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Hypolipidemia: A Word of Caution

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Introduction

Hypolipidemia is a decrease in plasma lipoprotein caused by primary (genetic) or secondary (acquired) factors. It is usually asymptomatic and diagnosed incidentally on routine lipid screening. The first report of hypocholesterolemia in the medical literature was in 1911 by Chauffard and coworkers, in patients with active tuberculosis [1]. Since then (about 95 years), only few dozens of studies were published in this regard. Unlike hyperlipidemia physicians are usually unaware of hypolipidemia, its causes and consequences. As the interest in aggressive management of hyperlipidemia increases, particularly with the available, relatively strong hypolipidemic drugs and the newer and probably stronger agents, the following question should be answered; how low can we go in serum levels. For the time being, it is difficult to give a certain limit for the safest and lowest level of serum cholesterol, but knowing the complications of hypolipidemia will raise awareness. What might appear as a simple mildly reduced serum lipid can be an indication of an underlying, serious problem.   A systematic search of Pubmed for all the studies in the English language as well as the abstracts of publications in other languages related to hypolipidemia was undertaken. The following words were used in the search: hypolipidemia, hypocholesterolemia, hypobetalipoproteinemia, and statins. Search results were reviewed.

Definition

The terms hypolipidemia, hypocholesterolemia and hypobetalipoproteinemia are used interchangeably in the literature, and refer to reduced plasma cholesterol. Most authors use the total serum cholesterol (TC) to define this condition. Yet, there is no consensus about the level below which a clinically significant hypocholesterolemia will ensue, and each author used a different cut-off value. Even so, most of the authors use a cut-off value between 120 mg/dl (3.1 mmol/l) and 150m/dl (3.88mmol/l) [2,3,4,5]. However some authors use higher levels up to 190mg/dl (4.9mmol/l) [6,7] while others use lower values such as 100mg/dl (2.59 mmol/l) [8,9,10].

Epidemiology

Hypolipidemia is generally uncommon but secondary causes are relatively common compared to the rare primary hypolipidemic disorders. The frequency of hypolipidemia depends on which plasma cholesterol level is used to define the condition. Among the 1,479 men selected from the National Health and Nutrition Examination Survey-I, the prevalence of hypocholesterolemia (<130mg/dl) was 1.8% in whites and 3.6% in blacks [3]. In another survey involving 772 firefighters 3.6% of blacks and 2.9% of whites were hypocholesterolemic [3]; both surveys demonstrate racial differences in the prevalence of hypocholesterolemia as it is more likely to be seen in blacks. In hospitalized patients the prevalence of hypocholesterolemia ranges from 0.5 to 6.2% [5,6,9,11]. It is more often seen in males and is linked to increased morbidity, longer hospitalization (hence greater cost), increased re-hospitalizations rate, and a greater number of associated diseases [6]. It is more commonly seen in the critically ill and post-operative patients, those with septicemia, malignancies, and inflammatory bowel disease [11] and is significantly associated with increased mortality.

Etiology and classification
Primary hypolipidemia

There are 3 rare primary disorders of hypolipidemia in which genetic mutations cause an underproduction or increased clearance of Low Density Lipoproteins (LDL) and result in lipid levels low enough to cause significant consequences. These conditions are: abetalipoproteinemia, hypobetalipoproteinemia and chylomicron.

Table-I: Causes of hypolipidemia

Primary disorders	Secondary disorders
Abetalipoproteinemia	Infection (acute or chronic)
Hypobetalipoproteinemia	Malabsorption and undernutrition
Chylomicron retention disease	Anemia
	Chronic inflammation
	Critical illnesses
	Malignancies
	Hyperthyroidism
	Chronic liver disease
	Gaucher disease
	Drug induced: statins

Secondary hypolipidemia

Multiple mechanisms have been described in different diseases and clinical conditions that are found to be associated with hypocholesterolemia (Table II).

Anemia

Hypocholesterolemia has been described in various types of chronic anemia [12-17]. Few studies have suggested that such patients have a lower incidence of atherosclerosis associated events [12]. Types of anemia that have been reported to be associated with hypocholesterolemia include: congenital dyserythropoietic anemia [12], congenital spherocytosis [12,13], sickle cell anemia [14], beta-thalassemia [12,15], aplastic anemia [16] and sideroblastic anemia [17]. The exact etiology of hypocholesterolemia in anemic patients is not known and the data are not sufficient, however several studies postulated different mechanisms [12,16-19], and some authors even suggest that hypocholesterolemia might be the cause rather than the consequence of anemia which is explained by the fact that cholesterol deficiency leads to rigidity of the erythrocytes [20] making them more prone to destruction. Hypocholesterolemia tends to occur in patients with chronic anemia and increased erythropoietic activity, and it has been suggested that this is due to increased cholesterol requirements by the proliferating erythroid cells [12]. Some researchers have demonstrated hypocholesterolemia in patients with aplastic anemia and correlated this with the elevated serum level of macrophage colony stimulating factor (M-CSF), which is known to have cholesterol-lowering activity, and they found that pretreatment total serum cholesterol and triglyceride levels nicely correlate with the counts of hemopoietic cells in the bone marrow. They concluded that low serum lipids suggest severe bone marrow failure in these patients and can help to predict the therapeutic response of each case of aplastic anemia [16]. Other researchers demonstrated a significant increase in serum cholesterol following splenectomy in patients with hypersplenism and preoperative hypocholesterolemia. They suggest a possible role of the spleen in lipid metabolism in these patients [19]. Bjerve et al reported a case of sideroblastic anemia and hypocholesterolemia due to autoantibodies against LDL causing an increased LDL catabolism [17]. Another animal study suggested that hypocholesterolemia in anemic mice is related to a decreased in vivo hepatic cholesterol synthesis [18].

Hyperthyroidism

Thyroid disorders are known to affect lipid metabolism hence thyroid dysfunction may result in changes in the composition and transport of lipoproteins [21]. Both overt and subclinical hyperthyroidism is associated with reduced serum levels of TC, LDL and high density lipoprotein (HDL) [21,22]. Hyperthyroidism can also be the underlying cause of unexplained improvement of hyperlipidemia [21]. These hypolipidemic changes in hyperthyroidism are explained by various effects of thyroid hormones on the lipoprotein metabolism. Despite the increased hepatic de novo cholesterol synthesis in hyperthyroid states due to augmentation of HMG-CoA reductase activity, levels of total and LDL cholesterol, are likely to diminish in patients with hyperthyroidism due to enhanced LDL receptor-mediated catabolism of LDL particles [21,22] and increased bile excretion of cholesterol [21]. Moreover, the triiodothyronine (T3) enhances the gene expression of the LDL receptor and hence the receptor activity [21]. Thyroid hormones also stimulate the enzyme lipoprotein lipase (LPL), which catabolizes the triglyceride-rich lipoproteins [21]. The end result of all previous changes, is reduction in serum level of TC, LDL and HDL. However triglyceride levels remain unchanged [21], while the effect on lipoprotein (a) is still controversial, because both decrease or no changes have been reported [21].

Table-II: mechanisms of secondary hypocholesterolemia

In chronic illness:
- chronic exposure to IL-6 , IL-10 and TNF
- undernutrition due to anorexia
In critically ill patients:
- downregulation of hepatic synthesis, due to decreased production of   cholesterol precursors.
- dilutional effects of fluid resuscitation
- loss of apoproteins in burns
- increased cholesterol catabolism
In cancer patients:
- elevated LDL receptor activity in malignant cells
- undernutrition due to anorexia
- effect of TNF
In anemia:
- increased cholesterol requirements by the proliferating erythoid cells
- elevated serum level of macrophage colony stimulating factor (M-CSF)
- hypersplenism
- autoantibodies against LDL causing an increased LDL catabolism
In thyrotoxicosis:
- enhanced LDL receptor-mediated catabolism of LDL particles
- increased bile excretion of cholesterol
- increased lipoprotein lipase, which catabolizes the triglyceride-rich lipoproteins
- increased LDL-receptor activity

Critical illness

Total cholesterol levels drop at the onset of acute illness and return to normal during recovery [23,24]. Multiple mechanisms influence hypocholesterolemia in critically ill patients and these include: downregulation of hepatic synthesis [25], probably due to decreased production of cholesterol precursors particularly lanosterol and lathosterol [26], loss of apoproteins in burns [27], and increased cholesterol catabolism [25,28]. Low cholesterol concentrations associated with high levels of cytokines such as interleukin (IL)-6 and IL-10 [28], Hypocholesterolemia have been reported in patients with acute severe pyelonephritis [29], major trauma [24,26], those with multiple organ dysfunction syndrome [25], burns [27], sepsis [30], and in patients undergoing surgical interventions [31] . More importantly, hypocholesterolemia is not only a marker for the disease severity but it may also predispose critically ill patients to sepsis and adrenal failure, and may carry a significantly increased risk of mortality. [23,28,30,32]. In meningococcal septicemia, Vermont et al demonstrated that total cholesterol, HDL, and LDL levels on admission correlate inversely with disease severity and cortisol level [30]. The severity of hypocholesterolemia in sepsis is directly related to the severity of acute phase response [33]. In patients with major trauma Dunham et al demonstrated that hypocholesterolemia improves with recovery from acute illness but continues with development of organ failure or occurrence of infection [24].

Malignancy

Several studies suggest an inverse relationship between serum cholesterol level and cancer mortality in patients with hematological and solid organ malignancies [34-39]. Elevated LDL receptor activity in malignant cells may be a contributing factor to hypocholesterolemia in some cancer patients [38]. The evidence relating hypocholesterolemia to increased risk of cancer is controversial. In a large prospective study of Japanese-American men followed for > 20 years, hypocholesterolemia was associated with increased risk of colonic cancer development; this relationship becomes stronger as the site of cancer shifts from the left to the right colon. The authors suggest that the preclinical effects of occult colonic cancer is responsible for this inverse relationship, but these effects do not explain why the association with hypolipidemia was stronger in patients who were later diagnosed with right-sided colon cancer [39]. Swanson et al also thought that hypocholesterolemia might be a predisposing factor for endometrial cancer [37]. In a large Japanese study of 9216 persons, hypocholesterolemia was significantly associated with an increased risk of liver cancer [40]. Moreover, several animal experiments have found that statins are carcinogenic at blood concentrations similar to those achieved by doses commonly used to treat hyperlipidemia, the carcinogenicity may be due to the effects of statins on cholesterol [41]. Furthermore, some human studies also connected the use of lipid lowering drugs to cancer development. The cholesterol and recurrent events trial (CARE), showed a significant increase in breast cancer, particularly recurrences [42], while the trial of Pravastatin in elderly individuals at risk of vascular disease (PROSPER), concluded that the benefit from fewer cardiovascular deaths was counterbalanced by the significant increase in cancer mortality [43]. Although several recent studies give reassuring evidences regarding the safety of statins with respect to carcinogenicity up to 10 years [44] but this period remains relatively short compared with the medically accepted latency period for cancer of 20 years [45]. In conclusion, evidence regarding the carcinogenicity of hypocholesterolemia from clinical studies in humans is inconclusive because of conflicting results and unsatisfactory duration of follow-up. The available evidence does not significantly support a direct cause-effect relationship between hypocholesterolemia and cancer [46], rather, the data suggest that low cholesterol levels may serve as a "marker," or prognostic indicator of the disease [47].

Malabsorption

Since dietary fats constitute the exogenous source of body lipids, undernutrition or fat malabsorption can lead to hypolipidemia. Brar et al demonstrated that celiac disease is associated with hypocholesterolemia and a gluten-free diet will result in rising of total cholesterol and HDL [48]. In patients with chronic pancreatitis, cholesterol absorption is markedly reduced primarily due to reduced intestinal lipolysis [49]. Bile acid malabsorption was also named as an additional factor in the development of hypocholesterolemia in patients with chronic pancreatitis [50]. Malabsorption is a common finding in patients with acquired immunodeficiency syndrome (AIDS) and fat malabsorption could be a contributing factor to the disease associated hypocholesterolemia. The pathogenesis of malabsorption in AIDS patients is multifactorial including primary enterocyte injury and exudative enteropathy [51].

Infection

Acute and chronic bacterial, viral, and parasitic infections all might induce hypocholesterolemia due to the chronic effect of proinflammatory cytokines on lipoprotein metabolism. In 1911, Chauffard et al were the first to report hypocholesterolemia in patients with tuberculosis. Since then, transient hypocholesterolemia and hypertriglyceridemia were frequently observed during the acute phase of bacterial infections [52]. In 1920, Kipp noted an association between the degree of hypocholesterolemia and the severity of infection [1]. These changes are mediated by different cytokines as IL-1 and tumor necrosis factor-alpha (TNF) which are involved in the acute phase response during sepsis [52]. In critically ill patients, decreasing cholesterol levels suggest the development of infection. Some authors believe that hypocholesterolemia is a more sensitive marker for the onset of infection than leukocytosis [24]. Moreover, hypocholesterolemia was significantly correlated with the intensity of the acute phase responses during sepsis (as C-reactive protein level) [52]. Since parasites need to feed on host cholesterol for a successful infection [3], theoretically parasitic infestation might cause low plasma cholesterol. Several authors have shown that hypocholesterolemia has the strongest positive predictive value (96%) of the biological parameters for malaria diagnosis, [53]. Visceral lieshmaniasis also has been reported to cause hypocholesterolemia [54]. Human immune deficiency virus (HIV) is associated with hypocholesterolemia during the asymptomatic phase and is associated with specific alterations in immune function, suggesting that hypocholesterolemia may be a useful marker of disease progression [4,55]. Hepatitis-C virus (HCV) is associated with significantly lower cholesterol levels (TC, LDL and HDL) when compared with those of normal subjects. Levels of apolipoprotein B (apoB) correlate negatively with HCV viral load and this finding is more pronounced in patients infected with HCV genotype 3 [56,57]. In a Japanese study, infection with genotype 1b was also associated with hypocholesterolemia [58]. It was postulated that hypobetalipoproteinemia associated with HCV is mediated by HCV core protein, which down-regulates triglyceride metabolism, leading to steatosis [59]. Clinically,hypocholesterolemia in genotype 3 is associated with a more severe steatosis, and higher grades of fibrosis pointing out a more aggressive disease [60]. It also increases the risk of hepatocellular carcinoma [61]. From the previous studies one can suggest that the presence of acquired ApoB deficiency in HCV-infected patients may be used as an indication for treatment of HCV as it is likely to be associated with a more progressive disease.

Chronic liver disease

Because hepatocytes are the most active site of lipid metabolism, hypolipidemia is frequently observed in severe chronic hepatic insufficiency [8]. A low serum cholesterol level is associated with a higher mortality rate in patients with liver cirrhosis [8,62]. Advanced chronic liver disease can cause a reduction in apolipoprotein A and apolipoprotein B levels. Isolated deficiency of apolipoprotein B indicates abetalipoproteinemia or familial hypobetalipoproteinemia; which can result in liver involvement in the form of elevated transaminases, fatty liver and cirrhosis, while deficiency of both apolipoprotein

A and apolipoprotein B is a manifestation of advanced chronic liver disease regardless of the etiology [63].

Chronic inflammation

Changes in plasma lipid levels are a well known phenomenon in the acute phase response to inflammation. Chronic inflammation also can produce hypocholesterolemia due to the chronic effect of proinflammatory cytokines on lipoprotein metabolism. Ettinger et al demonstrated that chronic IL-6 injection causes acquired hypocholesterolemia in nonhuman primates [64]. Bologa et al found a significant relationship between TNF and IL-6 and the degree of hypolipoproteinemia in hemodialysis patients [65]. Ripollés et al have demonstrated that serum cholesterol was significantly lower in patients with active inflammatory bowel disease than in the control group [66]. Hypocholesterolemia also has been reported in patients with rheumatoid disorders [67]. Moreover, the anorexia that accompanies the chronic inflammatory disorders may contribute to the hypolipidemic effect of the proinflammatory cytokines in producing hypolipidemia in these conditions.

Consequences of hypolipidemia

1- Effects on plasma membrane

Since about 44% of the human cell membrane is composed of lipids, they serve as a major structural component. Cell membranes are absolutely essential for the cell survival as well as for biological functions [68]. It is not known how very low plasma cholesterol levels would affect membrane composition and function but some indirect evidence might shed some light on this issue. Acanthocytes are dense, contracted red blood cells with several irregularly spaced thorny projections on the surface due to abnormal membrane fluidity. Acanthocytosis is a known clinical feature of abetalipoproteinemia and was also reported to be associated with hypolipidemia in celiac disease. In the later case acanthocytes disappeared two weeks after initiation of gluten free diet [69]. Acanthocytosis was also reported with hypobetalipoproteinemia in advanced chronic liver disease [63].The exact mechanism of formation of acanthocytes is unclear, but reversal of the usual phosphatidylcholine-sphingomyelin ratio is considered to be a possible mechanism [70]. In a recent animal study, the hypolipidemic agent Atorvastatin caused significantly lower cholesterol and higher phospholipid content of red blood cell membrane, thus decreasing the cholesterol to phospholipid ratio. Although these structural changes were not associated with any obvious adverse rheological alterations, but they show that hypolipidemia may be associated with cell membrane lipid changes [71].

2- Intracerebral hemorrhage (ICH)

Intracranial hemorrhage accounts for approximately 10% of all strokes, and carries a significantly high morbidity and mortality as the 30-day fatality rate reaches up to 50% [72]. Several studies have demonstrated that low cholesterol is a risk factor for ICH [73-75]. Others have reported that hypercholesterolemia is protective against ICH [76-78]. Iribarren et al [74] described the association between low serum cholesterol level and cerebral hemorrhage in elderly men. In another study of young patients hypocholesterolemia (</=160mg/dl) was found in 35% of the patients with ICH compared to only 13% having hypertension [7].

Hypocholesterolemia was more common in ICH patients aged < 20 years and in those with cryptogenic ICH [7]. Other authors have mentioned hypocholesterolemia <160mg/dl (4.14 mmol/l) as a contributing risk factor for Hypolipidemia intracerebral hemorrhage in previously healthy people [75].The causal relationship is unclear; however, some investigators have proposed that the interaction of high diastolic blood pressure and low cholesterol levels weakens the endothelium of the intracerebral arteries [75], while another study reported platelet hypoactivity is associated with hypocholesterolemia [79], therefore affected patients may be more prone to bleeding.

3- Adrenal failure

Cholesterol molecules are the precursors for adrenal steroid hormones. The adrenal gland requires a continuous supplement of cholesterol for the biosynthesis of adrenal corticosteroids, which can be supplied by LDL receptor-mediated uptake or through local synthesis [80]. Thus, at least theoretically; hypocholesterolemia will be associated with hypocortisolemia, and during stress cortisol production may not be high enough to protect against the cell damage. Hence critically ill patients will be predisposed to adrenal failure [23,30,81]. Although few human and animal studies support this hypothesis [30,81], several authors have shown that in reality this does not happen [80, 82,83]. Animal studies of the hypolipidemic drug Nafenopin have shown that despite significant lowering of serum cholesterol levels, this failed to alter blood corticosterone [82] and aldosterone [83] concentrations. This is probably because of the increased endogenous cholesterol synthesis as a result of compensatory smooth endoplasmic reticulum hypertrophy [82,83]. Furthermore, one study of adult patients receiving 80 mg of the potent HMG CoA reductase inhibitor Simvastatin for two months showed that despite a 36%, reduction in total cholesterol level, there was no adverse effect on ACTH-stimulated adrenal corticosteroid production [80]. In summary; the available evidence is insufficient to support or refute the hypothesis that hypocholesterolemia can lead to adrenal failure.

4- Sepsis

Hypocholesterolemia in healthy men is reported to be associated with significantly fewer circulating lymphocytes, total T cells, and CD8+ cells [84], thus the host immunity will be altered and the patient may be prone to infection. Harris et al reported that lipoproteins bind to and neutralize bacterial endotoxin lipopolysaccharide (LPS) [85]. LPS binds to LPS binding protein [86], activating the cell surface CD14 receptor [87] which stimulates the release of several proinflammatory cytokines, including TNF, IL-1, and IL-6 [88]. If LPS binds to lipoproteins, then cytokine release is decreased [89]. It is assumed that hypolipidemia impairs the LPS neutralization, hence predisposing to more severe inflammation. Recently Kitchens et al [90] demonstrated that despite hypocholesterolemia, circulating lipoproteins maintain their ability to bind and neutralize LPS. However in spite of this recent contradiction this issue remains unsolved as evidence remains inconclusive. Several authors report that hypocholesterolemia may be a predisposing factor to sepsis in the critically ill patient [23,30]. A significant relationship has been observed between preoperative

hypocholesterolemia and incidence of postoperative septic complications. Leardi et al reported that the highest incidence of postoperative septic complications is seen in patients with cholesterol levels below 105 mg/dl [10]. Moreover, a very low level of cholesterol is also considered to be a prognostic factor during infection, predicting an unfavorable outcome in elderly patients [52]. Hypocholesterolemia is the most frequently observed laboratory finding in fatal cases of pneumonia in the elderly [91], in a study conducted at a nursing home; hypocholesterolemia was the only admission feature associated with death due to bacteremia [2]. Pacelli et al reported hypocholesterolemia as an independent predictor of death in patients with intra-abdominal infection [92]. In neutropenic patients with fever, non-survivors had significantly lower serum cholesterol levels compared to survivors [93]. From these whole data one can conclude that hypocholesterolemia is a risk factor for infection in certain conditions as well as a prognostic indicator during sepsis.

5 - Disease mortality

Studies suggest that lipoproteins play a role in the binding and neutralization of endotoxins [85]. Epidemiologic studies have identified a relationship between hypocholesterolemia (< 130 mg/dL) and increased mortality from all causes [14]. Crook et al stated that, in hospitalized patients the lower the plasma cholesterol the higher the mortality, and they demonstrated an increase in the mortality rate from 39% to 71% as plasma cholesterol dropped from < 77.2mg/dl (2mmol/dl) to < 58mg/dl (1.5 mmol/l) [11]. A low baseline serum cholesterol level is associated with higher mortality rates in patients with liver cirrhosis. There is a significant relationship and increased risk of mortality in patients with HIV and HCV co-infections [62]. Hypocholesterolemia is also associated with increased mortality in patients with tuberculosis [94]. Several epidemiological studies suggest an inverse relationship between serum cholesterol levels and cancer mortality [34]. Following a severe trauma, dying patients appear to have progressive hypocholesterolemia [24]. In conclusion, hypocholesterolemia has a statistically significant relationship to mortality in the critically ill patient and is an independent predictor of mortality in this group.

The role of lipid lowering drugs

Lipid lowering drugs, particularly statins, are being more widely used to reduce the cardiovascular mortality. Recent studies show that cardiovascular risk reduction is proportional to the level of reduction of LDL. Therefore the American National Cholesterol Education Program recommends a more aggressive lipid lowering strategy for high risk patients with cardiovascular disease. This means that LDL should be < 70mg/dl (1.81 mmol/l). Although cholesterol lowering to this degree is more cardioprotective in high risk patients, other possible complications may neutralize or even outweigh this benefit. For example; hypocholesterolemia was associated with increased risk of colorectal cancer [36], endometrial cancer [37], and liver cancer [40]. Furthermore, some other studies directly link the use of lipid lowering drugs to cancer development. The CARE trial, showed a significant increase in breast cancer [42], while the trial of Pravastatin in elderly individuals at risk of vascular disease (PROSPER) concluded that the significant increase in cancer mortality counterbalanced the benefit of fewer cardiovascular deaths [43]. Moreover; high cholesterol has been found to be protective against intra

cerebral hemorrhage [76-78], therefore lipid-lowering medications may increase the risk of ICH (at least theoretically), and several studies have demonstrated that hypocholesterolemia is a risk factor for ICH [73-75]. Considering this evidence, one should be concerned about the potential deleterious effects of the drug-induced hypolipidemia. We should evaluate individual cases carefully in light of current strategies for aggressive hyperlipidemia treatment.

Conclusion

Hypolipidemia is a common disorder affecting about 2 - 3% of apparently healthy individuals and up to 6% of hospitalized patients. It might be a marker for an underlying, serious problem. Unexplained hypolipidemia should always be investigated for a possible cause. Several clinical conditions as well as lipid lowering drugs may result in clinically significant hypolipidemia. The evidence regarding the carcinogenicity of hypocholesterolemia from clinical studies in humans is inconclusive. The available data suggest that low cholesterol levels may serve as a prognostic indicator in cancer patients. Low cholesterol is a possible risk factor for ICH. Hypocholesterolemia is also a predisposing factor for infection in certain conditions as well as a prognostic indicator during sepsis. There is a positive relationship between low total serum cholesterol levels, and increased mortality from all causes particularly in critically ill patients. Hypolipidemia may predispose the critically ill patient to sepsis and adrenal failure and may carry a significantly increased risk of mortality. Currently, as we focus on aggressive management of hyperlipidemia we should at least keep an eye on the possible complications of drug-induced hypolipidemia.

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