ADVANCE IN SEPSIS MANAGEMENT

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Lt Col

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11 Oct 18

"Sepsis is a global healthcare problem. It is more common than heart attack, and claims more lives than any cancer, yet even in the most developed countries fewer than half of the adult population have heard of it. In the least developed countries, sepsis remains a leading cause of death.."

– Global Sepsis Alliance

U-Tryp
Ulinastatin
U-Turn Towards Life

ADDRESSING
UNMET NEEDS
IN MANAGEMENT OF

SEPSIS

MAGNITUDE OF THE PROBLEM

300/100,000
GLOBAL SEPSIS INCIDENCE RATE

40%
OF ICU ADMISSIONS ARE SEPSIS PTS.

>70%
OF SEPSIS POOL ARE SEVERE SEPSIS CASES

RECENT UPSURGE

- Dramatic annual increase of 8-13 % over last decade[1]
- Hospitalization rate for sepsis has more than doubled over the last 10 years[1]

PRIMARY SOURCES OF INFECTION

- Pneumonia
- Respiratory infection
- Abdominal infection
- Trauma & Wounds
- Catheter infection
- Urinary Track infection

ALRMING MORTALITY RATES

- Mortality is between 30% and 50 %, with deaths for septic shock being close to 85 %
- Every hour 36 patients die of sepsis

MANAGEMENT CHALLENGES

- Effective Antibiotic Cover for MDR infections
- Incorrect/delayed Diagnosis by physician
- Variability in Patient Response to treatment
- Cost of Therapy - a key challenge

CONSIDERING 300/100,000 INCIDENCE → **PATIENT POOL 20,000,000 CASES/YR**

(1)Angus, DC et al. *Critical Care Medicine*. 2001; 29:1303-1310 (2) World Sepsis Day Factsheet

U-Tryp
U-Turn Towards Life

"CYTOKINES STORM"

- Cytokines are signaling peptides, proteins, or glycoproteins, involved in either augmentation or suppression of inflammation that occurs in response to pathogens, non-self molecules or toxins.
- Several cells release cytokines including immune, epithelial, endothelial, and smooth muscle cells.
- Any impairment in cytokine production leads to uncontrolled inflammation within tissues and key organs, termed as a "cytokine storm"

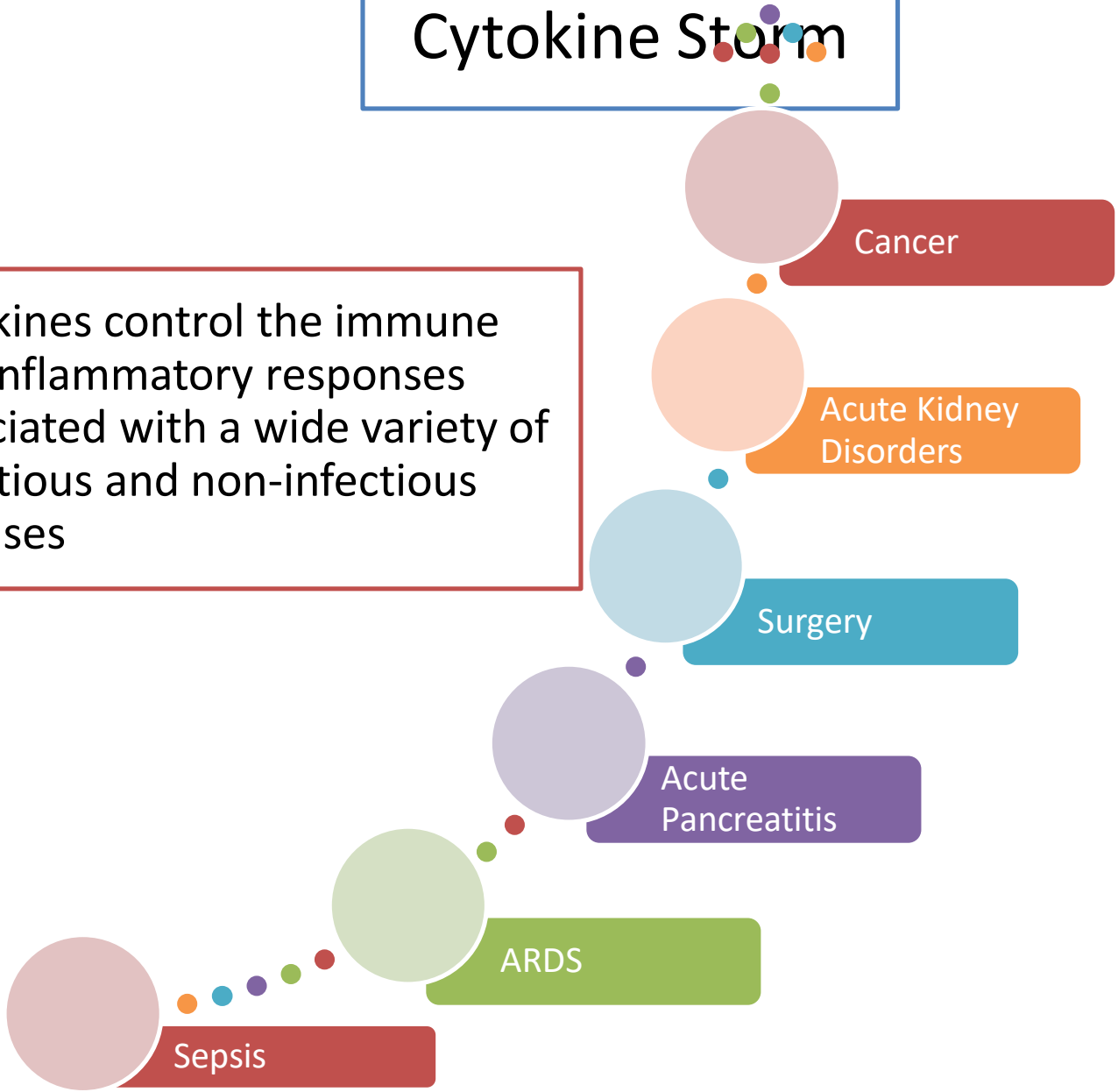
Table 1: Major types and actions of cytokines

Type	Actions
Interferons	Regulation of innate immunity, activation of antiviral properties, antiproliferative effects
Interleukins	Growth and differentiation of leukocytes, many are pro-inflammatory
Chemokines	Control of chemotaxis, leukocyte recruitment, many are proinflammatory
Colony-stimulating factors	Stimulation of hematopoietic progenitor cell proliferation and differentiation
Tumor necrosis factor	Proinflammatory, activates cytotoxic T lymphocytes

Source: Jennifer R. Tisoncik JR, Korth MJ, Cameron P. Simmons CP, Farrar J, Martin TR, Katze MG. Into the Eye of the Cytokine Storm. *Microbiol Mol Biol Rev*. March 2012;76(1):16-32.

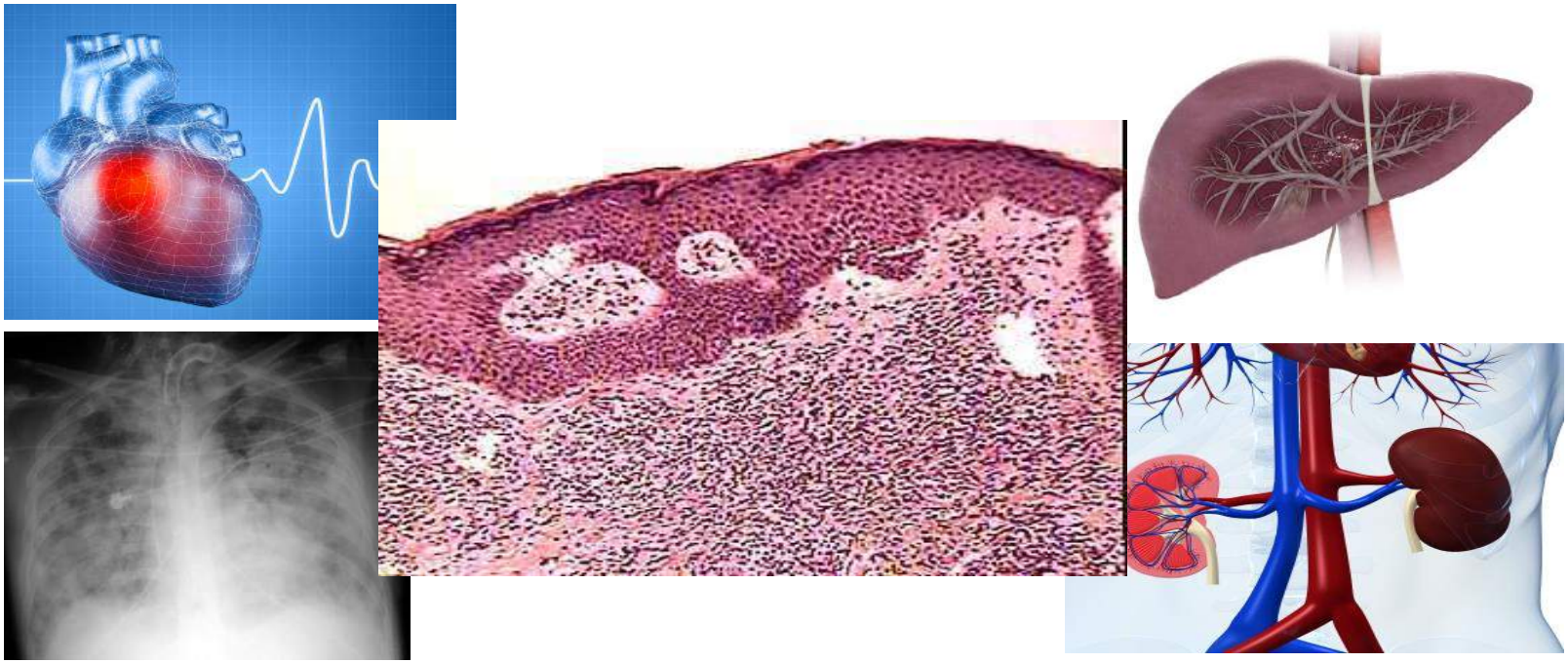
Cytokine Storm

Cytokines control the immune and inflammatory responses associated with a wide variety of infectious and non-infectious diseases



Cytokine and Cell-Mediated Organ Injury

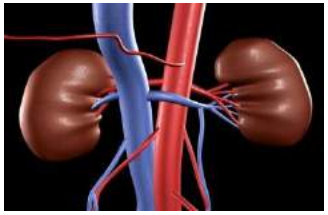
This leads to "Immune Confusion" and widespread inflammation with white blood cells infiltrating and damaging innocent bystander organs causing organ damage/failure

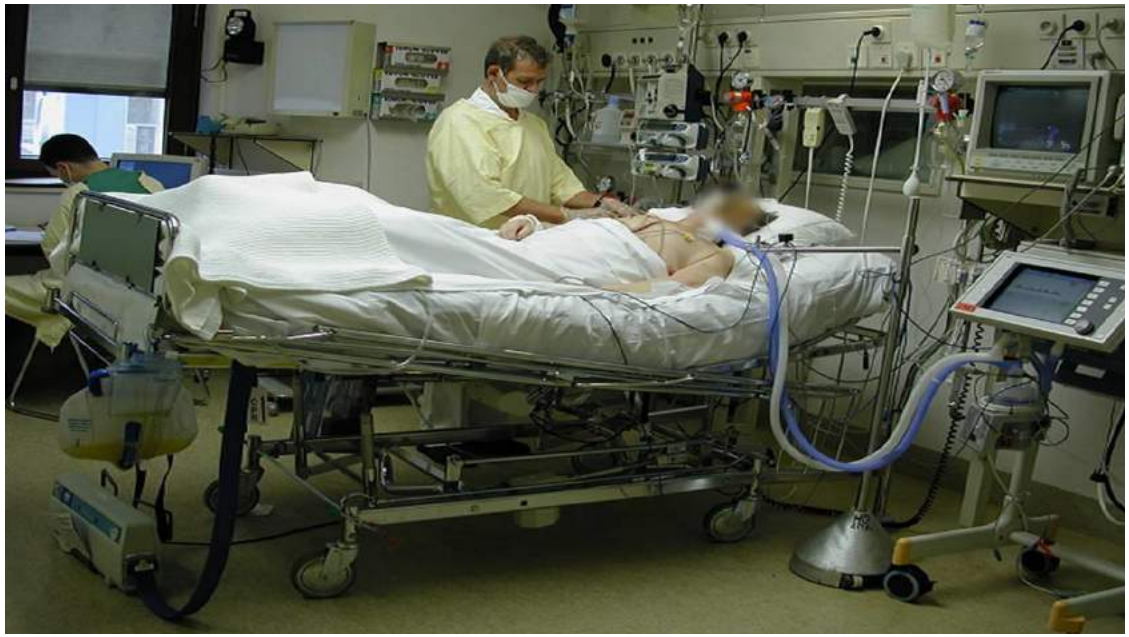


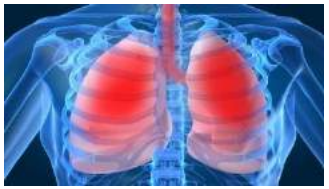
Role of cytokines during inflammation and infection

Organ Failure is the Top Cause of Death

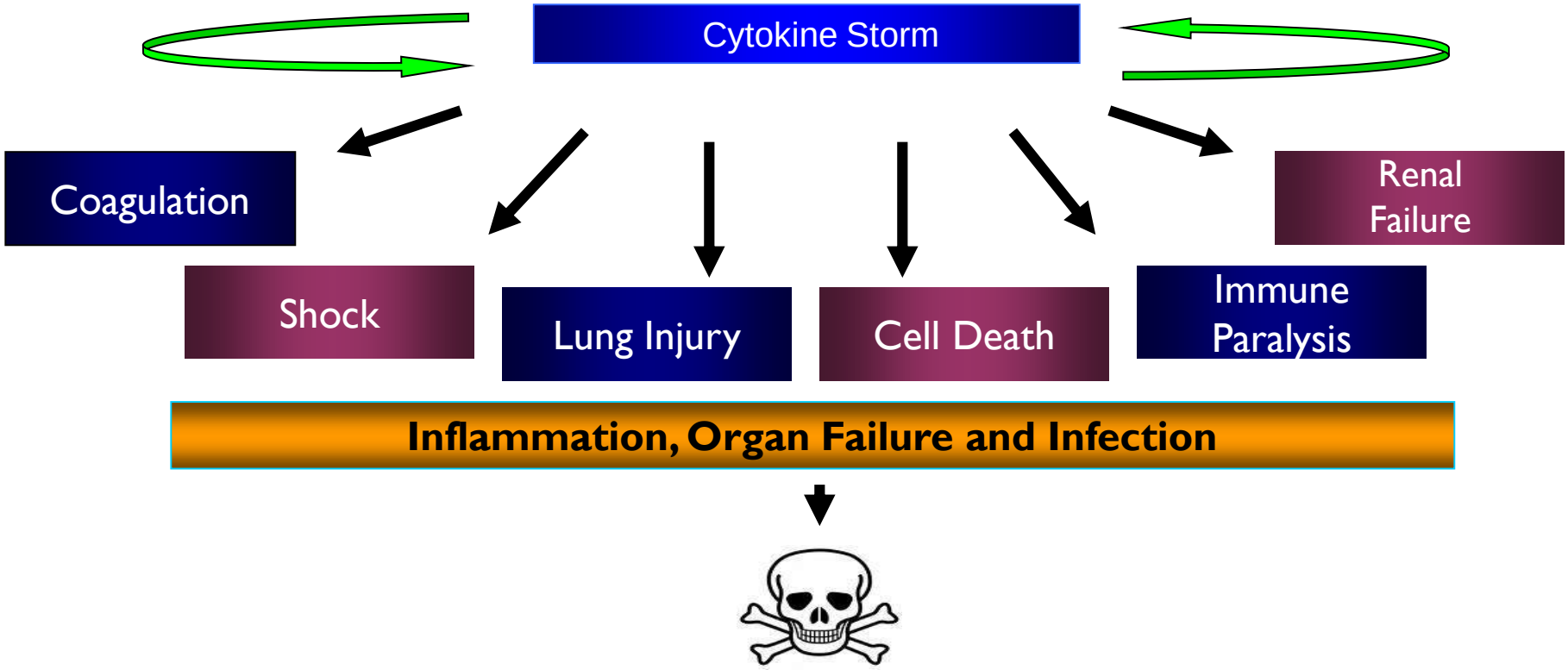
Organ Failure is responsible for nearly
50% of all deaths in the ICU



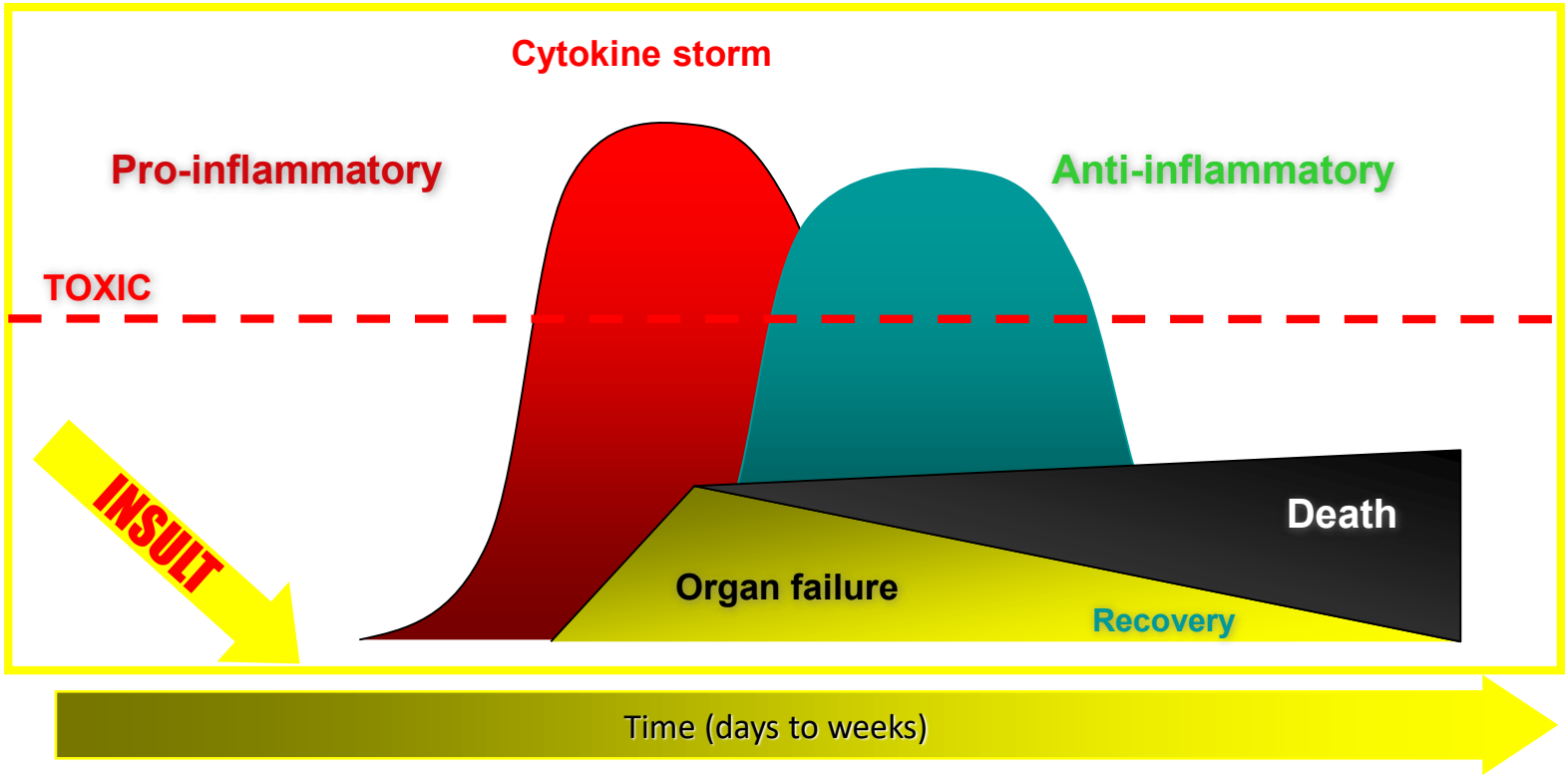




Cytokine Storm Causes Direct Organ Injury



Cytokine storm causes MOF



Gaps in Existing Therapies

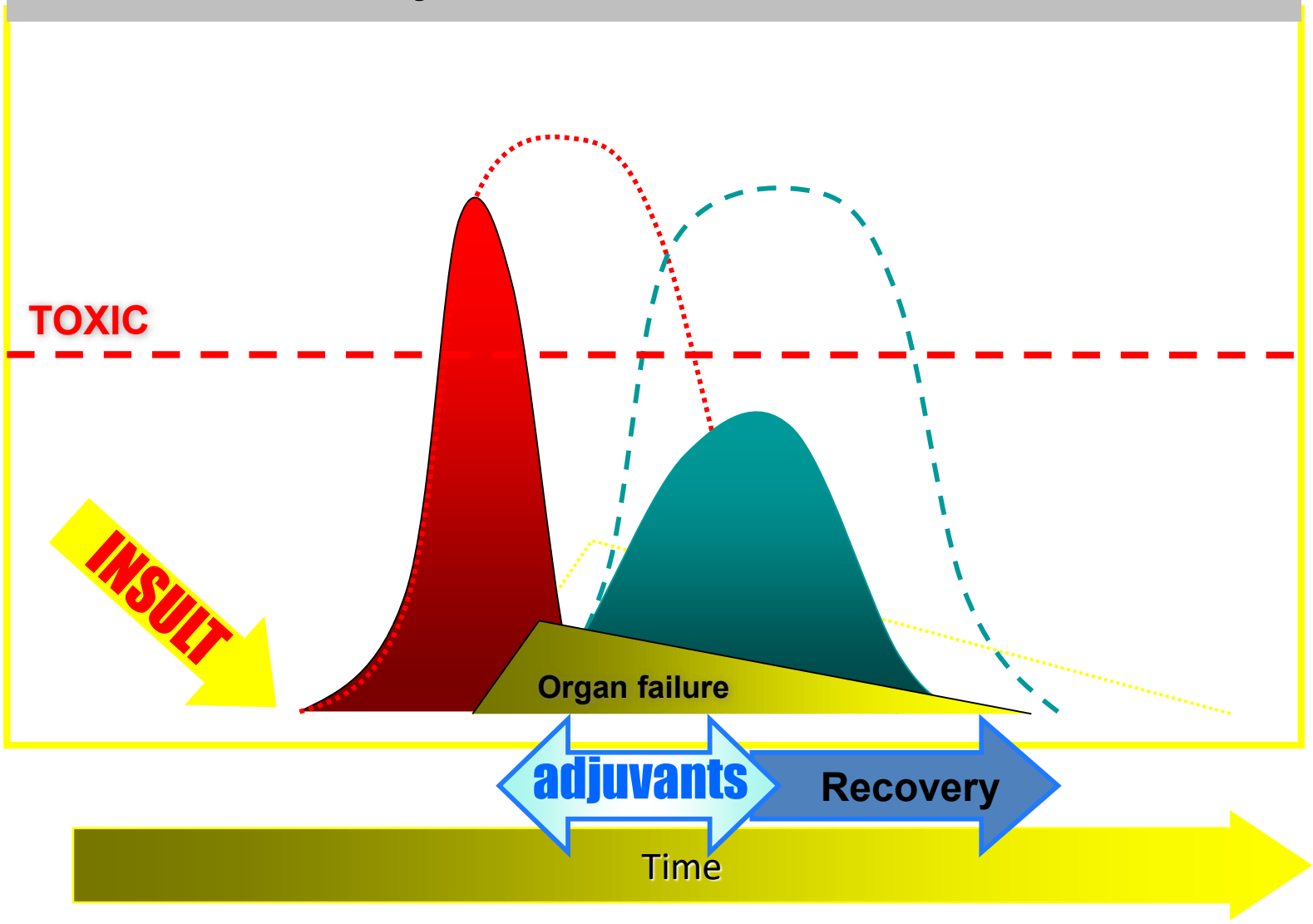
- Sepsis is regarded as a leading cause of morbidity and mortality throughout the world.
- Although bacteria play a leading role in sepsis, the direct cause of death in patients is not mere bacteria but rather the paralysis of the immune system and the systemic inflammatory response.
- Antibiotics & supportive ICU care are the only available routes of management for Sepsis.
- Many Anti inflammatory therapies have been introduced in the past but could not appeal due to their adverse events

Why Adjuvant Sepsis Therapy?

- an effective antibiotic therapy can not stop the septic process (domino effect)
- on the contrary: an effective antibiotic therapy can lead to an increased toxin release
- intensive care measures are symptomatic
- intensified use of invasive techniques
- increasing age of patients
- increasing severity of illness

Sepsis incidence and mortality are still high !

Organ-protective effect through controlled reduction of cytokine levels



Need for the Better Drug

Because treatment options like antibiotics that currently exist cannot

effectively treat sepsis infection there arises an urgent need to find a new

way to enhance the immune response and adjust the inflammatory

Reaction.

Drug which can reduce …

Mortality

Morbidity


U-Tryp
Ulinastatin
U-Turn Towards Life

Need for a Better Drug: U-Tryp

Because treatment options like antibiotics that currently exist cannot effectively treat sepsis infection there arises an urgent need to find a new way to enhance the immune response and adjust the inflammatory reaction

U-Tryp emerges as a "rescue" therapeutic option in Sepsis. It not only inhibits inflammatory markers but also promotes homeostasis and assists in immune modulation to prevent SIRS progression to multiple organ dysfunctions.

U-tryp also provides the following benefits in Sepsis:

- Reduces 28 day mortality in severe sepsis patients
- Reduces Duration of mechanical ventilation and Hospital stay thus reducing cost of care

U-Tryp: Introduction

Ulinastatin is a kind of glycoprotein extracted from human urine which acts as a Urinary Trypsin Inhibitor (UTI).

Physical Information:

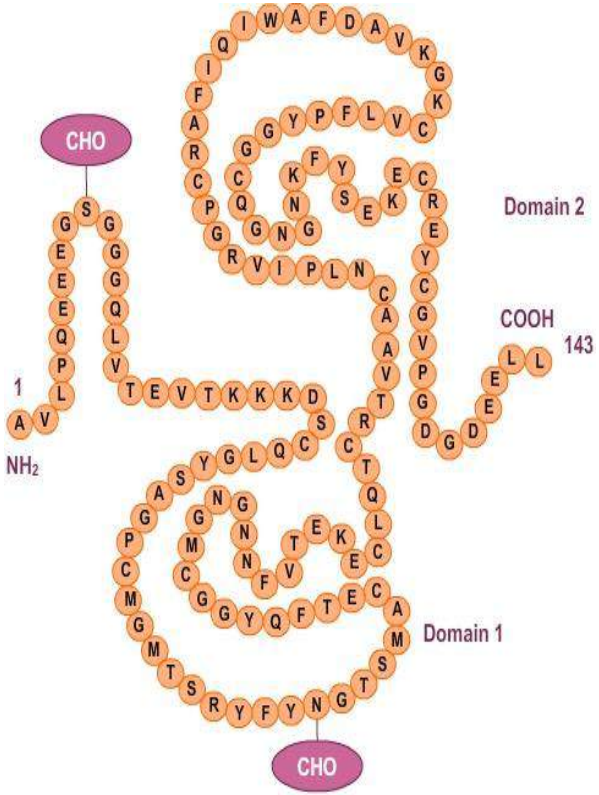
Ulinastatin for Injection is available as a clear, colourless liquid. It contains UTI of not less than 45,000 units per ml and not less than 2500 units per mg protein.

Chemical Information:

Molecular Weight: Ranges from 62 kDa to 72 kDa

Pharmaceutical Information:

Appearance: White or light yellow lyophilized powder or clear colourless liquid
pH: 6-8
Sterility: Sterile
Assay: 90% to 110% of label claim
Shelf life: 2 years under the storage conditions at 2°C-8°C



STRUCTURE OF ULINASTATIN

Indications

- Severe Sepsis
- Acute Pancreatitis

Mode of Action

U-Tryp Mode of Action

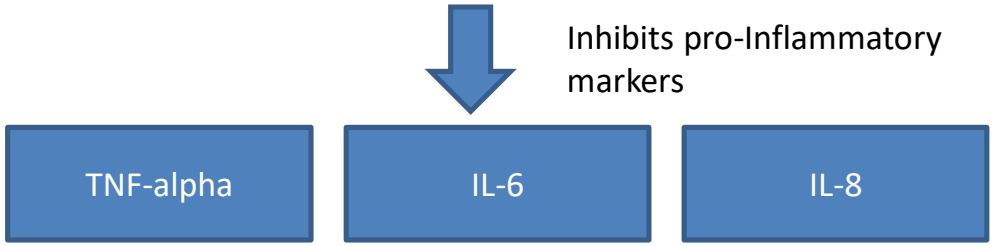
Inflammation

- Inhibition of the cytokines, reduction in the levels of TNF-α and Interleukin-6
- Suppresses the activity of neutrophil elastase and prevents the incidence of DIC
- Prevents progression to MOD's in Sepsis
- Reduces Polymorphonuclear Elastase levels and prevents new onset organ-dysfunction

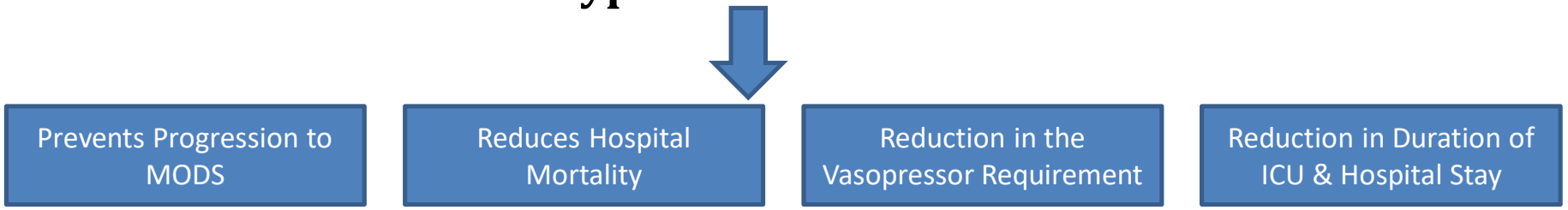
Coagulation Cascade

- U-Tryp also normalizes coagulation functions
- The PMNE (Polymorphonuclear Leukocyte Elastase) concentration correlates with the activities of coagulation and fibrinolysis.
- Ulinastatin inhibits PMNE release from granulocytes stimulated by several pathologic inflammatory processes; thus inhibiting the process of coagulation and fibrinolysis
- It acts on both thrombin and fibrin and hence balances the coagulation cascade

Direct Action: U-Tryp effectively controls Hyper-Inflammation



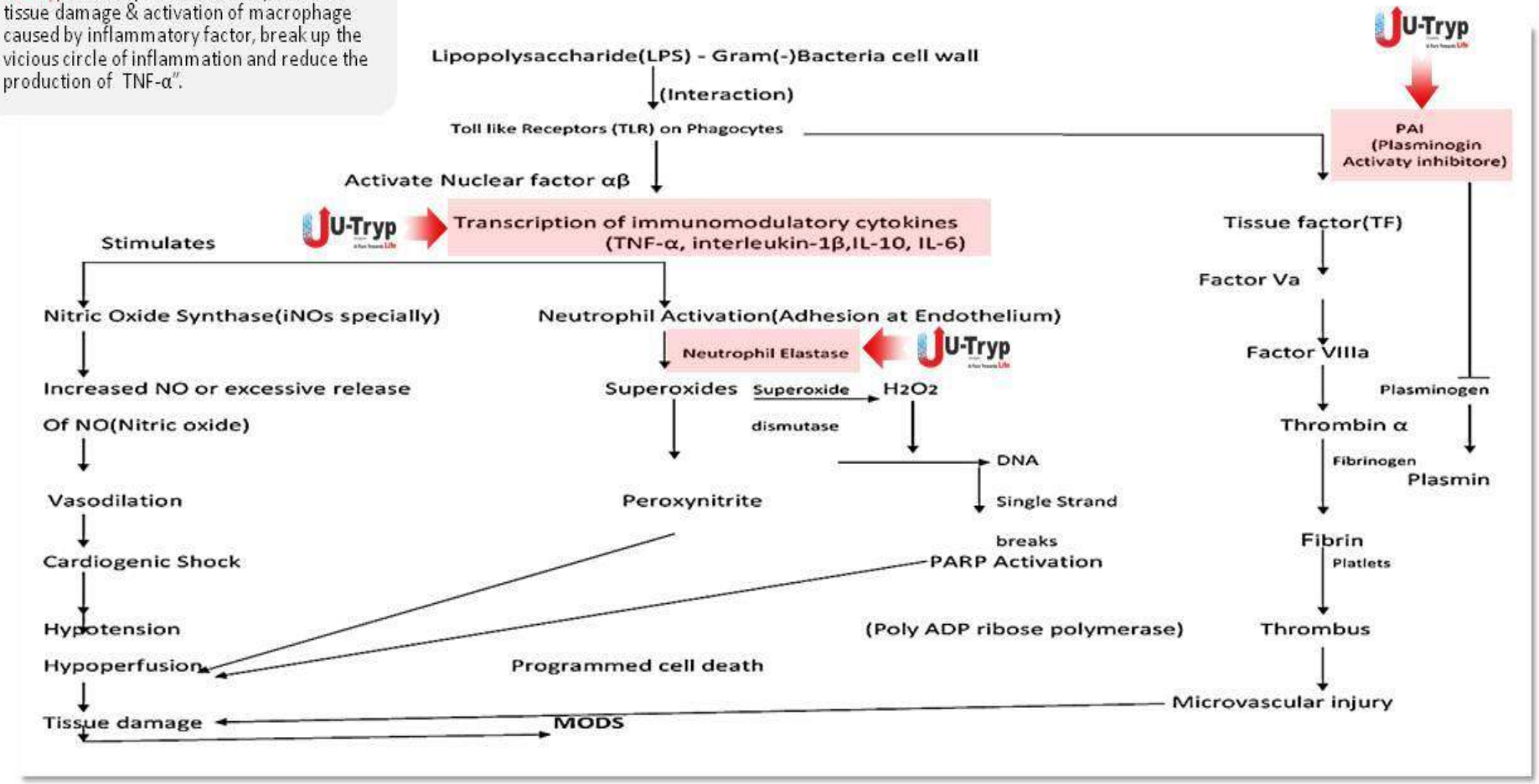
U-Tryp: Indirect Benefits



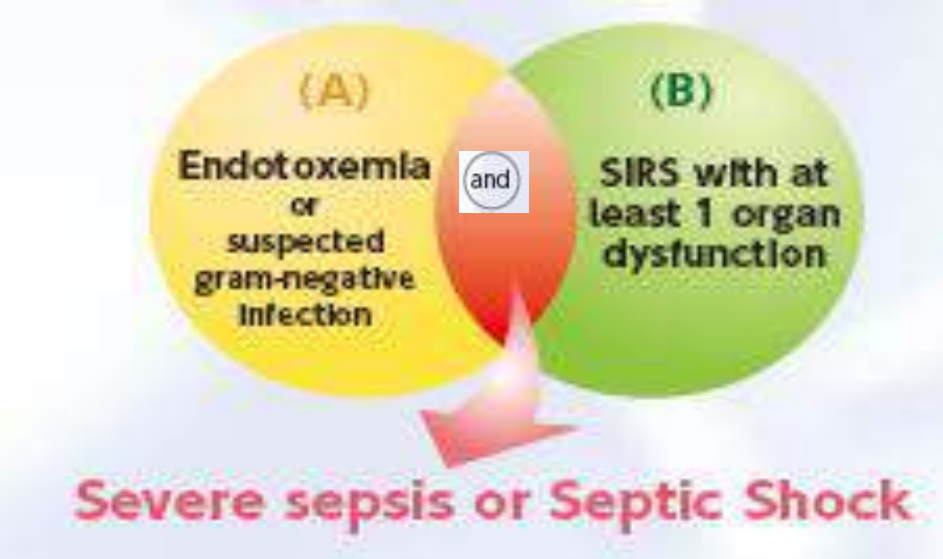
U-Tryp - ROLE IN SEPSIS

"U-Tryp inhibits protease activity, reduces tissue damage & activation of macrophage caused by inflammatory factor, break up the vicious circle of inflammation and reduce the production of TNF-α".

"U-Tryp inhibits PMNE release from granulocytes stimulated by several pathologic inflammatory processes; thus inhibiting the process of coagulation and fibrinolysis"



Utryp: Target Patients



Treatment of Sepsis or Septic Shock patients who fulfill the following:

Endotoxemia or suspected gram-ve bacterial infection

&

SIRS with at least 1 organ dysfunction

Effect of various Protease Inhibitors on inflammatory Mediators

Drug	TNF	IL-6	IL-8	CRP	Others
Aprotinin		+	+		
Gabexate mesylate	++	+			
Nafamostat	+	+			
Ulinastatin (UTRYP)	+	+	+	+	**IL2 and interferon Gamma**

(Journal of Gastroenterology and Hepatology **29** (2014) 1328–1337)

Ulinastatin (UTRYP) rationale

- Adjunctive therapies are indicated in the profound septic shock, indicated by high vasopressor requirement and multiple organ failure with at least two organs involved
- No improvement within a few hours after the commencement of resuscitation and antimicrobial therapy
- PCT values remain unchanged or increase in addition to not improving clinical conditions.

Ideal time to start adjuvant therapy

•Within 24 hours of diagnosis of sepsis

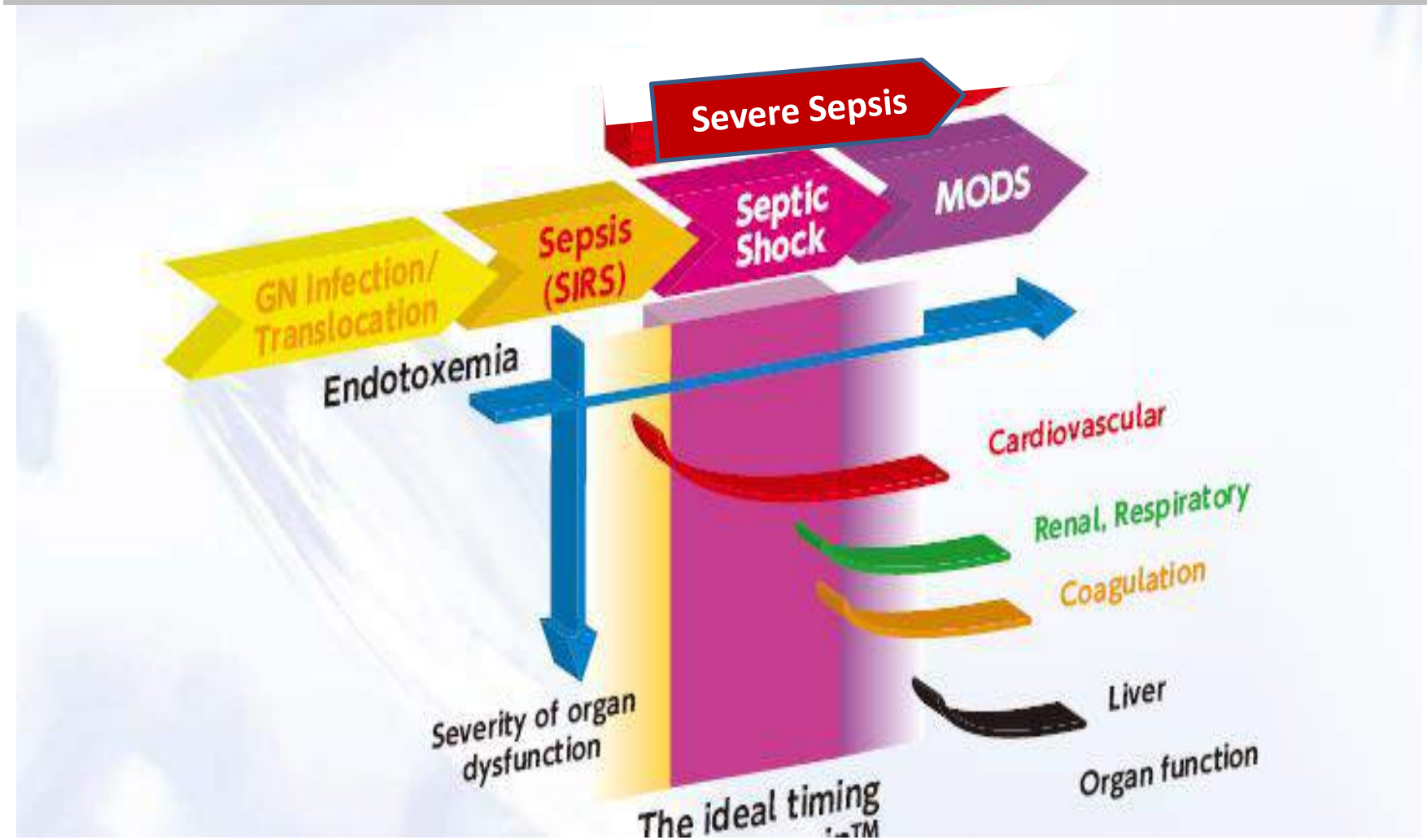
OR

•As early as possible after the onset of septic shock

OR

•Earlier in selective high risk group

Ideal Timing



When will you think about adjuvant therapy - Disease Dynamics

- Severe infections
- Selective severe infections
- Sepsis
- Septic shock
- Refractory shock

Ulinastatin (UTRYP DOSE – TIMING)

- High risk of death - Any of the following:
  - APACHE II ≥ 18

    APACHE II score >20 or one organ Failure

- Sepsis-induced organ failure
  - Septic shock
  - Sepsis induced ARDS
  - Sepsis induced DIC

- No absolute contraindications

- Weigh relative contraindications

Thymosine α1 & UTI strategy for Sepsis from Intraabdominal infection due to carbapenem resistant bacteria

The combination improves survival for patients infected with carbapenem resistant bacteria

Ying Z, Hao C, Yu L, Shu Z, Ya C, Lan L et al

(The Journal of Infectious Disease 2008;198:723-30)

UTI an alternative therapy for Inflammatory disorders

UTI has “rescue” therapeutic potential against endotoxin related inflammatory diseases as DIC, ALI, acute liver injury etc.

Ken-ichiro I, Hirohisa T Tokyo, Japan www.intechopen.com

SEPSIS

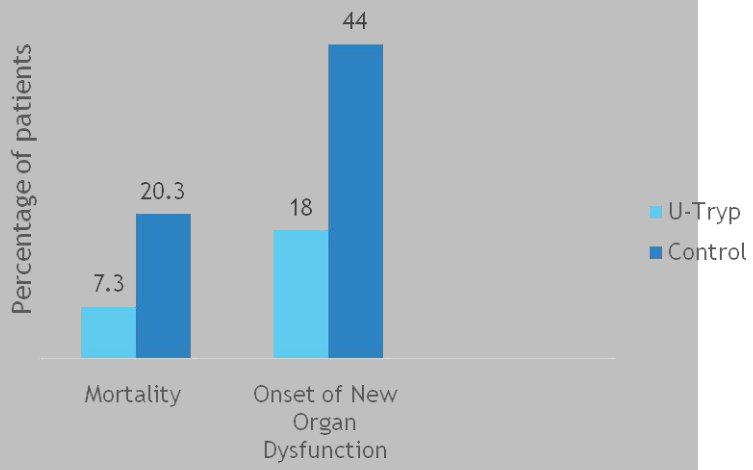
Indian Journal of Critical Care Medicine
Retrospective Study
First Author: Y.Mehta, 2014
n=100 patients with Severe Sepsis
50 Patients received U-Tryp 200000 units for 5 days along with antibiotics & standard care
50 patients received antibiotics and standard care

Key Observations:
Significant Reduction In APACHE II Score & SOFA Score Post Therapy in observed in U-Tryp group
12% Survival benefit observed with U-Tryp

SEPSIS

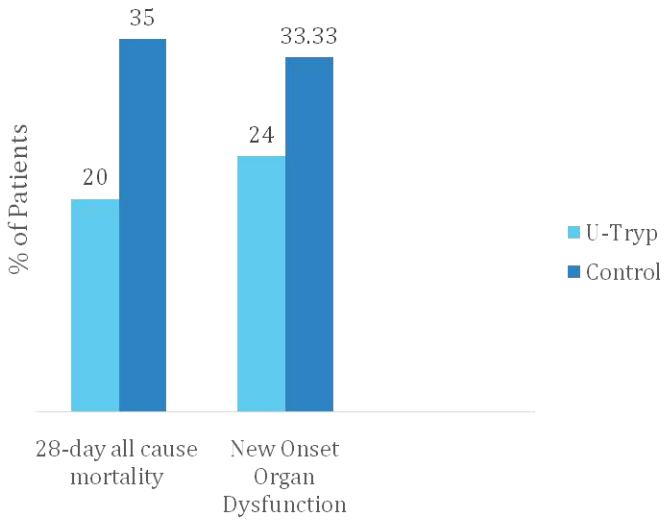
Intensive Care Medicine
Randomised Controlled Trial
First Author: Dilip R Karnad, 2014
n=114 Severe Sepsis Patients
55 Patients received U-Tryp 200000 units for 5 days along with antibiotics & standard care
59 Patients received Placebo

Key Observations:
Significant reduction in 28 day all cause mortality, 13% absolute mortality reduction
Significant reduction in New Onset Organ Dysfunction, 26% absolute reduction with U-Tryp



SEPSIS

European Congress of Clinical Microbiology & Infectious Disease
Observational Study,
1st Author: Y. Javeri, 2015
n=220 patients
100 patients received Ulinastatin , other 120 patients formed control group



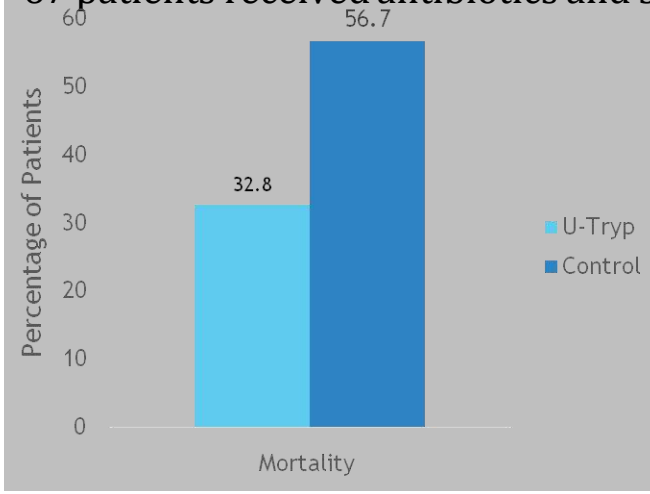
Key Observations:
-15% reduction in Absolute mortality
- 9.6% reduction in new onset organ dysfunction

SEPSIS

European Society of Intensive Care Medicine
Retrospective Cohort Study
1st Author: Y. Mehta, 2014
n= 134 Severe Sepsis Patients

67 Patients received U-Tryp 200000 units, twice a day for 5 days along with antibiotics & standard care

67 patients received antibiotics and standard care

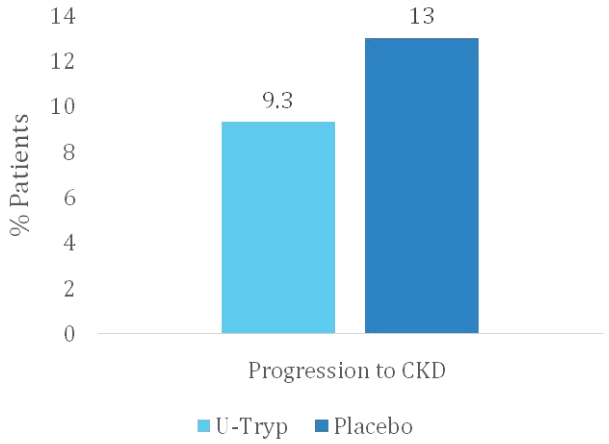


Key Observations:

1. 24% reduction in mortality in the U-Tryp group
2. Significant reduction in the duration of Vassopressor Requirement & ICU Stay
2. Significant improvement in SOFA Score (14%, p 0.003)
3.Significant improvement in Serum Creatinine levels

ACUTE KIDNEY INJURY

Nephrology Dialysis Transplantation 31 (Supplement 1): i147–i159, 2016
Retrospective Study
Ulinastatin: can it be the new therapeutic option in AKI?
1st Author: Sonia Gupta
n = 150 Acute Kidney Injury patients requiring ICU support
75 patients received 200000 IU U-Tryp thrice a day for 5 days



Key Observations:

- **Significant reduction in the duration of ICU stay observed ($p<0.01$)**
- **Significant reduction in the time to stoppage of renal replacement (<0.05)**
- **Lesser number of dialysis were required in the Ulinastatin group**

WJCCM World Journal of Critical Care Medicine

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.5492/wjccm.v3.i1.34

World J Crit Care Med 2014 February 4; 3(1): 34-41
ISSN 2220-3141 (online)

META-ANALYSIS

Ulinastatin for acute lung injury and acute respiratory distress syndrome: A systematic review and meta-analysis

Yu-Xin Leng, Shu-Guang Yang, Ya-Han Song, Xi Zhu, Gai-Qi Yao

Twenty-nine RCTs with 1726 participants were totally included, the basic conditions of which were similar

Oxygenation Index (WJCCM 2014)

- The basal oxygenation index in all studies were similar.
- After treatment with standard strategy or ulinastatin, the patients' oxygenation indexes were improved in all studies.
- The effect of Ulinastatin was more significant which was confirmed by the meta-analysis

Ulinastatin (UTRYP) in ARDS

- Reduces the levels of Cytokines critical in the development of inflammatory response
- Ulinastatin exerts organ protective activity
- Has significant effect in improving oxygenation
- Significantly decreases hospital mortality and length of ICU stay

Ulinastatin (UTRYP) in Sepsis

- Inhibition of the cytokines, reduction in the levels of TNF-α and Interleukin-6
- Suppresses the activity of neutrophil elastase and prevents the incidence of DIC
- Prevents progression to MOD's in Sepsis
- Reduces New onset organ-dysfunction.
- Reduces overall mortality in sepsis

U-Tryp – ORPHAN DRUG DESIGNATION

- Ulinastatin has been granted **ORPHAN DRUG STATUS** for the treatment of Acute Pancreatitis in EU
- Orphan Drug Status is granted after a stringent evaluation process by the EMA orphan drug committee which examines all aspects of:

1. **Quality of the product**
2. **Company credentials**
3. **Magnitude of disease burden**
4. **Urgency of requirement**

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 September 2014
EMA/COMP/443087/2014
Committee for Orphan Medicinal Products

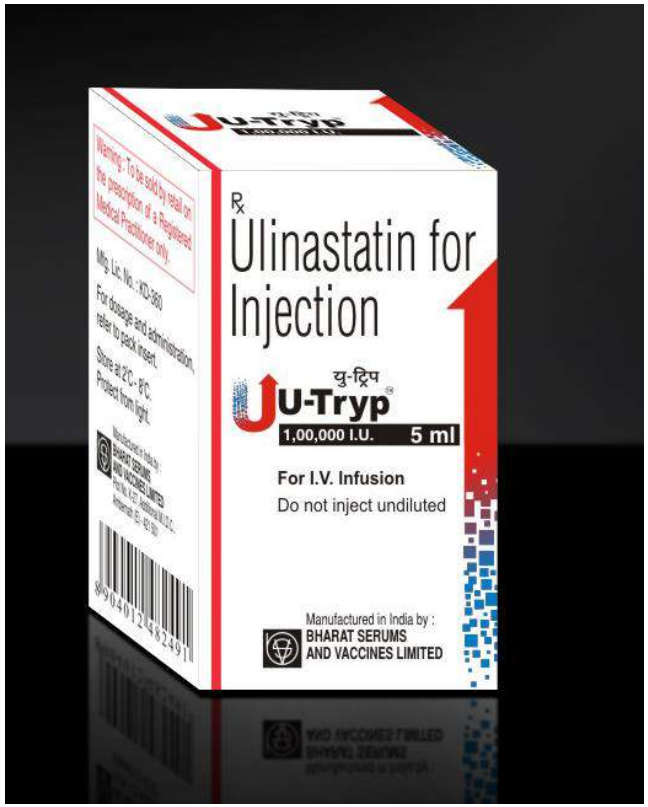
Public summary of opinion on orphan designation

Ulinastatin for the treatment of acute pancreatitis

On 22 August 2014, orphan designation (EU/3/14/1318) was granted by the European Commission to BSV BioScience GmbH, Germany, for ulinastatin for the treatment of acute pancreatitis.

Dosage & Administration

- **2 Vials of U-Tryp 100,000 IU to be administered 2 times a day for 5 days**
- **Dilution** – with 100 ml of Normal saline or 5 % Dextrose
- **Infusion Time -** over a period of 1 hr
- To be stored at 2-8° **C**



THANK YOU