Peri-operative Optimization: Does It Really Improve Outcome ?

Philadelphia Academy of Surgery

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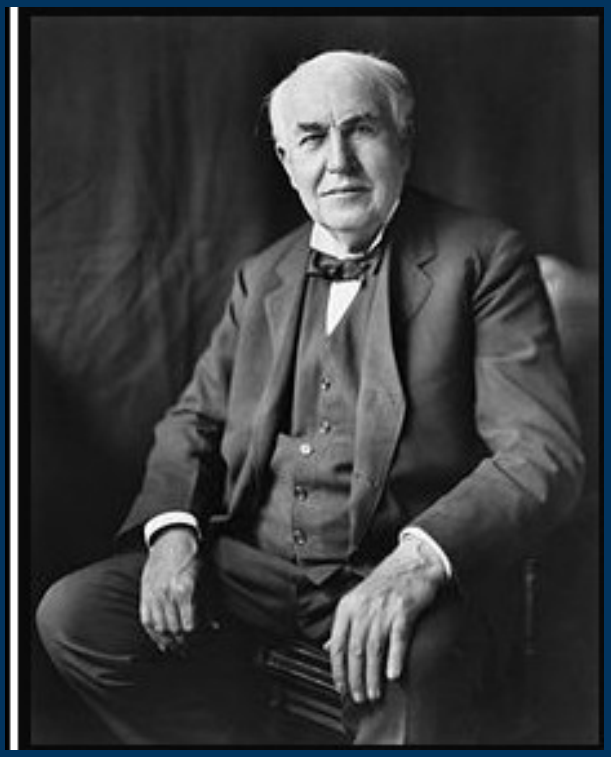
What procedures are *high risk* and have existing data to support pre-op risk reduction plan?

- Complex or re-operative colorectal (20-30%)
- Major UGI surgery (gastric, esophageal) (11-22%)
- Abdominal wall reconstruction (18-38 %)
- Pancreatic (14-22%)
- Major hepatobiliary
- Major head and neck surgery (>T3 lesions)
- GU (ex:cystectomy, prostatectomy, nephrectomy)
- Major re-operative or trauma orthopedics
- Bariatric procedures (GB, Sleeve)
- Spine procedure with hardware placement
- Major cardiothoracic
- Others selective by individual patient / procedure

Missed Opportunity to Improve Surgical Outcomes:
It is not easy to make changes !

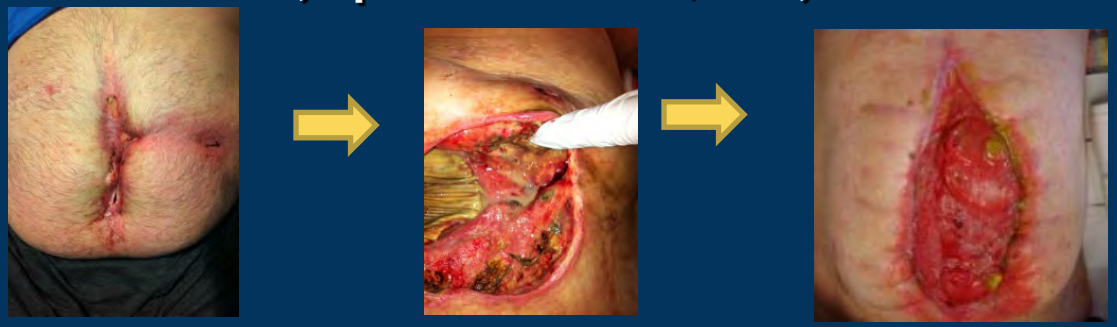
- **"Opportunity is missed by most people because it is dressed in overall and looks like work."**

  – Thomas Edison



Is optimization worth the effort ?
Example: Surgical Site Infections

- SSI: Incidence: 2.6 to 6% of all operations
  - Up to 20-30% for complex CRS, AWR, Pancreatic surgery
  - *S.aureus* is most common bacteria (30%)
    - » 70% will be resistant to at least one antibiotic
    - » MRSA responsible 23,000 deaths and 375,000 infections 2013
  - Infection increases length of hospital stay (mean of 7.3 days)
  - Patients who develop SSI 60% more likely to need ICU
  - 5 x increase risk of readmission to the hospital
  - Economics: Additional cost of SSI in ventral hernia repair
    - Minor superficial infection $ 400
    - Mesh infection $ 21,000 to 63,000
    - EC fistula, open abdomen $ 211,000



Alexander JW et al Ann Surg 2011 Kavanah KT 2014 Mangram AJ et al. 1999
.Bratzler DW CID 2004 Martindale, RG OHSU Database 2013 Savage JW 2013

Optimization of Outcome in Surgery: Phases of care

- Pre-op

- Immediate peri-op and intra-op

- Post-op

Surgeon Modifiable Factors for Preventing Complications "Protocols"

Pre-op

- Glycemic control
- Smoking cessation
- Clearing MRSA
- Nutrition
  - Metabolic prep (Arg/FO)
- CHO loading
- Weight loss
- Cardiac clearance
- Pulmonary
- Exercise

"prehabilitation"

Immediate Peri-op

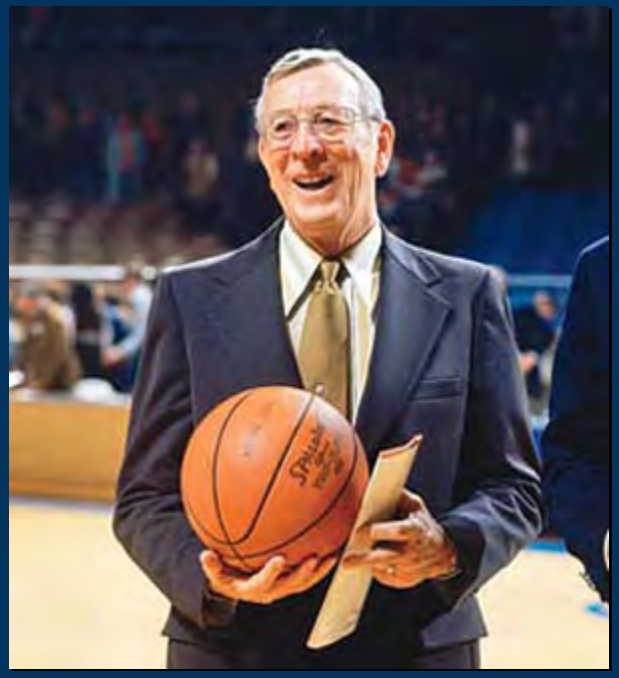
- Skin prep selection
- Antibiotics
- Glycemic control
- Intraop warming ?
- Elevated FiO_2 ?
- Suture choice
- Techniques
  - Halsted principles
  - Drains

Post-op

- DVT prevention protocol
- Resistance exercise
- High protein intake
- Early enteral feeding
- Prevention C.diff, AAD
- NPWT

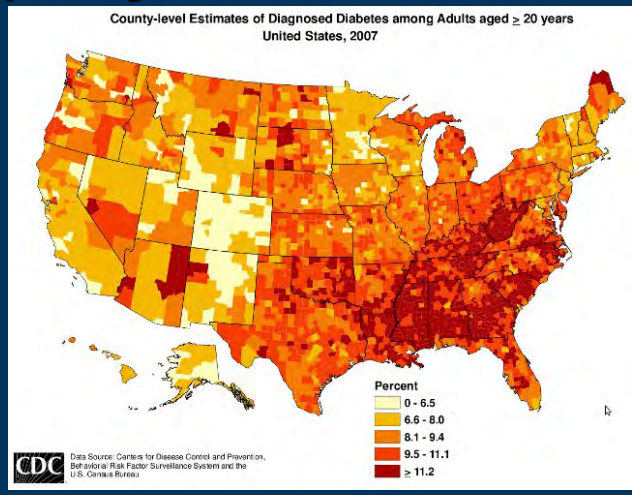
“Failure to prepare is preparing to fail”

John Wooden
UCLA Basketball

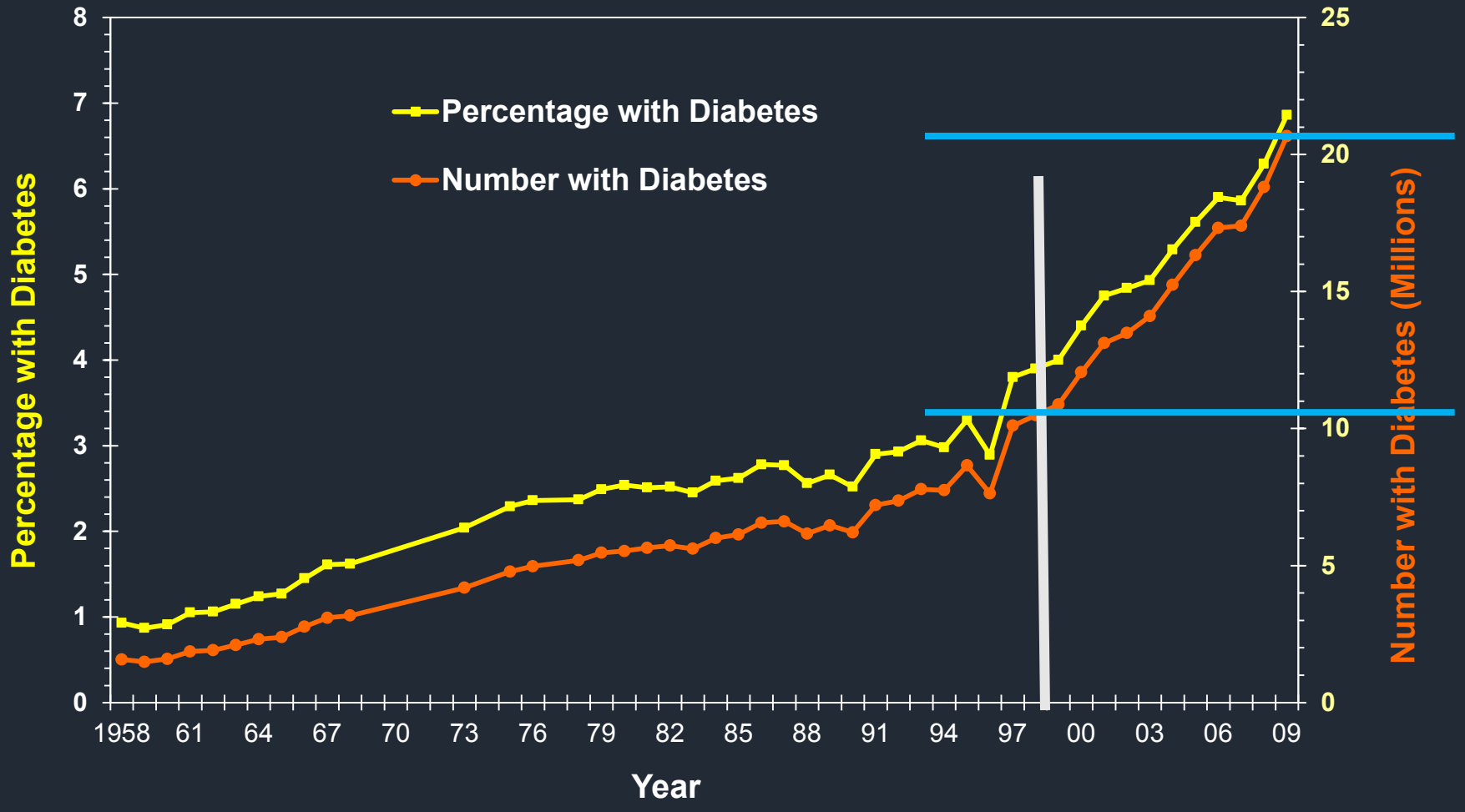


Perioperative Glycemic Control

- 25 million Americans have diabetes
- Another 7 million are unaware that they have the disease
- At least 25% of diabetic patients will require surgery.
- Mortality rates are 5 times greater than in non-diabetic patients, often related to the end-organ damage
  - microangiopathy (retinopathy, nephropathy, and neuropathy)
  - macroangiopathy (atherosclerosis)

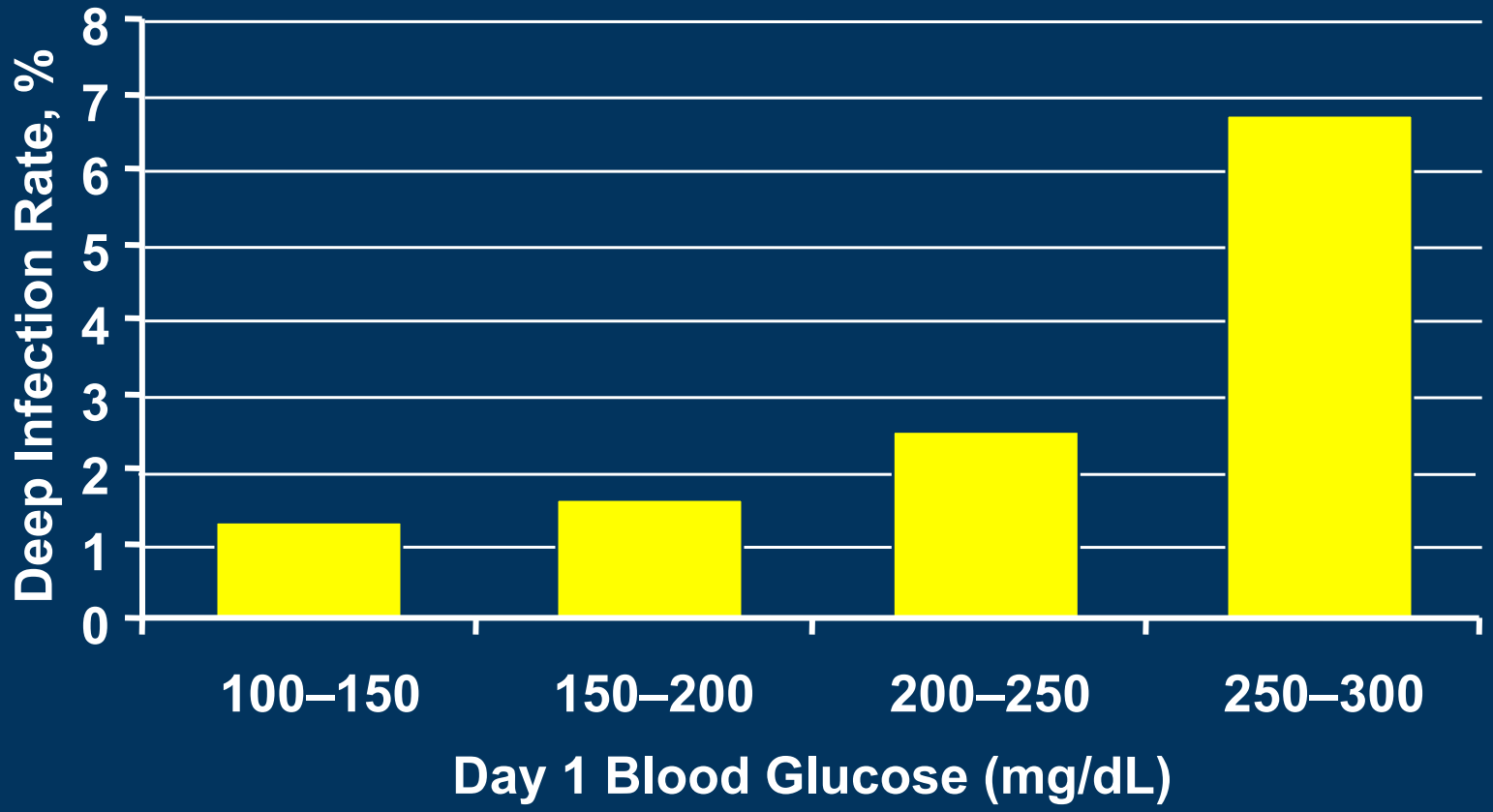


Number and Percentage of U.S. Population with Diagnosed Diabetes, 1958-2009



CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at http://www.cdc.gov/diabetes/statistics

SSIs and Glucose Levels in immediate post-operative period



Kerr KJ Ann Thor Surg 1997

SSIs and Glucose Levels

- **Incidence of SSI** [1] (N=>1000 CT surg patients)
  - Diabetes (known and undiagnosed) 5.8% (20/342)
  - Without diabetes 1.5% (10/658)
  - Diabetes with HbA1c ≥8% 7.9% (10/126)
  - Diabetes with HbA1c <8% 4.0% (7/174)

- **Post op infection increase by 30% for each 40 mg/dl over 110** [2] (general and vascular pts)

- **What are the mechanisms**
  - Glycosylation of proteins
  - Macrophage / neutrophil function
    - » Chemotaxis
    - » Oxidative burst
    - » phagocytosis
    - » Bacterial recognition
    - » Etc etc etc

1. Latham NEJM 2004
2. Ramos Ann Surg 2008

Peri-op glucose recommendations

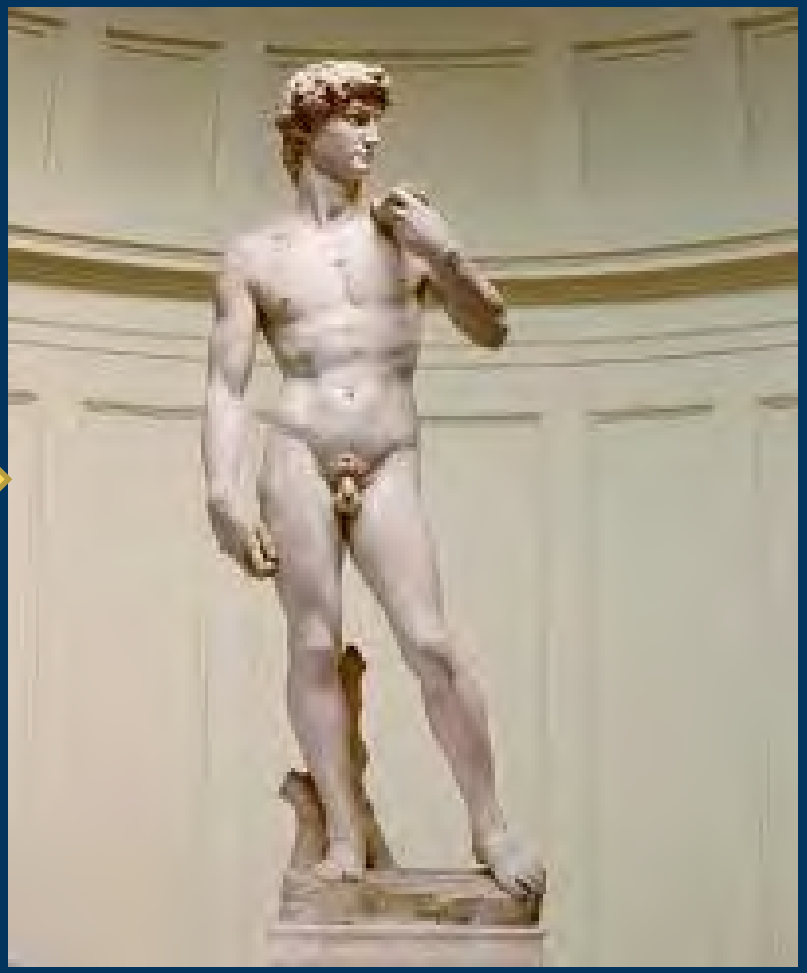
- **Recommendations:**
  - Remote pre-op setting (30 to 60 days preop)
    - Measure HbA1c with preop labs in high risk patients
    - If > 8.0 significant evidence to support postponing surgery for better control (> 7.5 infection curve rises sharply)
    - High risk surgical populations:
      - Bariatric, vascular, cardiac, AWR, obese
  - Immediate peri-op and post-op period
    - Target between 140 and 180 mg/dl is safe and rarely results in hypoglycemia
      - NSQIP suggests post op bit lower < 130mg/dl
      - N=11,633
    - Sweet spot 120 to 140 mg/dl

Marfalla, R JCEM 2012
Scopinaro, N Obes Surg 2011
Marsala, M J Cardiothor Vas Anes 2011
Moghissi, ES Am J Health Sys Pharm 2010
Kwon, S Ann Surg 2013

Proposed T2 DM Preop Management

- **Minor surgery, T2DM well controlled:**
  - No change in Rx
- **Major surgery, T2DM well controlled (Hb1Ac ≤ 6.5) :**
  - No oral medications on operative day, return to regimen promptly
  - If on insulin, halve dose operative day
  - Bring glucose levels to 120 – 160 mg/dl
- **Major surgery, T2DM not controlled:**
  - Delay surgery until glucose is between 120 -160 mg/dl
- **Emergency surgery:**
  - Apply short-acting insulin infusions, monitor closely (target 120-160mg/dl)
- **Very high glucose values (400-500 mg/dl):**
  - Address the underlying problem, i.e. an abscess, a leak, pulmonary infection, titrate with short acting insulin

Pre-operative weight loss ?



Ex: 63% of AWR's done in the obese (NSQIP database)
AWR in obesity increases risk of complications

surgical complications, wound complications, return to OR, renal, thromboembolic

(Pre-op data only available for bariatric surgery, no Level 1 data)

Nelson JA et al Am J Surg 2014
Bachler T et al Dig Surg 2014

CONGRATULATIONS
YOUR WEIGHT
IS NOW
STABLE

USA

USA Today 10-18-13

USA TODAY
FRIDAY, OCTOBER 18, 2013

NATION

Obesity rate in USA levels off

More than a third of adults are 35 pounds over a healthy weight

Nanci Hellmich
USA TODAY

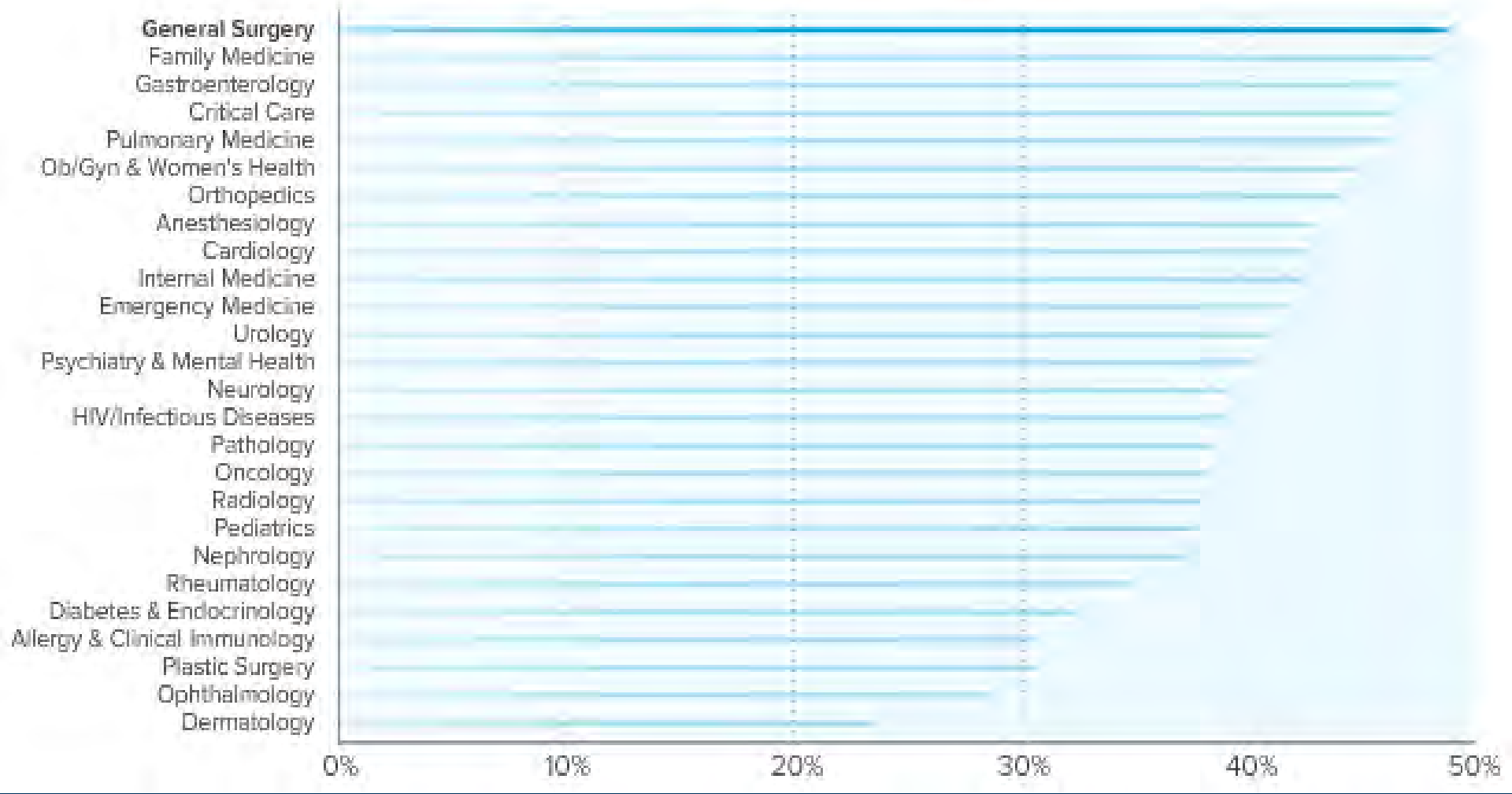
Obesity among U.S. adults is continuing to level off after several decades of skyrocketing growth, new government data show.

In 2012, about 34.9% of the people in this country were obese, which is roughly 35 pounds over a healthy weight. That is not significantly different from the 35.7% who were

OBESITY OVER TIME
Percentage of adults who were obese in:

to continue to create smart
to address this health probl
There has been no
change in obesity rates
when the obesity rate
32%, Ogden says.
The prevalence of
creased dramatically in
and 1990s after being re
ble in the USA betwee
1980 when about 15% c
into the category.
The latest statistics d
obesity rates for childre
cents, but there has be
cation in recent CDC
those rates have leveled
This new analysis is
from the National He
tion Examination Su
considered the gold

Which Physicians Are the Most Overweight?



Pre-op: Smoking Cessation

- **Benefit mostly shown in orthopedic / spine / plastics literature**
  - Data mixed in GS population 1990's vs 2000's literature
  - Timing of "last" cigarette is key
  - Cochrane analysis 2005 no specific effect
  - Cost of care increases for smokers vs never smokers
- **Clearly decreases collagen deposition**
  - Jorgensen LN, APMIS 2003;115:1-56, ePTFE human model
- **Prospective trial smoking abstinence [1]**
  - 228 incisional wounds (4 groups)
  - Non-smokers, smokers, abstinent +/- nicotine patch
  - Wound infection 12 vs 2 % with 4 wks of abstinence

- **Prospective trial [2]**
  - Wound complications 21% in non-smokers vs 41% in smokers
  - ITT analysis NNT to decrease complications =5
- **Periop surgery counseling is "teachable moment"**
- **Nicotine replacement "ok"**
- **Electronic cigarettes in question ?**

Sorensen LT et al Ann Surg 2003
Lindstrom D Ann Surg 2008
Mastracci TM JACS 2011
Goniewicz, ML BJS 2013
Khullar D JACS 2013
Warner DO JAMA 2014
Ann Int Med 2014

Where does nutrition fit into *surgical risk reduction* ?

- Appropriate and timely nutrition therapy can:
  - Attenuate the loss of lean body mass during stress
    - Fewer DVT, PE, less pneumonia, off ventilators (not proven)
    - Out of hospital earlier, less need for post D/C SNF
  - Early enteral nutrient delivery can:
    - Decrease mortality
    - Decrease infectious complications
    - Maintain mucosal barrier
    - Attenuate the metabolic response to surgical stress
  - Specific nutrients have a myriad of beneficial effects
    - Membrane stability, mucosal maintenance, etc etc
    - Decrease morbidity and mortality reported with;
      - » Fish oils, Arginine, Antioxidants , Glutamine ?
  - Probiotics
    - Decrease AAD, C.diff, VAP ! Maybe even anastomotic leaks ?

Martindale RG et al JPEN 2013
McClave S, Martindale RG CCM 2014

30 Day Hospital Readmissions: What role does nutrition play ?

(large database study in general surgery patients)

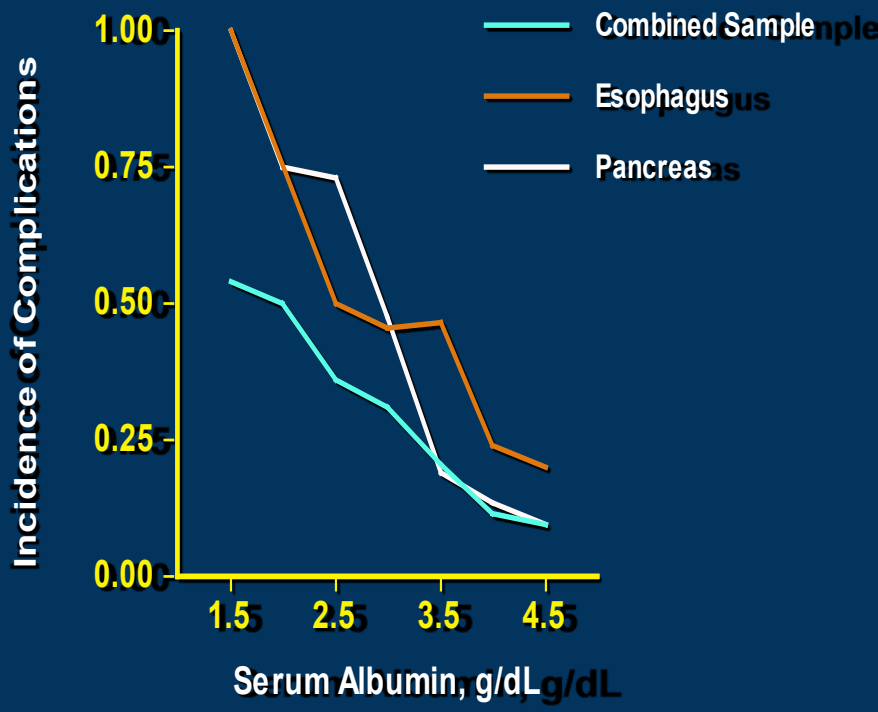
- Readmission is focus of payors, patients, and providers
  - Recently shown from 11 million Medicare beneficiaries 15.6% of patients are readmitted postop
- 27% GI complications
  - Prolonged ileus
  - Anastomotic leaks
  - Early post-op bowel obstruction vs PO ileus
- 19% MalNutrition related
  - Unable to maintain PO intake
- 21% Surgical site infections
  - Infection related complications
    - Wound breakdown etc.

Kassin MT et al JACS 2012
Kelly KN et al J GI Surg 2014

Predicting the high risk surgery patient

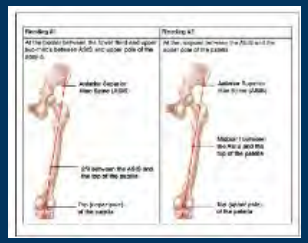
- **VA Preoperative Risk Assessment Study:**
- 87,078 pts / 67 variables
- Prospective data, 44 medical centers
- Albumin available in 61%
- Mean age 60.1 yrs
- 30 day mortality 0.67-5.9%
- Conclusion:
  - **Pre-operative albumin is single best predictor of overall operative risk**

J Amer Coll Surg 185:315-327, 1997



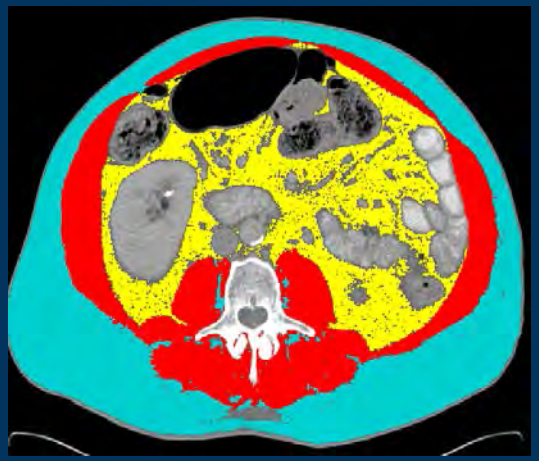
Kudsk K JPEN 2003

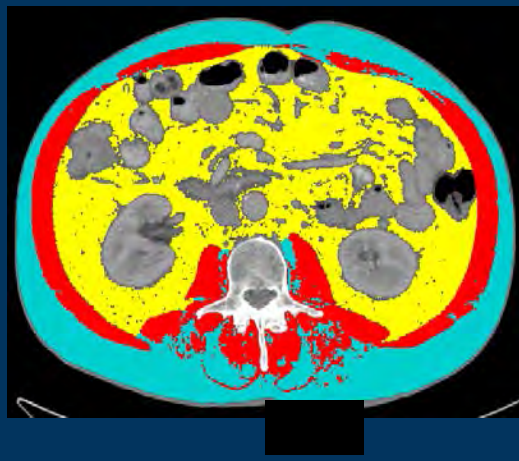
Body composition



Tillquist M JPEN 2013

The coming assessment tool !





"Impact of sarcopenia on outcomes"

Pancreatic surgery (1)

- N=557 pts
- Sarcopenia independently associated with mortality

Other diseases now have associated outcome and body composition.

Colorectal Ca, lymphoma, esophageal Ca, elderly trauma ICU, AWR ?

1) Peng P J GI Surgery 2012
2) Moisey LL CC 2013

Do we have PRCT evidence to support “pre-op Nutrition” ?

- Jie B et al
  - Nutrition 2012
  - Prospective Multicenter cohort study n=1085
  - Pre-op Nutrition therapy NRS-2002 (n=512 at risk)
  - 102 with NRS ≥ 5
  - Results
    - In NRS ≥ 5 complications ↓ 50.6 vs 25.6 %
    - In NRS ≥ 5 length of stay ↓ 17 to 13 days
    - No benefit in NRS < 5

Jie B et al Nutrition 2012

Peri-operative metabolic manipulation to improve outcome: fact or fantasy ?

- 35 articles met inclusion criteria
- Compared pre and post op vs pre op or post op alone
- Results: Arginine – Fish oil containing solutions
  - Significant reduction in overall infections
  - Significant reduction in hospital stay
  - Subgroup analysis shows consistent treatment effect regardless of type of surgery
  - Infection rates varied between formula types
    - +/- fish oils altering Arginase 1
  - No decrease in mortality
  - Greatest effect when given pre and post operatively

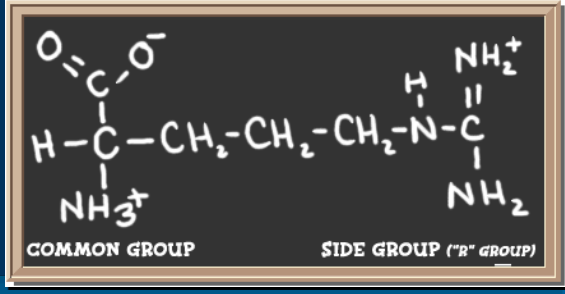
Drover J. Heyland D. et al JACS 2011

The Most Recent of the 9 Meta-analysis published on metabolic modulation in surgery: Immune and metabolic modulating formula in open GI surgery (meta-analysis)

- Analysis of 26 RCT (2496 patients)
  - Isonitrogenous / isocaloric formulations
  - Open GI surgery
  - GRADE system used to stratify quality of studies
- Results:
  - 5-7 days required to show benefit
  - 26/26 reported infectious complications (↓ 36%)
  - 20/26 reported non-infectious complications (↓18%)
  - 20/26 reported length of stay (↓LOS)
  - 26/26 reported no benefit in mortality

Marimuthu K et al Ann Surg 2012

Arginine Supplementation: Metabolic Manipulation

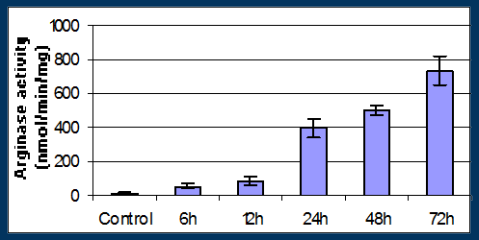


- **Animal Models**
- ↑ survival in sepsis
- ↑ survival in tumor bearing
- ↑ number and function of T cells
- ↑ delayed hypersensitivity
- ↑ allograft rejection
- ↑ macrophage phagocytic activity

- **Human Studies**
- Improved wound healing
- Net nitrogen retention during critical illness
- Enhanced lymphocyte proliferative response to mitogens
  - 70 fold increase in arginine uptake with stimulation
- Necessary for normal myeloid cell function
  - Macrophages, dendritic cells
- ↓ Clinical infections
- ↓ Postop length of stay

Post op arginine deficiency alters T-cell function

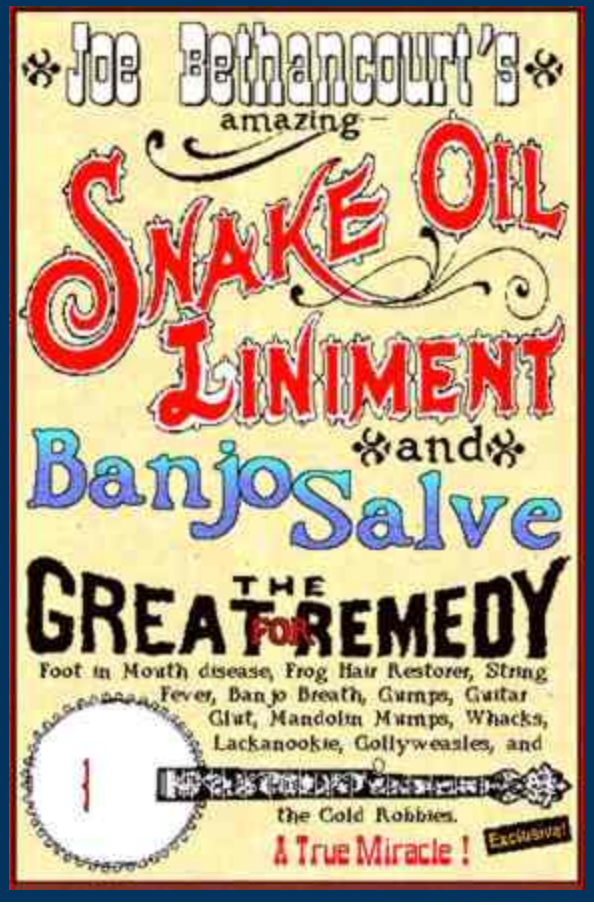
- Arginine Deficiency
  - Rapidly develops following injury or surgery
  - Primarily secondary to increase in Arginase I



- T-cell dysfunction
  - Decrease T-cell receptor with loss of zeta chain
  - Decrease production of interferon gamma
  - Anergy to recall antigens
  - Decrease immunologic memory

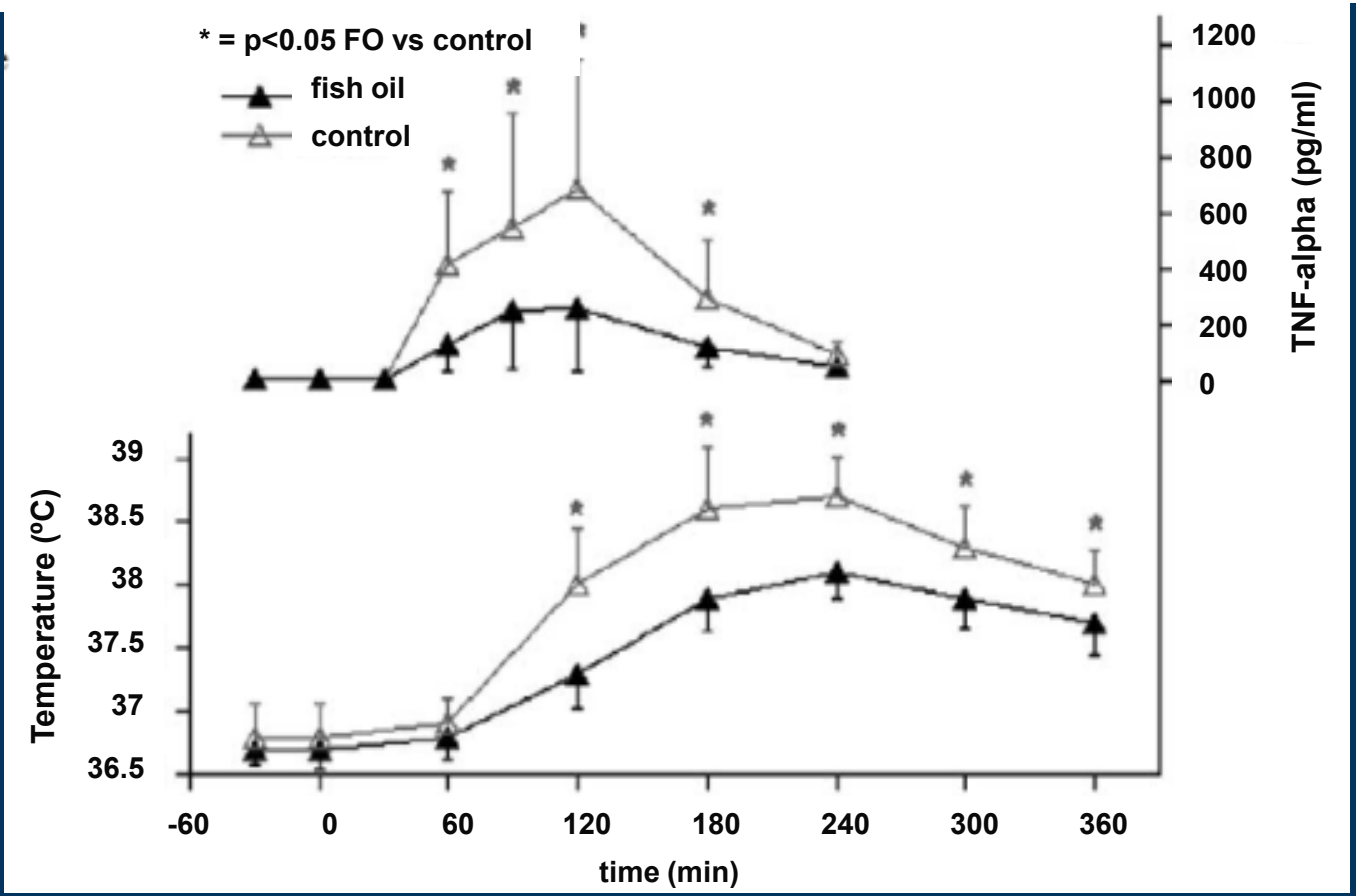
Zhu X et al Ann Surg 2013

Fish oil to lower the metabolic response to stress?



Thomas-Thi Pluess
Daniel Hayoz
Mette M. Berger
Luc Tappy
Jean-Pierre Revelly
Burkhard Michaeli
Yvon A. Carpentier
René L. Chioléro

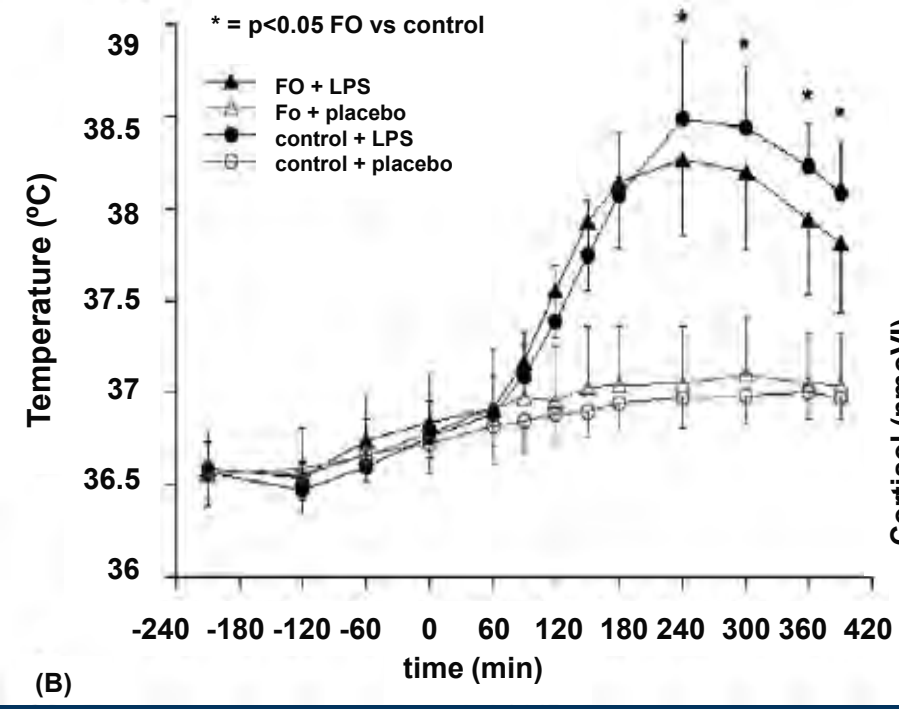
Intravenous fish oil blunts the physiological response to endotoxin in healthy subjects

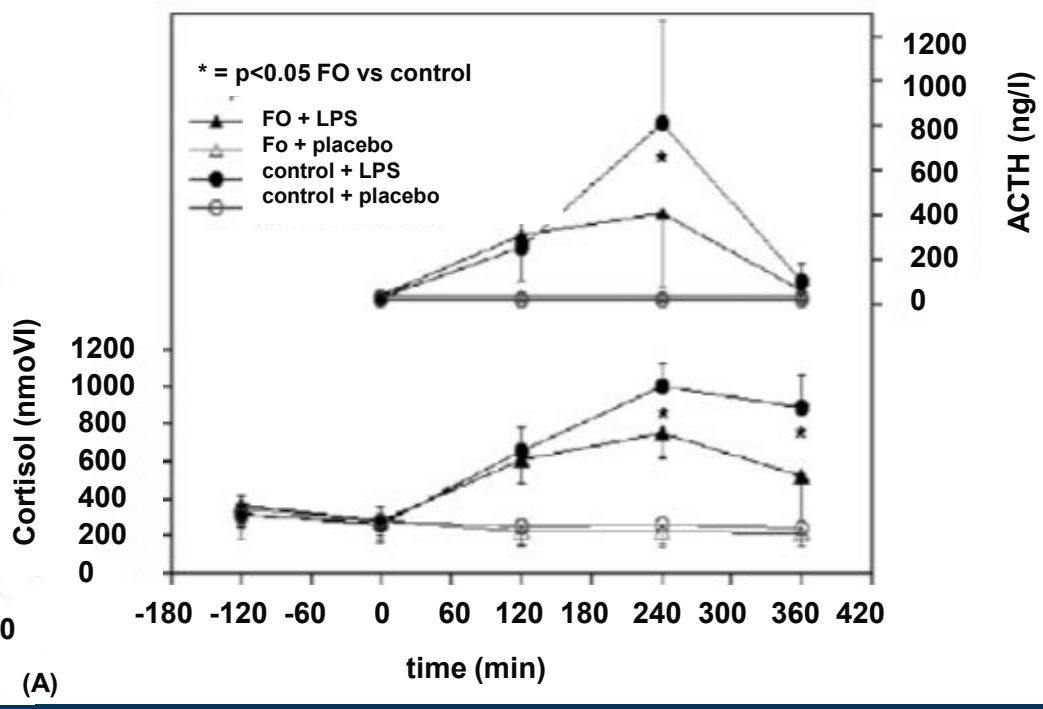


Intensive Care Med (2007 33:789-797

Effects of fish oil on the neuro-endocrine responses to an endotoxin challenge in healthy volunteers ☆

Burkhard Michaeli[a], Mette M. Berger[a,*], Jean-Pierre Revelly[a], Luc Tappy[b], René Chioléro[a]





Michaeli B. Clin Nutrition (2007) 26, 70-77

Three short perioperative infusions of n−3 PUFAs reduce systemic inflammation induced by cardiopulmonary bypass surgery: a randomized controlled trial[1–3]

Am J Clin Nutr 2013

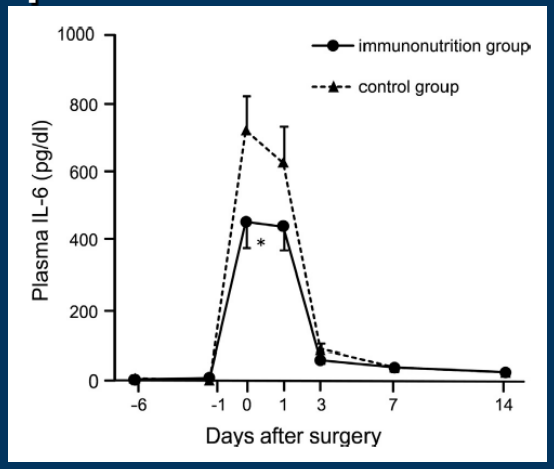
- PRBCT Evaluation influence of FO infusion in immediate peri-operative period in CABG
  - N=28 equal groups
  - Three 2 hour infusion with/in 12 pre-op period
  - Results: FO showed;
    - Pilot study not powered for clinical outcome
      - No change in mortality, clinical outcome, endogenous glucose production
    - Trend toward decrease APACHE, SOFA
    - Improved glycemic control
    - Decrease in lactate
    - Decrease in IL-6

Berger M et al Am J Clin Nutr 2013

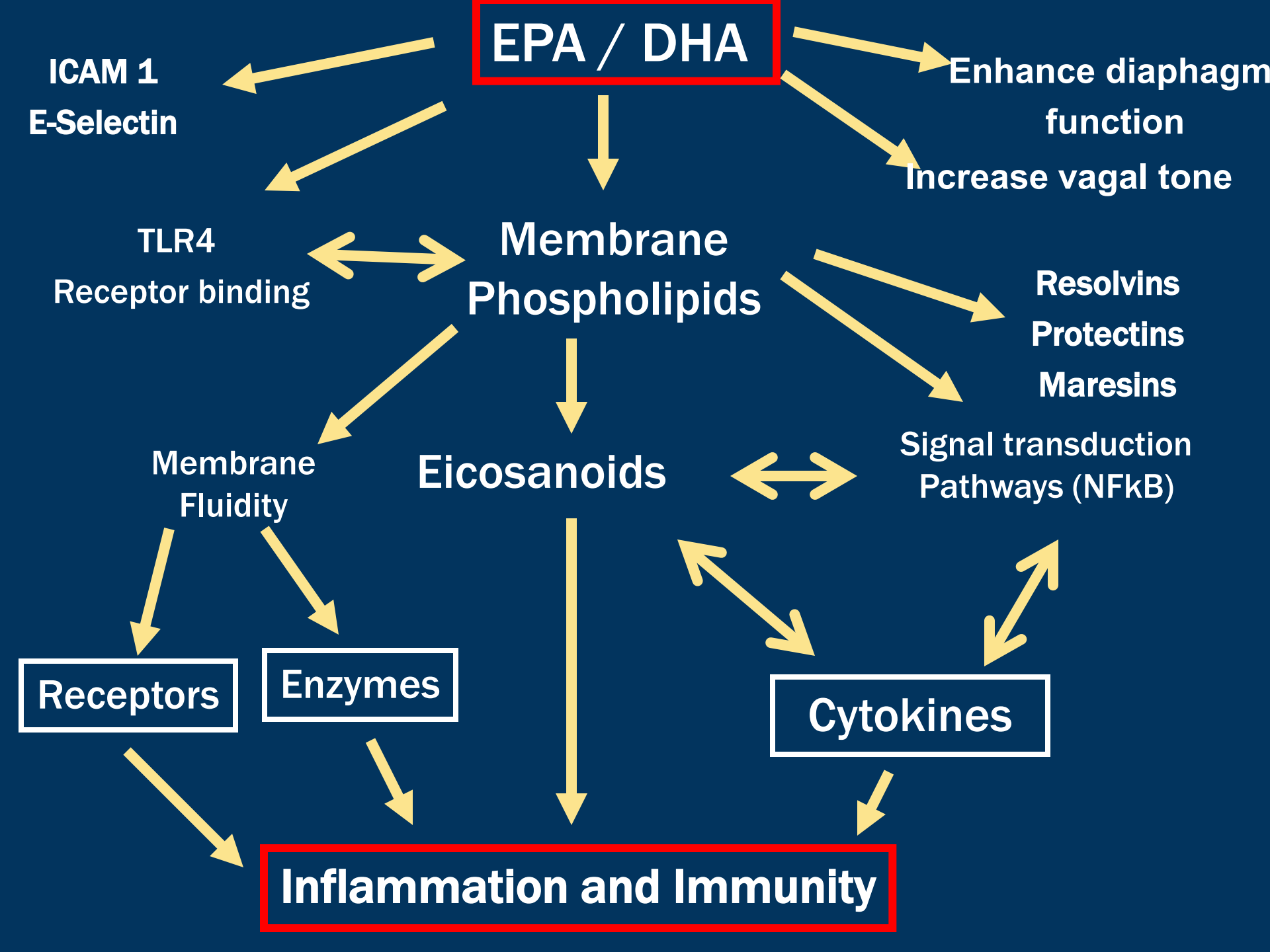
Preoperative immunonutrition decreases postoperative complications by modulating prostaglandin E_2 production and T-cell differentiation in patients undergoing pancreatoduodenectomy

Surgery 2014

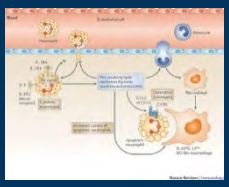
- N=50 RCT
  - PO 5 days preop
- Outcome
  - Attenuates metabolic response to surgery
  - Decrease infection
  - Decrease severity of complications



Aida T et al Surgery 2014


EPA / DHA
ICAM 1
E-Selectin
Enhance diaphagm function
Increase vagal tone
TLR4
Receptor binding
Membrane Phospholipids
Resolvins
Protectins
Maresins
Membrane Fluidity
Eicosanoids
Signal transduction Pathways (NFkB)
Receptors
Enzymes
Cytokines
Inflammation and Immunity

Resolvins, Lipoxins, Protectins, Maresins (SPM's)



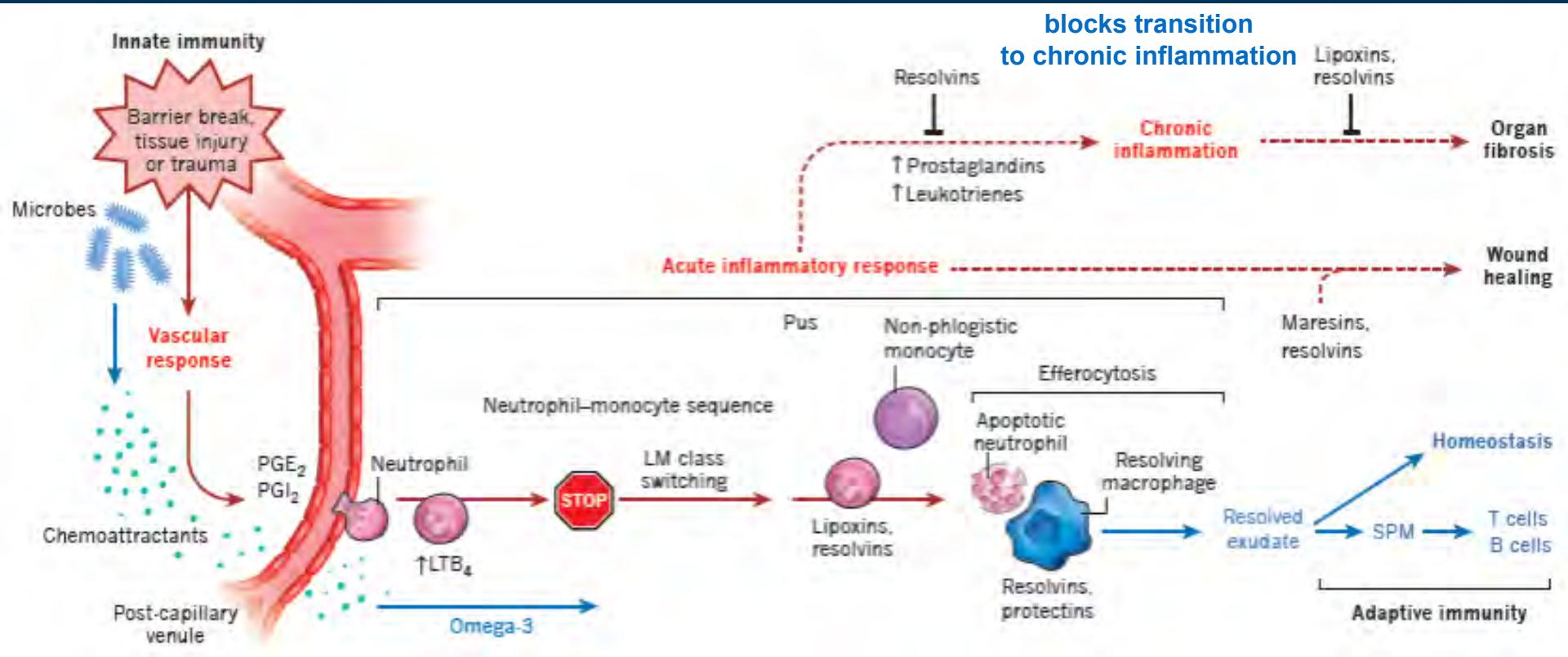
- Endogenous mediators generated from ω-3 PUFA's that promote the *active* resolution of inflammation
- Each SPM is a unique structure possessing precise stereochemistry that is essential for its biological activity
- SPM's exert pro-resolving actions in physiologic (picomolar-nanomolar) dose ranges and have multiple cellular targets, including:
- neutrophils, macrophages, dendritic cells,
- vascular smooth muscle cells, and endothelial cells
- Primary mechanism of action of SPMs is:
  - promote non-inflammatory efferocytosis (apoptoic cell removal)
  - Enhancing neutrophil and macrophage function

•Zhang MJ et al Ann Rev Nutr 2012

•Serhan C Nature 2014

SPM = Specialized pro-resolving mediators

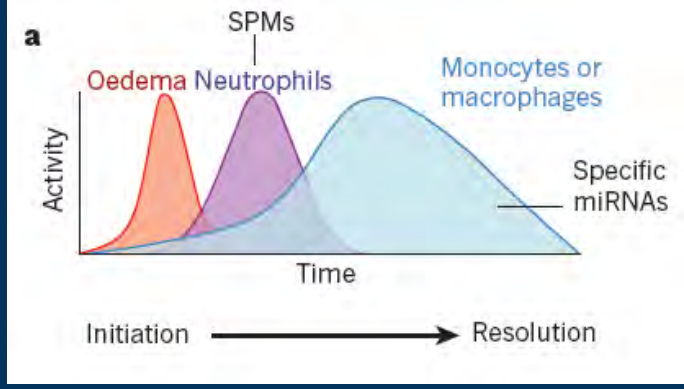
SPM's have multiple levels of activity



SPM: specific pro-resolving mediators
LM: Lipid mediators

Serhan C Nature 2014

Reported Benefits of SPM's



- Enhance resolution of inflammation
  - SPM's *do not block inflammation* they resolve and modulate it
    - » Highly conserved in evolution from planaria to human

- Produced from DHA and EPA substrate
  - SPM's have physiologic activity at nano-pico gram range
- Enhance bacterial killing of macrophages
- Accelerates removal of inflammatory debris
- Potentiates action of antibiotics
- Not immunosuppressive
- Decreases postop edema and pain

Serhan C Nature 2014

“Carbo” Loading Pre-op

- Principle is similar to preparation for major end sports event !
- Protocol:
  - 8 hours pre-op 800 cc isotonic CHO solution
  - 3 hours pre-op 300 cc isotonic CHO solution
- Reported outcomes:
  - No increase risk of aspiration
  - Protects lean body mass post op
    - » Maintain hand grip strength, “well being” etc
  - Decreases insulin resistance post op (up to 50%)
    - » Insulin resistance directly correlated with post op complications
    - » Multiple mechanisms
      - » Mitochondrial changes noted
      - » Via PDK4 ⇩ mPDC
-

Schricker T Ann Surg 2012
Bilku DK Ann R Coll Surg 2014
Lundquist et al 2011
Faria MS WJS 2009
Awad S Curr Opin Nutr2012
Sato AJCEM 2010

Pre-op Bathing / Decolonization Protocols

- **Antiseptic showers (preoperative)**
  - Reduced bacterial counts by 3.5 x 10^{10} from baseline[1]
  - Cochrane Database "no benefit" 2012 (n=>10,000)
    - Chlorhexidine vs soap
  - No consistent evidence that they affect SSIs[2,3]
  - Antiseptic skin cloths (no consistency in data)
- **Pre-op Staph *aureus* screening[4,5,6]**
  - Bode NEJM (2010) RCT
    - 6771 screened ITT analysis
    - ¼ of population + Staph aureus, ~2% MRSA
    - Mupirocin/Chlorhexidine x 5days = 44%↓ post op wound infection
  - Kim JBJS (2010)
    - 7019 pts screened, 22.6 + S.aureus 4.4% MRSA
    - Preop treatments decreased postop infection > 59%
  - Roa N J. Arthoplasty (2011)
    - >3000 prospective cohort
    - Decrease S.aureus infection 47%

1. Seal LA et al. *Am J Infect Control.* 2004;32:57–62.
2. Mangram AJ et al. *Am J Infect Control.* 1999;27:97
3. Webster j et al Cochrane Database Syst Rev 2012
4. Bode LG et al NEJM 2010;362:9-17
5. Kim, DH et al JBJS 2010;92
6. Roa N et al J. Arthoplasty 2011, 26;1501-7

- **Clustered randomization: 43 hospitals, 74 ICU's, 74,256 patients**
- **Three groups:**
  - **MRSA screen and isolation**
  - **Targeted decolonization – screen, isolate, decolonization of MRSA carriers**
  - **Universal decolonization – no screen, decolonization of all**
- **Conclusion:**
    - **Routine universal decolonization most effective**

Huang SS et al NEJM 2013

Bowel Preps: Mechanical

- 14 trails 4859 patients
  - 1* outcome anastomotic leak
  - 2nd outcome septic episodes
- Results:
  - No difference in leaks or pelvic abscesses
  - If all infections considered slight benefit to no mechanical bowel prep ($p<.02$)
- Conclusion: No benefit to bowel prep

- Similar conclusions from
  - 2011 Cochrane analysis (Guenaga KF et al)
- Several unanswered questions
  - No description of +/- antibiotic bowel prep (Michigan NSQIP study Englesby Ann Surg 2010)
  - C. difficile with MBP ?

Slim K et al Ann Surg 2009

What happened to the concept of antibiotic bowel prep ?

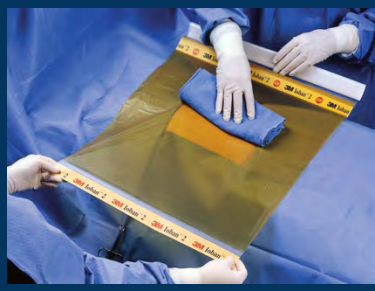
- Most large trials compared MBP to no MBP
  - Known that antibiotics decrease colonic bacteria
    - Mucosal associated CFU 1.8 x10^2 compared to 3.4x 10^7
- Englesbe et al MBP w and w/o antibiotics
  - Part of Michigan Surgical Quality Collaborative
  - N= 1553 patients, propensity matched cohort analysis
    "fancy statistics with many assumptions"
  - NOT a randomized trial but a observational study
  - Results: Antibiotic bowel prep reported to;
    - decrease SSI 4.5% vs 11.8%
    - Decrease organ space infection 1.8% vs 4.2%
    - Less prolonged ileus
    - No change in C.*difficile* infections

Englesbe MJ et al Ann Surg 2010

Preventing Infections in the Immediate Peri-op period

- Hair removal ?
  - Shaving vs clipping vs dipilatory
    - Multiple RCT
  - Timing of hair removal
  - Cochrane analysis 2006 Tanner J > 3000 pts clipping with lowest infection risk

- Skin Sealants ?
  - Decrease skin colonization at end of case
  - No change in SSI (study not powered adequately for SSI)
- Surgical site barriers(incise drapes, i.e. Iodine impregnated)
  - Webster J Cochrane Review 2008
    - » Possibly slight increase in infection cases > 4 hours
    - » Key appears to be adherence to skin edges
      - » 6 x increase in infection if drape edge lifts
      - » Studies done without Iodine impregnated drape
    - » Newer incise drapes with better adhesives



Alexander JW Ann Surg 2011

Skin Preparations

- Prospectively compared 3 commonly used preps general surgery cases (N=3209)
- Betadine® (povidone Iodine 10% in water)
- Chloroprep® (chlorhexidine 2% isopropyl alcohol 70%)
- Duraprep® (Iodine povacrylex, isopropyl alcohol)
- SSI followed for 30 days post-op, ITT
- Conclusion:
  - Duraprep lowest SSI,
  - Iodine solutions 4.8 %, chlorhexidine 8.2%

Swenson, BR, Sawyer RG et al
Infect Control Hosp Epidem 2009

- PRT 6 hospitals, clean contaminated cases
- 849 patients ITT analysis
- Primary outcome: SSI at 30 days
- Secondary outcome: type of SSI
- Results:
  - Chlorhexidine 9.5% vs Povidone-iodine 16.1%
  - Chlorhexidine better for superficial, and deep infections
  - No difference in organ space infections 4.4% v 4.5%

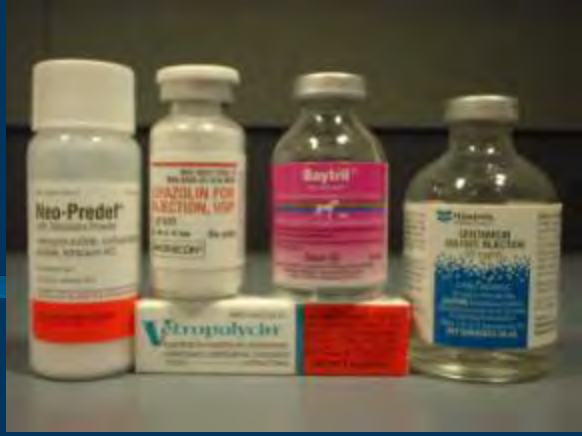
Darouiche RO. NEJM 2010;362:18-26

Subset analysis indicates Alcohol was key !! (Swenson JACS 2010)

Clinical outcome data consistent with skin bacterial count data

Recent study Hakkarainen TW JACS 2014 questions these studies ?

Uses of antibiotics

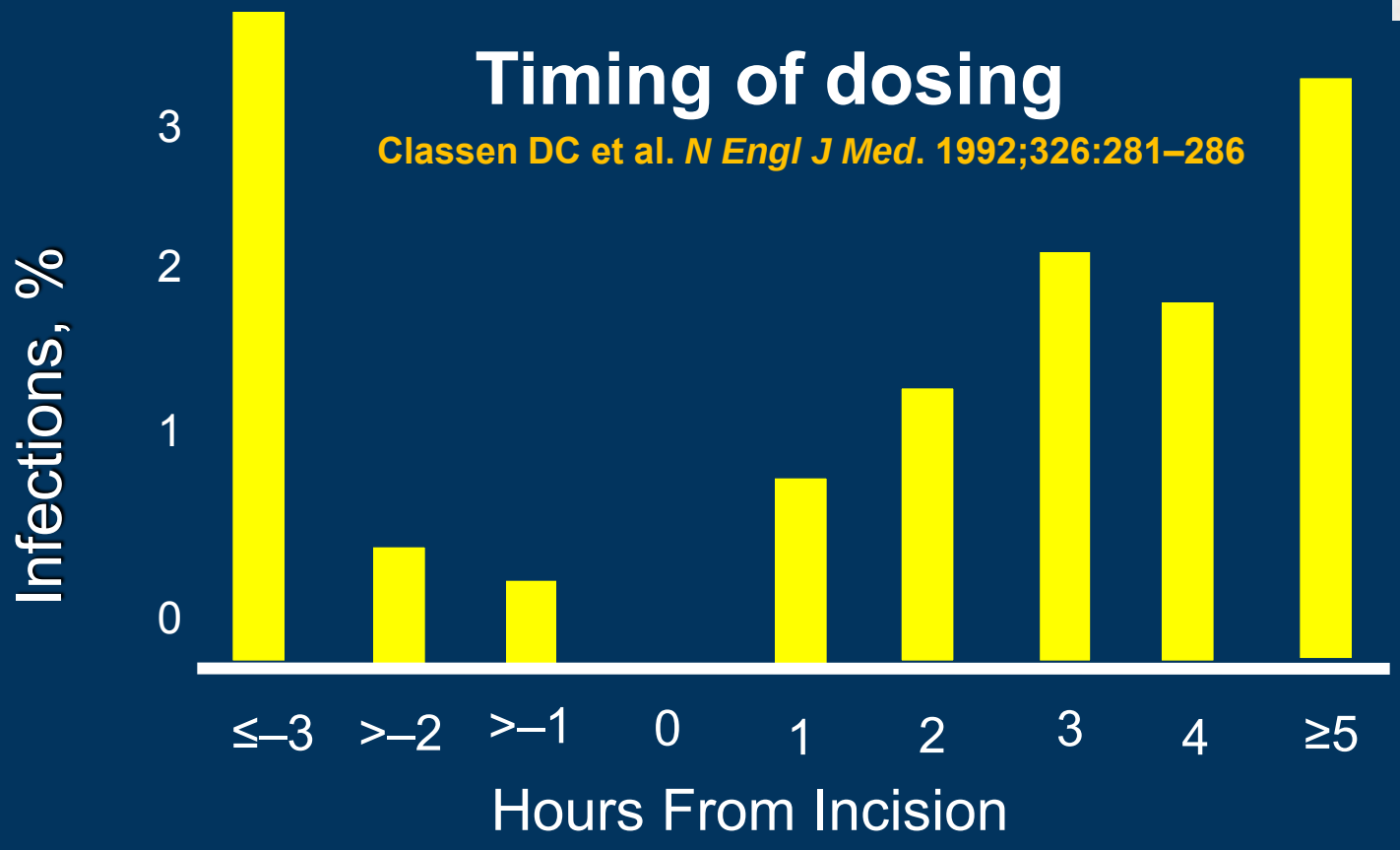


- Prophylaxis
- Empirical therapy
    - "carefully considered, presumptive treatment of (infectious) disease prior to establishment of diagnosis"
- Therapeutic

- "Primum Non Nocere"

- " First, do no harm"

Peri-operative Prophylactic Antibiotics:



Recent data 20 yrs following Classen study almost identical data; NSQIP database 4,453 patients. Give antibiotic close to incision

Koch CG et al JACS 2013

Short or "Long" Duration of Prophylaxis

Author / Yr	Surgery	Outcome
Enzler MJ 2011	Open fracture	No benefit after closure
Berbari EF 2012	Hip replacement	No benefit after wound closure
Fonseca S 2008	PRCT 12,000 Pts (GS, Ortho, H and N, Cardiac, GYN, Vascular, Neuro)	Single vs 24 hours No difference
Morrison S 2011	Closed fractures Meta-analysis (4 studies)	Single vs 24 hours No benefit of > single
Bratzler DW 2004	General surgery	No additional benefit once skin closed
Medical Letter 2009	General Surgery	Antibiotics should be stopped after < 24 h
Suehiro 2011	CRS, Hepatobiliary	No benefit > 24 hours
von Kasteren 2007	Hip arthroplasty	No benefit over 24 h
Burke 2001	General surgery	No more than 24 hours
Hendren S 2013	CRS part of SSI bundle	Fewer infections (part of bundle)

Consequences of Prolonged Prophylaxis

	All patients		Nontransplant patients	
Duration of prophylaxis	<1 day	>4 days	<1day	>4 days
No. of patients	180	94	143	25
No. of patients developing bacteremia (%)	6 (3%)	16 (17%) *P*<0.0001	5 (3%)	6 (24%) *P*=0.0001
No. of line infections (%)	4 (2%)	14 (15%) *P*<0.0001	4 (3%)	6 (24%) *P*<0.0001

Namias N et al. J Am Coll Surg. 1999;188:225-30.

What about "prophylaxis" until the drains come out ?

- No level one data !
  - No randomized clinical trials of > 100 patients

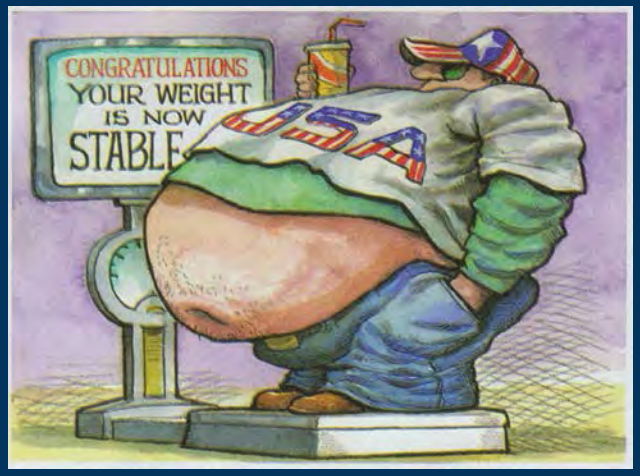
- Can data from Flaps, Breast reconstruction, chest tubes in elective chest surgery be extrapolated to other procedures ?
  - if yes
    - *No consistent* data showing prolonged "prophylaxis" until drains are out is beneficial

    - Chest tubes with mediastinal drains and cardiac leads 48 hours is recommended
      - Rec based on two large RCT with slight significant more infections in 24 h vs 48 h "prophylaxis"

Dosing of antibiotics in Obesity:

“one size does not fit all”

- Under dosing common when BMI > 30
  - Estimated in 60% of patients don’t reach serum levels for adequate prophylaxis



Anderson DJ, et al Infect Control Hosp Epidemiol 2008;29 (Suppl 1):S51-S61
Hanley MJ et al Clinical Pharmacokinetics 2010
Freeman JT Obesity Surg 2010

"Optimal" Use of Prophylactic Antibiotic Administration

- Use antibiotic when risk of infection is high or outcome is devastating if infection develops
- Don't start too early or too late !
- Give the right antibiotic / right dose
  - First generation cephalosporin for most
  - Caution: indiscriminate use of Vancomycin
    - less effective for MSSA
- Give IV as oral absorption may be unreliable
- Use of additional doses only when necessary:
  - Long procedures (> 2 or 3 hours)
  - Consider $t^{1/2}$ of antibiotic used
    - » Cefazolin 108 min, cefoxitin 48 min, cefotetan 3.5 hours
    - » Vancomycin 4-6 hours, cipro 4 hours, ertapenem 4 hours
  - "excessive" blood loss (spine, cardiac, liver procedures)
  - When cell saver is used

Bull AL et al Ann Surg 2012
Bratzler DW et al Am J Health Sys Pharm 2013

Prevention of Infection: Intra-op

- Surgeon hand hygiene
- Gowns, gloves, shoe protectors
- Wound protectors ?
- Antibiotic impregnated sutures?
- Intra-operative glucose control?
- Peri-operative temperature control?
- Intraoperative antibiotic irrigation?
- Placement of drains?
- Technique – Technique – Technique

1.Justinger C Surgery 2009:145;330-334

Prevention of Infection: Intra-op Surgeon Garb

- **Surgeon gloving**
  - Gloves: no randomized control trial ever done
    - » Clean vs sterile gloves (Moh's surgery)
  - Single vs double glove NS difference in SSI [1]
    - » Double gloves do decrease inner glove perforations
    - » Little if any data to support perforation increase SSI[3]
  - 15 to 25 % of gloves have hole within 1 hour of surgery[2]
  - Glove perforation associated with increase SSI only when no IV antibiotics given[5]

- **Masks**
  - Current masks have 2 filters for particulates <1µm
  - Masks ***NOT*** shown to decrease bacterial counts in OR
  - No PRCT to show decrease in SSI
  - Orr et al suggest increase infection with mask [4]
  - Tunevall 3088 patients RCT "no difference"

1. Tanner J Cochrane Database 2006
2. Harnoss, JS Am J Infect Control 2010
3. Eisen DB J Am Acad Derm 2011
4. Orr NW Ann R Coll Surg 1981
5. Misteli H Arch Surg 2009

Surgeon Garb

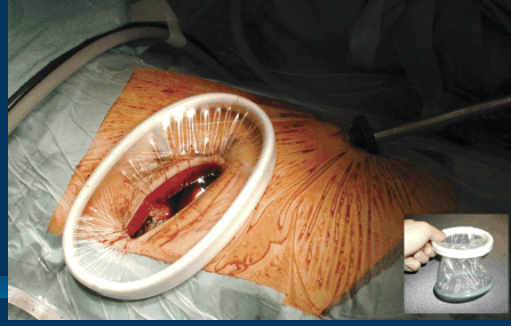
- OR shoes vs street shoes
  - Street shoes have more bacterial !
    - – Not the bacteria profile that cause SSI
  - OR only shoes never shown to yield fewer infections
- Shoe covers
  - Originally designed to prevent explosions (grounding strip)
  - They do decrease OR floor bacterial counts
  - NO study showing decrease SSI
  - Several studies showing increase in the surgeons hand contamination when shoe covers used

Prevention of Infection: Intra-op Surgeon Garb

- Head covering
  - Hair does harbor Staphylococcus
  - Beards and long hair do not increase bacterial counts in the OR
  - Not been shown to decrease SSI or even bacteria on the surgical field
- Gowns
  - Became common in early 1900's
  - Cotton gowns poor bacterial barriers
  - Standardization not uniform 2011

? Data

Intra-operative wound protectors

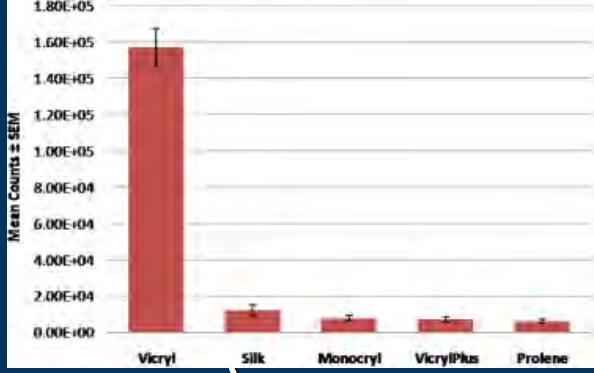


- Designed to protect from desiccation, contamination and mechanical trauma during procedure
- 4 RCT showing no benefit in reducing SSI
- 3 RCT showing benefit in reducing SSI

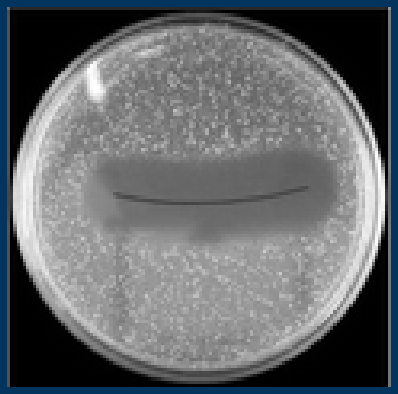
- **General conclusion:**
- When weighing quality of study using Grade System evidence leans toward no benefit.
- Some function as wound protector and retractor
- Use in clean contaminated and contaminated wounds *if* at all

Reid K Dis Colon Rectum 2010
Lee P Arch Surg 2009
Horiuchi T J Trauma 2007
Han J et al Zhong Wai 2014 (C)

Prevention of Infection: Intra-op



- Suture choice
- Antibiotic impregnated sutures[1]
  - Triclosan-coated N=2088 procedures (midline incisions)
  - Vicryl+ vs PDS (looped) Prospective trial
    - Two time periods (looped followed by Vicryl +)
  - decrease SSI (10.8% vs 4.9%)

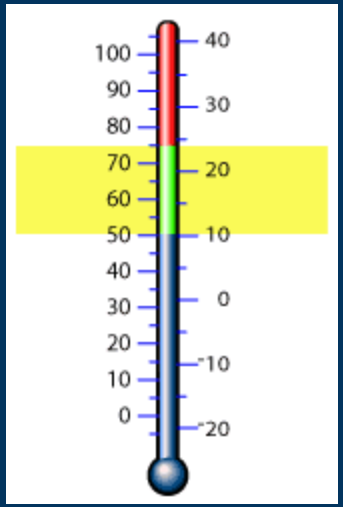


VS

- Coming soon: amphiphilic polymer PAMBM poly[(aminoethyl methacrylate)-co-(butyl methacrylate)] inspired by antimicrobial peptides found in skin
  - 2 abstracts look promising

Justinger C Surgery 2009
Li, Y Langmuir 2012
Masini BD J Surg Ed 2011

Temperature Control in the Perioperative Period ?



Historically: OR kept at low temperature and low humidity to prevent bacteria growing on surfaces. This was based on theory and not data !!!

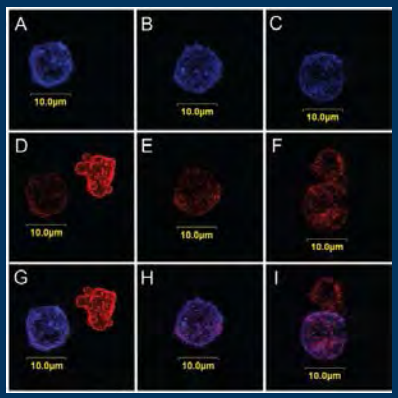
Current concept:

Euthermia maintains perfusion to skin

- Vasoconstriction decreases SubQ O2 tension
- seems to most effective if warming started in pre-op holding
- multiple studies support increase in O2 tension results in decrease infection
- 11.5% infection vs 2.0% if arrived in RR hypothermic (1)

Hypothermia decreases immune function (2)

- T Cell mediated Ab production
- Decreases non-oxidative and oxidative killing



(1) A Flores-Maldonado Arch Med Res 2001
(2) Qadan M Ann Surg 2009

Perioperative Normothermia Elective Surgery

- **200 CRS patients**
  - Control: Routine intraoperative thermal care (mean temperature 34.7°C)
  - Treatment: Active warming (mean temperature 36.6°C)
- Incidence of SSI
  - Control 19% (18/96)
  - Treatment 6% (6/104); *P*=0.009

Kurz A et al. *N Engl J Med.* 1996;334:1209–1215.

- **421 (breast, hernia, varicose veins) patients**
  - Intention to treat analysis
  - Three groups: forced air, local warming, control
  - 14% vs 5%
  - ? 14% infection in clean elective surgery

Melling AC et al Lancet 2001;358:876-880

Several retrospective studies do not confirm this benefit including the NSQIP database review (N=323)of non-colorectal GI surgery shows no difference in SSI
Retrospective chart review study Lehtinen SJ et al Ann Surg 2010

Trauma N=524 + correlation to temps <35 and incidence of SSI Seamon MJ Ann Surg 2012

Prospective trial 1008 colorectal procedures: No significant benefit
Melton GB et al Ann Surg 2013

Recent Cochrane Database Review 2014: No Clear Benefit
Alderson P et al Cochrane 2014

Supplemental Periop Oxygen (Hyperoxia)

Theory: O2 needed for neutrophil and macrophage killing of bacteria, added O2 to increase PP of O2 in tissue bed and increase oxidative destruction of bacteria; surgical wounds PP oxygen much lower than normal tissues

- **500 CRS patients**
  - 80% or 30% inspired oxygen during operation and for 2 hours post surgery
  - All patients received prophylactic antibiotics
- **Results**
  - Arterial and subcutaneous Partial Pressure O2 higher in 80% oxygen group
  - Lower incidence of SSIs with higher supplemental oxygen (5.2% vs 11.2%; *P*=0.01)

Greif et al. *N Engl J Med.* 2000;342:161–167.

- **DBRCT 300 patients, teaching hospitals**
  - CDC definition for infection
  - 30 % vs 80% intraop and 6 hrs post op via rebreather mask
- **Results:**
  - Infections: 24.4 % vs 14.4 %

Belda FJ et al JAMA 2005; 294:2036-2042

- **PROXI study 1400 PRT**
  - 80% vs 30% intraop and for two hours post op
- **Results**
  - No benefit in SSI reduction
  - 19.1% vs 20.1%

Meyhoff CS JAMA 2009

Meta-analysis of supplemental perioperative oxygen in reducing SSI:
Favors use in CRS and high risk. More prospective studies needed to confirm
Al-Niamimi et al J Eval Clin Practice 2009
Recent Cochrane Database Review 2014 No Clear Benefit

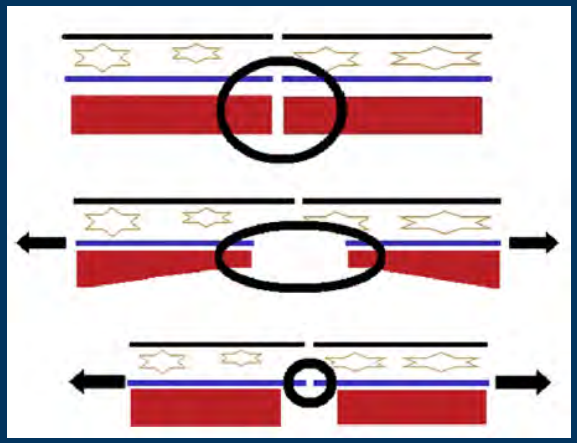
Operative Techniques to minimize risk !

Tenants of Halsted

- Aseptic Technique
- Atraumatic handling of tissues
- Sharp Anatomic Dissection
- Meticulous hemostasis
- Fine Non-Reactive Sutures in Minimal Amounts
  - Minimization of foreign body
- Avoidance of Tension
- Obliteration of dead space

Preventing complications:

- Choice of closure technique
  - Monofilament suture
  - Running suture
  - Approximate without strangulate
  - Close only the aponeurosis
  -
  - 5-8 mm from wound edge
  - 4-5 mm apart



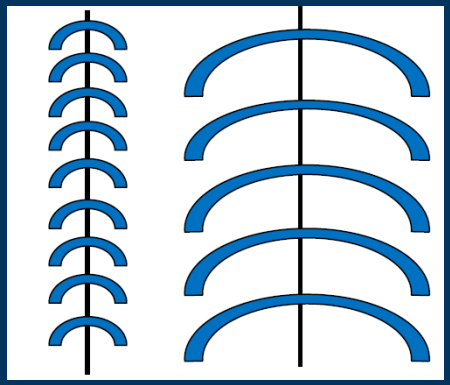


Table 1
Wound complications related to the size of stitches in a randomized trial

	Small Stitches	Large Stitches
Wound dehiscence	0% (0 of 356)	0.3% (1 of 381)
Surgical-site infection	5.2% (17 of 326)	10.2% (35 of 343)
Incisional hernia	5.6% (14 of 250)	18.0% (49 of 272)

Millbourn D et al Arch Surg; 2009
Israelsson LA SCNA 2013

Post op dressing and SSI

- Optimal post op dressing technique
  - 16 RCT, various techniques and wound classes
  - No evidence any one dressing better than any other

- Tissue adhesives and biologic glue for closure
  - 14 RCT with high methodological quality
  - NO statistical difference between adhesives and sutures (adults) regarding infections
  - Sutures had less skin dehiscence

Dumville JC et al Cochrane Database 2011
Coulthard P et al Cochrane Database 2010

Post-op NPWT on closed incisions

- Multiple small observational, retrospective and RCT
  - Mixed results best in Orthopedics
  - Some data on increasing blood flow to flap

  - PRCT NPWT vs standard dressing (1)
    - N=81 (37 dressing 44 NPWT)
    - High risk pt with multiple comorbidities
    - Mostly LE wounds
    - No change in infection, dehiscence, reoperation
  - Retrospective review of prospective database AWR (2)
    - N=119 all AWR
    - No benefit
  - Retrospective Ca Surg (4)
    - N=191 total procedures
    - Decrease SSI, wound complications

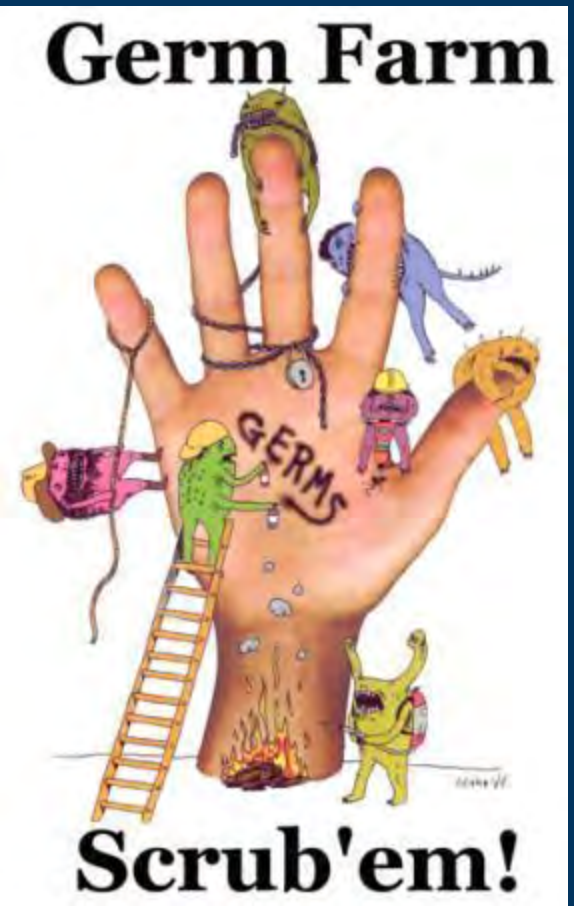
(1) Madsen GB Ann Surg 2012
(2) Pauli EM, Rosen et al Surg Infection 2013
(3) Tadisina KK, Singh D et al Eplasty 2013
(4) Blackman Au et al Am J Surg 2013

Miscellaneous: Fact or Fiction ?

Sacred cows make the best hamburger !

- Scrubs not leaving the OR ?
- Duration of surgery
  - » Multiple reports of association between time of surgery and infection risk
    - » Risk of bias extremely high
- Electrocautery ?
  - » Focused use no increase risk of infection
- Selective gut decontamination
  - » USA vs EU
- Single rooms in ICU decrease cross-contamination
- ETT with subglottic suction ability decrease VAP
- Blood transfusions
  - » Increase infections
  - » Multiple mechanisms
    - » Immune
    - » Changes in PP O_2
- Fluid management
  - » Restrictive vs liberal
    - » Restrictive decreases wound complications
- Active surveillance culturing for MRSA
  - » JAMA 2008
  - » Bundled infection control, population based vs MRSA based
  - » Bode NEJM 2010

Some say we should be killing bacteria in the ICU not eating them !!



More Antibiotics is Not the Answer: Myths of Antibiotic Prophylaxis

- If some is good more is better
- A large amount of contamination requires more and prolonged antibiotics
- “a few extra days of antibiotics can’t hurt”
- Sicker patients need more antibiotics
- Antibiotics can sterilize infected synthetic mesh
- Antibiotic bowel preps decrease SSI and complications
- Intra-abdominal irrigation with antibiotics decrease post-op infections

Interpreting Scientific Evidence: Different Perspectives May Result !

US Perspective

Interpreting Scientific Evidence: Different Perspectives May Result !

US Perspective

Canadian Perspective

More Antibiotics is Not the Answer: Myths of Antibiotic Prophylaxis

- If some is good more is better
- A large amount of contamination requ… re and prolonged antibiotics
- "a few extra days of antibi… t hurt"
- Sicker patients need … tibiotics
- Antibiotics can… nfected synthetic mesh
- Antibiotic … preps decrease SSI and com…
- …dominal irrigation with antibiotics …crease post-op infections

Maybe we should be giving back bacteria

Antibiotic Associated Diarrhea: Preventable or Inevitable ?

- Hempel S et al JAMA 2012
- Meta-analysis 82 RCT met criteria for inclusion
- Probiotics strains were poorly documented
- N=11,811 participants (pooled data)
- Conclusion:
  - Probiotics confer significant decrease in AAD ($p<.001$)
  - # needed to treat N=13

Hempel S et al JAMA 2012

Pathogenesis of CDAD

Antibiotic therapy

↓

Alteration in colonic microflora

↓

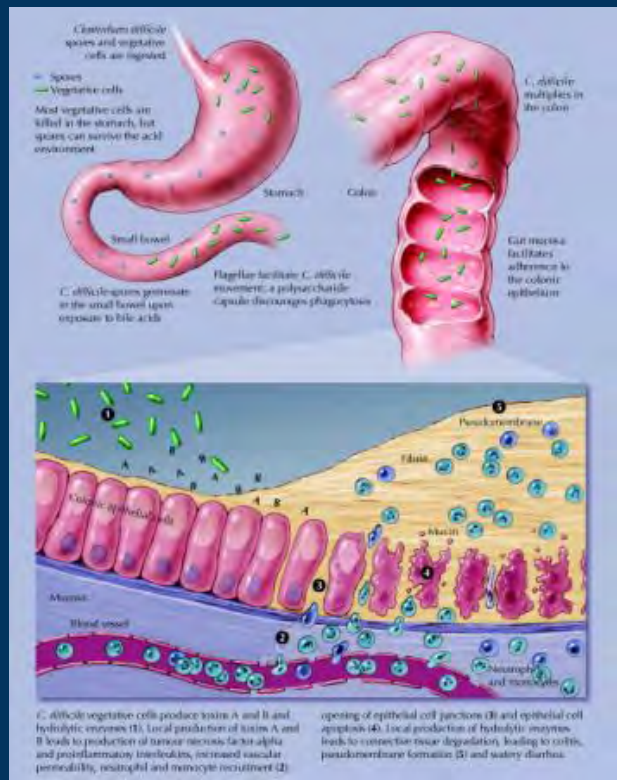
C. difficile exposure and colonization

↓

Release of toxin A and Toxin B

↓

Colonic mucosal injury and inflammation

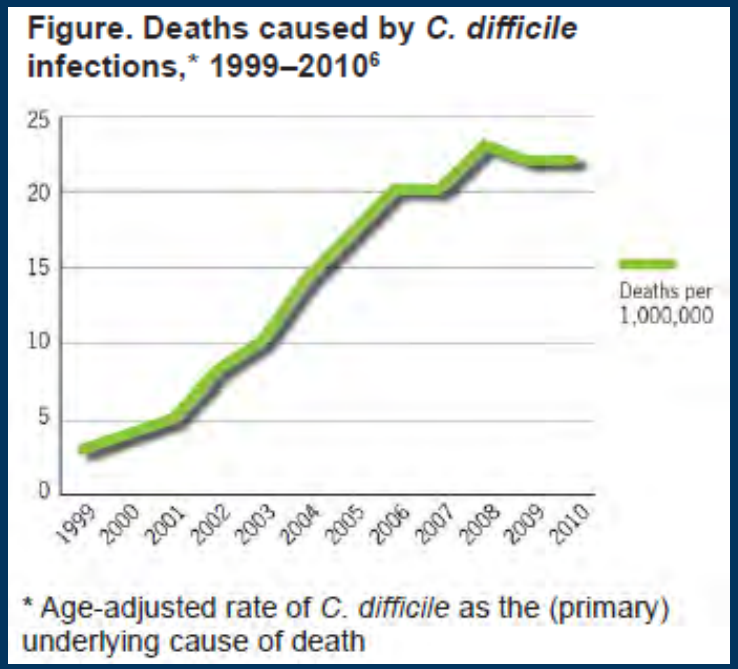


Spores can survive up to 5 months on surfaces

Badger, VO et al JPEN 2012

Emergence of B1/NAP1 Strain

- Produces 16-23 times C. diff. toxins A and B in vitro,
- represented 50% of isolated strains between 2001-2003
  - Produces a 3rd binary toxin
- Increased risk of relapse
- Less responsive to standard therapies



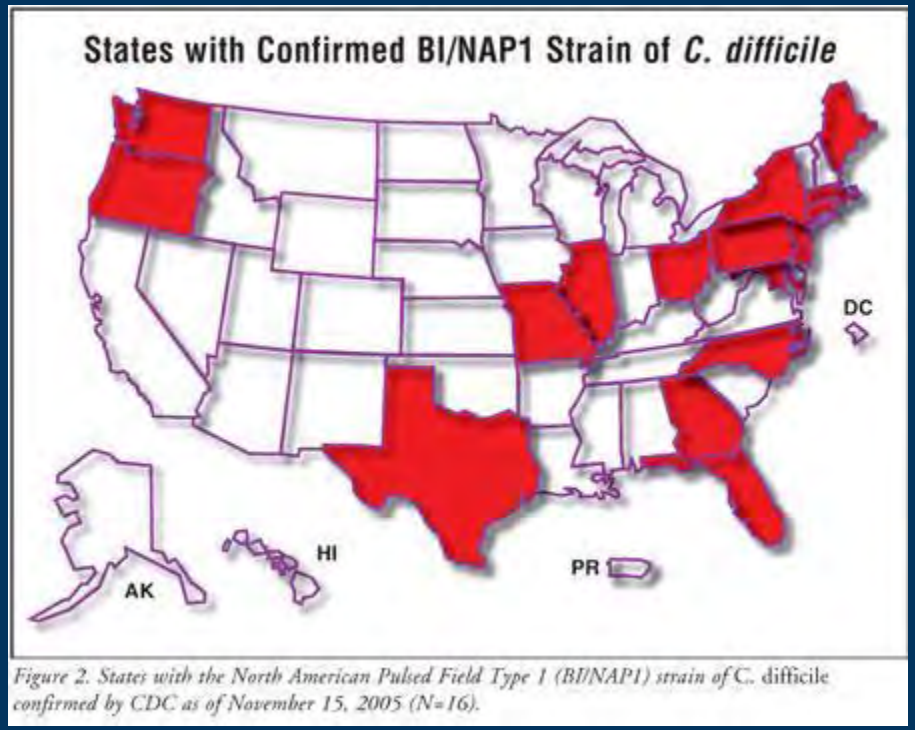
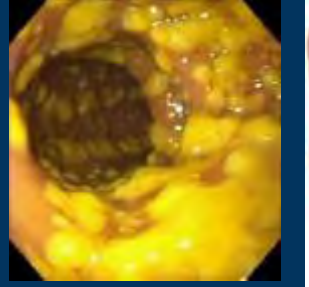


Figure 2. States with the North American Pulsed Field Type 1 (BI/NAP1) strain of C. difficile *confirmed by CDC as of November 15, 2005 (N=16).*

McDonald NEJM 2005
Johnson BC Ann Int Med 2012
Pattani R et al Medicine 2013

Use of probiotic preparations to prevent C.difficile Associated Diarrhea



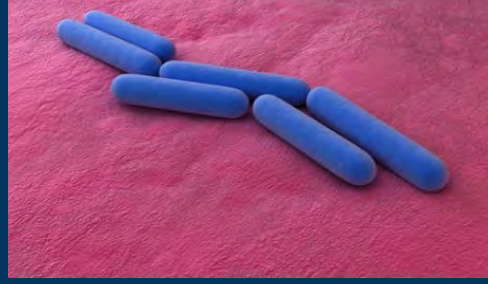
- RDBPCT N=135
- Age 74 all taking antibiotics
- 100 gm BID L. casei as drink
- Results:
  - AAD: 7/57 (12%) vs 19/56 (34%)
  - 21% relative risk reduction, NNT 5
  - C.diff 0/57 vs 9/53 (17%)

Hickson M, et al . BMJ 2007

- Meta-analysis 28 studies
- N=3818 patients
- "Moderate quality" of evidence probiotics as prophylaxis
  - decreases incidence of CDAD by 66%
  - No adverse influence by receiving probiotics

Johnston BC Ann Internal Medicine 2012

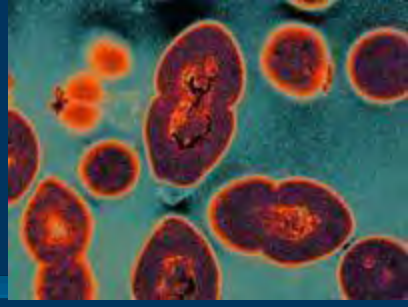
Probiotics: Importance of choosing the correct bacterial species
"Yoplait® just won't make it "



- PLACID Trial: MRDBPCT
- 17,480 screened 2,981 met criteria
  - > 65 yo
  - All received antibiotics
  - 75% received either placebo of probiotic for at least 14 days
    - » L.acidophilus x 2
    - » B.bifidum x 2
- Conclusion:
  - AAD 10.8 vs 10.4 %
  - CD 0.8 vs 1.2 %
  - Essentially no differences between groups

Allen SJ et al Lancet 2013

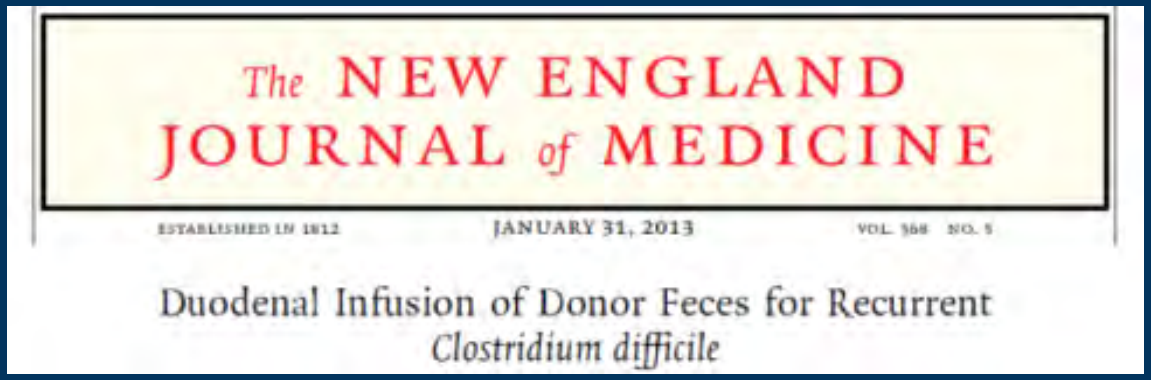
"Probiotic treatment of VRE: Randomized Controlled Trial."



- PRPCBT 27 VRE positive patients
- Yogurt (containing live Lactobacillus GG vs Pasteurized yogurt)
- 100 gm daily x 4 weeks
- Primary outcome measure: clearance of VRE
- Results:
  - L.GG group: 11/11 cleared VRE at 4 weeks, 3/11 reconverted + at 4 weeks
  - Control: 1/12 cleared
    - » Allowed to crossover at 4 weeks 8/11 crossed over
    - » 8/8 of the crossover group cleared in 4 weeks

Manley KJ, Fraenkel MB et al Med J Australia 2007;186:454-457
PRPCBT = Prospective Randomized Placebo Control Blinded Trial

The ultimate probiotic: Is stool from a "good friend" or family member the answer for refractory C. difficile diarrhea



- RTC 39 patients with proven refractory C. difficle
- 16 got Donor feces / 13 received QID vancomycin
- Results:
  - Feces group
    - 13/16 resolved with single infusion
    - 2/3 resolved with second infusion
  - Vancomycin group
    - 4/13 resolved

Nood EV NEJM 2013

Hamilton MJ et al
Frozen "fecal" prep for C.diff
43 consecutive, recurrent CDI
95% success
Am J Gastroenterology 2012

Prevention of GI Anastomosis Failure

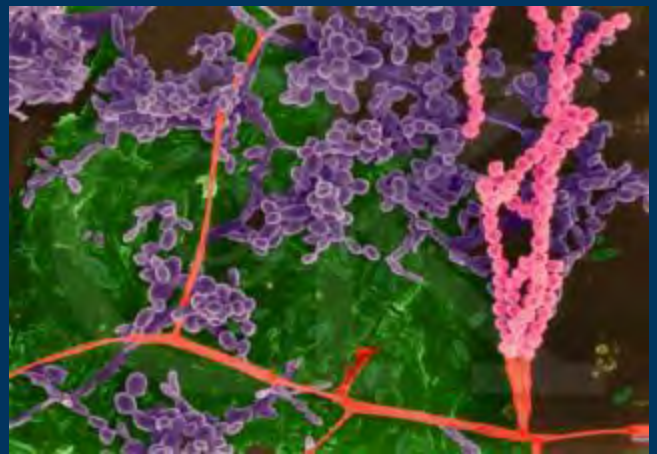
- Animal models (John Alverdy's group)
  - IR increases mortality with Pseudomonas after inoculation
    - Expression of barrier disrupting adhesin PA-IL
- Bacteria at sight of anastomosis change phenotype and become more aggressive and produce adhesins and enzymes with increase risk of anastomotic disruption
    - Altered by mechanical and antibiotic bowel prep, ischemia, narcotics etc

Fink D, et al J Trauma 2011
Morowitz MJ et al Ann Surg 2011
Stern JR et al J Surg Res 2013
Shogan, BD et al J GI Surg 2013

It time for a paradigm shift ?

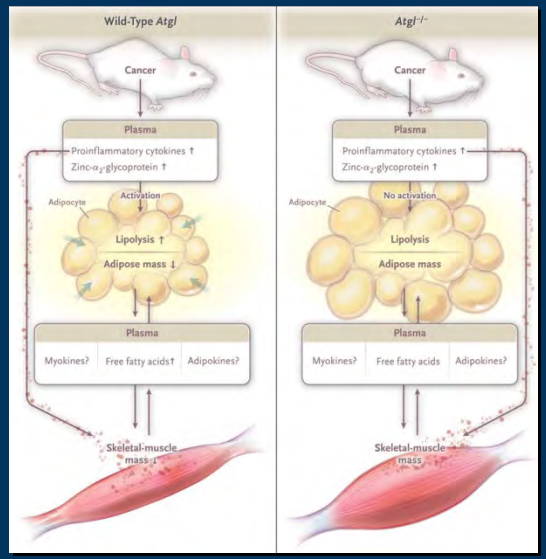
Supply adequate viable beneficial bacteria or a substrate which enhances these specific beneficial bacteria instead of trying to eliminate the pathogen ?

“Bioecological control”

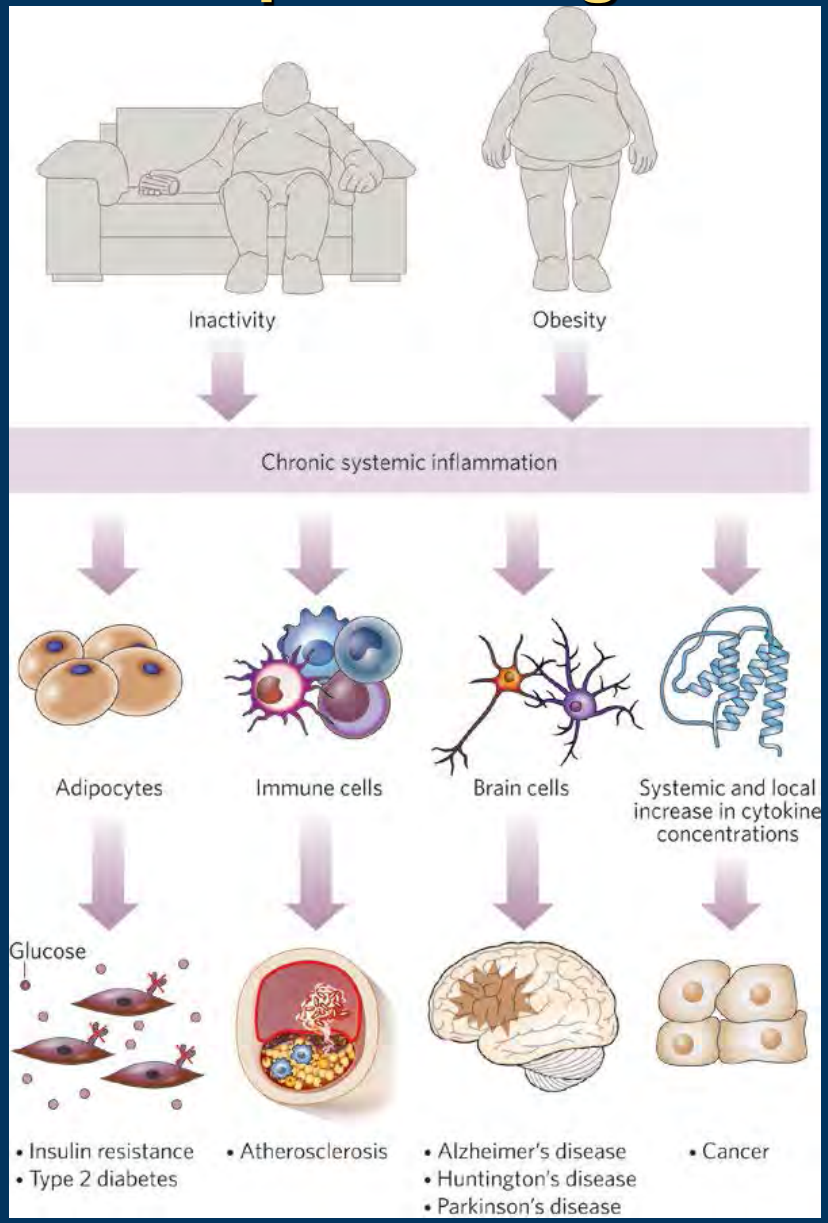


New approaches to protecting lean body mass

Arner P Science 2011



Fearon K NEJM 2011



Multiple mechanisms

↓ insulin resistance
FA mobilization

changes blood flow
↓ inflammation

↑ protein uptake by muscle

Biolo, G Lancet 2011
Baracos, V NEJM 2011

Pre-habilitation ?

- Systematic review 12 studies evaluating the effect of pre-op physical activity / exercise program on post op outcome
- Exercise:
  - Inspiratory muscle training
    - Diaphragmatic breathing, forced expiration
  - Various resistance exercise (4 to 8 weeks)
    - Most individualized with PT support

- Conclusion:
  - Decrease length of stay
  - Decrease total complications
  - Benefit seen in abdominal surgery and chest surgery

Valkenet K et al Clin Rehab 2011

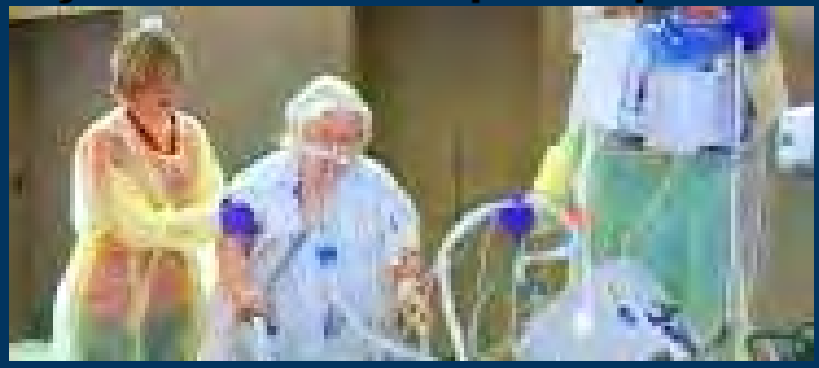
Can resistance exercise overcome the anabolic resistance associated with immobilization and surgery ?

- Exercise with appropriate AA and nutrition shown to be anabolic in multiple models
  - Burn (Wolfe 1990's)
  - Cancer (Biolo 2010)

- Resistance exercise;
  - Increases nutritive blood flow to muscle (decreases precapillary shunting)
  - Anti-inflammatory
  - Lowers insulin resistance
  - Increase nutrient uptake in multiple tissue beds
  - Possibly decrease myofiber necrosis

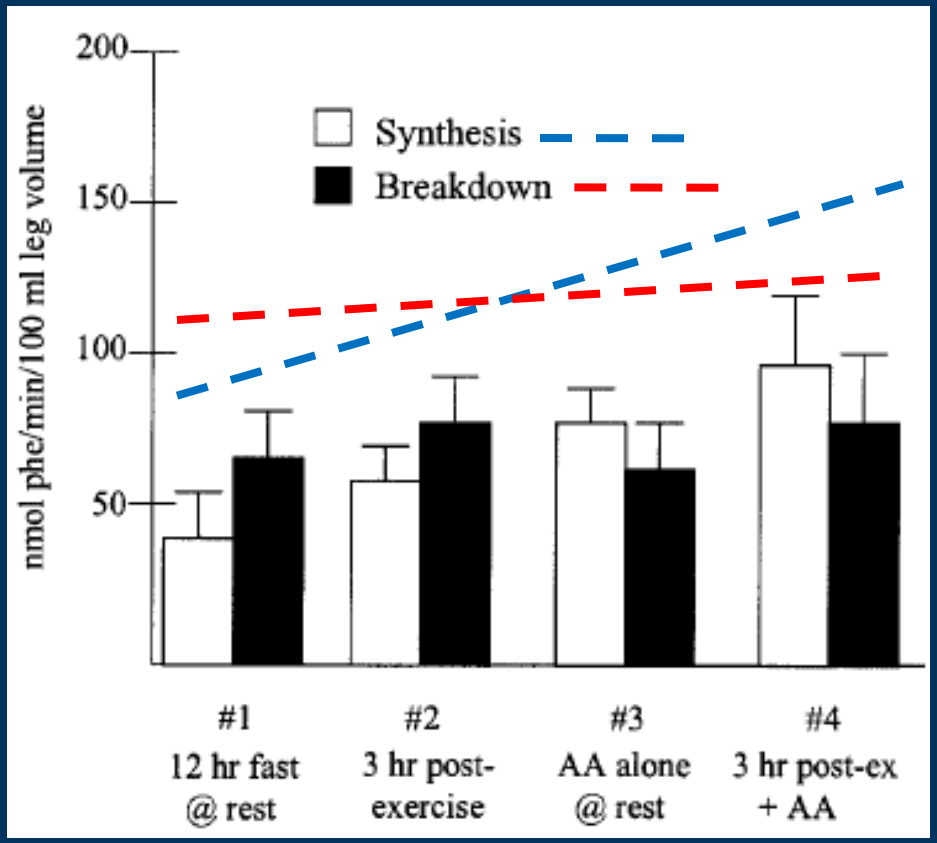
•Puthucheary ZA JAMA 2013

New approaches to protecting lean body mass ICU and post-op

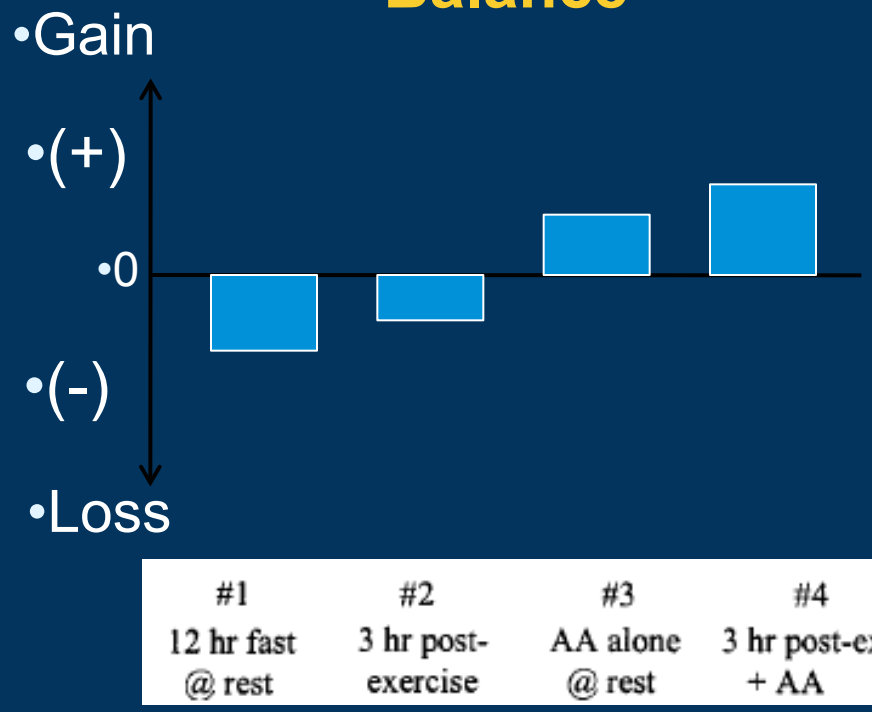


- Pohlman MC et al CCM 2010
  - N=122 pts exercise program
  - Conclusion: Safe
- Burtin, C et al CCM 2010
  - N=90
  - Conclusion: enhanced recovery
    - 6 minute walk, muscle function, safe
- Schweickert WD et al Lancet 2009
  - RCT N=104 pts with PT/OT
  - 59 vs 35% left hospital functional status
- Morris P et al CCM 2008
  - RCT N=330 pts
    - OOB 5 vs 11.4 days
    - ICU stay 5.5 vs 6.9 days
    - Hospital stay 11.2 vs 14.5 days

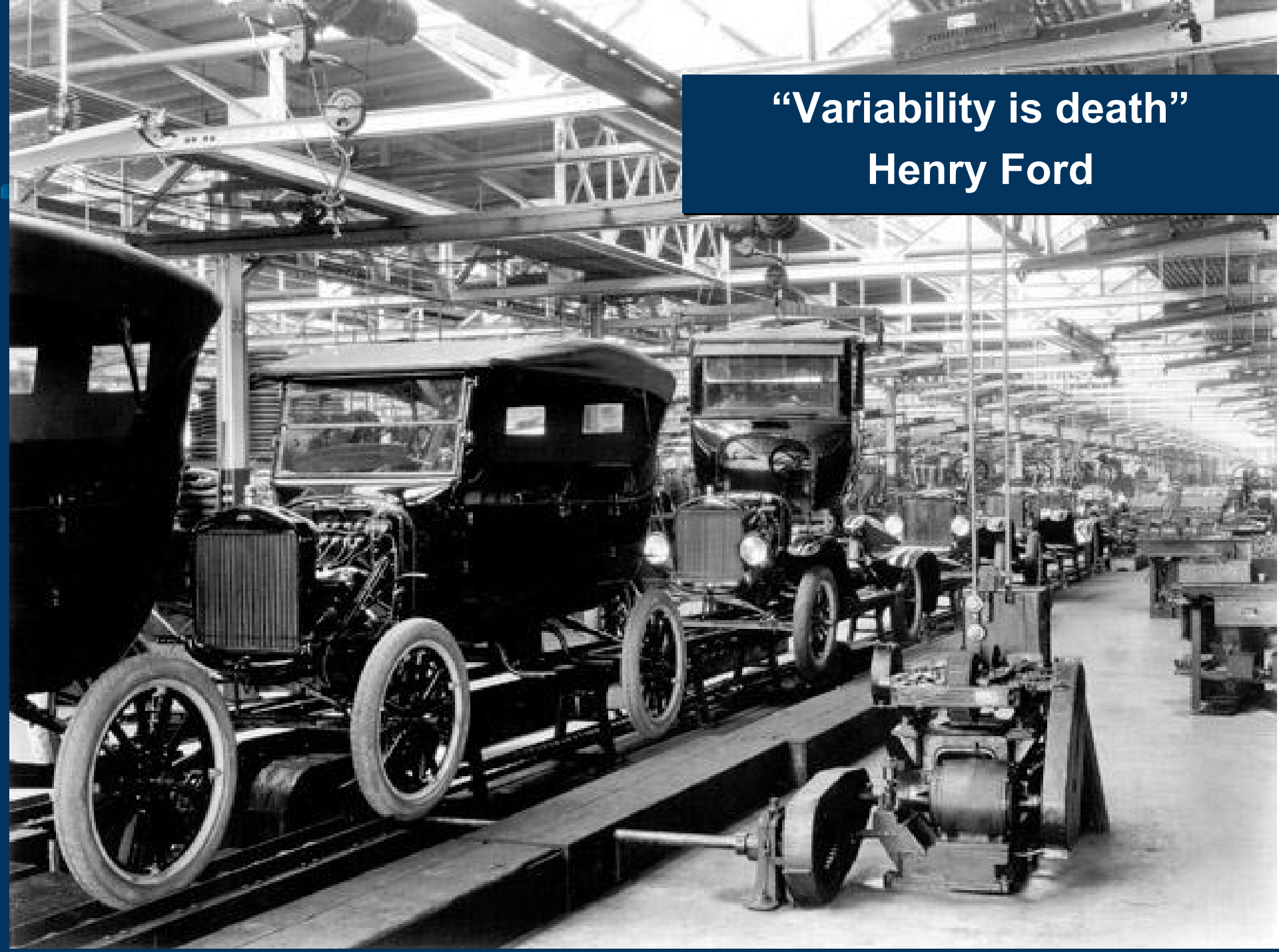
Muscle protein synthesis primarily determines changes in protein balance in healthy humans



- **Net Muscle Protein Balance**



- Rasmussen B & Phillips S, Exerc Sport Sci Rev 31:127, 2003.


“Variability is death”
Henry Ford

Current Protocols in Use at OHSU: Preop preparation protocols

- Preop MRSA Clearance Protocol
  - Mupiricin BID, Hibiclens shower x 5 days
  - (Bode NEJM 2010)
- Preop Nutrition Protocol
  - Impact AR® (Arginine, Fish Oil, RNA)
  - (Drover JACS 2011)
- Exercise program pre and post-op
  - Walking, resistance exercise
  - (Biolo Arch Surg 2011, Barocos NEJM 2012)
- Recent protocols (Jan 2014)
  - Pulmonary function (SBT) coming off vent post op
    - » Started in AWR now rolling out to others
  - Perioperative glycemic control
  - Selective use of antibiotics
    - – Prophylaxis ---- Emperic---- Therapeutic

Focus on Preventing Complications

Pre-op
- Smoking cessation
- Clearing MRSA
- Nutrition
- CHO loading
- Glycemic control
- Weight loss
- Cardiac clearance
- Pulmonary
- Exercise
- "prehabilitation"

Immediate peri-op
- Skin prep
- Antibiotics
- Glucose control
- Techniques
- Drains
- Closure technique

Post-op
- DVT prophylaxis
- Resistance exercise
- High protein intake
- Early enteral feeding
- NPWT

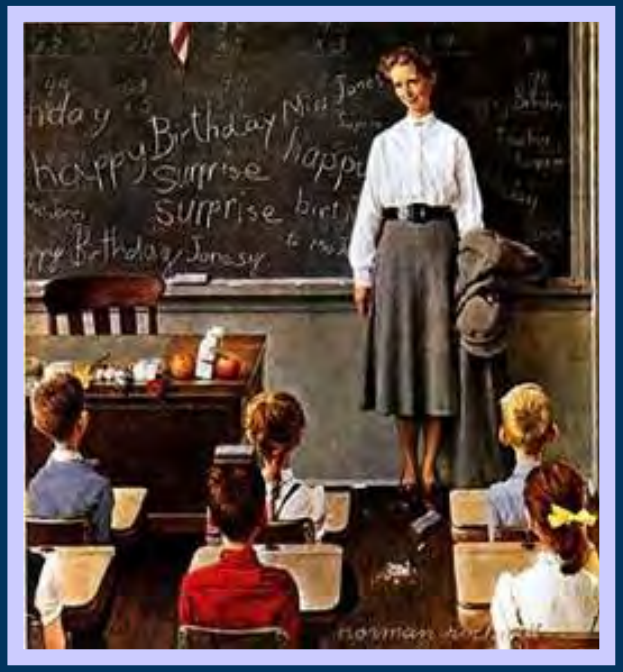
Summary / Conclusions

- **Solid data to support use**
- Smoking cessation
- Attention to nutrition
  - Pre and post op
  - Consider specific nutrients
- Glucose control
  - preop – intraop – postop
- Antibiotic prophylaxis
  - Choice of drug
    - » 1^{ST} generation in most
    - » Vanc in high risk populations
  - Duration of therapy
    - » Should stop when last suture placed
  - Redosing
    - » Consider $t^{1/2}$ of antibiotic being used
- Alcohol containing skin prep
- Minimize transfusions

- **Awaiting confirmation**
- Bowel preps
- Patient warming
- Peri-op hyper oxygenation
  - – O^2 sats > 96%
- Statins
- Carbo loading
- Topical antibiotic delivery
- Pre-habilitation

Following evidenced based Guidelines improves outcome:

1) Protocols
2) Feedback to individual surgeons decreases complications



"…, one of the greatest opportunities to improve patient outcomes will probably come not from discovering new treatments but from more effective delivery of existing therapies."

Pronovost PJ et al., Lancet 2004; 363:1061-7