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REVIEW ARTICLE

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Immunity from Intensive Care Perspective

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ARTICLE HISTORY

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Abbreviations

- **ICU:** Intensive Care Unit
- **SIRS:** Systemic Inflammatory Response Syndrome
- **NK:** Natural Killer Cell
- **MC:** Mast Cell
- **MAC:** Membrane Attack Complex
- **SIC:** Streptococcal Inhibitor of Complement
- **SPE:** Streptococcal Pyrogenic Exotoxins
- **TSS:** Toxic Shock Syndrome
- **WAT:** White Adipose Tissue
- **ATP:** Adenosine Triphosphate
- **MCA:** Middle Cerebral Artery
- **TLR4:** Toll Like Receptor 4
- **CR1:** Complement Regulator One
- **Tim3:** T Cell Immunoglobulin and Mucin-Domain Containing-3
- **BBB:** Blood Brain Barrier
- **ROS:** Reactive Oxygen Species
- **LPS:** Lipopolypsaccharide
- **MRGPRX2:** Mas-Related G Protein Coupled Receptors X2
- **CRH:** Corticotropin Releasing Hormone
- **HMGB1:** High Mobility Group Box 1
- **MDSC:** Myeloid Derived Suppressor Cells

Ensemble and analysis of past, recent publications. Evolutionary aspects, homeostatic functions, defense mechanisms and flaws, how immunity Participates in the pathogenesis of ICU conditions.

Characteristics of ICU Patients

- Severe Disturbance of Organ Homeostasis
- Frequently Multiorgan Dysfunction
- Presence of SIRS
- Primary or Secondary Viral, Bacterial, Fungal Infections
- Need for Invasive Accesses
- Surgical Stress
- Comorbidities
- Frailty by Age and Functional Status
- Need for Careful Indication and Titration of Potent Intravenous Medications
- Need for Continuous Monitoring
- Mechanical Organ Support
- Patient are not Divided by Specialty, But Depth and Multiplicity of System Dysfunction

Goal

- Monitoring and translation of the immune response in the complex environment of multiorgan dysfunction in a versatile environment with multitude of confounders.

In What Manner is Immunity Involved?

Immunity and hormonal regulation participate decisely in the tissue homeostasis with capacity to enhance and adapt the response to eliminate threat.

- Ischemia and Subsequent Reperfusion
- Infection and Sepsis
- Stress Response
- Immunosuppression
- Immune Deviation
- Immune Activation
- Destruction on Cellular and Tissue Level

Frequently, the clinical picture is driven by immune pathology.

The immune response is the consequence of neat effect of proinflammatory and regulatory mechanisms that are initiated early upon infection, but contribute to acute and eventual chronic phase phenotype.

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What is Monitored Routinely in ICU Regarding Immunity?

- Blood Count and Differential Blood Count, Neutrophils, Monocytes, Lymphocytes, Absolute Counts and Relative Contributions
- C Reactive Protein
- Procalcitonin

Not on Regular Base

- IL-6, Novel Occasionally
- C3, C4 Level of Complement Components
- Immunoglobulins and subtypes IgA, IgG, IgE, IgM

How Many Immune Modulating Therapies Exist in a Complex ICU Situation?

- **Direct:** Corticosteroids- Broadly Immune Suppressive, Inducing Lymphocyte Apoptosis
- **Immunoglobulins:** In Specific Indications
- **Indirect:** Potentially Variety/ For Example Ketamine Has Been Reported to Increase NK Cell Activation/

Is the Effect of Immune Modulation, are the Fluctuations of Immune Response /Other Than the Basics/ Monitored?

NO

Characteristics of Immune Response in ICU Patients

- Immune response that is tailored at elimination of pathogen
- Immune response reacting to tissue damage
- Killing via complement, NK, or CD8 mediated cell lysis via MAC/membrane attack complex/, perforins, granzymes may involve self: intracellular pathogens, collateral damage
- Increased vascular and tissue permeability that should serve immune cell migration, but also leads to extracellular fluid accumulation and disturbed tissue oxygenation
- Overactive immune response leading to energy and substrate exhaustion
- Exhausted adaptive immune response leading to chronicity
- Dysregulated immune response leading to fibrotic remodelling, worsening heart failure, pulmonary emphysema, etc.
- Organ dysfunction, leading to depressed immune response: liver failure
- A derailed immune response, that is due to pathogen evasion mechanisms
- Defective immune feedback, aggravating immune pathology
- It may become a double-edged sword, overt activation to eliminate pathogen may conclude in significant collateral damage.
- Derailed or dysregulated immune activation to SIRS without capability of ultimate pathogen clearance
- Silent, exhausted or suppressed phenotype promoting chronicity

How do Pathogens Modify the Immune Response?

Group a Streptococcus/GAS/, the Perfect Warrior and the Lonely Defense [1].

A Model to Demonstrate Pathogen Evasion Mechanisms and Immune Response Derailment

- **Capsule:** Prevention of C3 Deposition and Opsonization
- **CD44 on Epithelial Cells:** Mediates Adhesion
- **Cell Wall M Protein:** M1-Extracellular Sic /Streptococcal Inhibitor of Complement/, Disables Mac Associated Cell Lysis. There Are 80 Subtypes Based on M1 Variance, and M Protein Contributes to Delayed Manifestations Based on Molecular Mimicry.
- **Superantigens:** GAS is Equipped with 12 Different Superantigens that Bypass APCs, and Massively Stimulate Polyclonal T Cell Activation. SPE: B/ Streptococcal Pyrogenic Exotoxin / Activates pro IL-1beta, Eliciting TSS/Toxic Shock Syndrome/
- **Streptolysin O:** Massive Host Cell Apoptosis /Neutrophils, Macrophages/
- **Streptokinase:** To Lyse Fibrin Nets Created to Localize Infection
- **C5a protease:** Cleaves Anaphylatoxin 5a, Mediates Attachment

Effects are Diverse, Not Entirely "Suppressive", Enhancement of Inflammation and Obstruction to Phagocytosis and Killing.

Fine - Tuning Mast Cells is Essential for the Maintenance and Regulation of the Systemic and Immune Homeostasis [2].

- MCs Produce Mediators of Anaphylactic and Anaphylactoid Reactions
- **Classically Crosslinking IgE in Previously Sensitized Individuals:** fine particulate matter, various drugs, etc.
- Alternative MRGPRX2 receptors without previous need for sensitisation /nondepolarizing muscle relaxants,fluoroquinolones, vancomycin, substance P,etc/
- MCs /mast cells/ are Present in Abundance in Obese Patients Aggravating Immune Response, Wat /White Adipose Tissue/ Contains Increased Numbers with Significant Tryptase Activity.
- Underappreciated Role in severe Acute Pancreatitis
- **Secretory Products:** Tryptase participates beyond anaphylactic reactions in fibroblast proliferation and fibroblast migration, contribute to fibrosis via Tgf beta production
- In macrophage polarization in COPD /chronic obstructive pulmonary disease/
- Granzyme D in apoptosis and ROS production, decreased in TLR2 knock out
- **Histamine:** Sleep and wakefulness, Vaso - permeability, MDSC /myeloid -derived suppressor cells / and IL-10 promoter, part of tumour environment /MDSC, Mast cells, regulatory T cells/

Fine -Tuning Mast Cells is Essential for the Maintenance and Regulation of the Systemic and Immune Homeostasis

Mast Cells And the Heart, Infection

[1] **Pressure Overload of the Heart- Hypertension:** induces MC infiltration and proliferation, chronically leading to fibrosis and acutely to triggering ectopic pacemaker activity in assorted ways of arrhythmias and even coronary spasm, C5a induced apoptosis and coronary plaque rupture.

[2] **Brain:** increases BBB/ blood brain barrier/ permeability, perpetuating swelling, cell and toxin translocation.MC stabilization decreased the extent of brain swelling

[3] **Viral and Bacterial Infections:** Ambivalent: role in microbial clearance, but may worsen clinical picture by increasing airway reactivity and may serve as viral reservoir: HIV, EBV.

- Hormonal Interactions: MC Interacts with all Hormonal Systems.

  Acute stressors, via hypothalamic CRH /corticotropin releasing hormone/ and MC expressed CRH-Receptor mediate activation, degranulation, TNFalpha and IL-6 release, increased permeability, neuroinflammation.

- Mast cells stimulate aldosterone production influencing fluid, sodium, fluid and potassium homeostasis.
- Sex influences the immune response, but the reverse is true, as well. MCs are influenced by environmental endocrine disruptors, with a potential to switching phenotype.
- Even prenatal allergen exposure may influence adulthood social and sexual behaviour.

Innate Immune Recognition and Signaling During Times of Pandemic and Beyond from Intensive Care Perspective [3].

- SIRS may become a governing force of organ dysfunction during inflammation and sepsis
- While apoptotic cell engulfment by APCs is a relatively silent event, intracellular molecules released from injured and dying cells may trigger cytokine production.
- TLR4 engages in a particularly distinctive way in the manner, because beyond gram negative bacterial LPS recognition it serves as sensor for host damage associated triggers: Heat shock proteins, chaperon proteins, fibronectin, surfactant A, HMGB1, S100, etc.
- TLR4 engagement leads to triggering and aggravating many aspects of immune response via intracellular mediators: IL1beta, IL-6, TNF alpha IFN I, MHCI, II, costimulatory molecules, internalization, ROS activation.
- Balance between deleterious hyperinflammatory response and pathogen clearance may be tilted towards the former, creating significant collateral damage.
- While a proinflammatory environment is required for pathogen clearance, an overactive, overwhelming response- a cytokine storm- creates accessory injury. Primarily neutrophil mediated ROS production aggravates collateral damage and primes adaptive T cells for a immunosuppressive phenotype.

TLR4: Ischemia- Reperfusion Injury

- Ischemia- reperfusion injury: reperfusion injury worsens infarct size/ calcium overload, opening of mitochondrial permeability pores, oxidative stress, SIRS/.
- TLR4 engagement is present and inhibition leads to partial restoration of organ function, partial rescue of hippocampal neuronal death during global cerebral hypoxia.
- Coronary artery occlusion and reperfusion followed by apToll /small TLR4 inhibitor RNA/protected pigs form myocardial injury, dampened inflammatory cytokines, improved left heart function.
- Low grade TLR4 activation is needed for wound healing, oligodendrocyte differentiation, and osteoblast formation, but overt activation however leads to fibrosis.
- Sensing DAMPs triggers a profibrotic environment.

Portrayal of Multitasking Complement Regulator one in Critical Illness [4].

- CR1 or CD35 is a Phagocytic and complement regulatory protein in surface bound and soluble form.
- Provides assistance to pathogen and damaged self-engulfment / housekeeping/ and clearance by promoting adhesion and opsonization with limited proinflammatory potential.
- **Multiple recognition properties:** MBL, C1q, C3b and C4b fragments.
- With cell protective properties on erythrocyte surfaces and as immune-complex transporter, with age-dependent depletion in levels.
- Interaction with CRP +antigen/phosphatidylcholine of microbes, apoptotic cell membranes and nuclear antigens/ complexes in carriership to the spleen, **engagement with MDSC!!!**
- Insufficiency leads to dysregulated immune response, uncontrolled inflammation and impaired pathogen clearance.
- Highlights the importance of phagocytosis, and erythrocyte mediated clearance mechanisms in the immunity against pathogens , in controlling the extent of ischaemia reperfusion injury and SIRS.
- Primes B cells for somatic hypermutation and affinity maturation /with TLR4/
- Recombinant sCR1 with relatively shorter half-life, therefore more favourable therapeutic profile, in comparison to immunoglobulin derivatives, extensively studied in animal models, less in human ischmia-reperfusion injury with protective results.
- **St. Mutans Evasion Mechanisms:** disabling C3b deposition and CR1/CR3 mediated phagocytosis
- Phagocytosis may support survival of intracellular organisms
- **Involvement in Renal Failure:** comprehensive immuno-pathological characterization of many faces of AKI hasn´t been done yet.
- Hemodialysis patients demonstrate worse outcome that is associated with low CR1 levels. Continuous tick over activation of C3 on activating surfaces may represent a not desirable caveat in haemofilter application. Fortunately, the selective membrane permeability allows filtration of small complement components with anaphylactoid properties, such as C3a, C5a,

Cardiorespiratory Arrest, the Unmet Challenge [5].

11% out of hospital arrest survival

25% in-hospital arrest survival

18-40% of survivors demonstrate poor functionality

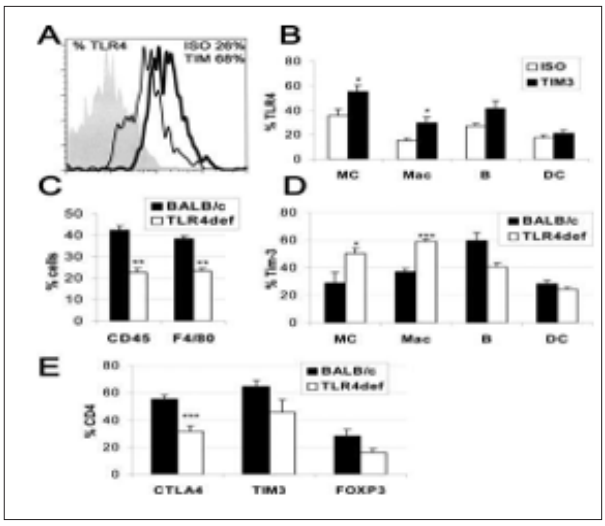
Brain receives 20% of cardiac output, as little as 30 seconds is sufficient for the emergence isoelectric eeg, that is cessation of brain activity.

- Ceased ATP production, SIRS, glutamate, membrane disintegration, apoptosis, swelling, discordant electric activity, collapse of vascular autoregulation.
- TLR4 mutant or deficient mice demonstrate better survival / 53% vs33%/ with diminished cell apoptosis
- C5a or C5aR blockade: murine ischemic stroke: decreased infarct volume, neutrophil influx, injury size
- MC/mast cell/ cell deficient and cromoglycate treated mice showed less cerebral swelling upon MCA/middle cerebral artery / occlusion

Apoptosis, SIRS, ischemia/reperfusion, energy depletion are major determinants of outcome- are they therapeutically addressed?

Cutting Edge: Cross-Regulation by TLR4 and T cell Ig Mucin-3

Determines Sex Differences in Inflammatory Heart Disease [6].



TLR4 and Tim3 participate as proximal and continuous contenders during the immune response to stimulation.They influence the extent and the phenotype of pathology in CVB3 myocarditis. Males present with an enhanced pathology, where TLR4 and IFN-gamma are increased, while females have a Tim3 and IL-4 dominant phenotype. Proinflammatory TLR4 and regulatory Tim3 crosstalk is demonstrated using TLR4 mutant mice and blockade using Tim3 MAB initially, with subsequent distinctive acute pathology.

Monoclonal Antibodies in ICU Management of Sepsis, Matters of Affinity, Targeting and Specificity [7].

Indication of polyclonal antibodies: sepsis with hypogammaglobulinemia, usually a mix of antibodies with low affinity, low specific concentration obtained from many healthy individuals and to create a background antibody defensive environment for patients with low immunoglobulinémias.

MABs act via neutralization, opsonization and phagocytic enhancement, antigen antibody complex formation for clearance, by mediating antibody dependent cellular cytotoxicity, by enhancing degranulation

1The Therapeutic and Preventive Potential of Monoclonal Antibodies in Sepsis

- Targeted at pathogen, HIV, SARS Cov-2, neutralizing antibodies to prevent entry to the host cell, therapeutic and preventive
- Targeted at immune modulation/ anti IL-6, checkpoint inhibitors/
- **Therapeutic Drug Carriership:** rifampicin linked to MABs / monoclonal antibodies/ to provide intracellular transport for intracellularly residing staphylococci.
- **Targeting Toxin Production:** Bezlotoxumab against Clostridium difficile toxin B.

2Diagnostic Monoclonal Antibodies: Well Established Applications.

3/Limitations: Pathogens Display an Array of Antigens each with Several Epitopes. Thereby a Cocktail of Monoclonal Antibodies would have Enhanced Efficacy.

- MABs may potentially have a long half-life, and with strong binding affinity their effect may be present well beyond need and positive potential
- MABs act on pathogens prior internalisation, upon engulfment such effect is not attainable. They may mediate immune pathology via anaphylactic reactions, via induction of overt cytokine production and in large doses likely suppress B cell function.
- High cost due to advanced technologies.

Phagocytosis: The process of engulfment, processing and presentation of microbes, which is accompanied by variable levels of inflammatory response

Targeted towards clearance of host debris and invader pathogens, while the former is constitutive, the latter is induced.The complement system provides important house -keeping functions. Phagocytosis is mediated by opsogenic and non-opsogenic receptors, that chiefly prime the cells to become phagocytic. TLR4 has been shown to internalize and participate in inducing MHCII presentation.

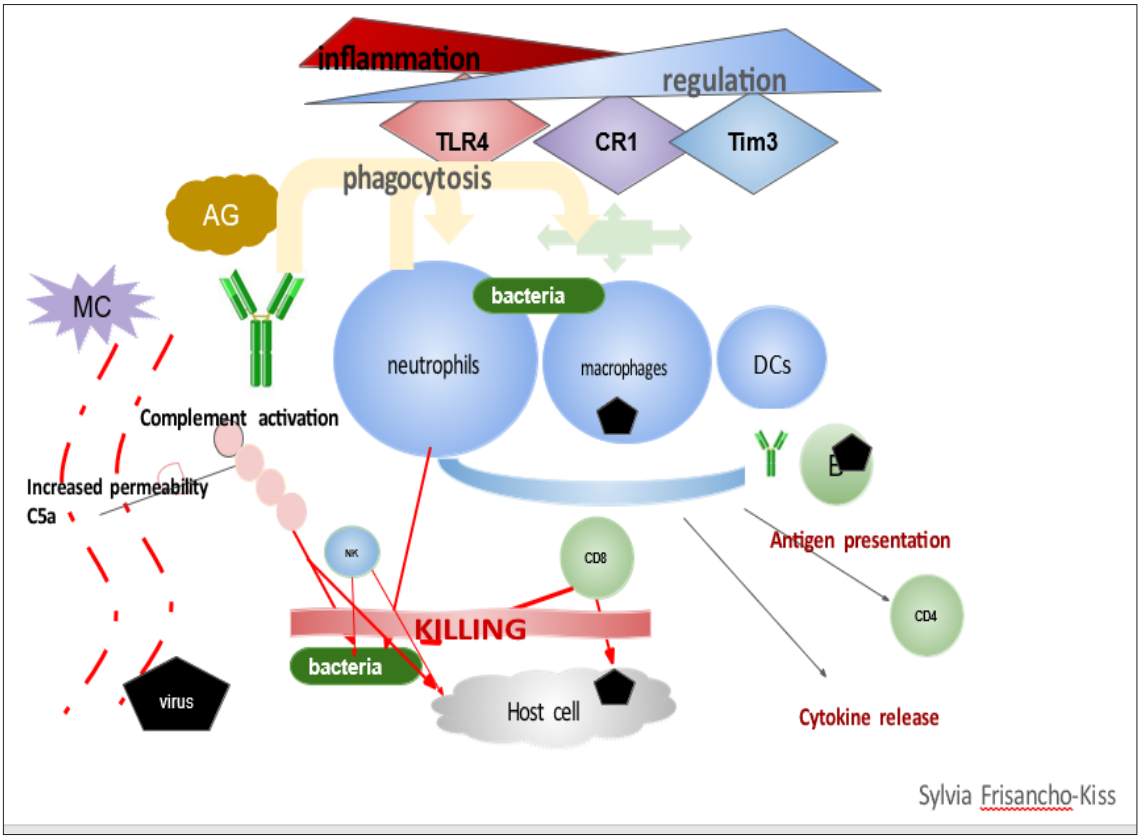
CR1 behaves as mediator of adherence, via high affinity towards C3b and C4b coated surfaces., but MBL, CRP and C1q, too are recognized by CR1 molecule.

Bacteria May Evade Phagocytosis: Klebsiella pneumoniae via capsule, Staphylococci via Staph pain B, cleaving CD11b from neutrophil surfaces.

Potential Mediators of Immune Pathology

- **Phagocytosis:** ROS production, NET production
- **CD8 Mediated Killing:** perforin, granzyme B
- Complement mediated killing (MAC)
- C5a and MC mediated increased vascular permeability, swelling, extravascular fluid retention
- Targeting intracellular pathogens/viral and bacterial/ inevitably lead to host cell elimination
- High neutrophil turnover / half-life 3 days and NET formation with proinflammatory properties.

- Mechanisms of molecular mimicry, particularly in recall responses
- Energy depletion
- **Viral Cytokines:** IL-10, pathogen evasion mechanisms.
- **MDSC formation:** CRP, Th2 related cytokines /IL-4, IL-10/.
- Regulatory T cell emergence. Upon CR1 engagement
- **Ischmia Reperfusion Injury:** higher complement activation in non-survivors
- **Lack of Regulators:** Tim-3, CR1



Effect of Organization, Hygiene, Monitoring and Stress on Patient Safety the Old Friend's Hypothesis or Viral Regulation of the Host Immune Response [8].

- The vast majority of ICU admitted patients with and inflammatory origin or comorbidity in my experience presented with an innate neutrophil phenotype that lacked stimulatory capacity and with a minute, albeit increased numbers in CD4 regulatory T cells.
- Why would such phenotype emerge initially?
- A plausible hypothetical explanation would be the old friend's hypothesis.
- While the bacterial pathogens patients are exposed are diverse, for the exception of few "rare" outliers there is a limited number of identifiable pathogens circulating in our regular community and healthcare environment. As per later, they may evolve and gain antibiotic resistant phenotype.
- For the purposes of innate immunity and for adaptive immunity in part, many constitutive component and features of pathogens are steady.
- An adaptation of the old friend's hypothesis is when a person is exposed to a pathogen orally that is not pathogenic via GIT route per se, a regulatory immune response may emerge. Similarly to oral desensitisation for allergens.

Effect of Organization, Hygiene, Monitoring and Stress on Patient Safety the Old Friends Hypothesis or Viral Regulation of the Host Immune Response

- While many viruses upon host encounter seasonally come and go,
- Several more conserved viruses integrate to host environments genomically or via episomes, where they behave silently, and re-activate periodically.
- 8-10% of our genome consists of retroviruses, that have become integral to self during evolution. They may produce viral particles, causing damage to the host and can divert the immune response,

- SSPE /subacute sclerosing panencephalitis/: morbilli, nowadays rare due to immunization.
- SSPE evolved decades after initial infection by morbillivirus, and led to irreversible, progressive, demyelinating brain damage. No infective virus had been found in the brain, but viral particles, that were sufficient to elicit degenerative and destructive pathology were recovered.
- A number of progressive disease phenotypes are currently not explained scientifically.
- One prominent example is ALS/amyotrophic lateral sclerosis/. If we are retroviruses in essence in a significant extent, do we have the answer whether they can behave upon the proper stimuli similarly to the paramyxovirus morbillivirus.

Environmental and social stress disturbs the host in many ways. And while a conditioning level of stress is desirable to develop resistance and coping mechanisms and strengthen the body and the soul, overt and cumulative stressors frequently lead to severe psychosomatic disorders.

Viruses, that are embedded in our cells may become reactivated upon stressors, upon activation they elicit disease by either direct pathogenic mechanisms, or by deterring the immune response in a number of ways.

Two prominent, deceptive players are DNA viruses EBV and CMV. Both are present in the cells in latent forms and generally the activation emerges in "immune suppressed" host, however alternative more subtle ways or immune suppression may also lead to reactivation. Stressors are the major contributors to reactivation.

EBV is more worrisome clinically, because it is "less appreciated "by clinicians, due to lack or solid applied scientific background knowledge of the many faces of the virus. The state of viral reactivation in form of circulating DNA is seldom examined and upon accidental discovery, there is no antiviral treatment available. Frustratingly, after treatment the virus still retrieves to a silent, intracellular, episomal phenotype.

Conclusions: What can We Propose in Order to Create Change?

- Monitor, in order to understand the in vivo immune response, tissue damage signals and pathogen loads in time, we are in the beginning of the effort.
- Adapt basic scientific knowledge gained in vitro, in animal models in artificial systems, translational immunology
- Understand the indirect effect of our interventions on the immune system
- Understand the effect of pathogens on the immune response, how they shape and evade the immune response
- **Influence The Immune Response:** using existing therapies
- Sirs, Diminish Early with Short Term, Tailored Therapy: TLR4 inhibition.Decreased binding of damage associated molecules/HMBG1, HSP/, stop dividing forces
- Substitute immunoglobulins primarily in immune deficiencies, either inborn or acquired , for example due to EBV carriership.
- **Enhance Phagocytosis:** using; low dose immunoglobulins
- Decrease permeability and anaphylactic potential: using C5a inhibitors
- Supplement immediate energy requirements using creatine phosphate
- Suggest novel therapies, based on thorough evaluation using translational immunology
- Indicate and follow therapies based on monitoring.

Conclusions

What is Holding us Back?

- The competitive, rather than cooperative phenotype of healthcare providers, scientific societies, professional organisations and cultures.
- The fear of increased health care related costs
- Lack of vision, lack of sharing technologies and knowledge.
- Fear of inconclusive results, unsubstantiated fear of non-sustainable results, obtained in artificial systems.
- Reluctance to adapt.
- Lack of professionals with combined specialties and lack of crosstalk
- Ill-defined goals and priorities
- Lack of resources

Translational immunology, looking at non-conventional clinical pathologies in human subjects may open new horizons. In ultimately humble outcomes, if no liveable therapies were found, even then, simple scientific understanding is a gain without doubt.

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