The Effect of Strict Blood Glucose Control on Biliary Sludge and Cholestasis in Critically Ill Patients

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Background and Aims: Cholestatic liver dysfunction and biliary sludge are common problems in critically ill patients. No specific strategies have been described to prevent cholestasis and biliary sludge in the intensive care unit (ICU). We examined liver dysfunction and biliary sludge prospectively in a large medical long-stay ICU population and hypothesized that tight glycemic control with intensive insulin therapy (IIT) reduces cholestasis and biliary sludge.

Methods: This study was a preplanned subanalysis of 658 long-stay (at least a fifth day) ICU patients out of a large randomized controlled trial (n = 1200), studying the effects of IIT on the outcome of medical critical illness. Patients were allocated to either IIT (glycemia 80–110 mg/dl) or conventional insulin therapy (CIT) requiring insulin above a glycemia of 215 mg/dl. Different patterns of liver dysfunction were studied based on daily blood sample analysis, and biliary sludge was evaluated by ultrasonography.

Results: On admission, cholestasis was present in 17% of patients (n = 649), increasing to 20% on d 10 (n = 347), whereas ischemic hepatitis decreased from 3.4% (n = 588) to less than 1% (n = 328). IIT significantly decreased biliary sludge on d 5 (50.4 *vs.* 66.4%, $P = 0.01$; n = 250). The difference did not remain significant on d 10 (57.4 *vs.* 66.2%, $P = 0.29$; n = 136). IIT also lowered the cumulative risk of cholestasis ($P = 0.03$).

Conclusions: Cholestatic liver dysfunction and biliary sludge are very common during prolonged critical illness but are significantly reduced by IIT. (***J Clin Endocrinol Metab* 94: 2345–2352, 2009**)

In critical illness, the development of liver dysfunction complicates the clinical picture and poses a clinical challenge both in diagnostic evaluation and in management. Liver dysfunction has been linked to an increased risk of mortality in the intensive care population (1). Notably, the excretory function of the liver appears to be impaired. This cholestasis may be associated with an impaired vasopressor response to hypotension, kidney injury, platelet dysfunction, gastric ulceration, hampered wound healing, and decreased endotoxin processing (2). The association between cholestasis and critical illness, especially sepsis and total parenteral nutrition (TPN), has also been established for a long time (3, 4).

The reported incidence of cholestasis during critical illness is highly variable, however, ranging from 0.6–54% (5). Factors contributing to this variability include the lack of clear diagnostic criteria for cholestasis, the small patient samples of retrospective studies, and the heterogeneity of the studied populations. Extrahepatic mechanical obstruction of the bile ducts is only a rare cause of cholestasis in the critically ill. Recent insight into the molecular mechanisms of cholestasis suggests that altered function of the hepatic bile acid transporters may be involved (4).

In the intensive care patient population, biliary sludge is often present. The prevalence is reported to vary from 6–75% in this population, as compared with less than 0.3% in healthy volunteers (6). Among patients requiring more than 5 d intensive care, biliary sludge is present in approximately half of them (7–9). Besides the duration of critical illness, clinical conditions such as

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Abbreviations: ALP, Alkaline phosphatase; ALT, alanine aminotransferase; APACHE, Acute Physiology and Chronic Health Evaluation; AST, aspartate aminotransferase; AUC, area under the curve; BMI, body mass index; CI, confidence interval; CIT, conventional insulin therapy; combPN+EN, combination of parenteral and enteral nutrition; CRP, C-reactive protein; exclPN, exclusively parenteral nutrition; GGT, γ-glutamyl-transferase; ICU, intensive care unit; IIT, intensive insulin therapy; IQR, interquartile range; PT, prothrombin time; TPN, total parenteral nutrition; ULN, upper limit of normality.

gastrointestinal surgery, TPN, liver cirrhosis, liver transplantation, bone marrow transplantation, high spinal cord injury, trauma, and administration of ceftriaxone are associated with an increased risk for biliary sludge (10). In intensive care unit (ICU) patients, biliary sludge may lead to acute complications such as biliary colic, acute necrotizing cholecystitis, cholangitis, and acute pancreatitis (11–14).

In animal studies, it was shown that hyperglycemia induces cholestasis (15). In nondiabetic volunteers without gallstones, acute hyperglycemia dose-dependently inhibits postprandial gallbladder motility.

Gallbladder dysmotility is also associated with an elevated fasting glycemia as well as with insulin resistance (16, 17). Chronic hyperglycemia in diabetic patients is known to cause gastroparesis and gallbladder dysmotility, especially in those with an associated autonomic neuropathy (18).

Recently, two large prospective, randomized, controlled trials, one in surgical and the other in medical ICU patients, demonstrated a reduction of morbidity and/or mortality with strict blood glucose control (between 4.4 and 6.1 mmol/liter, or 80–110 mg/dl) via intensive insulin therapy (IIT), as compared with conventional insulin therapy (CIT) (19, 20). The latter recommended insulinization only when glycemia exceeded 12 mmol/liter (215 mg/dl). A reduction of hyperbilirubinemia also appeared present (19).

The primary aim of this study was to further examine liver dysfunction and biliary sludge prospectively in a large medical ICU population using clear diagnostic criteria. Our hypothesis was that tight glycemic control, achieved by IIT, reduces cholestasis and biliary sludge in critically ill patients.

Patients and Methods

This study was a preplanned prospective subanalysis of hepatic dysfunction and biliary sludge during a large (n = 1200) randomized trial on the effects of IIT on the outcome of medical critical illness (20). The ultrasound study for biliary sludge started when the 633rd patient had been included. Then, patients who had been on the ICU for more than 4 d underwent ultrasonography on d 5 and 10, provided they were still in the ICU. The examinations took place only on weekdays and during working hours (Fig. 1). Day 5 was chosen because at that time point, sludge formation has been reported to occur in 47% of an ICU patient population (9). Moreover, this selection falls within the time frame required to bring about the clinical benefit of IIT, allowing us to investigate the relative contribution to outcome of biliary sludge and cholestasis. A total of 374 patients were not investigated because of unavailability of the radiologist; 12 patients were excluded because of technical difficulties, which did not allow ultrasonographic visualization of the gallbladder and 22 patients because they had no gallbladder. Hence, on d 5 after admission, 250 patients had an interpretable gallbladder ultrasonography, 113 patients in the CIT group and 137 in the IIT group. A second screening was performed on d 10, with only 136 patients with an interpretable ultrasound examination. Ultrasonography was performed by an independent radiologist, unaware of treatment allocation. The diagnosis of biliary sludge was based on the recognition of echogenic material layering in the most dependent portion of the gallbladder without acoustic shadowing or as a globular mass of low echogenicity within the gallbladder. No attempt was made to quantify sludge or to test for gallbladder motility.

Of the entire group of 658 long-stay patients (at least a fifth day in the ICU), blood samples were analyzed for liver function tests by routine

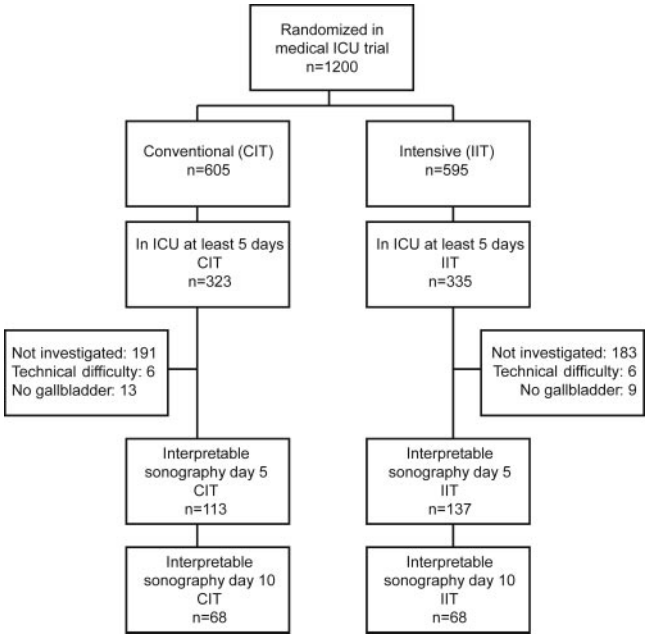

FIG. 1. Consort diagram of the preplanned subanalysis of a large (n = 1200) randomized controlled trial, where patients were randomized to either IIT or CIT (24). Only patients with an ICU stay of at least 5 d were selected for analysis of liver dysfunction. Biliary sludge was evaluated on d 5 in 250 patients with an interpretable sonography and in 136 patients on d 10.

laboratory assays. Total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl-transferase (GGT), alkaline phosphatase (ALP), and prothrombin time (PT) were daily recorded while in ICU.

The detailed protocol of the interventional study and the characteristics of the patients have been previously published (20).

Briefly, patients were allocated to either IIT or CIT. IIT aimed at blood glucose levels between 4.4 and 6.1 mmol/liter (80 and 110 mg/dl). CIT required insulin when blood glucose rose above 12 mmol/liter (215 mg/dl) and tapering or stopping of insulin when blood glucose decreased to less than 10 mmol/liter (180 mg/dl). Written informed consent was obtained from the closest family member. The protocol and consent forms were approved by the Institutional Ethical Review Board.

Definitions

Different definitions of hepatic dysfunction have been used in studies (1, 21–24). Therefore, the diagnostic criteria of the different patterns of liver dysfunction in this study were primarily based on the definitions of an international consensus conference (21, 24). Cholestasis was primarily defined as total bilirubin higher than 3 mg/dl [three times the upper limit of normality (ULN)]. As an alternative, cholestasis was defined as ALP higher than 400 IU/liter (1.5 × ULN) and GGT higher than 80 IU/liter (1.5 × ULN). Ischemic (or hypoxic) hepatitis was defined as AST higher than 800 IU/liter (20 × ULN) and ALT higher than 800 IU/liter (20 × ULN) and PT lower than 70%. Mixed pattern liver dysfunction was defined as total bilirubin higher than 3 mg/dl in combination with AST higher than 800 IU/liter, ALT higher than 800 IU/liter and PT lower than 70%. Chronic liver disease upon ICU admission was defined as preexisting cirrhosis on liver biopsy and/or imaging. Sepsis upon ICU admission was defined using the modified Bone criteria as a suspected or documented infection on admission day and fulfillment of at least two of the three Systemic Inflammatory Response Syndrome criteria for which data were available [1) receiving ventilatory support, 2) white blood cell count ≤ 4000/liter or ≥ 12,000/liter, 3) temperature ≤ 36 C or ≥38 C].

Statistical analysis

Statistical analysis was performed using Statview 5.0.1 (SAS Institute, Cary, NC). All quantitative values were assessed for normality.

Values with normal distribution and those that were normalized after logarithmic transformation were represented as mean ± SEM and compared using the Student's *t* test or ANOVA.

The others were represented as medians and interquartile range (IQR) (first to third) and compared by the nonparametric Mann-Whitney *U* test. Categorical variables (expressed as numbers and percentages) were compared between groups with χ^2 tests. The effect of the intervention on time to reach a specific biochemical criterion of liver dysfunction (as specified above) was assessed by cumulative hazard analysis and log-rank significance testing. This analysis assumed that patients who did not reach the diagnostic criterion before ICU discharge remained negative thereafter. The time course of the biochemical liver function tests was evaluated by repeated-measures ANOVA. Fisher's least significant difference test was used for multiple comparisons. During receiver operator characteristic analysis, the area under the curve (AUC) was calculated for hospital mortality.

Multivariate logistic regression analysis was performed to assess which factors could explain biliary sludge and cholestasis. Treatment allocation, baseline characteristics, diagnostic category, known risk factors, and other risk factors occurring during ICU stay with a *P* value <0.2 in univariate analysis were incorporated into the multivariate analysis. Factors with colinearity were left out of the analysis. For all tests a *P* value < 0.05 was deemed significant.

Results

Baseline characteristics and effect of tight glycemic control on mortality of patients with an ICU stay of at least 5 d

Table 1 summarizes the baseline characteristics of the 658 patients who stayed in the ICU for at least a fifth day. The two study groups, CIT and IIT, were comparable for baseline risk factors such as gender, age, body mass index (BMI), history of cancer or diabetes mellitus, on-admission blood glucose levels or kidney failure, and severity of illness as reflected by on-admission Acute Physiology and Chronic Health Evaluation (APACHE)-II and Therapeutic Intervention Scoring System-28 scores. The number of patients with chronic liver disease upon ICU admission was not different between IIT and CIT (6.6 *vs.* 7.4%, $P = 0.66$). In this long-stay cohort of patients, mean blood glucose in the IIT group was significantly lower than in the CIT group (108 ± 1 *vs.* 155 ± 1 mg/dl, $P < 0.001$). IIT reduced hospital mortality from 53.9 to 45.4% (absolute risk reduction of 8.5%, $P = 0.029$). There was no selection bias because outcome in the

TABLE 1. Baseline characteristics of the 658 patients who stayed in the ICU for at least a fifth day and the 250 patients with an interpretable sonography on the fifth day of ICU stay

	Patients who stayed in ICU ≥5 d			Patients with interpretable sonography on d 5		
	CIT	IIT	*P*	CIT	IIT	*P*
No. of patients	323	335		113	137	
Sex, n (% male)	206 (51.1)	197 (48.9)	0.19	71 (62.8)	89 (65.0)	0.73
Age, yr (mean ± SEM)	64 ± 1	62 ± 1	0.17	64 ± 2	62 ± 1	0.27
BMI, kg/m^2 (mean ± SEM)	24.7 ± 0.3	25.4 ± 0.4	0.08	25.2 ± 0.5	26.1 ± 0.6	0.24
APACHE-II score [median (IQR)][a]	23 (18–29)	23 (17–29)	0.36	24 (19–31)	24 (18–30)	0.98
TISS-28 score [median (IQR)][b]	30 (26–35)	31 (26–36)	0.33	30 (27–36)	32 (28–37)	0.13
Diagnostic category, n (%)			0.39			0.99
Cardiovascular	10 (3.1)	16 (4.8)		4 (3.5)	3 (2.2)	
Gastroenterological	73 (22.6)	54 (16.1)		15 (13.3)	17 (12.4)	
Hematological or oncological	33 (10.2)	34 (10.1)		14 (12.4)	17 (12.4)	
Metabolic	8 (2.5)	4 (1.2)		2 (1.8)	1 (0.7)	
Neurological	8 (2.5)	14 (4.2)		4 (3.5)	6 (4.4)	
Renal	8 (2.5)	11 (3.3)		3 (2.7)	3 (2.2)	
Respiratory	152 (47.0)	166 (49.5)		59 (52.1)	74 (54.0)	
Sepsis with unknown focus	28 (8.7)	32 (9.6)		11 (9.7)	14 (10.2)	
Others	3 (0.9)	4 (1.2)		1 (0.9)	2 (1.5)	
Sepsis on admission, n (%)	188 (58.2)	209 (62.4)	0.27	81 (71.7)	95 (69.3)	0.69
Kidney failure on admission, n (%)[c]	78 (24.1)	74 (22.1)	0.53	29 (25.7)	27 (19.7)	0.26
History of diabetes, n (%)	49 (15.2)	49 (14.6)	0.84	20 (17.7)	22 (16.1)	0.73
Blood glucose on admission, mg/dl (mean ± SEM)	162.7 ± 3.7	162.2 ± 3.6	0.92	162.0 ± 6.8	157.4 ± 5.3	0.58
Total bilirubin on admission, mg/dl [median (IQR)]	0.86 (0.42–2.34)	0.78 (0.43–1.71)	0.22	0.83 (0.49–2.08)	0.84 (0.43–1.55)	0.41
Creatinine on admission, mg/dl [median (IQR)]	1.38 (0.94–2.41)	1.26 (0.84–2.15)	0.11	1.46 (0.99–2.49)	1.31 (0.92–2.10)	0.11
Ureum on admission, mg/dl [median (IQR)]	70 (44–114)	69 (38–103)	0.37	75 (49–112)	69 (41–98)	0.25
CRP on admission, mg/dl [median (IQR)]	150 (55–245)	141 (50–233)	0.43	144 (60–247)	148 (50–237)	0.55

TISS, Therapeutic Intervention Scoring System.

[a] Higher APACHE-II scores indicate more severe illness.

[b] In the TISS-28 scoring system, each therapeutic intervention is assigned a number of points. Hence, a higher score indicates a greater number of therapeutic interventions.

[c] Kidney failure on admission was defined as dependence on dialysis or a serum creatinine higher than 2.5 mg/dl.

TABLE 2. Daily prevalence of cholestasis (total bilirubin > 3 mg/dl), ischemic hepatitis (AST > 800 IU/liter, ALT > 800 IU/liter, and PT < 70%) and mixed type liver dysfunction (mixed)

	d 1	d 2	d 3	d 4	d 5	d 6	d 7	d 8	d 9	d 10
Cholestasis	17.1 (649)	18.4 (648)	17.4 (650)	17.6 (649)	18.9 (639)	19.9 (564)	21.2 (491)	21.8 (426)	20.8 (395)	19.9 (347)
Ischemic hepatitis	3.4 (588)	3.1 (590)	2.5 (602)	1.0 (592)	0.4 (578)	0.2 (515)	0.2 (451)	0.5 (391)	0.0 (360)	0.6 (328)
Mixed	1.9 (587)	1.9 (587)	1.5 (601)	1.0 (588)	0.4 (576)	0.2 (511)	0.0 (451)	0.3 (390)	0.0 (359)	0.6 (324)

Data are represented as percentages (total number of patients shown in *parentheses*). Mixed type liver dysfunction is defined as the combination of cholestasis and ischemic hepatitis.

censored group, comprising the patients with an ICU stay of fewer than 5 d, was not affected by IIT ($P = 0.50$). Also, the two study groups of patients, CIT and IIT, who underwent ultrasonography on d 5 were comparable at baseline (Table 1).

Prevalence of liver dysfunction at different time points

Using strict diagnostic criteria, daily prevalence of the three major types of liver dysfunction was determined over the first 10 d (Table 2). On admission, 17.1% of all patients were characterized by a cholestatic liver pattern (total bilirubin > 3 mg/dl), increasing to 19.9% on d 10. The fraction of conjugated bilirubin in case of an elevated level of total bilirubin (>3 mg/dl), available only in about 30% of patients, was 75 ± 15%. The number of blood transfusions per patient and per day was comparable in both insulin study groups (0.14, $P = 0.74$). Prevalence of ALP/GGT definition of cholestatic liver dysfunction increased from 13.2 to 34.1% in 10 ICU days (data not shown).

Of patients with cholestasis assessed according to the bilirubin definition, 70.8 ± 5.0% also had cholestasis according to the ALP/GGT definition. Ischemic hepatitis had a reverse evolution, decreasing from 3.4% on admission to 0.6% on d 10. Only a minority of patients were hallmarked by the mixed pattern of liver dysfunction with prevalence between 0.0 and 1.9%.

Effect of IIT on biliary sludge and liver dysfunction

In the IIT group, 50.4% of ultrasonography-screened patients had biliary sludge on d 5 compared with 66.4% in the CIT group ($P = 0.01$) (Table 3). On d 10, this difference was no longer significant ($P = 0.3$). The prevalence of sonographically detectable gallstones was similar with 28 of 113 patients (24.8%) in the CIT group and 33 of 137 (24.1%) in the IIT group on d 5 ($P = 0.77$). On d 10, gallstones were detected in 24 of 68 patients (35.3%) of the CIT and in 19 of 68 (27.9%) of the IIT group ($P = 0.46$). No patient had dilated bile ducts as a sign of extrahepatic cholestasis.

IIT significantly decreased the cumulative risk of biochemical cholestasis, using both definitions (Fig. 2). Cumulative risk of ischemic hepatitis and mixed pattern liver dysfunction was not affected by IIT (data not shown).

TABLE 3. Prevalence of biliary sludge on d 5 and 10 in the IIT group *vs.* the CIT group

	IIT	CIT	*P*
d 5	50.4 (137)	66.4 (113)	0.01
d 10	57.4 (68)	66.2 (68)	0.3

Prevalence is represented as percentages with total number of patients shown in *parentheses*.

On d 5, patients with sludge did not have more cholestasis than those without sludge (17 *vs.* 20%, $P = 0.55$). The same conclusion holds for both randomization groups separately. In contrast, patients with sludge on d 10 had more cholestasis (total bilirubin > 3 mg/dl) on d 10 than those without sludge (26 *vs.* 8%, $P = 0.01$). In the CIT randomization group, a comparable observation was done (27 *vs.* 5%, $P = 0.03$), whereas IIT patients with sludge on d 10 did not have more cholestasis (25 *vs.* 12%, $P = 0.17$).

Factors clinically associated with biliary sludge and cholestasis in the ICU

Univariate analysis revealed that patients with biliary sludge on d 5 were those with more pronounced inflammation on d 5 [C-reactive protein (CRP) 94 mg/liter (IQR 46–189) *vs.* 69 mg/liter (IQR 32–148), $P = 0.016$] and more severe kidney injury on d 5 [plasma creatinine 1.27 mg/dl (IQR 0.93–2.31) *vs.* 1.08 mg/dl (IQR 0.74–2.03), $P = 0.015$] as compared with patients without biliary sludge. In multivariate analysis, IIT as well as female gender were independent protective factors for biliary sludge. A primary renal reason for ICU admission and a high d-5 CRP level were independently associated with increased risk of biliary sludge (Table 4).

Univariate analysis showed that patients with cholestasis on d 5 (total bilirubin > 3 mg/dl) were those with higher on admission APACHE-II scores [26 (IQR 22–34) *vs.* 22 (IQR 17–29), $P < 0.001$] and more inflammation on d 5, evidenced by significantly increased CRP levels [104 mg/liter (IQR 59–198) *vs.* 83 mg/liter (IQR 34–167), $P = 0.005$] than those without cholestasis. In addition, degree of renal dysfunction on d 5 was also higher in patients with cholestasis [plasma creatinine 1.63 mg/dl (IQR 1.09–2.56)] as compared with those without cholestasis [1.07 mg/dl (IQR 0.79–1.90)] ($P < 0.001$). In multivariate analysis, the independent risk factors for cholestasis were high APACHE-II scores (>23, being the median APACHE-II score), a gastrointestinal or hematooncological diagnosis upon admission, as well as hemodynamic instability and parenteral nutrition during the first 5 d. The protective effect of IIT on cholestasis present in univariate analysis was no longer significant after correction for risk factors including inflammation and kidney injury (Table 4).

The role of TPN in the development of cholestasis and biliary sludge in the ICU

Patients receiving exclusively parenteral nutrition (exclPN) (n = 67 on day 10) had a significantly higher cumulative risk of biochemical cholestasis (defined as total bilirubin >3 mg/dl) than

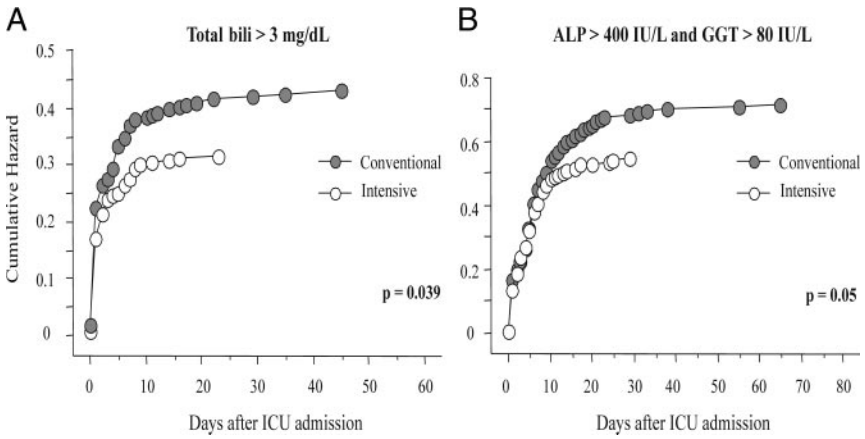

FIG. 2. Cumulative hazard plot for the effect of IIT *vs.* CIT on cholestasis. A, Total bilirubin (bili) higher than 3 mg/dl; B, ALP higher than 400 IU/liter and GGT higher than 80 IU/liter.

patients receiving the combination of parenteral and enteral nutrition (combPN+EN) (n = 228 on d 10) ($P = 0.004$) (Fig. 3A).

IIT could not prevent this increased risk of cholestasis in exclPN patients (Fig. 3, B and C). In IIT-treated patients, the prevalence of sludge on d 5 did not differ between patients receiving exclPN (10 of 18, 56%) or combPN+EN (59 of 119, 50%) ($P = 0.64$), whereas patients receiving CIT and combPN+EN showed significantly less sludge (62 of 99, 63%) on d 5 than patients receiving exclPN (13 of 14, 93%) ($P = 0.03$). On d 10, lower patient numbers did not allow us to draw conclusions.

Relationship between cholestasis and hospital mortality

Daily serum bilirubin concentrations were significantly higher and increased over time in hospital nonsurvivors *vs.* survivors ($P < 0.001$). In receiver operator characteristic analysis, assessing the predictive value of total bilirubin on d 5 for hospital mortality, the AUC was 0.60 [confidence interval (CI) 0.56–0.64, $P < 0.001$]. This was comparable to the AUC for hospital mortality in function of on-admission APACHE II [0.63 (CI 0.59–0.67, $P < 0.001$)] and sequential organ failure assessment (SOFA) scores [0.61 (CI 0.57–0.65, $P < 0.001$)]. In multivariate analysis, the impact of IIT on cholestasis did not explain the impact of IIT on mortality (data not shown).

Discussion

This study showed that in prolonged critically ill patients, IIT significantly reduced biliary sludge and cholestatic liver dysfunction. The different pattern of clinical predisposition to either biliary sludge or biochemical cholestasis suggests an at least par-

TABLE 4. Multivariate logistic regression analysis for the effect of different clinical factors on biliary sludge on d 5 and cholestasis (total bilirubin > 3 mg/dl) on d 5

	Risk for sludge, d 5		Risk for cholestasis, d 5	
Factor	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**
Randomization: IIT	0.02	0.49 (0.27–0.88)	0.33	0.79 (0.49–1.27)
APACHE-II score[a] > 23	0.33	0.73 (0.39–1.37)	0.02	1.83 (1.10–3.06)
TISS-28 score[b]	0.21	1.03 (0.98–1.09)	0.14	1.03 (0.99–1.07)
BMI	0.06	0.95 (0.90–1.01)	0.36	0.98 (0.93–1.03)
Gender: female	0.03	0.50 (0.27–0.94)	0.97	1.01 (0.62–1.65)
Diagnosis				
Gastrointestinal	0.17	4.13 (0.56–30.7)	0.003	23.6 (3.98–186.2)
Hemato-onco	0.08	6.14 (0.80–50.0)	0.01	15.2 (1.88–123.8)
Metabolic	0.28	5.86 (0.23–149.6)	>0.9	
Neurological	0.26	4.01 (0.35–45.6)	0.82	1.39 (0.08–26.0)
Renal	0.03	29.4 (1.38–623.9)	0.37	3.01 (0.27–33.2)
Respiratory	0.05	6.83 (1.02–45.8)	0.61	1.73 (0.22–14.0)
Sepsis with unknown focus	0.19	3.95 (0.52–30.1)	0.08	6.53 (0.78–54.7)
Others	>0.9		0.38	3.90 (0.19–79.1)
Sepsis on admission	0.15	1.78 (0.81–3.92)	0.80	0.93 (0.52–1.66)
Admission glycemia > 200	0.83	0.92 (0.42–2.00)	0.94	0.98 (0.53–1.79)
History of diabetes: Yes	0.32	1.55 (0.65–3.70)	0.66	0.85 (0.42–1.74)
CRP d 5	0.004	1.01 (1.00–1.01)	0.62	1.00 (0.99–1.00)
Creatinine d 5	0.26	1.18 (0.89–1.55)	0.06	1.18 (0.99–1.40)
Norepinephrine d 1–5	0.46	0.94 (0.79–1.11)	0.01	1.19 (1.04–1.37)
Antibiotics d 1–5	0.13	0.80 (0.60–1.07)	0.93	1.01 (0.82–1.25)
Parenteral nutrition d 1–5	0.16	1.14 (0.95–1.36)	0.03	1.22 (1.02–1.45)
Bilirubin d 1–5 (%)	0.91	1.00 (0.99–1.00)		

Hemato-onco, Hematological-oncological; OR, odds ratio; TISS, Therapeutic Intervention Scoring System.

[a] Higher APACHE-II scores indicate more severe illness.

[b] In the TISS-28 scoring system, each therapeutic intervention is assigned a number of points. Hence, a higher score indicates a greater number of therapeutic interventions.

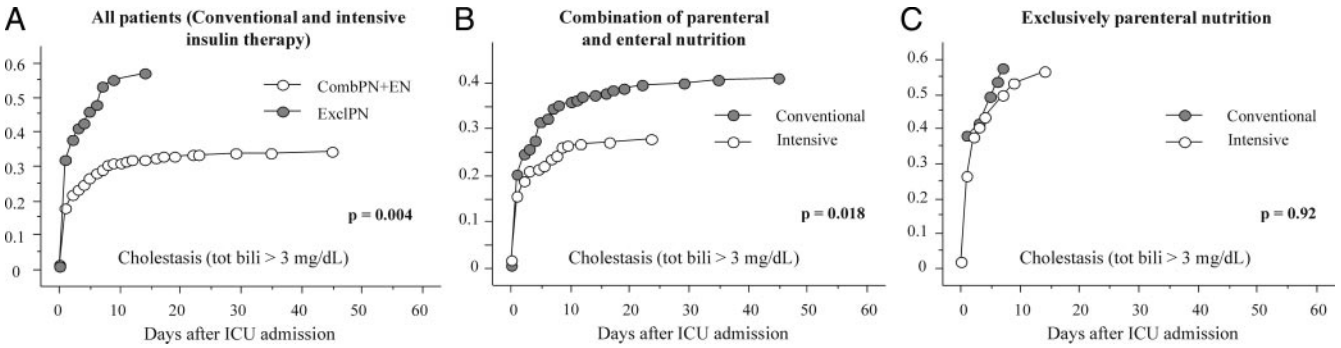

FIG. 3. A, Cumulative hazard for cholestasis in all patients (CIT and IIT) receiving either exclPN or combPN+EN; B, cumulative hazard plot for the effect of IIT *vs.* CIT on cholestasis in patients receiving the combination of parenteral and enteral nutrition; C, cumulative hazard plot for the effect of IIT *vs.* CIT on cholestasis in patients receiving exclPN. Cholestasis was defined as total bilirubin higher than 3 mg/dl.

tially dissimilar pathogenesis of these two abnormalities in the critically ill.

Our prevalence of biliary sludge of 66% is comparable with a reported prevalence of 47% after 5 d in an ICU trauma population (9). No method for prevention or treatment of biliary sludge in ICU patients has undergone extensive testing. Only preliminary data exist on the prevention of recurrence of biliary sludge and idiopathic pancreatitis by ursodeoxycholic acid (14). In our study, IIT decreased the prevalence of biliary sludge on d 5. However, on d 10, this difference lost statistical significance. Two factors may have contributed. First, on d 10, only 68 patients in each group were analyzed, limiting statistical power. Second, the prevalence of biliary sludge in the IIT group increased from d 5 to 10, possibly because these patients were more severely ill compared with the CIT patients, because IIT induces a survival benefit.

In multivariate analysis, IIT was an independent protective factor for sludge. Although diabetes and insulin resistance are known to predispose to gallbladder disease, multivariate analysis did not suggest that it was the previous history of diabetes or longstanding hyperglycemia that explained the development of biliary sludge but rather the insulin-titrated prevention of hyperglycemia during critical illness (25, 26). Although the on-admission renal diagnosis and the degree of inflammation on d 5 were significant risk factors for development of biliary sludge, the impact of IIT remained independent of these. Inflammation of the gallbladder is indeed known to be associated with increased stone formation by increased mucin glycoprotein synthesis (27). Also, female gender appeared to be a protective factor for biliary sludge, which is in contrast with findings in the non-critically ill patient population (28).

Although classically associated with biliary sludge, neither in univariate analysis nor in multivariate analysis could we confirm the role of PN or antibiotic use in the development of biliary sludge (29). However, IIT may be protective against parenteral nutrition-related development of sludge.

Different types of hepatocyte dysfunction clearly have a different prevalence and a different time course during prolonged critical illness. Unlike ischemic or mixed type liver dysfunction, which are less frequent, cholestatic liver dysfunction has a prevalence of about 17% on admission, going to 20% on d 10. Data on serial changes in bilirubin and other markers of liver dysfunction in a large long-stay cohort of ICU patients are scarce. Our findings confirm earlier small studies, reporting cholestasis to vary from 8–30%. This is explained by the varying time frame as well as the definition of cholestasis chosen in the study protocols (1, 22, 23). In contrast with the rising prevalence of cholestatic liver dysfunction, ischemic and mixed type liver dysfunction decrease with length of ICU stay, returning to less than 1% within 5 d, probably due to progressive stabilization of the hemodynamic status with time and treatment.

IIT decreased the cumulative risk of cholestatic, but not ischemic, liver dysfunction. This effect did not remain independent when correcting for other risk factors and for inflammation and kidney function, which were previously shown to be beneficially affected by IIT. Both insulin administration and glycemia are known to affect cholestasis. Animal data have shown that diabetes leads to the development of bile acid-independent cholestasis, probably as a consequence of hyperglycemia (15, 30). Plasma and cellular hyperosmolarity in combination with bile duct epithelial reabsorption might decrease bile acid-independent bile flow (31). In addition, insulin is thought to be choleretic and can partially restore the depressed bile flow (32).

In multivariate analysis, we found high on-admission APACHE-II scores, gastrointestinal or hematological diagnosis, and norepinephrine support or parenteral nutrition during the first 5 d to be statistical risk factors for developing cholestasis. Moreover, the risk to develop cholestasis was higher in patients receiving exclusively parenteral nutrition.

The association of cholestasis with parenteral nutrition is remarkable because parenteral nutrition-associated cholestasis is classically described in patients (mostly children) receiving parenteral nutrition for more than 2 wk (3). The pattern of risk factors for cholestasis on d 5 also clearly differs from the pattern of risk factors for sludge on d 5, suggesting that cholestasis and sludge are at least partially mediated by other factors. However, both complex pathological findings may partially share common pathophysiological mechanisms.

In agreement with others, we found that cholestatic liver dysfunction was associated with risk of death (1). However, in multivariate analysis, the effect of IIT on cholestasis did not explain the impact of IIT on hospital mortality. Previous research from our group has revealed that multiple other factors are involved in the survival benefit of IIT in the ICU. The effects of IIT on

inflammation, endothelial function, kidney injury, and weaning from mechanical ventilation may have had a larger impact (33, 34). However, this does not exclude the possibility that cholestatic liver dysfunction through other mechanisms may have contributed to the survival benefit of IIT. One can speculate that, *e.g.* the changes in the serum lipid profile induced by IIT may stimulate the clearance of the endotoxins in the liver (35). IIT may also exert its effect by improving the energy production of the liver because mitochondrial dysfunction is prevented by IIT (36).

The findings of this study may have important clinical implications. Critically ill patients often receive a plethora of drugs, which are often metabolized and excreted by the liver. Changes in cholestatic liver function may lead to alterations in drug efficacy or toxicity and potentially to drug-drug interactions in the ICU (37, 38). Moreover, therapeutic strategies aimed at improving cholestatic liver dysfunction may lead to improved survival of prolonged critically ill patients.

Our study has some limitations that should be addressed. First, because direct bilirubin was not available for all patients, we assessed cholestasis based on total bilirubin to avoid possible selection bias. Intrahepatic cholestasis is characterized by conjugated hyperbilirubinemia with a ratio of direct *vs.* total bilrubin of more than 70%, which was the case in our study population (39).

Second, we did not have ultrasound data on the status of the gallbladder upon ICU admission. However, a systematic bias in favor of the IIT group is highly unlikely, because a large set of baseline characteristics was similar in both treatment groups. Moreover, prevalence of gallstones on d 5, of which biliary sludge has generally been accepted as precursor, was comparable in both groups (10).

In conclusion, our study reveals that cholestatic liver dysfunction is more frequent than ischemic or mixed type liver dysfunction during prolonged critical illness. Cholestatic liver dysfunction is associated with hospital mortality. Strict glycemic control by IIT significantly reduced cholestatic liver dysfunction and biliary sludge in prolonged critical illness. Cholestasis and biliary sludge seem to be two different clinical entities in multivariate analysis.

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