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INTENSE SURGICAL OXIDATIVE STRESS

ALBUMIN

A synergistic key for postoperative recovery pathways.

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1- Introduction

In more recent times, pharmacological properties arising from albumin's complex structure have become a focus of attention by clinical researchers. In particular, albumin, through anti-inflammatory and antioxidant properties, has been proposed as an agent for the treatment of sepsis, cirrhosis and other inflammatory states. Intense surgical oxidative stress is one of them. Some evidence for these indications in the context of intense oxidative stress surgery has accrued from several small clinical observational or retrospective studies. Unfortunately, these studies have not been confirmed in large and randomised trials integrating the crucial key which is synergism of different surgery recovery pathways structured around serum albumin.

In this review, we will exhibit physiology of oxidative surgical stress and the perioperative recovery pathways to limit this stress, particularly the antioxidant pathway. Additionally, we will expose their physiology applied to the surgery context and therapeutic implications to mitigate postoperative complications especially nosocomial infections.

2- Postoperative recovery quadriptych pathway

Major surgery even performed by highly skilled surgeons induces traumatic stress due to surgical aggression that could lead to postoperative complications and death when the patient organism is not ready or prepared to support this intense corporeal stress. Cancer surgical resection often leads to major surgery whose postoperative complications could result from cancer-induced malnutrition and patient weakness exacerbated by intense surgical oxidative stress. Perioperative metabolic modulation around the onset of surgical stress attenuates the catabolic effect of major surgical insult.(1-2) (Finnerty CC 2013, Braga M 1999)

Perioperative enteral or parenteral nutrition before or/and after surgery improves both nutritional status and clinical outcomes, results in higher postoperative serum albumin levels, and shortens both time to first bowel action and length of hospital stay. Additionally, perioperative nutrition reduces the rate of both non-infectious and infectious complications.(3)



(Katona P, 2008). Nutritional support initiated early postoperatively from the first day is vital in maintaining nutritional status during the catabolic postoperative period. This is underscored by evidences for early and sustained feeding after surgery. Delivery of nutrition on the first postoperative day is an **independent predictor** of postoperative survival at five years. The advancement of oral intake has been identified as an independent determinant of early recovery after colorectal surgery.(3-4) (Katona P, Wischmeyer PE)

Immune-modulating nutrient-enriched products containing arginine, omega-3 polyunsaturated fatty acids (PUFAs), nucleic acids, vitamins and antioxidants (selenium) can modulate immune and inflammatory processes in burn, trauma, and major surgery. Additionally, it improves clinical outcomes.(5) (Drover 2011) Their biochemical effect includes increased cell stability, improved gastrointestinal mucosal integrity, enhanced cell-mediated immune response to stress, attenuation of the hypermetabolic response to surgery and improvement of blood flow to poorly vascularised and ischemic tissues.(6) (Evans DC, 2014) These immune-modulating nutrient-enriched products have shown their ability to decrease postoperative complications up to 50% in patients undergoing non-gastrointestinal major surgery, length of hospital and ICU stays (Drover 2011, Jie B 2012).(5,7) In the same vein, Buijs and al demonstrated a benefit on mortality outcome in a study focused on otorhinolaryngology surgery.(8) (Buijs N, 2010) Additionally, immune-modulating regimens reduced hospital resources consumed for surgical morbidity.(9) (Braga M, 2005) Consequently, this reduces the hospital capacity strain, increases income capacities and patient hospitalisation rate.

Arginine is a non-essential amino acid that plays a role in collagen synthesis, cell growth and proliferation such as for wound healing in surgery. Additionally, arginine is involved in the production of nitric oxide (NO), which regulates gene expression and stimulates cell-mediated immunity. NO is important for microvascular perfusion, particularly in postoperative and septic states. Arginine supplies are rapidly depleted during surgery and major metabolic stress. When arginine depletes, cells generate superoxide, instead of nitric oxide and superoxide leads to cell injury as a result.(5,8) (Drover JW 2011, Buijs N, 2010)

Omega-3 polyunsaturated fatty acids (PUFAs), EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) are anti-inflammatory acids. They reduce inflammation without escalating risk of infection. They modulate key processes of immunity, inflammation and oxidative defences. They reverse or reduce the loss of lean body tissue. They prevent oxidative injury in a variety of tissues. They modulate gene production of pro and anti-inflammatory mediators.(6) (Evans DC, 2014)

Oral source of Arginine and PUFAs are founded in a special oral nutritional supplement, the **Oral Impact®** (Nestlé Health Science, Issy-les-Moulineaux, France) (Figure 1). This is a nutrient enriched diet containing **Arginine**, PolyUnsaturated Fatty Acids (**ω3 PUFAs**) and nucleotides (Figure 1). In addition, it provides 340 calories per briquette. It acts as an immune-modulating product. Regimen consists of three briquettes per day for 7 to 10 days within 20 days preceding scheduled surgery. This is the only oral supplement delivered with a medical prescription for exceptional products and then redeemed.



Figure 1: Oral Impact ® briquette. Note the components on the briquette: **Arg** (arginine), **ω3** (PUFAs, PolyUnsaturated Fatty Acids) and, nucleotides.

Reducing postoperative complications remains worldwide an important concern. Eckart et al. has demonstrated that inflammation with CRP > 20 mg/L induced a 10-fold increase of the risk of poor postoperative outcome, NRS-2002 score ≥ 3 and serum albumin < 34 g/L also increased the risk of poor outcome by 3 folds. The combination of the three factors could predict well 30-days mortality with an area under the receiver observer characteristics curve of 0.82.(10) (Eckart A, 2019)

Indeed, many trials have demonstrated that perioperative hypoalbuminemia is an independent and major risk factor of postoperative complications.(11-13) (Panayi AC 2024, Goh SL 2015, Offodile AC 2014) The multiple protective actions of serum albumin explain this link between hypoalbuminemia and postoperative complications. Indeed, serum albumin exhibits immunomodulatory capacity by binding several bacterial products, antibiotic transportation, synergistic and potentiating action with antibiotic treatment, anti-inflammatory effects, anti-oxidation property by scavenging reactive oxygen species, kidney protection, cardiac protection, neuroprotection, preservation and stabilisation of the vascular endothelium glycocalyx integrity, preservation of microcirculation which is very important for wound healing, maintenance of normal capillary permeability, significant reduction of re-oxygenation injury and ischemia–reperfusion injury resulting in tissue damage following disruption of the glycocalyx.(14-15) (Aldecoa C 2020, Ferrer R 2018) Additionally, liver production of albumin is of 10-15 g per day and postoperative complications occurred in the first week following the surgery. The rate of human serum albumin synthesis depends on the blood oncotic pressure, as the human serum albumin concentration is detected by osmoreceptors in the hepatic interstitium. Moreover, the yield of human serum albumin biosynthesis is dependent upon hormone status, nutrition, and inflammation.(16-17) (De Simone G 2021, Fernandez J 2020) The liver cannot produce sufficient albumin to maintain a serum albumin at the normal level to avoid postoperative complications as Fernandez et al. showed by investigating serum albumin recovering kinetics (Figure 2).(17) Therefore, early infusion of albumin intravenously maintains the serum level at its normal value and promote effective interaction of albumin with the other recovery pathways: immunity, iron homeostasis, energy metabolism. Success in postoperative recovery pathways lies in synergistic multiple actions and not in a solitary



intervention. Therefore, a solely albumin infusion could not be efficient to prevent postoperative complication.

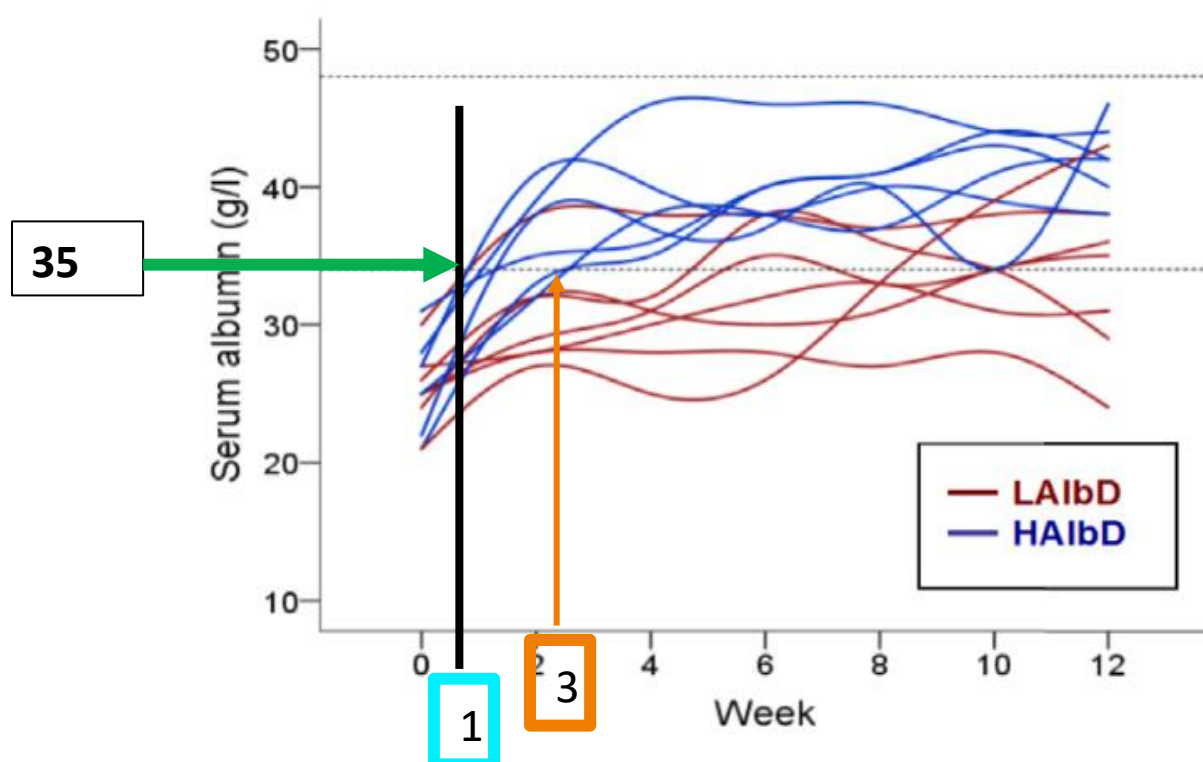


Figure 2: Kinetics of serum albumin recovering in cirrhotic patients with hypoalbuminemia receiving intravenously 20% albumin. Cure durations were in the range of a week. High posology (blue lines) was 1 vial (20 g) per day for one week, to be repeated. Recovering kinetics were as slow, one to three weeks, as hypoalbuminemia was severe and posology low (red lines, less than 1 vial per day). Serum albumin target was 35 g/L. From Fernandez et al.(17).

Moreover, serum albumin is catabolised when acting against inflammation, infection, reactive oxygen species released by surgery in per and postoperative periods due to the intense surgical stress. The resulting hypoalbuminemia is a recognised and independent major risk factor of nosocomial infection. Consequently, hypoalbuminemia deprives patients of the advantages of the serum albumin in stress situations and systemic inflammation response as observed after surgery.

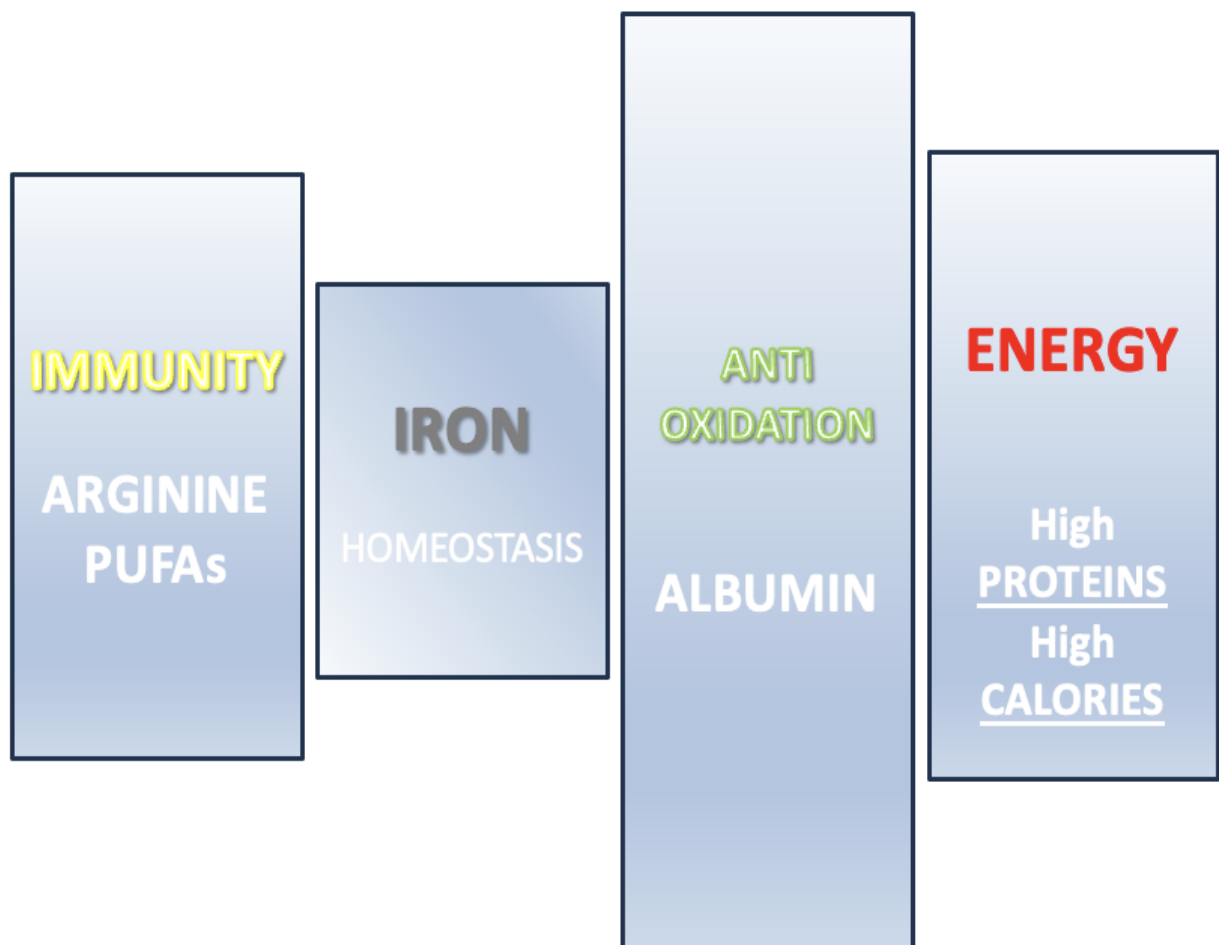


Figure 3: Postoperative recovery quadriptych pathway for intense oxidative stress surgery. This quadriptych illustrates recovery pathways synergism. Arginine and PUFAs (PolyUnsaturated Fatty Acids) are components of Oral Impact® diet for preoperative immune modulation.



Therefore, controlling serum albumin concentration at its normal level associated with the other recovery pathways would protect patients from major postoperative complications and prolonged length of stay.

Our clinical experience in gastro-intestinal and urologic surgery, and the ongoing IMPACTURO trial (ClinicalTrials.gov, NCT05520151, <https://classic.clinicaltrials.gov/ct2/show/NCT05520151>) standing for feasibility study, suggests that a perioperative recovery program based on a quadriptych pathways (immune modulation, iron control, proteins-calories support and postoperative albumin antioxidant pathway) could consistently reduce, below 10%, the incidence of major postoperative complications following laparotomies for radical cystectomy, nephrectomies (IMPACTURO trial) and others intense oxidative stress surgeries like laparotomy for gastro-intestinal surgery (Figure 3).

Studies with immunonutrients alone have demonstrated discrepancy in level of benefit, around 20% of major postoperative complications, suggesting a need of synergism with different components that have to be used in combination in a complete nutrition program to optimise immunonutrition efficacy.(4) (Wishmeyer PE, 2018)

Today, no prospective and randomised study has previously demonstrated that hypoalbuminemia treatment with 20% albumin infusion (antioxidant pathway), in a synergistic action with arginine (immune modulation), iron control, and proteins-calories support (energy), could reduce postoperative complications in intense oxidative stress surgery.

Recent recommendations of the American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Nutrition Screening and Therapy Within a Surgical Enhanced Recovery Pathway emphasizes this synergism.(4) (Wishmeyer PE, 2018)



3- Human albumin in surgery context

3-1- Perioperative endogenous and exogenous malnutrition

Malnutrition may be exogenous, related to insufficient food intake, or endogenous, related to an increase in nutritional requirements generated by hypercatabolism or an increase in energy expenditure. Moreover, malnutrition may be mixt, exogenous and endogenous, as in surgical context, cancer and inflammatory diseases.(18-19) (Argiles JM 2005, Heremmans KM 2019) Consequently, sarcopenia, asthenia, loss of weight and appetite, loss of patient autonomy, reduction of protein synthesis impairing wound healing, reduction of albumin synthesis, greatly increase the risk of major postoperative complications after surgery generating both intense catabolism and oxidative stress. Therefore, perioperative nutrition interventions appear mandatory to limit occurrence of postoperative complications and first of them, nosocomial infections.(3, 20) (Katona P 2008, Wiedermann CJ 2021) Additionally, hospital malnutrition is common worldwide concerning 40% of patients.(21) (Baker LA, 2003)

As a result, clinical screening of malnutrition is essential in the perioperative context. NRS-2002 is a recognised gold standard screening score. Items taken in account are age ≥ 70 years, body mass index < 18 , kinetics of weight loss $> 5\%$, sarcopenia and asthenia.(22-23) (Kondrup J 2003, Hersberger L 2020) A patient with a score ≥ 2 is considered malnourished. NRS-2002 is associated to the biologic screening especially serum albumin < 35 g/L. Hypoalbuminemia is a late sign of malnutrition, a pejorative health marker, and an independent major risk of postoperative complications. Clinical signs should alert and promote interventions prior to surgery. However, cachexia, especially that induced by cancer does not respond to conventional nutrition interventions particularly in the perioperative period. Benefit of surgery should therefore be balanced with induced-surgical stress and postoperative complications particularly death.

Recovery pathways will tend to minimise the induced-surgical stress, reduce catabolism and both favour anabolism and early physical mobilisation. Daily calories support at the level of 35



Cal/kg/day must be a permanent query for physicians. Energy from calories and proteins should be provided first orally, secondly by enteral nutrition and if that is not possible, by parenteral nutrition. Enteral nutrition through a feeding tube inserted percutaneously into the stomach or proximal small intestine by gastroenterologist, surgeon, or radiologist must be of worth considering.

Cutaneous catheter is a way of **nosocomial infection** in malnourished patients. To allow nutrition recovery before occurrence of catheter infection, hypoalbuminemia should be corrected concomitantly to make profit of antimicrobial effect of serum albumin with microbiota and peptides such as chromogranin and vasostatin. Therefore, human albumin should be infused intravenously to compensate the low production rate of the liver. Additionally, this helps enhancement of bowel transit and secondly, oral intake or enteral nutrition. These latter preserve intestinal trophicity. Finally, preserved intestinal trophicity prevent bacterial intestinal-translocation infection.

3-2- Physiology of intense surgical oxidative stress

Surgery can induce an intense oxidative stress related to hypercatabolism and intense inflammation with a systemic response. (1) (Finerty CC, 2013) In the absence of infection, this inflammatory response is sterile. The balance between defence and repair should be oriented to repair. Acute-phase response is characterised by decreased production of albumin by hepatocytes, reorientation of iron metabolism, and hormonal changes.

Inflammation must be artificially down regulated. Plasma concentration of C-Reactive Protein decreases when serum albumin increases (Figure 4) suggesting that an early control of CRP could be possible if serum albumin is early maintained even with albumin infusion. Figure 4 illustrates how crucial the first postoperative week is. The core point is at the middle of the first week.(24) (Mantovani A, 2023) In clinical practice, this is the moment when probability of complications, especially nosocomial infection, is high induced by dysbiosis, gut barrier



dysfunction, increased intestinal permeability and bacterial translocation in blood stream (Figure 5).(19) (Herremans KM)

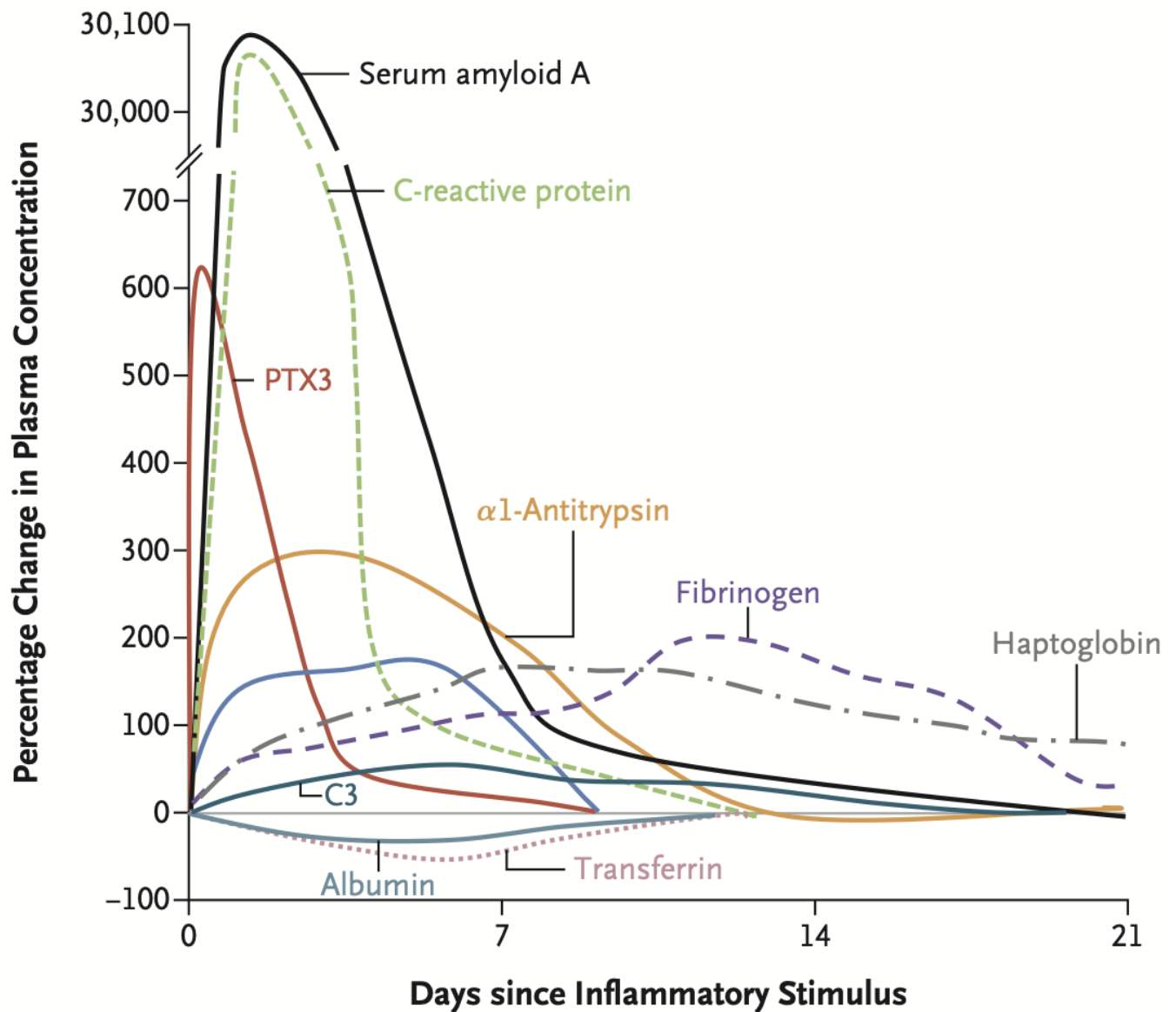


Figure 4: Kinetics of C-Reactive Protein and serum albumin in the inflammation acute-phase response to stress. From Mantovani et al.(24)

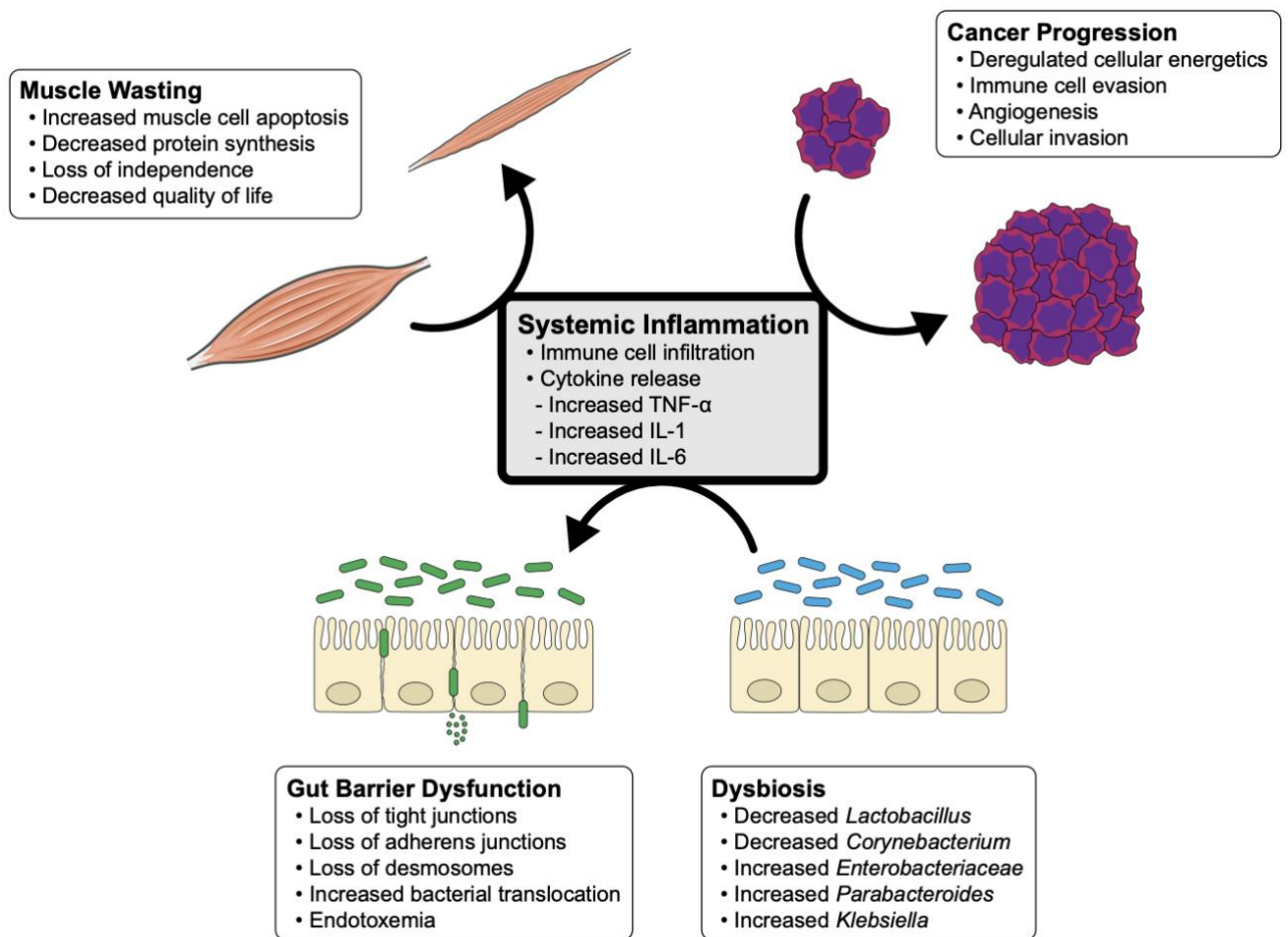


Figure 5: Mechanisms of cachexia in oxidative stress induced by cancer. Note gut barrier dysfunction leading to bacterial translocation, endotoxemia, and nosocomial infection. From Herremans et al.(19)

Cytokines (IL1, TNF- α , IL6) released by inflammation and catabolism products (reactive oxygen species, DAMPs (Damage-Associated Molecular Pattern) and PAMPs (Pathogen-Associated Molecular Pattern) greatly impair postoperative recovery by promoting major complications.

Additionally, inflammation induces a wide response of the neuroendocrine system, which leads to modifications in all the endocrine axes to mobilise energy and innate immunity. Cortisol, catecholamines, antimicrobial peptides from chromaffin cell of the adrenal medulla released along catecholamines, glucagon, and growth factor mobilise energy for both defence and repair. Endocrine and metabolic responses to inflammation allow the organism to survive. However, in chronic or prolonged inflammatory conditions, this systemic response contributes to the catabolic process, with skeletal muscle atrophy and cachexia as observed postoperatively, after intense and prolonged surgical oxidative stress.(19, 25) (Herremans KM 2019, Martin AI 2021).

3-3- Cachexia

Mechanisms of cachexia in cancer highlight metabolism pathways describing the oxidative surgical stress (Figure 5).(19) (Herremans KM, 2019)

Additional studies have exhibited a correlation between circulating IL-6 and suppression of protein synthesis and muscular atrophy. TNF- α has also been shown to accelerate apoptosis in muscle cells.

Cancer cachexia is a multifaceted clinical syndrome characterised by disequilibrium of inflammation, gut permeability and muscle wasting. In patients with cancer cachexia, elevations of acute phase reactants, such as C-reactive protein (CRP), fibrinogen and inversely, decrease of serum albumin, have been correlated with disease progression, decreased survival and poor quality of life (Figure 6).(26) (Raush V, 2021)

IL-6 is **multifunctional** and is involved in wound healing and tissue regeneration. However, chronic secretion of IL-6 has been correlated with tumorigenesis, muscle wasting and decreased survival time in patients with cancer cachexia. Patients with advanced cancer have elevated levels of IL-6 which correlate to weight loss and anaemia.(19) (Herremans KS, 2019)



Additionally, interleukin-6 is a potent inducer of acute-phase proteins production in the liver through reprogramming and reorientation of metabolic functions (e.g., decrease in albumin production and increased production of acute-phase proteins).(24) (Mantovani A, 2023)

Cachectic patients with gastric cancer involving the transverse mesocolon exhibited after surgery a higher level of bacterial translocation and increased systemic inflammatory cytokines. Increased intestinal permeability caused by variations in tight junction proteins may result in bacterial translocation. Tight junctions are the structural basis for the intestinal epithelium barrier. There is increasing evidence that bacterial translocation might contribute to the occurrence and development of cancer cachexia.(27) (Jiang Y, 2014)

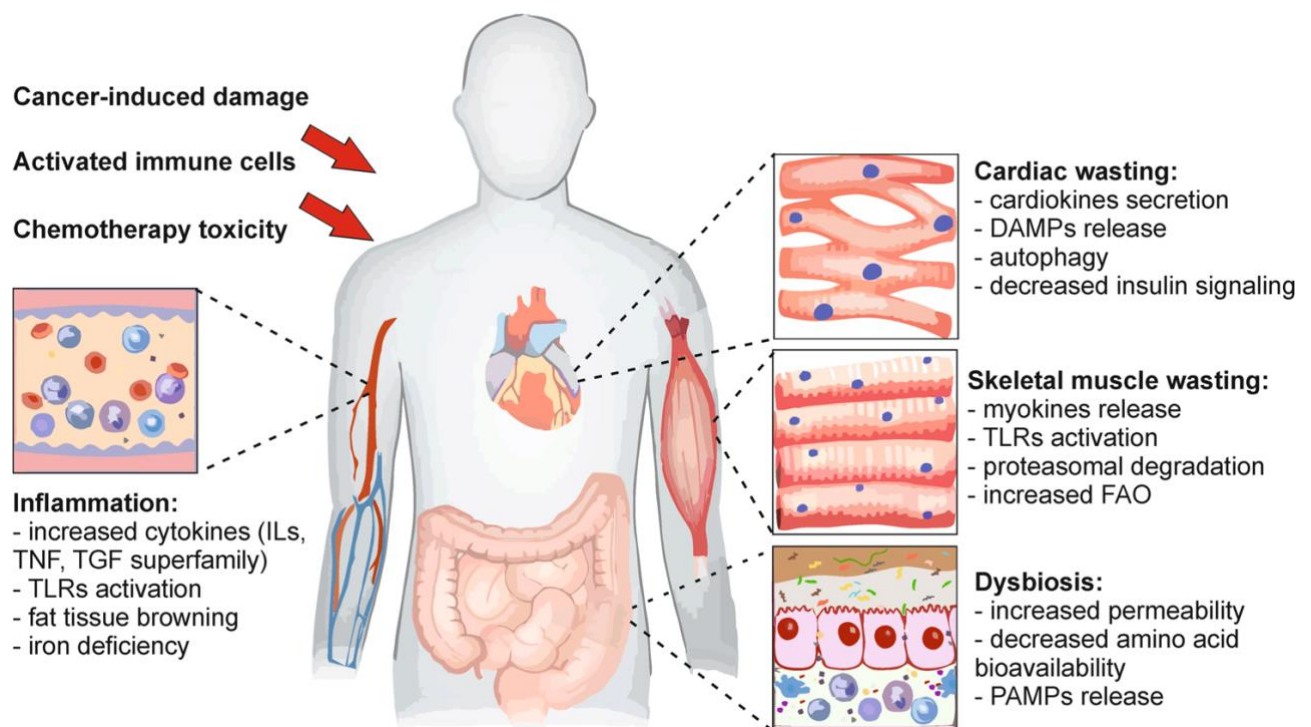


Figure 6: Inflammation induced by cancer and chemotherapy toxicity generates cardiac and skeletal muscle cachexia, gut permeability and bacterial translocation. IL, interleukins; TLR, Toll-like receptor. DAMP, Damage-Associated Molecular Patterns. PAMP, Pathogen-Associated Molecular Patterns. TNF, Tumor necrosis Factor; TGF, Transforming Growth Factor; FAO, fatty acid oxidation. From Rausch et al.(26)

3-4- Innate immunity

Immunity is carried out by granulocytes and monocytes (lymphocytes), collectively called myeloid cells. Upon pathogen invasion, myeloid cells are rapidly recruited into local tissues via various chemokine receptors, where they are activated for phagocytosis as well as secretion of inflammatory cytokines, thereby playing major roles in innate immunity (Figure 7).(28-29) (Jarczak D 2021, Kawamoto H 2004)

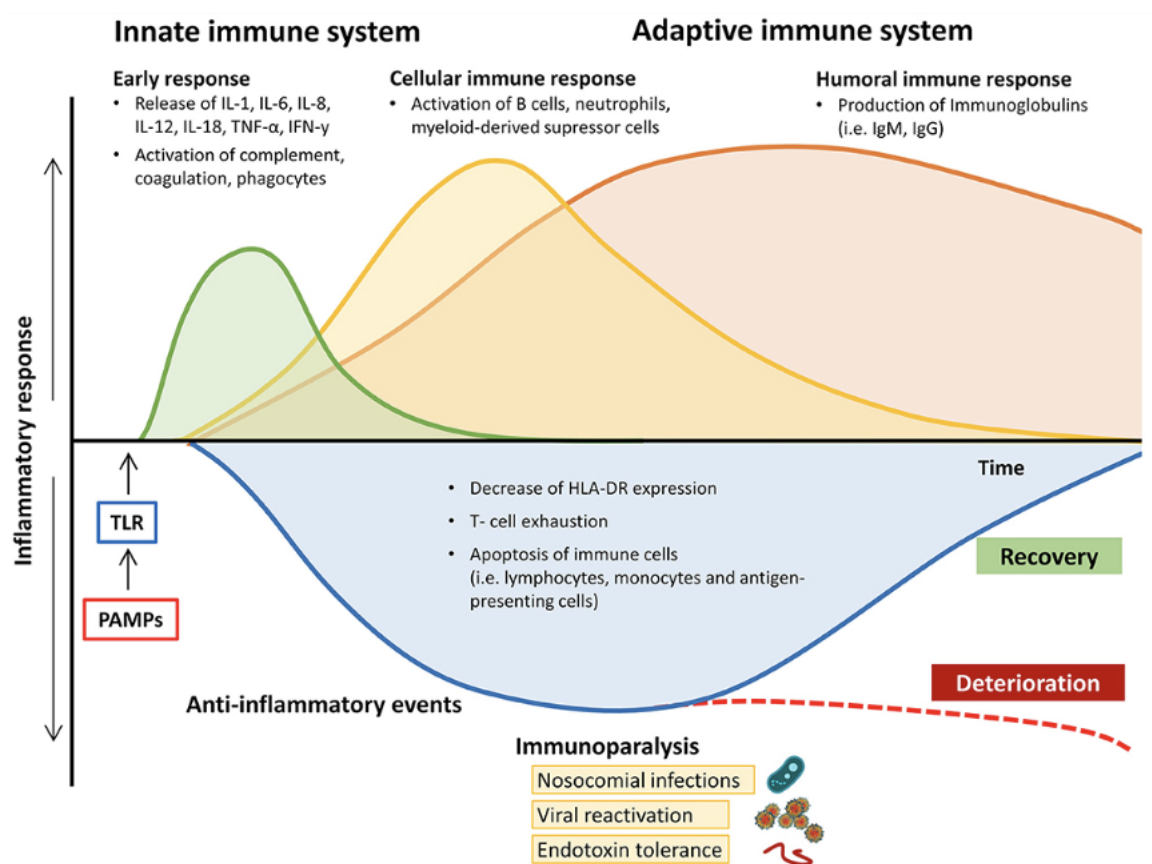


Figure 7: Changes in pro- and anti-inflammatory response of the immune system during course of sepsis and septic shock. HLA-DR, human leukocyte antigen-D related; IgM/G, immunoglobulin M/G; IL, interleukin; IFN- γ , Interferon γ ; PAMPs, pathogen-associated molecular patterns; TNF- α , tumor necrosis factor alpha; TLR, toll-like receptor. From Jarczak et al.(28) (Jarczak D, 2021)

Innate immunity is supported by non-oxidised peptides very sensible to ROS which degrade them. Antimicrobial peptides (AMPs) have been studied and used in clinical settings for infections treatment. Endogenous AMPs represent the defence first line of the innate immune system against pathogens (Figure 8). They also positively interfere with infection-associated inflammation. Interestingly, AMPs influence numerous biological processes, such as regulation of the microbiota, wound healing, induction of adaptive immunity, and regulation of inflammation. Numerous peptides identified in chromaffin secretory granules from the adrenal medulla possess antimicrobial activity: they are released by chromaffin cells during stress situations by exocytosis via activation of the hypothalamo-pituitary axis.(30-31) (Scavello F 2022, Zhang Q-Y 2021) Because these AMPs co-localised with catecholamines, they are released during stress for health. They play a role as first protective barrier against bacterial infection and then, act as factors of innate immunity shortly after infection development. Moreover, AMPs present in chromaffin cells act by destabilising the cell wall.(30) Likewise, combinations of cateslatin with classical antibiotics, such as Cefotaxime, Amoxicillin, Methicillin and Voriconazole show a synergistic effect.

The humoral arm of the innate immune system is made up of different classes of molecules, such as pentraxins, collectins, and ficolins, which functionally act as ancestors of antibodies (ante-antibodies) by initiating complement activation, opsonizing microbes and damaged cells, agglutinating or neutralizing microbes, and regulating inflammation.(24) (Mantovani A, 2023)

Albumin by scavenging ROS protects those peptides (chromogranin, vasostatin, catestatin, cateslytin) and potentiates the innate immunity which **acts synergistically with antibiotics**. Catestatin binds to the circulating albumin suggesting a synergistic action. The interaction catestatin/albumin improves the antimicrobial activity of the peptide against Candida Albicans.(30) (Scavello F, 2022) The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group has demonstrated that sterilize patients from bacteria with antibiotics is not sufficient to recover total health and avoid death.(32)



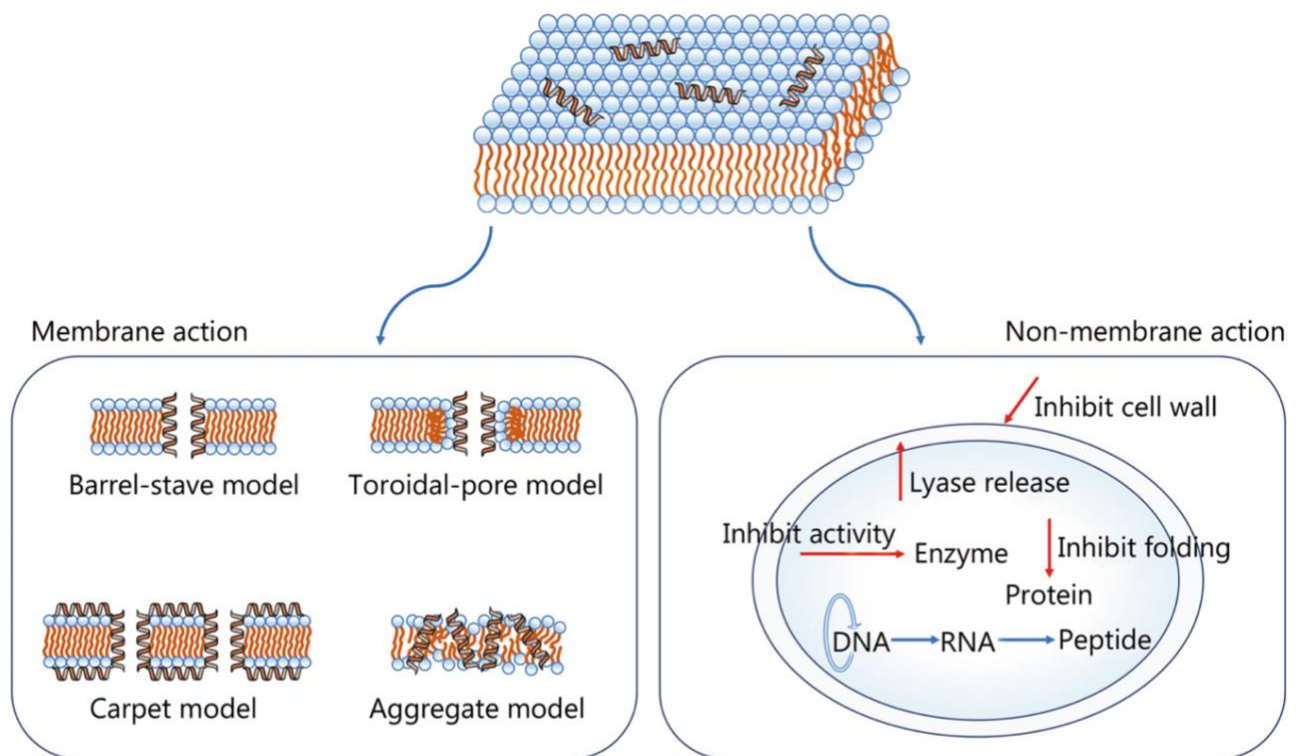


Figure 8: Action mechanism of non-oxidised antimicrobial peptides. The main target of AMPs is the cell membrane. Membrane permeability increased leading to cell death. Additionally, AMPs inhibit cell protein synthesis. From Zhang et al.(31)

3-5- Arginine, trauma, and surgery

Myeloid cells function needs substantially arginine. In myeloid cells, arginine is mainly metabolized either by inducible nitric oxide (NO) synthases (iNOS) or by arginase, enzymes that are stimulated by cytokines secreted by T helper lymphocytes. iNOS promotes arginine and NO. Arginase depletes arginine. Moreover, T lymphocytes depend on **arginine** for proliferation, zeta-chain peptide and T-cell receptor complex expression, and development of memory. Thus, activation of iNOS or arginase (or both) reflects the type of inflammatory response in a specific disease process like cancer. Myeloid cells expressing arginase have been

shown to accumulate in patients with cancer. Additionally, myeloid suppressor cells (MSC) expressing arginase have been described in cancer, infections, intra-abdominal sepsis, and trauma. Trauma is comparable to surgery. Arginase expression is also detected in mononuclear cells after trauma or surgery. MSC efficiently deplete arginine and generate ornithine. Through arginine depletion, MSC may control NO production and regulate other arginine-dependent biological processes. Low circulating arginine has been documented in trauma and cancer, suggesting that MSC may exert a systemic effect and cause a state of arginine deficiency. Likewise, T-cells cocultured with MSC express molecular and functional effects associated with arginine deficiency. Not surprisingly, T-cell abnormalities, including decreased proliferation and loss of zeta-chain, are observed in cancer and after trauma.(33) (Popovic PJ, 2007) Consequently, arginine intake prior to surgery appears a good recovery pathway to prevent postoperative nosocomial infections.

3-6- Iron

Acute-phase proteins are involved in the metabolism of iron, a nutrient required for a several host-cell functions as well as for growth of microbial pathogens. Acute-phase proteins function in iron metabolism include binding to the nutrient (iron), thus preventing utilisation of circulating free iron by pathogens and retention of iron inside cells.(24) (Matovani A, 2023) As a result, circulating iron is not available for haematopoietic function resulting in an inflammatory anaemia. Iron stocks are full but not functionally available. Treatment of inflammatory anaemia results in transfusion. Inflammation must be controlled postoperatively to release iron and promote its non-haematopoietic properties like wound healing and physical activity improvement crucial in postoperative period following intense oxidative stress surgery.(34-35) (Martín-Ontiyuelo C 2019, Boutou AK 2015) Albumin infusion could play an important role in this therapeutic pathway. Circulating iron must be maintained at a normal level. Iron deficiency in the inflammatory context that increases serum ferritin is monitored with the serum transferrin receptor which is upregulated meaning that free iron is low.



However, non-haematopoietic properties of iron are researched preoperatively by increasing serum level of ferritin above 100 ng/ml as recommended by the Superior Health Authority in France with intravenous administration of iron (Ferinject[®], Vifor Pharma, Paris La Défense, France).

3-7- Microcirculation

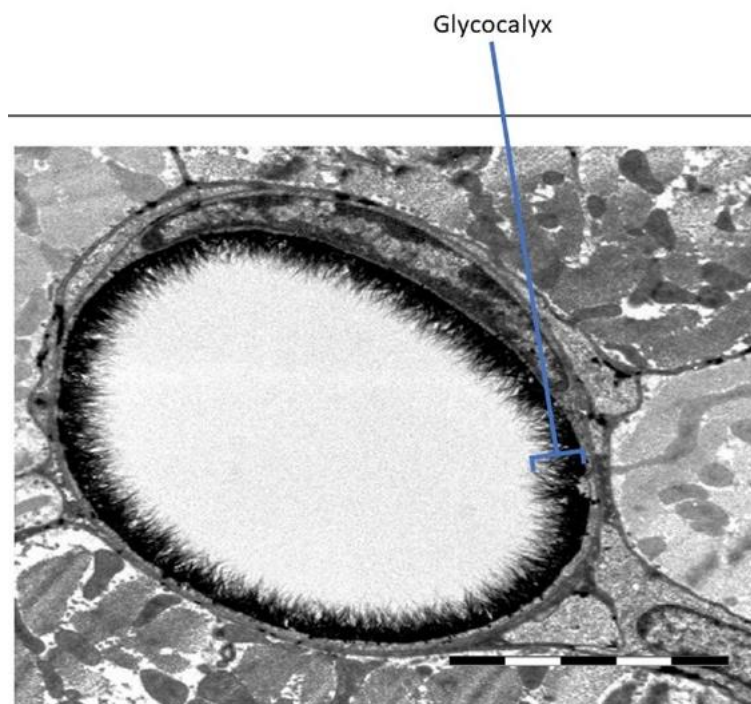


Figure 9: Electron micrograph of a cross-sectional image of a coronary endothelial glycocalyx (courtesy of B. van den Berg, Maastricht University). From Lekakis J et al.(34)

The vascular endothelium glycocalyx plays a major role in preservation of microcirculation integrity (Figure 9). Normal function of microcirculation favours wound healing, avoid fistula and anastomotic leakages. These postoperative complications prolong length of stay as well as sepsis.

Sepsis is a disease of microcirculation. Endotheliopathy is preceded by disruption of the glycocalyx mediated by reactive oxygen and nitrogen species and tumour necrosis factor- α (TNF- α). Disrupted glycocalyx exposes endothelium to leukocytes adhesion and impaired fibrinolysis. Reactive oxygen and nitrogen species activates matrix metalloproteinases (MMP) that cleave the glycocalyx. Sphingosine 1-phosphate released by red blood cells inhibits this MMP-mediated glycocalyx degradation and serum albumin mobilises Sphingosine 1-phosphate.(37- 38) (Farrugia A 2022, Zhang W-J 2002)

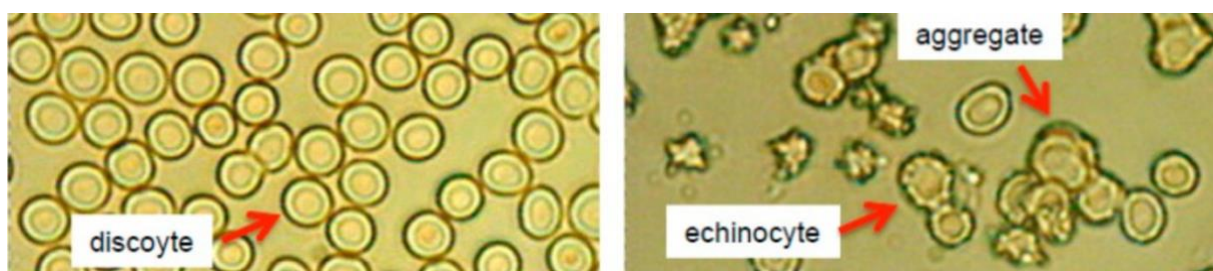


Figure 10: Sepsis alters erythrocytes morphology and blood flow in capillary network. Blood smears from a healthy volunteer (left) show normal red blood cell with discocyte morphology and a septic shock patient (right) with abnormal red blood cell morphology. Note the presence of echinocytes, red blood cell aggregates and abnormal red blood cells in the septic patient. From Bateman RM et al.(39)

A hallmark of sepsis is increased stopped-flow capillary. Several factors may be involved: (1) red blood cells adhesion to endothelial cells mediated by lipopolysaccharide (LPS) and intermittent flow conditions, (2) increased RBC intracellular Ca^{2+} , (3) redistribution of phosphatidylserine to the outer red blood cells membrane leaflet, (4) decreased red blood cells deformability, (5) increased platelet adhesion and increased coagulation. Increased red blood cells rigidity and a change in red blood cells deformability is an early indicator of sepsis. Sepsis dramatically alters cytoskeleton, membrane and red blood cells membrane surface properties (Figure 10). Decreased erythrocyte deformability in sepsis is associated with organ dysfunction and patient outcome. Taken together, these findings suggest a significant role for RBC injury

in sepsis induced-microvascular dysregulation and patient outcome. Moreover, sepsis decreases red blood cells glutathione indicating reduced potential to recycle oxidised antioxidants and protect protein thiol groups from oxidation. Antioxidants protect cells from damaging effects of oxygen free radicals and reactive oxygen species (superoxide anion, hydrogen peroxide, hydroxyl radical) on membranes (lipid peroxidation), proteins (oxidation of thiol groups) and DNA (strand breaking). These damages result in cell and organelle damage particularly if endogenous antioxidant defences are depleted.(39) (Bateman RM, 2017) Interestingly, washing stored red blood cells in an albumin solution improves their morphological and haemorheological properties (Figure 11). Albumin as described above remains the most powerful antioxidant circulating in blood.(40) (Reinhart WH, 2015)

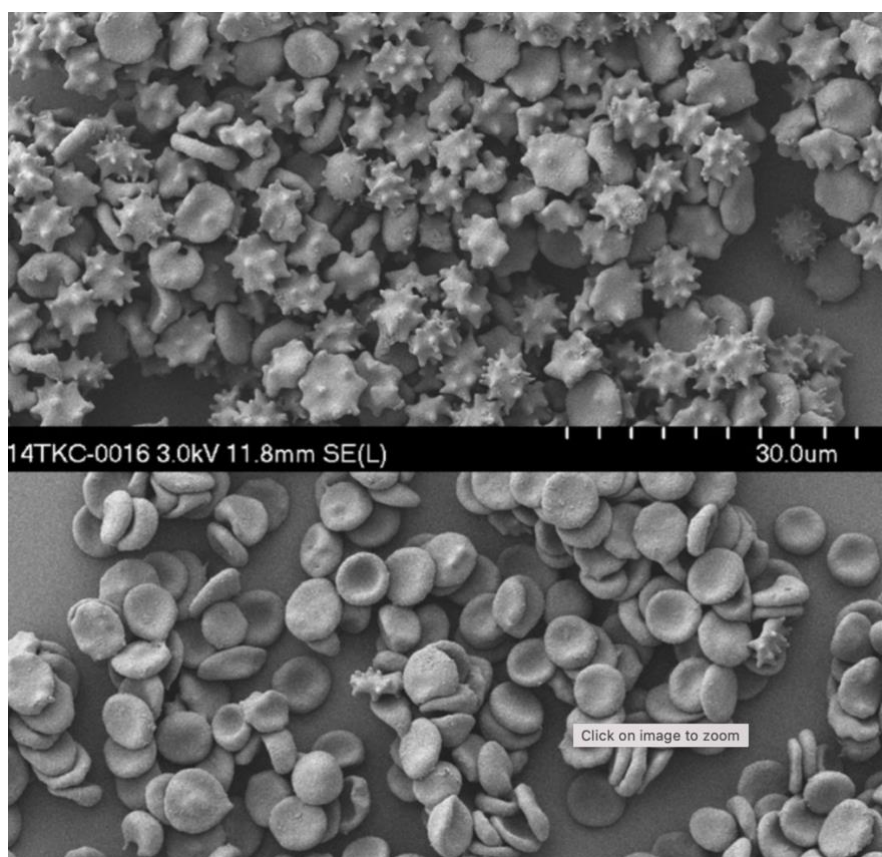


Figure 11: Washing stored red blood cells (up) in an albumin solution improves their morphological and haemorheological properties (down). From Reinhart WH et al.(40)

Therefore, preservation of the glycocalyx and vascular endothelium integrity is crucial. This consists of maintaining the vascular tone, endothelium permeability and haemostasis equilibrium. This could explain thrombosis in inflammatory states like COVID 19 or cancer. Consequently, nitric oxide (NO) resulting from arginine metabolism participates to preservation of vascular endothelium integrity, maintained vascular tone, and subsequently favour organ perfusion, oxygenation, and prevents thrombosis. This supports the resistance to hypoxia in addition of preventing anaemia.(41) (Kurhaluk N, 2023) NO is sensible to oxidation especially to reactive oxygen species emerging from inflammation. Antioxidation pathways protect NO from degradation or impairment of its synthesis.

3-8- Postoperative Complications following major surgery inducing intense oxidative stress

Postoperative complications are defined as a pathological clinical event occurring during hospital stay. These complications are classified in minor or major complications according to the Clavien-Dindo score.(42) (Dindo D, 2004).

The Clavien-Dindo score describes severity of postoperative complications as following:

- **Grade 1**: Events not requiring pharmacological treatment except symptomatic treatment as antiemetics, intestinal prokinetics, wound cares, physiotherapy, diuretics, analgesics, ...
- **Grade 2**: Requirement of pharmacological treatment such as antibiotics, blood transfusion or total parenteral nutrition.
- **Grade 3**: Requirement of surgical, endoscopic, or radiologic interventions.
- **Grade 4**: Requirement of admission in intensive care unit.
- **Grade 5**: Death.

Complications classified **Clavien-Dindo score 1-2** are considered as **minor**: nosocomial infection without impairment of physical conditions, wound infection without collection of pus, wound dehiscence, need of blood transfusion without bleeding, delayed signs of bowel activity,



postoperative paralytic ileus, need of postoperative nasogastric suction, delayed wound healing, arrhythmia, deep vein thrombosis.

Complications classified **Clavien-Dindo score ≥ 3** are considered as **major**: circulatory insufficiency, bleeding, deep collection of pus, nosocomial infection with impairment of physical conditions, intestinal obstruction, respiratory tract failure with dyspnoea or decrease of blood oxygen saturation $< 92\%$, pulmonary embolism, acute renal insufficiency with need of haemodialysis, postoperative reintervention, percutaneous drainage of a deep collection of pus, fistulas, anastomosis leakage, transfer to intensive care unit (ICU) and death.

3-9- Hypoalbuminemia models

3-9-1- Postoperative hypoalbuminemia and complications following intense oxidative stress surgery

Hypoalbuminemia is both an independent major risk and prognostic factor for poor postoperative recovery and, consequently, for prolonged length of stay.(11-13) (Panayi AC 2024, Goh SL 2015, Offodile AC 2014) The Wiedermann's review emphasizes that hypoalbuminemia is a major risk factor for nosocomial postoperative infection.(20) We clearly observe this relationship in clinical practice. Central catheters represent a recognised gateway of systemic infections. In clinical practice, central catheter infections occur more frequently and easily in patients with hypoalbuminemia or malnourished. In malnourished patients treated with parenteral nutrition via peripheral inserted central catheters (Midline or Piccline), in addition to oral intake to cover daily calorie requirements, catheter infection often ensues before obtaining the benefit of nutrition intervention reflected by normalisation of serum albumin and physical recovery. In these cases, fungal infections are common with Candida Albicans or other fungal pathogens.(43) (Karadag-Oncel E, 2015) Invasive fungal infections are an important cause of morbidity and mortality in hospitalised patients and in immunocompromised population as may be malnourished patients.



For many physicians, hypoalbuminemia still represents an indicator of malnourishment or a prognostic factor whereas serum albumin plays a key role in human body homeostasis with important therapeutic implications. Albumin non-oncotic properties are essential to functionally equilibrate the human body and organise its defence and repair against various damages.

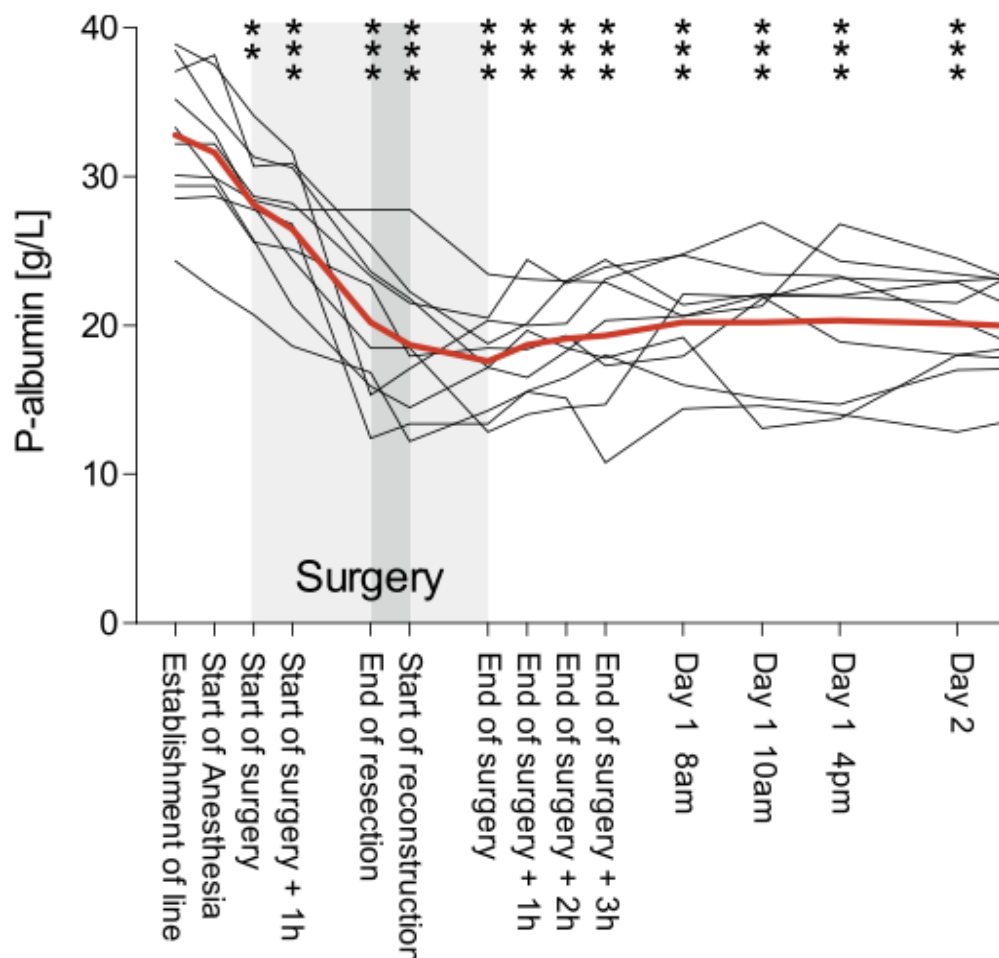


Figure 12: Deep decrease of plasma albumin concentration in per and postoperative periods of abdominal surgery with intense surgical oxidative stress. From Norberg A et al.(44)

Serum albumin is cleared in the liver when highly oxidised after struggling against inflammation, infection, reactive oxygen species released by surgery in per and postoperative periods due to intense surgical stress.(46) (Holte C, 2023) The resulting hypoalbuminemia is recognised as an independent high risk factor for nosocomial infection.

Consequently, hypoalbuminemia deprives patients of the advantages of the serum albumin in stress situations and systemic inflammation response as observed after surgery. These multiple actions of albumin consist of immunomodulatory capacity by binding several bacterial products, antibiotic transportation, synergistic and potentiating action with antibiotic treatment, anti-inflammatory effects, reduction of oxidation by scavenging reactive oxygen and nitrogen species, kidney protection, cardiac protection, neuroprotection, preservation and stabilisation of vascular endothelium glycocalyx integrity, preservation of microcirculation which is very important for wound healing, maintenance of a normal capillary permeability, significant reduction of re-oxygenation injury and ischemia–reperfusion injury resulting in tissue damage following disruption of the glycocalyx. This latter property is crucial for **free tissue flap transfer** in reconstruction surgery.

Therefore, controlling serum albumin concentration at its normal level in association with the other recovery pathways would protect patients from major postoperative complications and prolonged length of stay. Additionally, this review may contribute to a better understanding of perioperative cares of surgeries with intense oxidative stress especially concerning recovery pathways synergism.

The liver synthesises non-oxidised albumin with a yield below that required in acute phases of inflammation following damages, trauma or surgery. Liver protein synthesis is redirected to that of inflammation acute-phase proteins against non-oxidised albumin synthesis. During this period, serum albumin decreases.(24) (Mantovani A, 2023) Specifically, after surgery with intense oxidative stress, Motamed et al. have shown that serum albumin dropped significantly by 50% in the postoperative period following ovarian cancer, abdominal and otorhinolaryngology surgery.(46) (Motamed C, 2022) Norberg et al. shared this observation of



a 30 to 50% decrease in serum albumin from pre to postoperative periods (Figure 12).(44)
(Norberg A, 2016)

Maintaining postoperatively, a normal serum albumin in surgery with intense oxidative stress, by a 100%-pure non-oxidised albumin infusion appears, in present days, worldwide, a medical requirement. However, albumin must not be used solely but in a synergistic recovery program associating other recovery pathways: immunonutrition, iron homeostasis, proteins-calories support, and physical exercise. Therefore, to demonstrate the value of this analysis and perhaps evolve perioperative guidelines, a perioperative, prospective, rigorous, multicentric, and randomised trial is necessary and eagerly awaited.

In the prospective group of a recently completed before-after IMPACTURO multicentre trial (ClinicalTrials.gov, NCT05520151, <https://classic.clinicaltrials.gov/ct2/show/NCT05520151>), comparing the rate of postoperative complications following laparotomies for radical cystectomies and nephrectomies, infusions of 20% albumin solution was administered intravenously only when a complication occurred. The rate of complications is collected prior to albumin infusion. The retrospective group did not receive albumin infusions. Additionally, the prospective group is entered into a perioperative synergistic recovery program based on immune modulation, iron homeostasis and proteins-calories support. Therefore, the present IMPACTURO prospective group could stand for a feasibility study and a base for sample size calculation of a randomised trial.

Schaller et al. have designed a single centre, randomised, controlled, outcome assessor-blinded clinical trial in 2509 adult patients with a goal-directed perioperative albumin substitution versus standard cares to reduce postoperative complications and mortality(SuperAdd Trial).(47) (Schaller SJ, 2023) This study failed to demonstrate despite randomisation a difference between groups at interim analysis after inclusion of 100 patients in each group. This highlights clearly that correcting solely perioperative hypoalbuminemia is insufficient to enhance postoperative recovery. Perioperative hypoalbuminemia must be treated



synergistically and concomitantly with immune modulation, iron homeostasis and proteins-calories support as a quadriptych perioperative recovery pathway. A normal serum albumin, at least 35 g/L, is necessary to provide non-oxidised albumin which guarantees an efficient antioxidant action against surgical oxidative stress. Additionally, this study shows the methodologic way and the base of a future trial design which, furthermore, must not focus on mortality outcome.

Indeed, Haynes et al. pointed in a meta-analysis the result discrepancy related to the focus on mortality outcome. These small trials missed power to detect a significant difference as required when the outcome is mortality. However, these small trials demonstrate that treating hypoalbuminemia reduces morbidity which, in surgical context, is exhibited by postoperative complications.(48) (Haynes GR, 2003) Therefore, reducing postoperative complications decreases length of stay, releases surgical beds, and allows a certain admission capacity which limits both overcrowding in Emergency Services and cancellations of scheduled patients in operating rooms.

An additional meta-analysis conducted by Vincent et al. share the findings of Haynes et al. Therapeutic infusion of albumin reduced overall morbidity by decreasing the incidence of complications in acutely ill hospitalised patients of various categories including surgery or trauma, burns, high-risk neonates, hypoalbuminemia and ascites.(49) (Vincent JL, 2004)

Continuing in the surgical setting, the ongoing ALBICS trial intends to demonstrate that postoperative treatment of hypoalbuminemia by 20% human albumin infusion could reduce the risk of postoperative acute kidney injury after high-risk cardiac surgery. This is the kidney protective property of human albumin.(50) (Balachandran M, 2021) This property relies essentially on preservation of vascular endothelium integrity, stabilisation of intravascular fluids, inflammation modulation and antioxidation. Clinical practitioners routinely observe these properties in surgical settings. Furthermore, albumin infusion protects against rhabdomyolysis occurring after prolonged-duration surgeries.(51) (Nishida K, 2015) Finally, Vincent et al.,



through a meta-analysis, found an interest to treat postoperative hypoalbuminemia by albumin infusion. For each 10 g/L-serum-albumin decrease, they observed an increase in incidence of postoperative complication of 89%, length of stay of 71% and mortality of 137%.(52) (Vincent J-L, 2003)

Hypoalbuminemia exposes surgical patients to another great postoperative complication, the anastomotic leakage after major gastrointestinal surgery. The following factors were independently associated with increased risk of anastomotic leakage: 1)- serum albumin < 35 g/L, 2)- anaemia < 8 g/dl, 3)- hypotension, 4)- use of inotropes, and 5)- blood transfusion. The high-risk surgeries for anastomotic leaks seem pancreatic surgeries, esophagectomies, and colonic resections. Additionally, risk for anastomotic leak was greatly increased in patients requiring inotropic support in perioperative period and developing hypotension.(53) (Choudhuri AH, 2013). This is consisting with vascular protecting property and intravascular fluids volume stabilising effect of serum albumin found inter alia in the ALBIOS trial.(54-56) (Caironi P 2014, Loffel LM 2021, Hahn RG 2019) **Intraoperative albumin infusion stabilises blood pressure and reduce need of vasopressor to avoid hypotension.**(55)(Loffel LM 2021)

Hypoalbuminemia is believed to affect anastomotic healing by impairing collagen synthesis due to lack of essential amino acids. It is also believed to reduce host immunocompetence, increasing vulnerability for anastomotic leakage. Hypoalbuminemia as described previously appears in both malnutrition and inflammation, by reducing its rate of synthesis, increasing liver clearance of highly oxidised albumin, and in extreme cases, increase in transfer of albumin out of the vascular compartment. Sepsis induced by anastomotic leakage generates a vicious cascade of events: inflammation-induced anorexia, decrease in effective use of dietary proteins and energy intake, and catabolism of key somatic proteins and serum albumin.(57) (Choi JCW, 2023)



3-9-2- The critically ill patient model in intensive care units

Critically ill patients in intensive care units compared with surgical patients lead clinical practitioners, intensivists and anaesthesiologists, to different therapeutic approaches despite hypoalbuminemia and intense oxidative stress in the two categories of patients. Anyway, the quadriptych recovery pathway described above seems of worth considering for intensivists and anaesthesiologists.

The interest of 20% albumin infusion to restore decreased serum albumin in critically ill patients in intensive care units has been widely evaluated. These investigations failed to convince because the primary outcome was often probability of survival or 30 days-mortality. Therefore, groups were not significantly different due to a lack of power. However, other morbidity outcomes often showed significant differences.

This is pointed out by the ALBIOS trial results which found, in critically septic patients, that 20% albumin infusion, three vials per day, for one month to maintain serum albumin at 30 g/L, improved significantly cardiovascular criteria of the SOFA score (Sequential Organ-Failure Assessment) as compared with the crystalloid group. Additionally, time to suspension of vasopressor or inotropic agents administration was shorter and total doses of vasopressor or inotropic agents were decreased in the albumin group with equivalent fluid volume.(54) (Caironi P, 2014) The sample calculation was done on the basis of an estimated baseline mortality of 45%. The observed mortality was quite lower, 31.8%, in the albumin group and 32.0% in the crystalloid group. Therefore, the trial did not have a sufficient power to detect a difference in mortality. There was no mention about immunonutrition (arginine, PUFAs) or iron homeostasis to hold a synergistic quadriptych recovery pathway as mentioned previously. Moreover, the absence of significant difference in length of stay and acute kidney injury, in the ALBIOS trial, highlights that the solely albumin infusion is insufficient to make a significant clinical difference. Hemodynamic difference may have been due to oncotic effect of serum albumin. Nevertheless, Wiedermann CJ and Joannidis M found, in their meta-analysis, that mortality among patients receiving albumin was lower without reaching statistical significance in each of the three following trials: EARSS,



SAFE, and ALBIOS. However, this statistical significance was attained when considering the overall sample with a significant survival benefit (Figure 13).(58-59) (Wiedermann CJ 2014, Carpentier J 2011)

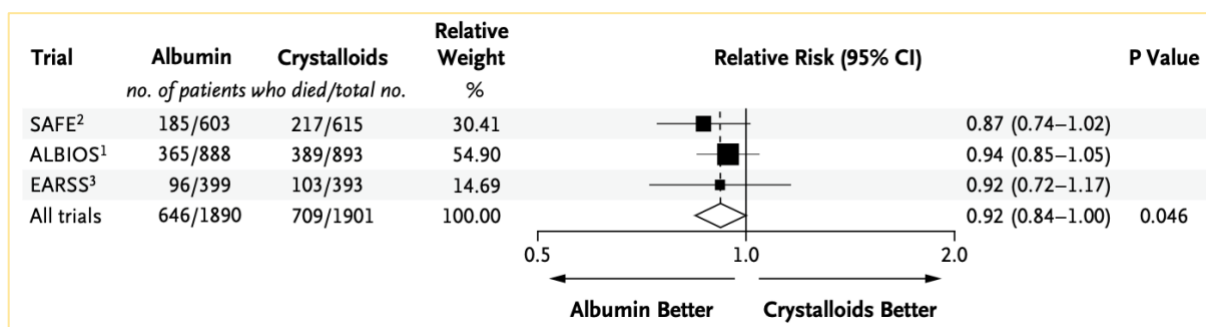


Figure 13: Meta-Analysis of mortality in large-scale randomized trials comparing albumin with crystalloids in adult patients with severe sepsis. From Wiedermann CJ and Joannidis M (58)

The meta-analysis of Delaney et al. involving predominantly small trials with different control fluids and patient populations found similarly a reduction of mortality in patients whom fluid resuscitation included albumin solution.(60)

In other critically ill patients with acute respiratory distress syndrome related to septic shock and hypoalbuminemia, Wang et al. exhibited that early infusion of 20% albumin solution is an independent factor for reduction of length of stay.(61) (Wang X, 2023) Dubois et al., found other positive results following infusion of 20% albumin solution in critically ill patients with hypoalbuminemia. They observed a better SOFA score in the albumin group, consistent with ALBIOS trials findings, and an improvement of intestinal tolerance of enteral nutrition, crucial for a complete recovery.(62) (Dubois MJ, 2006) Finally, Schneider et al. administered continuously 4% albumin solution in critically ill patients in septic shock and found a decline of nosocomial infections via the antimicrobial peptide vasostatin-1.(63) (Schneider F, 2019)



The model of critically ill patients to highlight non oncotic properties of albumin is not easy to analyse. However, beyond methodological bias, there are sufficient knowledges on serum albumin non-oncotic properties to conduct a large randomised trial evaluating a synergistic quadriptych postoperative recovery program in surgical setting.

3-9-3- The liver failure model: cirrhosis

The common model of hypoalbuminemia widely investigated is the liver deficiency of albumin production in cirrhosis. This albumin synthesis failure may be exacerbated by inflammation induced by a sepsis which prognostic is usually poor. Paucity of serum albumin explains greatly this poor prognostic.

Consequently, administration of 20% albumin solution in Gastro-enterology settings addresses four formal indications validated by Gastro-enterology Societies: 1)- Type 1 hepatorenal syndrome with ascites infection, needing albumin in conjunction with vasoconstrictors and antibiotics, 2)- Severe variceal haemorrhage, 3)- Spontaneous bacterial peritonitis treated by combination of albumin with antibiotics, 4)- At the time of large volume paracentesis.(64-65) (Bera C 2022, Angeli P 2010)

Fernandez et al. compared two groups of patients with cirrhosis and type 1 hepatorenal syndrome. They found significantly more patients (82.3%) recovering from acute liver failure with better kidney and circulatory functions in the albumin group than control group (33.3%), $p = 0.03$. Additionally, there was significantly less nosocomial infections in the albumin group than control group (6.6% vs 24.6%, $p = 0.007$). Of note, patients in the albumin group were more severely ill at baseline.(17) (Fernandez J, 2020) These findings are consistent with those of Sort et al. highlighting recovery properties of serum albumin beyond antibiotics efficiency. (66) (Sort P, 1999)



Solely antibiotic therapy for controlling recovery from sepsis is not sufficient. Despite a small sample size and using the classic model of critically ill patients with hypoalbuminemia, liver failure, and inflammation due to sepsis, Sort et al. study resulted in a reduction of mortality in patients receiving antibiotics and 20% albumin infusion. The albumin posology was 1.5 g/kg the first day and 1 g/kg the third day equivalent for a 70 kg-patient to 2 vials per day for 5 days. Notably, infection was resorbed in the two groups. However, mortality was significantly lower in the antibiotics - 20% albumin infusion group and additionally, they observed significantly more deaths in the group with solely antibiotic therapy.

In this way, non-specific impairments related to inflammation, vascular endothelial dysfunction, acute kidney injury, tissues injury induced by reactive oxygen, nitrogen species and other toxic substances like heme, deserve to be appropriately managed. In this inflammatory syndrome commonly known as the systemic inflammatory response syndrome (SIRS), serum albumin plays a key role and C-reactive protein level exceeding 150 mg/l on the critically first postoperative week, is the most sensitive biochemical marker.(67) (McDermott ED, 2015) Non-septic SIRS is induced by trauma and surgical oxidative stress. In septic surgical patients the non-septic SIRS is exacerbated by the septic-induced SIRS component of the global surgical oxidative stress.

Clinical physicians experience this situation in routine practice. Patients do not recover despite prolonged and various antibiotics therapy leading sometimes to antibiotics resistance. It appears that associating antibiotics therapy to immunonutrition, iron homeostasis, daily proteins-calories support (30 cal/kg/day) and normal serum albumin (35 g/L) could help patients to completely recover from a sepsis in a reasonable time. Ferrer et al. share this multimodal approach in using albumin therapeutic in patients with great clinical distress as could be patients with septic shock.(15) (Ferrer R, 2018) Treatment precocity seems equally of high importance and joins the concept of critically first postoperative week for complication occurring.(15, 57) (Ferrer R 2018, Wang X 2023)



The French Society of Anaesthesiology and Intensive Care (SFAR) recommends these indications of albumin infusion in patients with acute liver failure. (68) (Paugam-Burzt C, 2020) Meanwhile, Weiss et al. raise the beneficial effect of non-oncotic properties of albumin and point that the therapeutic effect of albumin infusion in patient with acute liver failure is not solely due to the circulatory oncotic property. (69) (Weiss E, 2018)

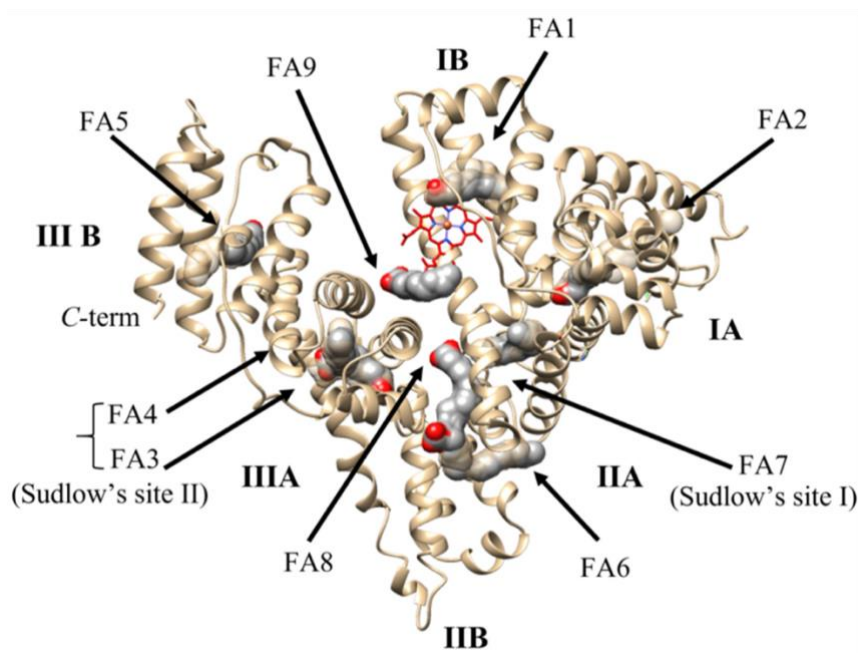


Figure 14: Three-dimensional structure of non-oxidised human albumin supporting protective properties for the human body. From De Simone G et al.(16)



3-10- Non-oncotic properties of human serum albumin.(15, 16, 70-71) (Ferrer R, De Simone G, Sun L, Evans TW)

Human serum albumin is the major protein of the human body, key of body homeostasis (Figure 14). It is a multimodal-acting protein and has other properties than equilibrium in body fluids via its oncotic action.

It regulates the acid-base balance in the body. Its molecular binding ability increases solubility of various endogenous and exogenous substances in plasma and permits their transportation or detoxification. This property depends on its three-dimensional structure (Figure 14). Therefore, albumin affects distribution, biologic activity, clearance of endogenous compounds (bile acids, long-chain fatty acids, bilirubin), pharmacodynamics and pharmacokinetics of drugs (non-steroidal anti-inflammatory drugs, antibiotics, furosemide). Other substances are bound and carried by serum albumin: metal ions (cobalt, copper, nickel), hormones, toxins, and lipopolysaccharide.

Albumin binding modifies structure conformation of ligands, rendering toxins neutral. This binding equally supports catalytic activity such as esterase, enolase, glucuronidase and peroxidase. These catalytic enzymatic properties are pertinent in the body. They affect proteins, lipids, cholesterol, reactive oxygen and nitrogen species and drugs. They may be in turn impaired by allosteric effectors, competitive inhibitors, pathologic situations, and ageing. In heme and iron metabolism, serum albumin binds and clears heme and iron deposits phagocytised by macrophages. Additionally, the complex albumin-heme-Fe⁺⁺⁺ is not inactive and expresses catalytic enzymatic properties.

Serum albumin binds and transports fatty acids and nucleic acids present in Oral Impact® briquettes (Figure 1). Preoperative Oral Impact intake needs non-oxidised albumin in plasma

to be effective. Arginine contained in Oral Impact® briquettes interacts with albumin to be effective. Therefore, the liver must synthesise and provide plasma with **non-oxidised albumin** pre and postoperatively especially in a surgical context in which its production yield is impaired.

Non-oxidised serum albumin, the reduced form of albumin, expresses the main antioxidant activity of the human plasma (70-80%). The free Cysteine residue in position 34 of the reduced albumin (mercaptalbumin – HMA) constitutes the major thiol pool in plasma. This free Cys34 thiol residue binds and scavenges reactive oxygen and nitrogen species.(37) (**Farrugia A, 2022**) An additional catalytic action improves its antioxidant property essential for plasma detoxification and prodrugs activation. Reactive oxygen and nitrogen species alter lipids, proteins, and DNA (desoxyribonucleic acid). Analbuminaemic rats are more sensible to oxidative stress and develop more frequently bladder, kidney, and stomach cancers. Reactive oxygen and nitrogen species maintain inflammation and impair vascular endothelium, microcirculation and consequently wound healing, anastomosis, and intestinal activity for early oral intake. **Their clearance is of major importance.** The other antioxidant minority encompasses transferrin, ceruloplasmin, ferritin, bilirubin, glutathione, vitamin C and E, superoxide dismutase, and catalase.

Oxidised albumin is cleared in the liver inducing hypoalbuminemia in inflammatory conditions. Patients with COVID-19 were particularly inflammatory and at high risk of mortality.(72) (**Violi F, 2021**) Johnson et al. recently confirm the pivotal role of serum albumin in the protection of the body in regard of increased vulnerability observed in hypoalbuminemic patients with COVID-19.(72) (**Johnson AS, 2022**) They report that this increased vulnerability is related to impairment of nutrient-carrying activity of serum albumin. In COVID-19 situation, low serum albumin concentrations affected directly and deeply the immune system participating to patient vulnerability as well as aging, diabetes, and obesity. In this context, albumin infusion could be proposed.(72)



Moreover, COVID-19 exposes patients to severe and deep thrombosis may be related to inflammation and decreased endothelium protection with low serum albumin because serum albumin is anti-thrombotic. Violi et al. investigations demonstrated that oxidative stress induced by the activation of NOX2, a reactive nitrogen specie, was associated to disease severity and thrombosis in patients with COVID-19.(74) (Violi F, 2020) Indeed, reactive oxygen or nitrogen species degrade nitric oxide (NO), a crucial molecule for vascular endothelial function, preservation of its integrity, adjustment of its permeability with an additional major role in haemostasis regulation. Reactive oxygen or nitrogen species activate an enzyme, arginase, which reroute arginine metabolism toward ornithine and urea production instead of NO synthesis by endothelial NO synthase.(75) (Chandra S, 2012)

Endothelial NO synthase is an enzymatic protein containing heme. It catalyses conversion of L-arginine in L-citrulline releasing nitric oxide. Of note, L-arginine is a component of Oral Impact®. Consequently, a normal level of serum albumin > 35 g/L seems required to optimise immune modulating action of Oral Impact® and NO production preoperatively.(39, 76) (Kurhaluk N 2023, Belinskaia DA 2020) Moreover, albumin is a major carrier for NO in the circulation through binding to the free thiol Cys34 residue and acts as a reservoir of NO for modulating vascular tone and preservation of endothelium integrity.(35, 77) (Farrugia A 2022, Minamiyam 1996)

Albumin protects the endothelium (Figure 15). Albumin is physiologically bound within the endothelium glycocalyx, protecting it against shedding and therefore, contributing to the maintenance of vascular integrity and normal capillary permeability, and preventing thrombosis.(14, 70) (Aldecoa C 2020, Sun L 2019) Clinical studies on the effect of human albumin in the glycocalyx and microcirculation has been conducted. A recent study involving patients with septic shock reported that, compared with saline, albumin improved skin endothelial cell function by improving microcirculatory blood flow. These beneficial effects may be independent of oncotic property of albumin since neither cardiac output nor skin blood flow differed between albumin- and saline-treated patients.(78) (Hariri G, 2018)

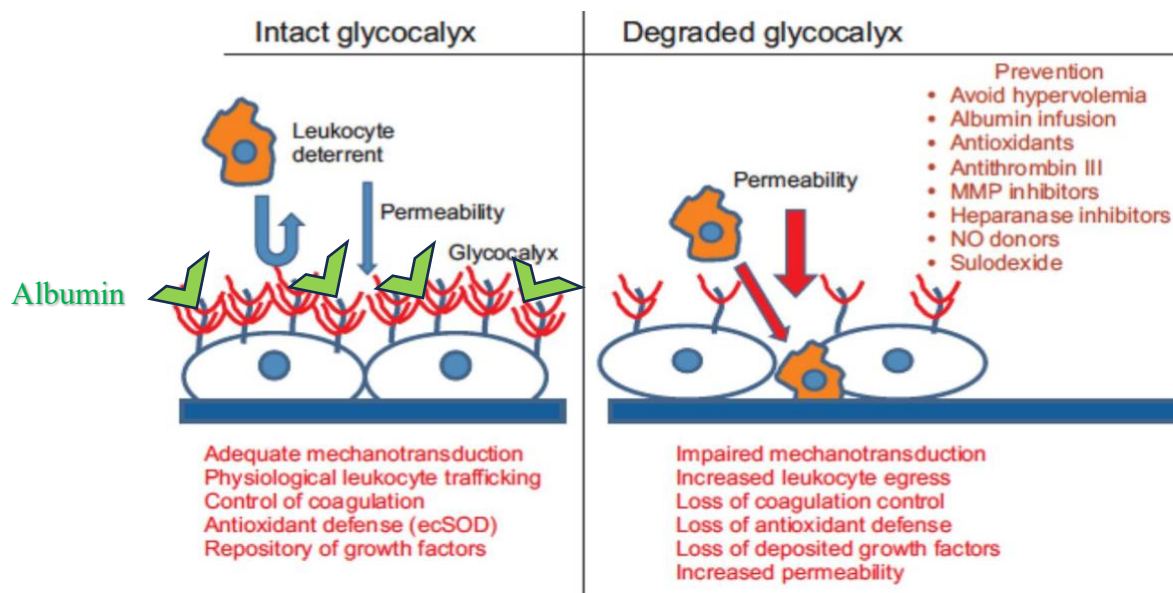


Figure 15: Pathologies and interventions associated with glycocalyx alterations. ecSOP, extracellular superoxide dismutase; MMP, matrix metalloprotease; NO, nitric oxide. Sulodexide is a heparinoid. From Aldecoa C et al.(14)

Additionally, albumin mobilises sphingosine 1-phosphate from red blood cells to inhibit glycocalyx cleavage mediated by matrix metalloproteinases and preserves red cells deformability reduced in sepsis and other conditions.(35, 37) (Farrugia A 2020, Bateman 2017) Alterations in erythrocytes deformability results in poor rheology, poor outcome in septic patients and exposes to thrombosis.(35, 79) (Farrugia A 2020, Donadello K 2015)

Likewise, serum albumin modulates inflammation response by mobilising omega-3 polyunsaturated fatty acids (PUFAs). PUFAs are provided by Oral Impact® in addition to arginine and nucleic acids. They constitute cell membranes. The most common are arachidonic acid, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Their metabolism follows two antagonist pathways. The first pathway is pro-inflammatory producing leukotrienes, reactive oxygen and nitrogen species, thromboxane A2, prostaglandins and cytokines. The second pathway is anti-inflammatory and immune modulating via three bioactive cytoprotecting lipids: lipoxin, resolvins and protectin (CD59).(80) (Das UN, 2015) Serum albumin mobilises PUFAs in oxidative stress situations from the liver and other tissues to release lipoxin, resolvins and protectin. These three bioactive cytoprotecting lipids reduce leukocytes extravasation, rolling through vascular endothelium (Figure 16).(80-82) (Das UN 2015, Dona M 2008, Filippi MD 2019) Lipoxin stimulates endothelial cell to produce nitric oxide and therefore, protects and stabilises vascular endothelium integrity and permeability.(80)

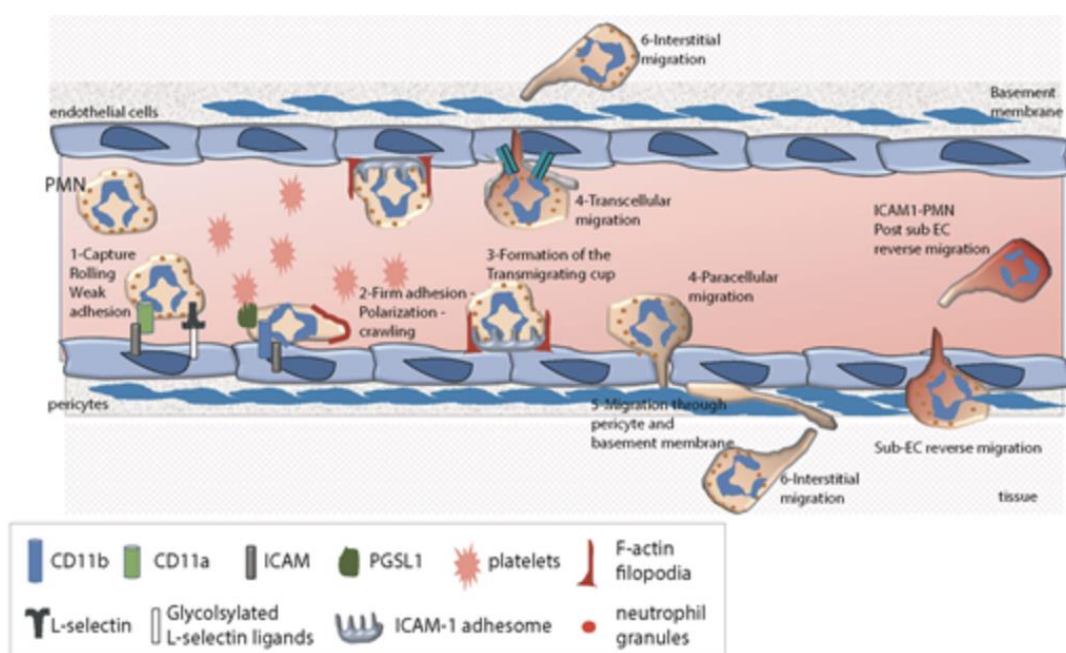


Figure 16: Leukocyte extravasation involving adhesion, lateral migration by rolling and crawling on the endothelium to find a permissive site into interstitial tissue. The migration process is reversible. PMN, polymorphonuclear neutrophil. From Filippi MD et al.(82)

Moreover, these bioactive cytoprotecting lipids promote cerebral cell surviving by stimulating neuroprotective genes. They inhibit cell apoptosis (cell death) induced by oxidative stress, cyclooxygenase 2, and production of tumor necrosis factor α (TNF α), the main inflammation cytokine in association with interleukin 1 and interleukin 6. Additionally, tumor necrosis factor α induces both hypoalbuminemia and a deficit of PUFAs in sepsis.(80) (Das UN, 2015)

Obviously, modulating immune system preoperatively with Oral Impact® while maintaining a normal serum albumin concentration, iron homeostasis and proteins-calories intake appears coherent physiologically and clinically to reduce postoperative complications induced by intense surgical oxidative stress.

Finally, the meta-analysis from He et al. argues this concept of multimodal perioperative recovery program to manage surgical oxidative stress.(83) (He ZW, 2023) Patients undergoing hepatectomy received an early parenteral nutritional support in the first critical postoperative week. Parenteral nutrients were rich in PUFAs. He et al. found that liver function was preserved in regard of albumin production and generated a positive cascade with exogenous PUFAs. Moreover, they found that inflammation was controlled, nosocomial infection rate and length of stay were reduced. Mortality was lower compared to the control group. Unfortunately, as usually, the study missed power to detect a significantly difference in mortality. However, the fistulae rate was not different between the two groups suggesting that, with standard anastomosis quality, all pathways for maintaining homeostasis and wound healing were not strictly controlled in all studies included in the meta-analysis.

In protection against nosocomial infection development, serum albumin greatly participates to antimicrobial early response via the human innate immunity. Innate immunity is present in various living species. It is supported by antimicrobial peptides (AMP) different from one species to another. In human, AMP are located in the chromaffin cells of the adrenal medulla. They modulate inflammation response to infections. Serum albumin inactivates toxin released by *Clostridium difficile* and *Streptococcus pyogenes*, and *Candida albicans*. This is a direct



antimicrobial action of serum albumin. In routine clinical practice, we observe frequently **Candida nosocomial infections** in patient with both hypoalbuminemia and infection of central catheters.(41) (Karadag-Oncel E, 2015)

Likewise, Austermeier et al. confirmed recently that serum albumin is the most abundant serum protein in humans. During inflammation, serum albumin levels decrease drastically, and low albumin levels are associated with poor patient outcome. They described the ability of albumin to neutralize hydrophobic microbial toxins and demonstrate that **albumin is a toxin-neutralizing protein** that may play a role during infections with toxin-producing microorganisms. Therefore, albumin can protect against damage induced by the pathogenic yeast *Candida Albicans* by neutralizing its cytolytic toxin, candidalysin. (84) (Austermeier S, 2021)

Similarly, Schneider et al. has found in critically ill patients in intensive care unit, with deep hypalbuminaemia < 20 g/L, that human albumin infusion protected patients from **bacterial nosocomial infections**. The peptide vasostatin-1 is recognised for its innate antimicrobial properties. It plays a pivotal role in the response against Gram positive bacteria infections. However, oxidised vasostatin-1 loses its antimicrobial activity. Interestingly, this suggests that oxidative processes observed in critically ill patients and patients undergoing intense oxidative stress surgeries expose them to **nosocomial infections**. Additionally, they found that management of oxidative stress by maintaining a circulating non-oxidised vasostatin-1 protected by albumin infusion decreased occurring of **nosocomial infections**.(59) (Schneider F, 2019)

This direct and indirect antimicrobial activity of human albumin could solely justify maintaining postoperative serum non-oxidised albumin at an optimal concentration, efficient to prevent **nosocomial infections** in synergism with the other recovery pathways.

Antimicrobial peptides have been clinically investigated in the treatment of infections. As described previously, they participate to the **regulation of microbiota**, involve wound healing,



induce adaptative immunity, modulate inflammation and express anti-cancer cytotoxic properties.(30) (Scavello F, 2022) In the surgical setting, these antimicrobial peptides are released in the bloodstream after skin incision for cardiac surgery, one of the most intense oxidative stress surgery.(85) (Stasiemski A, 2002) Albumin reduces circulating oxidised peptides and potentiates both their antimicrobial activity and antibiotic therapy. Notably, serum albumin as a reductant must be at the adequate concentration to reverse efficiently oxidation induced by surgical stress.

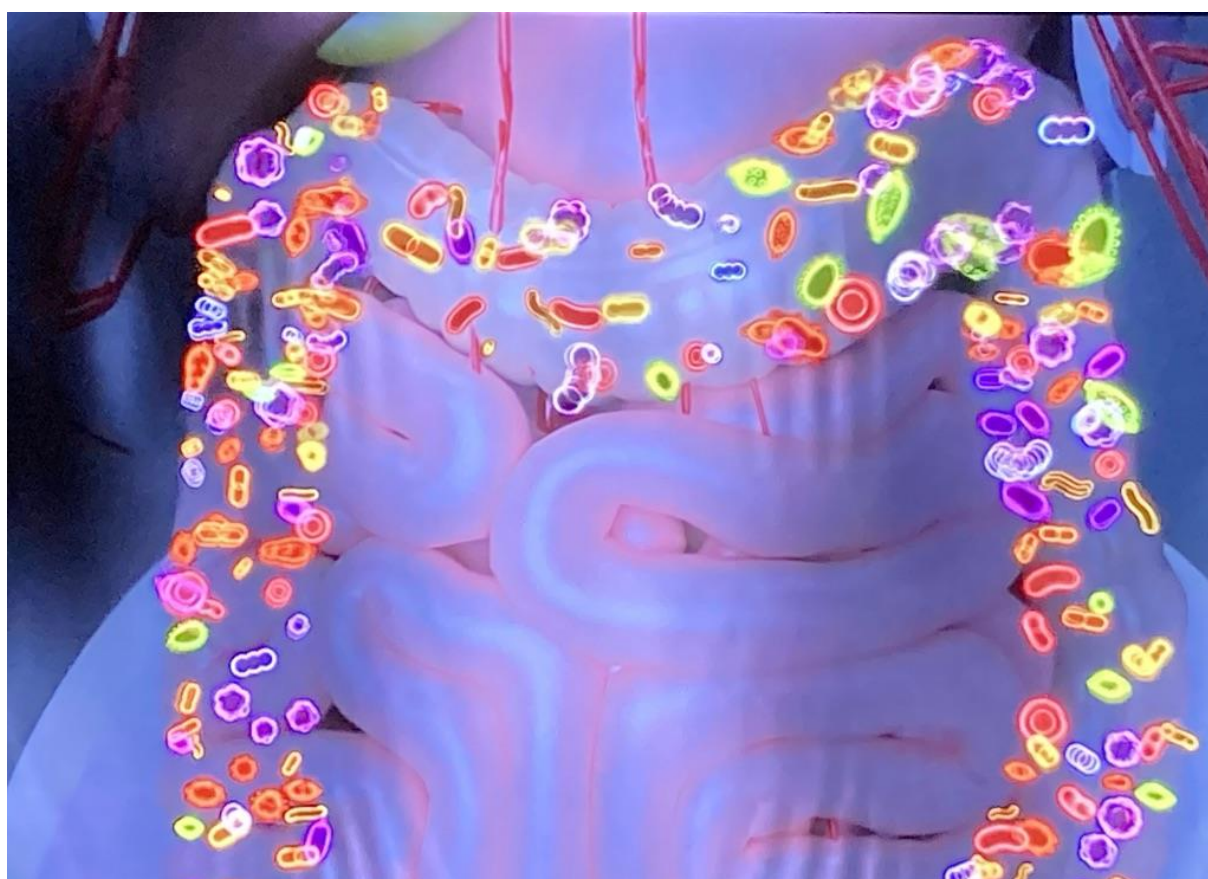


Figure 17: Microbiota.

The immune system interacts continuously with intestinal microbiota. Consequently, microbiota diversity appears determinant for immunity efficiency.

This **regulation of microbiota** may be pertinent in postoperative ileus prevention, a complication responsible of abdominal meteorism, dyspnoea by impairment of diaphragm excursion, insertion of a gastric tube for fluids and air aspiration, delay of oral intake and extension of length of stay. This could partially explain concomitant reduction of ileus during albumin infusion in our patients included in the IMPACTURO trial and conversely, occurrence of major postoperative ileus in patients with severe hypoalbuminemia below 20 g/L. These observations are consistent with results of Dubois et al. who found a better digestive tolerance to enteral caloric intake in patient receiving albumin infusion.(58) (Dubois MJ, 2006)

The multiple protective actions of the serum albumin (immunomodulatory capacity by binding several bacterial products, antibiotic transportation, **synergistic and potentiating action with antibiotic treatment**, anti-inflammatory effects, reduction of oxidation by scavenging reactive oxygen species, kidney protection, cardiac protection, neuroprotection, preservation and stabilisation of the vascular endothelium glycocalyx integrity, preservation of the microcirculation which is very important for wound healing, maintenance of the normal capillary permeability, significant reduction of re-oxygenation injury and ischemia–reperfusion injury resulting in tissue damage following disruption of the glycocalyx) depends on its three-dimensional structure integrity (Figure 14) and **its purity** when intravenously infused.(14-15) (Aldecoa C, 2020, Ferrer R 2018) Liver diseases induced by surgical trauma and oxidative stress lead to albumin post-translational modifications. This results to alteration of three-dimensional structure of albumin and impairment of its biological activity (Figure 18).



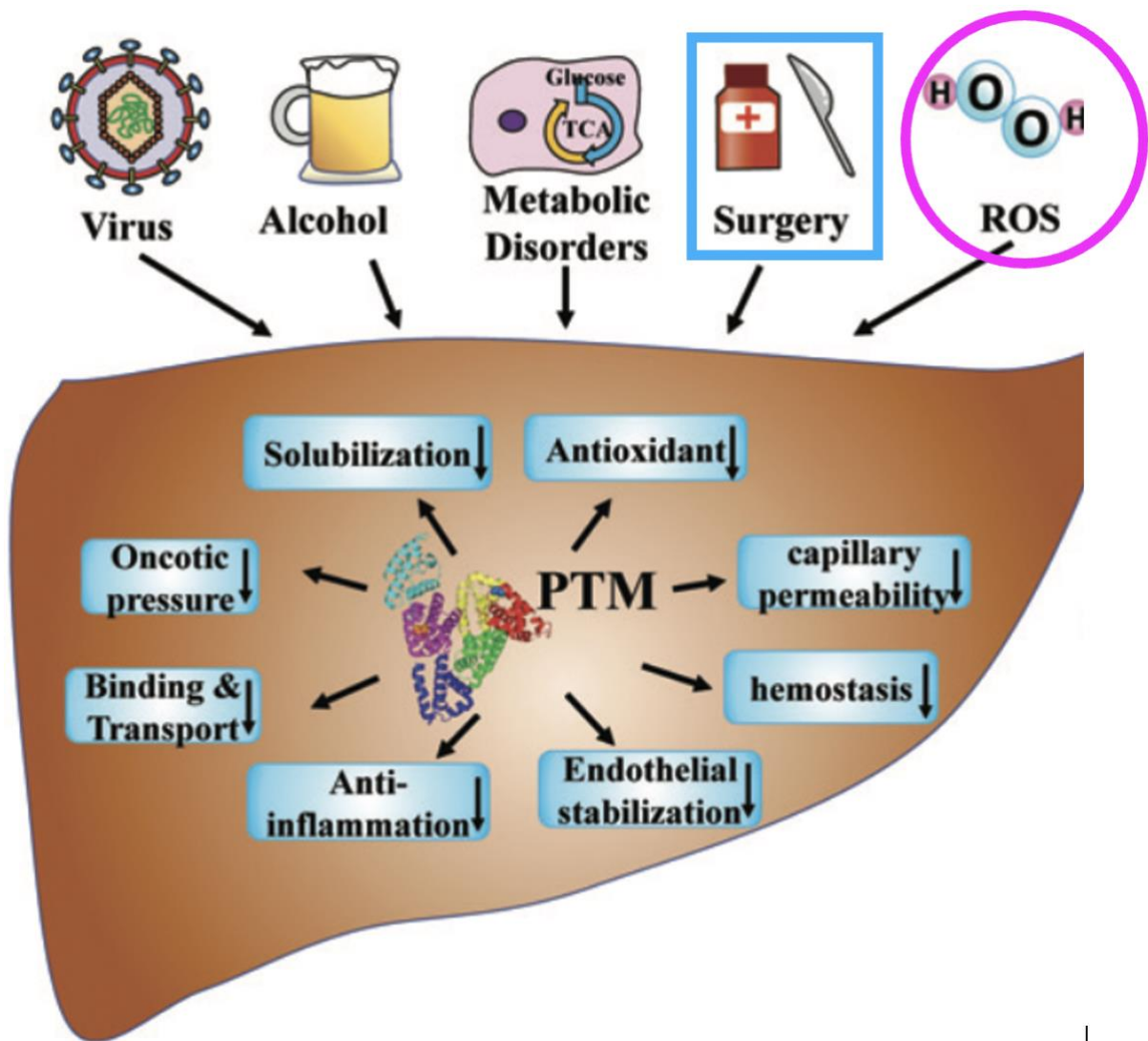


Figure 18: Alterations of albumin function in liver diseases.

Several factors result in post-translational modifications of albumin and alteration of its three-dimensional structure impairing its biological activity: surgical trauma, oxidative stress, metabolic disorders, alcohol intake, virus hepatitis. The impaired three-dimensional structure will cause decreased albumin function in maintaining plasma oncotic pressure, dissolving, binding, transporting endogenous and exogenous molecules, antioxidant, anti-inflammatory, haemostatic effects, endothelial stabilisation, and adjusting capillary permeability. PTM, post-translational modifications; ROS, reactive oxygen species. Details from Sun L et al.(70)

3-11- Albumin solution for intravenous administration

The 20% albumin solution VIALEBEX® (LFB biomédicament, Courtaboeuf, France) is the most antioxidant solution on the market.(35, 86-87) (Farrugia A 2022, Plantier JL 2016, Taverna M 2013) All the other albumin solution do not reach its antioxidant level. This could explain discrepancy in results provided by various studies for 30 years in addition to previously evoked methodological bias omitting synergism of the quadriptych postoperative recovery pathway. Taverna et al. pointed that earlier, 10 years ago.(87) Limited studies precise characteristics of albumin solution used. In the ongoing IMPACTURO trial, we used the 20% albumin solution VIALEBEX® (LFB biomédicament, Courtaboeuf, France).



Figure 19: The 20% Albumin solution, VIALEBEX® (LFB biomédicament, Courtaboeuf, France), 100 ml-vial containing 20 g of human albumin with high antioxidant power.



- 20% Human Albumin (VIALEBEX ®) (Figure 19)
- 100 ml-vials contains 20 g of human albumin.
- The solution has hyperoncotic properties.
- The product is extracted from plasma of human donors.
- Excipient with known properties: sodium (chloride and caprylate) 2.3 mg /ml, 115 mg per 50 mL-vial and 230 mg per 100 ml-vials.
- This is a solution for infusion. The solution is clear, slightly viscous, almost colourless, yellow, amber or green. Direct intravenous administration of the VIALEBEX solution 200 g/L is possible.
- The oncotic property of human albumin solution with 200 g/L is approximately about four times that of blood plasma. Consequently, when a concentrated albumin solution is administered, be cautious to ensure that patient fluid providing is optimized.
- Avoid dilution of albumin solution with water for injection. It could generate haemolysis in patients.
- Albumin manufactured via a well-established process, according to the specifications of the European Pharmacopeia, has been recognized for its viral safety.
- No case of viral contamination related to albumin, manufactured according to both the specifications of the European Pharmacopeia and well-established process, has been reported.
- No specific interaction between human albumin and any medication is reported.
- No sign of acute toxicity has been described previously in animal model experimentations.
- Human albumin is a normal component of the human plasma and acts as physiological albumin.
- **This solution is 100% pure.**

The process of plasma fractionation results in alterations in the albumin structure, including those parts of the molecule involved in antioxidant and anti-inflammatory effects. Albumin products from diverse manufacturers show heterogeneity in their ability to address these effects.



There are variations in fractionation chemistries adopted by different manufacturers. These manufacturing processes have contributed to variations in the physico-chemical properties of albumin. Heterogeneity in products may have contributed to variable clinical outcomes of clinical studies assessing the role of albumin in improving conditions such as sepsis and cirrhosis.(35) (Farrugia A, 2020)

3-12- Posology for administration of 20% albumin solution

The liver synthesises 10 to 15 g per day of albumin. The yield of the liver albumin synthesis depends on the hormonal status, nutritional conditions and inflammatory patient state.(16) (De Simone G, 2021) The yield of this synthesis becomes insufficient in presence of an inflammatory response or endogenous and/or exogenous nutritional deficiencies.

In present days, there is no specific recommendations concerning posology for administration of 20% albumin solution to address hypoalbuminemia. However, numerous studies allow defining the outlines of that posology with a maximum of safety and efficiency for therapeutic target, dose, duration of the cure, and kinetics of serum albumin recovery.

Therefore, Fernandez et al. investigated the recovering kinetics of low serum albumin in cirrhotic patients using weekly intravenous infusion of 20% albumin. The therapeutic target was a serum albumin concentration of 35 g/L. Cure durations were in the range of a week (Figure 3).(17) (Fernandez J, 2020) The high posology (blue lines, Figure 3) was one vial (20 g) of 20 % albumin per day for 1 week, to be repeated. Serum albumin recovering kinetics was slow, one to three weeks. It was as slow as hypoalbuminemia was severe and posology below 1 vial per day (red lines, Figure 3). Inflammatory cytokines in this study were considered. They decreased with the course of albumin cure. Additionally, inflammation affects kinetics of serum albumin recovering. This is observed in routine clinical practice.



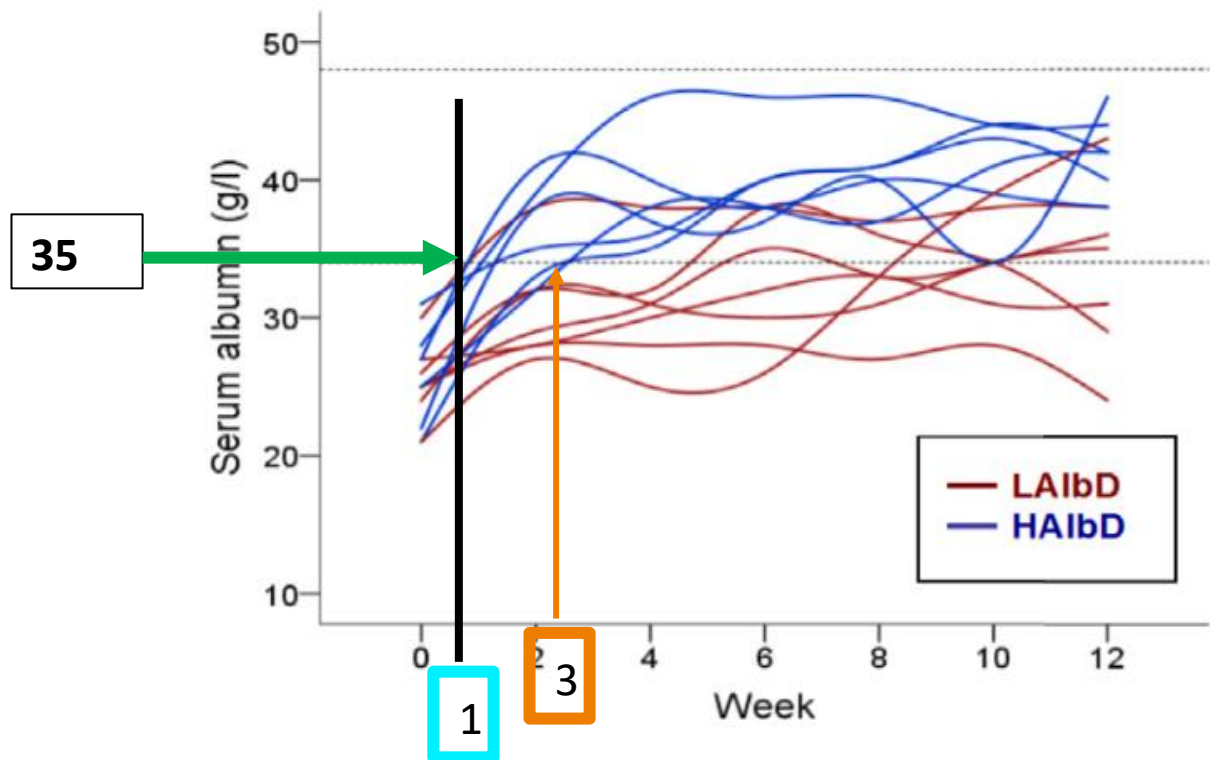


Figure 3 (reminder): Kinetics of serum albumin recovering in cirrhotic patients with hypoalbuminemia receiving intravenously 20% albumin. Cure durations were in the range of a week. High posology (blue lines) was one vial (20 g) per day for one week, to be repeated. Recovering kinetics were as slow as hypoalbuminemia was severe and posology low (red lines, below one vial per day), in the range of one to three weeks. Serum albumin target was 35 g/L. From Fernandez et al.(17)

Meanwhile, the ALBIOS study used a posology of three vials of 20% albumin per day for 28 days in critically ill patients with septic shock admitted in intensive care unit. No undesirable effects related to albumin infusion were observed.(54) (Caironi P, 2014) In the same way, Wong et al. evaluating terlipressine in type 1 of hepatorenal syndrome, administered 1 to 2 vials of 20% albumin per day for 14 days according to international recommendation of the Ascites Club.(88-89) (Wong F 2021, Angeli P 2015)

Additionally, the ALISAH trial went further, administering 25% albumin, 100 g over seven days to treat subarachnoid haemorrhage. This posology is equivalent to one vial of 20% albumin per day for 5 days. Tolerance was good.(90-91) (Suarez JI, 2012, 2015) Similarly to the ALBIOS trial, Dubois et al. administered two vials of 20% albumin per day for at least seven days to reach a serum albumin target of 30 g/L in critically ill patients with septic shock.(58) (Dubois MJ, 2006)

Finally, Schaller et al. initiated a study, SuperAdd, in adult surgery encompassing vascular, orthopaedic and abdominal surgery.(48) (Schaller SJ, 2023) This trial evaluated the impact of treatment of perioperative hypoalbuminemia on postoperative complications. Posology of 20% albumin was one vial per day until reaching serum albumin target of 30 g/L. The interim analysis at 100 patients, with optimal intravascular fluid volume, exhibited that this posology never allowed reaching the target. Additionally, 20% albumin posology really depends on the severity of the hypoalbuminemia. Serum albumin in the two groups were profoundly low, 21 and 22 g/L. Not surprisingly, there was not any significant difference in postoperative complications between the groups receiving or not albumin. Authors did not mention if other synergistic perioperative recovery pathways (immune modulation, iron homeostasis and proteins-calories support) were optimised in association with serum albumin recovering. Albumin solution seemed postoperatively administered alone and not adjusted to hypoalbuminemia severity.

This dose-dependent efficiency has been confirmed by the meta-analysis of Haynes et al. who included randomised studies evaluating the clinical benefit of treating hypoalbuminemia with 20% albumin infusions. They concluded that there was a real benefit to recover normal serum



albumin level in patients with hypoalbuminemia even in surgical context.(49) (Haynes GR, 2003)

Therefore, the ongoing trial IMPACTURO designed a protocol for administration of 20% albumin infusions. This protocol has been validated by the **French National Agency of Safety and Medication**.

- ✚ Serum Albumin blood samples at J1 – J3 – J5 – J7
- ✚ Protocol of *ALBUMINE 20%* infusion based on serum albumin values (g/l):
 - ✚ 35 – 25: 1 vial/day = 20 g/day for 5 days
 - ✚ 24 – 15: 2 vials/day = 40 g/day for 5 days
 - ✚ < 15: 3 vials/day = 60 g/day for 5 days.
- ✚ A control of serum albumin concentration is done at day 6.
- ✚ If the albumin serum concentration was < 35 g/l, a second 5-days cure of albumin 20% is initiated based on serum albumin values till the serum albumin concentration reached or overpassed 35 g/l.

4- Synergistic Perioperative Recovery Program

A synergistic perioperative recovery program should be based on the American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Nutrition Screening and Therapy Within a Surgical Enhanced Recovery Pathway. This program should rely on synergism of different components used in combination to optimise immunonutrition efficacy.(4) (Wishmeyer PE, 2018)

Figure 20 highlights an example of synergistic quadriptych perioperative recovery program.

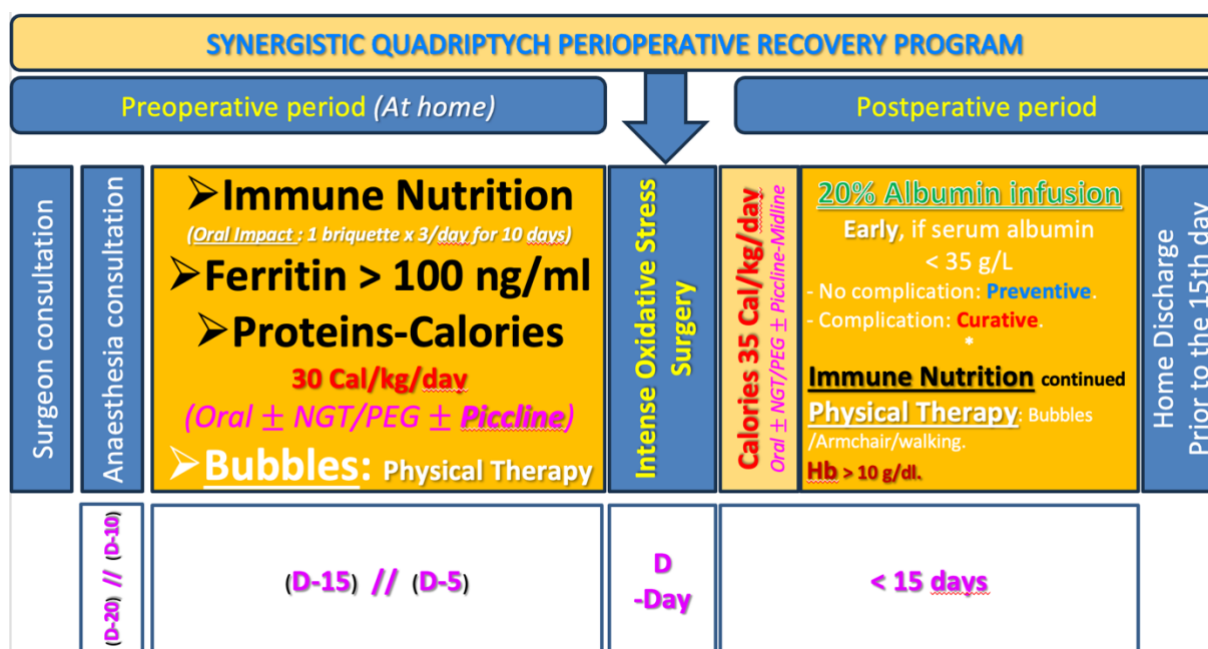


Figure 20: Protocol diagram of a synergistic quadriptych perioperative recovery program for intense oxidative stress surgery. NGT, nasogastric tube; PEG, percutaneous endoscopic gastrostomy, D, day.

4-1- Preoperative period

Once surgery is decided by a multidisciplinary staff, the surgeon should explain to the patient risks of postoperative complications. Thereafter, a dietician screens the patient nutritional status at home and makes a report to the anaesthesiologist. Nutritional status could be evaluated at the preoperative anaesthesia assessment with the NRS-2002 score two to four weeks before surgery. Patients should be given a special prescription of Oral Impact®: three briquettes (38.7 g of arginine and 1020 Cal for three briquettes) per day for seven to ten days. This number of calories should be accounted in the dietary requirements covered. Ideally, within the 20 days preceding surgery, patients should ingest Oral Impact® preoperatively for seven to ten days. A lap of couple days, one week, seems of worth considering, between the cure completion and surgery, to allow the body to integrate the immunonutrition effect and be ideally enhanced. If patient's intake was impaired by nausea, diarrhoea or glycaemic variability in diabetic patients, the daily number of briquettes should be reduced to 2 briquettes per days during the following



days of the cure. Therefore, duration of Oral Impact® intake will be prolonged and possibly in postoperative period. If surgery cannot be postponed or intake period cannot remain prior to surgery, patients will continue Oral Impact intake after surgery. All patients should be advised to consume regular food as desired in the preoperative period (30 Cal/kg/day). If dietary oral intake and Oral Impact did not cover the dietary proteins-calories requirements despite dietician efforts, additional parenteral nutrition should be conducted at home to provide the missing calories. A peripheral inserted central catheter (piccline) should be inserted during a one-day hospital admission to initiate a home parenteral nutrition for one or two weeks. Of note, piccline is the solely central catheter authorised out-of-hospital for parenteral nutrition. Risk of catheter infection must be controlled by out-of-hospital professional nurses and members of the dieticians' team.

However, for malnourished patients (serum albumin level < 35 g/L) with asthenia, sarcopenia, and decrease of oral intake or loss of appetite, an enteral nutrition should be proposed at home, preoperatively providing 30 Cal/kg/day. A nasogastric tube or suitably, a percutaneous enteral feeding tube (gastrostomy or jejunostomy) endoscopically, radioscopically, or surgically inserted should be proposed primarily. When patients do not tolerate enteral feeding or refused gastric tube, a frequent situation, parenteral nutrition should be proposed and conducted in addition of dietary oral intake to meet the dietary proteins-calories requirements.(32)

Iron homeostasis should be controlled if ferritin < 100 ng/ml in non-anaemic iron deficiency patients to promote wound healing and, additionally, endurance and physical activity tolerance.(35-36, 92-93) (Wright JA 2014, Surbek M 2023, Martín-Ontiyuelo C 2019, Boutou AK 2015) Iron (Ferinject®, Vifor Pharma, Paris La Défense, France) 1g should be administered intravenously if serum ferritin level < 100 ng/ml preoperatively. If hemoglobin level < 10.9 g/dl with no way to postpone surgery, a blood transfusion should be carried out before surgery in addition to intravenous iron supplementation.



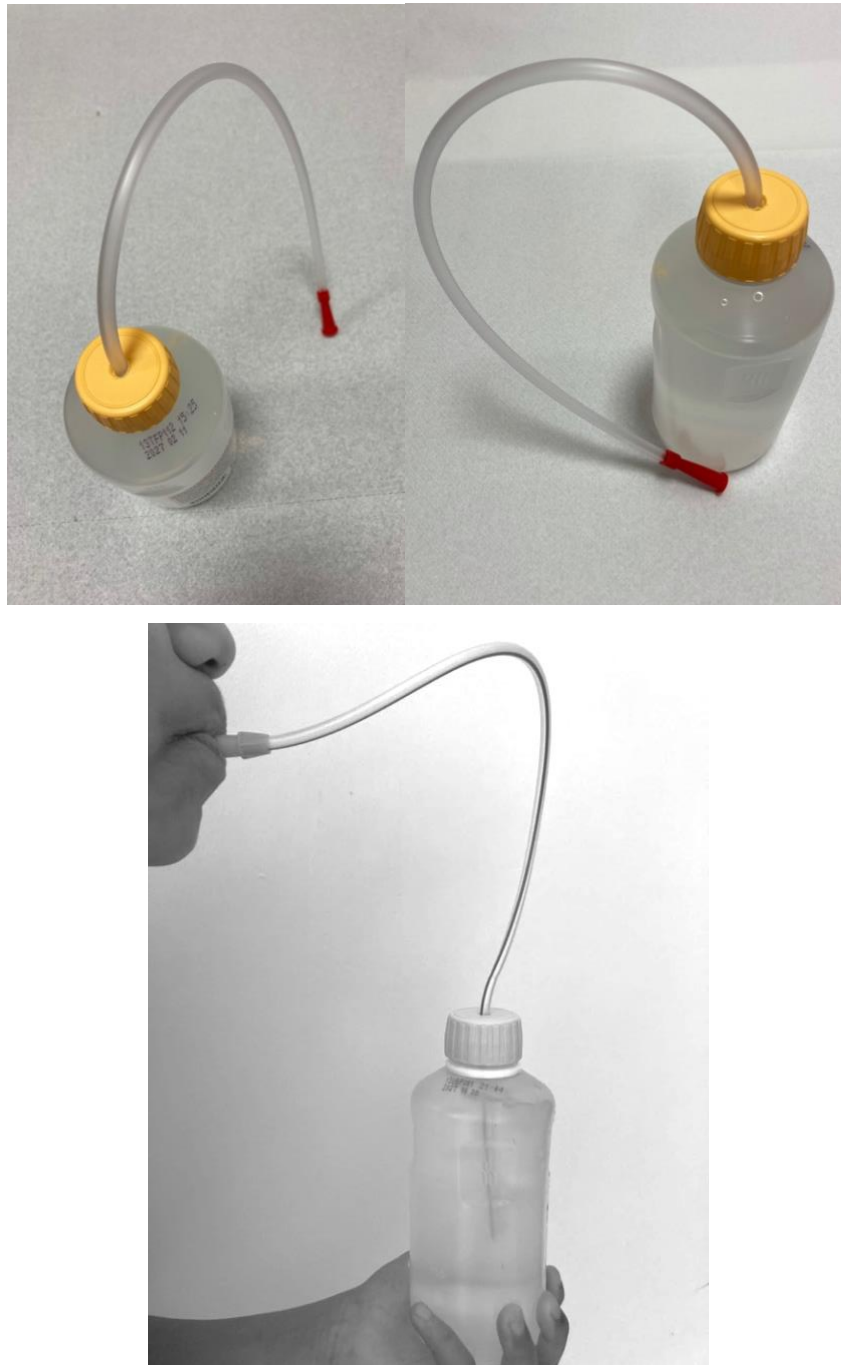


Figure 21: A bottle of water with a flexible small diameter pipe for incentive physical therapy: perioperative pulmonary kinesitherapy inducing positive expiratory pressure, mental mobilisation by focusing on bubbles and abdominal muscles contraction for expiration stimulating bowel activity and preventing postoperative paralytic ileus.

Preoperative physical exercises consisting in blowing bubbles in a water bottle with a straw through an airtight drilled hole on the bottle screw cap. Resistance to blowing bubbles is adjusted by turning the screw cap while blowing (Figure 21). Blowing bubbles should be performed at home preoperatively and continued in postoperative period as early as day one concomitantly with mobilisation in an armchair in agreement with surgeon. This simple exercise with a cheap stool recruits pulmonary alveoli, mobilises mental concentration by focusing on bubbles, and contracts abdominal muscles that enhances bowel activity highly important in postoperative period.

4-2- Postoperative period

During the postoperative period, optimisation of surgery recovery should be based on a quadriptych pathway combination and conducted **from the first day**, unrelated to preoperative nutritional status: 1- proteins-calories support (35 Cal/kg/day) as **early as day one** following surgery, 2- maintaining iron homeostasis, 3- maintaining antioxidant protection by treating postoperative hypoalbuminemia with intravenously administration of albumin 20% when any complication occurred and probably prior to any postoperative complication if the expected incidence is non-negligible.

Based on the range of hypoalbuminemia severity, 35-25, 24-15 or < 15 g/l, patients could receive 20 (one vial), 40 (two vials) or 60 (three vials) g/day for 5 days of 20% albumin pure solution (VIALEBEX®). A control of serum albumin concentration should be made at day 6. If serum albumin concentration keeps < 35 g/l, a second 5-days cure of 20% albumin pure solution (VIALEBEX®) is initiated until the serum albumin concentration reached or overpassed 35 g/l.

Proteins-calories support should be performed preferably orally under supervision of a dietician who could recommend, if necessary, additional parenteral nutrition as **early as day one** following surgery. Enteral nutrition should be equally the first option to meet energy requirements particularly if a percutaneous gastric or jejunal feeding tube has been inserted preoperatively. However, measures should be taken to provide patient energy requirement



within the lap of time enteral nutrition is not fully operational, particularly in the three first days following surgery. Rapid endogenous malnutrition must be anticipated. Likewise, high-protein oral nutritional supplements different from Oral Impact could complete the proteins-calories supplementation to reach 35 Cal/kg/day requirements.(4, 32) (Wischmeyer PE, 2018) The additional parenteral nutrition should be then interrupted once patients could meet energy requirements orally. Finally, concerns for infection risk related to parenteral nutrition should be minimised by nurse formation to care guidelines and implementation of a venous access unit inserting midline and picline. In the same way, parenteral nutrition fluid volume accumulation should be anticipated by small doses of diuretics to avoid oedema and especially inopportune pulmonary oedema in hypoalbuminemic elderly patients.

Of note, Drover et al. in their meta-analysis demonstrated that continuing immunonutrition on postoperative period increases benefit of the preoperative cure (Figure 22). This is of worth considering if Oral Impact intake is continued postoperatively. Effect on inflammation and oxidative stress could reduce rapid lowering of serum albumin and subsequently, need of albumin infusion.

In the postoperative period, maintaining iron homeostasis in the context of surgery inflammation is based on the dosage of soluble receptor of transferrin. An elevated concentration meant iron deficiency. Consequently, 1 g of iron (Ferinject®, Vifor Pharma, Paris La Défense, France) should be intravenously administered.



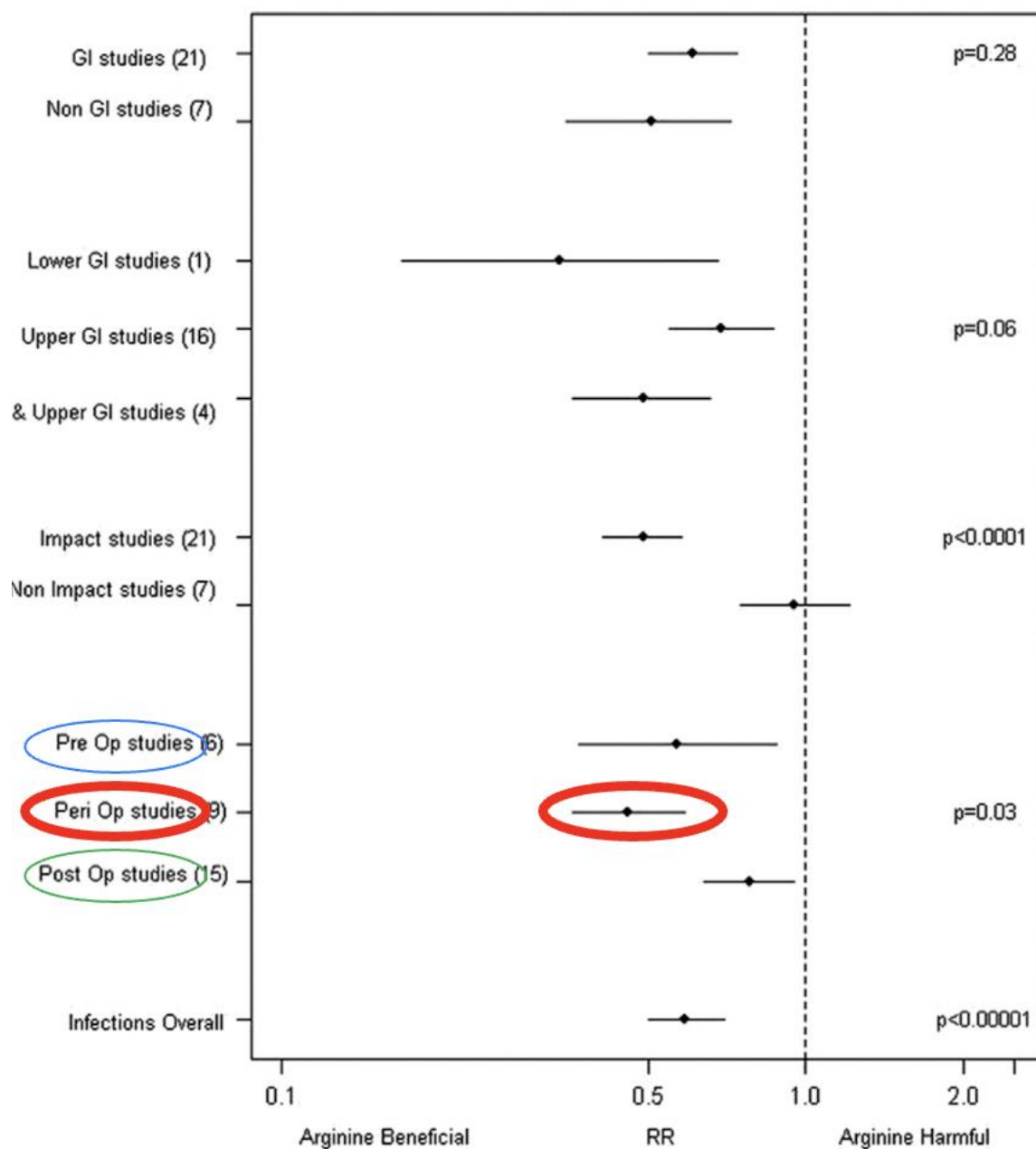


Figure 22: Meta-analysis demonstrating that immunonutrition effect increases with an additional postoperative cure of Oral Impact. From Drover et al.(5)

Pulmonary exercises consisting in blowing bubbles in a water bottle with a straw initiated preoperatively should be continued in postoperative period as early as day one concomitantly with mobilisation in an armchair in agreement with surgeon. This participates actively in prevention of paralytic ileus by contracting abdominal muscles and inducing mechanical massage of bowels.(94) (Singleton C, 2016) In addition to physical considerations, paralytic ileus is prevented by encouraging early gum chewing and oral intake from day one with hyperprotidic-hypercaloric oral nutrition supplements in small volumes of fluid particularly if caution on intestinal activity is required by surgeon with regard to anastomosis fragility.

Treatment of postoperative paralytic ileus could need erythromycin 1 g continuously for 24 hours and progressively decreased by steps of 250 mg per day when patients recovered oral intake autonomy. An additional gastric tube should be inserted if ileus becomes disabling with pain, agitation or dyspnoea.

5- Perspectives

5-1- Clinical Research

Various perioperative recovery protocols have been evaluated. Table 1 summarises results of these studies. Highly intense oxidative stress surgeries such as duodenopancreatectomy, esophagectomy, and cardiac surgery, inducing major postoperative complications, have been investigated to research pathways reducing postoperative complications.

None of these studies have used a synergistic quadriptych perioperative recovery program. This may explain results discrepancy.



However, and holistically, standard cares induce postoperative complications with an incidence ranging from 30 to 40%. This is equal when postoperative albumin infusion is administered solely. Preoperative immunonutrition reduces that rate of postoperative complications in a range from 15 to 20% (Table 1). Our database collecting cystectomies and nephrectomies since 2016 shows similar results. We observed a continuously decrease of postoperative complications below 20% from 2021 compared to the historical period with standard cares between 2016 and 2019 during which complication rate reached 40%. For patients undergoing cystectomies, the quadriptych recovery program with curative albumin infusion reduced the complication rate to 10% and 15% for patients undergoing nephrectomies with laparotomy or lumbotomy. Albumin infusion was administered early and only if a complication was developing. Development of laparoscopy for nephrectomy as mini-invasive surgical technique did not improve yet the current rate of postoperative complications.

Our data are consistent with those of Ascoli et al.(103) (Ascoli A, 2023) In a retrospective before-after case-control study, they compared two groups of patients undergoing otorhinolaryngologic cancer surgery with free or pedicled flap reconstruction and intense oxidative stress. The experimental group received immunonutrition preoperatively for seven days as part of a recovery program implemented in 2019. The control group received standard cares. Postoperatively, the two groups received in addition proteins-calories support and albumin infusion to treat hypoalbuminemia. They found a significant reduction of major postoperative surgical complications at the surgical site (Table 1). Likewise, multivariate analysis exhibited that immunonutrition has an independent protective effect for major surgical complications (OR 0.20, $p = 0.015$). Synergism with albumin antioxidant properties and proteins-calories support may have played a crucial role. Additionally, duration of antibiotic therapy was significantly lower in the immunonutrition group. Finally, multivariate analysis showed a significantly lower need of albumin infusion in the immunonutrition group ($p = 0.018$).

Design of the Ascoli's trial is similar to that of the ongoing IMPACTURO trial (ClinicalTrials.gov, NCT05520151, <https://classic.clinicaltrials.gov/ct2/show/NCT05520151>) conducted in the Territorial Hospital Group Grand Paris North East since November 2022 to November 2024. Two differences must be mentioned: the control group did not receive



albumin infusion and the postoperative hypoalbuminemia of the prospective experimental group was treated only if a complication occurred.

Nevertheless, further randomised studies are necessary to evaluate a synergistic quadriptych perioperative recovery program in intense oxidative stress surgeries like conventional laparotomy to confirm our current results concerning cystectomies and nephrectomies, and furthermore, in highly intense oxidative stress surgeries such as duodenopancreatectomy, esophagectomy, and cardiac surgery.

Indeed, the synergistic quadriptych perioperative recovery program described above and including antioxidant effect of postoperative 20%-albumin infusion deserves to be demonstrated in a randomised trial comparing a group of patients undergoing laparotomy for intense oxidative stress surgery and receiving the quadriptych recovery program to another, receiving standard cares.

Methodologically, there is two ways to administer 20% albumin postoperatively. The first administration modality is a preventive and early administration once serum albumin decreases from the first postoperative day below 35 g/L prior to a complication occurs. The second administration modality is curative. Postoperative hypoalbuminemia is treated only if a complication occurs and as part of complication treatment.

Reis et al. have found that serum albumin restoration is more rapid in the absence of complication than during a developing complication (Figure 22).(97) Consequently, amount of 20% albumin and subsequent costs increase substantially. Patients who rapidly normalise serum albumin in the first postoperative week are more protected from postoperative complications than those who fail. Additionally, it is currently unknown how to screen patients who will restore rapidly and spontaneously, in the first week, serum albumin and consequently, decrease dramatically probability of postoperative complication. Therefore, in intense



oxidative stress surgery, in which rapid decrease of serum albumin is expected postoperatively, from day one, it seems of worth considering to early maintain serum albumin at a normal level as part of a synergistic recovery program.

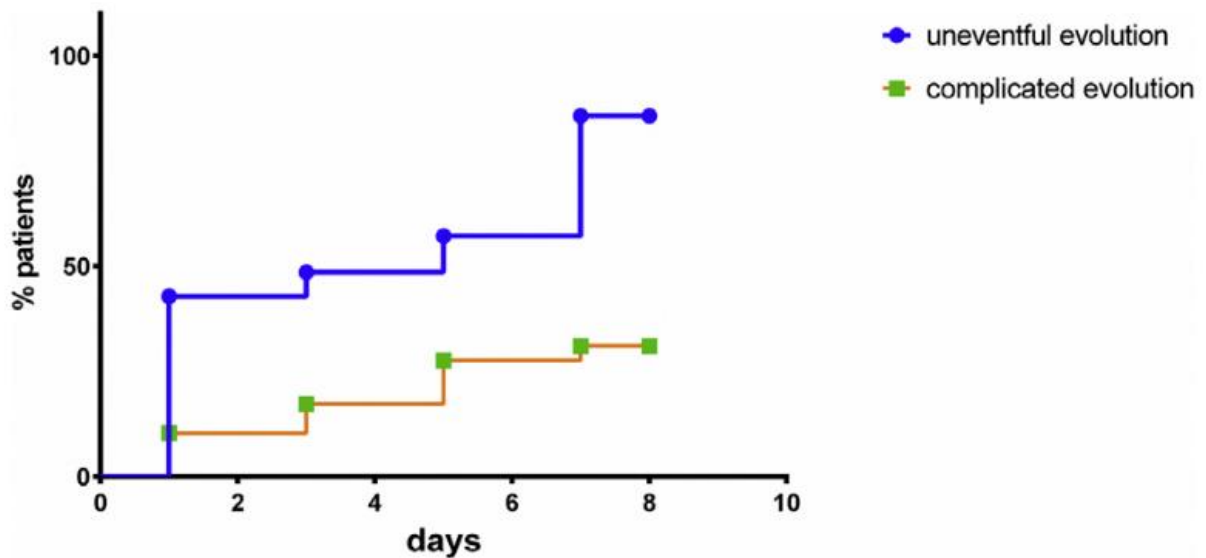


Figure 23: Dynamics of serum albumin restoration in patients whose postoperative evolution is uneventful or complicated. Patients who rapidly normalise serum albumin in the first postoperative week are more protected from postoperative complications. From Reis et al.(97)

Moreover, this such designed trial will contribute to a better understanding of perioperative cares in surgeries with intense oxidative stress especially recovery pathways synergism. Furthermore, reducing postoperative complications will permit to control length of stay, capacity of admittance and costs that represent a major issue in present days in hospitals.

Table 1: Incidence of postoperative complications following major abdominal surgery and other highly intense oxidative stress surgery.

Authors (year of publication)	Design	Sample size	Intervention protocol among Standard cares (proteins-calories-iron) Immune nutrition Albumin infusion	Surgery	Enrolment location	Outcomes	Results		
							Control group	Treated group	Difference <i>p</i>
CONTROL GROUP (STANDARD CARES)									
Wang Y ⁽⁹⁵⁾ (2018)	Observational study 2015 to 2017 (mean age 52 years)	193	No intervention Early decrease in postoperative serum albumin predicts severe complications in patients with colorectal cancer after curative laparoscopic surgery.	Elective minimally invasive colectomy	China	Severe postoperative complications Prolonged	19.7%	-	-
Offodile AC ⁽¹³⁾ (2014)	Retrospective Observational study The National Surgical Quality Improvement Program databases 2005 to 2011	2425	No intervention Risk Factors Associated with Prolonged Postoperative Stay following Free Tissue Transfer An Analysis of 2425 Patients from the American College of Surgeons National Surgical Quality Improvement Program Database	Free Tissue Transfer	Burlington, Massachusetts, USA	Length of stay (LOS)	36%	-	-
Goh SL ⁽¹²⁾ (2015)	Meta-analysis 87 studies 1980-2014	7227	No intervention Is low serum albumin associated with postoperative complications in patients undergoing esophagectomy for oesophageal malignancies?	esophagectomy	Worldwide	Mortality	21% (< 15 g/L)	11% (> 35 g/L)	P < 0.001
Labgaa L ⁽⁹⁶⁾ (2017)	Prospective cohort study	138	No preoperative intervention Is postoperative decrease of serum albumin an early predictor of complications after major abdominal surgery?	Major abdominal surgery	European centre	Postoperative complications	43% (60/138)	-	-



Reis TG (97) (2022)	Prospective cohort study 2008-2009	41	No preoperative intervention Postoperative ENTERAL nutrition	Head Neck cancer surgery	São Paulo Brazil	Postoperative complications	53.6%	-	-
Liu Z (98) (2022)	Prospective cohort study	206	No preoperative intervention	Gastrectomy	China	Postoperative complications	31.1%	-	-
Jie B (7) (2012)	Retrospective (A consecutive series of patients) 2007 - 2008. <u>Conclusion:</u> <i>Total parenteral nutrition (TPN) therapy decreased the overall risk of postoperative complications by approximately 10%</i>	1085	Seven-days Preoperative Total parenteral nutrition Impact of preoperative nutritional support on clinical outcome in abdominal surgical patients at nutritional risk.	selective abdominal surgery	Beijing China	Postoperative complications	50.6%	25.6% (pre- operative severely malnourished patients NRS 3-5)	0.008
								50% (pre- operative malnourished patients NRS 3-4)	NS
						LOS (days)	13.7	11.3	0.018
SOLELY POSTOPERATIVE ALBUMIN INFUSION									
Yu HM (99) (2017)	Prospective cohort study 2 Cohorts No randomisation	79	No preop intervention Postoperative intervention 39 patients: early enteral nutrition 40 patients: early parenteral nutrition 30-40 g Albumin infusion in the two groups	Esophagectomy	China	Postoperative complications	47.5% (19/ 40) PE	25.6% (10/39) EN	< 0.05



Schaller SJ (48) (2020)	Randomised (SuperAdd Trial) Interim analysis at 100 patients (50 x 2) Trial prematurely stopped.	2509	Solely Postoperative 20% albumin infusion A goal-directed perioperative albumin substitution versus standard of care.	Orthopaedic Gut Vascular surgery	Ulm Germany	Postoperative complications	34%	36%	NS
Xu W (100) (2020)	Prospective study No randomisation (Baseline Complications rate 30–60%)	163	Postoperative Calories Albumin infusion Group (n=61) for serum albumin > 30g/l Standard group (n=102) Hypoalbuminemia after pancreaticoduodenectomy does not predict or affect short-term postoperative prognosis	Pancreaticoduodenectomy	China	Major Postoperative complications (Clavien ≥ 3)	24.5% (n=102)	40.9% (n=61) 169 g 20% albumin (10%)	NS
Xu H (101) (2021)	Retrospective study (2012 – 2017)	315	Albumin infusion Perioperative Albumin Supplementation is Associated with Decreased Risk of Complications Following Microvascular Head and Neck Reconstruction	Microvascular Head and Neck Reconstruction	China	Postoperative complications LOS (days)	21.6%	6.5 % 12.5	< 0.001 < 0.001
SOLELY PREOPERATIVE IMMUNONUTRITION									
Braga M (2) 1999	Randomised double-blind phase 3 trial Meta-analysis	206	Perioperative immunonutrition in patients undergoing cancer surgery	cancer surgery	Italy	Nosocomial infections LOS (days)	30% (31/104)	14% (14/102)	0.009 0.01
Drover JW (5) 2011	Electronic databases Cochrane Controlled Trials Register from 1990 to 2010 <i>Infections are the most frequent cause of morbidity after surgery and up to 54% of all hospital-acquired infections occur in high- risk surgical populations.</i>	2780	Solely preoperative immune modulation. Perioperative Use of Arginine- supplemented Diets: A Systematic Review of the Evidence	Gastro-Intestinal surgery	USA	Nosocomial infections LOS (days)	27.7% (436/1248)	16.5% (253/1532)	< 0.00001 < 0.00001



Khaleel S.(102) 2021	Retrospective study	204	Preoperative immunonutrition	Radical cystectomy	USA	postoperative infection	45%	25%	0.003
Buijs N.(8) 2010	Randomised double-blind controlled trial <i>The incidence of postoperative complications within this population is 20-50%, which leads to prolonged hospital stays and a poorer prognosis.</i>	32	Perioperative immunonutrition Perioperative arginine-supplemented nutrition in malnourished patients with head and neck cancer improves long-term survival.	Head and neck cancer	Nederland	Long-term survival ≥ 10 years	-	-	0.019
IMMUNONUTRITION and ALBUMIN INFUSION									
Ascoli A.(103) 2023	Before-After case-control Retrospective Observational study Standard care group (2012-2019) N = 149 vs Immunonutrition group (2019-2021) N = 50	199	Immunonutrition preoperatively Albumin administration postoperatively in the two groups Immunonutrition in major oncologic head and neck surgery: Analysis of complications, plasmatic equilibrium, and costs.	Oncologic major otorhinolaryngologic surgery	Italia	Major surgical complications on the surgical site	20.1%	6.9%	0.026
						Minor surgical complication the on surgical site	17.4%	30.0%	0.069
						Medical complications (infections, organ failure, ...)	33.6%	36.0%	0.863
						Duration of antibiotics (days)	16	9	< 0.001
						LOS (days)	19.5	19.0	0.296
						Postoperative hypoalbuminemia treated by Albumin infusion	30.9%	22.0%	0.280



5-2- Experience Feedback 2016 - 2026

In our setting of territorial Hospital Group Grand Paris North-East, we experienced consequences of intense oxidative stress surgery specially in patients undergoing laparotomy for radical cystectomy and nephrectomy and sometimes laparoscopy for nephrectomy. During this decade, we experienced all types of minor and overall, major postoperative complications including patient death despite their admission in intensive care unit.

Therefore, in 2019, we aimed to dramatically reduce these major postoperative complications after radical cystectomies and nephrectomies by applying a synergistic perioperative antioxidative recovery program based on immunonutrition, in combination with other recovery pathways: physical exercise, iron homeostasis, calory requirement control and, albumin 20% infusion to maintain the crucial protective albumin antioxidant pathway.

Implementation of the Synergistic AntiOxidative Recovery Program was progressive with a first version lonely containing preoperative immunonutrition in half of patients. The COVID period covered 2020 and 2021. We began to prospectively collect outcomes with a stronger program, **Program 1**, containing pre or postoperative immunonutrition and 20% albumin infusion. In this Program 1, patients were completely or partially compliant with. In 2025, the Recovery Program evolution, **Program 2**, was exhaustive with immunonutrition continued in postoperative period and physical exercise by blowing bubbles in a special vial introduced prior and after surgery (Figure 20). However, Pharmacy was temporary reluctant to deliver 20% albumin for budget concerns and guidelines not yet updated. In 2026, this issue was addressed regarding in-hospital clinical results and the full program was applied with a good compliance not only in Urology but also in the other surgical specialties (otorhinolaryngology, abdominal surgery, free lap reconstruction, orthopedy). Outcomes collection in a database is still going on.

5-2-1- Methods

This experience feedback was a multicenter, before-after, case-control evaluation. Patients undergoing laparotomy or laparoscopy for radical cystectomy and nephrectomy were enrolled



into two cohorts: a retrospective cohort (2016 – 2018) and a prospective cohort (2022 – 2025).
One patient was included in December 2021.

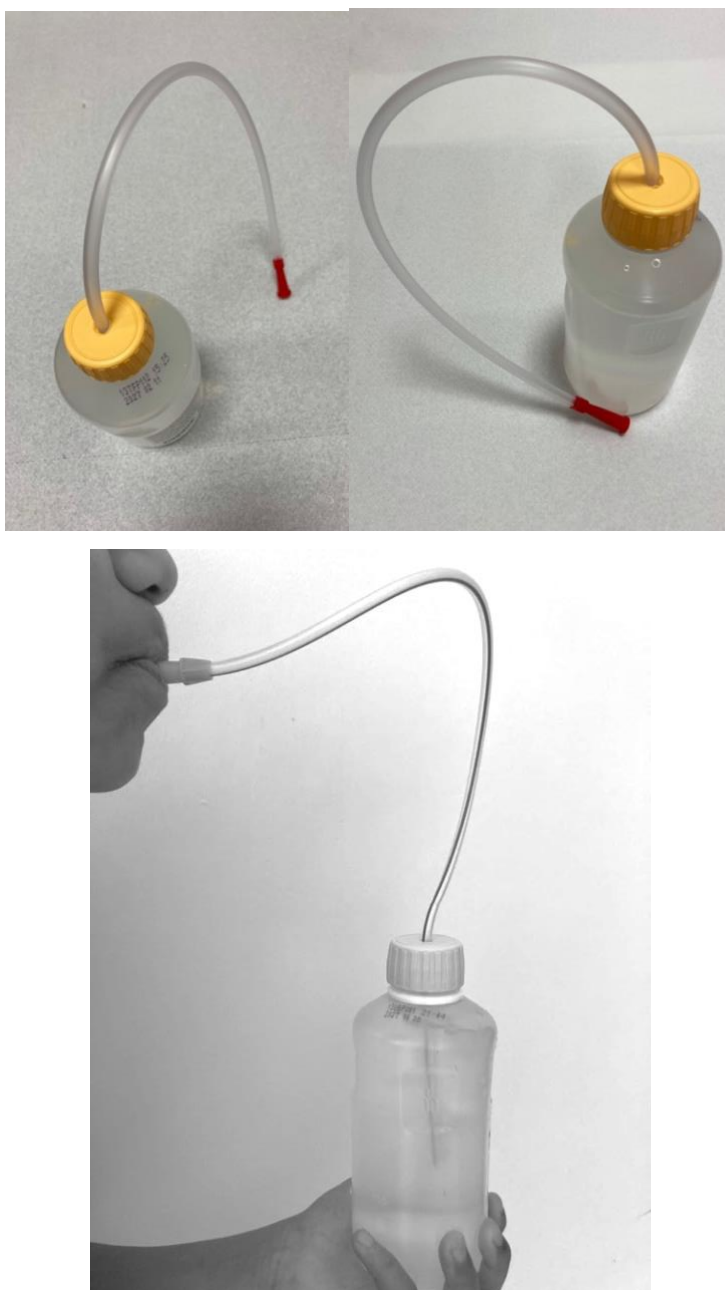


Figure 21: A bottle of water with a flexible small diameter pipe for incentive physical therapy: perioperative pulmonary kinesitherapy inducing positive expiratory pressure, mental mobilisation by focusing on bubbles and abdominal muscles contraction for expiration stimulating bowel activity and preventing postoperative paralytic ileus.

We conducted a comparison between historical standard cares and two synergistic Antioxidative and Perioperative Recovery Programs based on immunonutrition, postoperative curative Vialabex 20% albumin infusion (LFB Biomédicaments, Courtaboeuf, France) (Figure 19) to maintain serum albumin rate above 35 g/L when a minor or major complication occurred, physical exercise by blowing bubbles in a special bottle providing a positive expiratory pressure (Figure 21), iron homeostasis by maintaining serum ferritin > 100 ng/ml and calory requirement control (Table 2). Vialabex 20% albumin was 100% pure.

Physical exercise was performed by blowing bubbles through a flexible small diameter pipe in a special bottle providing a positive expiratory pressure. Bubbles escape from the bottle by slightly unscrewing the cap. This was made in addition to sitting in an armchair and walking in the surgery setting.

Additionally, dose of 20% albumin infusion was based on hypoalbuminemia range. For 35-25, 24-15 or < 15 g/l, patients received 20, 40 or 60 g/day for 5 days. A control of serum albumin concentration was made at day 6. If the albumin serum concentration was < 35 g/l, a second 5-days cure of 20% albumin was initiated till the serum albumin concentration reached or overpassed 35 g/l. This protocol was approved by the National Agency of Medication Safety on July 12, 2022. **Curative modality** of 20% albumin infusion consisted of administration only if a minor or major postoperative complication occurred. **Preventive modality** of 20% albumin infusion consisted of early administration, from day 1, prior to occurrence of a minor or major postoperative complication. This modality has not been used yet for budget concerns.

Figure 20 summarizes the patient care route and flow of the full basic Recovery Program. Transfusion of red blood cells was widely used to maintain hemoglobin above 10 g/dl.

Immune-modulating nutrient-enriched product was Oral Impact® (Nestlé Health Science, Issy-les-Moulineaux, France), ingested seven to ten days before surgery and pursued (Program 2) or not (Program 1) postoperatively (Table 1). Some patients in Program 1, not compliant with immunonutrition preoperatively, ingested Oral Impact briquettes in postoperative period.



Likewise, we nevertheless enrolled patients who partially comply with the program like those who have **partially** taken immunonutrition because of nausea, disgusting taste or difficult glycemia control in the Overall Program 1 group.

After surgery, patients returned directly in their hospitalization room without admission in Intensive Care Unit (ICU) for surveillance and postoperative first cares. The lonely indication of ICU admission was major clinical impairment. This was a secondary outcome of the present experience feedback.

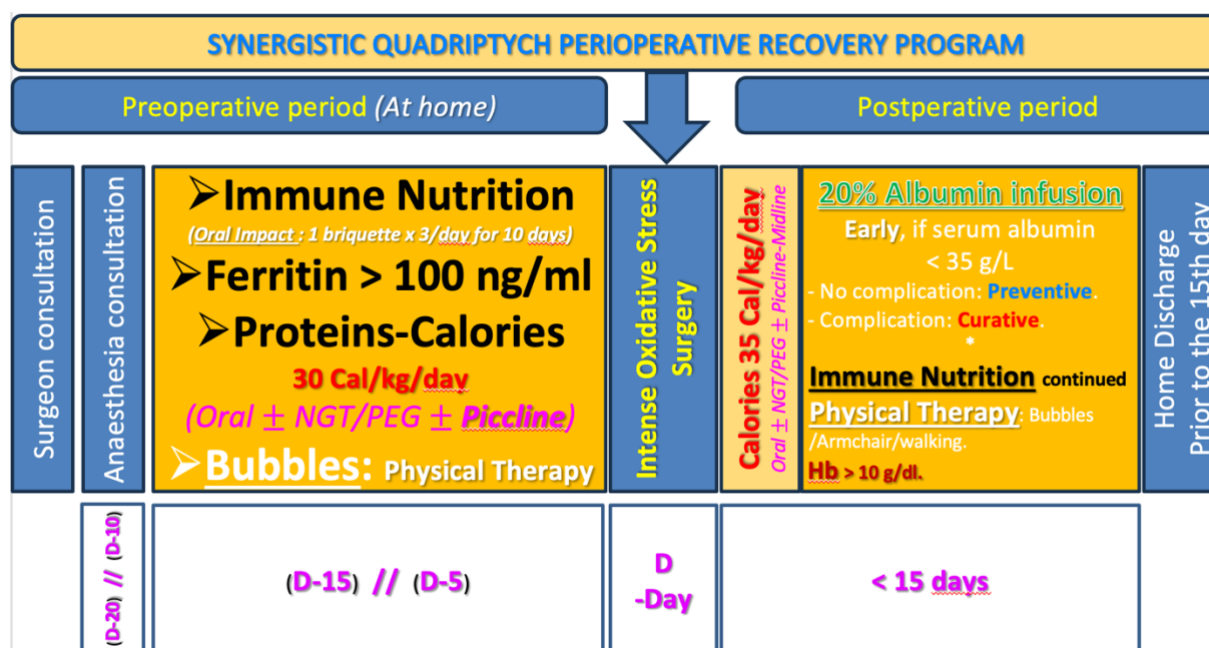


Figure 20: Care route and flow of the synergistic perioperative antioxidative recovery program. Protocol diagram of a synergistic quadriptych perioperative recovery program for intense oxidative stress surgery. NGT, nasogastric tube; PEG, percutaneous endoscopic gastrostomy, D, day.

	Historical Standard Cares	Program 1	Program 2
Immunonutrition.	None	Pre OR postoperatively	Pre AND postoperatively
Curative Albumin 20% infusion if minor or major complication occurred.	None	Only postoperatively	-
Physical Exercise by blowing bubbles in a special bottle providing a positive expiratory pressure.	None	-	Pre AND postoperatively
Calory requirement control.	Occasionally	Pre AND postoperatively	Pre AND postoperatively
Iron homeostasis.	None	Pre AND postoperatively	Pre AND postoperatively

Table 2: Synergistic Antioxidative and Perioperative Recovery Programs based on immunonutrition, postoperative curative 20% albumin infusion when a minor or major complication occurred, physical exercise, iron homeostasis and calory requirement control (35 Cal/kg/day).

The main outcome was the rate of major postoperative complications defined by a Clavien-Dindo Classification ≥ 3 (Figure 24).(42)

Secondary outcomes were intensive care unit admissions, mortality, length of stay (LOS), postoperative lowest serum albumin rate, paralytic ileus and wound healing delay.



We statistically compared mean $\pm$ standard deviation with the *t* Student test, proportions (number (percentage)) with a khi 2 test and proportion difference with a 95% confidence interval for an alpha error of 0.05.

Grades	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are drugs as antiemetics, antipyretics, analgesics, diuretics, and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic, or radiological intervention.
Grade III-a	Intervention not under general anesthesia.
Grade III-b	Intervention under general anesthesia.
Grade IV	Life-threatening complication (including CNS complications) requiring IC/ICU management.
Grade IV-a	Single organ dysfunction (including dialysis).
Grade IV-b	Multi-organ dysfunction.
Grade V	Death of a patient.

Figure 24: Clavien-Dindo Classification of postoperative complications. From Dindo et al.(42)



5-2-2- Results

We enrolled:

- 1- Retrospectively, 107 patients who have undergone laparotomy for cystectomy and nephrectomy from 2016 and 2018 in the retrospective control group,
- 2- Prospectively, 63 patients from 2022 to 2024 receiving prospectively the Program 1 whose 29 complied strictly with the Program 1. *One patient was included in December 2021.*
- 3- And, finally, prospectively, 22 patients in 2025 complying strictly with the Program 2.

Likewise, in 2026, data not published, seventeen patients have been currently included. No patient experienced major postoperative complications. There was not any need of 20% albumin infusion. Postoperative hypoalbuminemia was moderate with a mean at 28 g/L. We collected two laparotomies for cystectomies, 5 laparotomies and 10 laparoscopies for nephrectomies.

The incidence of major postoperative complications (Clavien-Dindo score ≥ 3) was significantly reduced in the two prospective groups compared to the retrospective control group (Figure 25 and Table 4) as well as in patients who underwent radical cystectomy (Figure 26 and Table 5).

Of note, in patients who underwent cystectomy and strictly compliant with the programs, rate of major postoperative has decreased from 40% to 10% (Program 1) and **zero% in 2025** (Program 2). Currently, in **2026**, data not published, this rate is stable at **zero%**.

The secondary outcomes are summarized in Tables 4 and 5.

The rate of ICU admission, mortality decreased (Figure 3). However, the lack of power did not allow this experience feedback evaluation to show a significant difference and in routine practice, the difference is clinically pertinent.



Similarly, the frequency of postoperative paralytic ileus has decreased without significant difference and, however, a clinically pertinent difference observed in routine practice.

Concerning length of stay (LOS), this latter significantly decreased in patients of the Program 1 who strictly complied with the program. LOS reduced of 4 days, from 12 to **8 days**. In contrary, **LOS did not decrease in patients of the Program 2** because serum albumin was excessively and significantly lower than that of patients of the Program 1 who received albumin infusion. Eleven patients of the Program 1 received postoperatively, early 20% albumin infusion as part of complication treatment, 5 nephrectomies and 6 cystectomies.

Currently, in **2026**, data not published, LOS is at **6 days**. The last one who underwent a cystectomy has discharged after one week, seventh day.

	Retrospective Control group	Overall Program 1	Strict Compliance Program 1	Program 2
	N= 107	N = 63	N = 29	N = 22
Age (years)	65.0 ± 13.4	61.3 ± 13.3	60.6 ± 11.8	65.9 ± 13.5
Weight (kg)	76.4 ± 18.2	79.6 ± 20.0	82.2 ± 20.8	74.4 ± 15.6
Height (cm)	170.1 ± 0.1	170.9 ± 11.0	171.5 ± 11.6	176.0 ± 8.2
Gender (male)	82 (76.6)	49 (73.1)	19 (67.9)	12 (54.5)
NRS-2002 (nutritional status)	0.8 ± 0.9	1.2 ± 1.3	0.9 ± 1.3	0.5 ± 0.8
Preoperative serum albumin rate	-	38.0 ± 5.0	38.6 ± 5.5	37.0 ± 5.3
Nephrectomy	52 (48.6)	44 (63.5)	19 (65.5)	10 (45.4)
Cystectomy	55 (51.4)	23 (36.5)	10 (34.5)	12 (54.6)
Laparoscopy (n)	0	0	0	2

Table 3: Baseline Patient Characteristics.

The mean serum albumin in patients of the Program 2 was 20 g/L, a mix of useful reduced albumin and useless oxidized albumin cleared by the liver.

The wound healing delay induced by this severe hypoalbuminemia was significantly more frequent in patients of the Program 2 than those of the Program 1.

Finally, in patients who underwent cystectomy, LOS was comparable in all the groups around 15 days despite a significantly reduction of major postoperative complications (Figure 26 and Table 5).

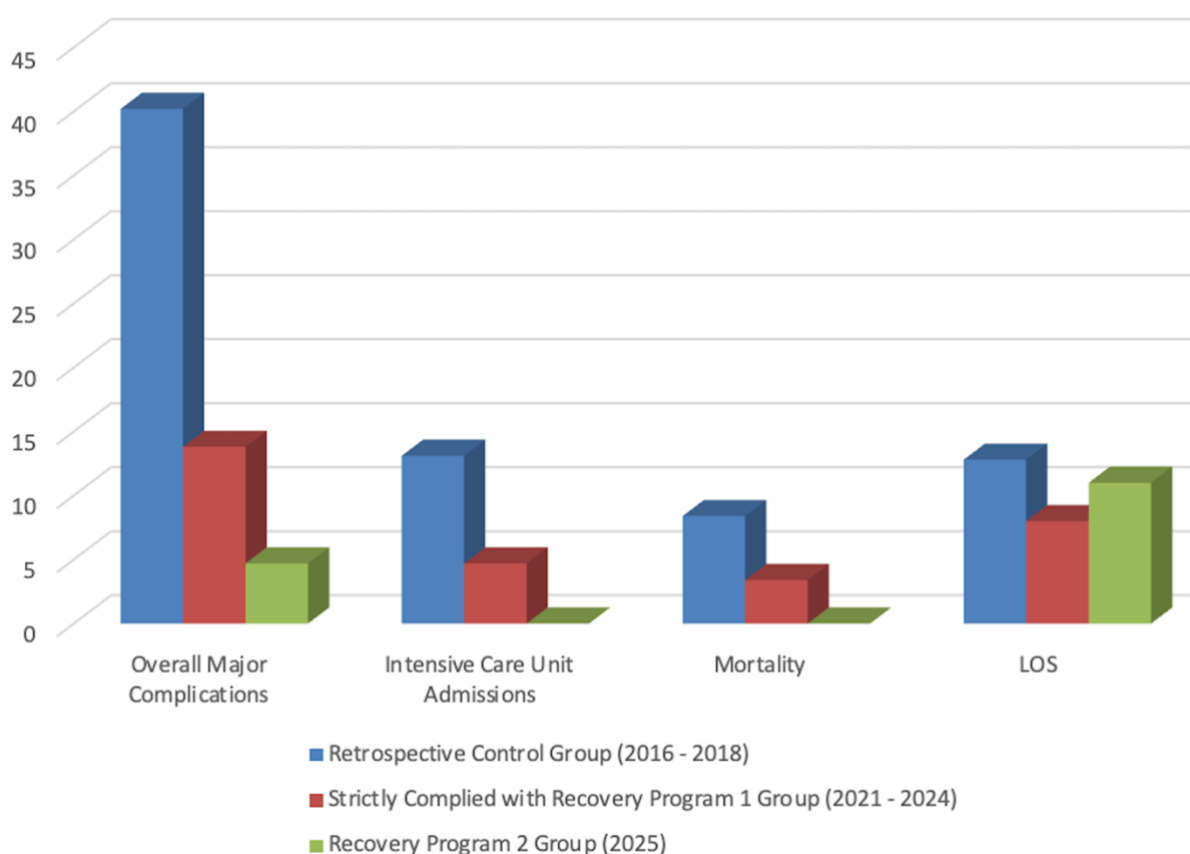


Figure 25: Benefits of a synergistic perioperative antioxidative recovery program on major postoperative complications in patients who underwent laparotomy for radical cystectomy or nephrectomy. LOS, length of stay. **Program 1:** Immunonutrition only pre or postoperatively, postoperative curative 20% albumin infusion when a minor or major complication occurred. **Program 2:** Immunonutrition pre and postoperatively, no postoperative 20% albumin infusion, physical exercise. 2 laparoscopies for nephrectomy. *One patient was included in December 2021.*



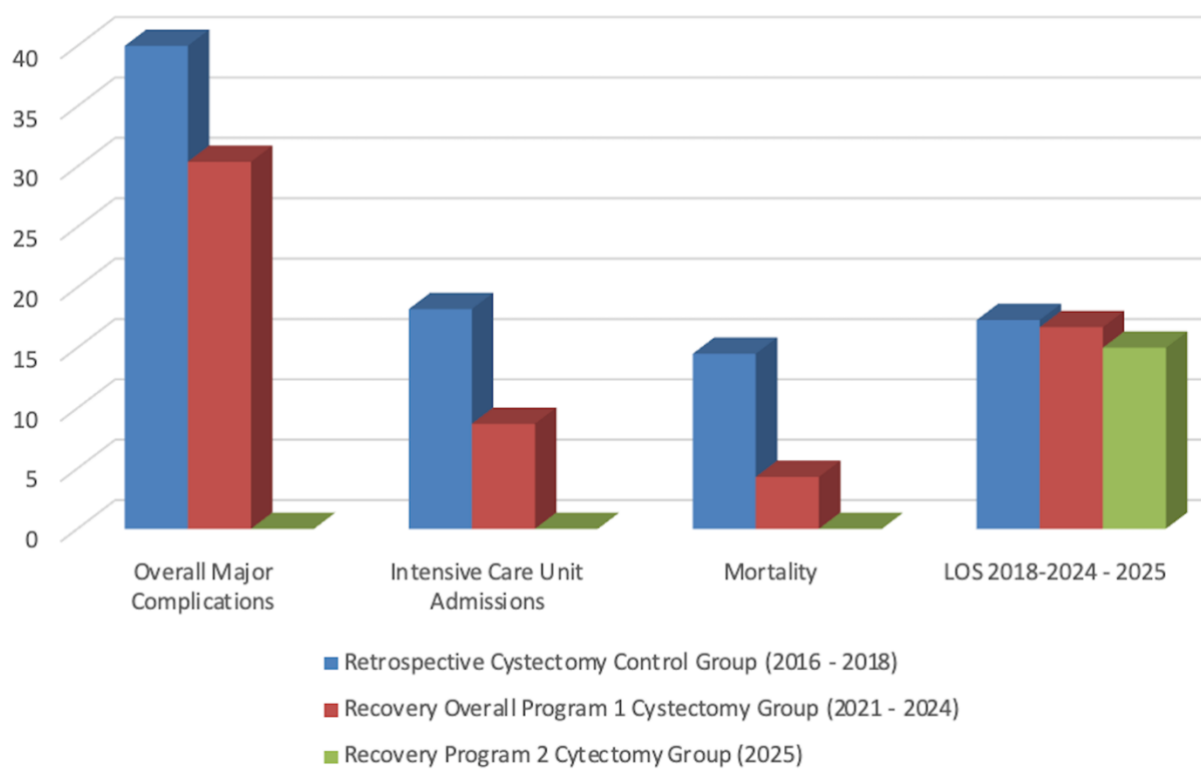


Figure 26: Benefits of a synergistic perioperative antioxidative recovery program on major postoperative complications in patients who underwent laparotomy for radical cystectomy. LOS, length of stay. **Program 1:** Immunonutrition only pre or postoperatively, postoperative curative 20% albumin infusion when a minor or major complication occurred. **Program 2:** Immunonutrition pre and postoperatively, no postoperative 20% albumin infusion, physical exercise. *One patient was included in December 2021.*

Groups	Retrospective N = 107	Prospective Overall Program 1 N = 63	Strict Compliance with the Program 1 N = 29	Prospective Program 2 N = 22
	2016-18	2021-2024		2025
	Standard cares	Pre or postoperative Immunonutrition Curative 20% Albumin infusion	Only Preoperative Immunonutrition Curative 20% Albumin infusion	Pre and postoperative Immunonutrition No Curative 20% Albumin infusion
		11(17.5)		1 (4.7)
Major Postoperative Complications (Clavien- Dindo score $\geq$ 3)	43 (40.2)	Difference = 22.7% IC95 [9.5% – 35.9%] p = 0.0010.*	4 (13.8) Difference = 26.4% IC95 [10.7% – 42.0%] p = 0.010*	Difference = 35.5% IC95 [22.4% – 46.4%] p = 0.0016*
Postoperative ICU admissions	14 (13.1)	4 (6.5) Difference = 6.6% IC95 [-2.0% – 15.5%] p=0.187	2 (6.8) Difference = 6.3% IC95 [-5.0% – 17.4%] p=0.434	1 (4.7) Difference = 8.4% IC95 [-2.2% – 19.3%] p=0.303
Postoperative Mortality	9 (8.4)	2 (3.0)	1 (3.4)	0 (0.0)
Postoperative LOS (days)	12.8 $\pm$ 7.4	12.0 $\pm$ 8.6 p = 0.250	8.0 $\pm$ 1.3 p = 0.0004*	11.0 $\pm$ 7.4 p = 0.130
Postoperative Paralytic Ileus	11 (10.3)	8 (12.7)	3 (10.3)	2 (9.0)
Postoperative wound healing delay	15 (14)	7 (11.1)	4 (13.7)	11 (50) p = 0.00012 ** p = 0.0049 ***
Postoperative lowest serum albumin rate	-	23 $\pm$ 1.5	24.2 $\pm$ 6.1	20 $\pm$ 5.0 p = 0.0057 ** p < 0.001 ***

Table 4: Postoperative outcomes of patients undergoing laparotomy for radical cystectomy and nephrectomy and benefiting from an Antioxidative Perioperative Recovery Program based on immunonutrition, postoperative curative 20% albumin infusion when a minor or major



complication occurred, physical exercise, iron homeostasis and calory support. **Program 1:** Immunonutrition only pre or postoperatively, postoperative curative 20% albumin infusion. **Program 2:** Immunonutrition pre and postoperatively, no postoperative 20% albumin infusion. ICU, intensive care unit, LOS, length of stay. The study was underpowered to detect a statistical significative difference between group despite a dramatic reduction of postoperative mortality and ICU admissions. *, **, ***, compared to the retrospective group, overall Program 1, Strict compliance with the Program 1. *One patient was included in December 2021.*



Radical Cystectomy				
Groups	Retrospective N = 55	Prospective Overall Program 1 N = 23	Strict Compliance with the Program 1 N = 10	Prospective Program 2 N = 12
	2016-18	2021-2024		2025
	Standard care	Pre or postoperative Immunonutrition Curative 20% Albumin infusion	Only Preoperative Immunonutrition Curative 20% Albumin infusion	Pre and postoperative Immunonutrition No Curative 20% Albumin infusion
				0 (0)
Major Postoperative Complications (Clavien-Dindo score $\geq$ 3)	22 (40.0)	7 (30.4) Difference = 9.6% IC95 [-13.2% – 32.4%] p = 0.420	1 (10.0) Difference = 30.0% IC95 [7.3% – 52.6%] p = 0.049*	Difference = 40.0% IC95 [27.0% – 52.9%] P = 0.007*
Postoperative ICU admissions	10(18.2)	2 (8.7%) Difference = 9.5% IC95 [-5.8% – 24.8%] p = 0.289	1 (10%) Difference = 8.2% IC95 [-13.0% – 29.0%] p = 0.460	0 (0) Difference = 18.2% IC95 [7.9% – 28.4%] p = 0.109
Postoperative Mortality	8 (14.5)	1 (4.3)	1 (10.0)	0 (0.0)
Postoperative LOS (days)	17.3 $\pm$ 6.7	16.7 $\pm$ 8.1 p = 0.250	14.9 $\pm$ 5.8 p = 0.146	15.0 $\pm$ 6.4 p = 0.140
Postoperative Paralytic Ileus	10 (18.2)	5 (21.7) p = 0.716	1 (10.0) p = 0.525	1 (8.3) p = 0.404
Postoperative wound healing delay	5 (9.1)	4 (17.4)	1 (10)	8 (66.7) p = 0.0012 ** p = 0.0071 ***
Postoperative lowest serum albumin rate	-	24.2 $\pm$ 6.3	23.8 $\pm$ 3.9	20 $\pm$ 3.2 p = 0.0192 ** p < 0.0103 ***

Table 5: Postoperative outcomes of patients undergoing laparotomy for radical cystectomy and benefiting from an Antioxidative Perioperative Recovery Program based on immunonutrition, postoperative curative 20% albumin infusion when a minor or major complication occurred,



physical exercise, iron homeostasis and calory support. **Program 1:** Immunonutrition only pre or postoperatively, postoperative curative 20% albumin infusion. **Program 2:** Immunonutrition pre and postoperatively, no postoperative 20% albumin infusion, physical exercise. ICU, intensive care unit, LOS, length of stay. The study was underpowered to detect a statistical significative difference between group despite a dramatic reduction of postoperative mortality and ICU admissions. *, **, ***, compared to the retrospective group, overall Program 1, Strict compliance with the Program 1. *One patient was included in December 2021.*

5-2-3- Discussion

We succeeded to reduce at 4.7 %, 2025, and currently at zero % in 2026, the rate of major postoperative complications in patients undergoing laparotomy and laparoscopy for radical cystectomy and nephrectomy.

This is the result of implementation of a synergistic antioxidative perioperative recovery program based on pre and postoperative immunonutrition by Oral Impact® intake in combination with other recovery pathways (20% albumin infusion, iron homeostasis, calory support and physical exercise).

There is not a study that previously reported a great reduction below the 6.5% rate of postoperative major complications obtained by Xu et al. in free lap reconstruction for oncological otorhinology surgery with lonely 20% albumin infusion.(101) (Xu H, 2021) The present experience feedback showed that it is possible to further decrease this rate near or at zero %. This needs to combine several postoperative recovery pathways including mental pathway. This latter may have been stimulated by explaining to patient that blowing bubbles was a good thing for a better postoperative recovery as well as not staying uselessly in bed, mobilizing in an armchair or walking to the toilets or into the surgical setting. The ludic effect of blowing bubbles as we observed when we test the exercise at the anesthesia consultation is effective. Patients have haggard eyes stimulated by the interest to make bubbles like when they were children.



5-2-3-1- Immunonutrition and reduction of postoperative complication following intense oxidative stress surgeries.

Immune-modulating nutrient-enriched products containing arginine, Omega-3 polyunsaturated fatty acids (PUFAs), nucleic acids, vitamins and antioxidants (selenium) can modulate immune and inflammatory processes in burn, trauma, major surgery and improve clinical outcomes.(5) (Drover 2011) Their biochemical effect includes increased cell stability, improved gastrointestinal mucosal integrity, enhanced cell-mediated immune response to stress, attenuation of the hypermetabolic response to surgery and improvement of blood flow to poorly vascularized and ischemic tissues.(6) (Evans DC, 2014) The Hamilton-Reeves study also identified that the patients undergoing cystectomy and receiving arginine- containing supplementation had significantly fewer Myeloid-Derived Suppressor Cells (MDSCs) than did their non-arginine-receiving counterparts. MDSCs are cells which, under normal conditions, rapidly expand upon physical injury and are known to inhibit T-cell responses. This inhibited T cell response lowers resistance to infection by depleting serum arginine through arginase-1, which is found within MDSCs.(104) (Hamilton-Reeves JM 2018) Furthermore, T lymphocytes are dependent on arginine for their proliferation, so these findings suggest that there are multiple mechanisms for infection prevention when patients undergoing cystectomy receive supplemental arginine.(105) (Hamilton-Reeves JM 2016) These immune-modulating nutrient-enriched products have shown their ability to decrease postoperative complications up to 50% in patients undergoing non-gastrointestinal major surgery, length of hospital and ICU stays.(5,7) (Jie B 2012, Drover 2011) In the same vein, Buijs et al. demonstrated a benefit on mortality outcome in a study focused on otorhinolaryngology surgery.(8) (Buijs N, 2010) Oral Impact effects have widely been investigated in patient undergoing abdominal surgery. Immune nutrition is efficiency regardless of the baseline nutritional status of the patients. Postoperative major complications were reduced from 27% to 10% in well-nourished patients and from 39% to 14% in malnourished patients.(2) (Braga M, 1999)

This is consistent with the clinical results of the experience feedback. However, the decrease in major postoperative complication is not as deep as expected may be because of lack of synergism with other recovery pathways as presented in this experience feedback reducing major complication rate near zero% and ICU admission and mortality to zero%.



Additionally, immune-modulating regimens reduced hospital resources consumed for surgical morbidity and consequently, could reduce the hospital capacity strain, increase income capacities and patient hospitalization rate.(9) (Braga M, 2005) Drover et al. metanalysis showed that preoperative administration of Impact reduced LOS by 1 day due to arginine load. Perioperative load of arginine by intake of impact before and after surgery reduced LOS by 2 days. This is consistent with the results of the present study in which length of stay (LOS) was reduced by 4 days. This is a major result, better than previous studies and probably related to the synergism of the recovery program used in this study. Synergism between arginine, PUFAs, controlled serum iron and serum albumin paired with early calories support and physical exercise may have play a substantial role in the results of the present clinical experience feedback.

5-2-3-2- Immunonutrition and reduction of postoperative complication following urology intense oxidative stress surgeries.

In urology surgery, few studies have investigated benefits of such a perioperative synergistic recovery program focused on immune modulation with Oral Impact and antioxidation pathway power to prevent major postoperative complications (Clavien-Dindo ≥ 3). Results are controversial concerning radical cystectomies related to small samples leading to lack of power, retrospective design, inclusion of patients operated with robot.(106-107) (Richt CR, 2019; Cozzy G, 2021).

Cozzi et al. did not find a significant difference in the rate of Clavien-Dindo ≥ 3 -patients between groups, immunonutrition versus standard care, 42% vs 38%.(107) (Cozzy G, 2021) This study was retrospective without consideration of antioxidant pathway power and, despite an immune diet continued postoperatively, the rate of Clavien-Dindo ≥ 3 -patients was high. However, the infection rate decreased significantly consistent with the immune diet effect, stabilization of gut barrier function and the gastrointestinal microbiome. Patient's resistance to postoperative infections is well-established in contrast to the other Clavien-Dindo ≥ 3 postoperative complications. Consequently, enhancing immune system by immunonutrition is worth considering, however not sufficient to reduced major postoperative complication (Clavien-Dindo ≥ 3). The other recovery pathways must be considered in a synergistic



combination. This may explain our excellent results in reducing frequency of Clavien-Dindo ≥ 3 postoperative complications at zero% and based on the synergism of five recovery pathways.

Similarly, two randomised controlled trials have been conducted showing a reduction in postoperative infections and not in major postoperative complications (Clavien-Dindo ≥ 3). The first true prospective randomised controlled trial investigating immunonutrition in patients undergoing radical cystectomies was performed by Hamilton-Reeves et al. Fourteen patients received a nutritional supplement containing arginine and were compared to fifteen patients who received a nutritional supplement without arginine. All patients received 5 days of their supplement before and after surgery. The count of Myeloid-Derived Suppressor Cells as main outcome was significantly reduced in the arginine group. The number of 30 days-late postoperative infections, as second outcome, decreased by 39% in patients receiving arginine-containing supplement (15% vs 53%, $p = 0.027$). No significant difference in 30 days-late major complications (Clavien-Dindo ≥ 3), 7% vs 0%. (104-105) ([Hamilton-Reeves JM 2018, 2016](#))

Likewise, Richt et al. conducted a prospective randomized controlled trial in patient undergoing radical cystectomy with 30 patients in each group. They did not find a significant difference in major complications (Clavien-Dindo ≥ 3), 19% versus 25%, after 60 days of preoperative immune diet (2 briquettes of Oral Impact per day).(106) ([Richt CR, 2019](#)) The patient antioxidant power was not enhanced. This may explain these poor results. Additionally, maintaining serum albumin in normal level or as high as possible was not taken in consideration as we did in our study. Therefore, synergism between immune and antioxidant pathways paired with calories support, iron homeostasis and perioperative physical exercise would have been of worth considering as we did in our urology surgical setting.

Additionally, Cianflone et al., in a 19 patients-sample observational study including 7 patients who undergone robotic surgical technic found a rate of 17 % in Clavien-Dindo ≥ 3 -patients who undergone laparotomy for radical cystectomy.(108) ([Cianflone F, 2025](#)) This is consistent with mini-invasive surgical technique inducing as well as laparotomy an intense oxidative stress that must be controlled by a synergistic perioperative and antioxidative recovery program.

The present experience feedback found 10% of Clavien-Dindo ≥ 3 -patients in a subgroup of 10 patients who undergone radical cystectomy and were strictly compliant with the recovery



program (Program 1) which did not include at this moment, in 2024, physical exercise and continuation of immunonutrition in postoperative period. 10% stand for one patient in a ten-patients group. This lone patient with preoperative chronic obstructive pulmonary disease who experienced an early postoperative major complication as an acute hypoxemic respiratory failure needing an admission in intensive care unit, at day one, presented an early severe hypoalbuminemia of 19 g/L. The other patients with hypoalbuminemia paired with postoperative complication received 20% albumin infusion in 2024. We believed at that moment, this rate could be reduced below 10% if immunonutrition was continued in postoperative period and serum albumin maintained as high as possible. We succeeded in 2025 owing to the synergism of different recovery pathways despite profound hypoalbuminemia leading to wound healing delay and prolonged length of stay. In 2026, hypoalbuminemia was less profound, at a mean of 28 g/L, without albumin infusion, probably by a better antioxidative synergism of the different recovery pathways. We believe that physical exercise played a crucial role in slowing down postoperative serum albumin drop. However, we cannot explain the physiological mechanism of this potential interaction.

Meanwhile, we did not find a study investigating efficacy of immunonutrition in patients undergoing either laparotomy or laparoscopy for nephrectomy.

5-2-3-3- Recovery Pathway synergism for an exhaustive postoperative recovery program.

A synergism of different recovery pathways explains the present results. This is a different approach of perioperative treatment (before and after surgery) with an oral diet enriched with arginine, omega-3 polyunsaturated fatty acids (PUFAs), **selenium** with its antioxidative action and RNA ribonucleic acids to obtain high levels of arginine and PUFAs at the time of intense oxidative surgical stress, when the depression of the host response is maximal. Additionally, arginine is involved in the production of nitric oxide (NO), which regulates gene expression and stimulates cell-mediated immunity. NO is important for microvascular perfusion, particularly in postoperative and septic states. Additionally, this significantly prevents early postoperative impairment of the host defence mechanisms, controls the overwhelming



inflammatory reaction, improves both intestinal microperfusion and postoperative gut mucosal oxygen metabolism and finally, modulates the metabolic response preventing protein catabolism and favouring synthesis of constitutive proteins instead of acute-phase proteins. (6) (Evans D, 2014)

Wischmeyer et al. defend this synergistic multimodal approach of perioperative recovery program associating immunonutrition, physical exercise, iron homeostasis and calories support. (3-4) (Wischmeyer PE)

Likewise, Akdemir et al. planned to investigate the superiority of a multimodal prehabilitation program versus standard-of-care in terms of reducing perioperative complications (proportion of Clavien-Dindo ≥ 2 -patients within 90 days after radical cystectomy in a multicenter, open label, prospective, randomized controlled trial including 154 patients with bladder cancer.(108) (Akdemir E, 2023)

This is probably the explanation of the poor results of previous studies (101-107) in reducing Clavien-Dindo ≥ 3 postoperative complications below 15% in different surgical specialties. The stability of our results confirm that this may be the right way.

5-2-3-4- Albumin antioxidant pathway

Serum albumin highlights inflammatory state, catabolism as a stress metabolism and reactive oxygen species production playing a key role in poor outcomes and mortality and justifying antioxidant supply and perioperative immunomodulation.(10) (Eckart A, 2020) It is well-established in present days that hypoalbuminemia is an independent and major risk factor for major postoperative complications. Eckart et al. has demonstrated that inflammation with CRP > 20 mg/L induced a 10-fold increase of the risk of poor postoperative outcome, NRS-2002 ≥ 3 and serum albumin < 34 g/L also increased the risk of poor outcome by 3 folds. The combination of the three factors could predict well 30-days mortality with an area under the receiver observer characteristics curve of 0.82.(10) (Eckart A, 2020)

Hypoalbuminemia is a mix of **useful antioxidative reduced albumin** and useless oxidized albumin cleared by the liver. The effective serum albumin concentration is probably lower than that measured.



Therefore, therapeutical strategies should aim to prevent postoperative decrease in serum albumin, either waiting a long time for serum albumin returns to a normal level or treating intravenously postoperative hypoalbuminemia by infusion of full-pure 20% albumin **preventively** in **high-risk patients** or **curatively** when a complication occurred. In the present experience feedback, eleven patients of the Program 1 received postoperatively and curatively an infusion of full-pure 20% albumin only when a postoperative complication occurred. All these patients discharged in a reasonable length of stay, 19 days, slightly prolonged by the treatment of the complication. This moderate additional cost has probably been widely outnumbered by health care resources saved by the marked reduction in morbidity using curatively postoperative of 20% albumin infusion paired to pre OR postoperative immunonutrition (Program 1).

However, solely postoperative 20% albumin infusion is not worthy. It deserves to be integrated in a synergistic recovery perioperative program as we did in the present clinical experience. Schaller et al. in a Randomized Clinical Trial, have investigated benefits of perioperative albumin substitution in patients undergoing orthopedic, vascular and abdominal surgery. They did not find significant difference in major Clavien-Dindo ≥ 3 -postoperative complications.(47) (Schaller SJ, 2023)

Similarly, Xu et al. and Ascoli et al. failed to reduce major Clavien-Dindo ≥ 3 -postoperative complications in otorhinolaryngology surgery setting with albumin supplementation without synergism with the other recovery pathways highlighted in our experience feedback.(101, 103) (Xu H, 2021; Ascoli A, 2023)

Serum albumin is the major powerful antioxidant in the organism. However, there are others antioxidant pathways like **selenium pathway** and **E vitamin pathway**. Selenium is present in Oral Impact briquettes ingested by patients pre and particularly, postoperatively. Its antioxidant action may explain why albumin infusion was spared since 2025 despite profound hypoalbuminemia (20 g/L) only inducing wound healing delay (Clavien-Dindo 2 complication) instead of major Clavien-Dindo ≥ 3 -postoperative complications. Selenium and physical exercise may compensate the deleterious effect of uncontrolled oxidative stress by lack of



antioxidative reduced albumin related to postoperative hypoalbuminemia, a mix of **useful antioxidative reduced albumin** and useless oxidized albumin cleared by the liver.

E Vitamin, tocopherol, is the most ingested in France. Tocopherol is one of the antioxidative pathways in the body. Glutathion is another providing thiol redox homeostasis. Prescription of tocopherol for pre and postoperative periods could worth considering. This is the next recovery pathway that will be aggregated within the synergism of our currently **Synergistic Perioperative and Antioxidative Recovery Program**. The expected effect and benefit will be to slow down postoperative serum albumin drop and limit the clinical deleterious effects of the postoperative induced-hypoalbuminemia encompassing **wound healing delay**. Tocopherol is easily available and could improve and consolidate our current excellent results in reducing at **zero%** major Clavien-Dindo ≥ 3 -postoperative complications.

5-2-3-5- Postoperative paralytic ileus

Postoperative paralytic ileus has greatly decreased in our urology surgical setting since the implementation of physical exercise by blowing bubbles in a special bottle and early mobilizing patient in an armchair and further encouraging them to walk around into the surgical setting. These physical exercises contract abdominal muscles and enhance intestinal activity and then avoid paralytic ileus.

Additionally, physical exercises were facilitated by an optimal pain control sparing morphine and including pre-incision TAP block (Transversus Abdominus Plan block) with 20 ml of ropivacaine 0.475% in each side of the incision.

5-2-4- Conclusion of the experience feedback

A strict compliance with a synergistic antioxidant perioperative recovery program based on immunonutrition in combination with other recovery pathways (20% albumin infusion, iron homeostasis, calory support and physical exercise) can greatly decrease major postoperative



complications incidence in patients undergoing laparotomy and thereby laparoscopy radical cystectomy and nephrectomy.

5-3- Health Economics

Reducing incidence of postoperative complications increases possibility of a patient turnover in a surgery setting. Hospital revenues come from homogeneous patient group pricing. Consequently, hospital revenues depend on the number of hospital patient stays. Each one corresponds to a homogeneous patient group. These revenues are counter-balanced by hospitalisation charges and costs which amount must be below revenues to obtain a positive economic balance.

Hospital charges and costs related to patient admission in a conventional surgery bed amount to approximately 1200€ per day based on the Technical Hospitalisation Data Agency (ATIH) reports. Therefore, a conventional surgery bed fully occupied by a patient for a year (full hospital year, 40 weeks, 280 days) costs approximately $1200\text{€/day} \times 280 \text{ days} = - 336.000\text{€}$ (Table 6).

Therefore, to balance this amount of charges and costs, hospital must increase patient turnover in each bed, number of homogeneous patient group and subsequently, related revenues.

Revenue from homogeneous patient group for a laparotomy is approximately 10.000€. Therefore, to balance charges and cost for a patient occupying a bed, patient turnover must be effective every week (Figure 27). Any postoperative complication extending length of stay will generate negative unbalance and a great economic deficit for hospital (Table 7).

A synergistic perioperative and antioxidative recovery program could help to reducing at zero % the rate of postoperative complication frequency, greatly limit negative unbalance.



Prolonged length of stay (LOS) does not increase prices of homogeneous patient group and thereby hospital revenues. LOS must be as short as possible leading to development of one-day admission program. For patients not eligible to one-day admission, shortening LOS depends on **surgery and perioperative medicine performances** in an optimized care organisation as prerequisite.

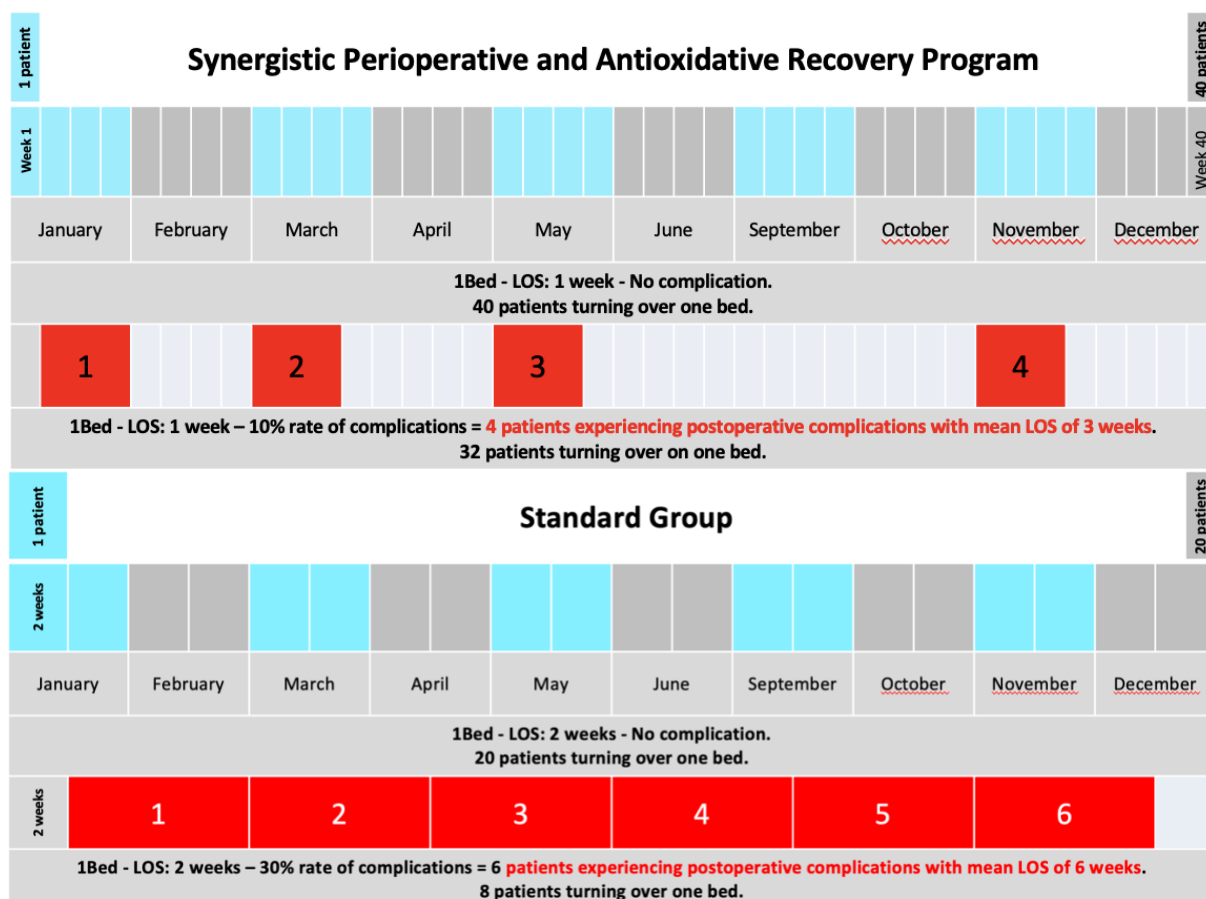


Figure 27: Impact of postoperative complications on length of stay and patient turnover on one bed of a surgery setting.

			Quadriptych recovery program	STANDARD
Price of homogeneous group of patients or homogeneous group stays (HGP/HGS) for laparotomy.			+ 10.000€ (ATIH) / patient	
Cost of one day in a surgery setting.			– 1200€ (ATIH) / day	
Length of Stay (LOS) for laparotomy. No complication.			1 week	2 weeks
LOS with Complications without death.			3 weeks	6 weeks
Cost of early cure of 20% albumin infusion based on serum albumin range 25-35 g/L: 1 vial / day for five days.			– 350€	-
Cost of late cure of 20% albumin infusion based on serum albumin	24-15 g/L	2 vials / day for five days	-	– 650€
	< 15 g/L	3 vials / day for five days		– 975€

Table 6: Prices and Costs of a laparotomy homogeneous group of patients turning over one bed in a surgery setting.

		REVENUE	COST		ACCOUNT BALANCE
			One Bed annual cost	Early cure of 20% albumin infusion	
Quadriptych recovery program group	40 HGP/years (No complications)	40 x 10.000€ = 400.000€	40 weeks = 40 x 7 days = 280 days x 1.200€ / day = - 336.000€	350€ x 40 patients = - 14.000€	+ 50.000€
	32 HGP/years (10% complications)	32 x 10.000€ = 320.000€		32 x - 350€ = - 11.200€	- 27.200€ (320.000 - 336.000 - 11.200)
Standard group	20 HGP/years (No complications)	20 x 10.000€ = 200.000€		-	- 136.000€
	8 HGP/years (30% complications)	8 x 10.000€ = 80.000€		-	- 256.000€

Table 7: Medico-economic analysis of patient hospitalisation for laparotomy involving impact of postoperative complications in a surgery setting.



6- Conclusion

Intense surgical oxidative stress induces endogenous malnutrition, patient weakness impairing oral intake and consequently, exogenous malnutrition. The subsequent severe hypoalbuminemia is an independent and major risk factor for postoperative complications following surgery even performed by highly skilled surgeons. With standard cares, complications occur in a mean rate of 30%. With a Synergistic Perioperative and Antioxidative Recovery Program associating immune nutrition, human albumin antioxidant power (reduced albumin) backed up by Oral Impact® selenium and potentially by tocopherol, proteins-calories support and iron homeostasis, perioperative physical exercise, it seems today possible to reduce the rate of postoperative complications at 0% and thereby:

- ✚ Reducing length of stay.
- ✚ Increasing patient turnover.
- ✚ Increasing number of homogeneous patient groups turning over beds.
- ✚ Increasing hospital revenues.
- ✚ Balancing hospitalisation charges and costs.
- ✚ And perhaps greatly limiting hospital economic deficit.



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Summary

Intense surgical oxidative stress induces endogenous malnutrition, patient weakness impairing oral intake and consequently, exogenous malnutrition. The subsequent severe hypoalbuminemia is an independent and major risk factor for postoperative complications following surgery even performed by **highly skilled surgeons**. With standard cares, complications occur in a mean rate of 30%. With a Synergistic Perioperative and Antioxidative Recovery Program associating immune nutrition, human albumin antioxidant power (reduced albumin) backed up by Oral Impact® selenium and potentially by tocopherol, proteins-calories support and iron homeostasis, perioperative physical exercise, it seems today possible to reduce the rate of postoperative complications at **0%** and thereby:

- ✚ Reducing length of stay.
- ✚ Increasing patient turnover.
- ✚ Increasing number of homogeneous patient groups turning over beds.
- ✚ Increasing hospital revenues.
- ✚ Balancing hospitalisation charges and costs.
- ✚ And perhaps greatly limiting hospital economic deficit.

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