THE ROLE OF IMMUNONUTRITION IN MAJOR ELECTIVE ABDOMINAL SURGERY

A DISSERTATION SUBMITTED TO

THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY

In partial fulfillment of the regulations for the award of the degree of

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BRANCH I: M.S (General Surgery)

DEPARTMENT OF GENERAL SURGERY

GOVERNMENT STANLEY MEDICAL COLLEGE AND HOSPITAL

THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY

CHENNAI

APRIL 2016

CERTIFICATE

This is to certify that the dissertation titled "THE ROLE OF IMMUNONUTRITION IN MAJOR ELECTIVE ABDOMINAL SURGERY" is the bonafide work done by **DR.T.JEYALAKSHMI** Post Graduate student (2013– 2015) in the Department of General Surgery, Government Stanley Medical College and Hospital, Chennai under my direct guidance and supervision, in partial fulfillment of the regulations of The Tamilnadu Dr. M.G.R. Medical University, Chennai for M.S., Degree (General Surgery) Branch - I, Examination to be held in April 2016.

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DECLARATION

I, **Dr. T.JEYALAKSHMI** solemnly declare that this dissertation titled "**THE ROLE OF IMMUNONUTRITION IN MAJOR ELECTIVE ABDOMINAL SURGERY"** is a bonafide work done by me in the Department of General Surgery, Government Stanley Medical College and Hospital, Chennai under the guidance and supervision of my unit chief. **Prof. Dr S.VISWANATHAN M.S HOD OF GENERAL SURGERY**

This dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the university regulations for the award of M.S., Degree (General Surgery) Branch - I, Examination to be held in April 2016.

Place: Chennai.

Date: September 2016 DR.T.JEYALAKSHMI

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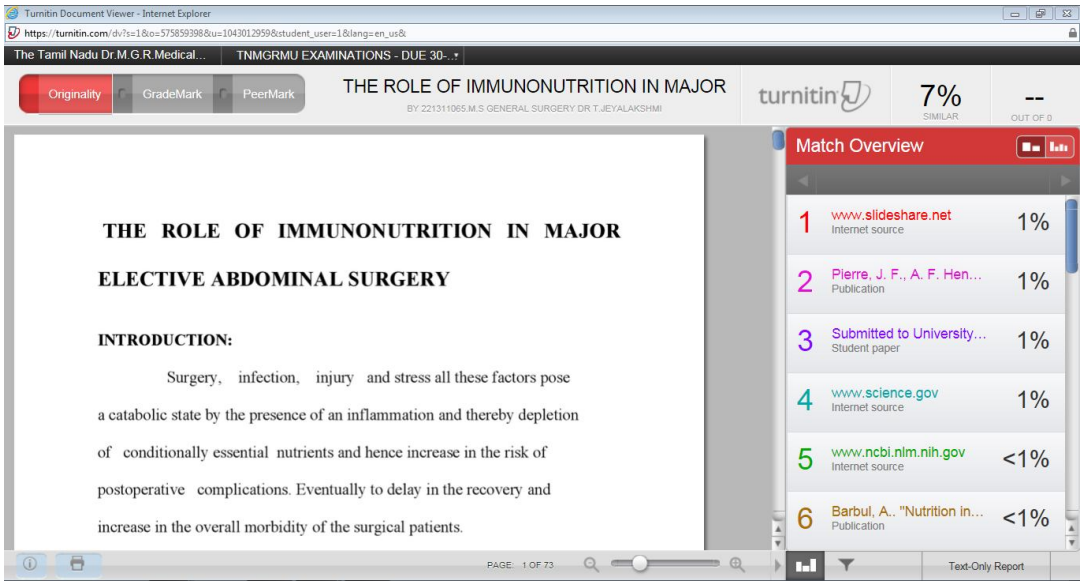
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THE ROLE OF IMMUNONUTRITION IN MAJOR
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INTRODUCTION:
Surgery, infection, injury and stress all these factors pose a catabolic state by the presence of an inflammation and thereby depletion of conditionally essential nutrients and hence increase in the risk of postoperative complications. Eventually to delay in the recovery and increase in the overall morbidity of the surgical patients.
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ABSTRACT

INTRODUCTION

Surgery, infection, injury and stress all these factors pose a catabolic state by the presence of an inflammation and thereby depletion of conditionally essential nutrients leading to increase in the risk of postoperative complications and eventually delay the recovery and enhance the overall morbidity of the surgical patients.

AIM

The study aims to investigate the effect of Immunonutrients on patients undergoing Elective Major Gastrointestinal surgery by assessment of changes in the clinical outcome in terms of postoperative complications compared to a normal diet.

MATERIALS AND METHODOLOGY

A prospective non randomnized study which included 50 patients who underwent major elective GI surgery for both benign and malignant diseases with IMN supplementation. The study group n=50 where administered 30 gms of IMN formula three times a day for 5 days preoperatively by oral route.The control group

were given a normal diet during the study period.The preoperative variables measured were weight,BMI.The post operative variables are the primary outcomes of infectious complications such as SSI,UTI,pneumonia ,wound abscess and anastomotic leaks were recorded in the prescribed proforma.\

CONCLUSION:

The study outcome has proved a beneficial reduction of infectious complications and substantial improvement with the immunonutrient formula and it emphazies the subset of malnourised patients are markedly benefitted .

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TABLE OF CONTENTS

ABBREVIATIONS

IMN	IMMUNONUTRIENTS
SMA	SUPERIOR MESENTRIC ARTERY
IMA	INFERIOR MESENTRIC ARTERY
DC	DENDRITIC CELL
GIT	GASTOINTESTINAL TRACT
TNF	TUMOUR NECROSIS FACTOR
IL	INTERLEUKIN
CRP	C REACTIVE PROTEIN
NO	NITRIC OXIDE
ZN	ZINC
HCL	HYDROCHLORIC ACID

INTRODUCTION

Surgery, infection, injury and stress all these factors pose a catabolic state by the presence of an inflammation and thereby depletion of conditionally essential nutrients leading to increase in the risk of postoperative complications and eventually delay the recovery and enhance the overall morbidity of the surgical patients.

Inspite of advancement of modern surgical practices, minimal surgical trauma and newer generations of antibiotics and improved perioperative care in the recent years, the increase in postoperative infection rate is still of great concern. The role of nutrition in the recovery from trauma or surgical insult has been researched by clinicians since the period of Hippocrates. Poor nutritional diet or deficiency of individual nutrients markedly alters the numerous factors of wound healing. The interaction of nutrition and wound healing is still not clearly deciphered. Efforts are made to develop wound-specific nutritional interventions and the pharmacological use of specific nutrients as modulators .

The role of Immunonutrients as a supplemental nutrition in elective gastrointestinal surgical patients and modulating the inflammatory response and improvement in postoperative outcome is to be evaluated .

AIM

The study aims to investigate the effect of Immunonutrients on patients undergoing Elective Major Gastrointestinal surgery by assessment of changes in the clinical outcome in terms of postoperative complications compared to a normal diet.

REVIEW OF LITERATURE

The **"GUT ORIGIN OF HYPOTHESIS"** mentions the leaky gut has a predominant role in the occurrence of sepsis with the concept of bacterial migration in vivo and in vitro .The intestinal barrier is of major importance as the distal small bowel and colon contain enormous concentration of bacteria. Under extreme clinical conditions like surgery and stress the intestinal barrier function is impaired, resulting in the movement of bacteria and toxins to the systemic circulation .This process of bacteria and its products moving across the intestinal mucosal barrier and with a systemic spread is known as bacterial translocation. Enteral nutrition supplies the intestinal mucosa and maintains Gut associated lymphoid tissue and decreases the bacterial translocation to the portal vein. The integrity of the mucosal barrier and functioning immune system are prerequisites for adequate gut function. The concept of gut barrier failure and bacterial translocation lead to the major impetus of initiation of early enteral feeding after injury. Enteral feeds maintain the intestinal structural integrity by increasing the mucosal mass, enhancing luminal epithelial cell proliferation ,maintaining villus height and stimulating the brush border enzymes.Enteral feeding preserves the intestinal barrier function better than parenteral route.

Malnutrition and immune dysfunction are synergistic and most often occur in hospitalized patients. Gastrointestinal malignant patients are more susceptible for malnutrition due to poor oral intake and cachexia. Immunonutition as a modality of intervention dates back to 3000 years in ayurvedic medicine. Malnutrition has increased the infection rate from 0.1% in the well nourished to 18% in the malnourished. The organisms measles, tuberculosis and pneumocystitis carnii are more susceptible in immune compromised patients. Malnutrition has an impact on wound healing. Protein catabolism can result in a delay in wound healing. A hypoalbumineamic patient experiences wound dehiscence ,with the albumin level of <2 gm/dl and protein supplementation can reverse this effect.

ANATOMY OF INTESTINE

Small Intestine:

The duodenum, jejunum, and ileum are the constituents of small intestine. The duodenum is anatomically distinct, but the jejunum (proximal two fifths) and ileum (distal three fifths) have no true anatomic border between them

The Duodenum

The duodenum hasfour parts: the first portion or the bulb, the second or descending portion, the third or transverse portion, and the fourth or ascending portion. The first portion begins at the pylorus and sweeps to the right; it is anchored by the hepatoduodenal ligament. The Blood is supplied from the supraduodenal & gastroduodenal arteries; both arise from hepatic artery.

The second portion of the duodenum travels posteriorly and is caudad to the level of first lumbar vertebra. The arterial supply is from the celiac axis through the gastroduodenal artery to the anterosuperior and posterosuperior pancreaticoduodenal arteries and from the superior mesenteric artery (SMA) through the anteroinferior and posteroinferior pancreaticoduodenal arteries.

Third portion begins as the duodenum sweeps to the left at the level L3 vertebra. It is associated with pancreas and superior mesenteric artery.

The fourth portion of the duodenum begins at the aorta, extends to the left, and passes ventral to the left psoas. It emerges into the peritoneum at the duodenojejunal flexure, which is fixed to the posterior abdominal wall at

the ligament of Treitz, Venous drainage from the duodenum is through the splenic, superior mesenteric, and portal veins.

Jejunum and Ileum

The jejunum and ileum comprise of the latter two parts of the small intestine (23). The jejunum origins at the duodenojejunal flexure. There is no clear line of division between jejunum and ileum (24).

The blood supply of the jejunum and ileum derives from the SMA, which has an extensive anastomotic network near the mesenteric border of the bowel called the marginal artery.

Jejunum	Ileum
located mainly in the upper left quadrant	located mainly in the lower right quadrant
Thick instestinal wall	Thin intestinal wall
longer vasa recta (straight arteries)	Shorter vasa recta (straight arteries)
less arcades (arterial loops)	More arcades (arterial loops)
red in colour	pink in color

The jejunum tends to have a single marginal artery from which arise long, relatively straight branches of the vasa recta. This pattern gradually blends into arcades that travel close to the mesenteric edge of the bowel and give rise to short branches in the ileum.

The intestine tends to become thinner and paler distally, along with a decrease in diameter. Lymphatic tissues to the small intestine, called Peyer's patches are most numerous in the distal ileum, whereas plicae circulares are more prominent in the proximal jejunum.

The vascular supply to the small intestine arises from SMA. The arterial branches derived from SMA pass through the two layers of the mesentery into the gut at the mesenteric margin of the small bowel.

In the jejunum, the arcades are comprised of long vasa recta (3 to 5 cm), whereas in the distal ileum the arcades are elongated and the vasa recta are relatively short. Venous drainage from the intestine parallels the arterial supply, with the superior mesenteric vein being the major venous collecting system; it also lies within the mesentery to the right of the SMA.

Innervation to the small intestine is through the autonomic nervous system and includes sympathetic, parasympathetic, and enteric divisions. Sympathetic fibers arising from thoracic segments of the spinal cord synapse in the celiac ganglion. Parasympathetic fibers arise from the vagus nerve and synapse in the submucosal (Meissner's) and myenteric (Auerbach's) plexus.

The Large Intestine

The large intestine originates from both the midgut and the hindgut. The colon is approximately 150 cm long, and its greatest caliber is 7.5 cm at the cecum, from where it gradually diminishes to 2.5 cm at the rectosigmoid.

The longitudinal muscle layer is concentrated to form three linear bands that are equidistant from each other and make up the taeniae coli. These shorter taeniae cause the circular muscle coat to be puckered and thrown into haustral sacculations because the length of the taeniae is less than that of the bowel wall.

The taeniae extend from the tip of the cecum to the rectosigmoid and are approximately 6 mm wide. Most of the colon, other than the appendix and cecum, is peppered with peritoneum-covered adipose pieces known as appendices epiploicae.

CECUM

The cecum is the commencement of the large intestine and just above the ileocecal valve. Its average axial diameter is approximately 6 cm, with a breadth of about 7.5 cm. Anteriorly, cecum is in contact with the anterior abdominal wall but may have greater omentum or coils of small intestine

overlying it. The cecum is mobile and has a complete covering of peritoneum, although this may be absent at the superior part.

ASCENDING COLON

The ascending colon is narrower than the cecum at its origin and is about 15 cm long. It then turns down, forward, and to the left, forming the hepatic flexure. The ascending colon is covered on all sides except its posterior surface. It is not uncommon for it to be completely covered with peritoneum and to contain a narrow mesocolon. The hepatic flexure has a vertical mobility of 2.5 to 7.5 cm with respiration.

TRANSVERSE COLON

The transverse colon begins at the hepatic flexure and passes across the abdomen into the left upper quadrant, where it curves acutely onto itself, down and backward, to form the splenic flexure. It is about 50 cm long, and in its course across the abdomen, it forms an arch with its concavity facing backward and up. The transverse colon is almost completely covered with peritoneum between the head of the pancreas and the splenic flexure.

The transverse colon merges into the descending colon at the splenic flexure.

This may be so acute that the distal transverse colon lies anterior to the descending colon. The splenic flexure is connected to the diaphragm by the phrenicocolic ligament, at the level of the 10th and 11th ribs.

DESCENDING COLON

Descending colon is 25 cm, long and starts at the splenic flexure up to the pelvic brim. It is covered by peritoneum over its anterior surface and side. On its anterior aspect, it is related to the coils of the small intestine, and in its lower portion, it is related to the anterior abdominal wall.

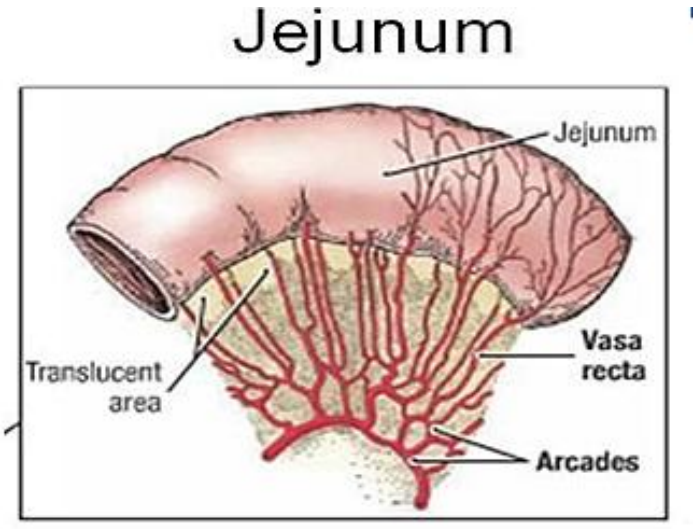
SIGMOID COLON

Sigmoid colon begins at the pelvic brim and forms a loop of about 40 cm that lies within the pelvis. It becomes continuous with the rectum at the level of S3 vertebra and is marked by lower end of the sigmoid mesocolon.

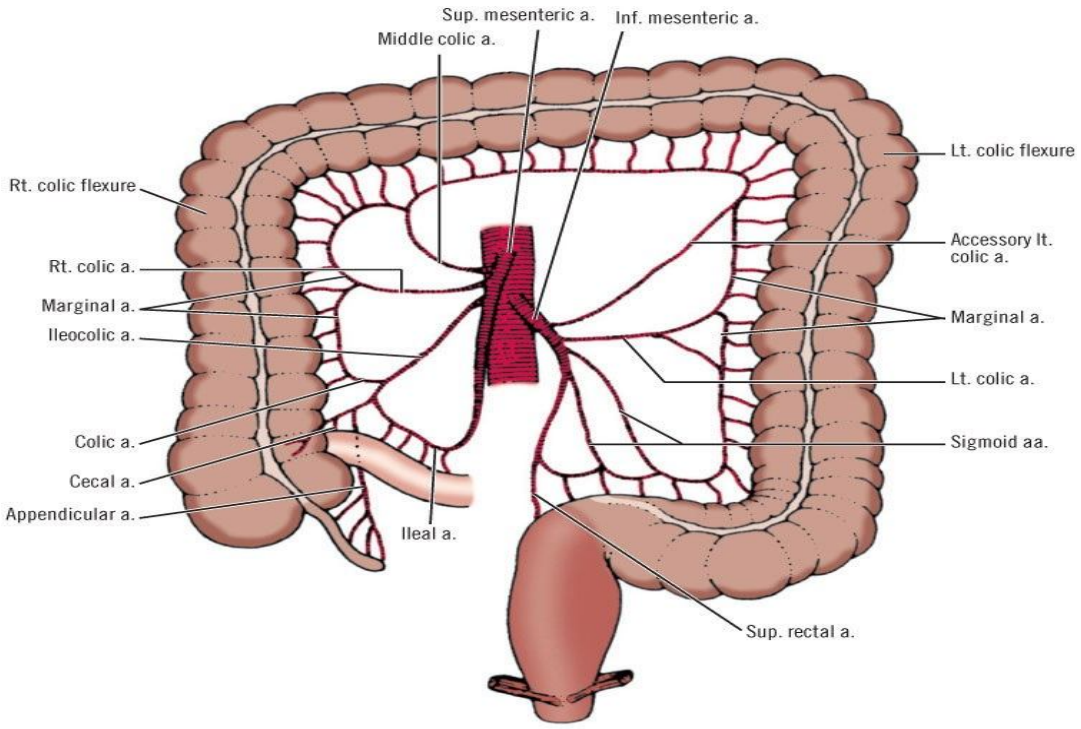
ARTERIAL SUPPLY

SMA supplies the colon to a level just short of the splenic flexure. IMA supplies the large intestine upto the mucous membrane of the upper third of the anal canal. The following branches are responsible for supplying the colon:

1. The ileocolic artery branches early from the superior mesenteric trunk. The artery then divides into anterior and posterior cecal arteries to supply cecum.
2. The right colic artery has its origin to the right of the root of SMA. At left side of colon, it branches into a descending branch, which anastomoses with the colic branch of the ileocolic artery, and an ascending branch, where it anastomoses with a branch of middle colic artery.



- **Less complex arterial arcades**
- **Longer Vasa Recta**
- **More plicae circulares, thicker, more highly folded**
- **No fat in mesentery**



vascular anatomy of large intestine

3. The middle colic artery is the most proximal branch of the SMA. It divides into right and left branch at the transverse colon. The right branch anastomoses with the ascending branch of the right colic artery, whereas the left branch anastomoses with a branch of the left colic artery.Inferior mesenteric artery arises opposite the L3 vertebra from the front of the aorta. The following branches supply the left side of the colon:

The first branch is the left colic artery. It then leaves as the upper branch, and lower branch. Both branches further divide into branches that anastomose with the left branch of middle colic artery.

Sigmoid arteries are three or four branches that arise from a common origin at the inferior mesenteric artery below the left colic artery. They pass forward in the sigmoid mesocolon and supply the sigmoid colon.

The marginal artery is the name given to a single arterial trunk made up of anastomoses around the concave border of the large intestine from the ileocecal junction to the rectosigmoid junction. The marginal artery is therefore made up of branches of both the superior and inferior mesenteric arteries.

VENOUS DRAINAGE

Veins from the right side of the colon flow into the superior mesenteric vein (SMV), which drains the midgut. Veins from the left side of the colon flow into the inferior mesenteric vein (IMV), which drains the hindgut.

PHYSIOLOGY OF GASTROINTESTINAL SYSTEM:

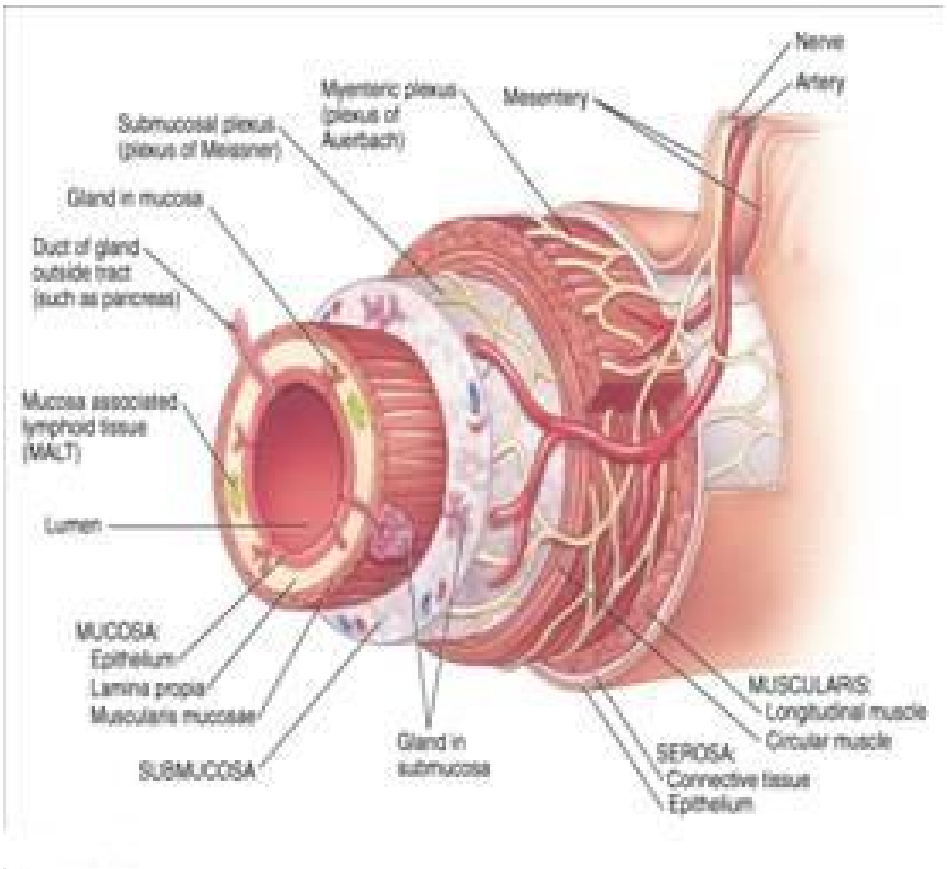
The mouth is the entry to the digestive system and food is physically broken and deglutition of the food is facilitated by moistening and initiation in the breakdown of carbohydrates and fats by the enzymes ptyalin and lingual lipase. It contains antimicrobial factors like IgA which neutralizes the bacteria in the food. PH of saliva is 6-8. Total salivary secretion is 1.5 litre. Saliva has the second highest concentration of potassium next to colon.

Stomach:

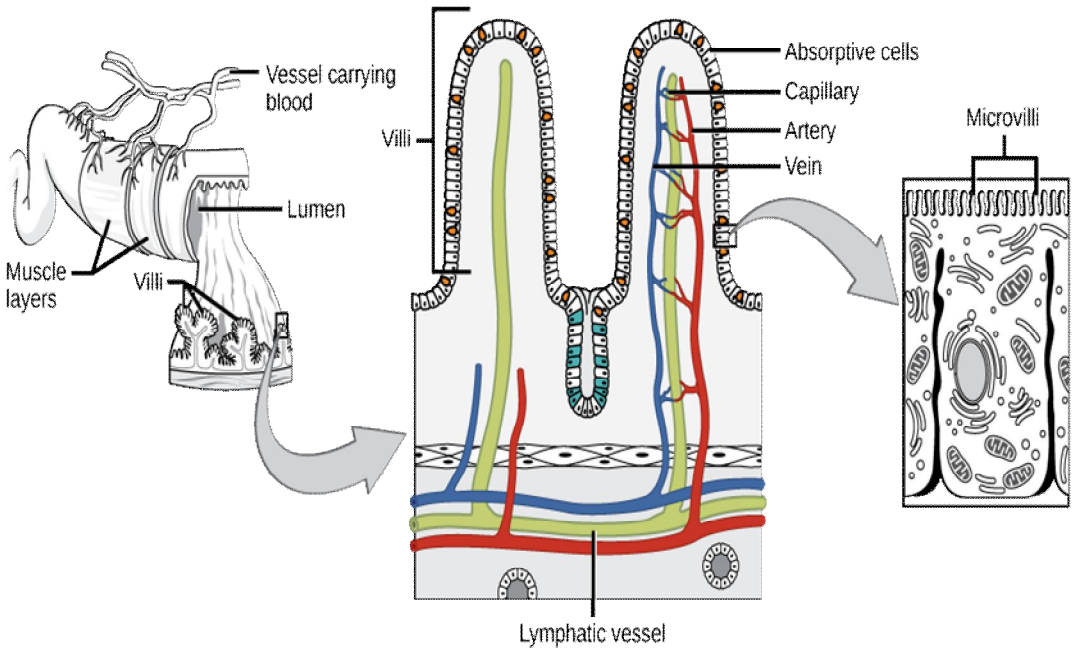
It contains numerous rugae and folds. The muscular contractions mixes and churns the food with the enzymes to form chyme. The parietal cells secrete HCL and intrinsic factor which breaks the particles of food ,initiates protein digestion by activating pepsinogen to pepsin. The absorption of vitamin B12 is depended on the Intrinsic factor and it occurs in the distal ileum. Gastrectomy patients develop pernicious anemia due to the lack of IF. Gastric juice amounts to 2litres .PH is 1-2. The surface area is 0.053 m2 small compared to the small intestine . Gastrin is the principal hormone

SMALL INTESTINE:

It is made up of four main layers-muosa, submucosa, muscularis propria and serosa. The inner layer is the mucosa and it is composed of the epithelium ,lamina propria and muscularis mucosae. The mucosa functions as a site of absorption of nutrients and water from the intestinal lumen. The **submucosa is** the **strength layer of the bowel wall** and is composed of the connective tissue. When completing a bowel anastomosis it is important to include bites through this layer of tissue to ensure integrity of the anastomosis.

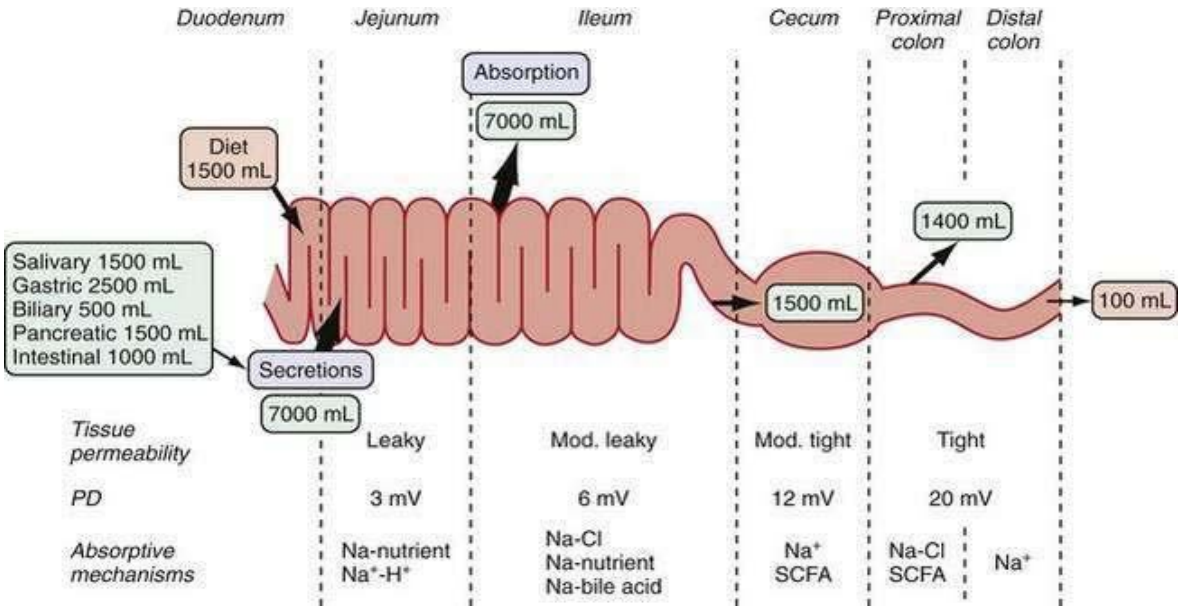


The maximum site of absorption are due to the numerous increased villi and micro villi which increase the surface area to 200 m2. Villi are finger like projections of the mucosa and are longest in the duodenum where most of the absorption occurs and shortest in the distal ileum. The carbohydrates are hydrolyzed by the enzymes in the brush border. Succus entericus are the small intestinal secretions which amounts to 2litres and the majority portion is water 98.5% and solids 1.5% .Paneth cells activate the enterokinase and which further releases the pancreatic zymogen granules for digestion. PH is 8-9. The acidic nature of the chyme is neutralized by the alkaline secretions .



LARGE INTESTINE:

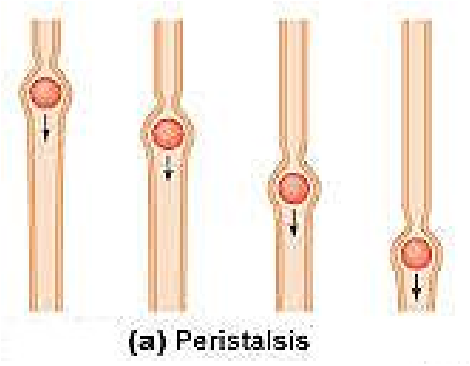
It contains the maximum number of bacteria in the entire GI system.



The amount of water excreted in the faeces is 150 ml.

MIGRATORY MOTOR COMPLEX:

Periodic and intense electrical activity are seen in the fasting stomach and intestine that lasts for 3-6 minutes and spreads from the stomach to the ileum. It is cyclical and repeated every 90 minutes and migrate at the rate of 5cm/minute. It clears the stomach and small intestine of luminal contents in preparation for the next meal. Gastric, pancreatic and bile flow increase during MMC. Food ingestion inhibits the MMC.



TYPES of contractions :

Segmental:

The **pacemaker are the interstitial cells of cajal** which are stellate mesenchymal cells that are present between the inner circular and outer longitudinal layer and initiates the frequency of the contractions.Pacemaker cells are absent in the esophagus and proximal portion of stomach. The cajal cells produce basal electrical rhythm which is the spontaneous fluctuation of the membrane potential between -65 and -45mv. The BER rarely causes muscle contraction but the superimposed spike potential increase the muscle tension. The rates of BER in the stomach-4/mt and duodenum is 16/mt. The segmental contractions moves the chyme to and fro and increases the exposure to mucosal surface and helps in mixing of the chyme with digestive juices.

HAUSTRATION:

They are mixing movements of the colon due to the circular muscle action and during the fasting period the colonic motility is minimal . The haustrations are formed due to the shorter length of the taenia coli which are the bands of the longitudinal muscle in comparison to the length of the intestine. They are slow segmenting , uncoordinated movements that occur approximately every 25 minutes .Fat component of the meal stimulates the colonic contraction.Protein ingestion inhibits colonic motility. Decending colon has the maximum postprandial increase in contraction.

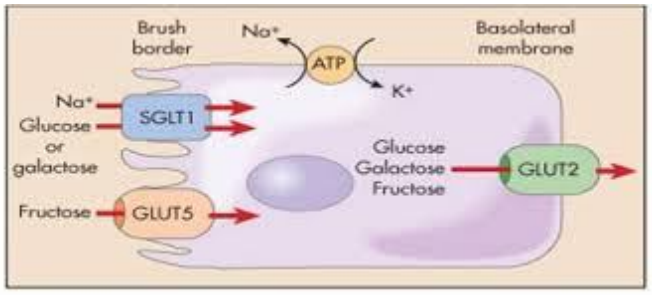
TRANSIT TIME :

The time taken for food to travel from the pharynx to esophagus is 6 seconds due to gravity and peristalsis. Water empties from the stomach in 12 mts.Gastric emptying time of the meal is 4 hours. The carbohydrate portion empties first followed by proteins and fat is the last. Chyme takes 3-4 hours to reach the ileum. Large intestine transit time is 2-4 days and with the increase in dietary fibre content ,it is reduced.

CARBOHYDRATE ABSORPTION:

The major portion of the diet contain starches (polysaccharides) ,sucrose and a small amount of lactose. Gycogen is animal starch but the 80% of food contains amylopectin and amylose. The average daily intake of carbohydrate is in the form of starch 64%,sucrose 26% and fructose 3%. Starch is digested by ptyalin from the saliva and this enzyme is inhibited by gastric juice. And cleaves the 1,4 linkage .Chyme is acted upon by the pancreatic amylase and it spares the 1,6 linkage hydrolization and the end products are Maltose, Maltotriose and limit dextrins. The three oligosaccharides are acted by the intestinal disaccharadise present in the microvilli of the ileum and degraded to oligosaccharides.Glucose is the primary energy source providing 30-40% of calories in atypical diet.The brain and redblood cells rely almost exclusively on a supply of glucose to function. Each gram of enteral carbohydrate provides 4kcal of energy.During fed states , hypoglycaemia leads to insulin secretion which promotes the glycogen synthesis. About 12hours of glycogen is available in the liver andd skeletal muscles, which provides a steady supply of glucose in between meals. In times of starvation and stress ,depleted glycogen stores cause the release of glucagons, which promotes the hepatic gluconeogenesis from aminoacids.If dietary

carbohydrates are not resumed ,glucagons promotes ketone body formation from lipids ,which the brain can utilize. A minimum intake of 400 calories of carbohydrate per day minimizes protein breakdown, which is administered in maintenance IV fluids during Nil per oral.

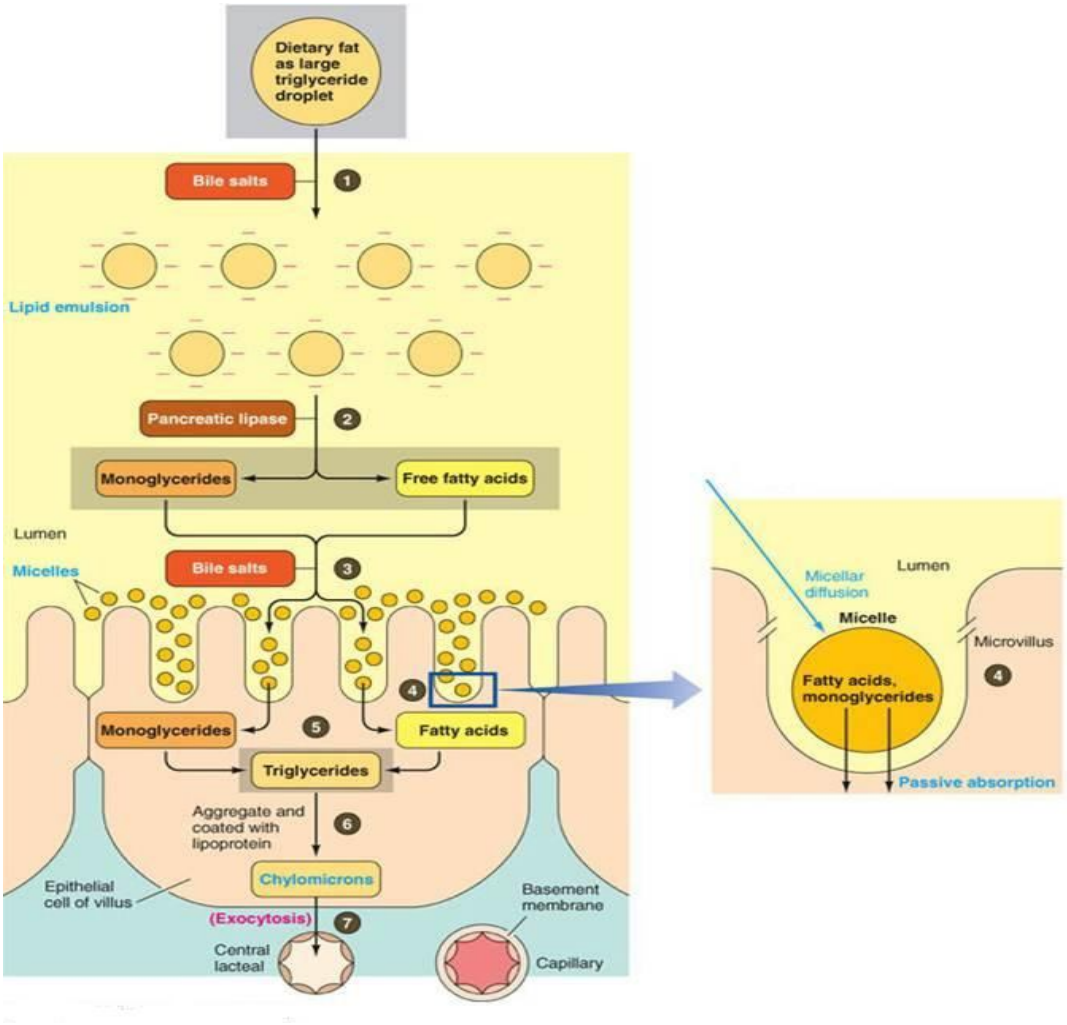


The glucose and galactose are absorbed by the Na+symport ,contrarily the fructose is absorbed by the facilitated diffusion. Insulin has no effect on the intestinal absorption of sugars. The maximum rate of glucose absorption from the intestine is 120 gm/hour.

LIPID DIGESTION:

Fatty acids are the functional units of lipid metabolism. Fats are ingested as triglycerides ,phospholipids ,cholesterol and cholesterol esters. Triglycerides are the most abundant .Pancreatic fluid provides enzymes integral in the digestive process of fat. Fat digestion also requires bile from the liver for emulsification, which is the process by which large fat globules are broken

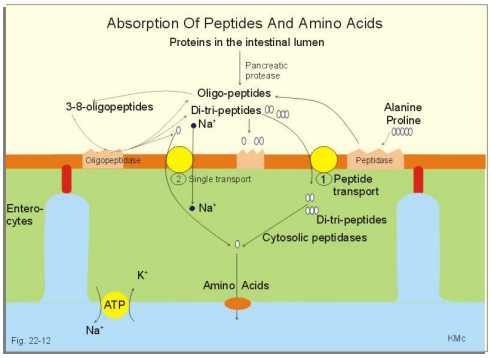
down into smaller sizes that are easier targets for water soluble enzymes.



The dietary fat is composed of large fat globules of triglygerides and is emulsified by the detergent action of bile salts into a suspension of small fat droplets. This lipid emulsification prevents the fat droplets from coalaescing and thereby increase the surface area for action by the pancreatic lipases. Furthur the lipase hydrolyzes the triglycerides into monoglycerides and free fattyacid. These water insoluble products are carried into the water soluble micelles and are presented to the intestinal epithelial cells. The monogl

yceride and fatty acid leaves the micelle and diffuses passively through the lipid bilayer of the luminal membrane. The resynthesis of the triglyceride occurs inside the epithelial cell .The TGL aggregates are coated with a layer of lipoprotein to form water soluble chylomicrons which are extruded through the basalmembrane of the cells by exocytosis. Chylomicrons are unable to cross the basement membrane of capillaries and instead enter the lymph vessels.

PROTEIN DIGESTION:



There are three main sources of protein : dietary, endogenous secretions and desquamated cells .Protein digestion begins in the stomach via pepsin and proceeds in the small intestine. Pancreatic proteases enter the duodenum in an inactive state as proenzymes. The proenzymes are activated by the brush border enzymes. The two main classes of enzymes are endopeptidase and exopeptidase. The most important is trypsinogen is

converted to the active enzyme trypsin by enterokinase.Once active it converts the other proenzymes into their active forms. Proteases break down the proteins into short oligopeptides and aminoacids. The brush border enzymes peptidases further hydrolyze the oligopeptides into free aminoacids, dipeptides, and tripeptides which can all be absorbed by enterocytes. Dipeptides and tripeptides are easily absorbed by the enterocyte because they are transported via a transmembrane H+ gradient.Aminoacids require an active Na+ transport. The majority of protein absorption takes place in the jejunum.

INFLAMMATION:

It is classified into acute and chronic. It is a series of molecular and cellular responses to eliminate foreign antigens or damaged (necrotic) cells and promote repair of damaged tissues. A protective response to initiate repair process and return the damaged tissue to useful function. In the absence of inflammation wounds and infection will never heal. The cardinal signs of acute inflammation was coined by CELSUS and are Rubor-redness is due to vasodilatation of small blood vessels ,Tumour-swelling (exudation of fluid),color-heat (increased blood flow due to vasodilation), DOLOR-Pain(stretching of tissue due to edema). The fifth

clinical sign was added by Rudolf Virchow as FUNCTIO LAESIO-loss of function.

PATHOPHYSIOLOGY OF ACUTE INFLAMMATION:

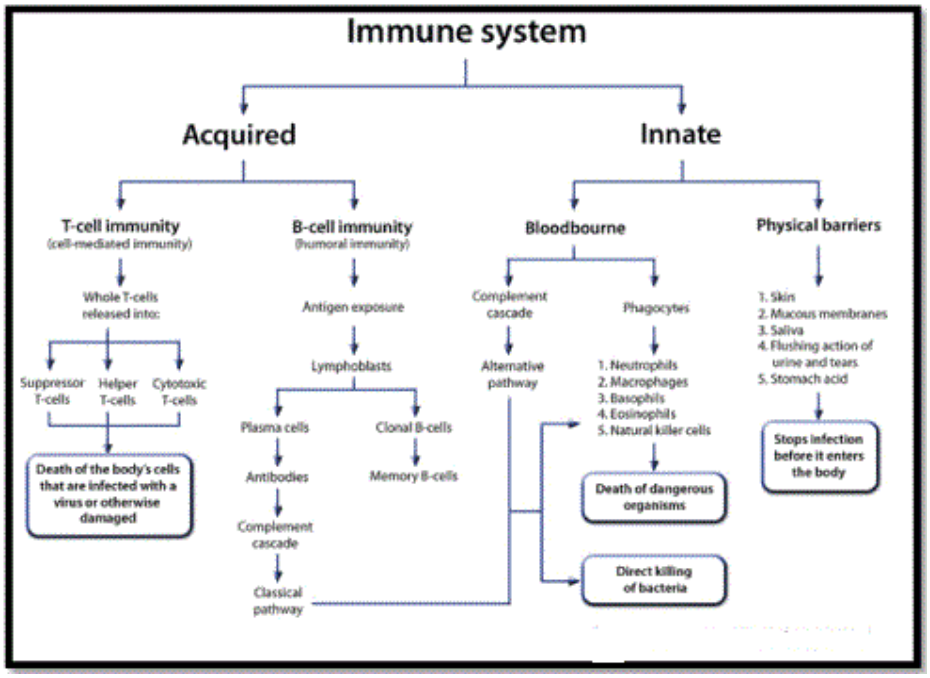
It has three major steps 1) vasodilation-alteration in vascular caliber that leads to increase in blood flow, earliest manifestation 2) vascular permeability-leads to escape of protein rich fluid (exudate) and leucocytes into extravascular spaces. Intravascular osmotic pressure reduces to exudation of proteins and osmotic pressure of interstitial fluid is increase and shift of fluid in the interstitial compartment. Fluid loss leads to increased viscosity of blood and stasis. 3)Extravasation of the leucocytes from the capillary circulation , and movement towards the foci of injury and their stimulation to eliminate the microbial organisms by-chemotaxis and phagocytosis. As stasis develops leucocytes accumulate along the endothelium known as margination. Next process is tumbling of leucocytes along the endothelium and finally adhesion of the leucocytes to the endothelium and pavementing. Leucocyte diapedesis is the process of transmigration across the endothelium and is regulated by the binding of adhesion factors–Selectins, Integrins and mucin like glycoproteins. Diapedes is predominantly occurs in the venules the exception in the lungs where it occurs in the capillaries. By chemotaxis the leucocytes migrate to

the site of injury and the chemoattractants are bacterial products and C5a,IL-8, LT4.Prolonged inflammation leads to destruction and healing of the tissue and diabetes, obesity, rheumatoid arthritis etc are examples. Chronic inflammation damages the organs and tissues ,the acute inflammation is an adaptive response.

METABOLIC RESPONSE TO TRAUMA:

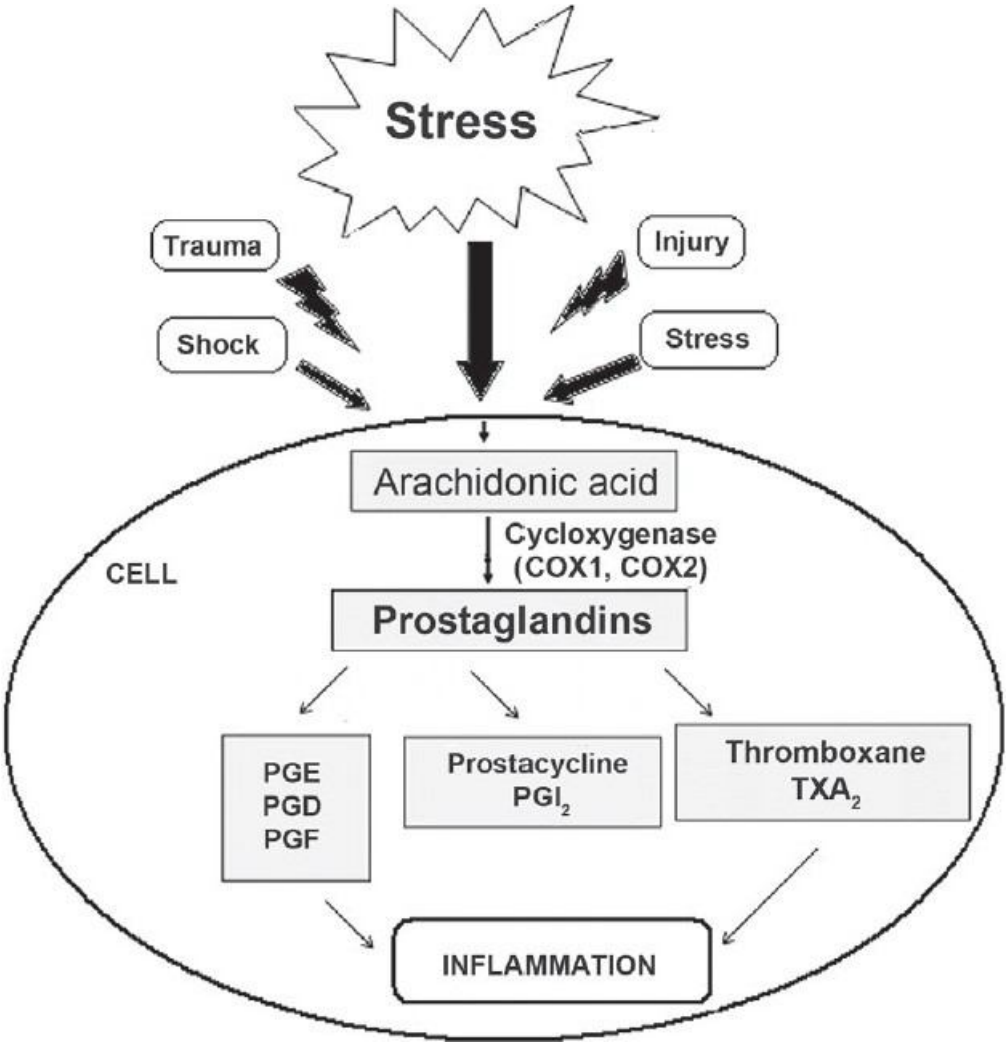
Surgical insult activates a complex cascade of metabolic host responses to meet the bodys homeostasis. The initial period is characterized by the protein breakdown ,increased utility of oxygen & ,insulin resistance . The changes that ensue are hyperglycaemia due to increased hepatic glucose production and skeletal muscle insulin resistance. There is a marked negative nitrogen balance due to the skeletalmuscle metabolism which leads to wasting of the lean body mass. Glutamine is the preferred energy source of enterocytes and immune cells and the antioxidant glutathione. Acute phase proteins and immune cells are produced in the liver at the expense of albumin. A redistribution of macronutrients from labile reserve(skeletal muscle and adipose tissue) to more active tissues for host defense, visceral protein synthesis and heat production. Injury is associated with a pronounced neuroendocrine response characterized by increased secretion of stress hormones as adrenaline and cortisol and also by

increased release of GH , ADH etc. Cortisol is the most important hormone with its widespread effects on glucose, aminoacid and fatty acid metabolism. There is no evidence to date that hormonl treatment can improve the outcome after major injury.



IMMUNE SYSTEM:

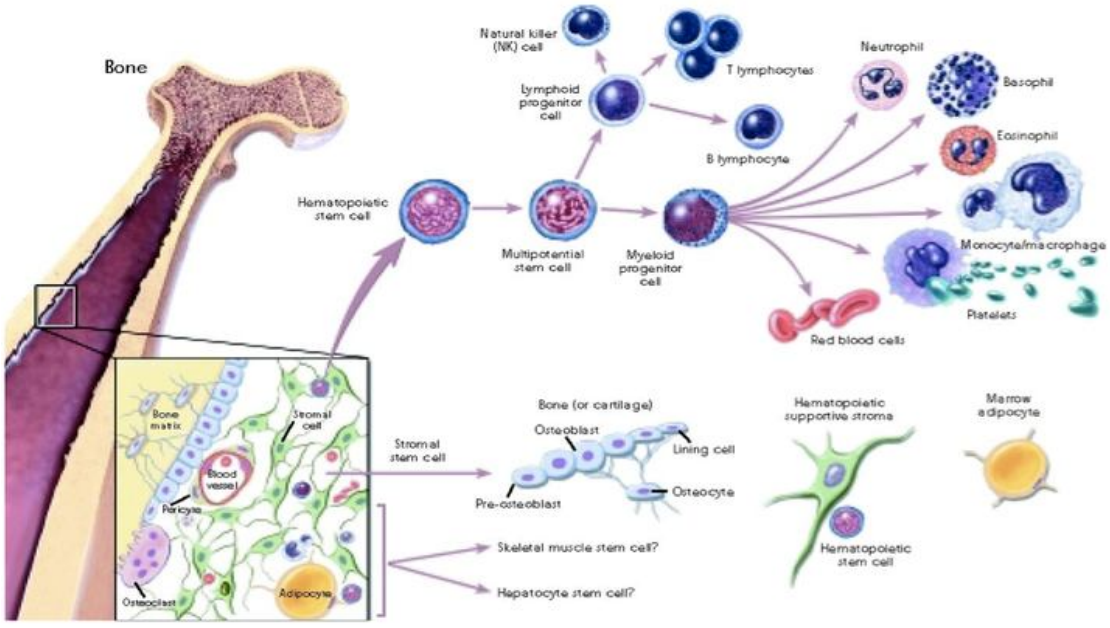
It is divided into the innate and acquired/adaptive immune responses. The fundamental function of the immune system is to combat against the infection and other foreign proteins (antigens) by its recognition of self antigens. If this mechanism fails it leads to autoimmune diseases.



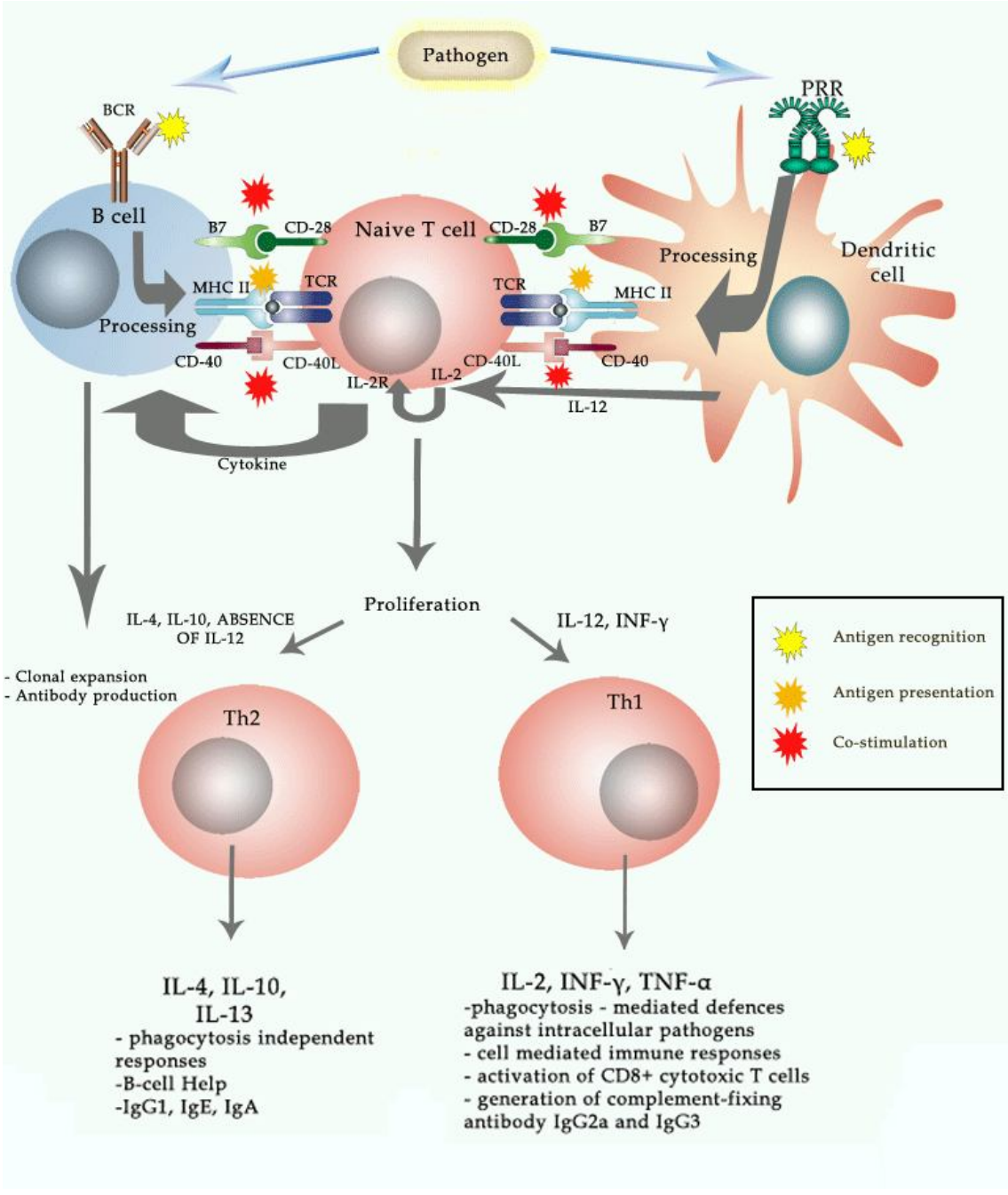
INNATE:

They are the first line of defense and are not specific to a particular pathogen and its specific elements are the epithelial barriers ,immune cells {neutrophils ,macrophages,dendritic cells and natural killer cells}. The evolutionary history suggests that the stimulation of NFkB is the main signaling pathway in innate immunity. It is activated quickly in response to invaders. The skin and epithelial lining of the lung and gut provide a

physical barrier from the outside world. Tight junctions between the neighbouring cells prevent early penetration by pathogen. The slimy mucous is primarily made of mucin and mucoproteins and protects against the pathogens adhering to the epithelium. The mucus layer consists of microbicidal substances that engulf and kill the pathogens. The most abundant antimicrobial peptides are defensins.



They are amino acids with a broad spectrum of antimicrobial activity including the ability to kill and inactivate the gram negative bacteria ,gram positive bacteria ,fungi ,parasites and also HIV. The innate mechanism depends on the identification of specific types of molecules that are common pathogens but are absent in the host .



These molecules are known as pathogen associated molecular patterns (PAMP) or microorganism associated molecular patterns(MAMP) and activate two types of responses –inflammatory and phagocytosis, both of

these responses occur rapidly even if the host has been never previously sensitized. The known examples of PAMPs are lipopolysaccharides (LPS) in gramnegative bacteria ,lipoteichoic acid in grampositive bacteria and double stranded RNA viruses. Pathogen associated molecules occur on the microbe surface in repeatitive sequences. The molecules are recognized by the dedicated receptors in the host known as pattern recognition receptors and are functionally divided into endocytic receptors which causes internalization and phagocytosis of microbes.

The signaling receptors activate the cellular signaling pathways and induce the expression of a multitude of immune responses. These include soluble proteins in the blood , as the complement system and the signaling receptors - membrane bound (toll like receptor family) and the G-protein coupled receptors. The toll like receptors functions in two aspects to initiate the phagocytosis and activates the progression of gene expression in the host for stimulating the innate response.

COMPLEMENT SYSTEM:

Complement system has 20 soluble proteins that are primarily produced in the liver, and circulates in the extracellular fluid and blood. They are inactive until they are stimulated by infection. Being a part of the innate immune system does not require prior immunization for activation. It

originally was identified by their ability to enhance and support the action of antibodies. It is rapidly activated in a nonspecific manner in one the three pathways –Classical, mannan-binding lectin and alternate pathway. In the classical pathway, it is activated by an IgG or IgM antibody –antigen complex.The alternate pathway does not rely on the antigen-antibody complex,but it is directly stimulated by bacterial cell wall components.The Mannan binding pathway is similar to the classical except that it is initiated by a cascade by the liver producing mannan lectin when bound to a pathogen surface.C3 is the pivotal component .Deficiency of c3 are subjected to repetitive bacterial infections. The initial complements and C3 are proenzymes which are activated in a step wise manner by proteolytic cleavage . A cascade ensues in the series and the next complement is generated as a serine protease. All the reactions occur on the surface of the pathogen. Activation of the complement cascade results in the formation of products that act to kill the microbes,attract the neutrophils by chemotactic action and stimulate both phagocytoses and bacterial killing through opsonization of bacteria and neutrophil degradation.

TOLL LIKE RECEPTORS:

Humans have 10 toll like receptor, stimulate the expression of molecules of both innate and inflammatory responses and adaptive

immune response. The receptors are host cell surface receptors responsible for inducing the gene expression in response to microbes .TLR are numerous on the surface of neutrophils and macrophages and on the epithelial lining of the respiratory tract and GIT . Phagocytic cells destroy the pathogens. The tissue macrophages reside abundantly in areas where infection are most susceptible like the lungs and gut. They are present abundantly in the connective tissues ,liverand spleen, as kupffer cells and act primarily as the frontline defense of the microbes . The neutrophils are absent in the normal healthy tissue but are abundant in the blood .It is swiftly recruited to the site of insult by the macrophages and peptides released by the pathogens. Macrophages & neutrophils have a plethora of cell surface receptors that recognizes & engulfs the pathogen. The pathogens are phagocytosed ,the macrophage and neutrophil releases enzymes to kill it eventually . The phagosome is fuse d with lysosomes which consists of acid hydrolases & lysozymes that disintegrate the bacterial cell wall protein. The phagocytes integrates the NADPH oxidase complex on the membrane and catalyzes the formation of toxic compounds like superoxide radical, hydroxyl, hypochlorite, H2O2. Macrophages continue to survey the tissues whereas the neutrophils are dead. The dead neutrophils are a major part of pus that is found in active wound infection sites. The Greenish hue of the pus is due to the presence of neutrophils and

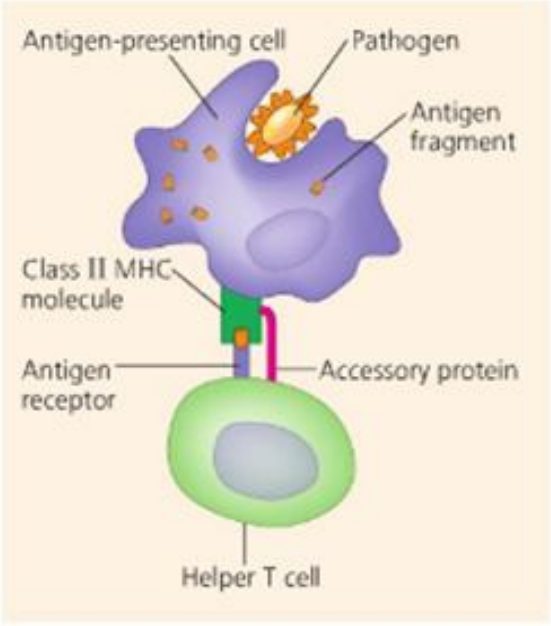
its copper containing myeloperoxidase enzyme. The activated macrophages recruit the other phagocytic cells to the site of injury. Pathogen invasion of tissue inevitably elicits an inflammatory response. Response per se is characterized by pain, redness, heat, swelling due to changes in the local blood vessels. Inflammatory responses are initiated by a number of signaling molecules. The action of TLR leads to the production of both lipid signaling prostaglandins and peptides like cytokines ,most of the cytokines produced by activated macrophages are chemokines. The Chemokines recruit the neutrophils to the site of infection, and others attract monocytes and DC. DC picks up the antigen from the invading pathogen and carries them to the lymph node and are presented to the lymphocytes to channelize the adaptive immune system. Other cytokines trigger fever like IL 1 and helps the immune system to combat the infections, as most of them are viral and bacterial pathogens which grow at low temperatures.The immune system functions more efficiently at high temperature. The proinflammatory signaling molecules stimulates the endothelial cells to express the proteins that trigger blood coagulation in the small blood vessels , and inturn the occlusion helps to prevent the organisms from entering the circulation and limiting its spread to the other parts of the body.

ADAPTIVE IMMUNE SYSTEM:

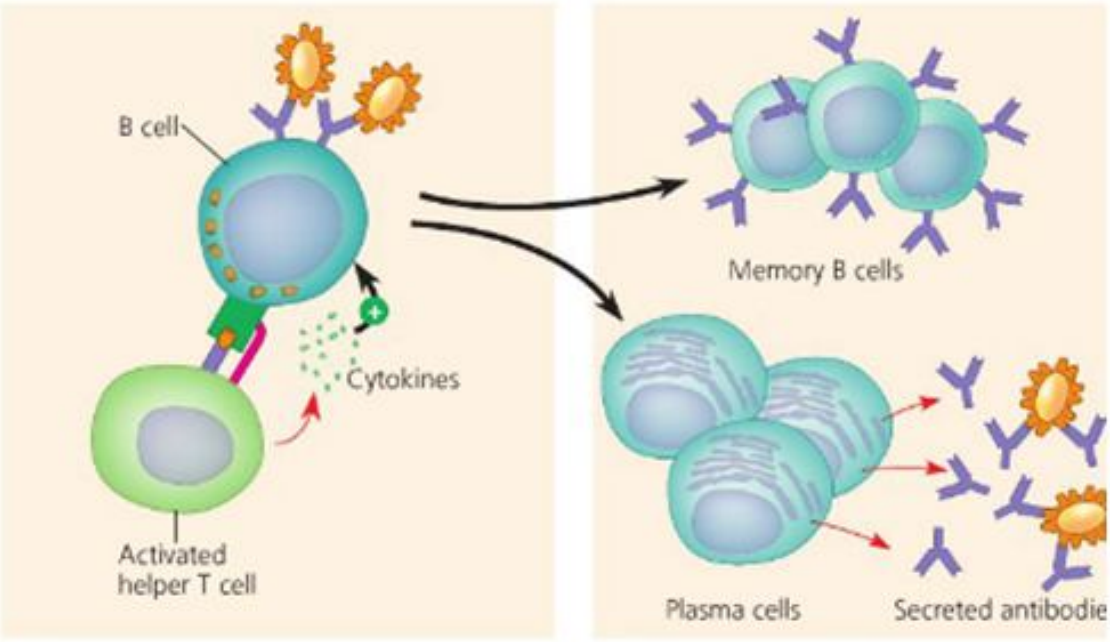
The role of adaptive immune response is to destruct the pathogens and are more specific in the production of B,T Lymphocytes and the response occurs in days to weeks .The responses are destructive ,it is crucial that the foreign cells are identified and host cells are spared. It consists of the humoral (extracellular microbes) and cell mediated immunity {intracellular microbes }

Activation of a B cell in the humoral immune response.

The protein antigens require activated helper T cells to initiate a humoral response. A macrophage or a dendritic cell can activate the helper T cell, which in turn activates the B cell to lead to antibody-secreting plasma cells



- The antigen presenting cell engulfs and destroys the pathogen, presents the antigen fragment complexed with a class II MHC molecule. The helper T cell recognizes the complex with the aid of cytokines ..

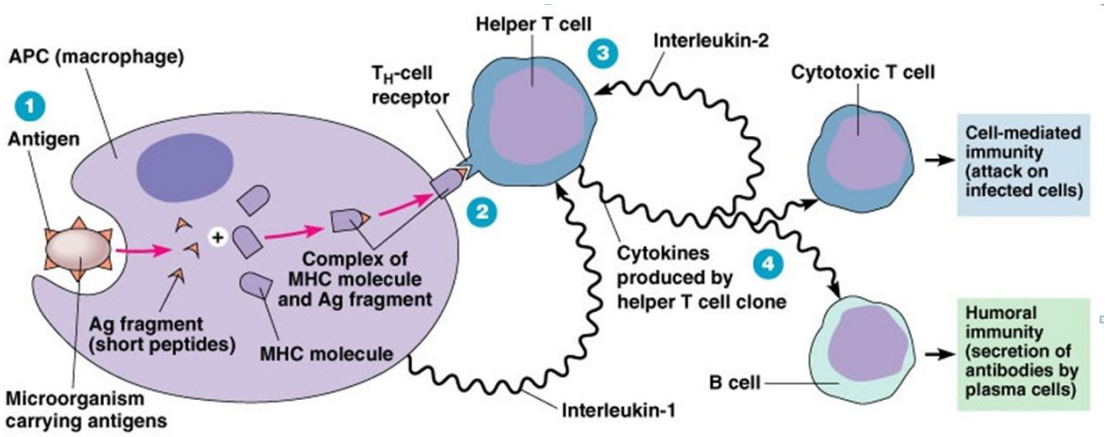


- The B cell receptors for the same epitope internalizes the antigen , It expresses the antigen fragment on the cell surface as a complex with the MHC class 11 molecule .An activated helper T cell bears the receptor specific for the displayed fragment and binds to the B cell .With the help of cytokines from the T cell, activates the B cell.

- The activated B cell differentiates into memory B cells and antibody – Secerting plasma cells. The secreted antibodies are specific for the same

antigen that initiated the response . The T lymphocytes of the adaptive immune system have evolved to provide a more competent means of defense and protection against subsequent re-infection with the same pathogen. There is a delay of 4-7 days occurs before the response takes effect , and the innate system has a definitive role in limiting the infection during this period. The stimulation of adaptive immune response starts when a pathogen is engulfed by an immature DC in the infected tissue. The specialized phagocytic cells resides in most tissues and are comparatively of a longer life span. DC are derived from the same Bone Marrow precursors as macrophages and shifts from the BM to the peripheral tissues to localize for the pathogens. Inevitably all tissue DC migrate through the lymphsystem to the regional lymph node and interact with naïve lymphocytes .If the DC fail to be activated ,they induce tolerance to the self antigen . The immature DC possess receptors on its surface that recognizes the pathogens such as bacterial cell wall p roteoglycans. Immature DC takes up extracellular material including any virus or bacteria that may be present by the receptor independent mechanism of macropinocytosis. The function of Dc is solely not the destruction of the pathogen but to sensitize the peripheral lymphoid stuctures and present to the T lymphocytes . .Highly effective APC secrete cytokines and activates the T lymphocytes that regulate both the innate and adaptive immune response.

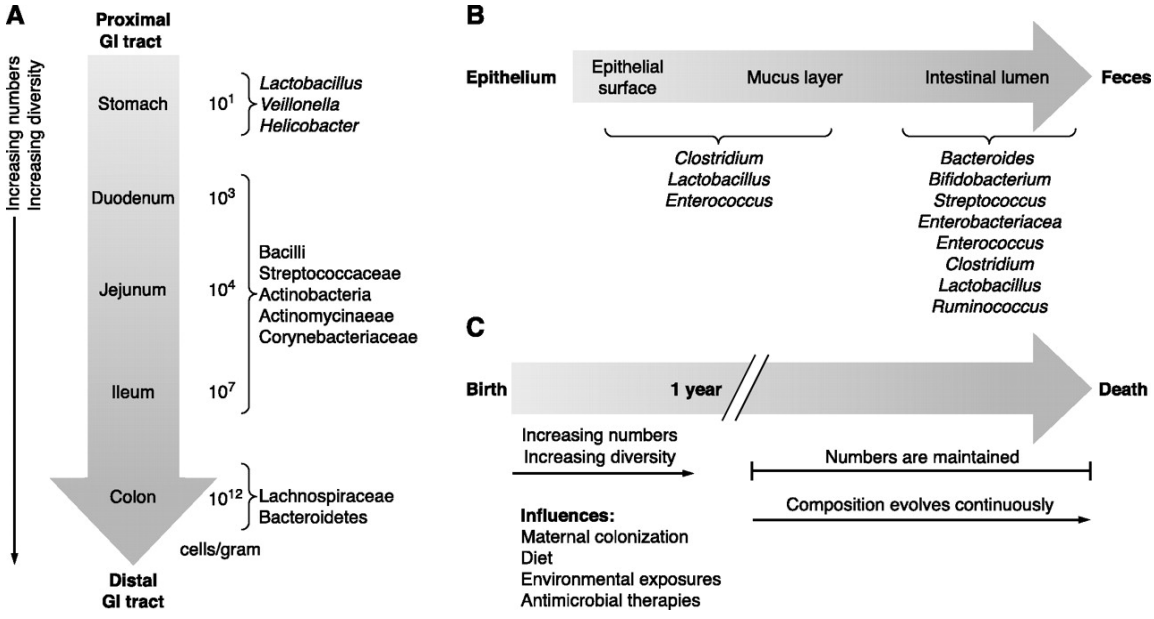
Tcells develop from the thymus and B cells develop in the BM in adults or the liver in the fetus. Inspite of their different origin both T & B cells arise from the same pluripotent haemopoetic stem cells and give rise to leucocytes .Primary lymphoid organs are the thymus and haemopoeitic tissue in the BM. Most lymphocytes die in the central lymphoid organs immediately after their development without ever functioning and the others mature and migrate via the blood to the peripheral lymphoid organs , GIT and respiratory tract epithelium. Peripheral lymphoid organs is the site where T& B cells react with foreign antigens.Both are instigated by antigens to proliferate and sustain into effector cells. Effector B cells are the Antibody mediated immunity which induce the plasma cells to generate the immunoglobins.There are two main classes of T cells –Cytotoxic and Helper T cells. Cytotoxic T cells kills the infected cells and the latter activates the macrophages, B cells and cytotoxic cells..B cells secrete antibodies that are transported and are distributed in the systemic circulation, where as T cells too are distributed to distant sites but its action is confined only on the neighbouring cells.



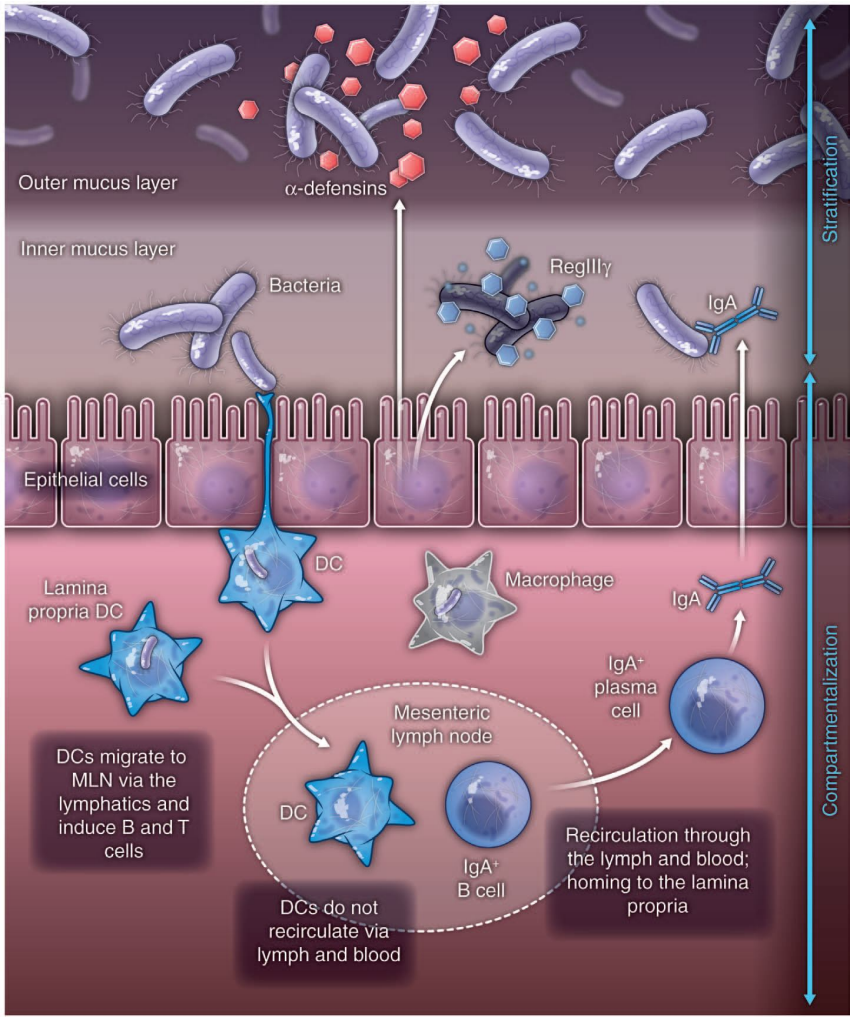
- An antigen – presenting cell (APC) encounters and ingests microorganism. Antigen fragments (shorts peptides)from the microorganism combine internally with MHC molecules and is presented on the surface of the APC
- A helper T (T_H) cell receptor binds to the complex, stimulating the APC to secrete interieukin-1
- The interieukin-1 stimulates the helper T cell to produce interleukin-2, which then stimulates the helper T cells to form a clonal of cells.
- Clonal cells in turn produce cytokines stimulating cells of both immune systems.

IMMUNOPHYSIOLOGY OF THE GUT:

The large numbers of microorganisms that inhabit mammalian body surfaces have a highly coevolved relationship with the immune system. Although many of these microbes carry out functions that are critical for host physiology, they nevertheless pose the threat of breach with ensuin pathologies. The mammalian immune system plays an essential role in maintaining homeostasis with resident microbial communities, thus ensuring that the mutualistic nature of the host-microbial relationship is maintained. The important function of the intestinal immune system is to control the exposure of bacteria to host tissues and thereby reducing the pathologic outcomes. This occurs at two levels –



- minimizing the direct contact between the intestinal bacteria and the epithelial cell surface by stratification.
- To confining the intestinal bacterium to the intestine and limiting the exposure to the systemic compartment by compartmentalization.



STRATIFICATION:

Intestinal epithelial goblet cells secret mucin glycoprotein that form a thick viscous coat to the cell surface. In the colon there are 2 distinct mucus layers, the outer layer consists of large number of bacteria, the inner layer is resistant to penetration. small intestine has no 2 mucus layers but Reg 111gamma is an antibacterial lectin expressed by the epithelial cells and limits the microbe penetration. It also depends on the IgA which specific for the intestinal bacterium is produced with the help of Dendritic cells. These bacterial laden DC interact with T,B cells of Peyers Patches ,inducing B cells to produce IgA and transcytosed across the epithelium and deposited on the apical surface. GIT with a surface area of 300-400m2 next only to respiratory tract is the largest surface connecting to the outer world. in The majority portion of the body's immune system about 60- 70% is localized to the GI lamina propria and mesenteric lymph nodes ,collectively referred as GALT.GI epithelial cells are replaced every 3-4days ,it adds to 55 million cells are renewed every minute.

Intestinal immune system:

It has two components-acquired or adaptive immune system-consists of peyers patches, IgA plasmocytes and lamina propria lymphocytes Effector pathway of intestinal epithelial cells, macrophages, eosinophils

and dendritic cells. Peyers patches are collections of lymphoid follicle located in the terminal ileum, appendix and colon.

CYTOKINES:

They are small proteins secreted by systemic immune cells macrophages, monocytes, lymphocytes and are crucial mediators in cell mediated immunity and inflammatory response. In healthy humans they are produced at low levels in plasma and function in a endocrine, paracrine or autocrine manner. They activate the intracellular signaling pathway NFkB gene expression which plays the cetral role in inflammatory cascade. They are not antigen specific and their effect can be inhibitory and stimulatory. The dominant proinflammatory cytokines are TNF,IL-1b,IL-6,IL-8,IL-12and IFN-gamma and the anti-inflammatory are IL-4,IL-10 and IL-13.The t-1/2 of circulating unbound cytokines is <5minutes to a few hours.TNF is the best described proinflammatory cytokine and is mainly produced by macrophages ,monocytes ,Tcells ,endothelial cells,fibroblasts and adipose tissue.It is the earliest cytokine secreted after trauma with a t-1/2 <20 minutes .It acts through its receptors TNF1 and TNF2.

Cytokines post elective surgey-

The acute phase response is related to the surgery related trauma or severity of the surgical related procedures. All the mediators of

inflammation peak post injury at about day 1 and 2 and return to baseline values by POD 6. Persistent pain, stress or a second insult will change the pattern.IL-1,IL6 & TNF are pluripotent cytokine which are intimately associated with the infection and inflammatory response.IL-6 can be produced by not only monocytes but also by endothelial cells and intestinal epithelial cells.The cellular and physiologic effects are diverse and induce fever, Tcell proliferation, promotion of differentiation of nerves and induction of synthesis of acute phase response in the hepatocytes.Circulatory concentrations of IL-6 dramatically increases after tissue injury like elective surgery, trauma & burns. The degree to which IL 6 is elevated correlates with the risk of post injury complications.

OXIDATIVE RADICALS:

They are a chemical species that have a single unpaired electron in the outermost orbit. Most of these are reduced reactive oxygen forms that are produced by the unavoidable byproducts of mitochondrial respiration. Reactive oxygen species are hydrogen peroxide, superoxide anionO2, and hydroxyl radical(OH).They are highly toxic and damage the cell membrane and nucleic acids and initiate autocatalytic reactions to propagate the chain of damage. The reduction –oxidation reaction during normal metabolic process are the rapid burst of superoxide which occurs in activated

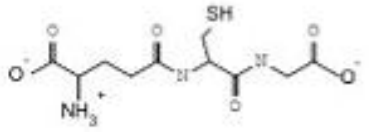
neutrophils during the process of inflammation with the help of NADPH oxidase. Transitional metals like cu and iron catalyze the free radical formation. NO generated in the endothelium and macrophages can act as a free radical. Cell injury is accomplished by lipid peroxidation and subsequent damage of the cellular and mitochondrial membrane, oxidative modification and degradation of intracellular proteins and DNA strand breakage.

ANTIOXIDANTS:

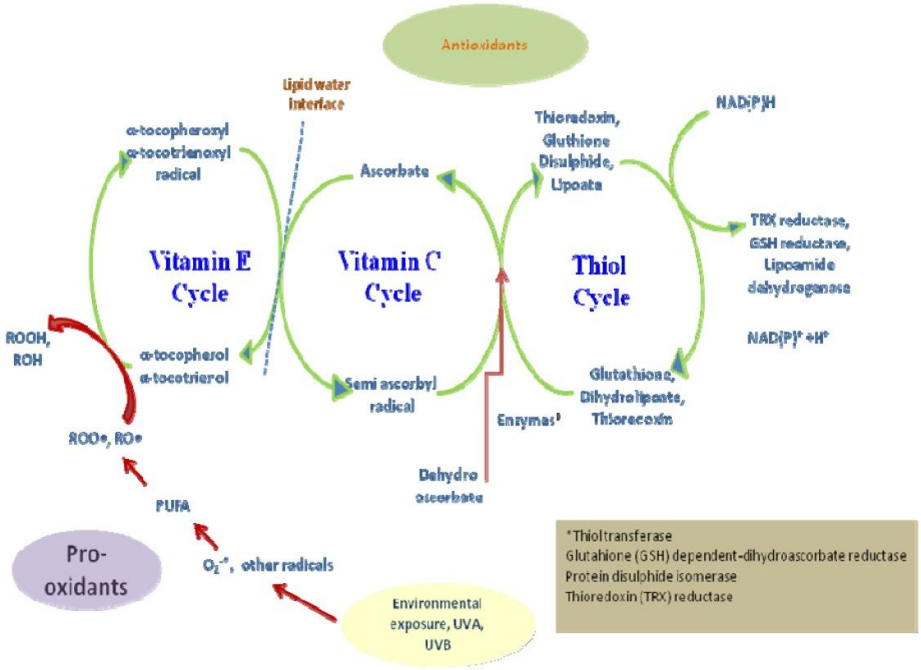
It is defined as any molecule capable of deactivating the free radicals before they attack the host cells .Humans have highly integrated antioxidant systems both enzymatic and non enzymatic which is symbiotic and protects the cells and organs against free radical injury .They are classified as endogenous and exogenous .The most efficient are enzymatic 1)glutathione peroxidase 2) catalase 3)superoxide dismutase. The nonenzymatic are vitamin C, E, Thiol, melatonin, carotenoids and natural flavenoids. However surgery, infection and inflammation promote oxidative stress and endogenous antioxidants may not be sufficient and dietary antioxidants are required to optimize the function.

MECHANISM OF NONENZYMATIC ANTIOXIDANTS

Gultathione :Y-Glutamyl - Cysteinyl-Glyaine



- The reduced form (GSH)is a strong antioxidant that protects cells against damage caused by free radicals and it recycles vitamin C and E .
- Serves as substrate for cof actor in GSH - linked enzymes
  1. Gultathione transfaminase (GST)
  2. Gultathione peroxidase (GPx)
- The oxidised form (GSSG) is catalysed by Glutathiane reductase (GSR)back to GSH using NADPH as reductant
- Glutathione is utilized by the white blood cells as an energy source used for lymphoproliferation glutathione helps to increase the resistance to bacterial and viral infections)
- Glutathione is a natural purifier (high concentrations are found in the liver for detox purposes)



VITAMIN C:

It is championed by Linus pauling in 1928 as an antiviral and anticancer nutrient .It functions as a booster to immune system. It is essential for collagen, carnitine and neurotransmitter synthesis. Humans cannot synthesize due to lack of an enzyme gulonolactone oxidase and is essential to be made available in the diet. History of scurvy occurred in sea voyagers and sailors and the British naval physician Lind documented citrus fruits cured the disease. Main sources are grapefruits, watermelon, papaya, citrus fruits, broccoli etc.US RDA is 40-60mg/day.

Antioxidant	Health benefits	Food sources
Selenium	Helps maintain healthy hair and nails, enhances immunity, works with vitamin E to protect cells from damage. Reduces the risk of cancer, particularly lung, prostate, and colorectal.	Garlic, seeds, Brazil nuts, meat, eggs, poultry, seafood, whole grains. The amount in plant sources varies according to the content of the soil.
Beta-carotene	Keeps skin healthy, helps prevent night blindness and infections, promotes growth and bone development.	Red, yellow-orange, and leafy green vegetables and fruits, including carrots, apricots, cantaloupe, peppers, tomatoes, spinach, broccoli, sweet potatoes, and pumpkin.
Vitamin E	Acts as the protector of essential fats in cell membranes and red blood cells. Reduces risk of cancer, heart disease, and other age-associated diseases.	Peanut butter, nuts, seeds, vegetable oils and margarine, wheat germ, avocado, whole grains, salad dressings.
Vitamin C	Destroys free radicals inside and outside cells. Helps in the formation of connective tissue, the healing of wounds, and iron absorption, and also helps to prevent bruising and keep gums healthy. May reduce risk of cataracts, heart disease, and cancer.	Peppers, tomatoes, citrus fruits and juices, berries, broccoli, spinach, cabbage, potatoes, mango, papaya.

SELENIUM:

It is an essential trace mineralrequired in microgram quantities and an important cofactor in 25selenoproteins included in immune,endocrine systems.It is readily bioavailable as an inorganic salt like selenate .Depressed selenium level in humans is associated with decreased IgG &IgM.Mostly macrophages &neutrophils require the selenodependent generation of ROS and decreased selenium causes a decrease in neutrophil

function.Th e reduced levels of selenium are inversely correlated with procalcitonin and CRP.Procalcitonin is a marker of inflammation and are produced by the thyroid gland and also the neuroendocrine cells of intestine &lung.It is also a cofactor in thioredoxin reductase that are essential for protection against the free radicals.

GUT DIRECTED THERAPIES;

The possibility that gut dysfunction or failure drives disease processes suggests that gut directed therapies to attenuate gut failure or preserve gut function may improve patient outcomes in day to day clinical practice. There are a number of methods by which at least in theory gut function might be modulated favourably these include:

- Physical methods such as early post operative mobilisation
- Drugs such as Prokinetics and avoidance of opiates
- Immuno nutrients such as glutamine, arginine, fish oils, antioxidants and trace elements
- Modulation of GI microflora by using synbiotics and selective gut decontamination.
- Combination approaches.

Immunonutition

Defined as the addition of specific nutrients in greater than normal concentrations, to modulate the immune function. It has been recently coined as pharmaconutrition. It constitutes of ARGININE, GLUTAMINE, FISH oil. BCAA, NUCLEOTIDES, vitamins and minerals and can be administered enterally and parenterally.

ORIGIN:

Nutritional immunology as a branch of science dates back to 1810 with the coincidence of lymphoid tissue atrophy and malnutrition. The discovery of vitamins in the early 1900s led to the contribution to immunity and other defenses. A hiatus in the progress of immunonutrients was noted during world war 2 and the resurgence of interest in the 1960s.Attempts of enteral nutritional therapy is documented for more than 3500 years back to 1500 BC,when the ancient Egyptians tied animal bladders to small clay or ceramic pipes to deliver medications and nutrients by rectal enemas. More than a millennium later in 400 BC greek physicians used apparatus to instill wine , whey, and barley, broth by rectum.

Macronutrients:

Arginine:

It was first discovered 100 years ago as a basic AA.

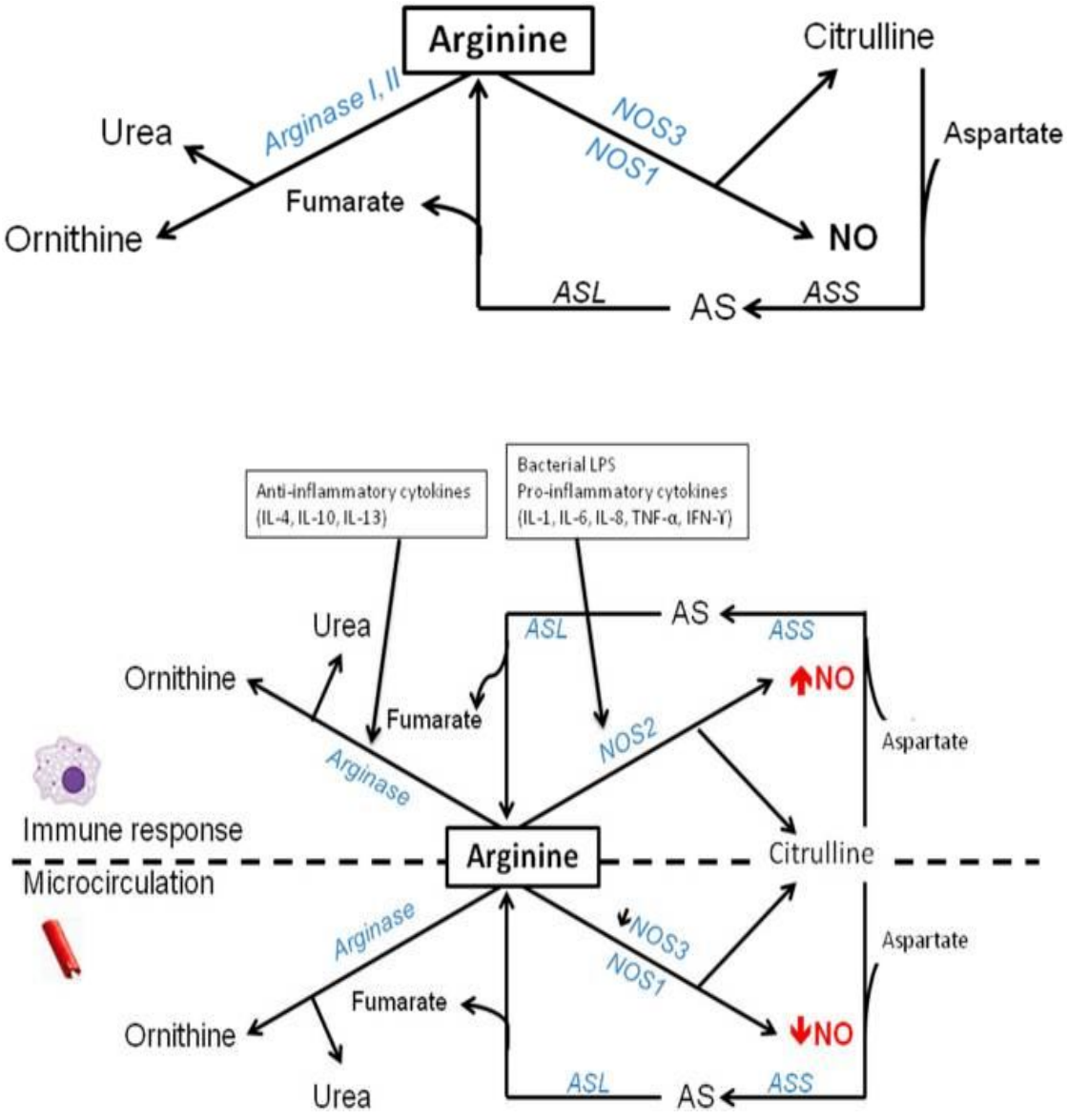
Naturally digested in diets at a rate of 3-5gm/day Most often found in meats and nuts. It is available as a denovo synthesis from citrulline and by protein breakdown. NO acts as a signaling pathway for immune cells and other cells.

PATHOPHYSIOLOGY FOLLOWING SURGERY

The Immature cells of myeloid origin appear in the circulation and lymph, and the cells secrete the enzyme arginase which further degrades arginine and leads to decreased T- lymphocyte function and producing decrease in CD4 cells and increase in IL-2and IFN-gamma.

ARGININE metabolism:

The Arginine Denova synthesis from L-citrulline is performed by the enzyme arginosuccinate synthase and arginosuccinate lyase ,both the enzymes are rate limiting . Arginine is degraded by the enzymes arginase to urea and ornithine. The biosynthesis of citrulline from L-ornithine depends on the enzyme OTC(ornithinecarbomoyl transferase).Arginine is degraded by the enzymes NOS to the biological active intermediate NO (endothelium derived factor).Nitric oxide is essential for GIT functions like bacteiostasis, increase in the immune defenses ,increases the mucus secretion, motility and splanchnic circulation.



- Improves wound healing
- Increases T Helpercells
- Secretagogue for GH,PRL,insulin
- Major metabolic fuel for enterocytes, colonocyte &immune cells

  Collagen synthesis

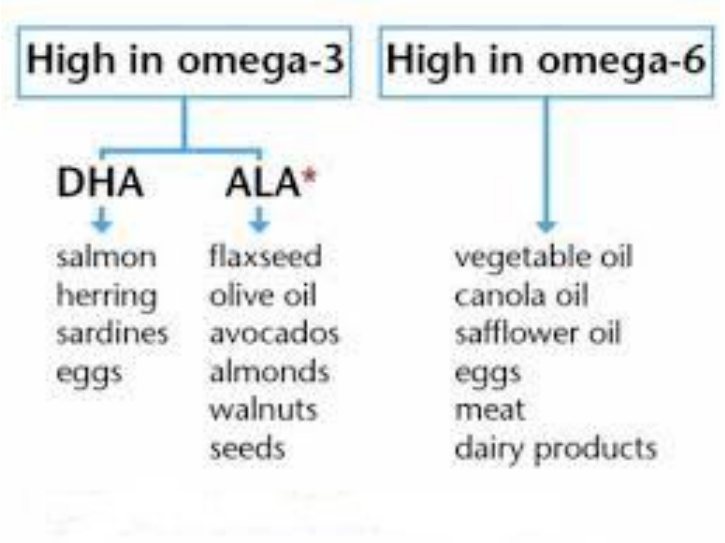
GLUTAMINE:

- Precursor of antioxidant glutathione
- Most abundant free AA
- Solubility of glutamine is low in aqueous state.
- Fuel for rapidly dividing cells.

Maintains gut barrier function Substrate for renal ammoniagenesis. It contributes to the formation of mucin & surface integrity of the intestinal epithelial cells .Increases the synthesis of heat shock proteins which are paramount for cellular recovery and protection of organ failure . Proves to be essential for the activation of the genes for heat shock proteins.

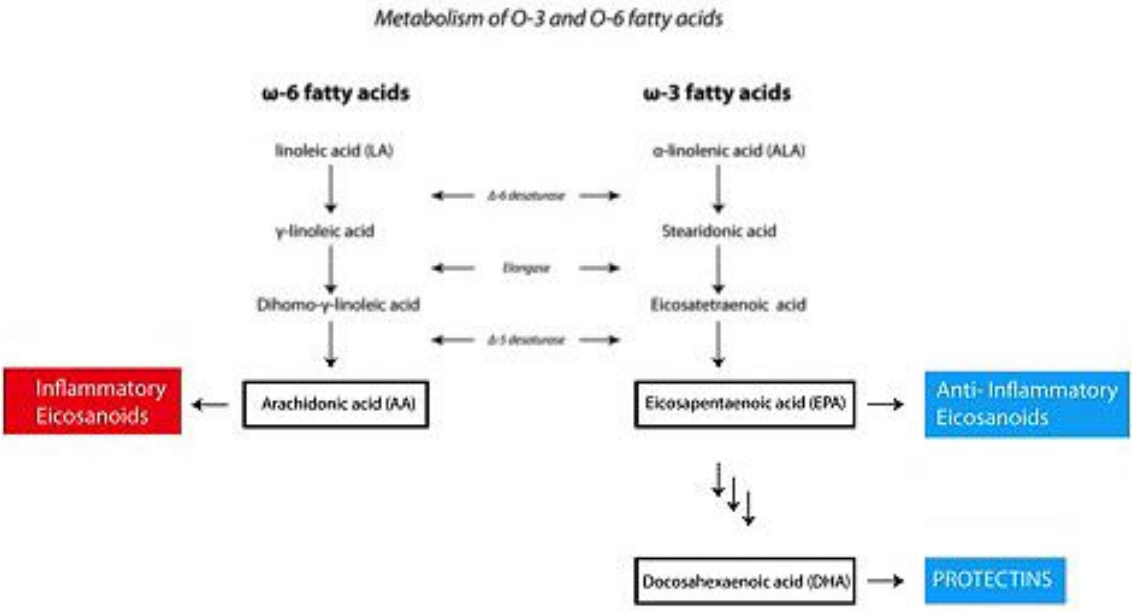
POLYUNSATURATED FATTY ACID:

The longchain omega -6 and omega-3 fattyacid compose the structure of cell membrane and stabilizes the cell and are the precursors of "eicosanoid and docosanoids" involved in the regulation of inflammation,immunity and platelet aggregation These include linoleic acid (omega -6) and alpha linolenic acid (omega 3).



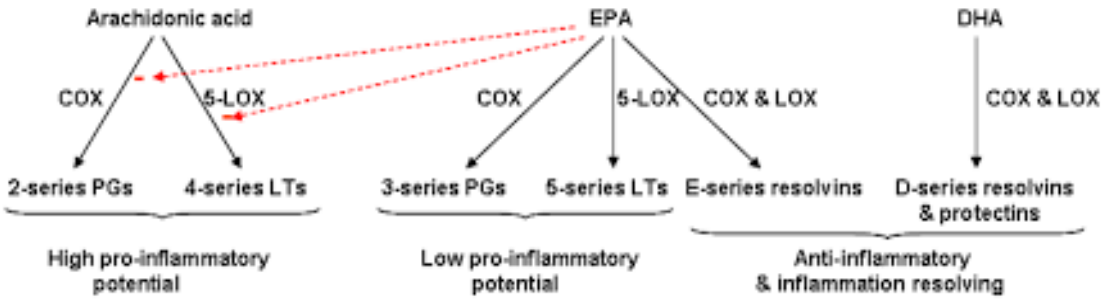
Omega 6&3 fatty acids cannot be synthesized in the body due to the carbons in the position 3 & 6.Arachinoid acid in the body is the major fatty acid content in the immune cell membrane and its predominant eicosanoids are PGE4 and LTB4. The membrane content of omega 3 FA is increased and it causes a changed pattern of production of eicosanoids ,which have a marked beneficial impact on the inflammation and immunity mechanism.Saturated and trans fat produce an elevated TNF –alpha. Flesh of oily fish is abundant with EPA &DHA, the good sources of preformed omega 3FA. Cold water fish like sardines ,mackerel and tuna are the richest source of EPA &DHA. The content of EPA &DHA varies according to the fish species. It is recommended to consume 2 portions of fish /week(one portion =140gm) and is found to have a protective effect on the cardiovascular and immune system. The Inuits of Greenland ingest a high fatty meal, inspite their

incidence of cardiovascular diseases are extremely minimal due to the purely fish based diet.



Omega 3 FA are_ anti-inflammatory and consists of alpha linolenic acid, EPA and DHA. Exception to this rule is Gamma linolenic acid is an "omega -6" but has an anti-inflammatory effect when administered exogenously. Omega 3 FA substitutes for the Arachidonic acid in the macrophages and neutrophil, and hence blunts the production of proinflammatory mediators. It competes for the cyclooxgenase and lipooxgenase and inhibits the production of Arachidonic acid metabolites. Resolvins and protectins are the byproducts of DOHA have shown to reduce cellular inflammation. The ideal ratio of omega 6:omega3 is 1:6 but modern

diets have as high as 20:1.The beneficial effects are demonstrated in conditions like crohns ,IGA nephropathy & atopic dermatitis .It has been noticed of proven benefit in critical care and cancer patients.



VITAMINS:

" A vitamin is a substance that makes you ill if you don't eat it"- "ALBERT SZENT_GYORGYI NOBEL PRIZE IN PHYSIOLOGY 1937" . These organic compounds are required in trace amounts in the diet and cannot be synthezised in organisms.It has diverse functions in the human system.

VITAMIN A:

The immune system functions effectively with the required amounts of micronutrients in the diet. It is well known and proved that vitamin A deficiency leads to suppression of the immune mechanism and alters the innate, Tcell and antibody mediated responses by the host cells. This enhances the susceptibility to infections as well as the morbidity. Later a

viscious cycle develops ,with the infections aggravating and reducing the vitamin levels by decreasing the intake and elevated losses. The mechanism of Vitamin A action on both types of the immune system is by the transretinoic acid,and nuclear retinoic acid recptors. Vitamin A deficiency leads to alteration of ,the integrity of mucosal epithelium and an enhanced capacity of the microbes to invade the eye,respiratory tract &GIT. The deficiency in children are more prone to diarrhoeal &respiratory disease like measles. It is observed with decreased phagocytosis &oxidative burst capacity of the macrophages , and a decline of the number & function of NK cells. Vitamin A supplementation antagonizes the proinflammatory mediators like IL-12 &TNF alpha. Also observed is the antibody mediated immunity decline. In humans antibody titre to various vaccines has shown improvement with vitamin A addition.

VITAMIN D:

The major role of the vitamin is its regulation of calcium and bone metabolism and is proved beyond doubt that its active metabolite 1,25-dihydroxycholecalciferol {vitamin D3} is as a strong immunoregulator. Majority of cells of the immune family express vitamin D receptors except B cells. Active form of vitamin D behaves as a immune system

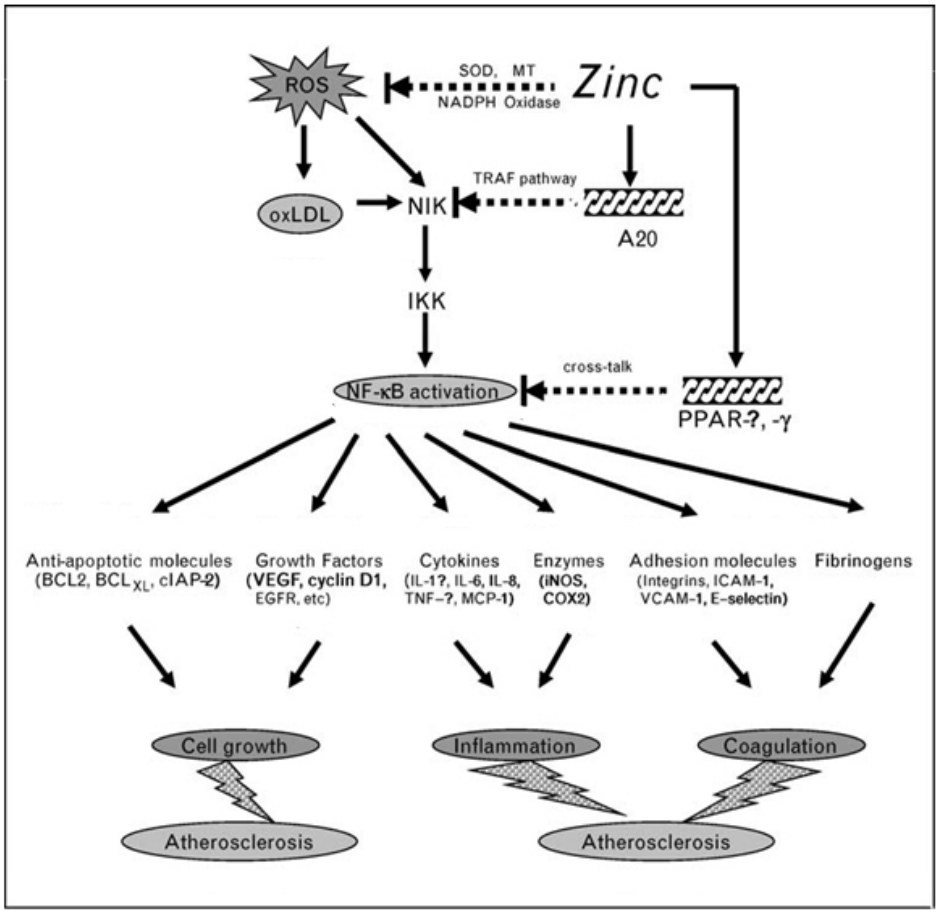
modulator ,reducing the excess expression of inflammatory cytokines and increases the oxidative burst of macrophages.

ZINC:

Raulin discovered the metal and its function in 1869. He observed that zn was required for the growth of aspergillus niger. Zinc deficiency was prevalent in Iran and the Arabian counties due to the whole grain and cereal based diet. Extreme Zn deficiency manifested as Acrodermatitis enteropathica with features of hypogonadism , alopecia, hepatosplenomegaly, dwarfism, anaemia ,impaired wound healing and mental retardation.

Humans contain 2-3 gm of zinc ,most of which is bound to proteins. The highest tissue content is found in the prostate, seminal fluid, uveal tissue and skin. More than 300 enzymes and 2000 transsignalling molecules contain the metal. Half of the body store of zinc is in the bones. There is no storage depot available and hence continuous supply is mandatory for metabolic needs, growth and tissue repair. It is available in fish, meat, eggs oyster. Legumes and cereals only contain moderate amounts and 20-40% is absorbed. It is absorbed from the duodenum and proximal jejunum and

excreted in faeces. Absorption is hampered by the presence of calcium, phytates , phosphates. Animal proteins and EDTA increase the absorption from the gut. Zn decrease the oxidative stress and inflammatory cytokines. NADPH oxidase are a group of plasma membrane associated enzymes which catalyze the production of O2- from O2 by utilizing NADPH as the electron donor. Zn is an inhibitor of this enzyme. Zn is an essential component of Thymulin , a thymic hormone involved in the maturation and differentiation of T cells. The expression of IL-2 &IFN- gamma[Th1] are depleted in Zn deficiency.



Zinc is a cofactor of catalytic, structural and regulatory proteins throughout the body ,especially immune system and wound healing. zinc deficiency can occur in high calorie PN and EN and manifests as abnormal sense of smell & taste , skin rash, failure to thrive, delayed wound healing and loss of hair. It is a vital cofactor to RNA &DNA polymerases and its deficiency leads to arrested cell cycle growths. Clinically deficiency manifests as decreased NK cell number and function and increased rate of infections. Within the intestine it has important antimicrobial roles of activatind the matrixmettaloproteinases which activates the antimicrobial defensins from

the intestinal paneth cells. It also has a structural role in the intestinal tight junction proteins, and holds the enterocytes and other epithelial cells. Zinc status is assessed by the serum concentration which is less than the intracellular concentration, normal serum Zn levelis 80-160microgm/l and less than 60 micro gm requires supplementation. Optimal zn dosing has not been determined, but recommended intakes are 2-5mg/dy in PN & 11-19mgday in EN.

POSTOPERATIVE COMPLICATIONS:

SEROMA:

They are the complications after a operative procedure and are attributed when large skin flaps are constructed like in axillary dissection , mastectomy and large ventral hernias with polypropylene mesh. Prevention of seromais by the placement of drains and like in other wound infections is opening of the sutures and healing by secondary intention.

Surgical site infection:

The incidence of SSI accounts to almost 40% of nosocomially acquired infections among surgical patients. The burden of infections leads to morbidity and increased healthcare costs. The surgical wound includes both the external and internal areas that involves the entire operative site. Wounds are divided into three categories 1) superficial, which includes the

skin and subcutaneous tissues 2)Deep, includes the fascia and muscles 3)Organ space, the internal organs of the body if the operation includes that area. The criteria for diagnosis is proposed by the CDC –superficial incisional-infection less than 30 days after surgery involves skin and superficial tissue plus one of he following purulent drainage, symptoms of erythema, pain and local edema and diagnosis by a surgeon. Deep incisional-less than 30 days after surgery with no implant and soft tissue involvement plus one of the features purulent drainage from the deep space but no extension into the organ ,abscesses found on direct ,radiologic examination or on reoperation and symptom of wound dehiscence. Oragan space is –infection <30 days with no implant and one of the following purulent drainage from the drain and cultured organisms from the organ space. SSI develop due to the contamination with micro organisms and the source is the inhabitant flora from skin and bowel. The source is exogenous if there is a break in the sterile technique. The microbiology varies with the types of procedures. Most of them are gram positive bacteria, staph aureus is the most common, coagulase negative staph and enterococcus spp. In Gi surgeries gram negative bacilli is the predominant species like E.coli, pseudomonas and enterobacter. Most SSi presents in the 5^{th} and 6^{th} POD. 80% of the infections occur within 30 days after the surgery. Both

superficial and deep SSIs are associated with erythema , redness, edema and drainage. The wound is often soft or fluctuant at the site.

CLASSIFICATION OF SURGICAL WOUNDS:

-- Classification of Surgical Wounds

CATEGORY	CRITERIA	INFECTION RATE
Clean	No hollow viscus entered	1%-3%
	Primary wound closure	
	No inflammation	
	No breaks in aseptic technique	
	Elective procedure	
Clean-contaminated	Hollow viscus entered but controlled	5%-8%
	No inflammation	
	Primary wound closure	
	Minor break in aseptic technique	
	Mechanical drain used	
	Bowel preparation preoperatively	
Contaminated	Uncontrolled spillage from viscus	20%-25%
	Inflammation apparent	
	Open, traumatic wound	
	Major break in aseptic technique	
Dirty	Untreated, uncontrolled spillage from viscus	30%-40%
	Pus in operative wound	
	Open suppurative wound	
	Severe inflammation	

The risk factors for postoperative wound infection are age, obesity ,diabetes emergency procedure, drains, inadequate antibiotic coverage ,preoperative hospitalization ,type of operation and prolonged operation ,malnutrition in the patient preoperatively, Inadequate skin antisepsis and defective sterilization. The administration of antibiotic one hour before the surgical incision is crucial to attain adequate tissue therapeutic levels. The intra-operative asepsis is a predominant factor in decreasing the postoperative wound infection. All operative personnel must ensure proper hand hygiene as a team. The proper skin preparation with a

antiseptic solution is essential along with the a careful sterile drape.The intraoperative surgical techniques to be followed are 1)careful tissue handling techniques , 2)precise dissection, hemostasis and thorough debridement of unhealthy tissues 3)avoidance of spillage of the intraluminal contents 4)maintenance of blood supply of the operated organ 5)elimination of foreign body 6)patient is kept in a euthermic state and hydrated 6)Irrigation of pus in the wound with normal saline. Treatment includes removal of the sutures and drainage and thorough wound washing with normal saline and for culture and sensitivity, meanwhile to start on empirical antibiotic therapy. If the deep fascia is involved and burst abdomen has ensued a reoperation is mandated.

Anastomotic leaks:

It is the most dreaded complication following Colorectal surgery.It is reported to 3-26%. Numerous conditions are associated with an elevared risk of leak. Mechanical bowel preparation results in structural alterations to the colonic mucosa and inflammatory changes in the bowel wall. The rationale of MBP prior to elective GI surgeries is debated due to the increased anastomotic leaks ,wound infections and resurgeries. The level of the anastomosis in the GI tract is of prime consideration as the ileocolic, ileorectal and small bowel are less prone compared to

esophageal ,.colorectal and pancreaticoenteral .In the esophagus the lack of serosa is a contributing factor ,the texturity of the pancreatic gland and the size of the pancreatic duct, the surgeon experience plays a major role.Intraluminal distension leads to the dehiscence of anastomosis. The Mechanical strength of the anastomosis is critical in the nascent period and is dependent on the sutures and staplers, as well as on the endothelial cells and fibronectin complex. The most fundamental bowel suturing technique is to ensure a watertight and airtight anstomosis. Intraabdominal drains if left for more than 24-48 hours predispose to infection. Defunctioning stomas does not contribute to the decrease in leak rate but reduces the perianastomotic complication. The clinical features suggestive of leak are fever ,tachycardia, peritonitis, fistula to skin, oliguria and abdominal distension. The clinical features are the result of loss of integrity of the anastomosis and seepage of intestinal contents. The leakage can be either diffuse involving the peritoneal cavity (uncontrolled leak) or shelled off by omentum ,abdominal wall and the contigous of bowel.If a surgical drain is placed it leads to an enterocutaneous fistula. The imaging modality of choice is water soluble contrast either oral ,IV or rectal contrast but now is supplanted by The clinical features suggestive of leak are fever ,tachycardia, peritonitis, fistula to skin, oliguria and abdominal distension. The imaging modality of choice is water soluble contrast either oral ,IV or rectal contrast

but now is supplanted by CT. Leaks are most common in 5-7 th POD. The leak rate is highest if the anastomotic site is 7cm from the anal verge.

Definition of anastomotic leaks:

- faecal fistula to skin
- fever >38 or septicaemia
- radiological signs of AL
- Intraperitoneal abscess or peritonitis

Principles of good and reliable anastomosis

- Excellent exposure and access to large bowel
- To ensure blood supply of the anastomosed stumps
- Prevention of sepsis or faecal contamination
- Suture or staplers are properly placed and confident of good approximation of all layers of the bowel(most important is the submucosa)
- To aim for tension free anastomosis “splenic flexure is released”
- distal obstruction is prevented

The surgical principles are to achieve a good vascularity and the are sutures must not be placed too tight or too deep and the bowel clamps should not include the mesentry. Submucosa is the strongest layer of the bowel wall and hence single layer technique is supported and

extramucosal interrupted sutures is the procedure of choice. Theoritically two layer anastomosis produces more tissue necrosis ,ischaemia and narrowing of the bowel lumen. The serosa of the small bowel should not be stipped of its mesentry for more than 3-4 cm. The marginal artery of colon and the last vascular arcade of the small bowel is left intact.

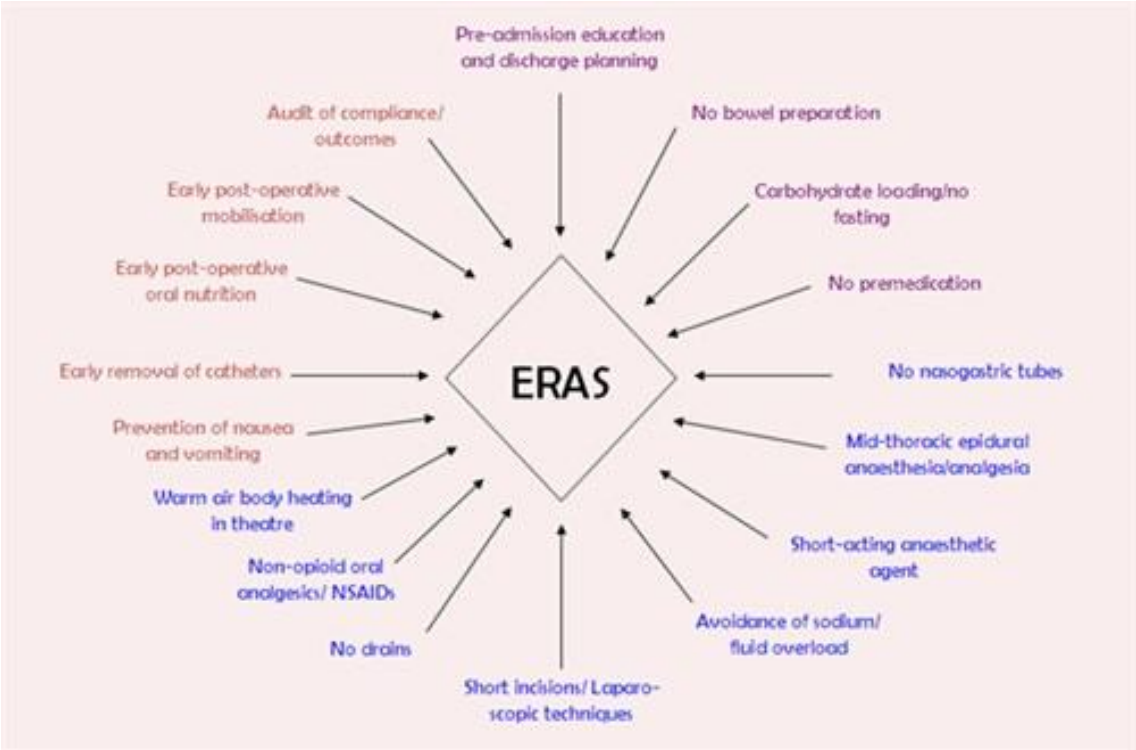
UTI:

It is a common postoperative event and a major predisposing factor is the presence of urinary catheter and the risk increases manifold with increased duration of catheterization {>2days}. E.coli is the most common source of infection with short term catheterization. High fever that occurs after 5-8days is more worrisome than early preoperative fever.In the first 48-72 hours of abdominal surgery, atelectasis is an important cause of fever.

PNEUMONIA:

It is diagnosed by the presence of fever, leucocytosis and purulent sputum production and an infiltrate on CXR.Pneumonias in postoperative patients are treated as nosocomial. Patients requiring more than 48 hours of ventilation are more prone.

Enhanced Recovery After Surgery :



The enhanced recovery after surgery programmes are the standard of care in elective surgical settings all over the world. It has also been advocated that the earliest return of bowel function is the benefit about the package by curtailing postoperative ileus, nausea and vomiting .The current preoperative fasting guideline mentions that a 2 hours of fasting period for clear fluids and a light meal is 6 hours .The prolonged preoperative fasting was advocated to prevent pulmonary aspiration but on the contrary it causes hyperglycaemia and increased stress response. They are in a more anabolic state and have less postoperative nitrogen and protein loss. The mechanical

bowel preparation leads to dehydration ,fluid &electrolyte disturbances especially in the old age and is not proved beneficial .It increases the risk of anastomotic leak and prolongs the postoperative ileus. Prophylaxis against thromboembolism is advocated with LMW heparin or unfractionated heparin. Prophlactic antibiotics is administered one hour prior to skin incision and is effective against both aerobes and anaerobes .A single dose is as effective as a multidose regimens but further doses should be given in prolonged cases >3 hours. The optimal combination of antibiotics is not established ,but a second generation cephalosporin and metronidazole are suggested. Postoperative nausea and vomiting by patient experience suggests are more stressful than pain. Risk factors are females, smoking and with a history of motion sickness. Surgical incisions-transverse or curved incisions cause less pain & pulmonary dysfunction than vertical incision.laparoscopic surgeries facilitate early recovery. Nasogastric tubes delay the recovery of bowel function.

JOURNAL REVIEW:

All these studies conducted worlwide are with preoperative immunonutrients in various GI surgeries and the results are variable due to the heterogenous populations .

- A study of preoperative oral IMN supplements in esophageal cancer patients –published in the journal of nutrition and health april 2014 vol 18 issue 4 pg 437-440.result shows a improved outcome.
- A study of 50 patients of colorectal carcinoma conducted in italy 2002 by BRAGA
- Gianotti of italy in 2002 studied 102 GI carcinoma patients
- Heril of japan in 2006 on colorectal ca patients .study population was 33.
- Gunerhan of turkey 2009 on 13 GI tumours patients.
- Mikagi of japan 2011 on 13 hepatocellular ca patients planned for liver resections ,the study was underarmed and reported improvement in the biochemical parameters.
- Fugitani of japan 2012 on 120 GI carcinoma patients
- Barker of Australia 2013 with a study population of 46
- Aida of Japan 2014 on whipples procedure of 25 patients.

PROUD STUDY-Is a RCT conducted by the germans to evaluate the effect of longterm preop IMN on liver transplantion patients and is in progress.

STUDY DESIGN:

Case Control study

SETTING:

Department of surgery and surgical gastroenterology at Stanley medical college, Chennai.

ETHICAL APPROVAL:

The study was approved by the Institutional committee in January 2015.

Inclusion criteria:

All patients above 13years of age.

Planned for elective major Gastro intestinal surgery

Exclusion Criteria :

- Intestinal obstruction.
- Vomiting and diarrhea.
- Diabetes mellitus.
- Pregnancy
- No evidence of liver and renal disease

Materials and Methodology:

A prospective non randomnized study which included 50 patients who underwent major elective GI surgery for both benign and malignant diseases with IMN supplementation. The study group n=50 where administered 30 gms of IMN formula three times a day for 5 days preoperatively by oral route.The control group were given a normal diet during the study period.The preoperative variables measured were weight,BMI.The post operative variables are the primary outcomes of infectious complications such as SSI,UTI,pneumonia ,wound abscess and anastomotic leaks were recorded in the prescribed proforma.

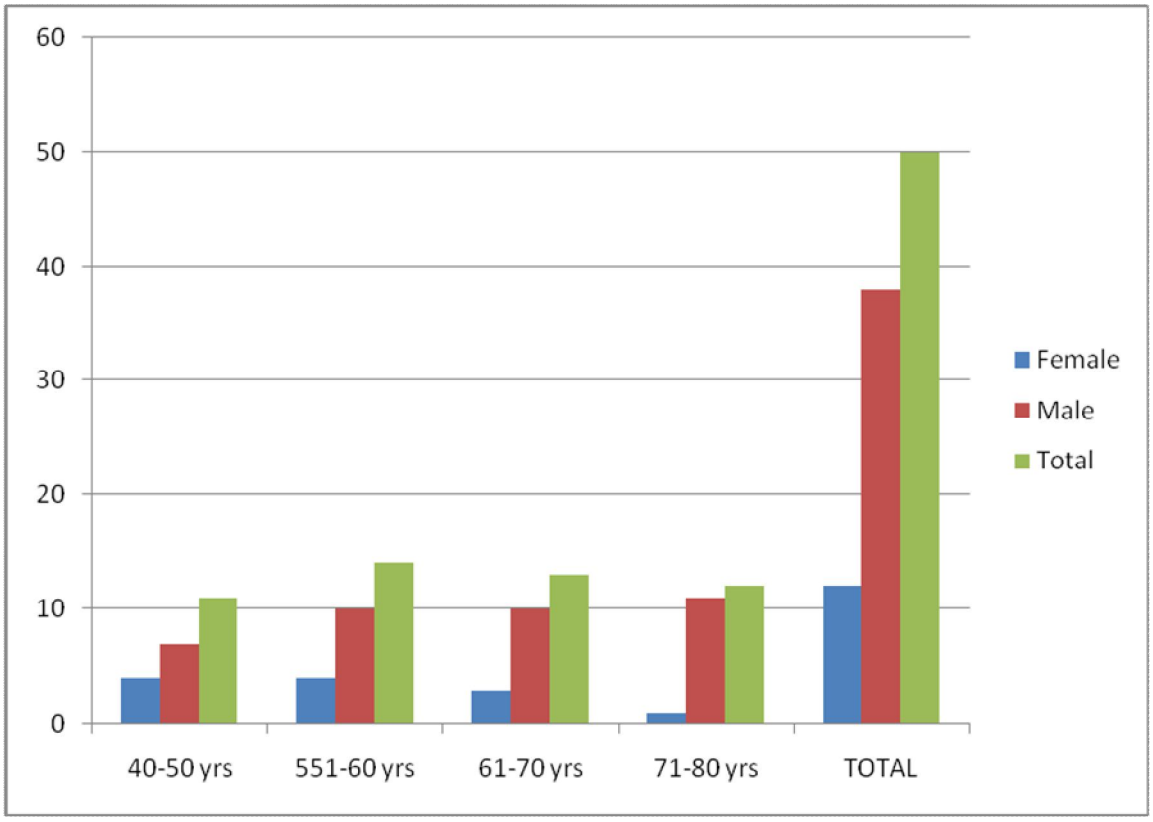
COMPOSITION OF IMMUNONUTRIENTS

Nutrients	Units	Per/100gm powder
Energy	Kcal	337.4
protein	gm	20
carbohydrate	gm	63
fat	gm	0.6
L-glutamine	Mg	500
l-arginine	Mg	3000
DHA	Mg	80
Linoleic acid	Mg	32
taurine	Mg	38
colostrum	Mg	2
vitamin C	Mg	83
vitaminE	Mg	33.3
vitamin K	Mg	50
vit A	Mcg	1812
biotin	Mcg	30
vit D	Mcg	2.2
Essential minerals		
Iron	Mg	18
Zinc	Mg	11
Selenium	Mg	15
Magnesium	Mcg	200
Calcium	Mg	1200
Copper	Mcg	410
molybdenum &chromium	Mcg	35
phosphorus-	Mg	700

RESULTS & OBSERVATIONS

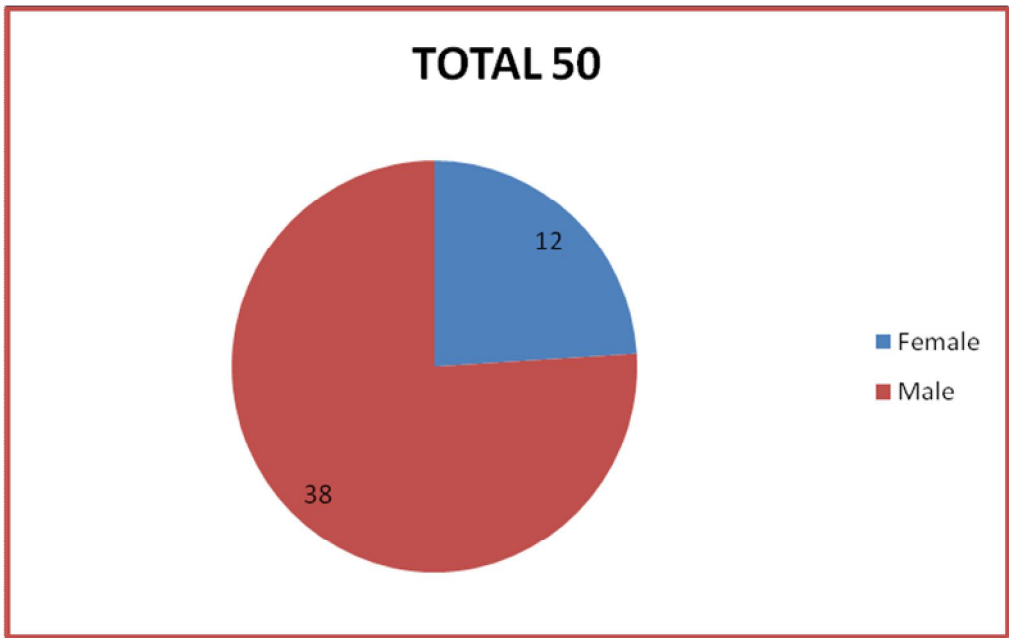
The age of the persons varies from 40 to 80 years. The age wise, sex wise distribution are appended in the diagram

Agewise sexwise distribution case group



The male persons are comparatively higher in number both in case groups and control groups as illustrated by the pie diagram below.

Sexwise case group



Surgeries are done as illustrated in the chart below according to the clinical diagnosis made earlier.

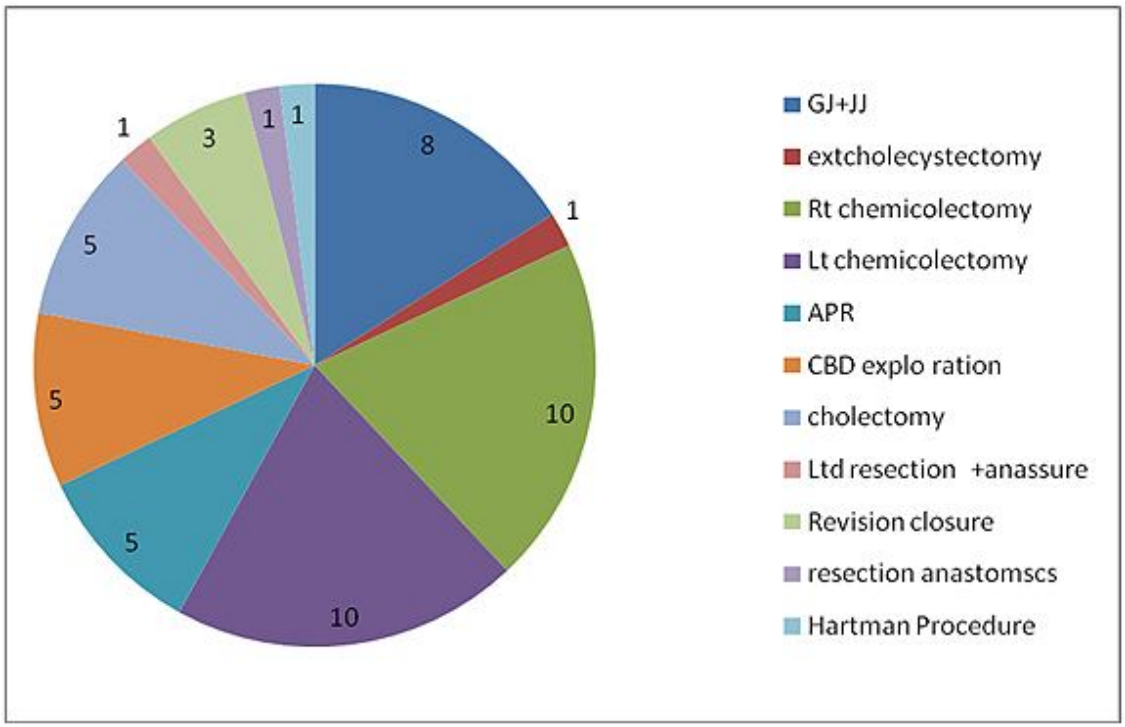
There were 11 types of surgeries done on 50persons of case group- the details of which are appended below.

Details of surgery

GJ+JJ	8
extcholecystectomy	1
Rt hemicolectomy	10
Lt hemicolectomy	10
APR	5
CBD Exploration	5
Cholecystectomy	5
Ltd resection +anastomosis	1
Revision closure	3
resection anastomosis	1
Hartman Procedure	1
Total	50

The detailed surgeries done are best illustrated by the diagram also for easy visibility.

Types of surgeries done 1



A similar number of surgeries were done on the control group of fifty persons alsoto monitor the effect of the intervention of nutrition on the case group.

The impact of nutrients

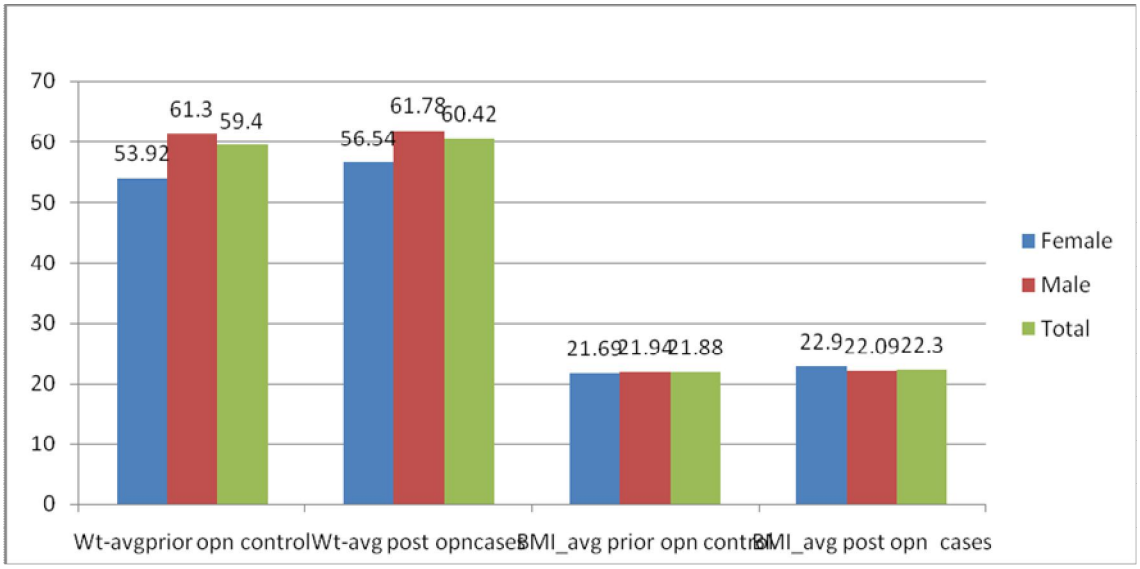
The data collected on the 50 patients of case group on parameters of weight and BMI are appended below- before and after the intervention of added immuno nutrition by oral intake.

Before operation –Case Group **After surgery and intervention of nutrition**

Patients	weight(avg)	BMI(avg)	weight(avg)	BMI(avg)
Female	53.92kgs	21.69	56.54	22.9
Male	61.3 kgs	21.94	61.78	22.09
Total	59.4 kgs	21.88	60.42	22.3

Group Statistics

	Group	N	Mean	Std. Deviation	Std. Error Mean
Hieght - Preop	Case	50	1.6470	.07702	.01089
	Control	50	1.6442	.06737	.00953
Weight - Preop	Case	50	59.40	5.901	.834
	Control	50	60.42	5.296	.749
BMI - Preop	Case	50	21.8776	1.46839	.20766
	Control	50	22.3704	1.82726	.25841
Height - Postop	Case	50	1.6470	.07702	.01089
	Control	50	1.6442	.06737	.00953
Weight - Postop	Case	50	60.42	5.296	.749
	Control	50	59.50	4.925	.696
BMI - Postop	Case	50	22.30305	1.746991	.247062
	Control	50	22.03404	1.732114	.244958



Others .**UTI**

There was an isolated incidence in the Case group with nutrients intake and it is only two with this symptom in the control group. hence there is no significant variance between the groups.

Pneumonia

Considering the attack of pneumonia only.. 5 patients got suffered in the case group whereas this is as high as 36 % in the standard group. **The p <0.05 is significant . The** P value is 0.001

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	10.767[b]	1	.001		
Continuity Correction [a]	9.237	1	.002		
Likelihood Ratio	11.498	1	.001		
Fisher's Exact Test				.001	.001
Linear-by-Linear Association	10.658	1	.001		
N of Valid Cases	98				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 10. 78.

Wound infection

The case group was affected by 36% and the control group by an enhanced level 50%. It can be confidently assessed that immunonutruients has a significant impact on the patients in reducing factors which help to increase the symptom of wound infection.

-

Crosstab

			Group		
			Case	Control	Total
Wound infection - Day 3	Yes	Count	15	24	39
		% within Group	31.3%	48.0%	39.8%
	No	Count	33	26	59
		% within Group	68.8%	52.0%	60.2%
Total		Count	48	50	98
		% within Group	100.0%	100.0%	100.0%

Abd abcess

Both the groups have registered a totally negative incidences during the study period making it irrelevant to comment on comparision.

Anastomotic Leak

The control group with absence of added nutrients intervention reported a occurance of one patient while it is none on the case group.

Others

The control group had a single instance complication.

Length of stay

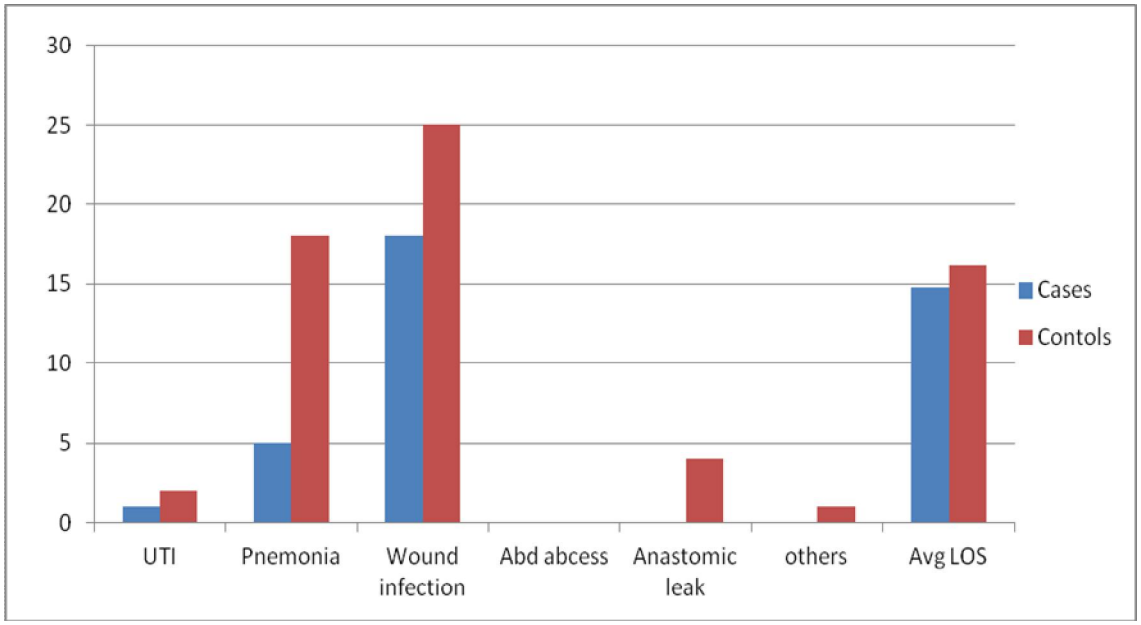
The average hospital stay of the case group was 14.82 days while that of control group was higher at 16.78 days, indicating a reduction of 12% on hospital stay . The lower number of hospital stay along with better quality of life at hospital undoubtedly help to conclude that the intervention with

immunonutrients on patients has a positive impact on healing.

The above said point are best illustrated by the table and the bar diagram shown below.

Post operative complications

Symptoms	Cases	Controls
UTI	1	2
Pneumonia	5	18
Wound infection	18	25
Abd abcess	-	-
Anastomotic leak	-	1
Avg Los	14.82	16.17



It is evident from the above data that after the intake of immunonutrients the weight of all categories of the sample group has marginally increased inspite of the cxpected correction on the lower side.

DISCUSSION:

Multiple studies and clinical research have demonstrated improved patient outcomes and reduced length of stay particularly in the elective GI surgery cases. The wound infections have marginally decreased in the study group compared to the control group(18vs25) and the incidence of pneumonia is elevated in the control group. The patients tolerated the Immunoenriched formula due to its palatability.One patient severely malnourished following an enterocutaneous fistula had benefitted remarkably and had no complications following revision ileostomy closure.The consensus view from multiple RCT and metaanalysis supports perioperative nutritional support in elective GI surgery patients.Daly et al has conducted two studies in 1992 &1995 with surgical patients as study population and demonstrated decreased wound infections and hospital stay.Braga et al in 1998 conducted in surgical patients n=110 and demonstrated decreased length of stay and also infectious complications. “XU et al 2006” with 60 patients on preoperative IMN had fewer postoperative complications 7%vs26%.LOS is <3 days.A study of

perioperative IMN in Elective GI surgery patients was conducted at Stanley Surgical gastroenterology unit by S.K perumal et al with 50 patients and the observed results are there was no difference in the postoperative infections but proved to be of benefit in malnourished group.Hence the study has similarity with the malnutrition component.The different composition of the IMN formulas available commercially and utilized in the numerous studies worlwide ,makes it difficult to comprehend the exact requirements in terms of dosage and route of administration which is beneficial in the recovery of the surgery patients.Although studies indicate that the amount of arginine required is >12 gm/1000 calories,glutamine 10to 30gm/day ,omega 3FA 1-4 gm/day for its beneficial outcome.

CONCLUSION:

The study outcome has proved a beneficial reduction of infectious complications and substantial improvement with the immunonutrient formula and it emphazies the subset of malnourised patients are markedly benefitted .

LIMITATIONS:

The limitation of the study is that biochemical markers like serum prealbumin and serum transthyretin the markers of the nutrional protein status was not measured .The more specific inflammatory markers

CRP,IL-6, TNF-alpha ,neopterin were not recorded in the postoperative setting and hence the biochemical variables of inflammation could not be extrapolated with the positive improvement in clinical outcome with respect to infections.

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Pre Operative Proforma

1. **Name :**
2. **Age / Sex :**
3. **History :**
4. **General Examination :**
5. **Systemic Examination :**
6. **Clinical diagnosis :**
7. **Comorbid illness :**
8. **Planned surgical procedure :**
9. **Weight and BMI :**

Weight	BMI

10. Biochemical investigations:

hb	TC	DC	LT	RFT

ORAL IMN FORMULA :

Day 1	2	3	4	5

Pre Operative Proforma

Surgical procedure done :

Weight and BMI :

POD DAY

	3	**7**	
UTI			
Pneumonia			
Wound inf			
Abd abscess			
Anastomotic leak			
Other			
Los			

T-Test

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Group Statistics

	Group	N	Mean	Std. Deviation	Std. Error Mean
Age	Case	50	60.44	4.949	.700
	Control	50	61.30	4.464	.631

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Age	Equal variances assumed	.051	.821	-.912	98	.364	-.860	.943	-2.731	1.011
	Equal variances not assumed			-.912	96.975	.364	-.860	.943	-2.731	1.011

Crosstabs

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Sex * Group

Crosstab

			Group		Total
			Case	Control	
Sex	Male	Count	38	37	75
		% within Group	76.0%	74.0%	75.0%
	Female	Count	12	13	25
		% within Group	24.0%	26.0%	25.0%
Total		Count	50	50	100
		% within Group	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.053[b]	1	.817		
Continuity Correction[a]	.000	1	1.000		
Likelihood Ratio	.053	1	.817		
Fisher's Exact Test				1.000	.500
Linear-by-Linear Association	.053	1	.818		
N of Valid Cases	100				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 12. 50.

Clinical Diagnosis * Group

Crosstab

			Group		
			Case	Control	Total
Clinical Diagnosis	Ca ascend	Count	20	20	40
		% within Group	40.0%	40.0%	40.0%
	ca rectum	Count	5	5	10
		% within Group	10.0%	10.0%	10.0%
	Ca stomach	Count	8	8	16
		% within Group	16.0%	16.0%	16.0%
	CB Calculi	Count	5	5	10
		% within Group	10.0%	10.0%	10.0%
	CBD Stone	Count	5	5	10
		% within Group	10.0%	10.0%	10.0%
	GB Cancer	Count	1	1	2
		% within Group	2.0%	2.0%	2.0%
	Loop ielost	Count	3	3	6
		% within Group	6.0%	6.0%	6.0%
	Sigmoid	Count	2	2	4
		% within Group	4.0%	4.0%	4.0%
	TB ileocaec	Count	1	1	2
		% within Group	2.0%	2.0%	2.0%
Total		Count	50	50	100
		% within Group	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	.000[a]	8	1.000
Likelihood Ratio	.000	8	1.000
N of Valid Cases	100		

a. 8 cells (44.4%) have expected count less than 5. The minimum expected count is 1.00.

Plannedsurgeical Procedure * Group

Crosstab

			Group		
			Case	Control	Total
Plannedsurgeical Procedure	APR	Count	5	5	10
		% within Group	10.0%	10.0%	10.0%
	CBD Exploration	Count	5	5	10
		% within Group	10.0%	10.0%	10.0%
	Cholecystectomy	Count	5	5	10
		% within Group	10.0%	10.0%	10.0%
	extcholecystectomy	Count	1	1	2
		% within Group	2.0%	2.0%	2.0%
	Gastrecto CJ+JJ	Count	8	8	16
		% within Group	16.0%	16.0%	16.0%
	Hartman procedure	Count	1	1	2
		% within Group	2.0%	2.0%	2.0%
	Limited resction	Count	1	1	2
		% within Group	2.0%	2.0%	2.0%
	Lthemicol ectomy	Count	10	10	20
		% within Group	20.0%	20.0%	20.0%
	Resection anastomo	Count	1	1	2
		% within Group	2.0%	2.0%	2.0%
	Revision closure	Count	2	2	4
		% within Group	4.0%	4.0%	4.0%
	Revision Closure	Count	1	1	2
		% within Group	2.0%	2.0%	2.0%
	Rthemicol ectomy	Count	10	10	20
		% within Group	20.0%	20.0%	20.0%
Total		Count	50	50	100
		% within Group	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	.000[a]	11	1.000
Likelihood Ratio	.000	11	1.000
N of Valid Cases	100		

a. 12 cells (50.0%) have expected count less than 5. The minimum expected count is 1.00.

Surgical Procedure done * Group

Crosstab

			Group		Total
			Case	Control	
Surgical Procedure done	APR	Count	5	5	10
		% within Group	10.0%	10.0%	10.0%
	CBD Exploration	Count	5	5	10
		% within Group	10.0%	10.0%	10.0%
	Cholecystectomy	Count	5	5	10
		% within Group	10.0%	10.0%	10.0%
	extcholecystectomy	Count	1	1	2
		% within Group	2.0%	2.0%	2.0%
	Gastrecto CJ+JJ	Count	8	8	16
		% within Group	16.0%	16.0%	16.0%
	Hartman procedure	Count	1	1	2
		% within Group	2.0%	2.0%	2.0%
	Limited resction	Count	1	0	1
		% within Group	2.0%	.0%	1.0%
	Limited resection	Count	0	1	1
		% within Group	.0%	2.0%	1.0%
	Lthemicol ectomy	Count	10	10	20
		% within Group	20.0%	20.0%	20.0%
	Resection anastomo	Count	1	1	2
		% within Group	2.0%	2.0%	2.0%
	Revision closure	Count	2	2	4
		% within Group	4.0%	4.0%	4.0%
	Revision Closure	Count	1	1	2
		% within Group	2.0%	2.0%	2.0%
	Rthemicol ectomy	Count	10	10	20
		% within Group	20.0%	20.0%	20.0%
Total		Count	50	50	100
		% within Group	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	2.000[a]	12	.999
Likelihood Ratio	2.773	12	.997
N of Valid Cases	100		

a. 14 cells (53.8%) have expected count less than 5. The minimum expected count is .50.

UTI - Day 3 * Group

Crosstab

			Group		
			Case	Control	Total
UTI - Day 3	Yes	Count	1	2	3
		% within Group	2.1%	4.0%	3.1%
	No	Count	47	48	95
		% within Group	97.9%	96.0%	96.9%
Total		Count	48	50	98
		% within Group	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.303[b]	1	.582		
Continuity Correction[a]	.000	1	1.000		
Likelihood Ratio	.310	1	.578		
Fisher's Exact Test				1.000	.515
Linear-by-Linear Association	.300	1	.584		
N of Valid Cases	98				

a. Computed only for a 2x2 table

b. 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1. 47.

Pneumonia - Day 3 * Group

Crosstab

			Group		
			Case	Control	Total
Pneumonia - Day 3	Yes	Count	4	18	22
		% within Group	8.3%	36.0%	22.4%
	No	Count	44	32	76
		% within Group	91.7%	64.0%	77.6%
Total		Count	48	50	98
		% within Group	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	10.767[b]	1	.001		
Continuity Correction[a]	9.237	1	.002		
Likelihood Ratio	11.498	1	.001		
Fisher's Exact Test				.001	.001
Linear-by-Linear Association	10.658	1	.001		
N of Valid Cases	98				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 10. 78.

Wound infection - Day 3 * Group

Crosstab

			Group		
			Case	Control	Total
Wound infection - Day 3	Yes	Count	15	24	39
		% within Group	31.3%	48.0%	39.8%
	No	Count	33	26	59
		% within Group	68.8%	52.0%	60.2%
Total		Count	48	50	98
		% within Group	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	2.868[b]	1	.090		
Continuity Correction[a]	2.211	1	.137		
Likelihood Ratio	2.887	1	.089		
Fisher's Exact Test				.103	.068
Linear-by-Linear Association	2.839	1	.092		
N of Valid Cases	98				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 19.10.

Abd abscess - Day 3 * Group

Crosstab

			Group		
			Case	Control	Total
Abd abscess - Day 3	No	Count	48	50	98
		% within Group	100.0%	100.0%	100.0%
Total		Count	48	50	98
		% within Group	100.0%	100.0%	100.0%

Chi-Square Tests

	Value
Pearson Chi-Square	.[a]
N of Valid Cases	98

a. No statistics are computed because Abd abscess - Day 3 is a constant.

Anastomotic Leak - Day 3 * Group

Crosstab

			Group		
			Case	Control	Total
Anastomotic Leak - Day 3	No	Count	48	49	97
		% within Group	100.0%	98.0%	99.0%
	4	Count	0	1	1
		% within Group	.0%	2.0%	1.0%
Total		Count	48	50	98
		% within Group	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.970[b]	1	.325		
Continuity Correction[a]	.000	1	1.000		
Likelihood Ratio	1.356	1	.244		
Fisher's Exact Test				1.000	.510
Linear-by-Linear Association	.960	1	.327		
N of Valid Cases	98				

a. Computed only for a 2x2 table

b. 2 cells (50.0%) have expected count less than 5. The minimum expected count is .49.

Others - Day 3 * Group

Crosstab

			Group		Total
			Case	Control	
Others - Day 3	Yes	Count	0	1	1
		% within Group	.0%	2.0%	1.0%
	No	Count	48	49	97
		% within Group	100.0%	98.0%	99.0%
Total		Count	48	50	98
		% within Group	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.970[b]	1	.325		
Continuity Correction[a]	.000	1	1.000		
Likelihood Ratio	1.356	1	.244		
Fisher's Exact Test				1.000	.510
Linear-by-Linear Association	.960	1	.327		
N of Valid Cases	98				

a. Computed only for a 2x2 table

b. 2 cells (50.0%) have expected count less than 5. The minimum expected count is .49.

UTI - Day 7 * Group

Crosstab

			Group		
			Case	Control	Total
UTI - Day 7	Yes	Count	1	2	3
		% within Group	2.1%	4.0%	3.1%
	No	Count	47	48	95
		% within Group	97.9%	96.0%	96.9%
Total		Count	48	50	98
		% within Group	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.303[b]	1	.582		
Continuity Correction[a]	.000	1	1.000		
Likelihood Ratio	.310	1	.578		
Fisher's Exact Test				1.000	.515
Linear-by-Linear Association	.300	1	.584		
N of Valid Cases	98				

a. Computed only for a 2x2 table

b. 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1. 47.

Pneumonia - Day 7 * Group

Crosstab

			Group		
			Case	Control	Total
Pneumonia - Day 7	Yes	Count	3	18	21
		% within Group	6.3%	36.0%	21.4%
	No	Count	45	32	77
		% within Group	93.8%	64.0%	78.6%
Total		Count	48	50	98
		% within Group	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	12.874[b]	1	.000		
Continuity Correction[a]	11.167	1	.001		
Likelihood Ratio	14.052	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	12.742	1	.000		
N of Valid Cases	98				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 10. 29.

Wound infection - Day 7 * Group

Crosstab

			Group		
			Case	Control	Total
Wound infection - Day 7	Yes	Count	15	24	39
		% within Group	31.3%	48.0%	39.8%
	No	Count	33	26	59
		% within Group	68.8%	52.0%	60.2%
Total		Count	48	50	98
		% within Group	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	2.868[b]	1	.090		
Continuity Correction[a]	2.211	1	.137		
Likelihood Ratio	2.887	1	.089		
Fisher's Exact Test				.103	.068
Linear-by-Linear Association	2.839	1	.092		
N of Valid Cases	98				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 19. 10.

Abd abscess - Day 7 * Group

Crosstab

			Group		
			Case	Control	Total
Abd abscess - Day 7	No	Count	48	50	98
		% within Group	100.0%	100.0%	100.0%
Total		Count	48	50	98
		% within Group	100.0%	100.0%	100.0%

Chi-Square Tests

	Value
Pearson Chi-Square	.[a]
N of Valid Cases	98

a. No statistics are computed because Abd abscess - Day 7 is a constant.

Anastomotic Leak - Day 7 * Group

Crosstab

			Group		
			Case	Control	Total
Anastomotic Leak - Day 7	No	Count	48	49	97
		% within Group	100.0%	98.0%	99.0%
	4	Count	0	1	1
		% within Group	.0%	2.0%	1.0%
Total		Count	48	50	98
		% within Group	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.970[b]	1	.325		
Continuity Correction[a]	.000	1	1.000		
Likelihood Ratio	1.356	1	.244		
Fisher's Exact Test				1.000	.510
Linear-by-Linear Association	.960	1	.327		
N of Valid Cases	98				

a. Computed only for a 2x2 table

b. 2 cells (50.0%) have expected count less than 5. The minimum expected count is .49.

Others - Day 7 * Group

Crosstab

			Group		
			Case	Control	Total
Others - Day 7	Yes	Count	0	1	1
		% within Group	.0%	2.0%	1.0%
	No	Count	48	49	97
		% within Group	100.0%	98.0%	99.0%
Total		Count	48	50	98
		% within Group	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.970[b]	1	.325		
Continuity Correction[a]	.000	1	1.000		
Likelihood Ratio	1.356	1	.244		
Fisher's Exact Test				1.000	.510
Linear-by-Linear Association	.960	1	.327		
N of Valid Cases	98				

a. Computed only for a 2x2 table

b. 2 cells (50.0%) have expected count less than 5. The minimum expected count is .49.

T-Test

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Group Statistics

	Group	N	Mean	Std. Deviation	Std. Error Mean
Hieght - Preop	Case	50	1.6470	.07702	.01089
	Control	50	1.6442	.06737	.00953
Weight - Preop	Case	50	59.40	5.901	.834
	Control	50	60.42	5.296	.749
BMI - Preop	Case	50	21.8776	1.46839	.20766
	Control	50	22.3704	1.82726	.25841
Height - Postop	Case	50	1.6470	.07702	.01089
	Control	50	1.6442	.06737	.00953
Weight - Postop	Case	50	60.42	5.296	.749
	Control	50	59.50	4.925	.696
BMI - Postop	Case	50	22.30305	1.746991	.247062
	Control	50	22.03404	1.732114	.244958

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Hieght - Preop	Equal variances assumed	.289	.592	.193	98	.847	.00280	.01447	-.02592	.03152
	Equal variances not assumed			.193	96.297	.847	.00280	.01447	-.02592	.03152
Weight - Preop	Equal variances assumed	.036	.851	-.910	98	.365	-1.020	1.121	-3.245	1.205
	Equal variances not assumed			-.910	96.876	.365	-1.020	1.121	-3.245	1.205
BMI - Preop	Equal variances assumed	.956	.331	-1.486	98	.140	-.49279	.33151	-1.15067	.16508
	Equal variances not assumed			-1.486	93.661	.141	-.49279	.33151	-1.15105	.16547
Height - Postop	Equal variances assumed	.289	.592	.193	98	.847	.00280	.01447	-.02592	.03152
	Equal variances not assumed			.193	96.297	.847	.00280	.01447	-.02592	.03152
Weight - Postop	Equal variances assumed	.162	.688	.900	98	.371	.920	1.023	-1.110	2.950
	Equal variances not assumed			.900	97.488	.371	.920	1.023	-1.110	2.950
BMI - Postop	Equal variances assumed	.000	.988	.773	98	.441	.269009	.347914	-.421415	.959432
	Equal variances not assumed			.773	97.993	.441	.269009	.347914	-.421415	.959433

T-Test

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Group Statistics

	Group	N	Mean	Std. Deviation	Std. Error Mean
LOS	Case	48	15.15	3.690	.533
	Control	50	16.78	4.349	.615

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
LOS	Equal variances assumed	1.908	.170	-2.002	96	.048	-1.634	.816	-3.254	-.014
	Equal variances not assumed			-2.009	94.592	.047	-1.634	.814	-3.249	-.019