ESPGHAN Committee on Nutrition Position Paper

Intravenous Lipid Emulsions and risk of Hepatotoxicity in Infants and Children: a Systematic Review and Meta-analysis

DR. Nguyen Thi Kim Ngan
Disgestive Department – Children's Hospital No.2

Content

1. Introduction
2. Materials and methods
3. Results
4. Conclusions
5. Recommendations

Introduction

- Parenteral Nutrition (PN): in patients not fully tolerating enteral nutrition/intestinal failure (IF) [1].
- PN-associated liver disease (PNALD): cholestasis and exclude other causes of liver injury [2,3].
- Cholestasis: direct bilirubin(>=2 mg/dL[34.2 mmol/L]) [4].
- The mechanism of PNALD is multifactorial: immature liver function, inflammatory mediators, short bowel syndrome, parenteral nutrition components (especially lipid emulsions)[5].

Introduction

- PNALD may develop in 40% to 60% of infants [6] and up to 85% of neonates [7] who require long-term PN.
- Intravenous lipid emulsion (ILE) prevents many complications: essential fatty acid deficiency, hyperglycaemia and hepatic steatosis [8,9].

Introduction

Different types of intravenous lipid emulsions:

	Intralipid 20%	ClinOleic 20%	Lipofundin 20%	SMOFlipid 20%	Omegaven 10%
Abbreviation	SO	OO/SO	MCT/SO	multicomponent FO-containing	FO
Year of introduction	1960s	1990s	1980s	2000s	1990s
	Oil source, %				
Soya bean	100	20	50	30	0
MCT	0	0	50	30	0
Olive	0	80	0	25	0
Fish	0	0	0	15	100
	Fatty acids (% of total fatty acid)				
Linoleic acid	53	18.7	29.1	37.2	4.4
Arachidonic acid	0.1	0.5	0.2	1.0	2.1
α-Linolenic acid	8	2.3	4.5	4.7	1.8
Eicosapentaenoic acid	0	0	0	4.7	19.2
Docosahexaenoic acid	0	0	0	4.4	12.1
n-6:n-3 ratio	7:1	9:1	7:1	2.5:1	1:8
Phytosterols (mg/L) based on Angsten et al (39)*	348±33	237 ± 8	NA	47.6	0
Phytosterols (mg/L) based on Xu et al (27)†	439.07 ± 5.72	274.38 ± 2.60	278.14 ± 5.09	207	No phytosterols, squalene 26.7 mg/L
α-Tocopherol (mg/L)	38	32	85 ± 20	200	150–296

FO, fish oil; MCT, medium-chain triglycerides; OO, olive oil; SO, soya bean oil.
* Data in the table are the mean value when an interval is given from the manufacturer (39).
† Independently evaluated concentration of 9 different phytosterols and sqalene (27).

*Fig. 1 Characteristics of commercially available intravenous lipid emulsions used in reported randomized controlled trials (*Journal of Pediatric Gastroenterology and Nutrition. 62(5):776-792, May 2016)

Introduction

Recent new generation of ILE (FO & SMOFLipid): promising results in the prevention and treatment of PNALD.

➡ The aim of the present article: summarizing the scientific evidence (23 RCTs) about role of different ILE in the pathogenesis and the effect of different types of ILE on PNALD.

Materials and Methods

- Journal of Pediatric Gastroenterology & Nutrition – Volume 62 - 5/2016
- A systematic review: PubMed, EMBASE, and Cochrane Central Register of Controlled Trials CENTRAL search up to March 2015.
- The primary outcome: incidence of cholestasis.
- Secondary outcomes: total and conjugated bilirubin and liver enzymes (ALT, AST, ALP, GGT) after the use of ILE.

Materials and Methods

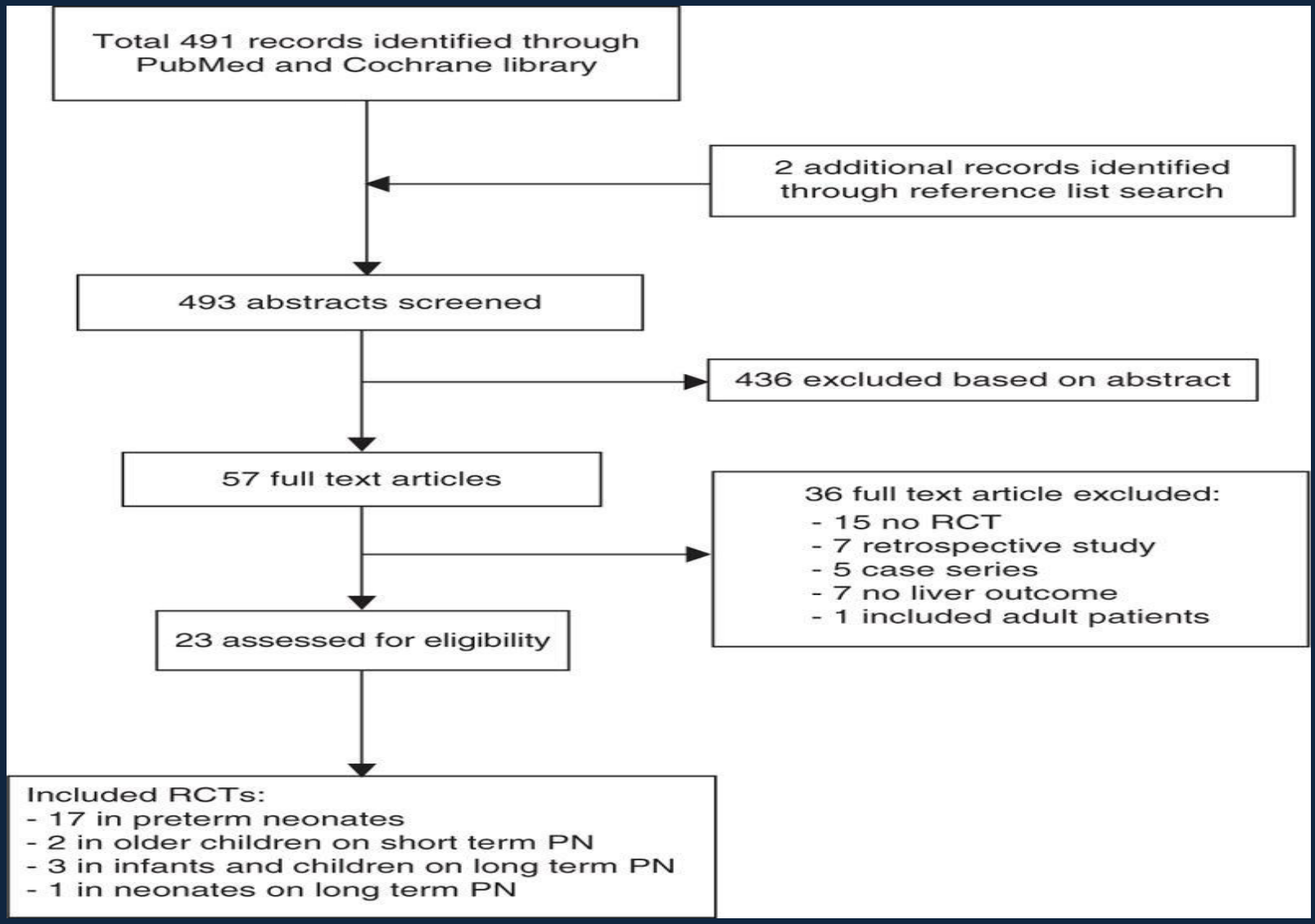

Fig. 2 Flow chart of search results.

Results

1. **Short-term (3–27 days) use in neonates including preterm infants**:17 RCTs

- 5 studies: between OO/SO (Clinoleic 20%) & SO (Intralipid 20%), 4 studies found no difference in the bilirubin and/or liver enzymes between groups. The largest study, however, found lower direct bilirubin after 7 days with OO/SO ILE.
- 2 studies compared MCT/SO-based (Lipofundin 20%) & SO (Intralipid 20%) with no difference between groups.

Results

1. **Short-term (3–27 days) use in neonates including preterm infants**:17 RCTs

- 6 studies compared multicomponent FO-containing IL (SMOFlipid 20%) to SO (Intralipid 20%).
- 2 studies found a greater decrease in bilirubin levels in SMOFlipid group, 1 study found lower GGT in SMOFlipid group. 3 studies found no difference in the cholestasis rate between groups.

Results

1. **Short-term (3–27 days)use in neonates including preterm infants**:17 RCTs

- Comparison of different ILEs: no difference in bilirubin levels and liver enzymes between groups.
- Primary outcome: 4 studies found no difference any experimental mixed ILE compared to solely SO ILE (Fig. 3)
- Secondary outcomes: All studies reported total bilirubin after the intervention and found no difference in overall effect and subgroup analysis (Fig. 4). Similarly, no difference for conjugated bilirubin, ALP, GGT, AST and ALT.

Results

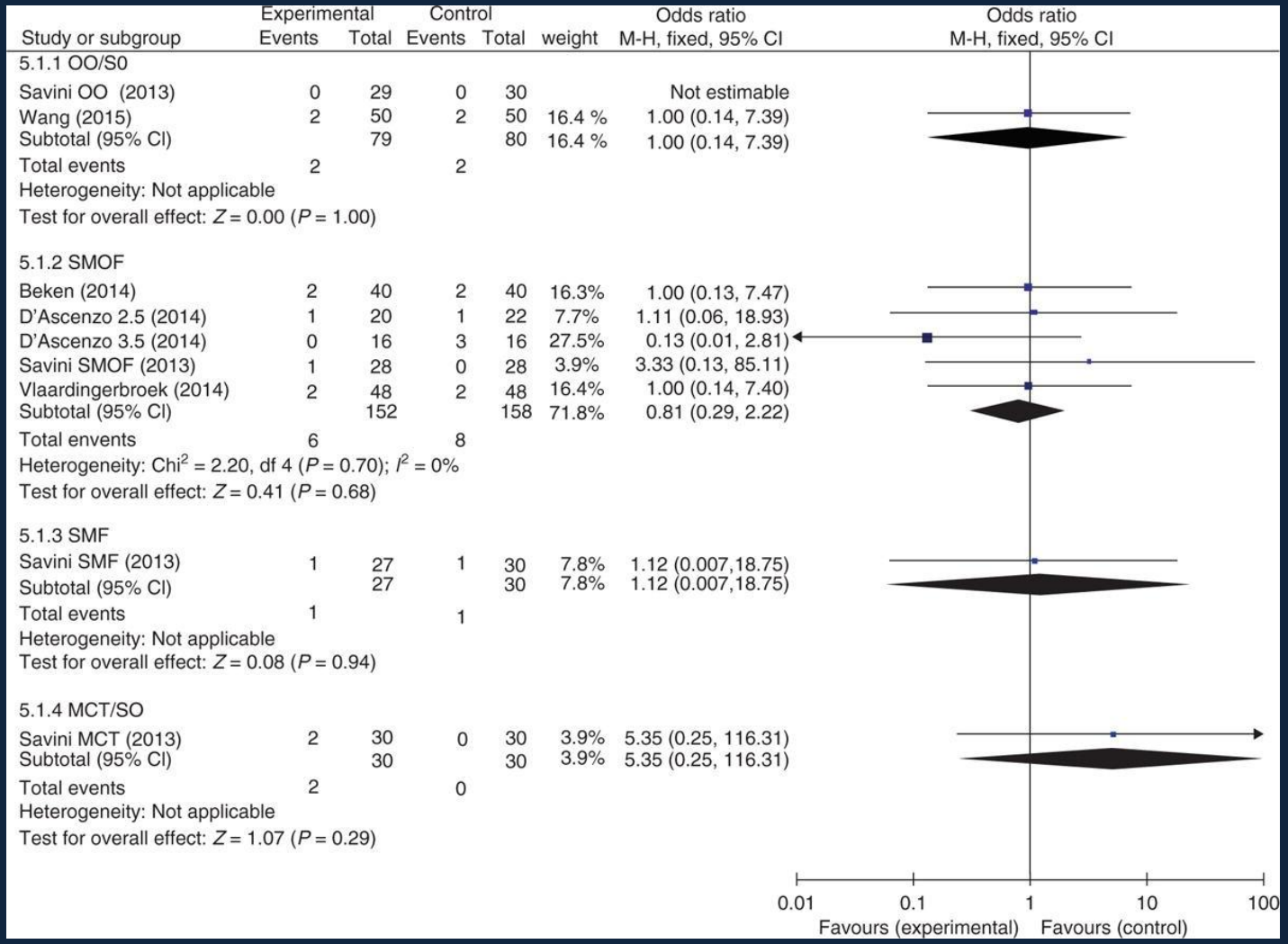

Fig. 3 Effect of mixed intravenous lipid emulsions on cholestasis rate in comparison to pure soya bean–based lipid emulsion in neonates including preterm infants

Results

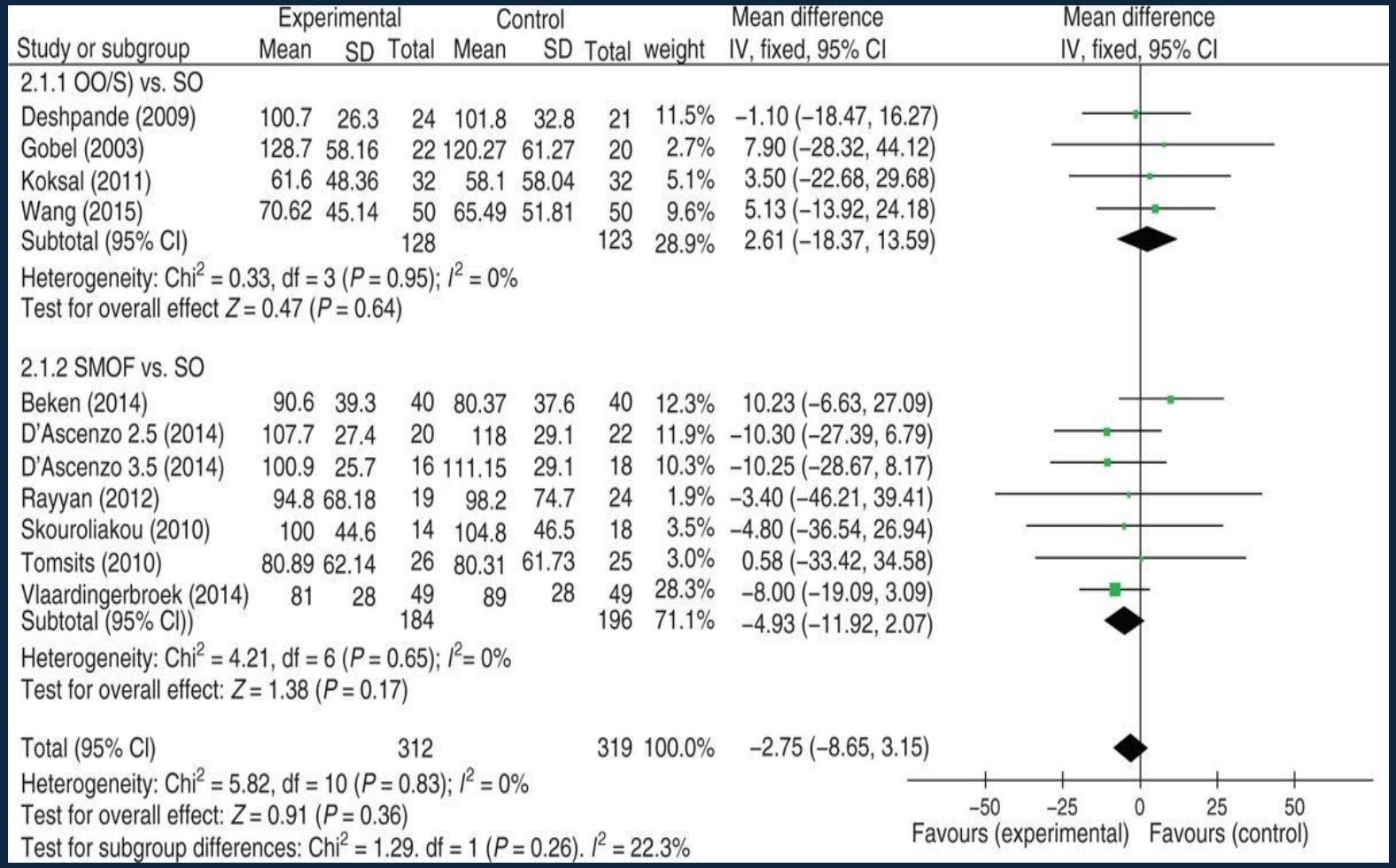

Fig .4 Effect of mixed intravenous lipid emulsions on total bilirubin levels (µmol/L) in comparison to pure SO-based lipid emulsion in neonates including preterm infants)

Results

2. Long-term use in neonates (more than 4 weeks):

- Only 1 RCT evaluated the use of FO ILE (Omegaven 10%) compared to SO ILE (Intralipid 20%) in neonates who required long-term PN. 19 neonates no difference in direct bilirubin and liver function between groups.

A Comparison of 2 Intravenous Lipid Emulsions: Interim Analysis of a Randomized Controlled Trial

Deepika Nehra, MD[1]; Erica M. Fallon, MD[1]; Alexis K. Potemkin, RN[1]; Stephan D. Voss, MD, PhD[2]; Paul D. Mitchell, MSc[3]; Clarissa Valim, MSc[3]; Mandy B. Belfort, MD, MPH[4]; David C. Bellinger, PhD[5]; Christopher Duggan, MD[6]; Kathleen M. Gura, PharmD[7]; and Mark Puder, MD, PhD[1]

Results

3. Children with short-term PN:

- 2 studies evaluated the safety and efficacy of different ILE in children (OO & MCT). None of the studies evaluated the influence of different ILE on liver function tests or bilirubin levels and none reported cholestasis rate.
- 1 study included children after bone marrow transplantation and compared MCT/SO (Lipofundin 20%) and OO/SO ILE (Clinoleic 20%) found no difference between groups in bilirubin levels and liver function tests.

Results

4. Infants and children with long-term PN:

- 3 RCTs: no difference in the liver enzymes, bilirubin levels between groups.
- The present study found a decrease in the bilirubin levels in the multicomponent FO-containing group and an increase in the SO group.
- Another study also showed a decrease in direct bilirubin and ALT levels in infants on FO compared with those on SO.

Conclusions

The ESPGHAN Committee on Nutrition (CoN) concludes:

- No evidence of a difference in total bilirubin, conjugated bilirubin, AST, ALT, ALP, and GGT between short-term use of OO/SO and SO ILE in infants and children (level of evidence 2A).
- No evidence of a difference in bilirubin, conjugated bilirubin, AST, ALT, ALP, and GGT between short-term use of multicomponent FO-containing ILE and SO ILE in neonates (level of evidence 2A).

Conclusions

- The use of multicomponent FO-containing ILE may contribute to a decrease in total bilirubin levels in children with prolonged PN (level of evidence 2B).
- Pure FO supply combined with a decrease or interruption of SO ILE may contribute to cholestasis recovery in children with PNALD (level of evidence 2B).

Recommendations

- Prevention and care of PNALD in children should not be focused exclusively on parenteral ILE intake.
- Based on available evidence, the CoN cannot currently recommend the use of any specific ILE for short-term use in infants and children for the prevention and treatment of PNALD (GR B).
- For children in whom long-term use of PN is expected, it appears prudent to use multicomponent FO-containing ILE (GR C).

Recommendations

- The present evidence base is inadequate to determine the optimal strategy for intravenous lipid supply in infants and children to prevent or treat liver complications.
- Studies on both the prevention and treatment of PNALD should be conducted in high-risk infants and children who are likely to require long-term PN, and should also consider additional extrahepatic outcomes such as growth and cognition.

References

- [1] D'antiga L, Goulet O. Intestinal failure in children: the European view. *J Pediatr Gastroenterol Nutr* 2013; 56:118–126.
- [2] Colomb V, Goulet O, Rambaud C, et al. Long-term parenteral nutrition in children: liver and gallbladder disease. *Transplant Proc* 1992; 24:1054–1055.
- [3] Peyret B, Collardeau S, Touzet S, et al. Prevalence of liver complications in children receiving long-term parenteral nutrition. *Eur J Clin Nutr* 2011; 65:743–749.
- [4] Klein CJ, Revenis M, Kusenda C, et al. Parenteral nutrition-associated conjugated hyperbilirubinemia in hospitalized infants. *J Am Diet Assoc* 2010; 110:1684–1695.
- [5] Moss RL, Amii LA. New approaches to understanding the etiology and treatment of total parenteral nutrition-associated cholestasis. Semin Pediatr Surg 1999; 8:140.
- [6] Kelly DA. Intestinal failure-associated liver disease: what do we know today? *Gastroenterology* 2006; 130:S70–S77.
- [7] Nehra D, Fallon EM, Puder M. The prevention and treatment of intestinal failure-associated liver disease in neonates and children. *Surg Clin North Am* 2011; 91:543–563.
- [8] Keim NL. Nutritional effectors of hepatic steatosis induced by parenteral nutrition in the rat. *JPEN J Parenter Enteral Nutr* 1987; 11:18–22.
- [9] Reif S, Tano M, Oliverio R, et al. Total parenteral nutrition-induced steatosis: reversal by parenteral lipid infusion. *JPEN J Parenter Enteral Nutr* 1991; 15:102–104.


Thank
You!