inflammatory cytokines [179].

Pre-clinical research has shown that endothelial dysfunction and reduced microcirculation contribute to inflammatory damage to several organs and tissues, as seen in the following instances, and are associated with the severity and duration of sepsis [170]. The pulmonary glycocalyx in endotoxemic mice was examined using intravitreal microscopy, which revealed deterioration via TNF-αdependent processes, such as HPase activation. Heparin-induced HPase inhibition, given three hours after endotoxin exposure, inhibited glycocalyx loss and neutrophil adhesion and reduced sepsis-induced acute lung injury (ALI) and mortality in mice [180]. HPase expression was elevated in epithelial cell models of ARDS caused by lipopolysaccharide (LPS); LPS-induced HS degradation and tight junction damage were decreased by N-acetylated heparin [181]. HPase also plays a role in septic acute kidney injury, and competitive inhibitors of HPase (heparin and a non-anticoagulant heparin) decrease the loss of glomerular filtration [182]. A non-anticoagulant heparin was also found to attenuate intestinal injury, inhibit neutrophil infiltration, and suppress the production of inflammatory cytokines in a similar model [184]. In a mouse model of sepsis, intestinal injury was decreased following inhibition of heparanase by unfractionated heparin [183]. Circulating high mobility group box 1 protein (HMGB1) binds extracellular lipopolysaccharide (LPS) and facilitates its cytosolic transport into cell cytoplasm, which triggers caspase-11 in gram-negative bacterial sepsis. Regardless of its anticoagulant qualities, heparin may inhibit caspase-11-dependent immunological responses and death in endotoxemic mice via interfering with the HMGB1-LPS interface [185]. Highly sulphated HSn nonasaccharide, asynthetic13C-labeled, was utilised to ascertain quick removal of HS pieces from the bloodstream in a model of sepsis in mice. Instead of targeting and penetrating the cortex and other non-neuronal tissues, this non-asparthetide specifically targeted and pierced the hippocampus blood–brain barrier after sepsis [186]. Cognitive impairment in sepsis patients has been linked to levels of circulating highly sulphated HS fragments [187].

Heparanase Inhibitors as Heparin Mimics Heparin mimetics are highly sulphated, structurally distinct analogues of glycosamino-glycans [188], which can be synthetic, naturally occurring, or often semi-synthetic in origin. A recent review of HPase inhibitors [189] can be suggested as a good starting point for this field, describing a number of heparin-derived or heparin mimetics based on bacterial HS-like polysaccharides, naturally occurring sulphated polysaccharides, semi-synthetic heparin mimetics based on bacterial HS-like polysaccha Although not for sepsis, a number of glycol-split heparin types have advanced to clinical studies [189]. One of these compounds, roneparstat, has been examined lately and is an effective heparanase inhibitor [190].

Viral Sepsis with Heparanasein These severe endothelial diseases linked to cytokine

release syndrome [82] are sufficiently comparable to sepsis as explained above. Heparin and its mimetics are being studied in the development of treatment approaches to this disease. The SARS-CoV-2 virus targets endothelial cells, causing both viral-mediated apoptosis and disruption of the glycocalyx [82]. Patients with COVID-19 had higher HPase activity, which is linked to the severity of the illness. Prophylactic LMWH was linked to lower HPase activity [191]. Roneparstat has been shown to inhibit the production of inflammatory cytokines from human macrophages associated with SARS-CoV-2 in the setting of viral sepsis, as well as to

Both HPase [193] and anti-viral infectivity [194] are features of the heparin mimic pixatimod, which also has dual potential modes of action in the treatment of COVID-19 [192]. Another factor linked to the coagulopathy seen in COVID-19 patients is HPase [195].

3. ClinicalTrialsofHeparin inSepsis

Heparin's clinical studies in sepsis have used an empirical approach.Li and Ma [196] reviewed experimental and clinical data in 2017 and concluded that there was conflicting evidence supporting the beneficial use of heparin in treating sepsis. This might have been caused by an inadequate meta-analysis of mostly non-randomized studies.However, they were generally hopeful about the potential of heparin to lower mortality in sepsis.The overall effect of heparin was also found to be unclear in a 2019 overview of systematic studies [197], which raised the possibility that demographic heterogeneity among trial participants contributed to the issue. A meta-analysis of eleven randomised trials of LMWH in sepsis conducted more recently revealed a decrease in the 28-day mortality rate, the incidence of multiple organ dysfunction (MODS), and inflammatory responses [46].Reductions in 28-day mortality and MODS were seen in another meta-analysis, this one using unfractionated heparinin sepsis [45].In another study, LMWH at a therapeutic dose decreased major thromboembolism and death among inpatients with COVID-19 with very elevated D-dimer levels, but this effect was not observed in ICU patients [36]. In severe COVID-19, a therapeutic dose of heparin was not found to have any benefit to critically ill patients when compared with a preventative dose [35].
Recent trials' findings support cautious hope. Since heparin is a strong anticoagulant, the therapeutic dose—typically 1 mg/kg twice daily—is the largest dosage that may be considered for clinical trial usage.It's possible that this regimen won't keep enough heparin in the bloodstream to benefit from anti-inflammatory processes that depend on competition with endothelial cell surface HS. Its local concentration is high because it is abundant in the glycocalyx. For an exogenous HS mimic, like heparin, to be as effective as possible, it must be present in excess. According to studies on heparin derivatives for illnesses other than sepsis, heparin derivatives and mimetics with lower anticoagulant activity may be safe at far larger doses than heparin itself.Based on a Phase 1 study, 300–400 mg/kg of the modified heparin roneparstat has been advised [198], a trial of the modified LMWH sevuparin utilised a dosage of 18 mg/kg/day [199], and 100 mg/kg of pixatimod was well tolerated [200]. Therefore, the use of heparin, an anticoagulant, to treat coagulopathy may become more difficult if heparin mimic compounds are introduced as anti-inflammatory medicines in the treatment of sepsis. Until one or more heparin mimetics are licensed for anti-inflammatory usage, we have no method of evaluating the possibility that a high dosage of a moderately antithrombotic heparinoid (such a dalaproid) may be useful in both inflammatory and coagulation settings.
Heparin may also be used in methods that prevent it from entering the bloodstream.Nebulised heparin is used to provide direct access to the lung epithelium and related pathogens without entering the circulation [14]. Another is the method described above for the extracorporeal removal of pathogens from the blood [65], in which the therapeutic heparin is immobilised on a column.

4. ConcludingRemarks

Some of the processes that may underlie heparin's antibacterial and anti-inflammatory properties have been described in the paragraphs above. The proportionate contributions of these processes to the therapeutic advantages of heparin therapy in sepsis and similar disorders are yet unclear to us. However, it is possible that safe and efficient heparin-based therapies for sepsis may eventually be made accessible due to the combination of innovative delivery techniques and advancements in anti-inflammatory heparin mimics.

References

1. Rudd,K.E.;Johnson,S.C.;Agesa,K.M.;Shackelford,K. A.;Tsoi,D.;Kievlan,D.R.;Colombara,D.V.;Ikuta,K.S.; Kissoon,N.;Finfer,S.; et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: Analysis for the Global Burden of Disease Study.*Lancet* **2020**, *395*, 200–211. [CrossRef] [PubMed]
2. Singer, M.; Deutschman, C.S.; Seymour, C.W.; Shankar-Hari, M.; Annane, D.; Bauer, M.; Bellomo, R.; Bernard, G.R.; Chiche, J.D.; Coopersmith, C.M.; et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *J. Am. Med. Assoc.* **2016**, *315*, 801–810. [CrossRef] [PubMed]
3. Giustozzi,M.;Ehrlinder,H.;Bongiovanni,D.;Borova c,J.A.;Guerreiro,R.A.;Gąsecka,A.;Papakonstantin ou,P.E.;Parker,W.A.E. Coagulopathy and sepsis: Pathophysiology, clinical manifestations and treatment.*Blood Rev.***2021**,*50*, 100864.[CrossRef] [PubMed]
4. Wada, H.; Thachil, J.; Di Nisio, M.; Mathew, P.; Kurosawa, S.; Gando, S.; Kim, H.K.; Nielsen, J.D.; Dempfle, C.E.; Levi, M.; et al. Guidance for diagnosis and treatment of DIC from harmonization of the recommendations from three guidelines.*J. Thromb. Haemost.* **2013**, *11*, 761–767. [CrossRef] [PubMed]
5. Iba, T.; Arakawa, M.; Di Nisio, M.; Gando, S.; Anan, H.; Sato, K.; Ueki, Y.; Levy, J.H.; Thachil, J. Newly Proposed Sepsis-Induced

CoagulopathyPrecedesInternationalSocietyonThrombosisandHaemostasisOvert-DisseminatedIntravascularCoagulation andPredictsHighMortality. *J.IntensiveCareMed.* **2020**,*35*,643–649. [CrossRef]
6. Iba,T.;Umemura,Y.;Wada,H.;Levy,J.H.RolesofCoagulationAbnormalitiesandMicrothrombosisinSepsis: Pathophysiology, Diagnosis,andTreatment. *Arch.Med.Res.***2021**,*52*,788–797. [CrossRef]
7. Jarczak,D.;Kluge,S.;Nierhaus,A.Sepsis-PathophysiologyandTherapeuticConcepts.*Front.Med.***2021**,*8*,628302.[CrossRef]
8. Vagionas, D.; Papadakis, D.D.; Politou, M.; Koutsoukou, A.; Vasileiadis, I. Thromboinflammation in Sepsis and Heparin: A ReviewofLiteratureandPathophysiology. *InVivo***2022**,*36*,2542–2557. [CrossRef]
9. Tree,J.A.;Turnbull,J.E.;Buttigieg,K.R.;Elmore,M.J.;Coombes,N.;Hogwood,J.;Mycroft-West,C.J.;Lima,M.A.;Skidmore, M.A.; Karlsson, R.; et al. Unfractionated heparin inhibits live wild type SARS-CoV-2 cell infectivity at therapeutically relevant concentrations.*Br.J.Pharm.***2021**,*178*,626–635. [CrossRef]
10. Mycroft-West,C.J.;Su,D.;Pagani,I.;Rudd,T.R.;Elli,S.;Gandhi,N.S.;Guimond,S.E.;Miller,G.J.;Meneghetti,M.C.Z.;Nader, H.B.; et al.Heparin Inhibits Cellular Invasion by SARS-CoV-2:Structural Dependence of the Interaction of the Spike S1 Receptor-BindingDomainwithHeparin. *Thromb.Haemost.***2020**,*120*,1700–1715. [CrossRef]
11. Sheehan, J.R.;Calpin,P.;Kernan,M.;Kelly,C.;Casey,S.;Murphy,D.;Alvarez-Iglesias,A.;Giacomini,C.;Cody,C.;Curley,G.;etal. The CHARTER-Ireland trial: Can nebulised heparin reduce acute lung injury in patients with SARS-CoV-2 requiring advanced respiratorysupportinIreland: Astudyprotocolandstatisticalanalysisplanforarandomisedcontroltrial. *Trials***2022**,*23*,774. [CrossRef]
12. Van Haren, F.M.P.; van Loon, L.M.; Steins, A.; Smoot, T.L.; Sas, C.; Staas, S.; Vilaseca, A.B.; Barbera, R.A.; Vidmar, G.; Beccari, H.; et al. Inhaled nebulised unfractionated heparin for the treatment of hospitalised patients with COVID-19: A multicentre case seriesof98patients.*Br.J.Clin.Pharm.***2022**,*88*,2802–2813.[CrossRef]
13. Van Haren, F.M.P.; Laffey, J.G.; Artigas, A.; Page, C.; Schultz, M.J.; Cosgrave, D.; McNicholas, B.; Smoot, T.L.; Nunes, Q.; Richardson, A.; et al. Can nebulised HepArin Reduce morTality and time to Extubation in patients with COVID-19 Requiring invasive ventilation Meta-Trial (CHARTER-MT): Protocol and statistical analysis plan for an investigator-initiated internationalmeta-trialofprospectiverandomisedclinicalstudies.*Br.J.Clin.Pharm.***2022**,*88*,3272–3287.[CrossRef]
14. VanHaren,F.M.P.;Page,C.;Laffey,J.G.;Artigas,A.;Camprubi-Rimblas,M.;Nunes,Q.;Smith,R.;Shute,J.;Carroll,M.;Tree,J.; etal.Nebulisedheparinasatreatmentfor COVID-19:Scientificrationaleandacallforrandomisedevidence.*Crit.Care***2020**,*24*, 454.[CrossRef]
15. Mulloy, B.; Hogwood, J.; Gray, E.; Lever, R.; Page, C.P. Pharmacology of Heparin and Related Drugs.*Pharm.Rev.***2016**, *68*, 76–141.[CrossRef]
16. Wang,P.;Chi,L.;Zhang,Z.;Zhao,H.;Zhang,F.;Linhardt,R.J.Heparin:Anolddrugfornewclinicalapplications.*Carbohydr. Polym.***2022**, *295*, 119818. [CrossRef]
17. Chen,D.Heparinbeyondanti-coagulation.*Curr.Res.Transl.Med.***2021**,*69*,103300.[CrossRef]
18. Cao,M.;Qiao,M.;Sohail,M.;Zhang,X.Non-anticoagulantheparinderivativesforCOVID-19treatment.*Int.J.Biol.Macromol.* **2023**,*226*,974–981.[CrossRef]
19. Jiang,L.;Zhang,T.;Lu,H.;Li,S.;Lv,K.;Tuffour,A.;Zhang,L.;Ding,K.;Li,J.P.;Li,H.;etal.Heparinmimeticsaspotential interventionforCOVID-19andtheirbio-manufacturing. *Synth. Syst. Biotechnol.* **2023**,*8*,11–19. [CrossRef]
20. Wheeler,A.P.;Bernard,G.R.Treatingpatientswithsevere sepsis.*N. Engl.J.Med.***1999**,*340*,207–214.[CrossRef]
21. Levi, M.; de Jonge, E.; van der Poll, T. Sepsis and disseminated intravascular coagulation.*J. Thromb.Thrombolysis* **2003**, *16*, 43–47.[CrossRef] [PubMed]
22. Strauss,R.;Wehler,M.;Mehler,K.;Kreutzer,D.;Koebnick,C.;Hahn,E.G.Thrombocytopeniainpatientsintheme dicalintensivecare unit: Bleeding prevalence, transfusion requirements, and outcome. *Crit. CareMed.* **2002**, *30*, 1765–1771. [CrossRef] [PubMed]
23. Lee,K.H.;Hui,K.P.;Tan,W.C.Thrombocytopeniainsepsis:Apredictorofmortalityintheintensivecareunit.*Singap.Med.J.* **1993**,*34*,245–246.
24. Mavrommatis,A.C.;Theodoridis,T.;Orfanidou,A.;Roussos,C.;Christopoulou-Kokkinou,V.;Zakynthinos,S.Coagulation system and platelets are fully activated in uncomplicated sepsis.*Crit.Care Med.***2000**, *28*, 451–457.[CrossRef]
25. Francois, B.; Trimoreau, F.; Vignon, P.; Fixe, P.; Praloran, V.; Gastinne, H. Thrombocytopenia in the sepsis syndrome:Role of hemophagocytosisandmacrophagecolony-stimulatingfactor. *Am.J.Med.***1997**,*103*,114–120. [CrossRef]
26. Zimmerman, G.A.;McIntyre, T.M.;Prescott, S.M.;Stafforini, D.M. The platelet-activating factor signaling system and its regulatorsinsyndromesofinflammationandthrombosis. *Crit.CareMed.***2002**,*30*,S294–S301. [CrossRef]
27. Zaid,Y.;Merhi,Y.ImplicationofPlateletsinImmuno-ThrombosisandThrombo-Inflammation. *Front.Cardiovasc.Med.***2022**,*9*, 863846.[CrossRef]
28. Gray,E.;Cesmeli,S.;Lormeau,J.C.;Davies,A.B.;Lane,

D.A.Lowaffinityheparinisanantithromboticagent.*Thromb.Haemost.* **1994**,*71*,203–207.
29. Periayah,M.H.;Halim,A.S.;MatSaad,A.Z.MechanismActionofPlateletsandCrucialBloodCoagulationPathwaysin Hemostasis.*Int.J.Hematol.Oncol.StemCellRes.* **2017**,*11*,319–327.
30. Versteeg,H.H.;Heemskerk,J.W.;Levi,M.;Reitsma,P.H.Newfundamentalsinhemostasis.*Physiol.Rev.* **2013**, *93*,327–358. [CrossRef]
31. Krisinger,M.J.;Goebeler,V.;Lu,Z.;Meixner,S.C.;Myles,T.;Pryzdial,E.L.;Conway,E.M.Thrombingeneratespreviously unidentifiedC5productsthatsupporttheterminalcomplementactivationpathway. *Blood***2012**,*120*,1717–1725. [CrossRef]
32. Mast,A.E.TissueFactorPathwayInhibitor:MultipleAnticoagulantActivitiesforaSingleProtein.*Arter.Thromb.Vasc.Biol.***2016**, *36*,9–14.[CrossRef]
33. Levi,M.;Poll,T.Coagulationinpatientswithseversepsis.*Semin.Thromb.Haemost.***2015**,*41*,9–15.[CrossRef]
34. Marietta, M.; Vandelli, P.; Mighali, P.; Vicini, R.; Coluccio, V.; D'Amico, R. Randomised controlled trial comparing efficacy and safety of high versus low Low-Molecular Weight Heparin dosages in hospitalized patients with severe COVID-19 pneumonia and coagulopathy not requiring invasive mechanical ventilation (COVID-19 HD): A structured summary of a study protocol. *Trials* **2020**, *21*, 574. [CrossRef]
35. Goligher, E.C.; Bradbury, C.A.; McVerry, B.J.; Lawler, P.R.; Berger, J.S.; Gong, M.N.; Carrier, M.; Reynolds, H.R.; Kumar, A.; Turgeon, A.F.; et al.Therapeutic Anticoagulation with Heparin in Critically Ill Patients with COVID-19.*N.Engl.J.Med.* **2021**, *385*,777–789. [CrossRef]
36. Spyropoulos, A.C.; Goldin, M.; Giannis, D.; Diab, W.; Wang, J.; Khanijo, S.; Mignatti, A.; Gianos, E.; Cohen, M.; Sharifova, G.; et al. Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-Dose Heparins for Thromboprophy- laxisinHigh-riskHospitalizedPatientsWithCOVID-19: TheHEP-COVIDRandomizedClinicalTrial. *J.Am. Med. Assoc. Intern. Med.* **2021**,*181*,1612–1620. [CrossRef]
37. Sholzberg,M.;Tang,G.H.;Rahhal,H.;AlHamzah, M.;Kreuziger,L.B.;Áinle,F.N.;Alomran,F.;Alayed, K.;Alsheef,M.;AlSumait, F.; et al. Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unitadmission in moderately ill patients with covid-19 admitted to hospital: RAPID randomised clinical trial. *BMJ Clin. Res. Ed.* **2021**,*375*, n2400. [CrossRef]
38. Billett, H.H.; Reyes-Gil, M.; Szymanski, J.; Ikemura, K.; Stahl, L.R.; Lo, Y.; Rahman, S.; Gonzalez-Lugo, J.D.; Kushnir, M.; Barouqa, M.;etal. AnticoagulationinCOVID-19: EffectofEnoxaparin,Heparin,andApixabanonMortality. *Thromb. Haemost.* **2020**,*120*, 1691–1699. [CrossRef]
39. D'Ardes,D.; Carrarini, C.; Russo, M.; Dono, F.; Speranza, R.; Digiovanni, A.; Martinotti, G.; Di Iorio, A.; Onofrj, M.; Cipollone, F.;etal.Lowmolecularweightheparininin COVID-19patientspreventsdeliriumandshortenshospitalization.*Neurol.Sci.***2021**,*42*, 1527–1530. [CrossRef]
40. Miesbach, W.; Makris, M. COVID-19: Coagulopathy, Risk of Thrombosis, and the Rationale for Anticoagulation.*Clin. Appl. Thromb./Hemost.* **2020**, *26*, 1076029620938149. [CrossRef]
41. Mattioli, M.; Benfaremo, D.; Mancini, M.; Mucci, L.; Mainquà, P.; Polenta, A.; Baldini, P.M.; Fulgenzi, F.; Dennetta, D.; Bedetta,S.; et al. Safety of intermediate dose of low molecular weight heparin in COVID-19 patients.*J.Thromb. Thrombolysis***2021**, *51*, 286–292. [CrossRef] [PubMed]
42. Sadeghipour, P.; Talasaz, A.H.; Rashidi, F.; Sharif-Kashani, B.; Beigmohammadi, M.T.; Farrokhpour, M.; Sezavar, S.H.; Payande- mehr, P.; Dabbagh, A.; Moghadam, K.G.; et al. Effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on ThromboticEvents,ExtracorporealMembraneOxygenationTreatment,orMortalityAmongPatientsWithCOVID-19Admitted to the Intensive Care Unit: The INSPIRATION Randomized Clinical Trial. *J.Am. Med. Assoc.* **2021**, *325*, 1620–1630. [CrossRef]
43. Lopes,R.D.;deBarros,E.S.P.G.M.;Furtado,R.H.M.;Macedo,A.V.S.;Bronhara,B.;Damiani,L.P.;Barbosa,L.M.;deAveiroMorata,J.; Ramacciotti, E.; de Aquino Martins, P.; et al. Therapeutic versus prophylactic anticoagulation for patients admitted to hospitalwith COVID-19 and elevated D-dimer concentration (ACTION): An open-label, multicentre, randomised, controlled trial.*Lancet* **2021**, *397*, 2253–2263. [CrossRef] [PubMed]
44. Di Castelnuovo, A.; Costanzo, S.; Antinori, A.; Berselli, N.; Blandi, L.; Bonaccio, M.; Cauda, R.; Guaraldi, G.; Menicanti, L.; Mennuni,M.;etal.Heparinin COVID-19PatientsIsAssociatedwithReducedIn-HospitalMortality:TheMulticenterItalianCORIST Study. *Thromb. Haemost.* **2021**, *121*, 1054–1065. [CrossRef]
45. Fu,S.;Yu,S.;Wang,L.;Ma,X.;Li,X.Unfractionatedheparinimprovestheclinicalefficacyinadultsepsispatients: Asystematic review and meta-analysis. *BMCAnesthesiol.* **2022**, *22*, 28. [CrossRef]
46. Li,X.;Liu,Z.;Luo,M.;Xi,Y.;Li,C.;Wang,S.;Yang,R. Therapeuticeffectoflow-molecular-weightheparinonadultsepsis:A meta-analysis. *Ann.Palliat.Med.***2021**,*10*,3115–3127. [CrossRef]
47. Iba, T.; Miyasho, T. Danaparoid sodium attenuates the increase in inflammatory cytokines and preserves organ function inendotoxemic rats. *Crit. Care* **2008**, *12*, R86. [CrossRef]
48. Hagiwara,S.;Iwasaka,H.;Hidaka,S.;Hishiyama,S.; Noguchi,T.Danaparoidsodiuminhibitssystemicinflammationand prevents endotoxin-induced acute

lung injury in rats. *Crit. Care***2008**, *12*, R43. [CrossRef]
49. Iba,T.;Kidokoro,A.;Fukunaga,M.;Nagakari,K.;Suda,M.;Yoshikawa,S.;Ida,Y.Antithrombinameliorate sendotoxin-induced organdysfunctionmoreefficientlywhencombinedwithdanaparoidsodiumthanwithunfractionatedheparin. *IntensiveCare Med.***2005**, *31*, 1101–1108. [CrossRef]
50. Myllylahti, L.; Pitkänen, H.; Magnani, H.; Lassila, R. Experience of danaparoid to treat vaccine-induced immune thrombocytopeniaand thrombosis, VITT. *Thromb. J.* **2022**, *20*, 4. [CrossRef]
51. Bertini, S.; Alekseeva, A.; Elli, S.; Pagani, I.; Zanzoni, S.; Eisele, G.; Krishnan, R.; Maag, K.P.; Reiter, C.; Lenhart, D.; et al. PentosanPolysulfate Inhibits Attachment and Infection by SARS-CoV-2 In Vitro: Insights into Structural Requirements for Binding. *Thromb. Haemost.***2022**, *122*, 984–997. [CrossRef]
52. Weiss,R.J.;Esko,J.D.;Tor,Y.Targetingheparinandheparansulfateproteininteractions.*Org.Biomol.Chem.***2017**,*15*,5656–5668. [CrossRef]
53. Gallagher, J.T. Heparan sulphate:A heparin in miniature.In*Heparin—A Century of Progress*; Handbook of Experimental PharmacologyBookSeries;Springer: Berlin/Heidelberg,Germany,2012;pp. 347–360. [CrossRef]
54. Rudd, T.R.; Hughes, A.; Holman, J.; Solari, V.; Ferreira Ede, O.; Domingues, R.M.; Yates, E.A. Heparan sulphate, its derivatives and analogues share structural characteristics that can be exploited, particularly in inhibiting microbial attachment. *Braz. J. Med. Biol. Res.* **2012**, *45*, 386–391. [CrossRef]
55. Van Belkum, A.; Almeida, C.; Bardiaux, B.; Barrass, S.V.; Butcher, S.J.; Çaykara, T.; Chowdhury, S.; Datar, R.; Eastwood, I.; Goldman,A.;etal.Host-PathogenAdhesionastheBasisofInnovativeDiagnosticsforEmergingPathogens.*Diagnostics***2021**,*11*, 1259. [CrossRef]
56. Sanchez, H.; Hopkins, D.; Demirdjian, S.; Gutierrez, C.; O'Toole, G.A.; Neelamegham, S.; Berwin, B. Identification of cell-surface glycansthatmediatemotility-dependentbindingandinternalizationof*Pseudomonasaeruginosa*byphagocytes. *Mol.Immunol.* **2021**, *131*, 68–77. [CrossRef]
57. Lorè, N.I.; Veraldi, N.; Riva, C.; Sipione, B.; Spagnuolo, L.; De Fino, I.; Melessike, M.; Calzi, E.; Bragonzi, A.; Naggi, A.; et al. Synthesized Heparan Sulfate Competitors Attenuate *Pseudomonas aeruginosa* Lung Infection.*Int. J. Mol. Sci.***2018**,*19*, 207. [CrossRef]
58. Bucior, I.; Mostov, K.; Engel, J.N. Pseudomonas aeruginosa-mediated damage requires distinct receptors at the apical and basolateralsurfacesofthepolarizedepithelium. *Infect.Immun.***2010**,*78*,939–953. [CrossRef]
59. Bucior, I.; Pielage, J.F.; Engel, J.N. *Pseudomonasaeruginosa*pili and flagella mediate distinct binding and signaling events at the apicalandbasolateralsurfaceofairwayepithelium. *PLoSPathog.***2012**,*8*,e1002616. [CrossRef]
60. Dzvova, N.; Colmer-Hamood, J.A.; Griswold, J.A.; Hamood, A.N. Heparinase Is Essential for *Pseudomonas aeruginosa* Virulence duringThermalInjuryandInfection. *Infect.Immun.***2018**,*86*,e00755-17. [CrossRef]
61. Shi, H.; Tang, J.; An, C.; Yang, L.; Zhou, X. Protein A of *Staphylococcus aureus* strain NCTC8325 interacted with heparin.*Arch. Microbiol.***2021**,*203*,2563–2573. [CrossRef]
62. Porayath,C.;Suresh,M.K.;Biswas,R.;Nair,B.G.;Mishra,N.;Pal,S.Autolysinmediatedadherenceof*Staphylococcusaureus*with Fibronectin,GelatinandHeparin. *Int. J.Biol. Macromol.* **2018**,*110*,179–184. [CrossRef][PubMed]
63. Hess,D.J.;Henry-Stanley,M.J.;Erlandsen,S.L.;Wells,C.L.Heparansulfateproteoglycansmediate*Staphylococcusaureus* interactionswithintestinalepithelium.*Med.Microbiol.Immunol.***2006**,*195*,133–141.[CrossRef][PubMed]
64. Seffer, M.T.; Eden, G.; Engelmann, S.; Kielstein, J.T. Elimination of *Staphylococcus aureus* from the bloodstream using a novel biomimeticsorbenthaemoperfusiondevice. *BMJCaseRep.***2020**,*13*,e235262. [CrossRef][PubMed]

65. Eden,G.;Schmidt,J.J.;Büttner,S.;Kümpers,P.;Hafer, C.;Rovas,A.;Koch,B.F.;Schmidt,B.M.W.;Kielstein, J.T.Safetyandefficacy of the Seraph®100 Microbind®Affinity Blood Filter to remove bacteria from the blood stream: Results of the first in human study.*Crit. Care* **2022**, *26*, 181. [CrossRef]
66. Andermatt, R.; Bloemberg, G.V.; Ganter, C.C.; Mueller, N.J.; Mueller, A.M.S.; Muellhaupt, B.; Kielstein, J.T.; David, S. Elimination of Herpes Simplex Virus-2 and Epstein-Barr Virus With Seraph 100 Microbind Affinity Blood Filter and Therapeutic Plasma Exchange: An Explorative Study in a Patient With Acute Liver Failure. *Crit. CareExplor.* **2022**, *4*, e0745. [CrossRef]
67. Chen,L.;Kraft,B.D.;Roggli,V.L.;Healy,Z.R.;Woods,C .W.;Tsalik,E.L.;Ginsburg,G.S.;Murdoch,D.M.;Sulima n,H.B.;Piantadosi,C.A.; et al. Heparin-based blood purification attenuates organ injury in baboons with *Streptococcus pneumoniae* pneumonia. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2021**, *321*, L321–L335. [CrossRef]
68. Lin,G.L.;McGinley,J.P.;Drysdale,S.B.;Pollard,A.J.E pidemiologyandImmunePathogenesisofViralSepsis. *Front.Immunol.* **2018**,*9*,2147.[CrossRef]
69. Kwizera, A.; Adhikari, N.K.J.; Angus, D.C.; Dondorp, A.M.; Dünser, M.W.; Festic, E.; Haniffa, R.; Kissoon, N.; Martin-Loeches, I.; Lundeg, G. Recognition of Sepsis in Resource-Limited Settings. In *Sepsis Management in Resource-Limited Settings*; Dondorp, A.M.,Dünser, M.W., Schultz, M.J., Eds.; Springer: Cham, Switzerland, 2019; pp. 69–84.
70. Monferrer,A.;Kretzmann,J.A.;Sigl,C.;Sapelza,P.;L iedl,A.;Wittmann,B.;Dietz,H.Broad-SpectrumVirusTrappingwith Heparan Sulfate-Modified DNA Origami Shells. *ACSNano***2022**, *16*, 20002–20009. [CrossRef]
71. Ancsin, J.B.; Kisilevsky, R. A binding site for highly sulfated heparan sulfate is identified in the N terminus of the circumsporozoiteprotein:Significance for malarial sporozoite attachment to hepatocytes.*J. Biol. Chem.* **2004**, *279*, 21824–21832.[CrossRef]
72. Kobayashi, K.; Kato, K.; Sugi, T.; Takemae, H.; Pandey, K.; Gong, H.; Tohya, Y.; Akashi, H. Plasmodium falciparum BAEBL binds toheparansulfateproteoglycansonthehumanerythro cytesurface.*J.Biol.Chem.***2010**,*285*,1716–1725.[CrossRef]
73. Leitgeb, A.M.; Charunwatthana, P.; Rueangveerayut, R.; Uthaisin, C.; Silamut, K.; Chotivanich, K.; Sila, P.; Moll, K.; Lee, S.J.; Lindgren, M.; etal. Inhibition ofmerozoite invasionandtransientde-sequestration bysevuparininhumans with*Plasmodium falciparum*malaria.*PLoSONE***2017**,*12*,e0188754. [CrossRef]
74. Saiwaew,S.;Sritabal,J.;Piaraksa,N.;Keayarsa,S.;Ru engweerayut,R.;Utaisin,C.;Sila,P.;Niramis,R.;Udo msangpetch, R.; Charunwatthana, P.; et al.Effects of sevuparin on rosette formation and cytoadherence of *Plasmodiumfalciparum*infected erythrocytes. *PLoSONE***2017**,*12*,e0172718. [CrossRef]
75. Ventura-Santana, E.; Ninan, J.R.; Snyder, C.M.; Okeke, E.B. Neutrophil Extracellular Traps, Sepsis and COVID-19—A Tripod Stand.*Front. Immunol.* **2022**,*13*,902206. [CrossRef]
76. Kearns, F.L.; Sandoval, D.R.; Casalino, L.; Clausen, T.M.; Rosenfeld, M.A.; Spliid, C.B.; Amaro, R.E.; Esko, J.D. Spike-heparan sulfateinteractionsinSARS-CoV-2infection. *Curr.Opin.Struct.Biol.***2022**,*76*,102439. [CrossRef]
77. Parafioriti, M.; Ni, M.; Petitou, M.; Mycroft-West, C.J.; Rudd, T.R.; Gandhi, N.S.; Ferro, V.; Turnbull, J.E.; Lima, M.A.; Skidmore, M.A.; et al. Evidence for multiple binding modes in the initial contact between SARS-CoV-2 spike S1 protein and cell surface glycans.*Chemistry***2023**,*29*,e202202599. [CrossRef]
78. Dwivedi, R.; Sharma, P.; Farrag, M.; Kim, S.B.; Fassero, L.A.; Tandon, R.; Pomin, V.H. Inhibition of SARS-CoV-2 wild-type (Wuhan-Hu-1)andDelta(B.1.617.2)strainsbymarinesulfatedglyc ans.*Glycobiology***2022**,*32*,849–854.[CrossRef]
79. Dwivedi,R.;Sharma,P.;Eilts,F.;Zhang,F.;Linhardt,R.J. ;Tandon,R.;Pomin,V.H.Anti-SARS-CoV-2andanticoagulantpropertiesof *Pentacta pygmaea* fucosylated chondroitin sulfate depend on high molecular weight structures. *Glycobiology* **2022**, *33*, 75–85.[CrossRef]
80. Zhang, F.; He, P.; Rodrigues, A.L.; Jeske, W.; Tandon, R.; Bates, J.T.; Bierdeman, M.A.; Fareed, J.; Dordick, J.; Linhardt, R.J. PotentialAnti-SARS-CoV-2ActivityofPentosanPolysulfateandMucopolysaccha idePolysulfate.*Pharmaceuticals***2022**,*15*,258.[CrossR ef]
81. Shute, J.K.; Calzetta, L.; Cardaci, V.; di Toro, S.; Page, C.P.; Cazzola, M. Inhaled nebulisedunfractionated heparin improveslung function in moderate to very severe COPD: A pilot study. *Pulm. Pharm. Ther.* **2018**, *48*, 88–96. [CrossRef]
82. Calabretta, E.; Moraleda, J.M.; Iacobelli, M.; Jara, R.; Vlodavsky, I.; O'Gorman, P.; Pagliuca, A.; Mo, C.; Baron, R.M.; Aghemo, A.;etal.COVID-19-inducedendotheliitis:Emergingevidenceandpossible therapeuticstrategies.*Br.J.Haematol.***2021**,*193*,43–51. [CrossRef]
83. Eder, J.; Bermejo-Jambrina, M.; Vlaming, K.E.; Kaptein, T.M.; Zaderer, V.; Kemper, E.M.; Wilflingseder, D.; Reitsma, S.; deBree, G.J.; Cohn,D.M.;etal. InhalationofLowMolecularWeightHeparinsasProph ylaxisagainstSARS-CoV-2. *mBio***2022**,*13*,e02558-22. [CrossRef] [PubMed]
84. Bertanha, M.; Rodrigues, L.D.S.; Mellucci Filho, P.L.; Moroz, A.; Pardini, M.; Sobreira, M.L.; Durigon, E.L.; Machado, R.R.G.; Grotto,R.M.T.;Lima,M.A.;etal. Nebulizedenrichedheparintotreatnocriticalpatients withSARS-CoV-2: Triple-blindclinical trial.*Medicine***2021**, *100*, e28288. [CrossRef] [PubMed]
85. Jarczak,D.;Nierhaus,A.CytokineStorm-Definition,Causes,andImplications.*Int.J.Mol.Sci.***202 2**,*23*,11740.[CrossRef]

[PubMed]
86. Fajgenbaum,D.C.;June,C.H.CytokineStorm.*N.Engl.J.Med.***2020**,*383*,2255–2273. [CrossRef][PubMed]
87. Hotchkiss,R.S.;Monneret,G.;Payen,D.Sepsis-inducedimmunosuppression:Fromcellulardysfunctionstoimmunotherapy. *Nat.Rev.Immunol.***2013**,*13*,862–874.[CrossRef]
88. Farrugia, B.L.; Lord, M.S.; Melrose, J.; Whitelock, J.M. The Role of Heparan Sulfate in Inflammation, and the Development of BiomimeticsasAnti-InflammatoryStrategies.*J.Histochem.Cytochem.***2018**,*66*,321–336.[CrossRef]
89. Nguyen,K.G.;Gillam,F.B.;Hopkins,J.J.;Jayanthi,S.;Gundampati,R.K.;Su,G.;Bear,J.;Pilkington,G.R.;Jalah,R.;Felber, B.K.;etal. Molecularmechanismsofheparin-inducedmodulationofhumaninterleukin12bioactivity. *J.Biol.Chem.***2019**,*294*, 4412–4424. [CrossRef]
90. Litov,L.;Petkov,P.;Rangelov,M.;Ilieva,N.;Lilkova, E.;Todorova,N.;Krachmarova,E.;Malinova,K.;Gospodinov,A.;Hristova, R.; et al. Molecular Mechanism of the Anti-Inflammatory Action of Heparin. *Int. J.Mol. Sci.* **2021**, *22*, 10730. [CrossRef]
91. Collins,L.E.;Troeberg,L.Heparansulfateasaregulatorofinflammationandimmunity.*J.Leukoc.Biol.***2019**,*105*,81–92. [CrossRef]
92. Chousterman,B.G.;Swirski,F.K.;Weber,G.F.Cytokinestormandsepsisdiseasepathogenesis. *Semin. Immunopathol.* **2017**,*39*, 517–528. [CrossRef]
93. Shi, C.; Wang, C.; Wang, H.; Yang, C.; Cai, F.; Zeng, F.; Cheng, F.; Liu, Y.; Zhou, T.; Deng, B.; et al. The Potential of Low Molecular WeightHeparintoMitigateCytokineStorminSevereCOVID-19Patients: ARetrospectiveCohortStudy. *Clin.Trans.Sci.***2020**, *13*, 1087–1095. [CrossRef]
94. Liew,P.X.;Kubes,P.TheNeutrophil'sRoleDuringHealthandDisease.*Physiol.Rev.***2019**,*99*,1223–1248.[CrossRef]
95. Nathan,C.Neutrophilsandimmunity:Challengesandopportunities.*Nat.Rev.Immunol.***2006**,*6*,173–182.[CrossRef]
96. Papayannopoulos,V.Neutrophilextracellulartrapsinimmunityanddisease.*Nat.Rev.Immunol.***2018**,*18*,134–147.[CrossRef]
97. Semeraro, N.; Ammollo, C.T.; Semeraro, F.; Colucci, M. Sepsis-associated disseminated intravascular coagulation and thromboembolicdisease.*Mediterr.J.Hematol.Infect.Dis.***2010**,*2*,e2010024.[CrossRef]
98. Chang,J.C.Sepsisandsepticshock:Endothelialmolecularpathogenesisassociatedwithvascularmicrothrombosticdisease. *Thromb.J.***2019**,*17*,10.[CrossRef]
99. Beristain-Covarrubias, N.; Perez-Toledo, M.; Thomas, M.R.; Henderson, I.R.; Watson, S.P.; Cunningham, A.F. UnderstandingInfection-InducedThrombosis: LessonsLearnedFromAnimalModels. *Front. Immunol.* **2019**,*10*,2569. [CrossRef]
100. Galli,E.;Maggio,E.;Pomero,F.VenousThromboembolisminSepsis:FromBenchtoBedside.*Biomedicines***2022**,*10*,1651. [CrossRef]
101. Jaimes,F.;DeLaRosa,G.;Morales,C.;Fortich,F.;Arango,C.;Aguirre,D.;Munoz,A.Unfractionedheparinfortreatmentof sepsis: Arandomizedclinicaltrial(TheHETRASEStudy). *Crit. CareMed.* **2009**,*37*,1185–1196. [CrossRef]
102. Voynow, J.A.; Zheng, S.; Kummarapurugu, A.B. Glycosaminoglycans as Multifunctional Anti-Elastase and Anti-Inflammatory Drugs in Cystic Fibrosis Lung Disease. *Front. Pharm.* **2020**, *11*, 1011. [CrossRef]
103. Juschten,J.;Tuinman,P.R.;Juffermans,N.P.;Dixon,B.;Levi,M.;Schultz,M.J.Nebulizedanticoagulantsinlunginjuryincriticallyill patients—An updated systematic review of preclinical and clinical studies.*Ann. Transl. Med.* **2017**, *5*, 444.[CrossRef] [PubMed]
104. Bazzoni,G.;BeltranNunez,A.;Mascellani,G.;Bianchini,P.;Dejana,E.;DelMaschio,A.Effectofheparin,dermatansulfate,and relatedoligo-derivativesonhumanpolymorphonuclearleukocytefunctions. *J.Lab.Clin.Med.***1993**,*121*,268–275. [PubMed]
105. Brown,R.A.;Lever,R.;Jones,N.A.;Page,C.P.Effectsofheparinandrelatedmoleculesuponneutrophilaggregationandelastaserelease in vitro. *Br. J. Pharm.* **2003**, *139*, 845–853. [CrossRef] [PubMed]
106. Freischlag,J.A.; Colburn, M.D.; Quinones-Baldrich, W.J.; Moore, W.S. Heparin, urokinase, and ancrod alter neutrophil function.*J. Vasc. Surg.* **1992**, *16*, 565–572. [CrossRef]
107. Laghi Pasini, F.; Pasqui, A.L.; Ceccatelli, L.; Capecchi, P.L.; Orrico, A.; Di Perri, T. Heparin inhibition of polymorphonuclear leukocyte activation in vitro.A possible pharmacological approach to granulocyte-mediated vascular damage.*Thromb. Res.* **1984**,*35*, 527–537. [CrossRef]
108. Piccardoni,P.;Evangelista,V.;Piccoli,A.;deGaetano,G.;Walz,A.;Cerletti,C.Thrombin-activatedhumanplateletsreleasetwo NAP-2variantsthatstimulatepolymorphonuclearleukocytes. *Thromb.Haemost.***1996**,*76*,780–785. [CrossRef]
109. Skinner,M.P.;Lucas,C.M.;Burns,G.F.;Chesterman, C.N.;Berndt,M.C.GMP-140bindingtoneutrophilsisinhibitedbysulfated glycans.*J.Biol. Chem.* **1991**,*266*,5371–5374. [CrossRef]
110. Koenig, A.; Norgard-Sumnicht, K.; Linhardt, R.; Varki, A. Differential interactions of heparin and heparan sulfate glycosamino-glycans with the selectins. Implications for the use of unfractionated and low molecular weight heparins as therapeutic agents. *J. Clin. Investig.* **1998**, *101*, 877–889. [CrossRef]
111. Page, C.; Pitchford, S. Neutrophil and platelet complexes and their relevance to neutrophil recruitment and activation.*Int. Immunopharmacol.***2013**,*17*,1176–1184.[CrossRef]
112. Kornerup, K.N.; Salmon, G.P.; Pitchford, S.C.; Liu, W.L.; Page, C.P. Circulating platelet-neutrophil complexes are important for subsequentneutrophilactivationandmigration. *J.Appl.Physiol.***2010**,*109*,758–767. [CrossRef]
113. Clark, S.R.; Ma, A.C.; Tavener, S.A.; McDonald, B.; Goodarzi, Z.; Kelly, M.M.; Patel, K.D.;

Chakrabarti, S.; McAvoy, E.; Sinclair,G.D.; et al. Platelet TLR4 activates neutrophil extracellular traps to ensnare bacteria in septic blood. *Nat. Med.* **2007**, *13*, 463–469.[CrossRef]

114. Caudrillier,A.;Kessenbrock,K.;Gilliss,B.M.;Nguyen,J.X.;Marques,M.B.;Monestier,M.;Toy,P.;Werb,Z.;Looney,M.R.Platelets induce neutrophil extracellular traps in transfusion-related acute lung injury.*J. Clin.Investig.***2012**, *122*, 2661–2671.[CrossRef]
115. Ley,K.;Cerrito,M.;Arfors,K.E.Sulfatedpolysaccharidesinhibitleukocyterollinginrabbitmesenteryvenules.*Am.J.Physiol.* **1991**, *260*,H1667–H1673.[CrossRef]
116. Giuffre,L.;Cordey,A.S.;Monai,N.;Tardy,Y.;Schapira,M.;Spertini,O.Monocyteadhesiontoactivatedaorticendothelium: Role ofL-selectinandheparansulfateproteoglycans. *J.CellBiol.* **1997**,*136*,945–956. [CrossRef]
117. Bonfanti, R.; Furie, B.C.; Furie, B.; Wagner, D.D. PADGEM (GMP140) is a component of Weibel-Palade bodies of human endothelialcells.*Blood* **1989**, *73*, 1109–1112. [CrossRef]
118. Lorant,D.E.;Topham,M.K.;Whatley,R.E.;McEver, R.P.;McIntyre,T.M.;Prescott,S.M.;Zimmerman,G. A.Inflammatoryrolesof P-selectin. *J.Clin. Investig.* **1993**,*92*,559–570. [CrossRef]
119. Wang,L.;Brown,J.R.;Varki,A.;Esko,J.D.Heparin's anti-inflammatoryeffectsrequireglucosamine6-O-sulfationandare mediatedbyblockadeofL-andP-selectins. *J.Clin. Investig.* **2002**,*110*,127–136. [CrossRef]
120. Hostettler, N.; Naggi, A.; Torri, G.; Ishai-Michaeli, R.; Casu, B.; Vlodavsky, I.; Borsig, L. P-selectin- and heparanase-dependent antimetastaticactivityofnon-anticoagulantheparins.*FASEBJ.***2007**,*21*,3562–3572.[CrossRef]
121. Riffo-Vasquez, Y.;Somani, A.;Man, F.; Amison,R.; Pitchford, S.; Page, C.P.ANon-AnticoagulantFractionofHeparinInhibits LeukocyteDiapedesisintotheLungbyanEffectonPlatelets.*Am.J. Respir.Cell Mol.Biol.***2016**,*55*,554–563.[CrossRef]
122. Maugeri, N.; Di, F.G.; Barbanti, M.; de Gaetano, G.; Donati, M.B.; Cerletti, C. Parnaparin, a low-molecular-weight heparin, preventsP-selectin-dependentformationofplatelet-leukocyteaggregatesinhumanwholeblood.*Thromb. Haemost.* **2007**, *97*, 965–973.
123. Ley, K.; Laudanna, C.; Cybulsky, M.I.; Nourshargh, S. Getting to the site of inflammation: The leukocyte adhesion cascade updated.*Nat. Rev. Immunol.* **2007**,*7*,678–689. [CrossRef][PubMed]
124. Massena, S.; Christoffersson, G.; Hjertstrom, E.; Zcharia, E.; Vlodavsky, I.; Ausmees, N.; Rolny, C.; Li, J.P.; Phillipson, M. A chemotactic gradient sequestered on endothelial heparan sulfate induces directional intraluminal crawling of neutrophils. *Blood* **2010**, *116*, 1924–1931. [CrossRef] [PubMed]
125. Lever, R.; Lo, W.T.; Faraidoun, M.; Amin, V.; Brown, R.A.; Gallagher, J.; Page, C.P. Size-fractionated heparins have differential effectsonhumanneutrophilfunctioninvitro. *Br. J.Pharm.* **2007**,*151*,837–843. [CrossRef][PubMed]
126. Veraldi, N.; Hughes, A.J.; Rudd, T.R.; Thomas, H.B.; Edwards, S.W.; Hadfield, L.; Skidmore, M.A.; Siligardi, G.; Cosentino, C.; Shute, J.K.; et al. Heparin derivatives for the targeting of multiple activities in the inflammatory response. *Carbohydr. Polym.* **2015**,*117*, 400–407. [CrossRef]
127. Redini, F.; Tixier, J.M.; Petitou, M.; Choay, J.; Robert, L.; Hornebeck, W. Inhibition of leucocyte elastase by heparin and its derivatives.*Biochem. J.***1988**, *252*, 515–519. [CrossRef]
128. Lahrsen,E.;Schoenfeld,A.K.;Alban,S.Degradation ofEightSulfatedPolysaccharidesExtractedfromRed andBrownAlgaeand ItsImpactonStructureandPharmacologicalActivities. *ACSBiomater.Sci.Eng.***2019**,*5*,1200–1214. [CrossRef]
129. Massberg, S.; Grahl, L.; von Bruehl, M.L.; Manukyan, D.; Pfeiler, S.; Goosmann, C.; Brinkmann, V.; Lorenz, M.; Bidzhekov, K.; Khandagale,A.B.;etal.Reciprocalcouplingofcoagulationandinnateimmunityvianeutrophilserineproteases.*Nat.Med.***2010**, *16*, 887–896. [CrossRef]
130. Marchetti, M.; Falanga, A. Leukocytosis, JAK2V617F mutation, and hemostasis in myeloproliferative disorders.*Pathophysiol. Haemost.Thromb.***2008**,*36*,148–159. [CrossRef]
131. Rasmuson,J.;Kenne,E.;Wahlgren,M.;Soehnlein,O.; Lindbom,L.Heparinoidsevuparininhibits*Streptococcus*-inducedvascular leakthroughneutralizingneutrophil-derivedproteins.*FASEBJ.***2019**,*33*,10443–10452.[CrossRef]
132. Fisher,J.;Linder,A.Heparin-bindingprotein:Akeyplayerinthepathophysiologyoforgandysfunctioninsepsis.*J.Intern.Med.* **2017**,*281*,562–574.[CrossRef]
133. Kaplan, M.J.; Radic, M. Neutrophil extracellular traps: Double-edged swords of innate immunity. *J.Immunol.* **2012**, *189*, 2689–2695.[CrossRef]
134. Brinkmann, V.; Reichard, U.; Goosmann, C.; Fauler, B.; Uhlemann, Y.; Weiss, D.S.; Weinrauch, Y.; Zychlinsky, A. Neutrophil extracellulartrapskillbacteria.*Science***2004**,*303*,1532–1535.[CrossRef]
135. Urban, C.F.; Ermert, D.; Schmid, M.; Abu-Abed, U.; Goosmann, C.; Nacken, W.; Brinkmann, V.; Jungblut, P.R.; Zychlinsky, A. Neutrophil extracellular traps contain calprotectin, a cytosolic protein complex involved in host defense against *Candida albicans*.*PLoSPathog.* **2009**,*5*,e1000639. [CrossRef]
136. Hakkim, A.; Furnrohr, B.G.; Amann, K.; Laube, B.; Abed, U.A.; Brinkmann, V.; Herrmann, M.; Voll, R.E.; Zychlinsky, A. Impairment of neutrophil extracellular trap degradation is associated with lupus nephritis.*Proc. Natl. Acad. Sci. USA***2010**, *107*,9813–9818. [CrossRef]
137. Gupta, A.K.; Hasler, P.; Holzgreve, W.; Gebhardt, S.; Hahn, S. Induction of neutrophil extracellular DNA lattices by placentalmicroparticlesandIL-8andtheirpresenceinpreeclampsia.*Hum.Immunol.***2005**,*66*,1146–1154.[CrossRef]
138. Kessenbrock,K.;Krumbholz,M.;Schonermarck,U.;

Back,W.;Gross,W.L.;Werb,Z.;Grone,H.J.;Brinkmann,V.;Jenne,D.E. Nettingneutrophilsinautoimmunesmall-vesselvasculitis. *Nat. Med.* **2009**,*15*,623–625. [CrossRef]
139. Delgado-Rizo, V.; Martinez-Guzman, M.A.; Iniguez-Gutierrez, L.; Garcia-Orozco, A.; Alvarado-Navarro, A.; Fafutis-Morris, M.Neutrophil Extracellular Traps and Its Implications in Inflammation: An Overview. *Front. Immunol.* **2017**, *8*, 81. [CrossRef]
140. Long, Y.; Zhang, Y.; Gong, Y.; Sun, R.; Su, L.; Lin, X.; Shen, A.; Zhou, J.; Caiji, Z.; Wang, X.; et al.Diagnosis of Sepsis with Cell-free DNA by Next-Generation Sequencing Technology in ICU Patients. *Arch. Med. Res.* **2016**, *47*, 365–371. [CrossRef]
141. Alhamdi,Y.;Abrams,S.T.;Cheng,Z.;Jing,S.;Su,D.;Liu,Z.;Lane,S.;Welters,I.;Wang,G.;Toh,C.H.CirculatingHistonesAre MajorMediatorsofCardiacInjuryinPatientsWithSepsis. *Crit.CareMed.***2015**,*43*,2094–2103. [CrossRef]
142. Saukkonen,K.;Lakkisto,P.;Pettila,V.;Varpula,M.;Karlsson,S.;Ruokonen,E.;Pulkki,K.;FinnsepsisStudy,G.Cell-freeplasma DNAasapredictorofoutcomeinseveresepsisandsepticshock. *Clin. Chem.* **2008**,*54*,1000–1007. [CrossRef]
143. Rhodes,A.;Cecconi,M.Cell-freeDNAandoutcomeinsepsis.*Crit.Care***2012**,*16*,170. [CrossRef] [PubMed]
144. Fuchs,T.A.;Brill,A.;Duerschmied,D.;Schatzberg,D.;Monestier,M.;Myers,D.D.,Jr.;Wrobleski,S.K.;Wakefield,T.W.;Hartwig,J.H.; Wagner, D.D. Extracellular DNA traps promote thrombosis. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 15880–15885. [CrossRef][PubMed]
145. Napirei, M.; Ludwig, S.; Mezrhab, J.; Klockl, T.; Mannherz, H.G. Murine serum nucleases—Contrasting effects of plasmin and heparinontheactivitiesofDNase1andDNase1-like3(DNase1l3). *FEBSJ.***2009**,*276*,1059–1073. [CrossRef][PubMed]
146. Brill, A.; Fuchs, T.A.; Savchenko, A.S.; Thomas, G.M.; Martinod, K.; De Meyer, S.F.; Bhandari, A.A.; Wagner, D.D. Neutrophil extracellulartrapspromotedeepveinthrombosisinmice.*J.Thromb.Haemost.***2012**,*10*,136–144.[CrossRef]
147. Varju,I.;Longstaff,C.;Szabo,L.;Farkas,A.Z.;Varga-Szabo,V.J.;Tanka-Salamon,A.;Machovich,R.;Kolev,K.DNA,histones and neutrophil extracellular traps exert anti-fibrinolytic effects in a plasma environment. *Thromb. Haemost.* **2015**, *113*, 1289–1298.[CrossRef]
148. Komorowicz, E.;Balázs,N.;Tanka-Salamon,A.;Varga,Z.;Szabó,L.;Bóta,A.;Longstaff, C.;Kolev,K.Size-andcharge-dependent modulationofthelyticsusceptibilityandmechanicalstabilityoffibrin-histoneclotsbyheparinandpolyphosphatevariants. *J. Thromb.Haemost.***2021**,*19*,1307–1318.[CrossRef]
149. Longstaff,C.;Hogwood,J.;Gray,E.;Komorowicz,E.;Varjú,I.;Varga,Z.;Kolev,K.Neutralisationoftheanti-coagulanteffectsof heparinbyhistonesinbloodplasmaandpurifiedsystems. *Thromb.Haemost.***2016**,*115*,591–599. [CrossRef]
150. Hogwood, J.; Pitchford, S.; Mulloy, B.; Page, C.; Gray, E. Heparin and non-anticoagulant heparin attenuate histone-induced inflammatoryresponsesinwholeblood. *PLoSONE***2020**,*15*,e0233644. [CrossRef]
151. Sharma, N.; Haggstrom, L.; Sohrabipour, S.; Dwivedi, D.J.; Liaw, P.C. Investigations of the effectiveness of heparin variants as inhibitorsofhistones.*J.Thromb.Haemost.***2022**,*20*,1485–1495.[CrossRef]
152. Wildhagen,K.C.;GarciadeFrutos,P.;Reutelingsperger,C.P.;Schrijver,R.;Areste,C.;Ortega-Gomez,A.;Deckers,N.M.;Hemker, H.C.; Soehnlein, O.; Nicolaes, G.A. Nonanticoagulant heparin prevents histone-mediated cytotoxicity in vitro and improves survivalinsepsis. *Blood***2014**,*123*,1098–1101. [CrossRef]
153. Yang,X.;Li,L.;Liu,J.;Lv,B.;Chen,F.ExtracellularhistonesinducetissuefactorexpressioninvascularendothelialcellsviaTLRand activation of NF-kappaB and AP-1.*Thromb.Res.***2016**, *137*, 211–218.[CrossRef]
154. Gould, T.J.; Lysov, Z.; Swystun, L.L.; Dwivedi, D.J.; Zarychanski, R.; Fox-Robichaud, A.E.; Liaw, P.C.; Canadian Critical Care TranslationalBiology,G.ExtracellularHistonesIncreaseTissueFactorActivityandEnhanceThrombinGenerationbyHuman Blood Monocytes. *Shock***2016**, *46*, 655–662. [CrossRef]
155. Ekaney,M.L.;Otto,G.P.;Sossdorf,M.;Sponholz,C.;Boehringer,M.;Loesche,W.;Rittirsch,D.;Wilharm, A.;Kurzai,O.;Bauer,M.; etal. Impactofplasmahistonesinhumansepsisandtheircontributiontocellularinjuryandinflammation. *Crit.Care***2014**,*18*, 543.[CrossRef]
156. Freeman, C.G.; Parish, C.R.; Knox, K.J.; Blackmore, J.L.; Lobov, S.A.; King, D.W.; Senden, T.J.; Stephens, R.W. The accumulation ofcirculatinghistonesonheparansulphateinthecapillary glycocalyxofthelungs.*Biomaterials* **2013**,*34*,5670–5676.[CrossRef]
157. Zhu,C.;Liang,Y.;Li,X.;Chen,N.;Ma,X.Unfractionatedheparinattenuateshistone-mediatedcytotoxicityinvitroandprevents intestinalmicrocirculatorydysfunctioninhistone-infusedrats.*J.TraumaAcuteCare***2019**,*87*,614–622.[CrossRef]
158. Fabian,I.;Aronson,M.Polycationsaspossiblesubstitutesforprotamineinheparinneutralization.*Thromb.Res.***1980**, *17*,239–247. [CrossRef]
159. Pal,P.K.;Starr,T.;Gertler,M.M.Neutralizationofheparinbyhistoneanditssubfractions.*Thromb.Res.***1983**,*31*,69–79.[CrossRef]
160. Wang, F.; Zhang, N.; Li, B.; Liu, L.; Ding, L.; Wang, Y.; Zhu, Y.; Mo, X.; Cao, Q. Heparin defends against the toxicity of circulating histonesinsepsis.*Front.Biosci.LandmarkEd.***2015**,*20*,1259–1270.
161. Mandel,J.;Casari,M.;Stepanyan,M.;Martyanov,A.;

Deppermann,C.BeyondHemostasis: PlateletInnateImmuneInteractions and Thromboinflammation. *Int. J.Mol. Sci.* **2022**, *23*, 3868. [CrossRef]
162. Chen,Z.;Zhang,H.;Qu,M.;Nan,K.;Cao,H.;Cata,J.P. ;Chen,W.;Miao,C.Review:TheEmergingRoleofNeutrophil ExtracellularTrapsinSepsisandSepsis-AssociatedThrombosis.*Front.CellInfect.Microbiol.* **2021**,*11*,653228.[CrossRef]
163. Jiao,Y.;Li,W.;Wang,W.;Tong,X.;Xia,R.;Fan,J.;Du, J.;Zhang,C.;Shi,X.Platelet-derivedexosomespromoteneutrophil extracellular trap formation during septic shock. *Crit. Care***2020**, *24*, 380. [CrossRef] [PubMed]
164. McDonald, B.; Davis, R.P.; Kim, S.-J.; Tse, M.; Esmon, C.T.; Kolaczkowska, E.; Jenne, C.N. Platelets and neutrophil extracellular trapscollaboratetopromoteintravascularcoagulationduringsepsisinmice.*Blood* **2017**,*129*,1357–1367.[CrossRef][PubMed]
165. Yuan, F.; Yang, Y.; Zhou, H.; Quan, J.; Liu, C.; Wang, Y.; Zhang, Y.; Yu, X. Heparanase in cancer progression: Structure, substrate recognitionandtherapeuticpotential. *Front.Chem.***2022**,*10*,926353. [CrossRef][PubMed]
166. Masola,V.;Greco,N.;Gambaro,G.;Franchi,M.;Onisto ,M.Heparanaseasactiveplayerinendothelialglycocalyxremodeling. *MatrixBiol.Plus***2022**,*13*, 100097.[CrossRef][PubMed]
167. Sullivan, R.C.; Rockstrom, M.D.; Schmidt, E.P.; Hippensteel, J.A. Endothelial glycocalyx degradation during sepsis: Causes and consequences. *MatrixBiol.Plus***2021**,*12*,100094. [CrossRef]
168. Drost,C.C.;Rovas,A.;Kümpers,P.Protectionandrebuildingoftheendothelialglycocalyxinsepsis—Scienceorfiction?*Matrix Biol. Plus* **2021**, *12*, 100091. [CrossRef]
169. Oshima,K.;King,S.I.;McMurtry,S.A.;Schmidt,E.P. EndothelialHeparanSulfateProteoglycansinSepsis: TheRoleofthe Glycocalyx.*Semin. Thromb. Hemost.* **2021**,*47*,274–282. [CrossRef]
170. Goligorsky,M.S.;Sun,D.GlycocalyxinEndotoxemiaandSepsis.*Am.J.Pathol.***2020**,*190*,791–798.[CrossRef]
171. Kiyan,Y.;Tkachuk,S.;Kurselis,K.;Shushakova,N.; Stahl,K.;Dawodu,D.;Kiyan,R.;Chichkov,B.;Haller, H.Heparanase-2 protectsfromLPS-mediatedendothelialinjurybyinhibitingTLR4signalling. *Sci. Rep.* **2019**,*9*,13591. [CrossRef]
172. Freeman,C.;Parish,C.R.Humanplateletheparanase: Purification,characterizationandcatalyticactivity. *Biochem.J.***1998**,*330 Pt 3*, 1341–1350. [CrossRef]
173. Sanderson, R.D.; Yang, Y.; Suva, L.J.; Kelly, T. Heparan sulfate proteoglycans and heparanase—Partners in osteolytic tumorgrowthandmetastasis. *MatrixBiol.* **2004**,*23*,341–352. [CrossRef]
174. Lindahl, U.; Li,J.P. Heparanase—Discovery andTargets.*Adv.Exp.Med.Biol.***2020**,*1221*, 61–69.[CrossRef]
175. Gong,F.;Jemth,P.;EscobarGalvis,M.L.;Vlodavsky,I.; Horner,A.;Lindahl,U.;Li,J.P.Processingofmacromolecularheparinbyheparanase.*J. Biol. Chem.* **2003**, *278*, 35152–35158. [CrossRef]
176. Ilan,N.;Elkin,M.;Vlodavsky,I.Regulation,functionandclinicalsignificanceofheparanaseincancermetastasisandangiogenesis. *Int.J.Biochem.CellBiol.***2006**,*38*,2018–2039.[CrossRef]
177. Eustes,A.S.; Campbell,R.A.; Middleton,E.A.; Tolley,N.D.; Manne,B.K.; Montenont,E.; Rowley,J.W.; Krauel,K.; Blair,A.; Guo,L.; et al. Heparanase expression and activity are increased in platelets during clinical sepsis. *J.Thromb. Haemost.* **2021**, *19*, 1319–1330.[CrossRef]
178. Vlodavsky, I.; Barash, U.; Nguyen, H.M.; Yang, S.M.; Ilan, N. Biology of the Heparanase-Heparan Sulfate Axis and Its Role in DiseasePathogenesis. *Semin.Thromb.Hemost.***2021**,*47*,240–253. [CrossRef]
179. Goodall,K.J.;Poon,I.K.;Phipps,S.;Hulett,M.D.Solubleheparansulfatefragmentsgeneratedbyheparanase triggertherelease ofpro-inflammatorycytokinesthroughTLR-4. *PLoSONE***2014**,*9*,e109596. [CrossRef]
180. Schmidt, E.P.; Yang, Y.; Janssen, W.J.; Gandjeva, A.; Perez, M.J.; Barthel, L.; Zemans, R.L.; Bowman, J.C.; Koyanagi, D.E.; Yunt,Z.X.; et al. The pulmonary endothelial glycocalyx regulates neutrophil adhesion and lung injury during experimental sepsis. *Nat. Med.***2012**, *18*, 1217–1223. [CrossRef]
181. Li, J.; Qi, Z.; Li, D.; Huang, X.; Qi, B.; Feng, J.; Qu, J.; Wang, X. Alveolar epithelial glycocalyx shedding aggravates the epithelial barrieranddisruptsepithelialtightjunctionsinacuterespiratorydistresssyndrome.*Biomed.Pharmacother.***2021**,*133*,111026. [CrossRef]
182. Lygizos, M.I.; Yang, Y.; Altmann, C.J.; Okamura, K.; Hernando, A.A.; Perez, M.J.; Smith, L.P.; Koyanagi, D.E.; Gandjeva, A.;Bhargava,R.;etal.Heparanasemediatesrenaldysfunctionduringearlysepsisinmice.*Physiol.Rep.***2013**,*1*,e00153.[CrossRef]
183. Chen,S.;Zhang,X.;Sun,Y.;Hu,Z.;Lu,S.;Ma,X.Unfractionatedheparinattenuatesintestinalinjuryinmousemodelofsepsisbyinhibiting heparanase. *Int. J. Clin. Exp. Pathol.* **2015**, *8*, 4903–4912. [PubMed]
184. Chen, S.; He, Y.; Hu, Z.; Lu, S.; Yin, X.; Ma, X.; Lv, C.; Jin, G. Heparanase Mediates Intestinal Inflammation and Injury in a Mouse ModelofSepsis. *J.Histochem. Cytochem.* **2017**,*65*,241–249. [CrossRef][PubMed]
185. Tang,Y.;Wang,X.;Li,Z.;He,Z.;Yang,X.;Cheng,X.;Peng,Y.;Xue,Q.;Bai,Y.;Zhang,R.;etal.Heparinpreventscaspase-11-dependentsepticlethalityindependentofanticoagulantproperties.*Immunity***2021**,*54*,454–467.e456.[CrossRef][PubMed]
186. Zhang, X.; Han, X.; Xia, K.; Xu, Y.; Yang, Y.; Oshima, K.; Haeger, S.M.; Perez, M.J.; McMurtry, S.A.; Hippensteel, J.A.; et al. Circulatingheparinoligosaccharidesrapidlytargetthehippocampusinsepsis,potentiallyimpactingcognitivefunctions. *Proc. Natl.Acad.Sci.USA***2019**,*116*,9208–9213. [CrossRef]
187. Hippensteel, J.A.; Anderson, B.J.; Orfila, J.E.; McMurtry, S.A.; Dietz, R.M.; Su, G.; Ford, J.A.;

Oshima, K.; Yang, Y.; Zhang, F.; et al. Circulatingheparansulfatefragmentsmediatesepticcognitivedysfunction. *J.Clin.Investig.***2019**,*129*,1779–1784. [CrossRef]
188. Mohamed,S.;Coombe,D.R.HeparinMimetics:TheirTherapeuticPotential.*Pharmaceuticals***2017**,*10*,78.[CrossRef]
189. Cassinelli,G.;Torri,G.;Naggi,A.Non-AnticoagulantHeparinsasHeparanaseInhibitors.*Adv.Exp.Med.Biol.***2020**,*1221*, 493–522.[CrossRef]
190. Noseda, A.; Barbieri, P.Roneparstat: Development, PreclinicalandClinicalStudies.*Adv. Exp. Med. Biol.* **2020**, *1221*, 523–538. [CrossRef]
191. Buijsers, B.; Yanginlar, C.; de Nooijer, A.; Grondman, I.; Maciej-Hulme, M.L.; Jonkman, I.; Janssen, N.A.F.; Rother, N.; de Graaf, M.; Pickkers, P.; et al. Increased Plasma Heparanase Activity in COVID-19 Patients. *Front. Immunol.* **2020**, *11*, 575047. [CrossRef]
192. Xiang,J.;Lu,M.;Shi,M.;Cheng,X.;Kwakwa,K.A.;Davis,J.L.;Su,X.;Bakewell,S.J.;Zhang,Y.;Fontana,F.;etal.Heparanase Blockade as a Novel Dual-Targeting Therapy for COVID-19. *J.Virol.* **2022**, *96*, e0005722. [CrossRef]
193. Chhabra, M.; Wilson, J.C.; Wu, L.; Davies, G.J.; Gandhi, N.S.; Ferro, V. Structural Insights into Pixatimod (PG545) Inhibition of Heparanase,aKeyEnzymeinCancerandViralInfections. *Chemistry***2022**,*28*,e202104222. [CrossRef]
194. Guimond,S.E.;Mycroft-West,C.J.;Gandhi,N.S.;Tree,J.A.;Le,T.T.;Spalluto, C.M.;Humbert,M.V.;Buttigieg,K.R.;Coombes, N.; Elmore, M.J.; et al. Synthetic Heparan Sulfate Mimetic Pixatimod (PG545) Potently Inhibits SARS-CoV-2 by Disrupting the Spike-ACE2 Interaction. *ACSCent. Sci.* **2022**, *8*, 527–545. [CrossRef]
195. Kinaneh, S.; Khamaysi, I.; Karram, T.; Hamoud, S. Heparanase as a potential player in SARS-CoV-2 infection and induced coagulopathy. *Biosci.Rep.***2021**,*41*,BSR20210290. [CrossRef]
196. Li,X.;Ma,X.Theroleofheparininsepsis:Muchmorethanjustananticoagulant.*Br.J.Haematol.***2017**,*179*,389–398.[CrossRef]
197. Murao,S.;Yamakawa,K.ASystematicSummaryofSystematicReviewsonAnticoagulantTherapyinSepsis. *J.Clin.Med.***2019**,*8*, 1869. [CrossRef]
198. Galli, M.; Chatterjee, M.; Grasso, M.; Specchia, G.; Magen, H.; Einsele, H.; Celeghini, I.; Barbieri, P.; Paoletti, D.; Pace, S.; et al. Phase I study of the heparanase inhibitor roneparstat: An innovative approach for ultiple myeloma therapy. *Haematologica* **2018**,*103*, e469–e472. [CrossRef]
199. Biemond, B.J.; Tombak, A.; Kilinc, Y.; Al-Khabori, M.; Abboud, M.; Nafea, M.; Inati, A.; Wali, Y.; Kristensen, J.; Kowalski, J.; et al. Sevuparin for the treatment of acute pain crisis in patients with sickle cell disease: A multicentre, randomised, double-blind, placebo-controlled,phase2trial.*LancetHaematol.***2021**,*8*,e334–e343.[CrossRef]
200. Dredge, K.; Brennan, T.V.; Hammond, E.; Lickliter, J.D.; Lin, L.; Bampton, D.; Handley, P.; Lankesheer, F.; Morrish, G.; Yang, Y.;etal. APhaseIstudyofthenovelimmunomodulatoryagentPG545(pixatimod)insubjectswithadvancedsolidtumours. *Br.J. Cancer***2018**,*118*,1035–1041. [CrossRef]