

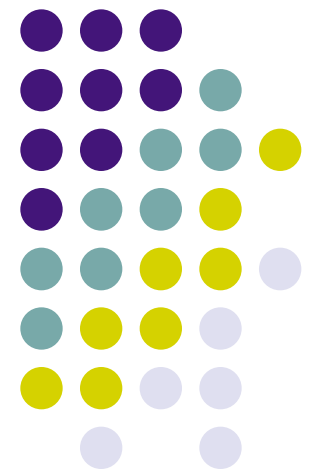
Parenteral Nutrition and Liver Disease

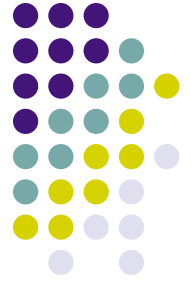
Melanie Stapleton MD FRCPC

Assistant Clinical Professor

University of Calgary

June 5, 2010





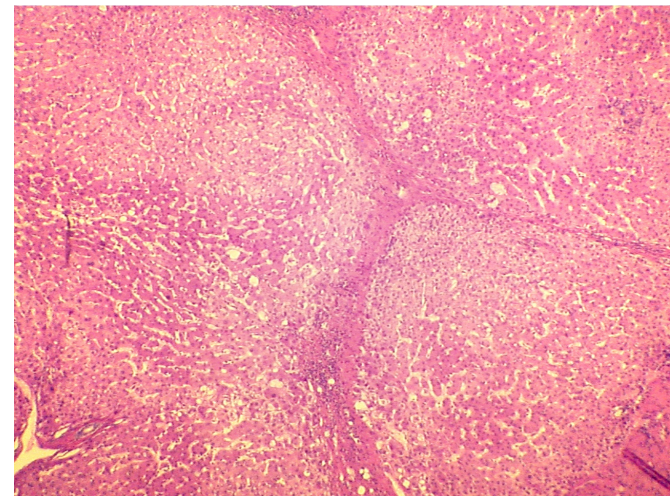
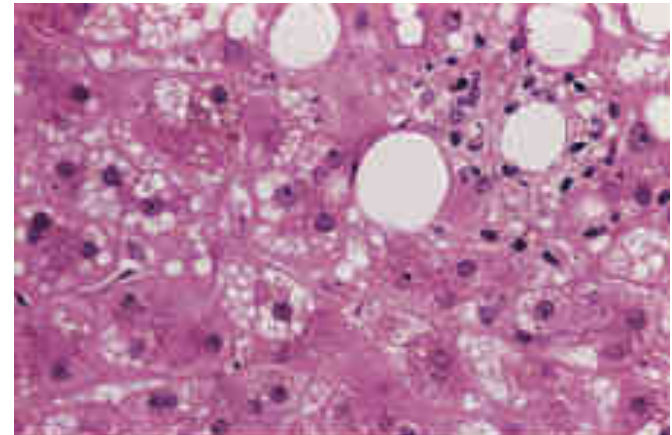
Objectives

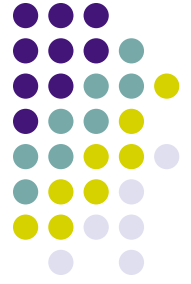
- Describe the pathophysiology of PNALD and the basis for proposed therapies
- Describe the novel pharmacological approaches for treating PNALD under investigation
- Describe the use of ω 3-rich lipid sources as a potential method of prevention and treatment for PNALD

Parenteral Nutrition Associated Liver Disease



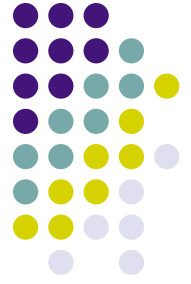
- Range of liver abnormalities
 - Steatosis
 - Steatohepatitis
 - Cholestasis
 - Cirrhosis
 - Portal hypertension





PNALD

- Risk factors
 - Prematurity
 - GI surgery/short gut
 - Duration of PN
 - Sepsis
 - Lack of enteral/oral intake
 - IUGR (neonates)
 - Excess amino acid intake
 - PN composition
 - ω 6 PUFA, phytosterols



PNALD - Pathophysiology

- Short gut, sepsis
 - Animal data – increased proinflammatory cytokines produced in setting of short gut and infection
 - Bacterial endotoxins
- Lack of enteral nutrition
 - Decreased gut hormone secretion
 - Decreased bile flow, biliary stasis

CJ Aprahamian et al. *J Ped Surg* 2007; 42: 992

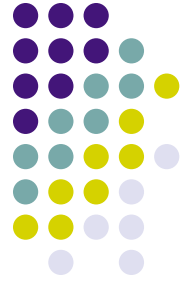
V Colomb et al. *JPEN* 2000; 108: 652



PNALD - Incidence

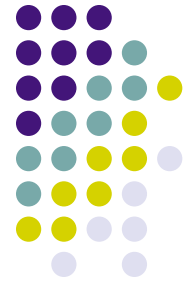
- Earlier reports of very high incidence
 - 65% of adults with elevated liver enzymes after median 6 months
 - 42% of adults complicated liver disease after median 17 months
 - Cirrhosis, bilirubin > 60 $\mu\text{mol/L}$, encephalopathy or complications of portal hypertension
 - Not similar population to current practice
 - Most >1g lipid/kg/day
- More data suggests ~10-15% will develop liver abnormalities on long term PN

M Cavicchi et al. *Ann Int Med* 2000; 132: 525
C Chung et al. *Clin Liver Dis* 2002; 6: 1067



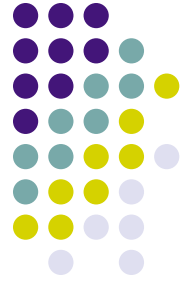
PNALD - Incidence

- Younger age – increased incidence
 - Related to immaturity of liver in neonates, esp. preemies
 - 2/3 of neonates on PN will develop total bili > 34 μ mol/L
 - Can develop within 2 weeks



PNALD - Incidence

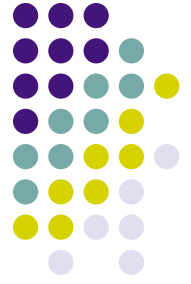
Bilirubin	N	Transplanted	Deaths
>34 μ mol/L, but decreased to normal	57	3	3
>34 μ mol/L, no decrease	19	11	11



PNALD - Prevention

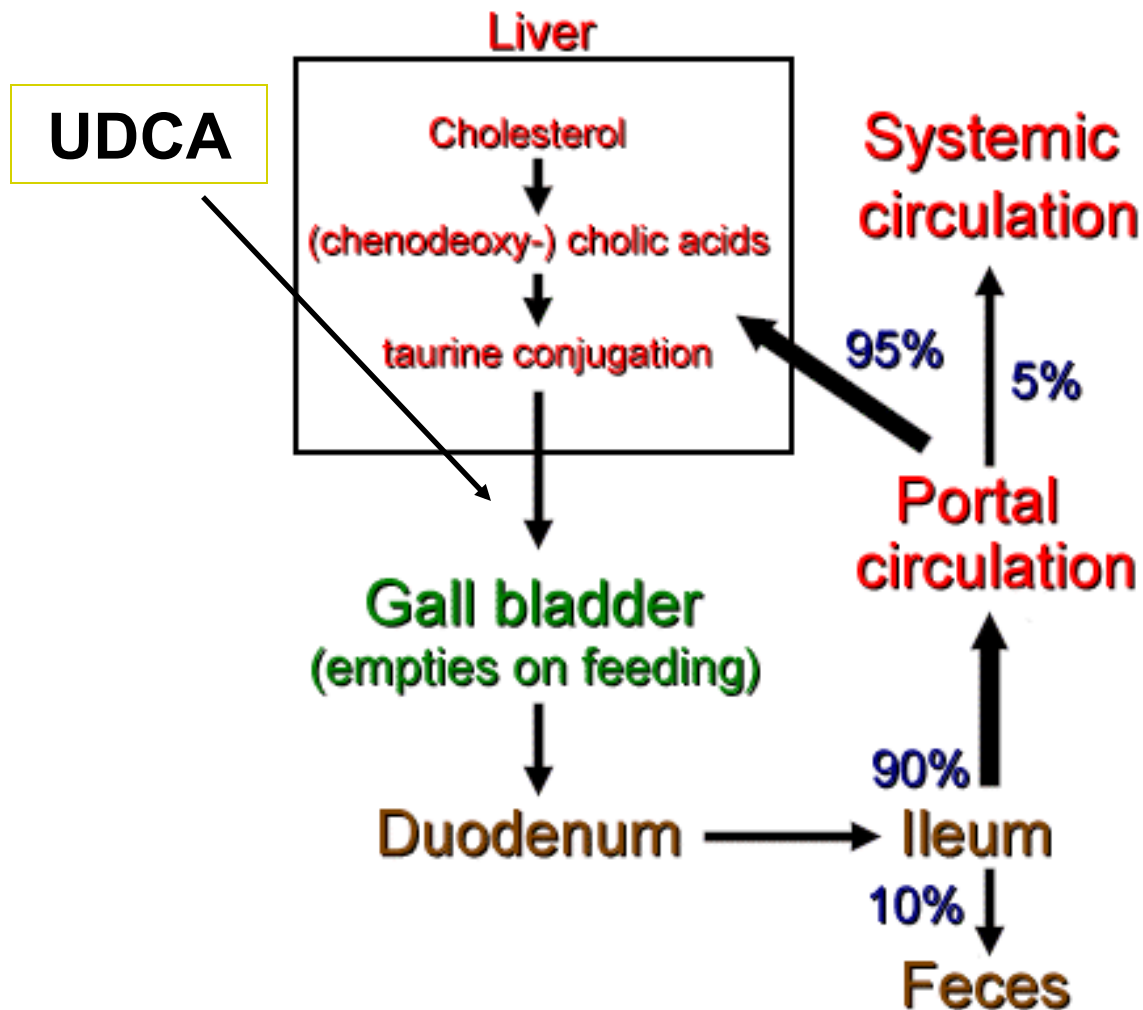
- Standard approaches
 - Early enteral nutrition
 - Control of bacterial overgrowth
 - Lipid dosing $<1\text{g/kg/day}$
 - Minimizing total energy intake from PN
 - Cycling PN

PNALD – Prevention/Treatment

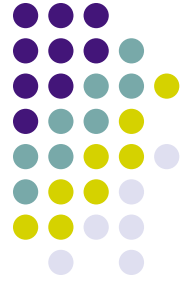


- Novel approaches
 - Ursodeoxycholic acid
 - Synthetic bile acid
 - Useful in other cholestatic liver diseases
 - Neonates and children
 - Two pilot studies suggesting benefit, but no benefit in a very small controlled trial
 - Adults
 - No controlled trials
 - Less consistent evidence of benefit
 - Excellent side effect/safety profile

PNALD – Prevention/Treatment



PNALD – Prevention/Treatment



- Novel approaches
 - CCK-octapeptide
 - GI hormone that increases gallbladder contractility and increases bile flow; no benefit in a controlled trial in children
 - Erythromycin
 - Antibiotic and motilin agonist used for promotility characteristics; may have some benefit in very low birthweight infants
 - N-Acetyl Cysteine
 - Methionine may have role in hepatotoxicity; single promising case series

DH Teitelbaum et al. *Pediatrics* 2005; 115: 1332

PC Ng et al. *Gastro* 2007; 132: 1726

DR Mager et al. *J Pediatr Gastroenterol Nutr* 2008; 46: 220



PNALD – Fish Oil

- Why blame soy-based lipids for PNALD?
 - Observational data
 - Cholestasis worsens with increasing dose of soy oils
 - Cholestasis improves with decreasing or discontinuing soy lipids



PNALD – Fish Oil

- Why blame soy-based lipids for PNALD?
 - Evidence of increased oxidative stress
 - Animal models – ROS can damage hepatocytes and cause cholestasis
 - Humans – large amounts of ω 6 PUFAs from soy oils contains little α tocopherol or other antioxidants
 - Increases levels of peroxidation markers

MG Roma et al. *Ann Hepatol* 2008; 7: 16

V Linseisen et al. *Clin Nutr* 2000; 19: 177

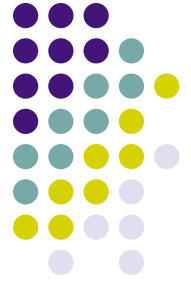


PNALD – Fish Oil

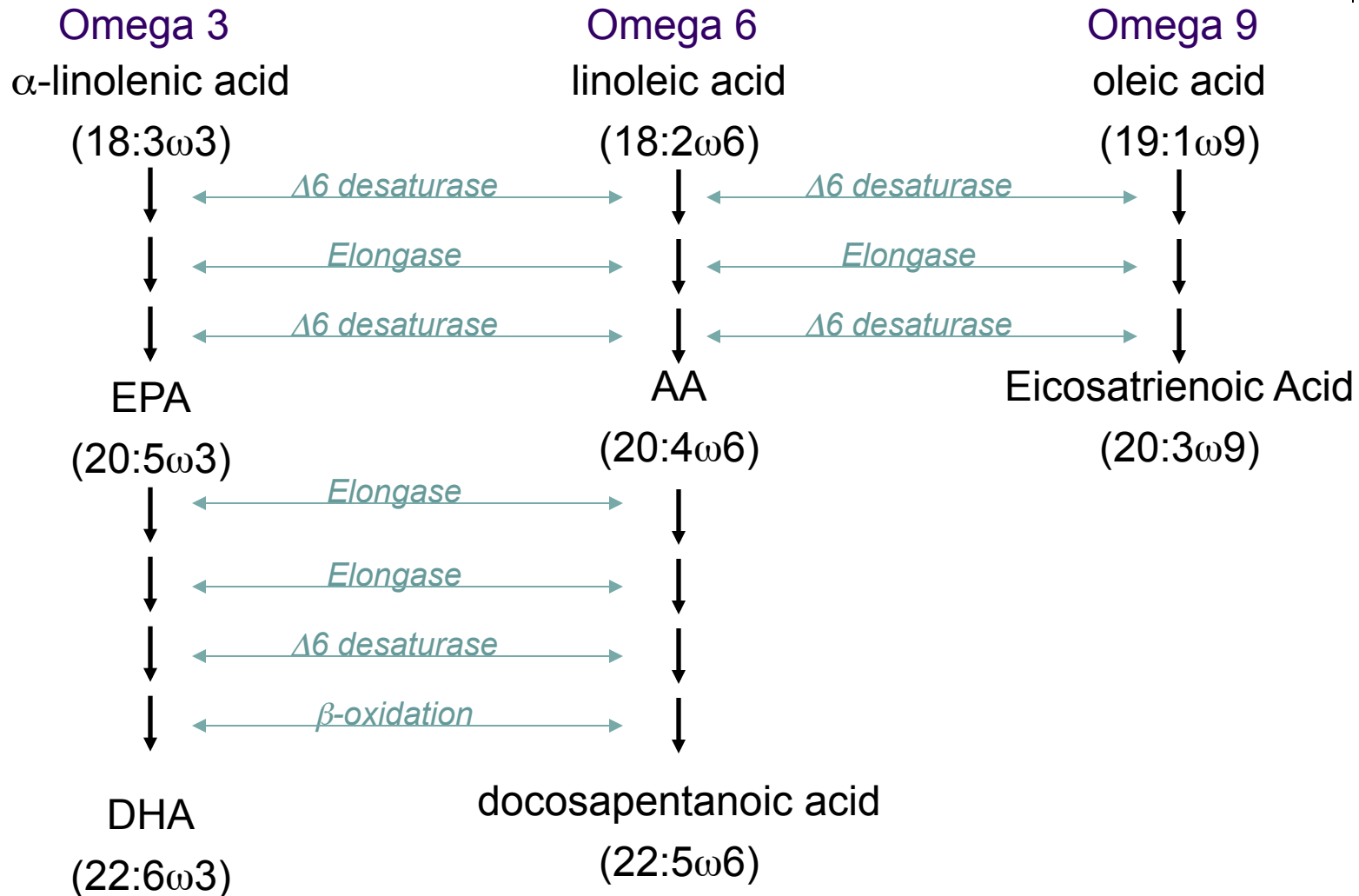
- Why might fish oils be any improvement?
 - Animal model showing decreased inflammatory enzymes with parenteral ω 3s
 - Animal models showing attenuation of fatty liver and prevention of steatosis
 - Fish oils contain high amounts of DHA and EPA
 - Increase production of anti-inflammatory cytokines
 - Leukotrienes B5, C5, D5
 - Prostaglandin E3, I3
 - Thromboxane A3
 - Decrease $\text{TNF}\alpha$ and IL6

SL Yeh et al. *Nutrition* 1997; 13: 32

IP Alwayn et al. *Pediatr Res* 2005; 57: 445



PNALD – Fish Oil





PNALD – Fish Oil

	Intralipid	Liposyn II	ClinOleic	SMOF Lipid	Omegaven
<i>Oil Source (g)</i>					
Soybean	10	5	2	3	0
Safflower	0	5	0	0	0
MCT	0	0	0	3	0
Olive Oil	0	0	8	2.5	0
Fish Oil	0	0	0	1.5	10
<i>α tocopherol (mg/L)</i>	38	NR	32	200	150-296
<i>Phytosterols (mg/L)</i>	348±33	383	327±8	47.6	0
<i>Fat Composition (g)</i>					
Linoleic	5.0	6.5	0.9	2.9	0.1-0.7
αlinolenic	0.9	0.4	0.1	0.3	<0.2
EPA	0	0	0	0.3	1.28-2.82
DHA	0	0	0	0.05	1.44-3.09
Oleic	2.6	1.8	2.8	2.8	0.6-1.3
Palmitic	1.0	0.9	0.7	0.9	0.25-1
Stearic	0.35	0.34	0.2	0.3	0.05-0.2
Arachadonic	0	0	0.03	0.05	0.1-0.4



PNALD – Fish Oil

- Soy oil has been primary lipid used in PN since introduction
 - 2005 – first reported use of Omegaven monotherapy
 - 2006 – case reports of reversal of PNALD and cholestasis in infants by switching from soy lipid to fish oil

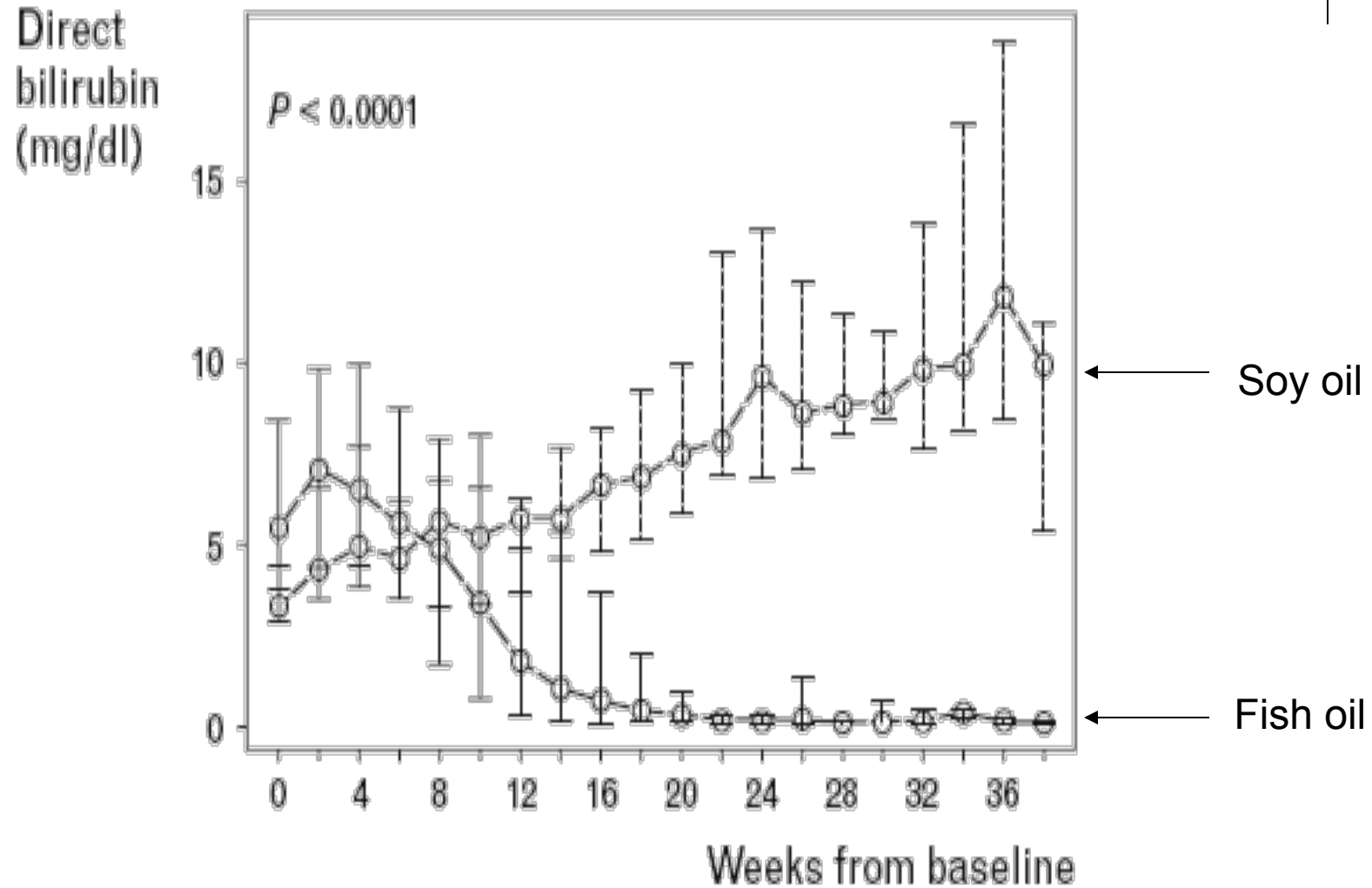


PNALD – Fish Oil

- 2009
 - Open label trial of Omegaven
 - 42 infants receiving soy based lipid for SBS
 - Bilirubin $>34 \mu\text{mol/L}$
 - 19/42 had reversal of cholestasis
 - Compared to control group 2/49 (historic)
 - Occurred 6x faster
 - 0/42 receiving fish oil went on to transplant vs 2/49
 - No EFAD deficiency, growth retardation, hypertriglyceridemia or coagulopathy

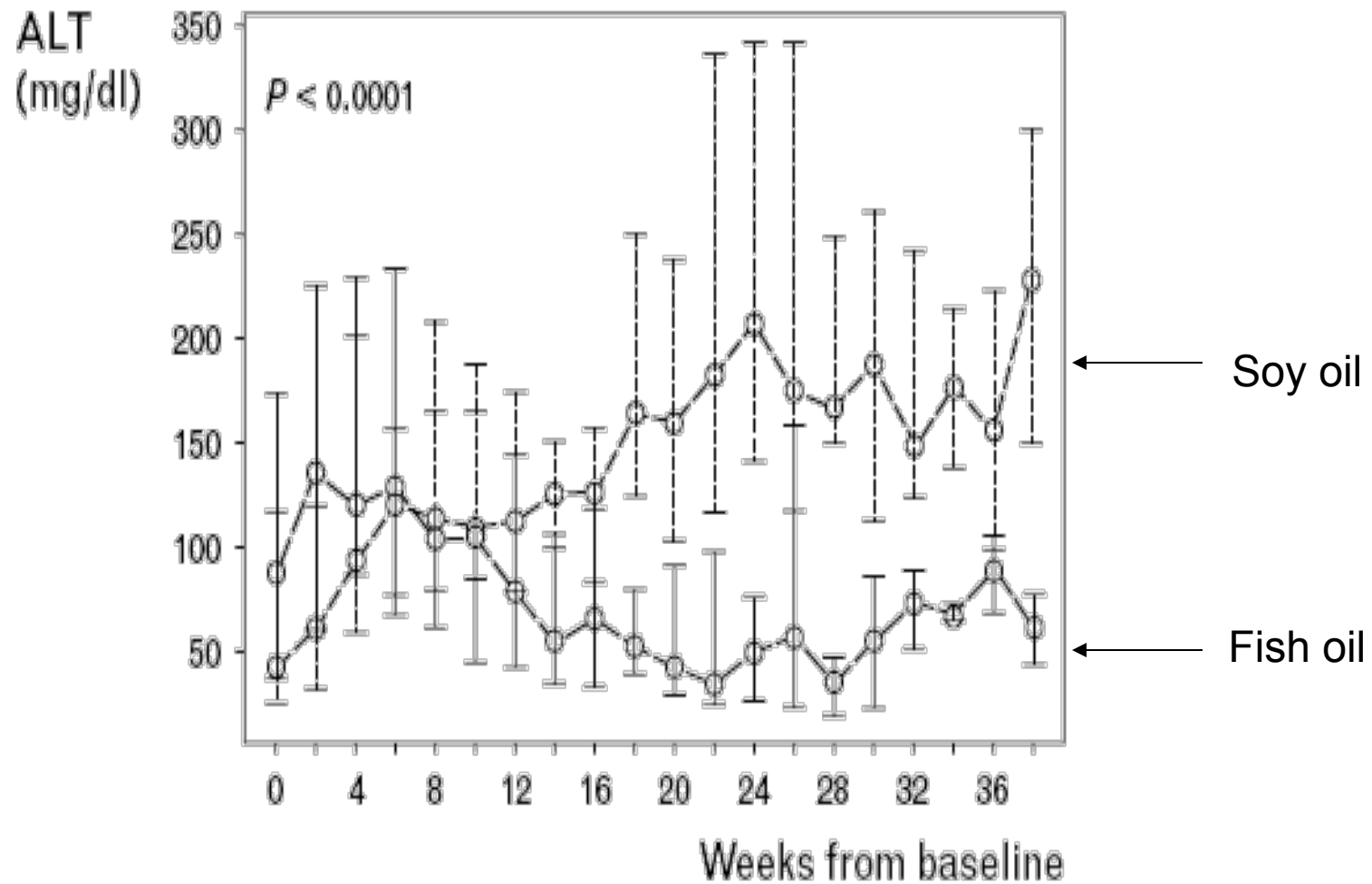
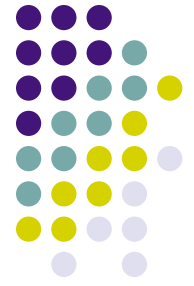


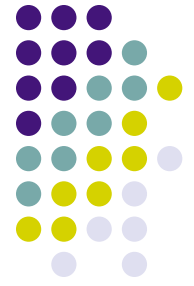
PNALD – Fish Oil



M Puder et al. *Ann Surg* 2009; 250: 395

PNALD – Fish Oil





PNALD – Fish Oil

- Two randomized controlled trials are currently being done
 - Soy lipid (Intralipid) vs fish oil (Omegaven)PN in neonates and infants requiring PN >3 weeks (<http://www.clinicaltrials.gov/ct2/show/NCT00512629>)
 - Started in Boston in 2007
 - SMOF Lipid vs Intralipid (http://niddk.nih.gov/federal/ddicc/minutes6_25_02.pdf)



PNALD – Fish Oil

- Is there any reason to be cautious about the use of fish oil as lipid source?
 - EFAD
 - ALA and linoleic acid are not supplied by 100% fish oil
 - EFAD has not been seen in children on Omegaven
 - No evidence that this is generalizable to older children or adults, nor to patients on long-term home PN



PNALD – Fish Oil

- Is there any reason to be cautious about the use of fish oil as lipid source?
 - Idiosyncratic reactions
 - Hemolytic anemia developed in an infant on Omegaven for PNALD
 - 8 red cell transfusions
 - Transfusions discontinued after Omegaven stopped
 - 6 months after discontinuation, normal blood smear
 - Theorized to be due to changes in red cell membrane lipid composition

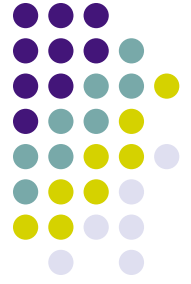


PNALD – Fish Oil

- Confounding factors – phytosterols
 - Plant sterols, only found in vegetable sourced lipids
 - Found in increased levels in serum of children with PNALD
 - In both animal and in vitro models, can be directly hepatotoxic
 - Is the benefit of fish oil the addition of ω 3 or removal of phytosterols?

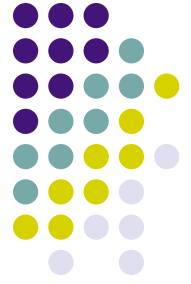
PT Clayton et al. *Nutrition* 1999; 14: 158

BA Carter et al. *Pediatr Res* 2007; 62: 301



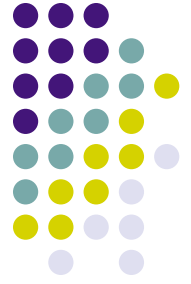
Conclusions

- Despite new and exciting advances in prevention and treatment of PNALD, prevention and treatment depends, not on a single intervention, but a multidisciplinary approach to correcting modifiable risk factors, recognizing unmodifiable risk factors, and early intervention (nutritional and pharmacological) to prevent end stage liver disease, liver transplant, and death.



Conclusions

- PNALD is likely different in adults and children, as the pathophysiology of PNALD seems to be different
 - Be wary of extrapolating data from pediatric studies to adults



Conclusions

- Sources of ω 3 fatty acids are an exciting new development in prevention/treatment of PNALD
 - Currently available only on compassionate release/special application from Health Canada
 - Good evidence (and even more evidence coming) for use in neonates and infants
 - Need some controlled data in adults before assuming benefit is same

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**“Large doses of fish oil are very good for your heart.
Especially when you get the urge to swim upstream.”**