ANOTHER CASE OF N/V AT NH. . .

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Overview

- Case Presentation
- Pathophysiology
- Treatment

Case Presentation

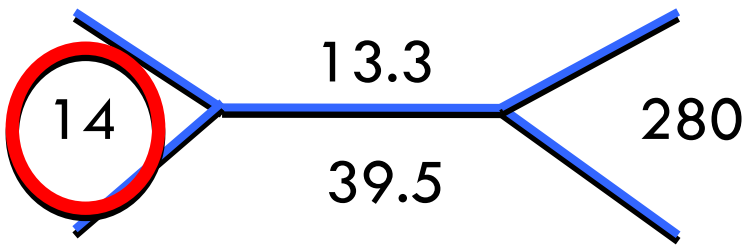
- 44aaF admitted with Acute Pancreatitis
- PMH:
  - DM 2 – on insulin x 5 years
  - Hypothyroidism
  - Obesity (BMI = 30)
  - Hyperlipidemia
  - h/o Acute Pancreatitis (no h/o chronic panc)
- Social Hx:
  - No tobacco/alcohol/illicits

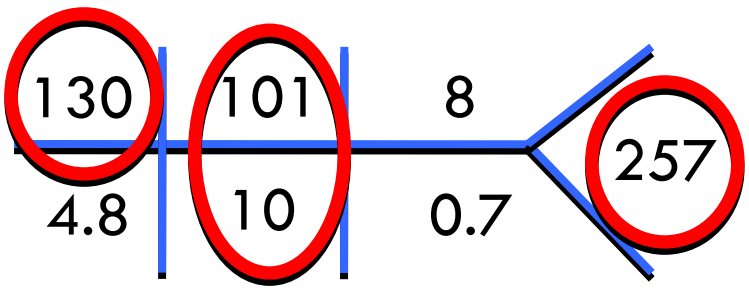
Case Presentation

- PE:
  - AF, normocardic, 98% RA
  - Mild distress secondary to pain
  - Heart/lung exam normal
  - Diffuse abd pain, no abd scars, no r/g, no distension, + BS
  - No edema

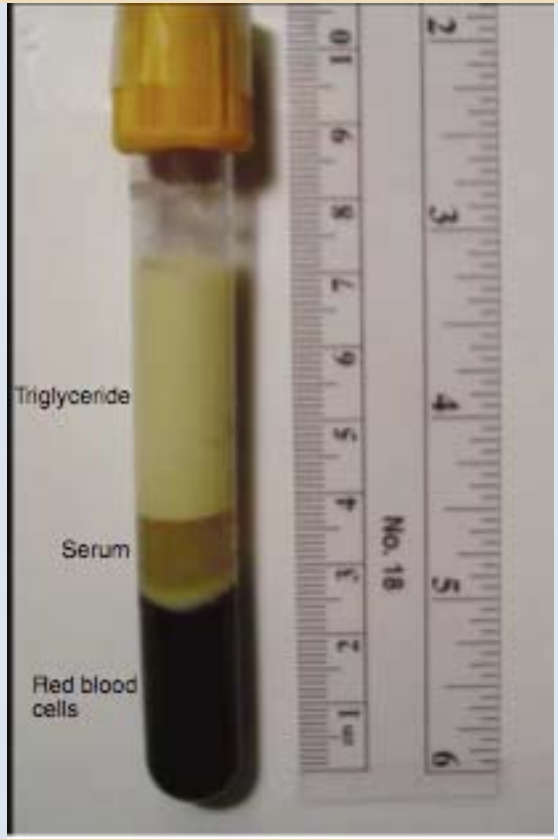
Case Presentation

- Labs:





- AST 18
- ALT 4
- AP 84
- TB 0.5
- ALB 3.7
- TP 6.9
- Lipase 180
- Amylase 80
- LDH 286
- Ca 9.0
- INR 1.1
- HgbA1c 11.3
- HCG neg
- 7.4/27/92
- UA:
  + ketones



TRIGLYCERIDES = 3500 mg/dL

CHOL 595 HDL 19 LDL ?

CT Imaging

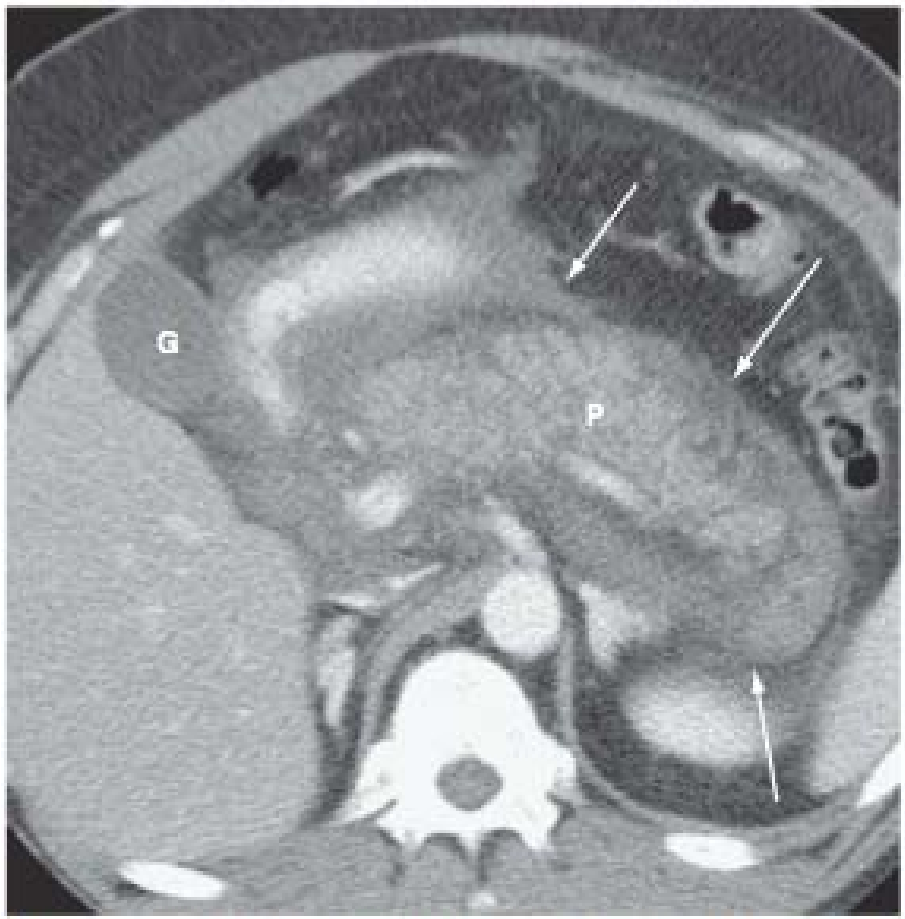


Figure 58-1. Acute interstitial pancreatitis. Contrast-enhanced computed tomography shows diffuse swelling of the pancreas (P) with peripancreatic inflammatory changes (*arrows*). The pancreas was well perfused without evidence of necrosis. G, gallbladder.

Severity of AP

- Ranson Criteria = 1
  - One point for glucose >200
  - Age<55, WBC < 16K, AST<250, LDH< 35
- Apache II Score Day 1 = 7
- CTSI Score = 2

Table 58-2 Ranson's Prognostic Criteria[14,215]

NON-GALLSTONE PANCREATITIS (1974)	GALLSTONE PANCREATITIS (1982)
At Admission	
Age >55 yr	Age >70 yr
White blood cells >16,000/mm^3	>18,000/mm^3
Blood glucose >200 mg/dL	>220 mg/dL
Serum lactate dehydrogenase >350 IU/L	>400 IU/L
Serum aspartate aminotransferase >250 IU/L	>250 IU/L
During Initial 48 hr	
Hematocrit decrease of >10 %	>10%
Blood urea nitrogen increase of >5 mg/dL	>2 mg/dL
Serum calcium <8 mg/dL	<8 mg/dL
Arterial pO_2 <60 mm Hg	NA
Serum base deficit >4 mEq/L	>5 mEq/L
Fluid sequestration >6 L	>4 L

Table 58-7 Computed Tomography (CT) Grading System of Balthazar and CT Severity Index (CTSI)

Balthazar Grades	
Grade A	Normal pancreas consistent with mild pancreatitis
Grade B	Focal or diffuse enlargement of the gland, including contour irregularities and inhomogeneous attenuation but without peripancreatic inflammation
Grade C	Grade B plus peripancreatic inflammation
Grade D	Grade C plus associated single fluid collection
Grade E	Grade C plus two or more peripancreatic fluid collections or gas in the pancreas or retroperitoneum

CTSI = Balthazar Grade Score Plus Necrosis Score*

Balthazar grade score:

A = 0
B = 1
C = 2
D = 3
E = 4

Necrosis score:
Absence of necrosis = 0
Necrosis of up to 33% of pancreas = 2
Necrosis of 33% to 50% = 4
Necrosis of >50% = 6

[Sleisenger and Fordtran]

ACUTE PANCREATITIS

1&2) Alcohol and Gallstones

3) Hypertriglyceridemia (1-5% of cases)

~ cause of over 50% of gestational pancreatitis

HTG = Hypertriglyceridemia
HTGP = HTG Pancreatitis

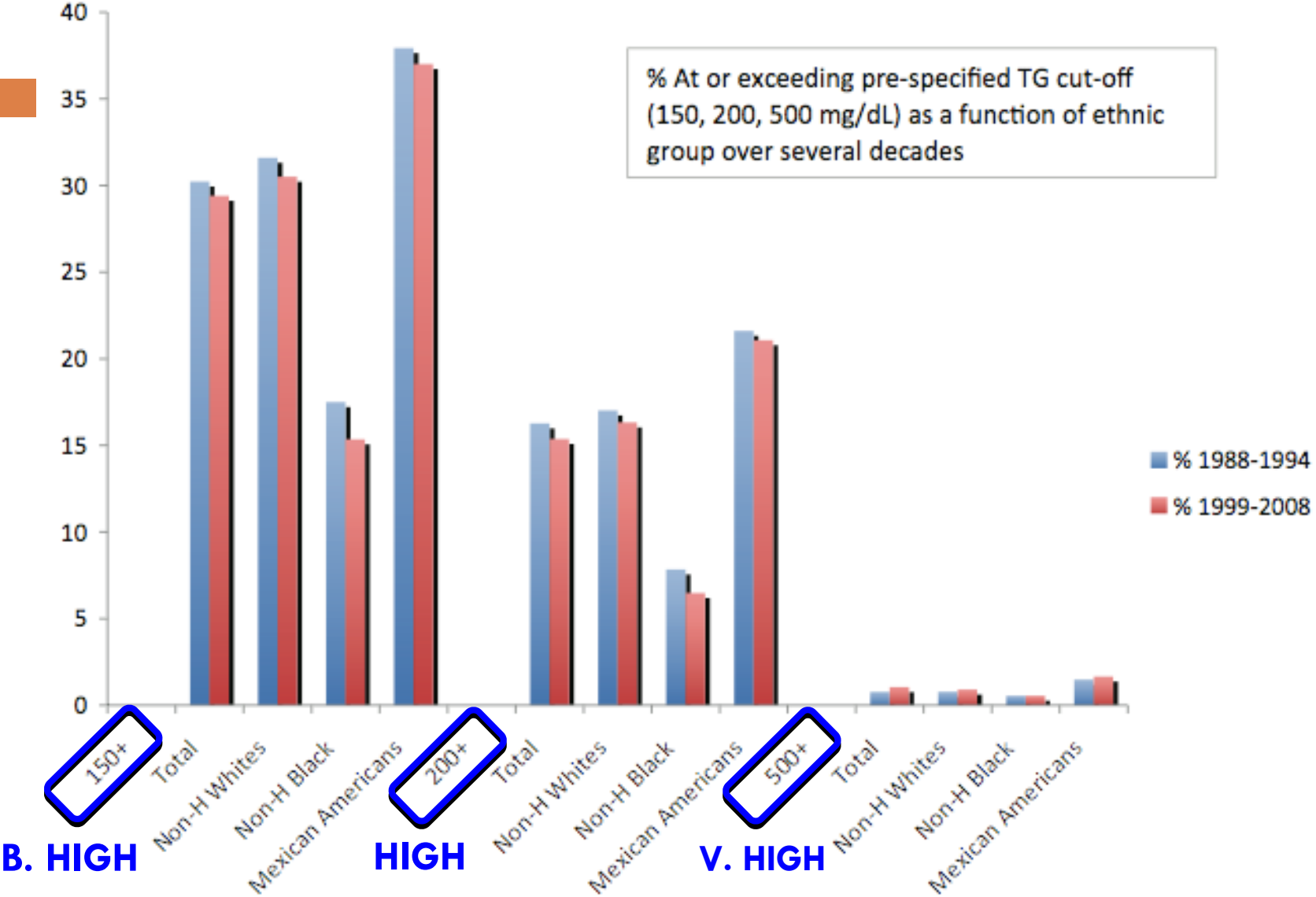
Definition of HTG

TG Designate	1984 NIH Consensus Panel	1993 NCEP Guidelines	2001 NCEP Guidelines
Desirable	<250	<200	<150
Borderline-high	250–499	200–399	150–199
High	500–999	400–999	200–499
Very high	>1000	>1000	≥500

Elevated TG levels are an independent risk factor for CV disease!

[Circulation –AHA Statement Triglycerides and CV Risk]

Prevalence of HTG

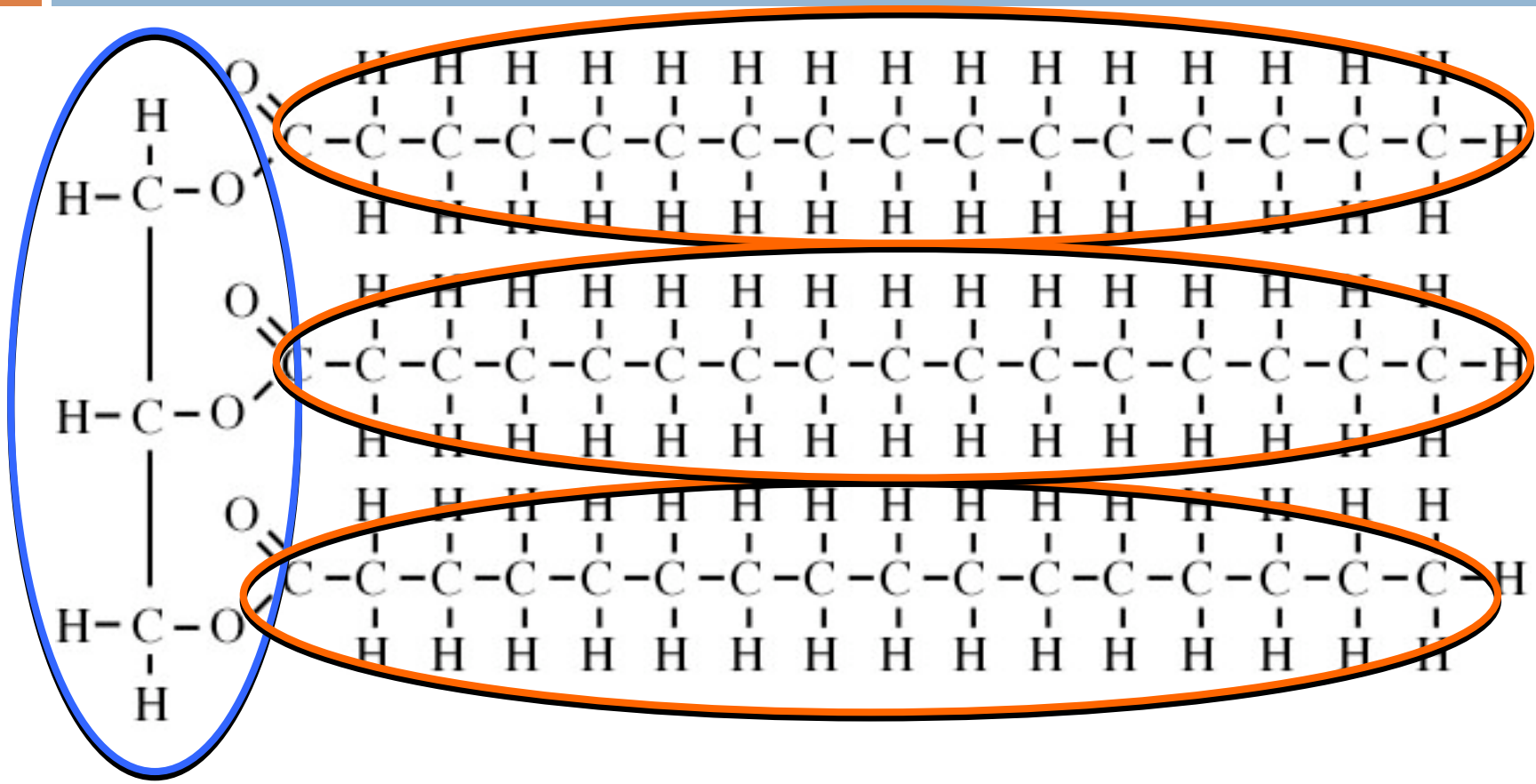


[Circulation –AHA Statement Triglycerides and CV Risk]

Cholesterol Summary

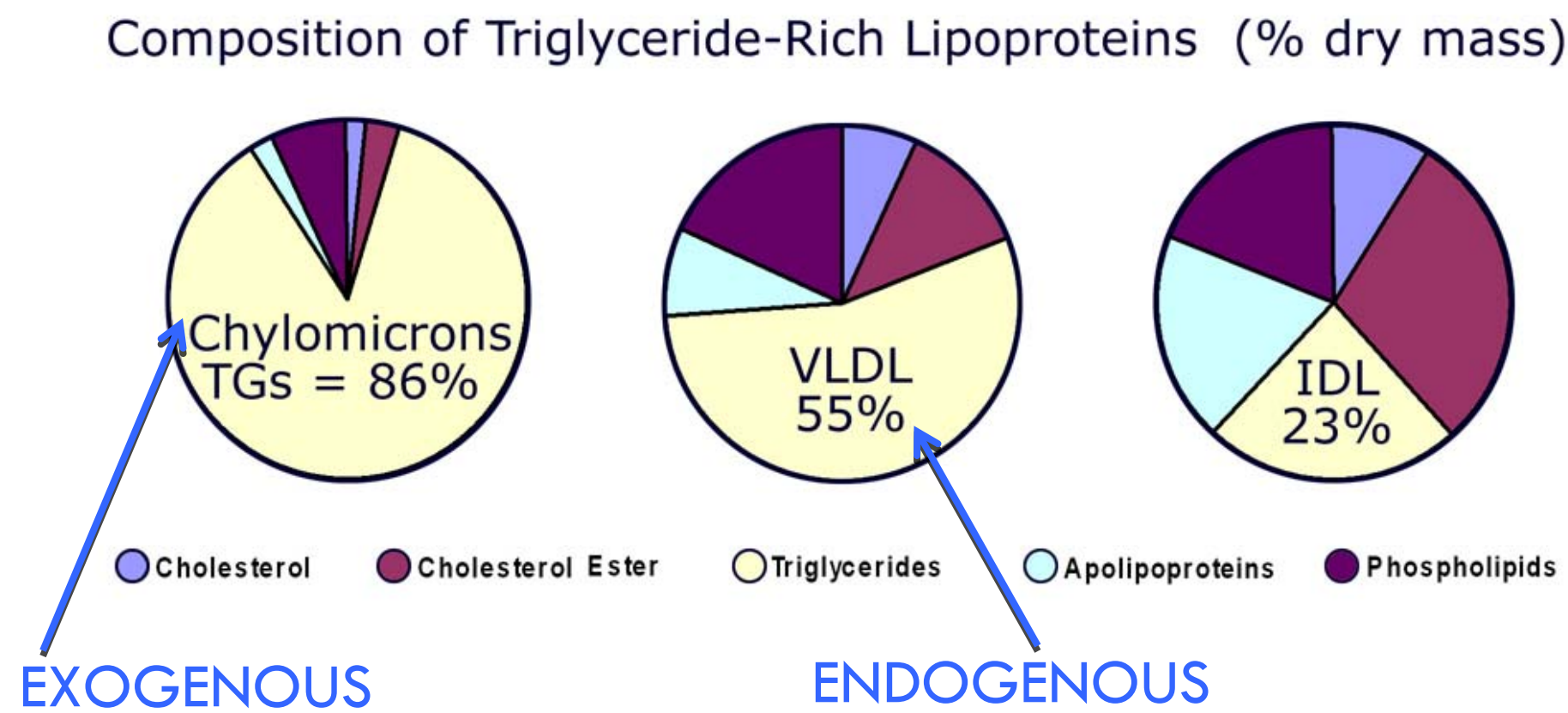
- Chylomicrons ⊙ Carry diet-derived lipids to the body
- VLDL ⊙ Carry liver-derived lipids to the body
- LDL ⊙ Carry cholesterol to the body
- HDL ⊙ Carry cholesterol back to liver

A Trip Back to Biochem. . .



TG = Glycerol + 3 Fatty Acids

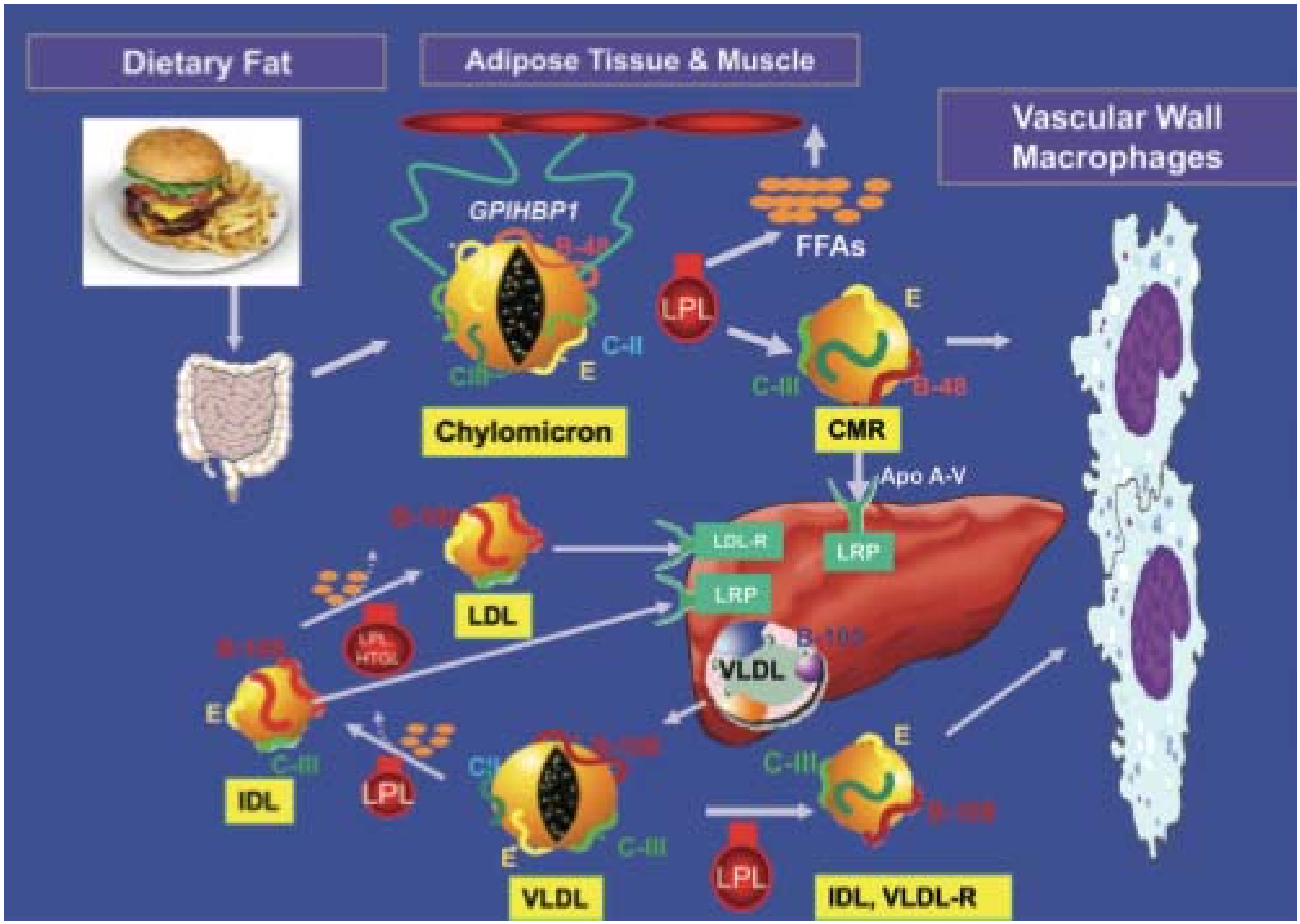
How are Triglycerides Carried?



[Medscape: Hypertriglyceridemia]

[Circulation –AHA Statement Triglycerides and CV Risk]

Triglyceride metabolism



1° Causes of HTG: Fredrickson Classification

Type	Synonym	Defect	Serum abnormality	Clinical Features	Treatment	Serum appearance
Type 1	Familial Hyperchylomicronemia	Low ~~LDL~~ LPL Altered ApoC2	Chylomicron ↑	Pancreatitis, Lipemia retinalis, skin eruptions, Xanthoma, Hepatosplenomegaly	Diet	Creamy top layer
Type IV	Familial Hyperlipemia	↑VLDL production, ↓elimination	VLDL↑		Statins, Niacin, Fibrate	
Type V	Endogenous hypertriglyceridemia	↑VLDL production, ↓LPL	VLDL & Chylomicron↑		Niacin, Fibrate	Creamy top layer & Turbid bottom

Type I : Exceedingly rare, TG > 1K, often > 10K

Type IV : Familial hypertriglyceridemia

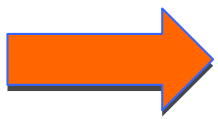
Type V : Assoc with DM

} TG > 1K

[Pedi Cardiology]

2° Causes of HTG

- Acute Hepatitis
- Alcohol
- CKD
- Glycogen Storage d/o
- High-carb diets
- Hypothyroidism
- HIV
- Ileal Bypass Surgery
- Multiple Myeloma
- Nephrotic Syndrome
- Obesity
- Pregnancy
- SLE
- Uncontrolled DM



2° Causes - DRUGS

Alpha-interferon

Atypical anti-psychotics

Beta-blockers

Bile Acid Resins

Estrogens (oral)

HIV anti-virals

Immunosupppressives

L-aspariginase

Retinoids

Propofol

Steroids

Tamoxifen

Thiazides

TPN

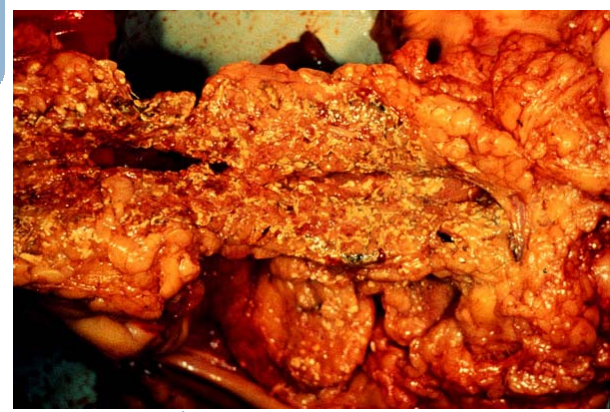
How high? (to cause pancreatitis. . .)

- A – over 500 mg/dL
- B – over 1000 mg/dL
- C – over 1500 mg/dL

How does HTG cause pancreatitis?

Chylomicrons/TG in plasma

Large size impairs blood flow



Degraded by Panc Enzymes

Release of FFA, Inflamm Med, and Free Radicals

Amylase/Lipase levels in HTGP

~Serum and urinary amylase level are spuriously low or normal

~Lipase levels tend to parallel amylase levels

~If serum is diluted, may be able to get a more reliable value

[HTG also falsely lowers measured Na levels]

ORIGINAL PAPER doi: 10.1111/j.1368-5031.2005.00645.x

Hyperlipidaemia and outcome in acute pancreatitis

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Department of Surgery,[1] Hepatobiliary Unit, Department of Clinical Biochemistry,[2] Manchester Royal Infirmary, Manchester, UK

	Alcohol-induced AP	*Non-alcohol AP*	*p-value*
Number of patients	14	29	
Mean (SEM) total cholesterol (mmol/l)	7.2 (2.2)	4.7 (0.3)	p = 0.97 (*U*-test)
Number with elevated cholesterol	8	10	p = 0.19 (Fisher's test)
Mean (SEM) HDL (mmol/l)	1.08 (0.2)	1.07 (0.1)	p = 0.95 (*U*-test)
Number with elevated HDL	2	3	p = 1.00 (Fisher's test)
Mean (SEM) Triglyceride (mmol/l)	3.07 (1.0)	1.26 (0.11)	p = 0.03* (*U*-test)

1000 mg/dL

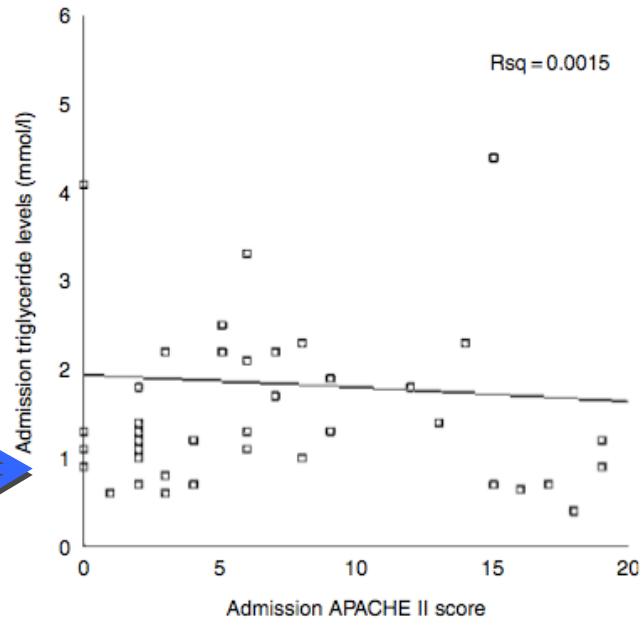


Figure 1 Scatter plot of admission triglyceride levels and admission APACHE II score

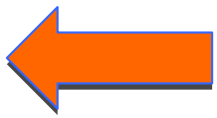
~Prosp. observational study

~43 pts with AP enrolled

~Sig difference in TG level in Etoh-induced vs. others

~No correlation with level of HTG and severity of AP

Overview

- Case Presentation
- Pathophysiology
- TREATMENT 

Behavioral Therapy

Table 11. Effects of Nutrition Practices on Triglyceride Lowering

Nutrition Practice	TG-Lowering Response, %
Weight loss (5% to 10% of body weight)	20
Implement a Mediterranean-style diet vs a low-fat diet	10–15
Add marine-derived PUFA (EPA/DHA) (per gram)	5–10
Decrease carbohydrates	
1% Energy replacement with MUFA/PUFA	1–2
Eliminate *trans* fats	
1% Energy replacement with MUFA/PUFA	1

TG indicates triglyceride; PUFA, polyunsaturated fatty acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; and MUFA, monounsaturated fatty acid.

[Circulation –AHA Statement Triglycerides and CV Risk]

Pharmacotherapy

Table 12. Effect of Lipid-Lowering Therapies on Triglyceride Reduction[504,480a–480d]

Drug	% Triglyceride Reduction
Fibrates	30–50
Immediate-release niacin	20–50
Omega-3	20–50
Extended-release niacin	10–30
Statins	10–30
Ezetimibe	5–10

[Circulation –AHA Statement Triglycerides and CV Risk]

What did we do for our patient?

- NPO
- Aggressive IVF
- Pain Management
- Anything else ?

(OK so this is a patient before his kidney transplant . . .)

PLASMAPHARESIS!!

ISSN 1007-9327 CN 14-1219/R World J Gastroenterol 2004 August 1;10(15):2272-2274

Therapeutic plasma exchange in patients with hyperlipidemic pancreatitis

Jui-Hao Chen, Jiann-Horng Yeh, Hsin-Wen Lai, Chao-Sheng Liao

Table 1 Demographic characteristics

	Group I (*n*=34)	Group II (*n*=60)	*P* value
Age (yr)	40.8±6.8	42.3±8.9	0.394
Initial TG	1 922±1 287	1 913±612	0.966
DM (%)	38(13/34)	55(33/60)	0.118
Alcohol (%)	44(15/34)	28.3 (17/60)	0.121
Ranson >3(%)	20.6(7/34)	36.7(22/60)	0.105
Balthazar D, E (%)	54.2(13/24)	41.3(19/46)	0.305

94 Patients with AP 2/2 Severe Hypertriglyceridemia

Group 1 – before 1999 – plasmapharesis unavailable

Group 2 - after 1999 – plasmapharesis available

ISSN 1007-9327 CN 14-1219/R World J Gastroenterol 2004 August 1;10(15):2272-2274

Therapeutic plasma exchange in patients with hyperlipidemic pancreatitis

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Table 2 Comparison of mortality and morbidity between patients before and after availability of plasma exchange

	Group I (%, *n*=34)	Group II (%, *n*=60)	*P* value
Mortality (%)	5.9(2/34)	6.7(4/60)	0.881
Systemic complications (%)	17.6(6/34)	18.3(11/60)	0.934
Local complications (%)	11.8(4/34)	6.7(4/60)	0.395

RESULTS:

NO CHANGE IN MORTALITY OR SYSTEMIC/LOCAL COMPLICATIONS

NO CHANGE IN COHORT OF PTS WITH SEVERE PANCREATITIS

CAVEAT:

PLASMAPHARESIS PERFORMED ~3 DAYS AFTER PRESENTATION

Studies on Plasmapharesis

Overview of the currently available studies (≥10 patients) on the use of apheresis in severe HTG

Author	Kyriakidis et al, 2006 [12]	Yeh et al, 2003 [13]	Yeh et al, 2003 [14]	Chen et al, 2004 [15]	Gubensek et al, 2009 [16]
Number of Patients included	10	18	17	20 74 control	50
Triglyceride levels	significantly reduced	significantly reduced, by 62%	significantly reduced by 66% (1. setting) and 83% (2. setting)	reduced by 66%	significantly reduced
Outcome	8 in good condition, 1 required surgery, 1 died	All in good condition	13 good condition, 2 required drainage 2 died	3/20 vs 3/74 died; p=n.s. Systemic and local complications comparable	5/50 died (Mortality 4% if APACHE II <8, 42% if APACHE II >8)
Method	Plasma exchange (FFP)	Plasma exchange (FFP and albumin) and Double membrane filtration	Plasma exchange (FFP and albumin)	Plasma exchange (FFP and albumin)	Plasma exchange (albumin)

GOOD OUTCOMES WITH PLASMAPHARESIS WITH FEW AE
SUGGESTS TIMING OF APHERESIS IS IMPT –
IDEALLY DONE **WITHIN 48 HOURS** OF DX

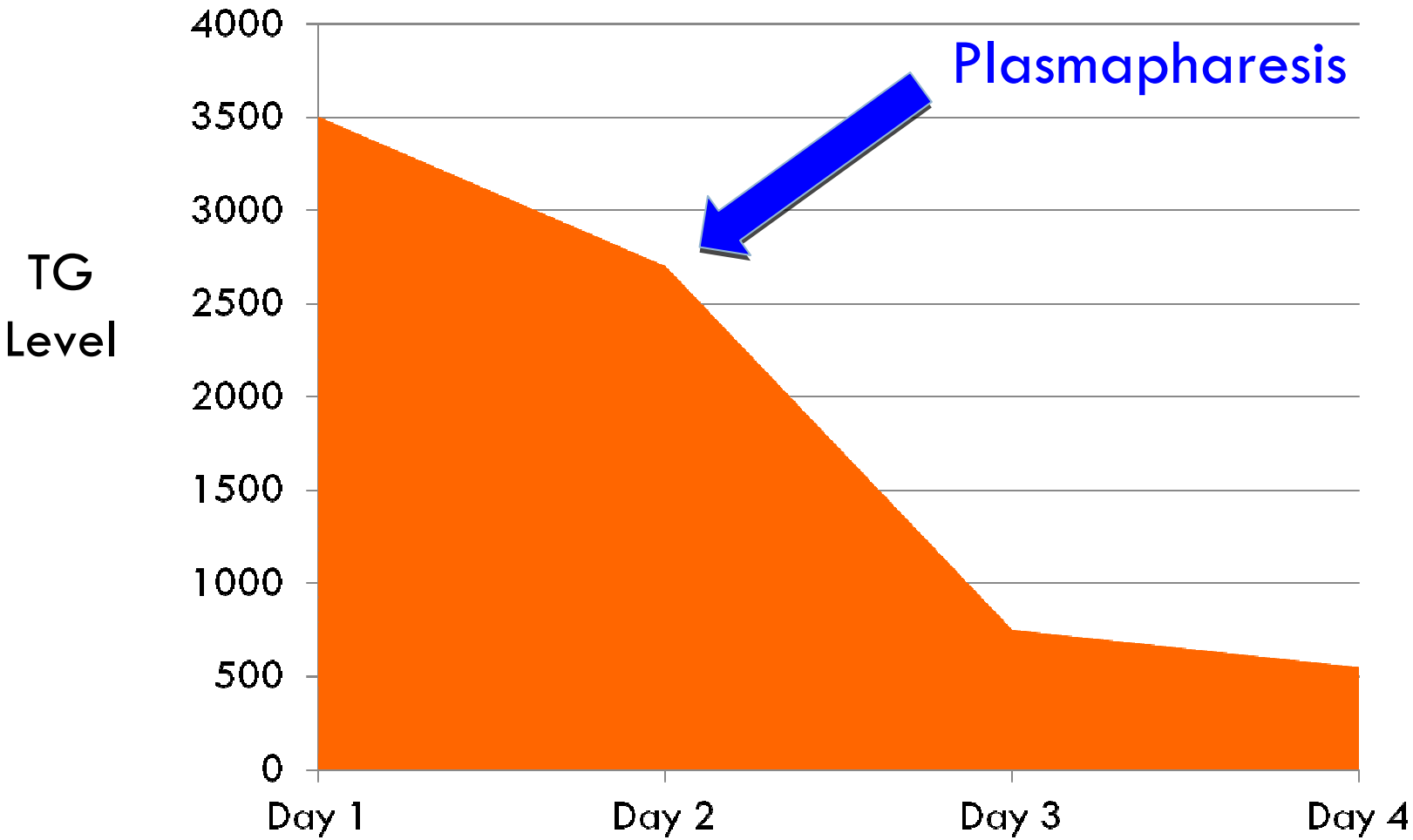
[Ewalk, Kloer Atherosclerosis Supp 10 (2009)]

Plasmapharesis Considerations

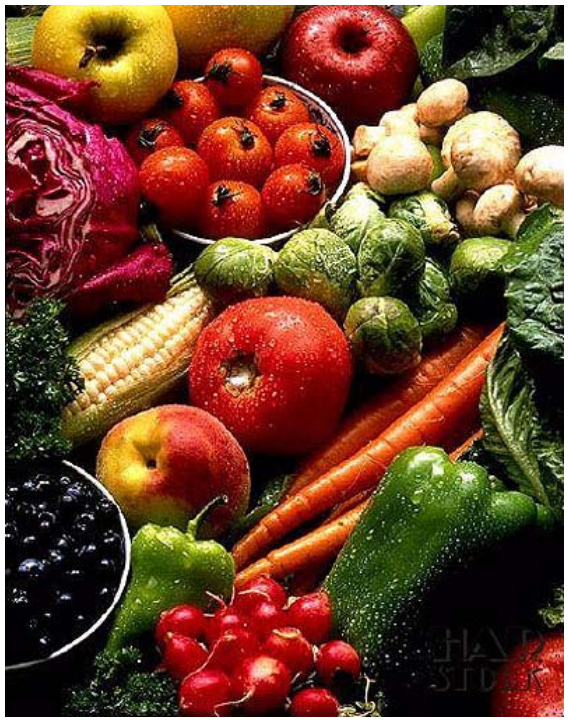
- Double-membrane filtration vs plasma exchange
- In general, 2-3L plasma are removed
- Fluid replacement with FFP vs albumin
- Single versus multiple sessions
- Also been used for prevention with some success

- AE: limited, generally safe

F/U on Case Presentation



2 Days After Plasmapharesis . . .



EATING LOW-FAT/HIGH-FISH DIE

5 Days Post-Plasmapharesis

HOME!!!

Other therapies

- IV Insulin
  - Activates LPL (accelerates chylomicron degradation)
  - For any diabetic patient
  - Goal to maintain euglycemia rapidly
  - Consider gtt
- Heparin
  - Stimulates release of LPL into circulation, but then increases hepatic degradation of LPL
  - Controversial

Medium Chain TGs (MCTs)

- 6-12 Carbons on 2/3 of the Fatty Acids
- Passively diffuse from GI tract to Portal System
- Avoids the rise in TG levels associated with dietary intake of TGs
- May have an adjunct role with fish oils

2 months later →

- Diagnosed with non-obstructive jaundice
- AST 350 , ALT 400 , TB 6
- What happened?

SUSTAINED-RELEASE NIACIN

SIGNIFICANT AE:

A: HEPATOTOXICITY!
must dc the drug

Niacin and the Liver

Table 4
Pathways and potential of niacin toxicity by formulation

Formulation	Primary metabolic pathway	Toxic metabolites produced or toxic process initiated	Toxicity potential	
			Hepatotoxicity	Cutaneous flushing
Immediate release	Conjugation	Prostaglandins	Extremely low	High
Extended release	Conjugation > amidation	Prostaglandins > nicotinomide and pyrimidine metabolites	Low	Low
Sustained release	Amidation	Nicotinomide and pyrimidine metabolites	High	Very low

[Bhardwaj and Chalasani Clin Liver Dis 11(2007) 597–613]

Lipid Lowering Agents and Heptatotoxicity

Lipid-lowering agent or class	Mechanism of action	Typical pattern of biochemical derangement	Typical histologic appearance of injury	Avg. length of use before injury	Avg. recovery time	Hepatotoxicity potential
Statins	Inhibits HMG-CoA reductase (involved in cholesterol synthesis)	Hepatocellular (although cholestatic and mixed injury are seen as well)	Few cases have shown inflammation of portal tracts with mild piecemeal necrosis and mild, focal periportal fibrosis	Often within first several months	2–3 months (but usually within 10 weeks)	Serious liver injury is very rare
Niacin (especially SR formulation)	Decreases hepatic TG esterification and LDL/VLDL production	Mostly hepatocellular but may be mixed injury	Generally varying patterns of necrosis, but may also include centrilobular cholestasis or steatosis	1 week–48 months	1–2 months	Common with SR formulation but rare with IR or ER
Fibrates (especially fenofibrate)	Inhibits hepatic TG synthesis; decreases hepatic FFA extraction (gemfibrozil)	Hepatocellular injury (especially with gemfibrozil) but mixed pattern of injury seen with fenofibrate	Fenofibrate can cause ductopenia, chronic hepatitis, and fibrosis (especially in combination with statin medications)	ND	ND	Serious liver injury is very rare
Ezetimibe	Inhibits absorption of cholesterol at small intestine	Rare cholestatic hepatitis or acute autoimmune hepatitis	n/a	ND	ND	Very low, but seen in higher frequency than previously thought

Abbreviations: ER, extended release; FFA, free fatty acid; IR, intermediate release; LDL, low-density lipoprotein; n/a, data not available; ND, inadequate patient data to reliably quantify; SR, sustained release; TG, triglyceride; VLDL, very low-density lipoprotein.

[Bhardwaj and Chalasani Clin Liver Dis 11(2007) 597–613]

Statins and the Liver

Box 1. Summary of recommendations of the liver expert panel to the National Lipid Association on statin safety

- Asymptomatic increases in aminotransferases are a class effect of statins, and they do not indicate liver dysfunction.
- Liver failure causing death or hospitalization or requiring liver transplantation is very rare from statins.
- Current evidence does not support routine monitoring of liver enzyme levels and liver biochemistries in patients receiving statins.
- Presence of chronic liver disease and Child's A cirrhosis should not be considered a contraindication for statin use.
- Current evidence supports the use of statins to treat hyperlipidemia in patients who have nonalcoholic fatty liver disease and nonalcoholic steatohepatitis.

From Vuppalanchi R, Chalasani N. Statins for hyperlipidemia in patients with chronic liver disease: are they safe? Clin Gastroenterol Hepatol 2006;4(7):838–9; with permission.

THE END ☺