Serum Total Cholesterol Levels Would Predict Nosocomial Infections After Gastrointestinal Surgery

Mitsuaki Morimoto^{1,2} · Yoshikazu Nakamura² · Yoshikazu Yasuda¹ · Alan T. Lefor¹ · Takashi Nagaie³ · Naohiro Sata¹ · Yoshinori Hosoya¹ · Hisanaga Horie¹ · Koji Koinuma¹

Received: 9 May 2014 / Accepted: 26 May 2015 / Published online: 5 June 2015
© Association of Surgeons of India 2015

Abstract It has been suggested that total cholesterol levels and the use of statin medications are associated with the incidence of complications after gastrointestinal surgery. The aim of this study was to determine if preoperative total cholesterol levels are associated with a higher risk of postoperative infections and mortality. A total of 2211 patients undergoing general surgical procedures between December 2006 and November 2008 at Iizuka Hospital and between January 2010 and March 2012 at Jichi Medical University Hospital were reviewed. Multiple logistic regression models were used to evaluate serum total cholesterol and other variables as predictors of postoperative nosocomial infections. Serum total cholesterol concentrations lower than 160 mg/dl were associated with an increased incidence of superficial and deep incisional surgical site infections. Serum total cholesterol levels showed a reverse J-shaped relationship with the development of organ space surgical site infection and pneumonia. There was no discernible effect of serum cholesterol levels on the postoperative mortality observed in this cohort of patients. Decreased serum albumin was one of the strongest risk factors for the development of nosocomial infection after surgery. Postoperative pneumonia was not observed in patients taking statin medications whose cholesterol levels were <200 mg/dl. Serum total cholesterol may be a valid predictor of surgical

outcome. Preoperative statin use may affect the development of postoperative pneumonia in patients with total cholesterol levels below 200 mg/dl.

Keywords Pneumonia · Surgical site infections · Statins · Total cholesterol

Introduction

Hypercholesterolemia has been associated with an increased incidence of coronary-heart-disease-related death and inversely related to deaths caused by some cancers, respiratory disease, digestive disease, and trauma [1, 2]. Low serum cholesterol is related to the development of organ dysfunction and mortality in critically ill surgical patients [3]. Some studies have demonstrated that very low density lipoprotein (VLDL) and chylomicrons, as well as high-density lipoprotein (HDL), (low-density lipoprotein (LDL) and cholesterol, can protect against endotoxin-induced sepsis [4–12]. We undertook this study to evaluate these parameters as predictors of the development of nosocomial infections in a group of 2211 patients undergoing various general surgical procedures.

Methods

This study was performed at Iizuka Hospital and at Jichi Medical University Hospital and was approved by the research ethical review committees of both institutions. The study population of 1031 patients from Iizuka Hospital was recruited from patients admitted to the General Surgery Service from December 2006 through November 2008. The study population of 1180 patients from Jichi Medical University Hospital was selected from patients admitted to the Department of

✉ Mitsuaki Morimoto
mittyyone2000@yahoo.co.jp

¹ Department of Gastrointestinal Surgery, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke, Tochigi 329-0498, Japan

² Department of Public Health, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke, Tochigi 329-0498, Japan

³ Department of Surgery, Iizuka Hospital, 3-83 Yoshio-machi, Iizuka, Fukuoka 820-8505, Japan

Gastrointestinal Surgery between January 2010 and March 2012, for a total enrolment of 2211 patients. Critically ill patients with systemic inflammatory response syndrome (SIRS) or diffuse peritonitis or patients undergoing emergency surgery can become hypocholesterolemic at an early point in their

illness [3]. Emergency surgery is associated with a higher incidence of wound infection [13]. Patients who underwent emergent operations were excluded from this study.

Variables that were considered to have a possible relationship with postoperative complications were assessed (listed in

Table 1 Baseline characteristics of study subjects according to postoperative nosocomial infections and mortality

		Incisional SSIs (<i>n</i> =168)			Organ space OSI (<i>n</i> =124)			Pneumonia (<i>n</i> =73)			Death (<i>n</i> =8)			Total
		<i>n</i>	%	<i>P</i> value	<i>n</i>	%	<i>P</i> value	<i>n</i>	%	<i>P</i> value	<i>n</i>	%	<i>P</i> value	
Age	–64	55	5.7	0.003	39	4.1	0.005	21	2.2	0.011	1	0.1	0.149	962
	65+	113	9.0		85	6.8		52	4.2		7	0.6		1249
Sex	Female	53	6.3	0.082	31	3.7	0.002	14	1.7	0.001	4	0.5	0.488	839
	Male	115	8.4		93	6.8		59	4.3		4	0.3		1372
Current smokers	Non-smoker	127	7.5	0.776	87	5.1	0.082	51	3.0	0.162	7	0.4	0.690	1691
	Smoker	41	7.9		37	7.2		22	4.3		1	0.2		516
Current drinkers	Non-drinker	152	7.6	0.891	113	5.6	0.843	68	3.4	0.452	7	0.3	0.546	2001
	Drinker	16	7.7		11	5.3		5	2.4		1	0.5		207
ASA	1–2	135	7.4	0.331	98	5.3	0.165	47	2.6	0.000	4	0.2	0.029	1835
	3–5	32	8.8		26	7.2		25	6.9		4	1.1		362
BMI ≥ 30.0 kg/m ²	–29.9	162	7.6	0.759	119	5.6	0.747	72	3.4	0.454	8	0.4	1.000	2128
	30.0+	4	6.6		4	6.6		1	1.6		0	0.0		61
Statin use	Non-statin use	155	7.9	0.106	111	5.7	0.695	70	3.6	0.043	8	0.4	0.373	1955
	Stat in use	13	5.1		13	5.1		3	1.2		0	0.0		256
Albumin level	–3 g/dl	40	16.3	0.000	28	11.4	0.000	25	10.2	0.000	5	2.0	0.991	245
	3.1–3.5 g/dl	40	11.8	0.000	23	6.8	0.030	12	3.5	0.033	1	0.3	0.992	340
	3.6–4.0 g/dl	49	7.2	0.007	39	5.7	0.080	21	3.1	0.045	2	0.3	0.992	684
	4.1–4.5 g/dl	29	3.9		28	3.7		11	1.5		0	0.0		750
	4.6+ g/dl	10	5.2	0.407	6	3.1	0.678	4	2.1	0.545	0	0.0	1.000	192
Cholesterol level	–160	82	13.4	0.000	57	9.3	0.000	35	5.7	0.000	6	1.0	0.992	612
	161–200	50	6.1	0.137	36	4.4	0.435	24	2.9	0.116	2	0.2	0.993	826
	201–240	24	4.2		20	3.5		9	1.6		0	0.0		568
	240+	12	5.9	0.345	11	5.4	0.252	5	2.4	0.435	0	0.0	1.000	205
Preoperative diagnosis	Benign	38	7.7	0.952	24	4.8	0.398	9	1.8	0.035	0	0.0	0.131	496
	Neoplasm	130	7.6		100	5.8		64	3.7		8	0.5		1715
Laparoscopic surgery	Open surgery	146	9.0	0.000	115	7.1	0.000	68	4.2	0.000	8	0.5	0.121	1631
	Laparoscopic surgery	22	3.8		9	1.6		5	0.9		0	0.0		578
Site of operation	Liver and biliary tract	42	7.1	0.544	38	6.4	0.027	11	1.9		1	0.2	0.993	591
	Pancreas	16	13.9	0.041	19	16.5	0.000	3	2.6	0.601	1	0.9	0.992	115
	Stomach, duodenum	34	6.0	0.832	20	3.5		17	3.0	0.207	1	0.2		564
	Lower GI tract	70	8.4	0.299	36	4.3	0.466	24	2.9	0.223	3	0.4	0.993	832
	Esophagus	6	5.5		11	10.1	0.004	18	16.5	0.000	2	1.8	0.992	109
Operation time	–120 min	16	4.4		6	1.7		10	2.8		1	0.3		361
	121–300 min	82	6.6	0.133	48	3.9	0.048	28	2.3	0.570	2	0.2	0.657	1243
	301+ min	70	11.5	0.000	70	11.5	0.000	35	5.8	0.036	5	0.8	0.318	607
Blood loss	–100 ml	43	14.0		20	6.5		13	4.2		2	0.7		307
	101–500 ml	59	20.9	0.011	39	13.8	0.002	25	8.9	0.014	3	1.1	0.521	282
	501+ ml	66	27.8	0.000	65	27.4	0.000	35	14.8	0.000	3	1.3	0.372	237
Blood transfusion	Absent	133	7.0	0.004	93	4.9	0.000	40	2.1	0.000	3	0.2	0.002	1913
	Present	35	11.7		31	10.4		33	11.1		5	1.7		298

ASA the American Society of Anesthesiologists, BMI body mass index

Table 1). Patients were interviewed at the outpatient office or within the first 24 h after hospital admission. Preoperative data evaluated included age, gender, height, weight, smoking status, alcohol consumption, and medications. The operative variables evaluated are shown in Table 1 and are classified into five anatomic groups: esophagus; stomach and duodenum; small intestine, colon, and rectum (lower gastrointestinal tract); liver and biliary tract including gallbladder; and pancreas. Patients who received a statin medication more than 1 month before surgery were regarded as being in the statin therapy group. Serial blood samples were obtained under fasting conditions before admission for scheduled surgery, as well as at admission. Total cholesterol levels were classified into four categories (quartiles) according to the guidelines of the American Heart Association (<159, 160–199, 200–239, and >240 mg/dl). The lower limit of the total cholesterol level was considered to be 160 mg/dl. Hypercholesterolemia (above 240 mg/dl) and borderline blood total cholesterol were generally accepted under the American Heart Association guidelines. These data and data from the surgical operation and clinical records were recorded in a database. Normal range of human serum albumin is 3.8–5.3 g/dl. Serum albumin levels were divided into five categories (<3, 3.1–3.5, 3.6–4, 4.1–4.5, and >4.6 g/dl) for further examination of the contribution of serum albumin.

In this study, postoperative tissue and wound complications were defined as surgical site infections (SSIs) and pneumonia according to the Centers for Disease Control and Prevention (CDC) criteria [14, 15]. SSIs were divided into superficial and deep incisional SSIs and organ space SSI. These infectious diseases were identified by a search of clinical records or a

medical database. Nosocomial infection surveillance was extended to 30 days after surgery. Postoperative mortality associated with surgery was monitored up to 60 days.

Statistical Analyses

Univariate relationships between biochemical variables and nosocomial infection were tested using odds ratios (ORs) and their 95 % confidence intervals (CIs). Logistic regression analyses were used to adjust for potential confounders. To assess the statistical significance of trends in the multivariate analyses, quartiles of serum total cholesterol levels, quintiles of serum albumin levels, and other variables were introduced in the logistic regression model. Data were analyzed using SPSS software (IBM Corp, Armonk NY, USA, SPSS statistic 21)

Results

A total of 2211 patients who underwent general surgical procedures were reviewed, including 1372 (62 %) men and 839 (38.0 %) women. The overall incidence of postoperative nosocomial infections was 14 % ($n=316$). Among these, superficial and deep incisional SSIs were most common ($n=168$; 7.6 %). The second most frequently seen infection was organ space SSIs ($n=124$; 5.6 %), and pneumonia was diagnosed in 73 patients (3.3 %). Postoperative mortality occurred within 60 days in 0.36 % ($n=8$). None of the preoperative variables were associated significantly with postoperative mortality in multivariate logistic regression analyses.

Table 2 Variables associated with superficial and deep incisional SSIs following elective surgery analyzed by logistic regression models

Parameters	Units	No. of patients		Univariate analysis			Multivariate analysis		
		Infected	total	OR	95 % CI	P value	OR	95 % CI	P value
Alb (mg/dl)	<3	40	245	4.85	2.94–8.02	0.000	3.36	1.82–6.21	0.000
	3.1–3.5	40	340	3.32	2.02–5.45	0.000	2.77	1.57–4.86	0.000
	3.6–4.0	49	684	1.92	1.20–3.07	0.007	1.80	1.08–3.00	0.023
	4.1–4.5	29	750		Reference			Reference	
	4.6+	10	192	1.37	0.65–2.85	0.407	1.66	0.77–3.57	0.200
Cholesterol (mg/dl)	<159	82	612	3.51	2.19–5.61	0.000	2.50	1.45–4.33	0.001
	160–199	50	826	1.46	0.89–2.41	0.137	1.38	0.81–2.34	0.241
	200–239	24	568		Reference			Reference	
	240+	12	205	1.41	0.69–2.87	0.345	1.66	0.79–3.49	0.178
Operation time (min)	<120	16	361		Reference			Reference	
	121–300	82	1243	2.26	0.88–2.64	0.13	1.49	0.79–2.82	0.22
	301+	70	607	13.10	1.61–4.92	0.000	3.00	1.43–6.29	0.004
Statin use	Present	13	168	0.62	0.35–1.11	0.109	0.69	0.38–1.28	0.241

ASA the American Society of Anesthesiologists, OR odds ratio, CI confidence interval

Table 3 Variables associated with organ space SSI following elective surgery analyzed by logistic regression models

Parameters	Units	No. of patients		Univariate analysis			Multivariate analysis		
		Infected	Total	OR	95 % CI	P value	OR	95 % CI	P value
Operation time (min)	–120	6	361		Reference			Reference	
	121–300	48	1243	3.92	1.01–5.60	0.05	2.28	0.88–5.93	0.09
	301+	70	607	22.48	3.32–17.95	0.00	5.46	1.93–15.51	0.00
Operative variables	Liver, biliary tract, gallbladder	38	591	1.87	1.07–3.25	0.03	1.61	0.88–2.96	0.13
	Pancreas	19	115	5.38	2.77–10.46	0.00	2.64	1.28–5.44	0.01
	Stomach, duodenum	20	564		Reference			Reference	
	Small intestine, colon, rectum	36	832	1.23	0.71–2.15	0.47	1.24	0.69–2.23	0.47
	Esophagus	11	109	3.05	1.42–6.57	0.00	1.99	0.86–4.64	0.11
Statin use	Present	13	124	0.89	0.49–0.60	0.695	1.00	0.53–1.88	0.995

ASA the American Society of Anesthesiologists, OR: odds ratio, CI confidence interval

Tables 2, 3, and 4 show the significant parameters that were related to the development of superficial and deep incisional SSIs, organ space SSIs, and pneumonia in multivariate logistic regression analyses. The analysis of factors associated with the development of superficial and deep incisional SSIs following surgery disclosed that the lowest quartile (<159 mg/dl) total serum cholesterol level, low serum albumin (<4.0 mg/dl), and operation time (>300 min) were independent predictors of the development of infections (Table 2). The duration of the operation (>300 min) and pancreatic surgery were significant predictors for the development of organ space SSIs (Table 3). Blood transfusion, esophageal surgery, American Society of Anesthesiologists (ASA) score, and the lowest quintile albumin levels were associated with the development of pneumonia in multivariate logistic regression analyses (Table 4).

Both the lowest and highest total serum cholesterol levels were associated with a higher incidence of postoperative nosocomial infections (Fig. 1). Pneumonia did not occur in the statin use group, and there was a decreased tendency to develop other infections. In particular, patients with normal total cholesterol levels (<200 mg/dl) using statin medications had a lower incidence of pneumonia (Fig. 2).

Discussion

The findings of this study suggest an inverse relationship between total serum cholesterol levels and the incidence of nosocomial infections. In multivariate analysis, a statistically significant inverse association was noted between serum total

Table 4 Variables associated with pneumonia following elective surgery analyzed by logistic regression models

Parameters	Units	No. of patients		Univariate analysis			Multivariate analysis		
		Infected	Total	OR	95 % CI	P value	OR	95 % CI	P value
Alb (mg/dl)	–3	25	245	7.63	3.70–15.76	0.000	2.48	1.01–6.11	0.048
	3.1–3.5	12	340	2.46	1.07–5.63	0.000	0.99	0.39–2.48	0.975
	3.6–4.0	21	684	2.13	1.02–4.45	0.007	1.14	0.52–2.54	0.742
	4.1–4.5	11	750		Reference			Reference	
	4.6+	4	192	1.43	0.45–4.54	0.407	1.78	0.52–6.09	0.360
Transfusion	Positive	33	298	5.83	3.61–9.41	0.000	2.52	1.37–4.64	0.003
Operative variables	Liver, biliary tract, gallbladder	11	591		Reference			Reference	
	Pancreas	3	115	1.41	0.39–5.14	0.601	0.89	0.23–3.52	0.871
	Stomach, duodenum	17	564	1.64	0.76–3.53	0.207	1.62	0.70–3.70	0.255
Small intestine	Colon, rectum	24	832	1.57	0.76–3.22	0.223	1.27	0.58–2.76	0.549
	Esophagus	18	109	10.43	4.77–22.80	0.259	10.14	3.90–26.37	0.000
ASA	3–4	25	362	2.82	1.71–4.65	0.000	1.87	1.02–3.41	0.042
Statin use	Present	3	73	0.32	0.10–1.02	0.054	0.40	0.12–1.34	0.138

ASA the American Society of Anesthesiologists, OR odds ratio, CI confidence interval

Fig. 1 The rate of postoperative nosocomial infections categorized by preoperative cholesterol level

cholesterol levels and the incidence of superficial and deep incisional SSIs. This relationship is shown in Fig. 1. Serum total cholesterol levels did not correlate with the development of organ space SSI or pneumonia, which may partially explain the observed lower rates of these two types of infection. While the consequences of elevated cholesterol levels are well understood with respect to the increased risks of coronary disease and thromboembolic stroke, the nature and implications of associations between low serum cholesterol and non-cardiovascular causes of death represent a complex problem and continue to be an active area of research [1, 2]. Hypocholesterolemia has also been associated with the development of nosocomial infections, especially during the postoperative period [16–18].

Several non-mutually exclusive explanations for the inverse association between total cholesterol and infections are possible. First, low total serum cholesterol may contribute to

the development of infections. Circulating cholesterol-rich lipoproteins and triglyceride-rich lipoproteins have the capacity to bind and detoxify bacterial lipopolysaccharide (LPS) [10]. HDL has been shown to compete with LPS binding protein (LBP) for binding to LPS. The LPS-LBP complex attaches to the CD-14 receptor on cells, which, in turn, stimulates TNF production [6]. In vitro and in vivo models of endotoxemia in rodents have shown that lipoproteins, such as LDLs, VLDLs, HDLs, lipoprotein, triglycerides, and chylomicrons, can modulate the bioactivity of LPS [9–12]. Second, cholesterol is the precursor of five major classes of steroid hormones. Cholesterol affects gluconeogenesis and immune function; its transport forms, the lipoproteins, also serve as vehicles for fat-soluble vitamins, antioxidants, drugs, and toxins. These hormones are synthesized from cholesterol mostly in the adrenal gland and gonads in response to tissue-specific trophic hormones. These steroidogenic tissues are unique in that they require cholesterol not only for membrane biogenesis, maintenance of membrane fluidity, and cell signaling but also as the starting material for the biosynthesis of steroid hormones [19, 20]. Cortisol levels are especially low in children with severe septic shock, which is not yet understood. Relative adrenal insufficiency may be involved in this mechanism [21, 22]. High cholesterol may be protective, possibly through a beneficial influence on the immune system.

Preoperative hypoalbuminemia is well known to be significantly associated with the development of and is an independent risk factor for the development of postoperative SSI [23]. Multivariate analysis of the relationship between serum albumin and the development of superficial and deep incisional SSIs showed that preoperative serum albumin <3.0 mg/dl increased the risk of SSI by 4.2-fold in this study. Numerous

Fig. 2 The incidence of postoperative nosocomial infections in patients with total serum cholesterol <200 mg/d between those treated with and without statins

studies have showed a high risk of developing pneumonia after esophageal surgery [24, 25]. Esophageal surgery was also shown to be a significant risk factor for the development of pneumonia in this study.

Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are commonly prescribed medications. Consistently favorable results from randomized clinical trials strongly support the use of statins in the primary and secondary prevention of cardiovascular events [26, 27]. However, it has become clear that, in addition to their beneficial lipid-lowering effects, they are associated with a multitude of other pharmacological actions that may contribute to their clinical benefits; i.e., pleiotropic actions, including anticoagulant, immunosuppressive, and antiproliferative effects. These effects could conceivably affect wound healing or the risk of other wound complications after surgery or injury [28]. Prior therapy with statins has been associated with a significantly reduced risk of sepsis, including severe and fatal sepsis, and pneumonia [29].

Hospital mortality rates for inpatient cancer surgery in the USA were between 2.1 and 9.1 % from 2006 to 2007 [30]. This study showed lower mortality rates ($n=8$, 0.36 %) after surgery. There were no significant differences in the numbers of deaths. However, although they were not significant, it would be reasonable to consider that extremely low levels of total cholesterol are important in predicting in-hospital mortality after surgery.

To investigate the actual effect of statins on infection, the incidence of infections was compared between the statin- and non-statin-treated groups of patients whose cholesterol levels were <200 mg/dl. The use of statin medications might have helped to lower the lipid level in this group, more than the subgroup of patients whose cholesterol levels were over 200 mg/dl. The use of statins did not significantly suppress the development of superficial and deep incisional SSIs and organ space SSI. However, postoperative pneumonia did not occur in patients receiving statins (Fig. 2). The results of this study did not demonstrate whether this is a consequence of the pleiotropic effect of statin medications or the innate cholesterol-producing ability of the patient because most patients discontinued statin use during the postoperative period. It is possible that preoperative use of statins may offer a protective effect for the prevention of pneumonia.

The main limitation of this study is that the patients were recruited during different time periods from two institutions. However, serum cholesterol and albumin levels exhibited reversed J-shaped relations with nosocomial infections in the two institutions. The clinical implications of these associations are difficult to predict at this time. However, the associations demonstrated here further illuminate the complex interplay of lipids and the development of infections, suggesting the need for further study and evaluation. Due to clinical efforts to control serum lipid levels to achieve beneficial cardiac effects, it is unreasonable to imagine that a patient with low lipid levels would be treated with extra fat to raise lipid levels prior

to surgery. However, the targeting of extremely low levels of total cholesterol to realize the benefit of a lower incidence of vascular disease may have deleterious effects on patients undergoing elective surgery. Appropriate levels of total cholesterol should be determined for each individual patient, based on input from a variety of medical viewpoints. Screening lipid profiles in patients undergoing general surgical procedures may be a useful predictor of nosocomial infections after surgery. While this study has limitations, the data may provide a clue concerning the influence of cholesterol levels on the development of postoperative nosocomial infections.

Conflict of Interest Mitsuaki Morimoto and the other coauthors have no conflicts of interest.

References

1. Jacobs D, Blackburn H, Higgins M, Reed D, Iso H, McMillan G et al (1992) Report of the conference on low blood cholesterol: mortality associations. *Circulation* 86:1046–1060
2. Iribarren C, Jacobs DR Jr, Sidney S, Claxton AJ, Feingold KR (1998) Cohort study of serum total cholesterol and in-hospital incidence of infectious diseases. *Epidemiol Infect* 121:335–347
3. Bonville DA, Parker TS, Levine DM, Gordon BR, Hydo LJ, Eachempati SR (2004) The relationships of hypocholesterolemia to cytokine concentrations and mortality in critically ill patients with systemic inflammatory response syndrome. *Surg Infect* 5: 39–49
4. Tobias PS, McAdam KP, Soldau K, Ulevitch RJ (1985) Control of lipopolysaccharide-high-density lipoprotein interactions by an acute-phase reactant in human serum. *Infect Immun* 50:73–76
5. Casas AT, Hubsch AP, Rogers BC, Doran JE (1995) Reconstituted high-density lipoprotein reduces LPS-stimulated TNF alpha. *J Surg Res* 59:544–552
6. Casa AT, Hubsch AP, Doran JE (1996) Effects of reconstituted high-density lipoprotein in persistent gram-negative bacteremia. *Am Surg* 62:350–355
7. Pajkrt D, Doran JE, Koster F, Lerch PG, Arnet B, van der Poll T et al (1996) Antiinflammatory effects of reconstituted high-density lipoprotein during human endotoxemia. *J Exp Med* 184:1601–1608
8. Galbois A, Thabut D, Tazi KA, Rudler M, Mohammadi MS, Bonnefont-Rousselot D et al (2009) Ex vivo effects of high-density lipoprotein exposure on the lipopolysaccharide-induced inflammatory response in patients with severe cirrhosis. *Hepatology* 49:175–184
9. Harris HW, Grunfeld C, Feingold KR, Rapp JH (1990) Human very low density lipoproteins and chylomicrons can protect against endotoxin-induced death in mice. *J Clin Invest* 86:696–702
10. Rauchhaus M, Coats AJ, Anker SD (2000) The endotoxin-lipoprotein hypothesis. *Lancet* 356:930–933
11. Schvartz YSH, Polyakov LM, Dushkin MI (2008) Modification and clearance of low density lipoproteins during the formation of endotoxin-lipoprotein complexes. *Exp Biol Med* 145:430–432
12. Navab M, Hough GP, Van Lenten BJ, Berliner JA, Fogelman AM (1988) Low density lipoproteins transfer bacterial lipopolysaccharides across endothelial monolayers in a biologically active form. *J Clin Invest* 81:601–605
13. Sørensen LT, Hemmingsen U, Kallehave F, Wille-Jørgensen P, Kjaergaard J, Møller LN et al (2005) Risk factors for tissue and

- wound complications in gastrointestinal surgery. *Ann Surg* 241: 654–658
14. Sørensen LT, Hemmingsen U, Kallehave F, Wille-Jørgensen P, Kjaergaard J, Møller LN (1988) CDC definitions for nosocomial infections. *Am J Infect Control* 16:128–140
 15. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR, Hospital Infection Control Practices Advisory Committee (1999) Guideline for prevention of surgical site infection. *Infect Control Hosp Epidemiol* 20:250–278
 16. Delgado-Rodríguez M, Medina-Cuadros M, Gómez-Ortega A, Martínez-Gallego G, Mariscal-Ortiz M, Martínez-Gonzalez MA (2002) Cholesterol and serum albumin levels as predictors of cross infection, death, and length of hospital stay. *Arch Surg* 137:805–812
 17. Delgado-Rodríguez M, Medina-Cuadros M, Martínez-Gallego G, Sillero-Arenas M (1997) Total cholesterol, HDL-cholesterol, and risk of nosocomial infection: a prospective study in surgical patients. *Infect Control Hosp Epidemiol* 18:9–18
 18. Canturk NZ, Canturk Z, Okay E, Yirmibesoglu O, Eraldemir B (2002) Risk of nosocomial infections and effects of total cholesterol, HDL cholesterol in surgical patients. *Clin Nutr* 21:431–6
 19. Hu J, Zhang Z, Shen WJ, Azhar S (2010) Cellular cholesterol delivery, intracellular processing and utilization for biosynthesis of steroid hormones. *Nutr Metab* 1:47
 20. Kraemer FB (2007) Adrenal cholesterol utilization. *Mol Cell Endocrinol* 265–266: 42–5
 21. Vermont CL, den Brinker M, Kâkeci N, de Kleijn ED, de Rijke YB, Joosten KF et al (2005) Serum lipids and disease severity in children with severe meningococcal sepsis. *Crit Care Med* 33:1610–1615
 22. Ravnskov U (2003) High cholesterol may protect against infections and atherosclerosis. *QJ Med* 96:927–934
 23. Hennessey DB, Burke JP, Ni-Dhonocho T, Shields C, Winter DC, Mealy K (2010) Preoperative hypoalbuminemia is an independent risk factor for the development of surgical site infection following gastrointestinal surgery. *Ann Surg* 22:325–329
 24. Griffin SM, Shaw IH, Dresner SM (2002) Early complications after Ivor Lewis subtotal esophagectomy with two field lymphadenectomy: risk factors and management. *J Am Coll Surg* 194:285–297
 25. Ando N, Ozawa S, Kitagawa Y, Shinozawa Y, Kitajima M (2003) Improvement in the results of surgical treatment of advanced squamous esophageal carcinoma during 15 consecutive years. *Ann Surg* 232:225–32
 26. Auerbach I, Behar S, Motro M (1997) The effect of pravastatin on coronary events after myocardial infarction. *N Engl J Med* 336:962
 27. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW (1995) Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 333:1301–1307
 28. Landmesser U, Bahlmann F, Mueller M, Spiekermann S, Kirchhoff N, Schulz S et al (2005) Simvastatin versus ezetimibe: pleiotropic and lipid-lowering effects on endothelial function in humans. *Circulation* 111:2356–2363
 29. Hackam DG, Mamdani M, Li P, Redelmeier DA (2006) Statins and sepsis in patients with cardiovascular disease: a population-based cohort analyses. *Lancet* 367:413–418
 30. Wong SL1, Revels SL, Yin H, Stewart AK, McVeigh A, Banerjee M, et al (2015) Variation in hospital mortality rates with inpatient cancer surgery. *Ann Surg*. 261: 632–636