The effects of IVFE treatment on hospital-acquired infections in critically-ill patients

Matthew Lennart, Lisa Lin, Nick Strayer

April 11, 2016

Introduction and Background

Lipid emulsions are a means to provide nutrients to patients that are unable to eat due to severe trauma or prolonged sedation by delivering essential fatty acids intravenously 1. Intravenous fat emulsions (IVFE) have also proved an effective therapy for cardiovascular collapse onset by an overdose of local anesthetic2. Previous studies establish that lipid emulsions can increase the risk for complicating infections for small prospectively selected cohorts of patients by as much as a factor of five1, 3, 4. This study seeks to establish if lipid emulsions should be withheld as a therapy of last resort.

The negative side effects of lipid emulsions manifest themselves in different ways. The mechanisms range from acting as an immunosuppressant in patients with severe trauma3, 5 to rendering patients hyperglycemic, which is well correlated with increased infection risk4. The lipid emulsion formula can promote the growth of blood based, gastrointestinal, respiratory, and skin site bacterial infections1, 6, 7. Infection rates can differ based on the formulation of the emulsion, whether it be soy based, coconut based, olive based, or fish oil based5. The flow rate of an emulsion also may affect infection rates4.

There is a link between hospital acquired infections and increased inpatient length of stay8, 9, but there is more than one way to acquire an infection in the hospital. While the tie between IVFE's and infection risk is a direct one1, 6, 7, this may not be the case for the length of stay, as it is a noisy metric10. There are many external factors, such as staffing11 and the use of residents during the course of care12, that can affect the length of stay within a hospital. Hospitals are also subject to different cost and capacity pressures that add variability to the average length of stay between hospitals13. Workflow and the enforcement of evidence based care pathways also affects the length of stay14 and those practices vary between institutions15. The deviation in length of stay both within and between institutions make it an imperfect outcome measure in the context of assessing the risk of lipid emulsions.

The risk of acquiring an infection in the hospital is not related to IVFE treatment alone. The use of a ventilator increases a patient's risk for pneumonia and other infections16, 17, 18. This establishes intubation as a confounding variable when assessing infection risk. Reflexively, the longer a patient stays in a hospital the greater their risk for acquiring an infection they were not admitted with19, 20. Thus, time within the hospital is also an important factor to account for.

The state of current research establishes that the use of a lipid emulsion, its chemical composition, and its flow rate all may play a factor in patient complications. This study aims to evaluate how the use of soy based lipid emulsion affects the odds of acquiring different etiological categories of infection.

Source of Data

These data are a retrospective look at hospital patients, from the years 2001 to 2005, who had a stay in the surgical intensive care unit (SICU) of three or more days.

The following were datapoints collected and available for the analysis. There were no missing data for any of the variables except for 59 unrecorded values for race.

Variable	Description
avgexp	Average amount of soybean oil IVFE received by the patient during the first 3 days of their SICU stay
maxexp	Maximum daily IVFE received by the patient during the first 3 days of their SICU stay
age	Age in years
gender	Gender
race	Race
bmi	Body mass index (weight divided by height squared)
apache2	Acute Physiology and Chronic Health Evaluation Score at Admission
glucose	Blood glucose level at admission
hosp.los	Hospital length of stay
hosp.death	Indicator of death in the hospital
unit.los	Length of stay in the surgical ICU
unit.death	Indicator of death in the surgical ICU
ventdays.hosp	Days spent on ventilator while in hospital
ventdays.unit	Days spent on ventilator while in surgical ICU
ventfree.unit	Days not on the ventilator while in the surgical ICU
bsi.inf	Bloodstream infection
eent.inf	Eye, ear, nose, throat infection
gi.inf	GI infection
lri.inf	Lower respiratory infection
pneu.inf	Pneumonia
ssi.inf	Surgical site infection
sst.inf	Skin structure infection
sys.inf	Systemic infection
uti.inf	Urinary tract infection

For the outcomes of blood and gastro-intestinal infection, total ventilator days and length of stay are potential confounders. This is due to the nature of hospital transmitted diseases[CITATION]. For lower resperatory infection ventilator days was considered a confounder.

Potential confounders for infection outcomes: total ventilator days (blood, gastrointenstinal, lower-resperatory, pnuemonia), length of stay (blood, gastrointenstinal), unit length of stay (pnuemonia), hospital length of stay (Urinary Tract).

Statistical Methods:

The primary outcome was the status of various infections in a patient's medical record. All the infections were assumed to be hospital-acquired. All outcomes were recorded as binary result (infection or not). The primary predictor was a dichotomized indicator of lipid emulsion treatment during the first 3 days of a patient's SICU stay. The basic demographics of the two groups were analyzed and compared. The analysis was done in statistical software STATA (StataCorp 2015). Logistic regression was performed for the binary outcomes. The rule of thumb of 10 to 20 events occurring for each additional variable in the model was considered for outcomes selection and models building. A P-value cutoff of 0.05 was used for significance. In addition confidence intervals of odds ratio are reported. To assess model fit a Hosmer-Lemeshow chi-square goodness of fit test was performed on each model (D. W. Hosmer et al. 1997).

Results

The study divided the patients into two groups, a cohort that received lipids intravenously at some point during their admission and a control group that did not. The summary statistics from Table 2 suggest that the secondary variables: age, APACHE II score, gender, and BMI are balanced in proportion between the IVFE group and the control group. The confounding variables of total encounter length of stay, SICU length of stay, and total number of days on a ventilator are all unevenly distributed across the cohort and control groups. These variables are well established in the medical literature as contributing risk factors for hospital acquired infections. [CITATIONS]

Table 2: Patient Statistics.

	Lipids	median	No Lipid	median
Gender Female	225 (42%)		516 (39%)	
Gender Male	313 (58%)		791 (61%)	
Age	58.66 ± 1.27	60.16	58.39 ± 0.84	59.4
BMI	28.71 ± 0.77	26.63	27.84 ± 0.44	26.1
Glucose Level	170.55 ± 5.1	160.00	189.73 ± 3.8	176.0
Hospital Length of Stay	21.19 ± 1.19	17.17	14.44 ± 0.72	10.2
Unit Length of Stay	11.49 ± 0.84	8.16	6.97 ± 0.36	4.8
Days on Ventilator (Hospital)	11.56 ± 1.06	7.00	5.96 ± 0.58	2.0
Days on Ventilator (Unit)	8.52 ± 0.88	4.81	3.38 ± 0.39	0.9

Gender is presented as a count (percentage of lipids group), all others are average with 95% confidence intervals and medians. BMI = Weight(KG)/Height(M)^2.

The similarity in the distribution of the secondary variables between the groups is further visualized in Figure 1. The figure suggests that these elements are well controlled for, and the study's models need not account for them.

The outcome variables are not evenly distributed between case and control groups. The systemic, skin structure, and otolaryngology (Ear, Nose and Throat) infections did not meet the minimum threshold of 20 cases needed for sufficient power[CITATION]. The study did not attempt to model the effect of lipid emulsion on the risk of these infections.

Table 3: Lipid Occurance and Infections.

	Occured	Did not Occur
Lipid Emulsion	1307	538
Death in Hospital	1683	162
Death in Unit	1740	105
Blood Stream infection	1791	54
Eye, Ear, Nose, Throat infection	1844	1
Gastrointestinal infection	1806	39
Lower Resperatory infection	1831	14
Pneumonia	1706	139
Surgical site infection	1796	49
Skin structure infection	1844	1
Systemic infection	1845	1845
Urinary tract infection	1806	39

The confounding variables did not show signs of colinearity, as evidenced in Figure 2. This indicates that the model does not need interaction terms. Additionally the study was unable to conclude any significant

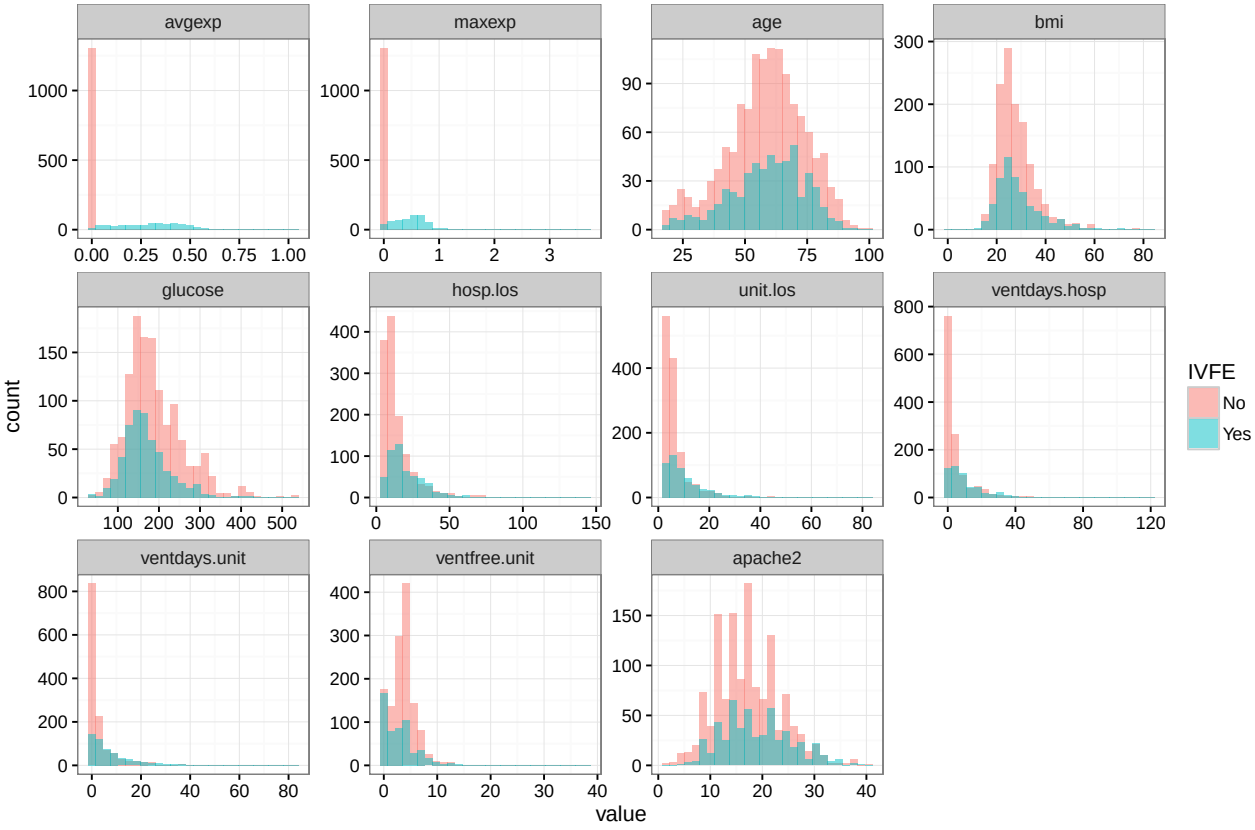

Figure 1: Distribution of continious variables.

marginal interactions between its predictors.

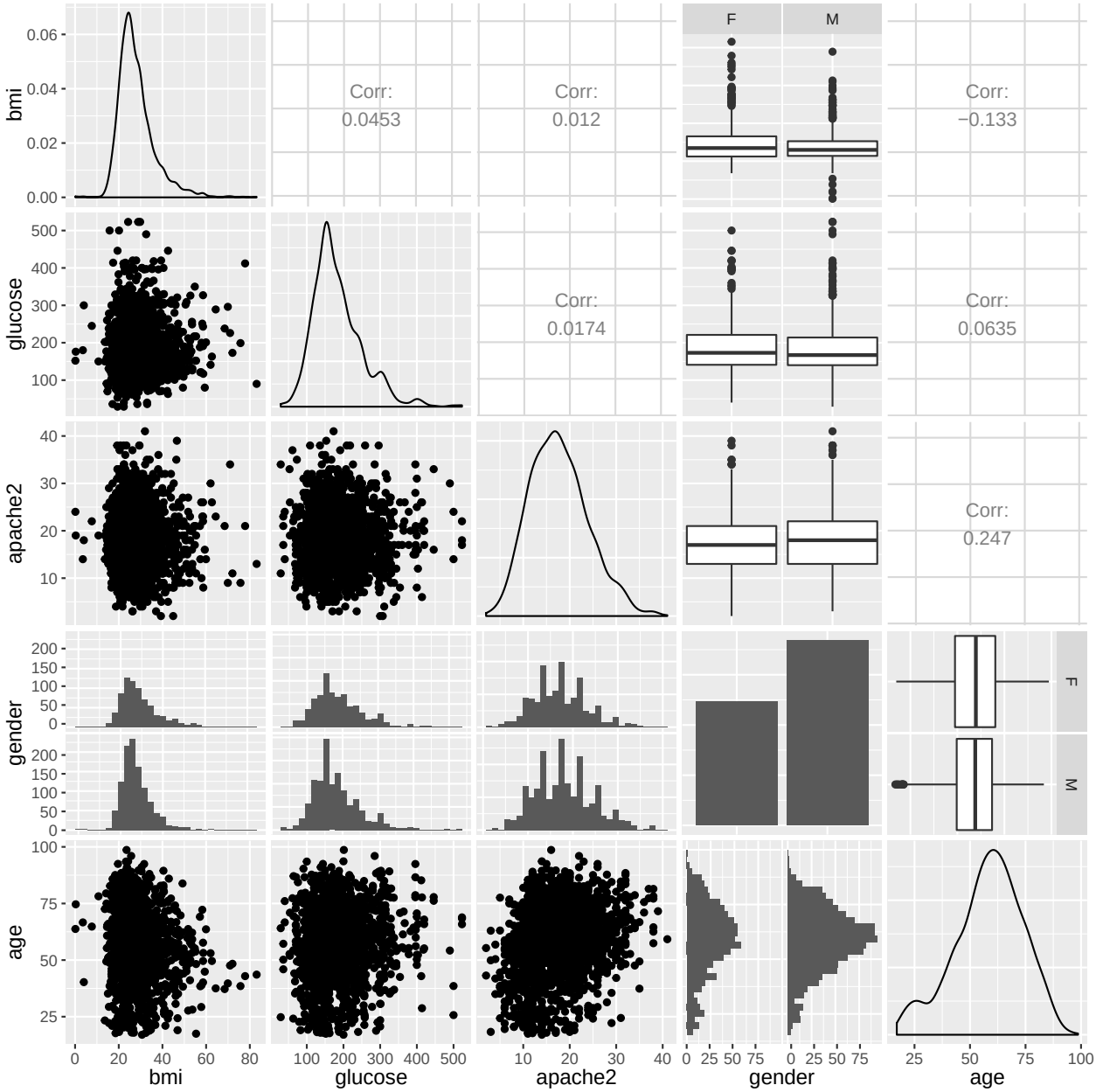

Figure 2: Relationships between potential confounders.

The study found that the use of a lipid emulsion increased the risk for hospital acquired blood-stream infections, lower-respiratory infections, surgical-site infections, and gastrointestinal infections. Lipid emulsions were not found to significantly affect the risk for hospital acquired pneumonia or urinary-tract infections. More information on these results including confidence interval bands for the odds ratios are shown in Table 3.

Table 4: Model odds ratios.

Infection Type	Odds Ratio	95% CI Lower	95% CI Upper	P-Value	Hosmer-Lemeshow chi2
Bloodstream	1.9	1.03	3.3	0.038	0.021

Infection Type	Odds Ratio	95% CI Lower	95% CI Upper	P-Value	Hosmer-Lemeshow chi2
Lower respiratory	13.0	2.88	58.6	0.001	0.003
Pneumonia	1.5	0.99	2.3	0.058	<0.001
Gastrointestinal	3.5	1.75	7.0	<0.001	0.081
Surgical site	2.6	1.47	4.8	0.001	0.354
UTI	1.7	0.87	3.36	0.121	0.068

Hosmer-Lemeshow chi2 (D. W. Hosmer et al. 1997) Figure 3 graphically displays these results

Discussion

These models suggest that IVFE treatment should be saved as a last resort. There are significant increases in the odds of contracting the majority of hospital acquired infections observed in this study. This is consistent with previous studies of IVFE complications. By reserving this therapy as a last result, these results can help guide the standard of care practices to reduce the rate of hospital-contracted infections and by result, shorten length of stay for critically ill patients (McClave et al. 2009). This has the potential to make care safer and more cost efficient [CITATION].

One of the strengths of the study is its incorporation of significant confounding variables such as the number of days intubated and length of stay. These confounders are largely absent from previous research. It has been shown that mechanical ventilation is a risk factor for Pneumonia and Lower Respiratory Infection (Craven et al. 1986).

Another strength is to consider the causal pathways when selecting outcomes. Hospital length of stay and ICU length of stay were shown to be primary outcomes from previous studies (Battistella et al. 1997). However, it has been shown that infection status is correlated to increased hospital length of stay (McClave et al. 2009). Thus, if these variables were treated as outcomes, we will overestimate the association between primary predictor and outcomes.

The major limitations of the study includes the dichotomization of the main predictor, few events observed for certain infections and its retrospective nature. By dichotomizing the main predictor, we are losing some information; however, the data are highly skewed with a majority of values at zero (see figure 1, first panel). The skewness of the data will potentially introduce bias for the analysis.

Due to the nature of logistic regression, infection events with very few observations are not able to be modeled properly. For some infections investigated, the number of events observed were below the threshold for modeling. Therefore, the potential association of main predictor and these events is not able to be confidently inferred.

Due to confidentiality, the client did not disclose the origins of the institutions for the patients. This may lead to some potential bias in patients selection.

References

Battistella, Felix D, John T Widergren, John T Anderson, John K Siepler, Jo C Weber, and Kathleen MacColl. 1997. "A Prospective, Randomized Trial of Intravenous Fat Emulsion Administration in Trauma Victims Requiring Total Parenteral Nutrition." *Journal of Trauma and Acute Care Surgery* 43 (1). LWW: 52–60.

Craven, Donald E, LAUREEN M Kunches, Vetal Kilinsky, DEBORAH A Lichtenberg, BARRY J Make, and WILLIAM R McCabe. 1986. "Risk Factors for Pneumonia and Fatality in Patients Receiving Continuous Mechanical Ventilation." *The American Review of Respiratory Disease* 133 (5): 792–96.

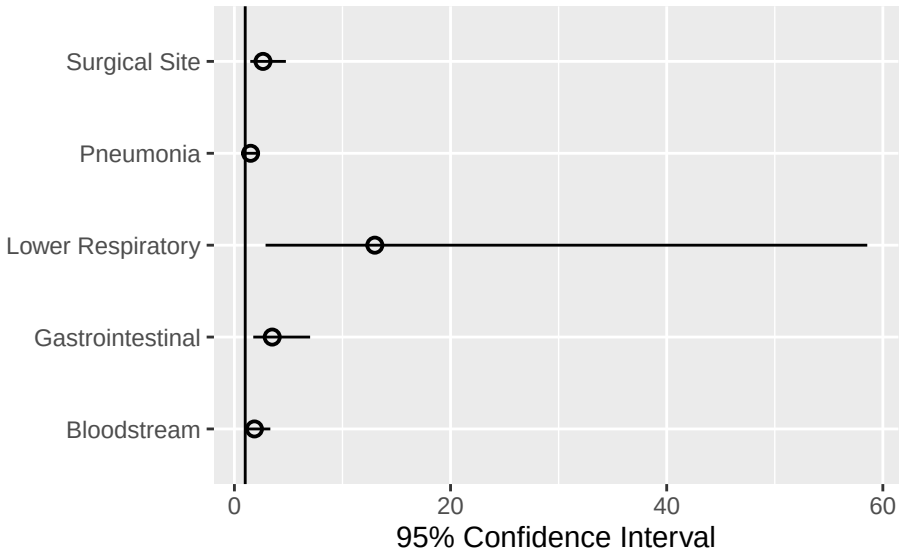

Figure 3: Odds Ratios and Confidence Intervals by Infection

Hosmer, David W, Trina Hosmer, Saskia Le Cessie, Stanley Lemeshow, and others. 1997. "A Comparison of Goodness-of-Fit Tests for the Logistic Regression Model." *Statistics in Medicine* 16 (9): 965–80.

McClave, Stephen A, Robert G Martindale, Vincent W Vanek, Mary McCarthy, Pamela Roberts, Beth Taylor, Juan B Ochoa, et al. 2009. "Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN)." *Journal of Parenteral and Enteral Nutrition* 33 (3). Sage Publications: 277–316.

StataCorp. 2015. *STATA* (version 14).