The Many Roles of Cholesterol in Sepsis: A Review

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Authors' contributions

MS conceived the idea for the article. DH performed the initial literature search and drafted the first version of the manuscript. DH, AK, AP, MB and MS revised subsequent drafts of the manuscript. All authors have approved the final version of the manuscript.

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The authors are performing laboratory studies investigating the potential of cholesterol as a therapy for sepsis and have no current commercial conflicts.

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Abstract

Rationale: The biological functions of cholesterol are diverse, ranging from cell membrane integrity and signalling, immunity, to the synthesis of steroid and sex hormones, Vitamin D, bile acids and oxysterols. Multiple studies have demonstrated hypocholesterolemia in sepsis, the degree of which is an excellent prognosticator of poor outcomes. However, the clinical significance of hypocholesterolemia has been largely unrecognized.

Objectives/Methods: We undertook a detailed review of the biological roles of cholesterol, the impact of sepsis, its reliability as a prognosticator in sepsis, and the potential utility of cholesterol as a treatment.

Measurements and Main Results: Sepsis affects cholesterol synthesis, transport and metabolism. This likely impacts upon its biological functions including immunity, hormone and vitamin production, and cell membrane receptor sensitivity. Early preclinical studies show promise for cholesterol as a pleiotropic therapeutic agent.

Conclusions: Hypocholesterolemia is a frequent condition in sepsis and an important early prognosticator. Low plasma levels are associated with wider changes in cholesterol metabolism and its functional roles, and these appear to play a significant role in sepsis pathophysiology. The therapeutic impact of cholesterol elevation warrants further investigation.

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Keywords

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Introduction

Sepsis, the dysregulated host response to infection resulting in organ dysfunction [1], is a major worldwide cause of mortality [2] and morbidity. Current management focuses on adequate fluid resuscitation, organ support, and treating the infection with antibiotics and source control. To date, no available treatments that directly target underlying pathophysiological mechanisms have been clearly demonstrated to improve outcomes.

Cholesterol, a sterol lipid, plays an integral role in multiple body functions including maintenance of cellular membrane processes, immunity, signalling, pathway regulation, and as a precursor for the synthesis of steroid hormones, Vitamin D, bile acids and oxysterols. Sepsis-induced hypocholesterolemia was first recognized a century ago [3]; multiple studies demonstrate a worse prognosis associated with the magnitude of decline. However, mechanisms by which plasma levels fall, the impact on organ functionality, the relationship of plasma cholesterol to intracellular concentrations, and the potential role of cholesterol as a therapeutic all require elucidation.

There is increasing interest in the therapeutic possibilities of lipoproteins and modulation of cholesterol transport in sepsis, particularly in immune-inflammatory modulation and pathogen scavenging. There has, however, been little focus on cholesterol itself rather than its carriers. In this article, we provide an overview of the biology of cholesterol, its possible roles in sepsis pathophysiology, and its potential utility as a specific adjunctive treatment.

Cholesterol synthesis, structure, metabolism and functional roles

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Cholesterol consists of four linked aromatic hydrophobic rings, a small hydrophilic hydroxyl group, and a hydrophobic chain. Due to its high hydrophobicity, cholesterol is only present within cells predominantly as a component of lipid membranes or bound to lipid-binding proteins [4] (Figure 1). Animals obtain cholesterol through diet and, primarily, by endogenous synthesis. Cholesterol synthesis is a multistep (~30 reaction) process that is highly energy-consuming; synthesis of one cholesterol molecule requires 18 acetyl-CoA, 36 ATP, 16 NADPH and 11 oxygen molecules. Endogenous cholesterol synthesis is tightly regulated by negative feedback (Figure 2). Hydroxymethylglutaryl-coenzyme A reductase (HMG-CoA reductase), the target of statin therapy, is the rate-limiting enzyme within the pathway and the predominant mechanism by which cells adapt to changes in cholesterol bioavailability.

To enable transport in plasma, cholesterol must be bound to lipoproteins or albumin. Lipoproteins are categorized into chylomicrons, chylomicron remnants, very-low (VLDL), low (LDL) and high-density (HDL) lipoprotein by density, size and the type of particle-forming and other associated proteins. Cholesterol bound to LDL is transported from liver to peripheral tissues whereas HDL carries cholesterol to the liver and steroidogenic tissues - "*reverse cholesterol transport*" [4]. Mammalian cells lack an enzyme system to catabolize and recycle cholesterol and its derivates. The liver clears cholesterol from the circulation via LDL and HDL receptors [5]. It is then metabolized or excreted either unmodified or as bile acids, a large proportion of which is reabsorbed.

Cholesterol and its metabolites provide multiple biological functions (Figure 3):

(i) Cholesterol is an integral part of cell membranes, and plays a crucial role in modulating membrane thickness, permeability, fluidity and functionality [6, 7]. Within the

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membrane, cholesterol distributes non-homogeneously, accumulating within lipid rafts. These small, highly dynamic, sterol- and sphingolipid-enriched membrane micro-domains attract many transmembrane proteins such as ion channels, transporters and receptors, including G-protein coupled receptors (GPCRs) [7]. Alterations in membrane cholesterol affect the membrane's physical properties and influence the presence and activity of transmembrane proteins such as the sodium-potassium-ATPase and ß-adrenergic receptors [7].

(ii) Both cholesterol and its lipoprotein carriers have immunomodulatory properties including binding of endotoxin and other toxins [8, 9]. This scavenging mechanism may play an important role in neutralizing toxins as part of the innate immune system response, preventing activation of Toll-like receptors (TLRs) by pathogen-associated molecular patterns (PAMPs). Of note, key receptors regulating the immune response such as Toll-like receptors and T- and B-cell receptors are localized within lipid rafts [10].

(iii) Cholesterol is the only steroidogenic substrate used to synthesize adrenocortical (glucocorticoids, aldosterone) and sex hormones (e.g. estrogen, progesterone, testosterone) and vitamin D through multi-step processes [11]. During a triggered stress response, approximately 80% of circulating cortisol may be derived from plasma cholesterol [12].

The impact of Vitamin D on multiple diseases, including musculoskeletal disorders, insulin resistance and metabolic syndrome, and on cardiovascular and immunological dysfunction has been studied extensively [13].

(iv) Conversion of cholesterol to bile acids involves 17 distinct enzymatic steps within hepatocytes and is the principal route of cholesterol metabolism. Bile acids undergo

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enterohepatic recirculation, allowing recycling with *de novo* hepatocyte synthesis compensating for physiological intestinal losses. Bile acids aid metabolite excretion by the liver, absorption of lipids, hydrophobic nutrients and fat-soluble vitamins, and prevent bacterial overgrowth within the small bowel and biliary tree. They also regulate multiple functions within various liver cell types, e.g. cell differentiation and regeneration [14].

(v) Oxysterols represent a large family of oxidized derivatives of cholesterol with multiple biological actions, including immunomodulation [15]. Cholesterol can be oxidized either enzymatically or non-enzymatically by reactive oxygen species. Oxysterols can exert their functions through GPCRs, nuclear receptors and other molecular pathways, regulating many processes from cytokine production to virus entry into cells [16, 17]. Oxysterols modulate neutrophil, B- and T-cell functionality, enhance innate immunity and regulate production of the anti-inflammatory cytokine, IL-10 [17, 18].

Cholesterol levels fall during sepsis, in line with severity and outcome

Reductions in total plasma cholesterol, high-density (HDL-C) and low-density lipoprotein cholesterol (LDL-C) are well recognized in sepsis [19-28]. Levels are decreased at the time of diagnosis [21] and often decline further during the disease course [25]. Serum HDL-C levels reach a nadir around day 3 post-admission, whereas LDL-C is lowest at the time of diagnosis [21]. Variable recovery in serum levels occurs over subsequent days [25]. The kinetics of VLDL-C in sepsis are poorly characterized in human sepsis.

Multiple studies report a greater mortality risk in patients with lower levels of total, HDL- and LDL-cholesterol [23-28]. Of note, a recent genetic study suggested that low LDL levels in sepsis may be associative rather than causal of an increased mortality risk [27]

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while low HDL cholesterol may be a causal factor [29]. Increased LDL clearance may contribute to a lower sepsis mortality via enhanced pathogen lipid clearance [27].

Survivors show a slow return to almost normal values over the disease course. The magnitude of fall is associated with a higher incidence of multi-organ dysfunction, an increased duration of ICU stay and more nosocomial infection [23, 26]. Elevated serum markers of inflammation correlate negatively with cholesterol levels [20, 24, 28].

Infusion of recombinant TNF-alpha or IL-6 into cancer patients also produced large falls in plasma cholesterol in inverse correlation to markers of inflammation [30, 31]. Animal experiments can replicate these findings and can be used as a therapeutic test bed. However, this is model-dependent as some rodent models injected with endotoxin or TNF-alpha actually demonstrate hypercholesterolemia [32]. However, we and others have found large falls in total and HDL cholesterol levels in rats given a more realistic peritonitis insult [33-35]. Hypocholesterolemia has also been demonstrated in septic models using primates, sheep and dogs [36-38].

Why does serum cholesterol fall in sepsis?

Biological mechanisms leading to hypocholesterolemia in sepsis remain incompletely understood. Apart from decreased intake and impaired intestinal absorption of fat in critical illness [39], decreased synthesis, impaired cholesterol transport, increased metabolism and depletion through toxin scavenging may be implicated.

Data on the impact of sepsis on cholesterol synthesis are limited and conflicting. Old studies in rodent models reported increased hepatic cholesterogenesis [32, 40] and concurrent hypercholesterolemia [32]. Vasconcelos et al however noted a decrease in HMG-

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CoA reductase activity compared to healthy, fed rats [40]. Our currently unpublished data reveal decreased expression of transcriptional regulators (SREBP-1, SREBP-2, INSIG) and enzymes (HMG-CoA reductase) within the hepatic cholesterol synthesis pathway in our rat peritonitis model.

Pro-inflammatory cytokines may contribute to hypocholesterolemia by reducing hepatic synthesis of apolipoproteins that bind cholesterol to form lipoproteins [41]. Falls in plasma LDL-C are commonly but variably reported whereas low HDL-C is a consistent finding. Those changes suggest reverse cholesterol transport, i.e. transfer of cholesterol from peripheral tissues to the liver, may be more affected [19]. Figure 4 illustrates different cholesterol metabolic and transfer pathways affected by sepsis. Transporters (e.g. the ATP-binding cassette (ABC) transporter superfamily which transforms lipid-poor apolipoprotein A1 (apoA-1) particles into mature HDL particles) and enzymes such as lecithin-cholesterol acyltransferase (LCAT), which converts free cholesterol to more hydrophobic cholesterol esters enabling incorporation into HDL, are affected by sepsis [22, 41]. The binding capacity of HDL is also affected by alterations in its structure and protein composition, and by accumulation of oxidized lipids [42].

Cholesteryl ester transfer protein (CETP) mediates triglyceride and cholesteryl ester transfer between triglyceride-rich lipoproteins and HDL particles, with lower plasma CETP levels increasing the proportion of HDL cholesterol. However, total circulating cholesterol levels are unaffected [43]. Literature on the relevance of changes in plasma CETP levels in sepsis and relationship to outcomes is conflicting [29, 44-46].

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Similarly, conflicting patient data are seen with regard to alterations in plasma proprotein convertase subtilisin kexin 9 (PCSK9) levels, an enzyme that degrades hepatic LDL and adipocyte VLDL receptors, resulting in hypercholesterolemia [47-49].

Cholesterol metabolism can be increased in sepsis by enzymatic and non-enzymatic oxidation. Cholesterol-25-hydroxylase is strongly induced by inflammation and its product, 25-hydroxycholesterol [50]. The acute-phase protein phospholipase A2 (PLA2) rises during inflammation and promotes increased metabolism of cholesterol esters and apolipoproteins, thereby reducing serum cholesterol [51]. PLA2 activity is enhanced by another acute-phase reactant, serum amyloid A (SAA), which also affects cholesterol transport [52]. Sepsis however decreases bile flow [53]. Impaired biotransformation and hepatobiliary transport of bile acids occur within hours of induction of polymicrobial sepsis [54]. As a consequence, bile acids can be elevated in the blood compartment.

Impact of sepsis on the biological roles of cholesterol

As described earlier, cholesterol and its various metabolites exert many complex biological functions, many of which are disrupted during sepsis. The specific contribution of cholesterol deficiency to these abnormalities requires further elucidation, but there is sufficient direct and circumstantial evidence to suggest cholesterol deficiency may play an important role.

• *Cell membrane function*

The cholesterol composition within lipid rafts modifies intrinsic function and downstream signaling, such as the adrenergic receptor pathway. Cholesterol depletion in human neutrophil cell membranes induced a more pro-inflammatory phenotype including

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priming, enhanced activation, increased adhesion and oxidant production [55, 56]. Raft-dependent signaling of multiple cell types may be altered due to changes in membrane cholesterol levels affecting, for example, GPCR density and activity [6, 7]. This may be of particular relevance in septic shock where myocardial and vascular hyporeactivity to exogenous catecholamines is a defining characteristic, with the magnitude of hyporesponsiveness associated with increased mortality [57].

- *Immunomodulatory and anti-bacterial properties of cholesterol*

Notwithstanding the scavenging and immunosuppressive roles of HDL and other lipoproteins, a low cholesterol may itself negatively impact on innate and adaptive immune cells [58]. Intracellular cholesterol plays a pivotal role in TLR signaling in macrophages [59]. The cholesterol concentration within membrane lipid rafts significantly impacts on raft levels of TLR-4 and -9 [59]. Depletion of the ABC-A1 transporter in knockout macrophages, impacting on intracellular cholesterol transport, was associated with enlarged, cholesterol-containing lipid rafts that were rich in TLR-4 and hyperresponsive to LPS [59]. In lymphocytes, enrichment of cholesterol in lipid rafts was associated with increased formation of an immune synapse between signalling complexes and T-cell receptors. Low serum and low membrane cholesterol concentrations also influence natural killer cell (NK cell) function [60].

- *Steroid, sex hormone and vitamin D deficiency*

Adrenal insufficiency is a recognized complication in patients with sepsis and septic shock and associated with increased mortality [61]. Even though plasma cortisol levels are frequently raised, there is decreased responsiveness to ACTH stimulation, particularly in

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eventual non-survivors [62], suggesting the possibility of diminished reserves. As mentioned earlier, some 80% of circulating cortisol during stress is derived from plasma cholesterol [12]. The contribution of hypocholesterolemia in sepsis is uncertain as the downstream cortisol production pathway may also be compromised, e.g. expression of steroidogenic acute regulatory protein (StAR), the rate-limiting step in steroidogenesis which orchestrates transport of cholesterol from outer to inner mitochondrial membranes [63]. Pharmacological suppression of HDL-C does however disrupt adrenal steroidogenesis [64]. Nonetheless, human data are conflicting [65-67].

Falls in sex hormone [68] and vitamin D levels [69] are also well recognized in sepsis and carry prognostic and potential therapeutic implications. Pharmacological activation of the estrogen receptor-beta improved survival in pneumonia and peritonitis models of sepsis [70]. Administration of high-dose vitamin D to critically ill patients with severe vitamin D deficiency have produced conflicting outcomes [71, 72]. An association has been described between low cholesterol and low testosterone in male septic shock patients [73], however causation remains unclear. Low LDL-C levels have also been linked to low testosterone levels in chronically ill patients [68].

- *Bile acids*

Impaired biotransformation and hepatobiliary transport of bile acids occur within hours following induction of polymicrobial sepsis [54]. In septic patients, bile acids are significantly elevated and predictive of poor outcomes [74]. This appears to relate to diminished or even obstructed bile flow from liver rather than increased synthesis. To what extent changes in cholesterol levels in different body compartments during sepsis alter the complex mechanisms of bile acid metabolism remains to be elucidated.

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Cholesterol supplementation and lipoprotein therapies

The idea of a lipid treatment for infection is not new, whether this be cholesterol, HDL or analogues, oxysterols or phospholipid emulsions. Indeed, Bayer took out a patent for cholesterol therapy for blackwater fever (malaria) in 1910. The possible impact of cholesterol therapy on a wide range of infectious diseases was suggested soon after [75].

Published studies remain relatively scanty and are often based on model systems. What benefit derives from the lipoprotein itself or from elevation of cholesterol levels is unclear.

Cholesterol nanoparticles elevated intracellular levels and prevented the cytotoxic effect of the pneumococcal antigen, pneumolysin on hepatocytes [76]. Administration of 25-hydroxycholesterol decreased viral load and improved outcomes in a porcine viral pneumonitis model [77]. In terms of carriers of cholesterol, intravenous application of reconstituted HDL or HDL mimetics (based on apolipoprotein A-1) reduced organ damage, improved hemodynamics and survival in a variety of septic or endotoxemic rodent models [35, 78-83]. Inhibition of CETP with anacetrapib preserved high-density lipoprotein cholesterol levels and improved survival in septic mice [46]. Pharmacological inhibition of PCSK9 has however delivered variable results. Whereas improved survival was noted in a murine polymicrobial peritonitis model [47], no protection was afforded in a murine endotoxin model [84].

Human studies are limited. Reconstituted HDL decreased proinflammatory cytokine release in human volunteer endotoxemia [85]. A multicenter study enrolling nearly 1400 patients with presumed Gram negative sepsis [86] reported that a 10% phospholipid-

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lipoprotein emulsion that contained no cholesterol, given with the aim of neutralizing endotoxin, failed to deliver any benefit. A two-centre Phase I/II clinical protocol has been recently published [87] in which an anti-inflammatory lipid emulsion containing fish oil is being administered intravenously to septic patients with the objective of raising plasma cholesterol levels. The impact of cholesterol infusions on lipoprotein levels (HDL-C, LDL-C, VLDL-C) remains unknown. More experimental *in vitro* and *in vivo* studies are needed to address mechanisms, feasibility, dose finding and possible adverse events.

Statin therapy for sepsis – is there a paradox?

How can the above arguments related to cholesterol therapy be reconciled with the putative benefits of statins in critical illness, agents which are conventionally used to treat hypercholesterolemia? Statins inhibit HMG-CoA reductase, the rate-limiting enzyme in the mevalonate pathway which commences with acetyl CoA. This pathway later splits into branches that synthesize cholesterol, heme A, ubiquinone, dolichol and other isoprenoids. Statins also affect other pathways either directly related or not to mevalonate, such as endothelial NO synthase activation [88]. Thus, other than lowering cholesterol, statins have multiple other immunomodulatory, antinflammatory and metabolic effects such as activation of PPARs, increased production of endothelial NO, reduced synthesis of endothelin-1 and thromboxane A2, and NADPH oxidase inactivation [88-90]. These may be both beneficial or harmful, e.g. statin-induced myopathy has been linked to reductions in ubiquinone and thus mitochondrial functionality or alterations in sarcolemma and/or membrane binding proteins [91]. The impact of statins on mortality in cardiovascular disease specifically related to cholesterol lowering is questioned [92].

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With respect to sepsis, epidemiological studies reported an association with improved survival from sepsis in patients on pre-existing statin treatment, however, this likely relates to population lifestyle differences [93-95]. Two randomized controlled, multicenter trials found no benefit from *de novo* statin therapy in sepsis [96, 97]. Notably, plasma cholesterol levels were markedly subnormal in both atorvastatin and control groups (2.4 vs 2.6 mmol/l, respectively) [96]. The HARP-2 trial of patients with ARDS, of whom 40% had sepsis, showed no outcome effect from simvastatin [98]. Of note, a post-hoc analysis suggested patients with a hyperinflammatory phenotype could benefit [99], indicating non-cholesterol lowering effects may be more pertinent. Based on current evidence, we cannot recommend continuation or addition of statins in sepsis; prospective randomised studies are needed to clarify their potential utility in specific patient subsets.

Conclusions

Low cholesterol levels are a well-recognized manifestation of sepsis and septic shock. The magnitude of hypocholesterolemia relates to disease severity and outcome and is an early prognostic marker. Several pathophysiologic mechanisms can participate in the development of hypocholesterolemia in sepsis and its impact on multiple downstream biochemical pathways. Further studies are needed to extend our knowledge about the importance and interactions of these mechanisms and the role of cholesterol ± lipoproteins as therapeutics.

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Figure legends

Fig. 1 Cholesterol structure and location within cell membranes

Fig. 2 Cholesterol synthesis and metabolism pathways and impact of sepsis

ABC1; ATP-binding cassette transporter-1, AMP; adenosine monophosphate, AMPK; AMP-activated protein kinase, ApoA1; apolipoprotein A1, HDL; high-density lipoprotein, HMGCoA reductase; Hydroxymethylglutaryl-coenzyme A reductase, INSIG; insulin-induced gene-1 protein, LDL; low-density lipoprotein, SIRT-1; sirtuin-1, SREBP; sterol regulatory element-binding protein, SCAP; SREBP cleavage-activating protein, VLDL; very low-density lipoprotein.

* plasma levels may be normal or raised for adrenocorticoid hormones and bile acids but this may relate to decreased metabolism/excretion rather than increased production. Cortisol levels frequently fail to augment with exogenous ACTH stimulation

Fig. 3 Functional roles of cholesterol

Fig. 4 Impact of sepsis on cholesterol transport

VLDL; very low-density lipoprotein, LDL; low-density lipoprotein, HDL; high-density lipoprotein; LDL-R; low-density lipoprotein receptor; ABC, ATP-binding cassette transporter; SR-BI, scavenger receptor B type 1; LCAT; lecithin-cholesterol acyltransferase; CETP; cholesteryl ester transfer protein; PCSK9; proprotein convertase subtilisin kexin 9.

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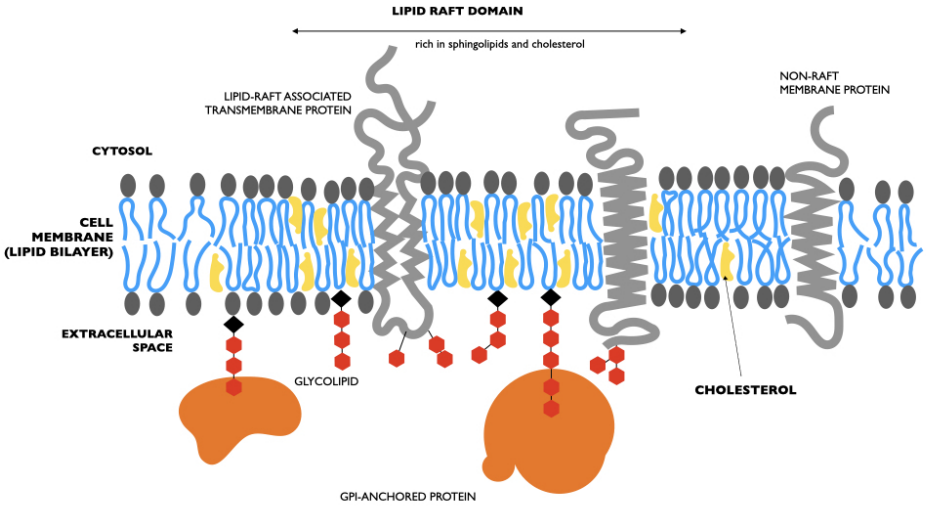

Fig. 1: Cholesterol structure and location within cell membranes

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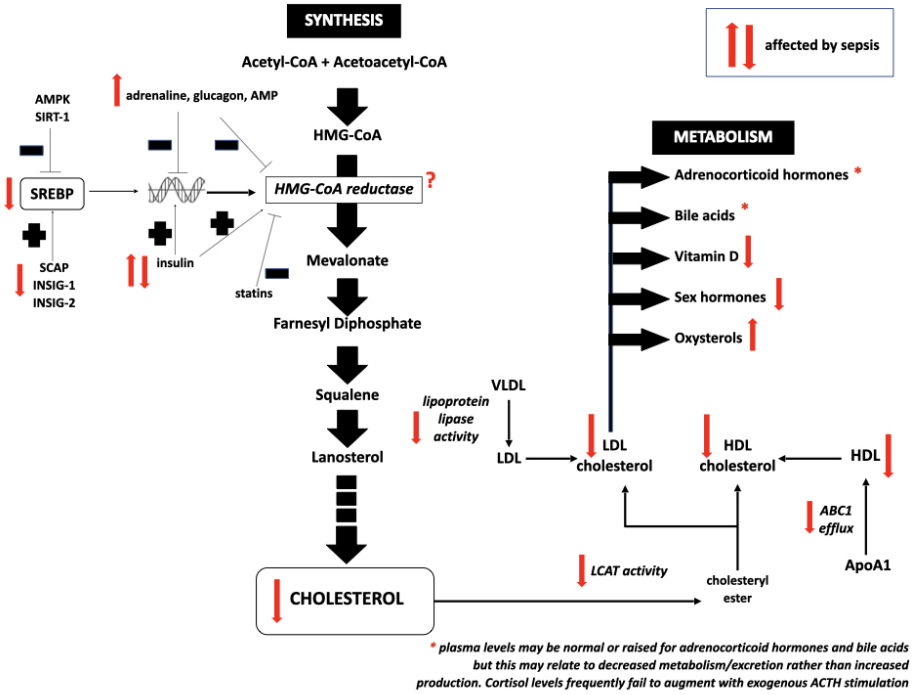

Fig 2: Cholesterol synthesis and metabolism pathways and impact of sepsis

361x270mm (72 x 72 DPI)

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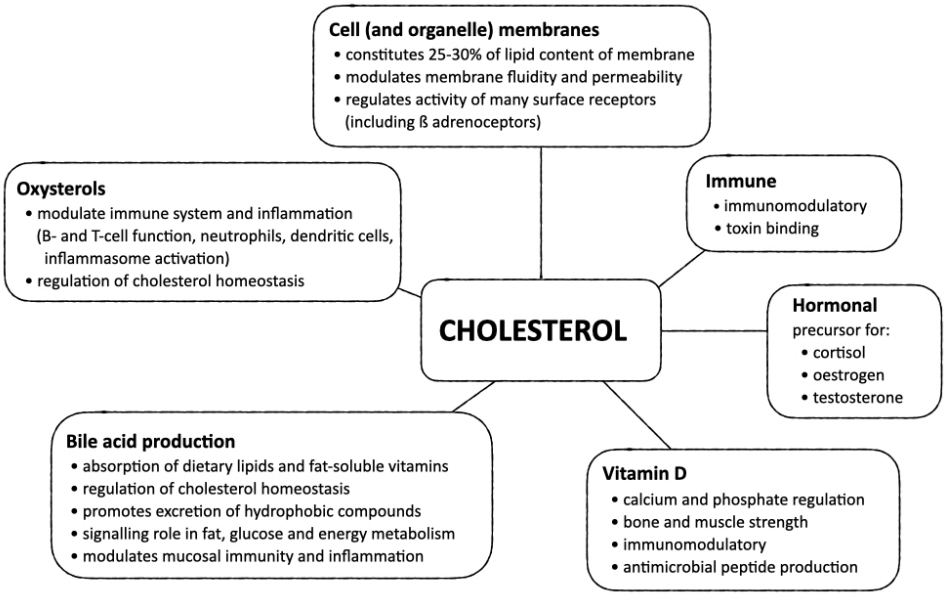

Fig 3: Functional roles of cholesterol

361x270mm (72 x 72 DPI)

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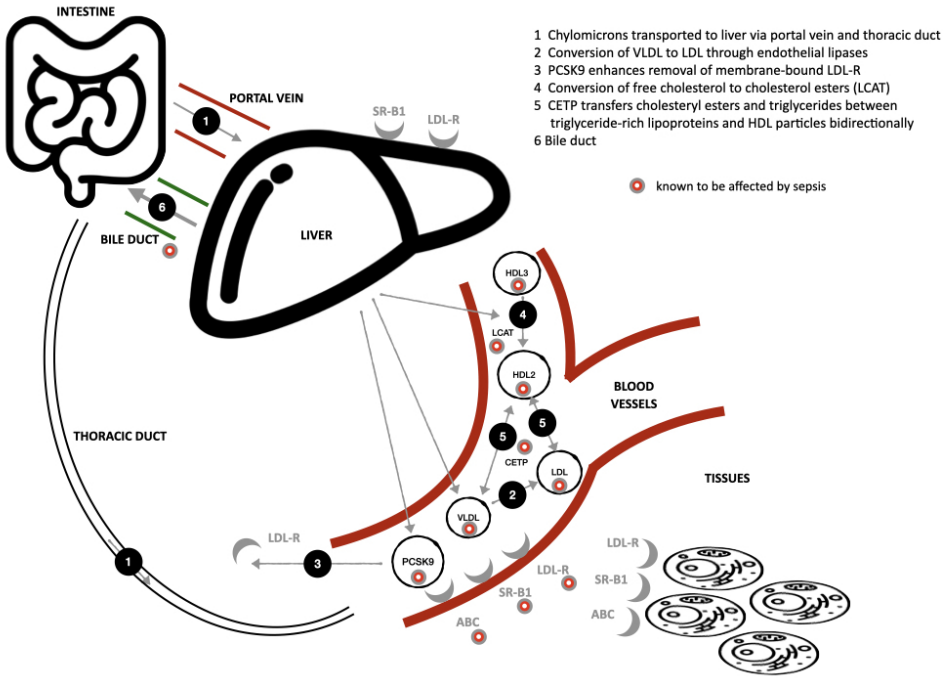

Fig 4: Impact of sepsis on cholesterol transport

361x270mm (72 x 72 DPI)

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