Biological Therapies and Onset of Sepsis, Severe Sepsis and Septic Shock: *What Kind of Evidence?*

Giorgio Tulli M.D. 2008

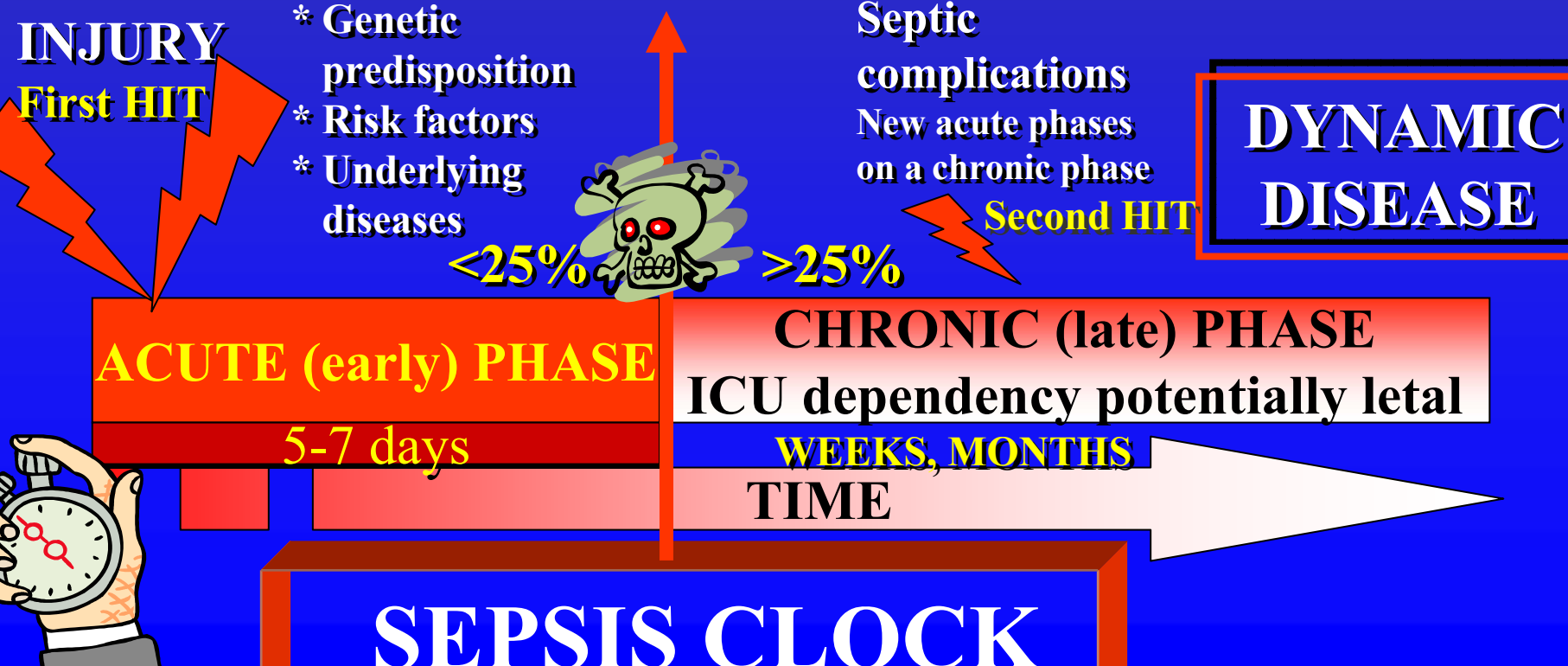
Critical Illness (e.g. Severe Sepsis) is any condition requiring **SUPPORT** of failing vital organ systems without which **DEATH** would ensue.

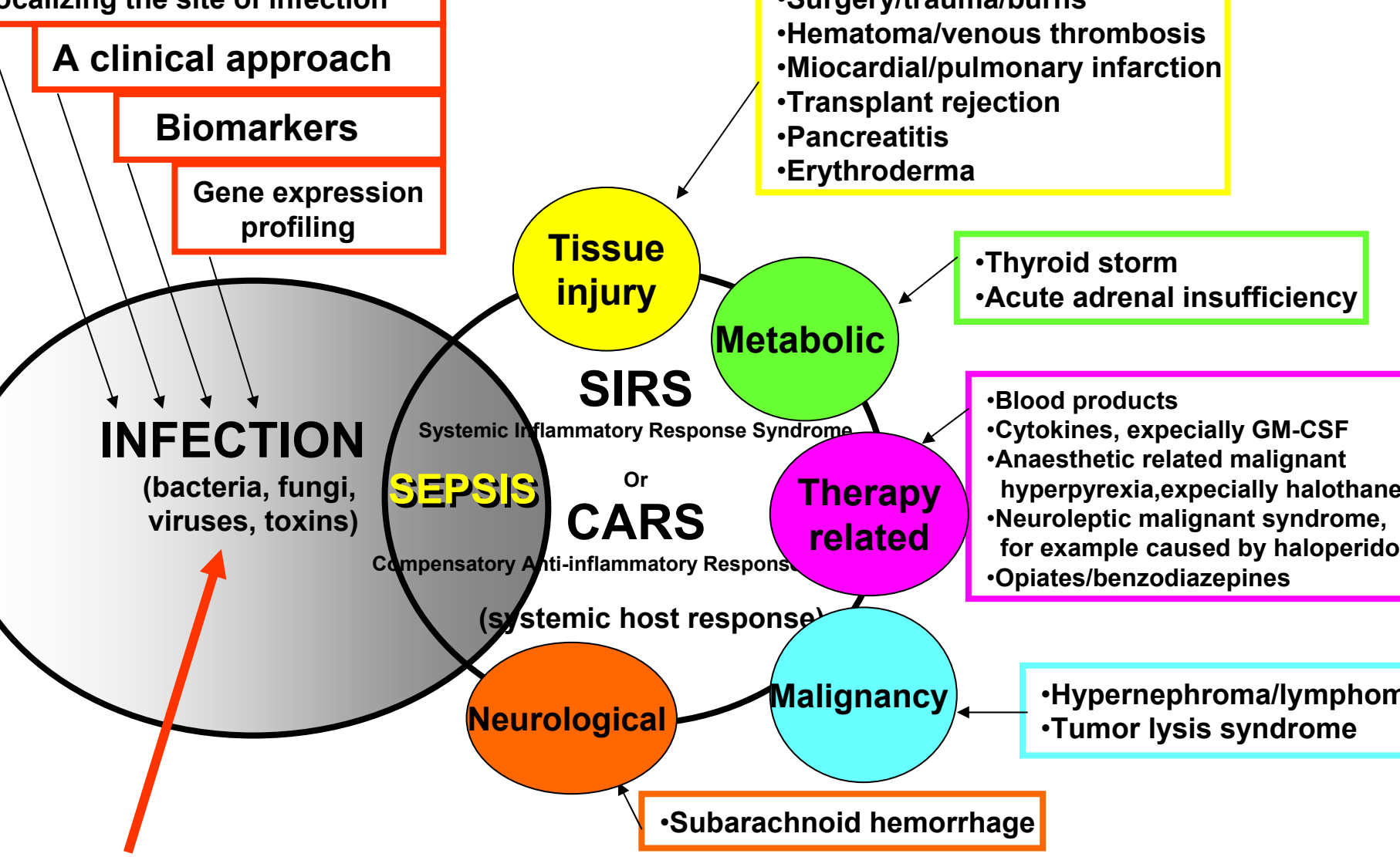
This condition is an ultimate example of acute, severe, physical stress.

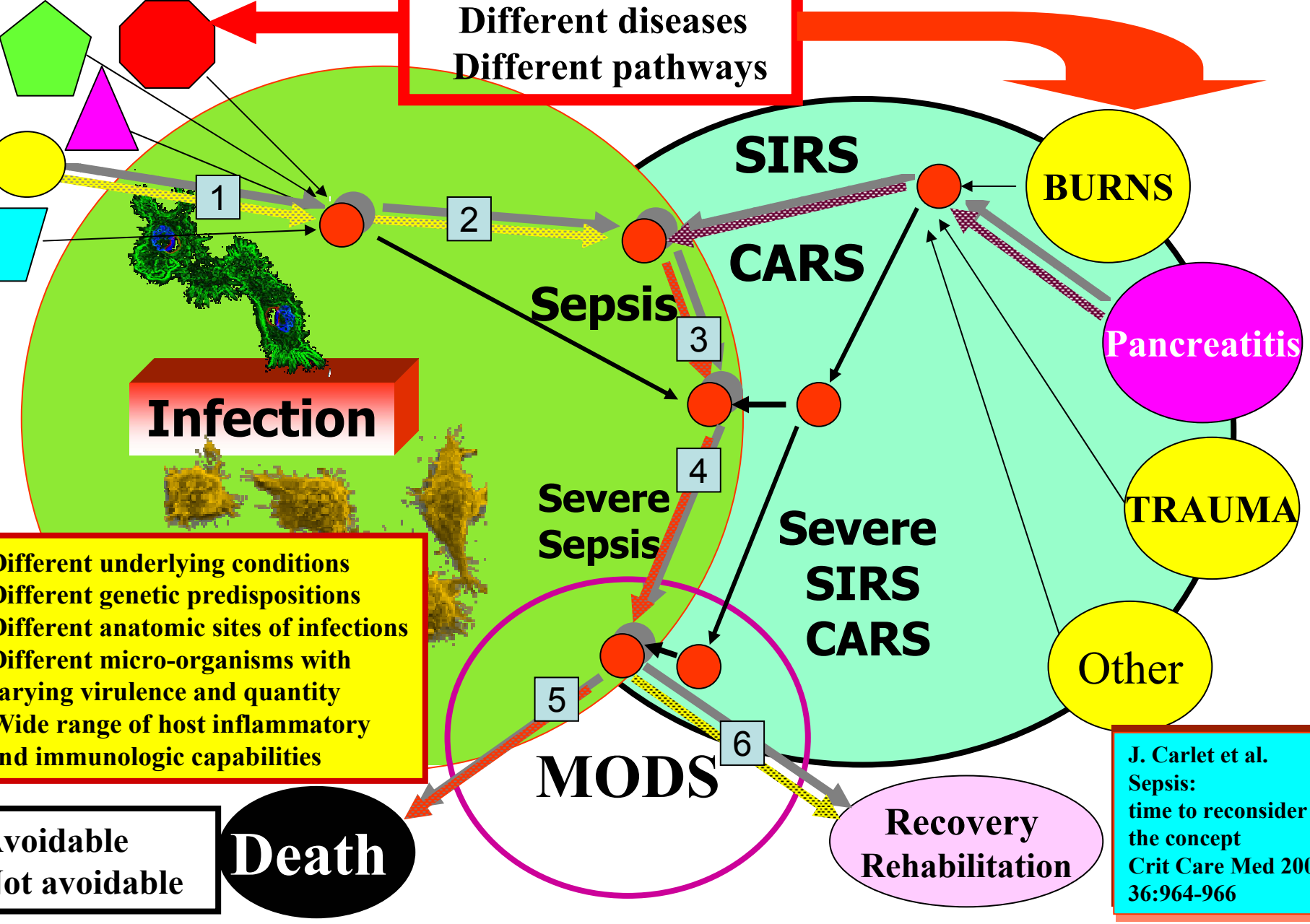
f onset of recovery does not follow within hours or few days (5-7d ?)

f Intensive Care, Critical Illness often becomes prolonged and

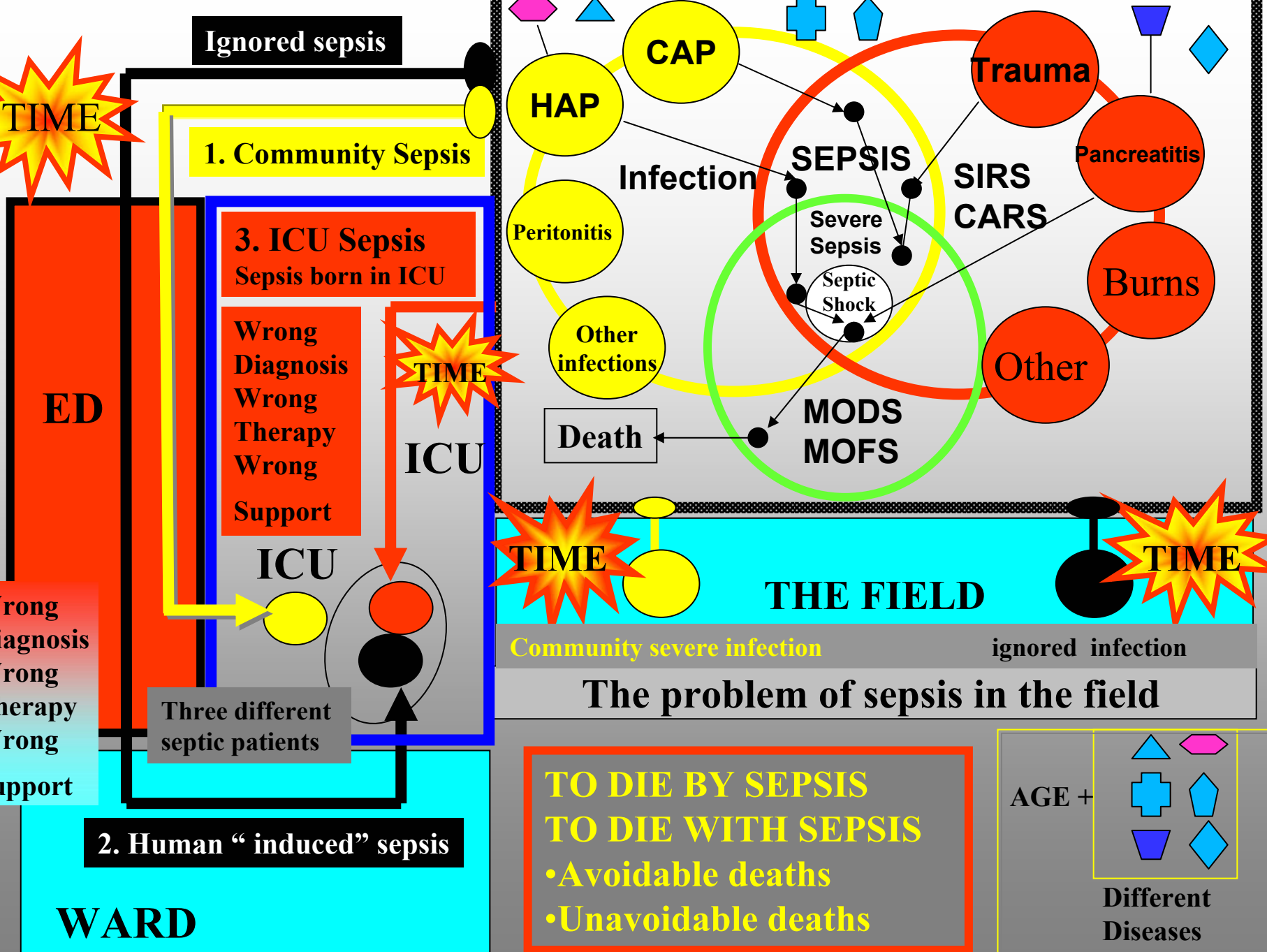
rgan systems support is frequently needed for several weeks, months




ocalizing the site of infection
A clinical approach
Biomarkers
Gene expression profiling
•Surgery/trauma/burns
•Hematoma/venous thrombosis
•Miocardial/pulmonary infarction
•Transplant rejection
•Pancreatitis
•Erythroderma
Tissue injury
Metabolic
•Thyroid storm
•Acute adrenal insufficiency
SIRS
Systemic Inflammatory Response Syndrome
Or
CARS
Compensatory Anti-inflammatory Respons
(systemic host response)
INFECTION
(bacteria, fungi, viruses, toxins)
SEPSIS
Therapy related
•Blood products
•Cytokines, expecially GM-CSF
•Anaesthetic related malignant hyperpyrexia,expecially halothane
•Neuroleptic malignant syndrome, for example caused by haloperido
•Opiates/benzodiazepines
Malignancy
•Hypernephroma/lymphom
•Tumor lysis syndrome
Neurological
•Subarachnoid hemorrhage
nterpreting the microbiological findings
Distinguishing colonization from infection
Prior antibiotic therapy
Correctly identifying unfamiliar organisms
Determining the significance of mixed culture results
nterpreting the importance of organisms normally of low virulence
Poor sensitivity
Delay of up to 48 hr
SIRS vs SEPSIS
Differential diagnosis



SEPSIS IS A CONCEPT THAT DELINEATES A GROUP OF DISEASES
SEPSIS IS NOT A SINGLE DISEASE, IT IS A CATEGORY


Ignored sepsis
TIME
1. Community Sepsis
3. ICU Sepsis
Sepsis born in ICU
Wrong Diagnosis
Wrong Therapy
Wrong Support
TIME
ICU
ED
ICU
rong
iagnosis
rong
herapy
rong
upport
Three different septic patients
2. Human " induced" sepsis
WARD
CAP
HAP
Trauma
Pancreatitis
Infection
SEPSIS
SIRS
CARS
Peritonitis
Severe Sepsis
Septic Shock
Burns
Other infections
Other
Death
MODS
MOFS
TIME
TIME
THE FIELD
Community severe infection
ignored infection
The problem of sepsis in the field
TO DIE BY SEPSIS
TO DIE WITH SEPSIS
•Avoidable deaths
•Unavoidable deaths
AGE +
Different Diseases

Systemic inflammatory response syndrome	Two or more of the following: ● Body temperature >38·5°C or <35·0°C ● Heart rate >90 beats per minute ● Respiratory rate >20 breaths per minute or arterial CO_2 tension <32 mm Hg or need for mechanical ventilation ● White blood cell count >12 000/mm³ or <4000/mm³ or immature forms >10%
Sepsis	Systemic inflammatory response syndrome and documented infection (culture or gram stain of blood, sputum, urine, or normally sterile body fluid positive for pathogenic microorganism; or focus of infection identified by visual inspection—eg, ruptured bowel with free air or bowel contents found in abdomen at surgery, wound with purulent discharge)
Severe sepsis	Sepsis and at least one sign of organ hypoperfusion or organ dysfunction: ● Areas of mottled skin ● Capillary refilling time ⩾3 s ● Urinary output <0·5 mL/kg for at least 1 h or renal replacement therapy ● Lactates >2 mmol/L ● Abrupt change in mental status or abnormal electroencephalogram ● Platelet counts <100 000/mL or disseminated intravascular coagulation ● Acute lung injury—acute respiratory distress syndrome ● Cardiac dysfunction (echocardiography)
Septic shock	Severe sepsis and one of: ● Systemic mean blood pressure <60 mm Hg (<80 mm Hg if previous hypertension) after 20–30 mL/kg starch or 40–60 mL/kg serum saline, or pulmonary capillary wedge pressure between 12 and 20 mm Hg ● Need for dopamine >5 µg/kg per min or norepinephrine or epinephrine <0·25 µg/kg per min to maintain mean blood pressure above 60 mm Hg (80 mm Hg if previous hypertension)
Refractory septic shock	Need for dopamine >15 µg/kg per min or norepinephrine or epinephrine >0·25 µg/kg per min to maintain mean blood pressure above 60 mm Hg (80 mm Hg if previous hypertension)

Definitions of Sepsis 1992

Critical Care Medicine 1992;20:864-874

The Sepsis Continuum

TIME IS THE ISSUE TIME IS THE TISSUE - TIME IS ORGAN

TIME

A clinical response arising from a nonspecific insult, with ≥2 of the following:

- **T >38°C or <36°C**
- **HR >90 beats/min**
- **RR >20/min**
- **WBC >12,000/mm³ or <4,000/mm³ or >10% bands**

SIRS with a presumed or confirmed infectious process

Sepsis with organ failure

Refractory hypotension

Recovery

MODS/MOF

DEATH

Roger Bone et al. Chest 1992;101:1644.

Infection (defined as a pathological process induced by a micro-organism) (documented or suspected)

and some of the following:

General parameters:

Fever (core temperature > 38.3 °C)
Hypothermia (core temperature < 36 °C)
Heart rate > 90 bpm or > 2 SD above the normal value for age
Tachypnea > 30 bpm
Altered mental status
Significant edema or positive fluid balance (> 20 ml/Kg over 24 hours)
Hyperglycemia (plasma glucose > 110 mg/dl or 7.7 nM/l) in the absence of diabetes

Inflammatory parameters

Leukocytosis (white blood cell count > 12,000/µl)
Leukopenia (white blood cell count < 4,000/µl
Normal white blood cell count with > 10% immature forms
Plasma C reactive protein > 2SD above the normal value
Plasma procalcitonin > 2SD above the normal value

CRP
PCT

DIAGNOSTIC CRITERIA FOR SEPSIS
2001 SCCM/ESICM/ACCP/ATS/SIS
International Sepsis Definitions Conferen
Intensive Care Med (2003)
29: 530-538

DIAGNOSIS
24 items

Hemodynamic parameters

Arterial hypotension (values above 70% are normal in children –normally 75-80%- and should therefore not be used as a sign of sepsis in newborns or children) (SBP < 90 mmHg, MAP < 70, or SBP decrease > 40 mmHg in adults or < 2 SD below normal for age)
Mixed venous oxygen saturation > 70%
Cardiac index > 3.5 l $min^{-1}m^{-2}$ (values of 3.5-5.5 are normal in children and should therefore not be used as a sign of sepsis in newborns or children)

Organ dysfunction parameters

Arterial hypoxemia (PaO2/FiO2 <300)
Acute oliguria (urine output < 0.5 $mlKg^{-1}h^{-1}$ or 45 mM/l for at least 2h)
Creatinine increase ≥0.5 mg/dl
Coagulation abnormalities (INR > 1.5 or aPTT > 60 sec)
Ileus (absent bowel sounds)
Thrombocytopenia (platetel count < 100,000/µl)
Hyperbilirubinemia (plasma total bilirubin > 4 mg/dl or 70 mmol/l)

PaO2/FiO2
RIFLE (Cystatin C and NGAL)
DIC SCORE
PROTEIN C

Tissue perfusion parameters

Hyperlactatemia (> 3 mmol/l)

LACTATE

2003

Simplified Organ Failure Assessment
SOFA Score

Organ system /Score	1	2	3	4
CNS GCS	13-14	10-12	6-9	<6
RESPIRATORY SYSTEM Pa/FiO_2 (mmHg)	< 400	< 300	< 200 with support	< 100
CARDIOVASCULAR SYSTEM Hypotension	MAP < 70 mmHg	Dopa < 5 o Dobutamin	Dopa > 5 o Adr < 0,1 o Noradr < 0,1	Dopa > 15 Adr > 0,1 Noradr > 0,1
COAGULATION Platelets ($10^3/mm^3$)	< 150	<100	<50	<20
LIVER Bilirubin(mg/dl)	1,2-1,9	2,0-5,9	6,0-11,9	>12
RENAL SYSTEM Creat(mg/dl) o Diur	1,2-1,9	2,0-3,4	3,5-4,9 o < 500 ml/24h	> 5,0 < 200 ml/24 H

TIME IS ORGAN

"Errors are not in the art but in the artificers"

Newton's PRINCIPIA

DEFINITION
DIAGNOSIS

"We ought to spend more time to search for an accurate diagnosis rather than search for the Magic Bullet for the treatment of Sepsis"

Roger Bone. Sir Isaac Newton, Sepsis, SIRS and CARS Crit Care Med 1996; 24:1125-112

Early diagnosis of Sepsis

has been estimated that as many
s 60% of critically ill patients
evelop SIRS manifested by
achycardia, tachypnea, fever
nd/or leukocytosis

Is there a living infection ?

History
Examination

Clinical diagnosis
of suspected living infection

Biomarkers (procalcitonin, endotoxin)
eptifast/VYOO

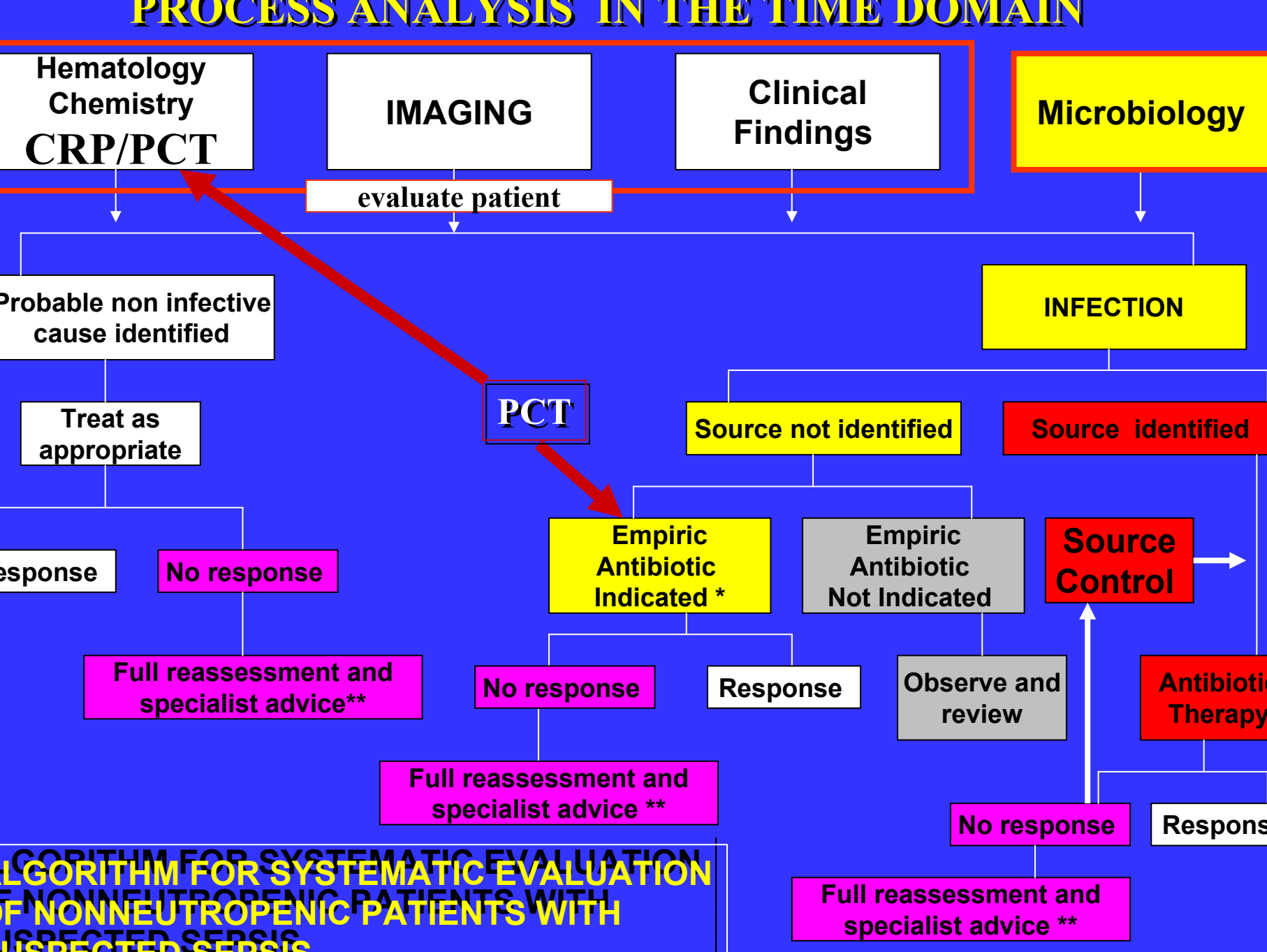
Clinical diagnosis
of probable living infection

Appropriate cultures
(always before antibiotics)

6 hours BUNDLE

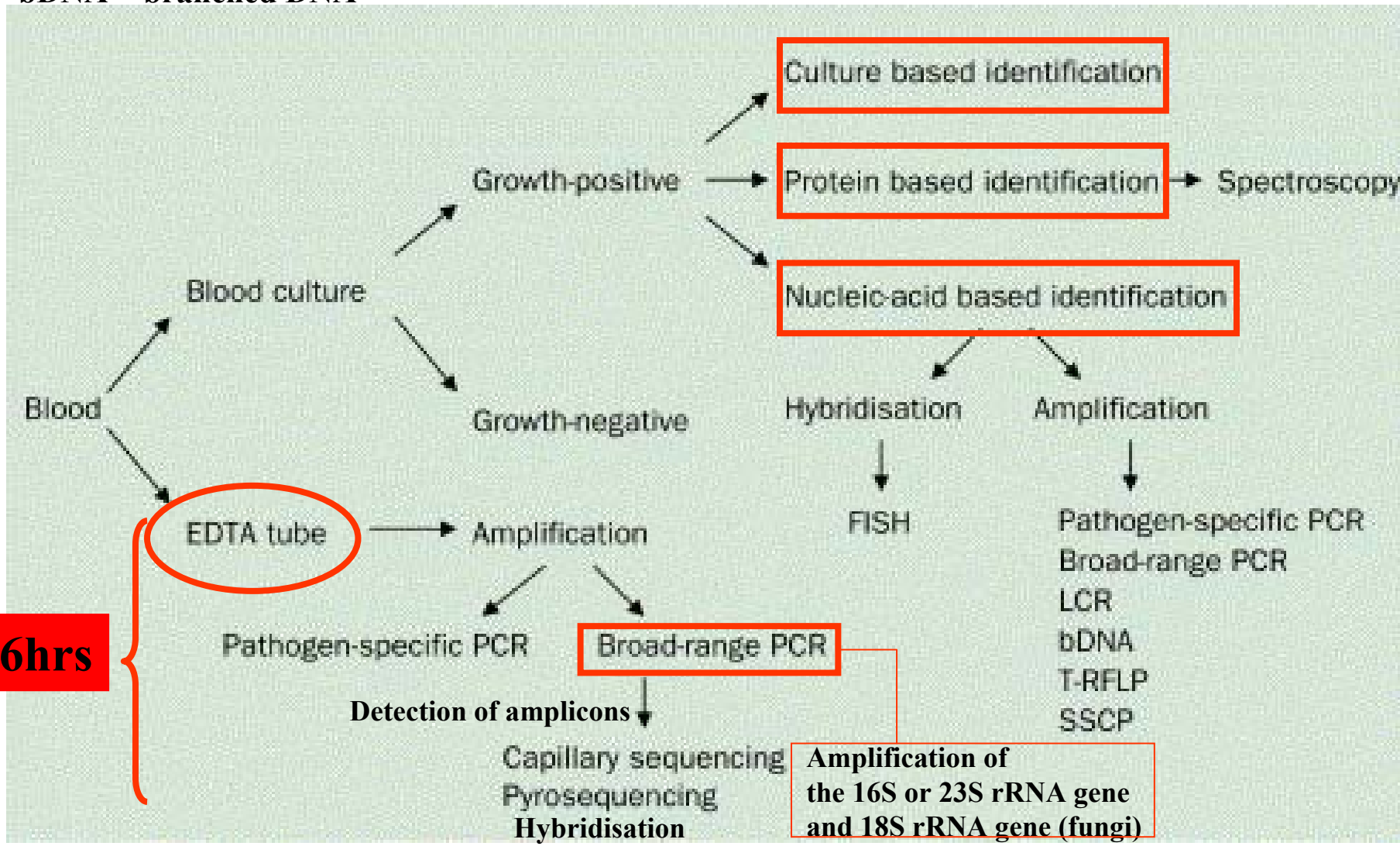
Clinical diagnosis
of certain living infection

The problem of the early diagnosis of a living infection


PROCESS ANALYSIS IN THE TIME DOMAIN
Hematology
Chemistry
CRP/PCT
IMAGING
Clinical
Findings
Microbiology
evaluate patient
Probable non infective
cause identified
INFECTION
PCT
Treat as
appropriate
Source not identified
Source identified
esponse
No response
Empiric
Antibiotic
Indicated *
Empiric
Antibiotic
Not Indicated
Source
Control
Full reassessment and
specialist advice**
No response
Response
Observe and
review
Antibioti
Therapy
Full reassessment and
specialist advice **
No response
Respons
Full reassessment and
specialist advice **
LGORITHM FOR SYSTEMATIC EVALUATION
F NONNEUTROPENIC PATIENTS WITH
USPECTED SEPSIS

Techniques for laboratory detection of bloodstream infections

- **FISH = fluorescent in situ hybridisation**
- **LCR = ligase chain reaction**
- **bDNA = branched DNA**
- **T-RFLP = terminal restriction fragment lenght polymorphis**
- **SSCP = single strand conformation polymorphism**

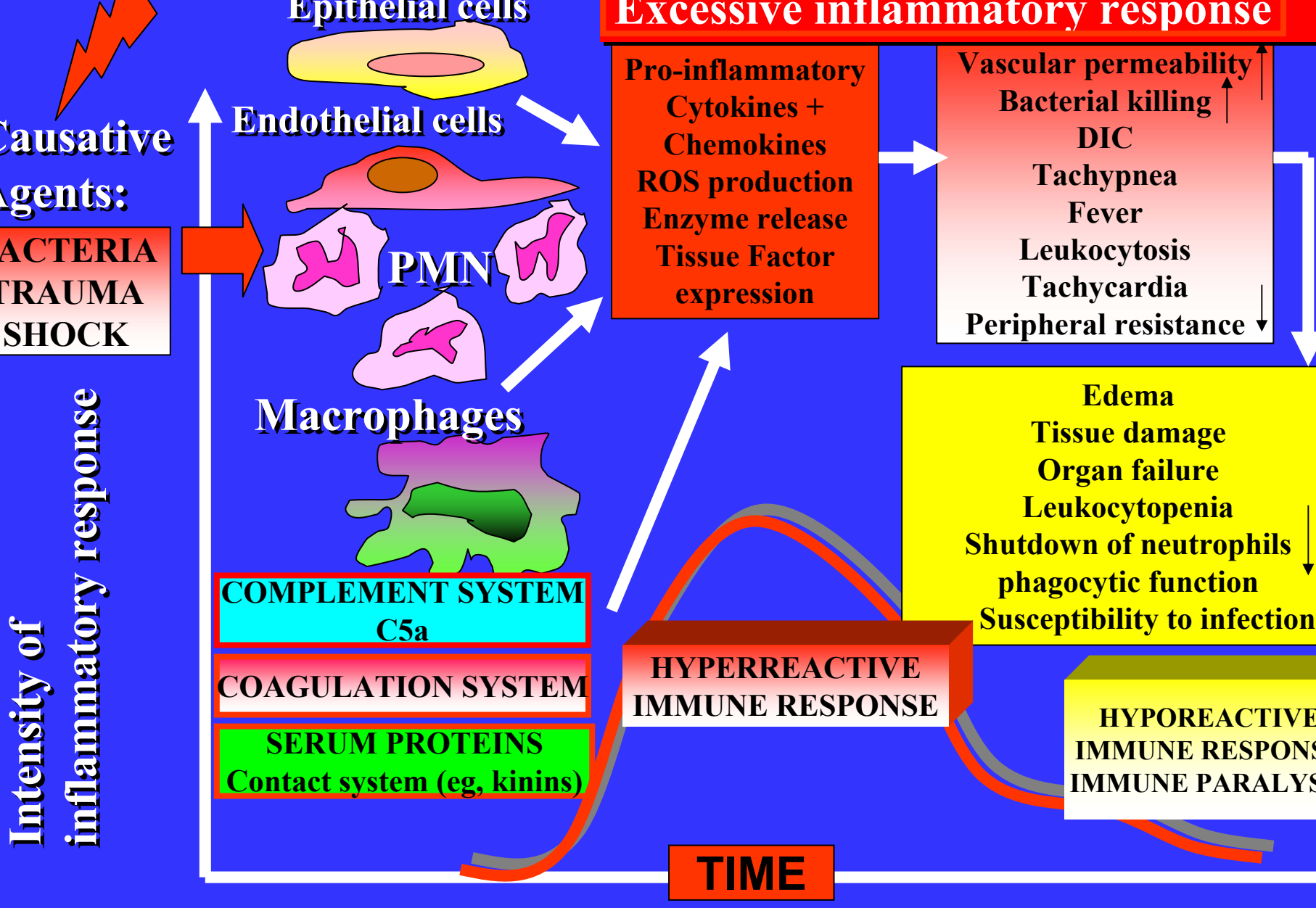


Sepsis:
a disorder due to uncontrolled inflammation

In 1972, Lewis Thomas described Sepsis in the following way:

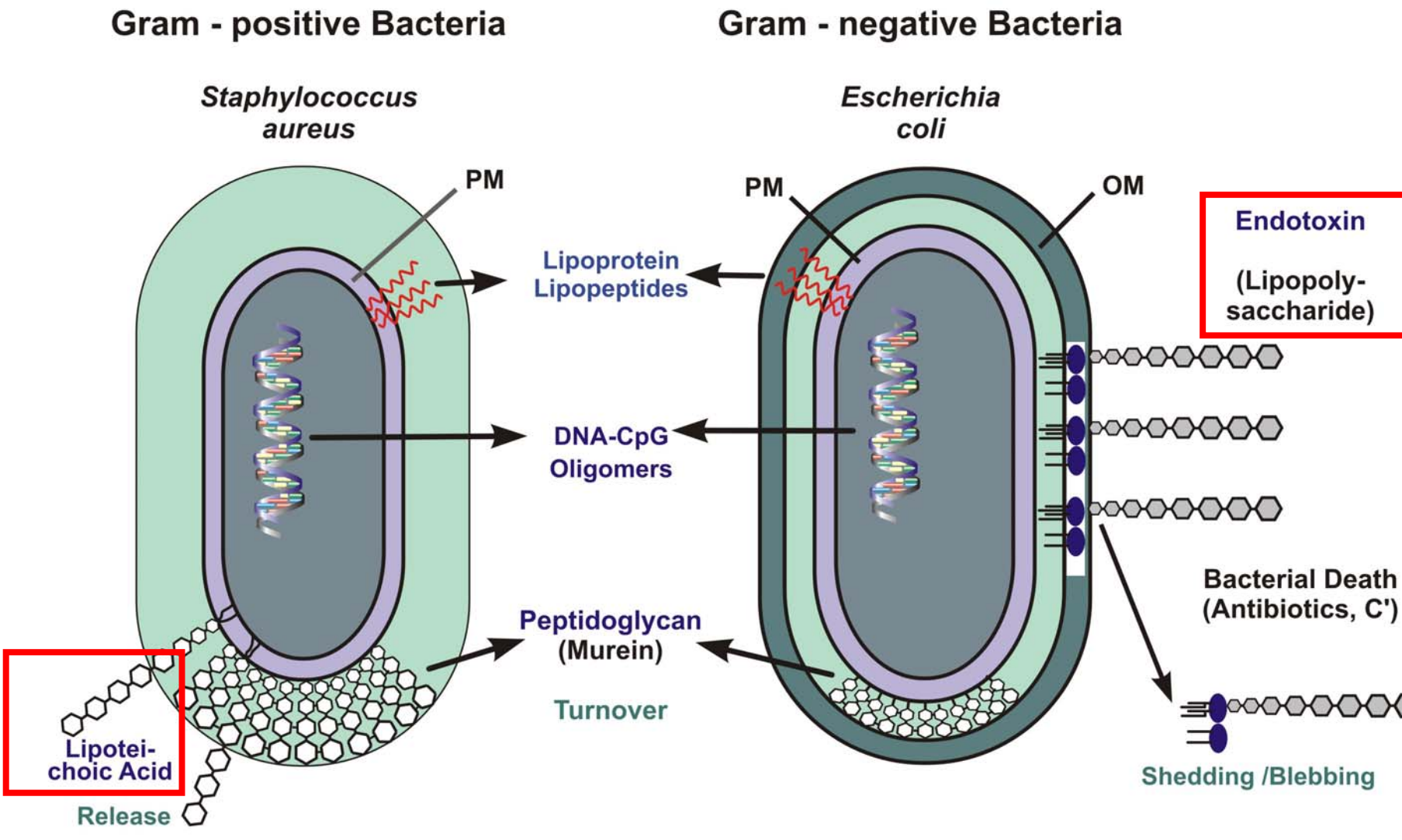
" It is our response to the micro-organisms presence that makes the disease. Our arsenals for fighting off bacteria are so powerful… that we are more in danger from them than the invaders"

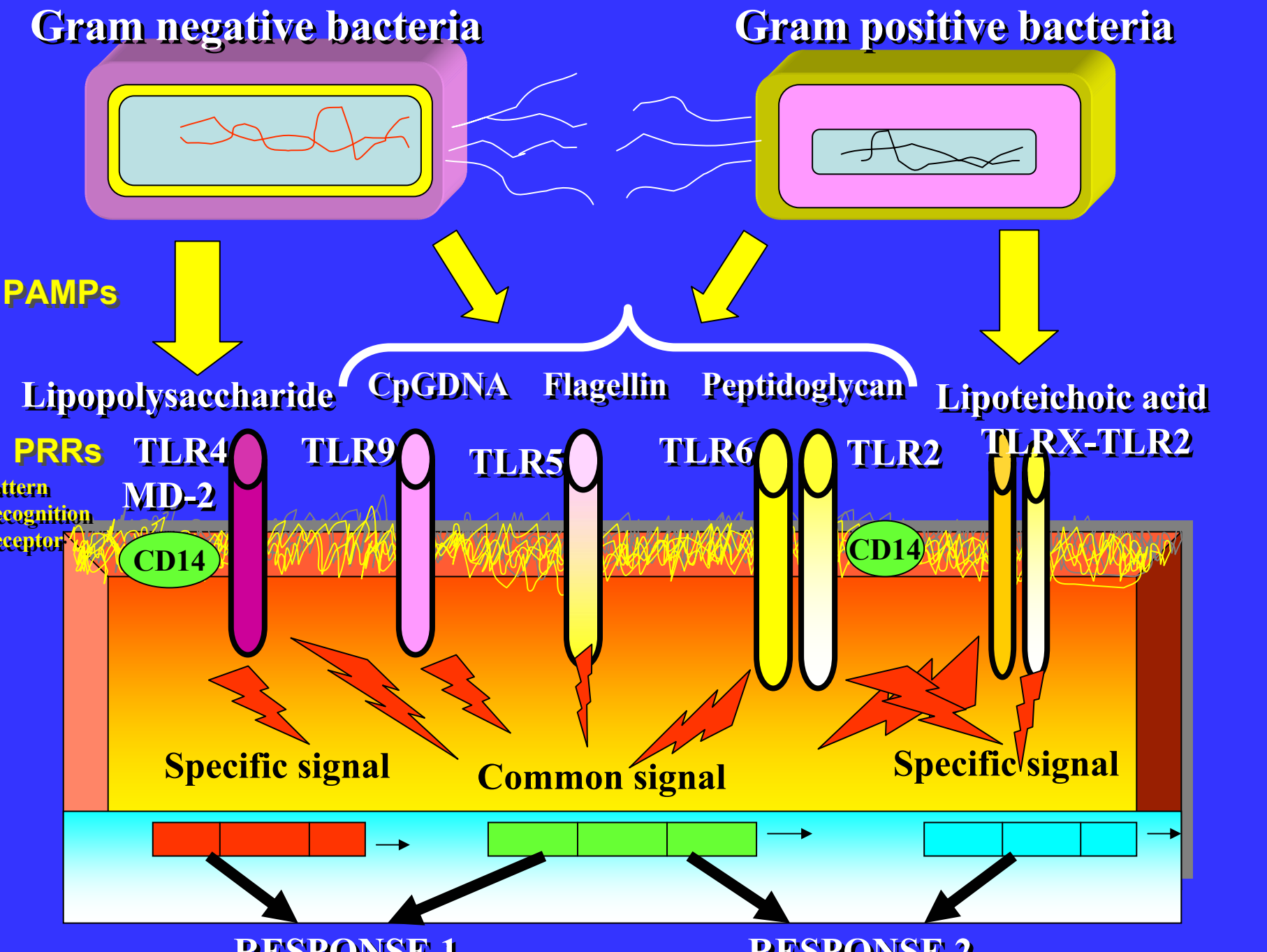
Lewis Thomas Germs N Engl J Med 1972; 287:553-555

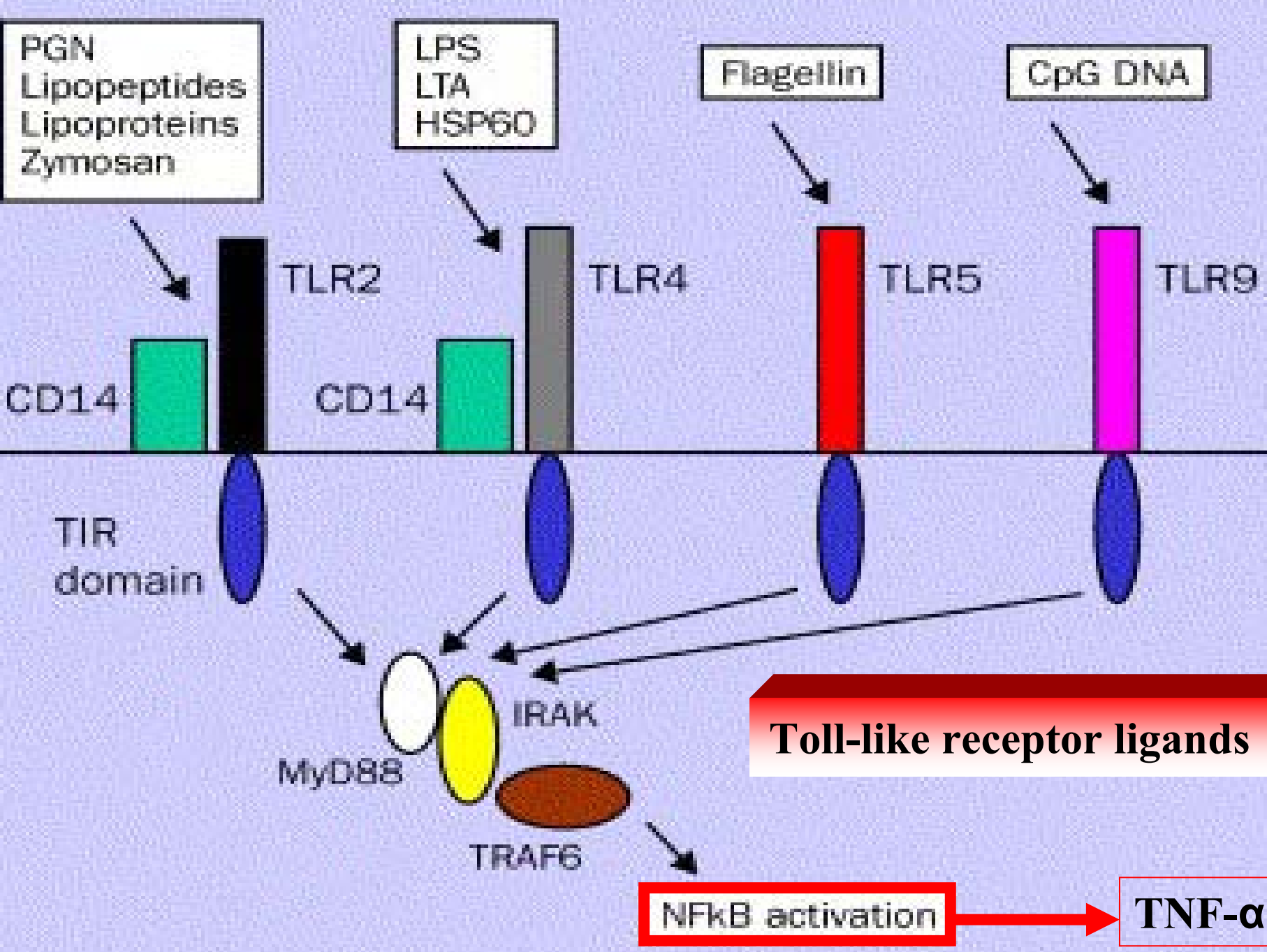


Dynamic time-course of the inflammatory response during Sepsis

PAMPs of Gram-positive and Gram-negative Bacteria

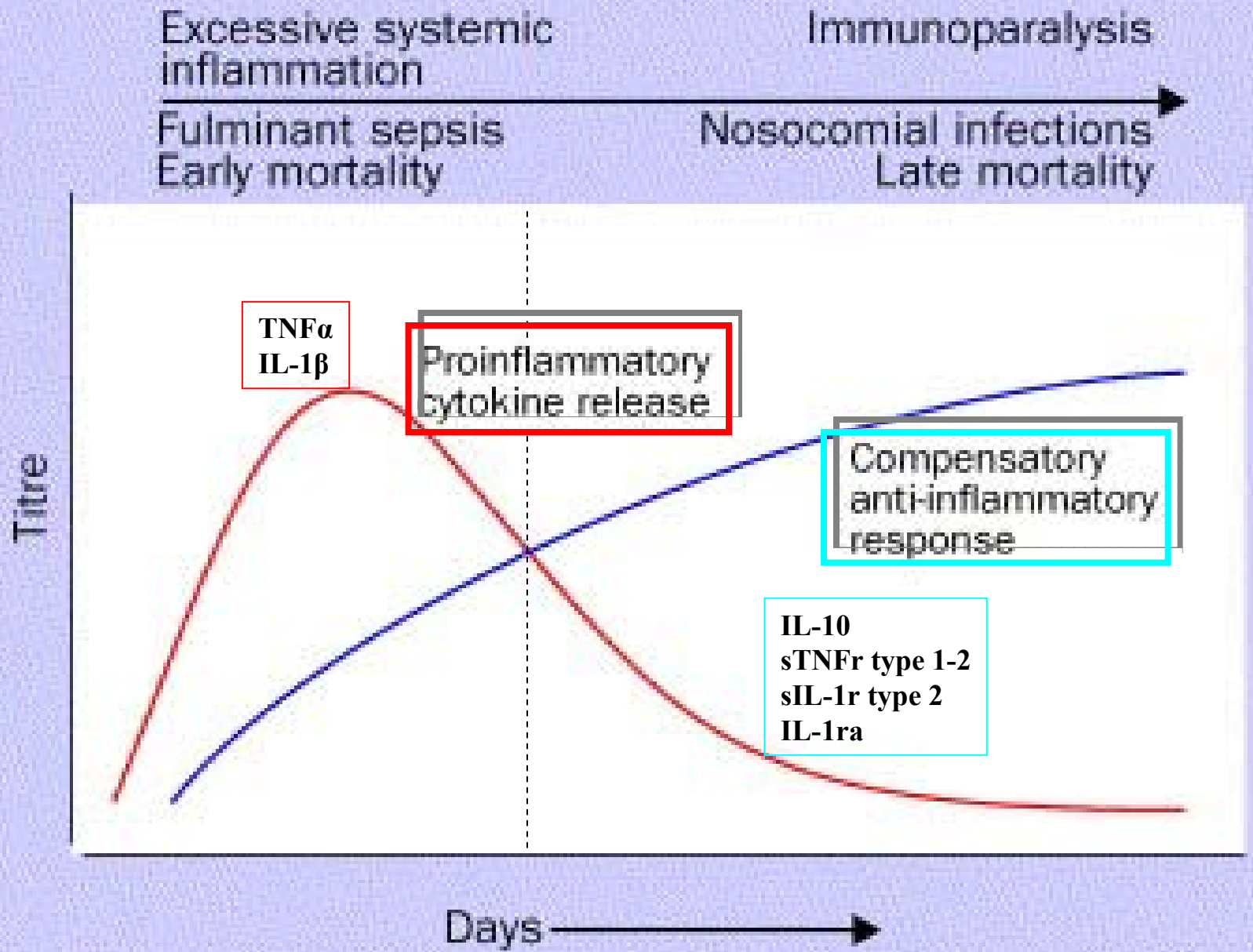



Gram negative bacteria
Gram positive bacteria
PAMPs
Lipopolysaccharide
CpGDNA
Flagellin
Peptidoglycan
Lipoteichoic acid
PRRs
TLR4
MD-2
TLR9
TLR5
TLR6
TLR2
TLRX-TLR2
CD14
CD14
Specific signal
Common signal
Specific signal

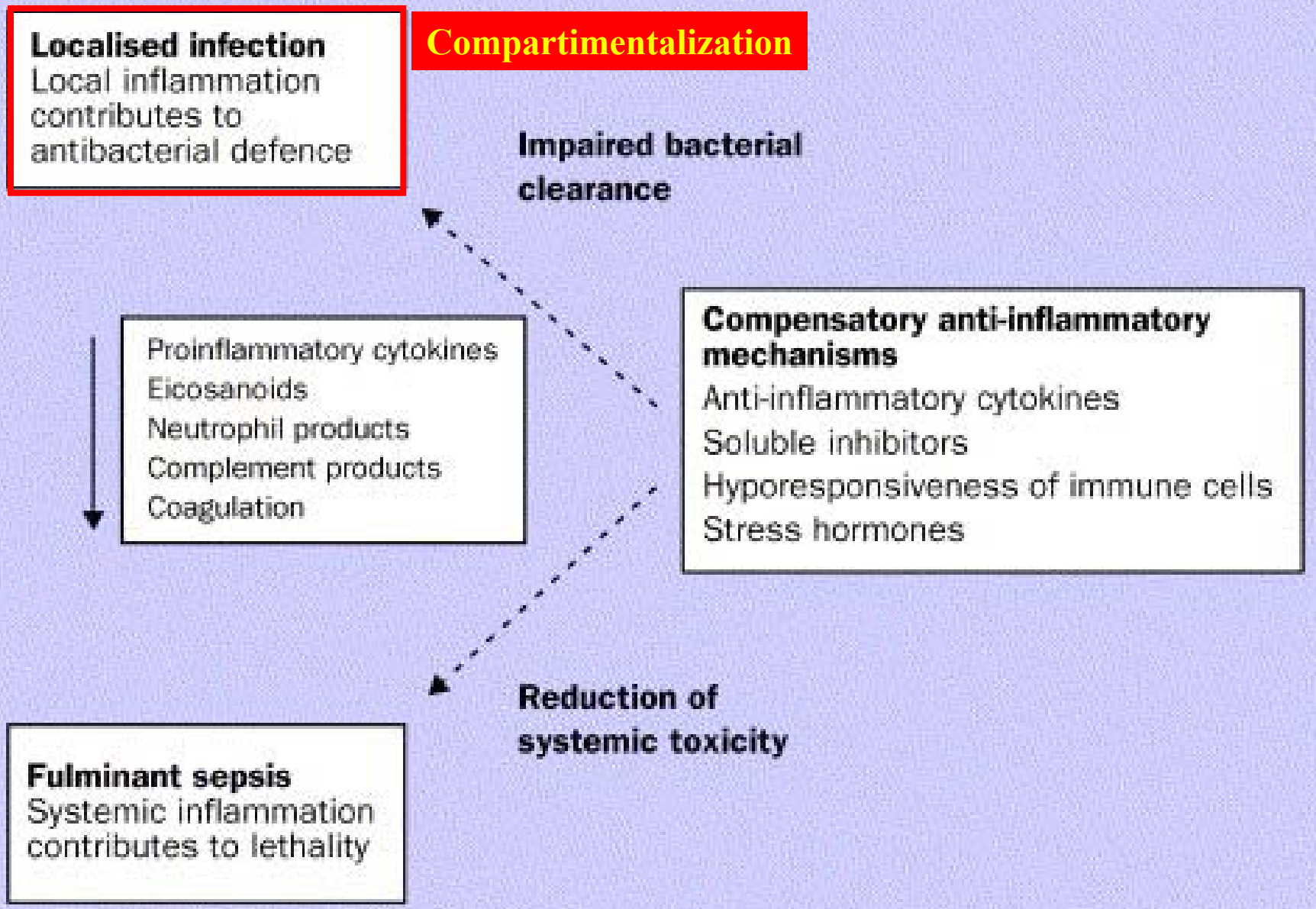


Toll-like receptor ligands

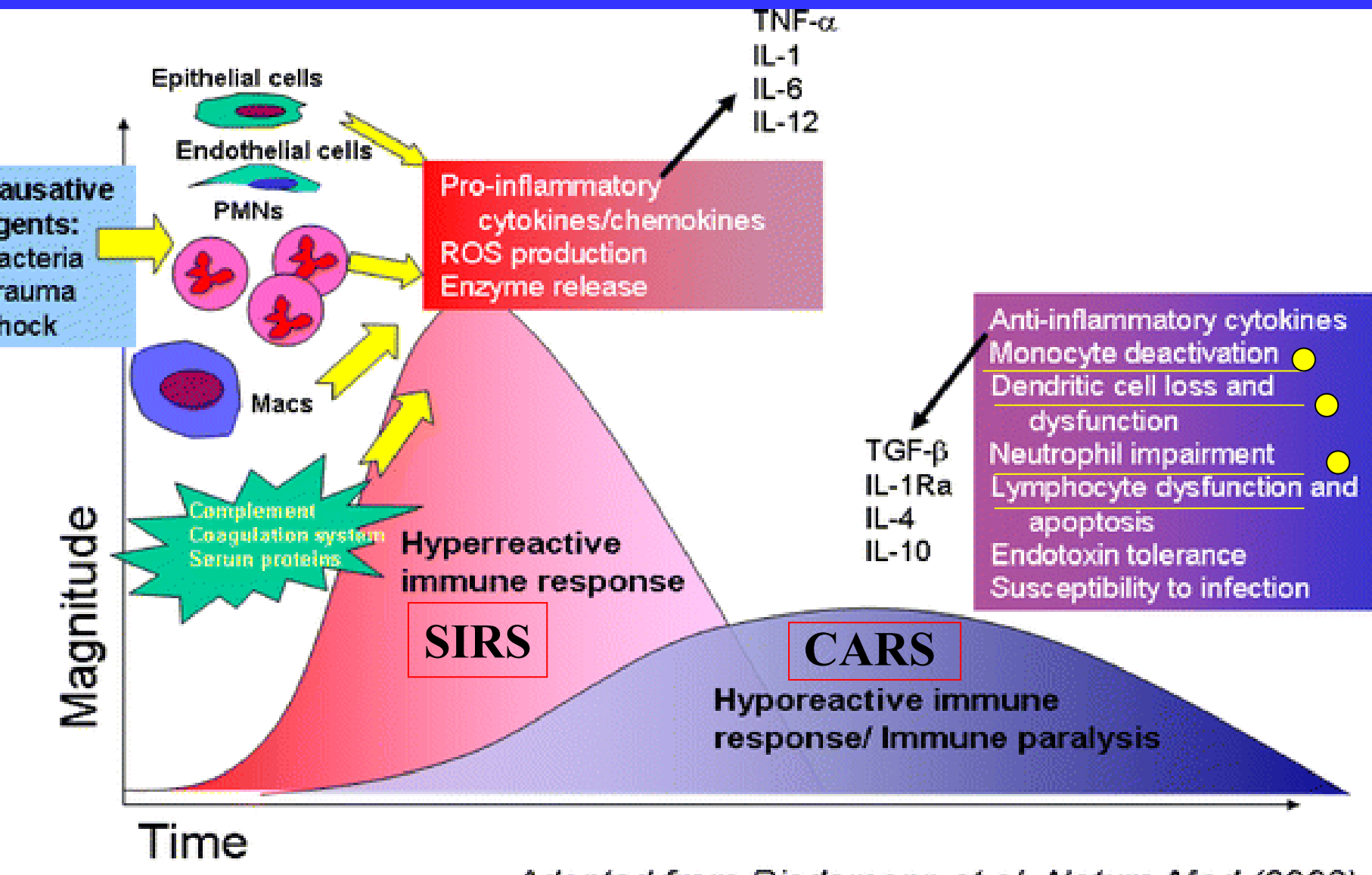
PROINFLAMMATORY AND ANTI-INFLAMMATORY EVENTS DURING SEPSIS

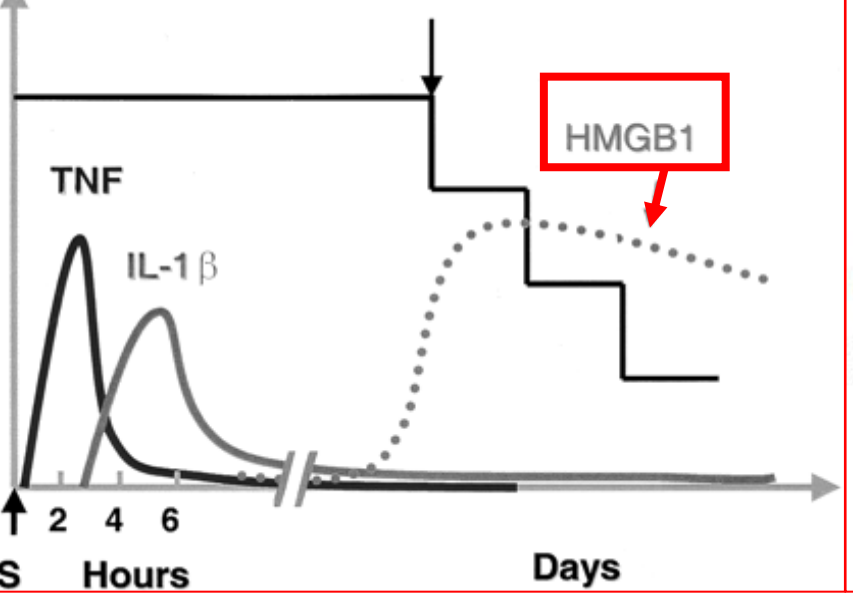


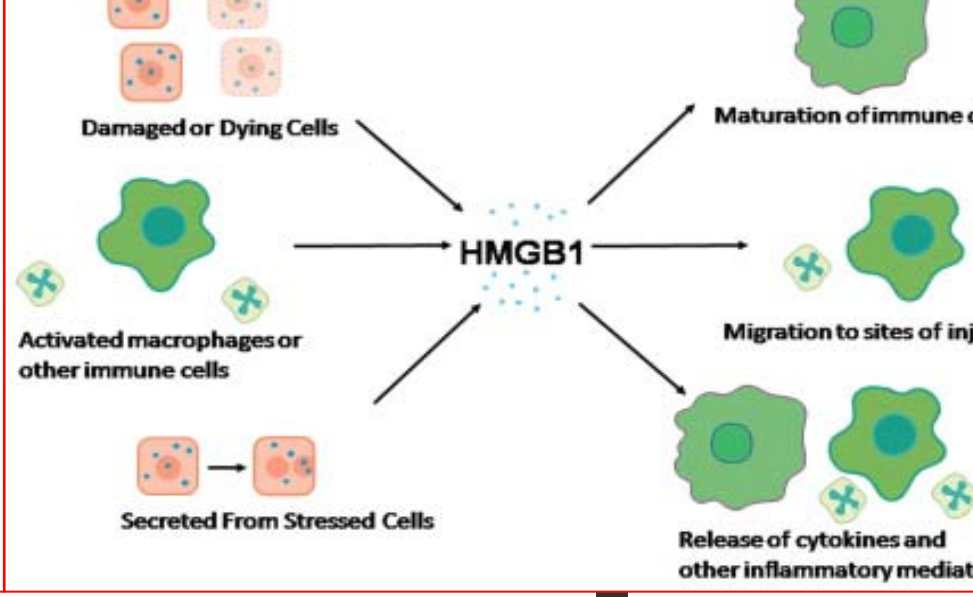
roinflammatory and anti-inflammatory mechanisms during localised and systemic infection

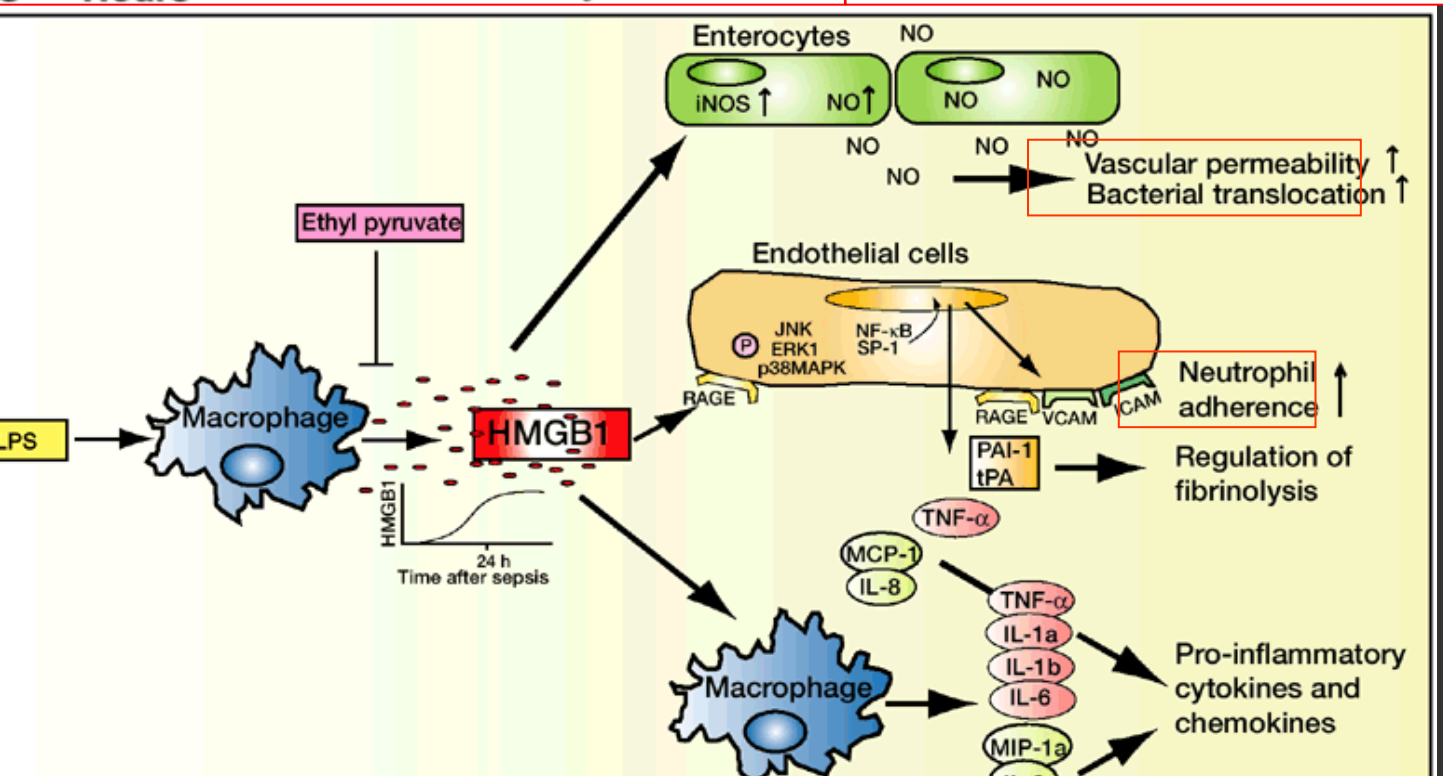


Dynamic of the septic inflammatory response
The immunologic response to sepsis over time




HMGB1
TNF
IL-1 β
2
4
6
Hours
Days


Damaged or Dying Cells
HMGB1
Activated macrophages or other immune cells
Secreted From Stressed Cells
Migration to sites of inj
Release of cytokines and other inflammatory mediat

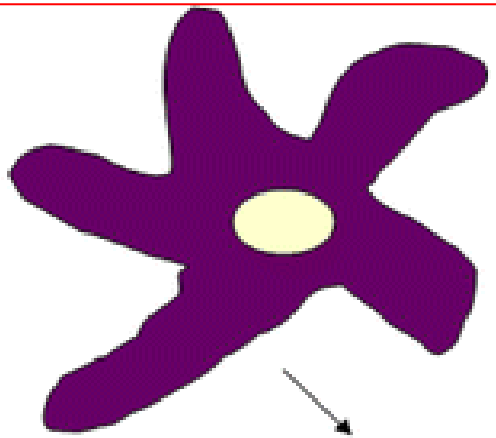

Enterocytes
NO
iNOS
Vascular permeability
Bacterial translocation
Ethyl pyruvate
Endothelial cells
JNK
ERK1
p38MAPK
NF-κB
SP-1
RAGE
VCAM
CAM
Neutrophil adherence
Macrophage
HMGB1
PAI-1
tPA
Regulation of fibrinolysis
TNF-α
MCP-1
IL-8
IL-1a
IL-1b
IL-6
Pro-inflammatory cytokines and chemokines
MIP-1a
24 h
Time after sepsis

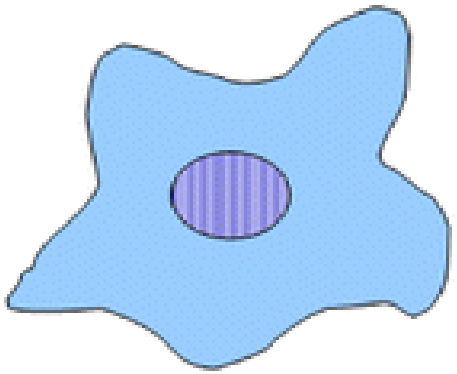
HMGB1

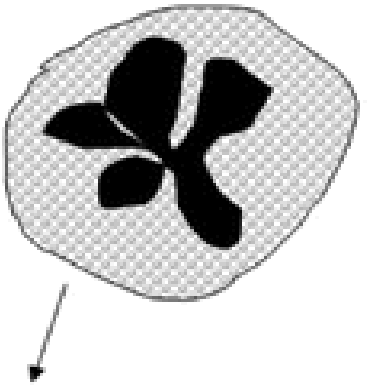
Mechanisms of sepsis induced immunosuppression

Sepsis-induced alterations in immune cell function.

In septic patients, multiple aspects of leukocyte function are disrupted, leading to susceptibility to secondary infections among survivors of sepsis







Dendritic cell:

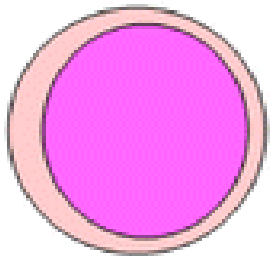
- Apoptotic loss
- Impaired T1 responses

Neutrophil:

- Diminished neutrophil adherence/migration
- Decreased activational marker expression

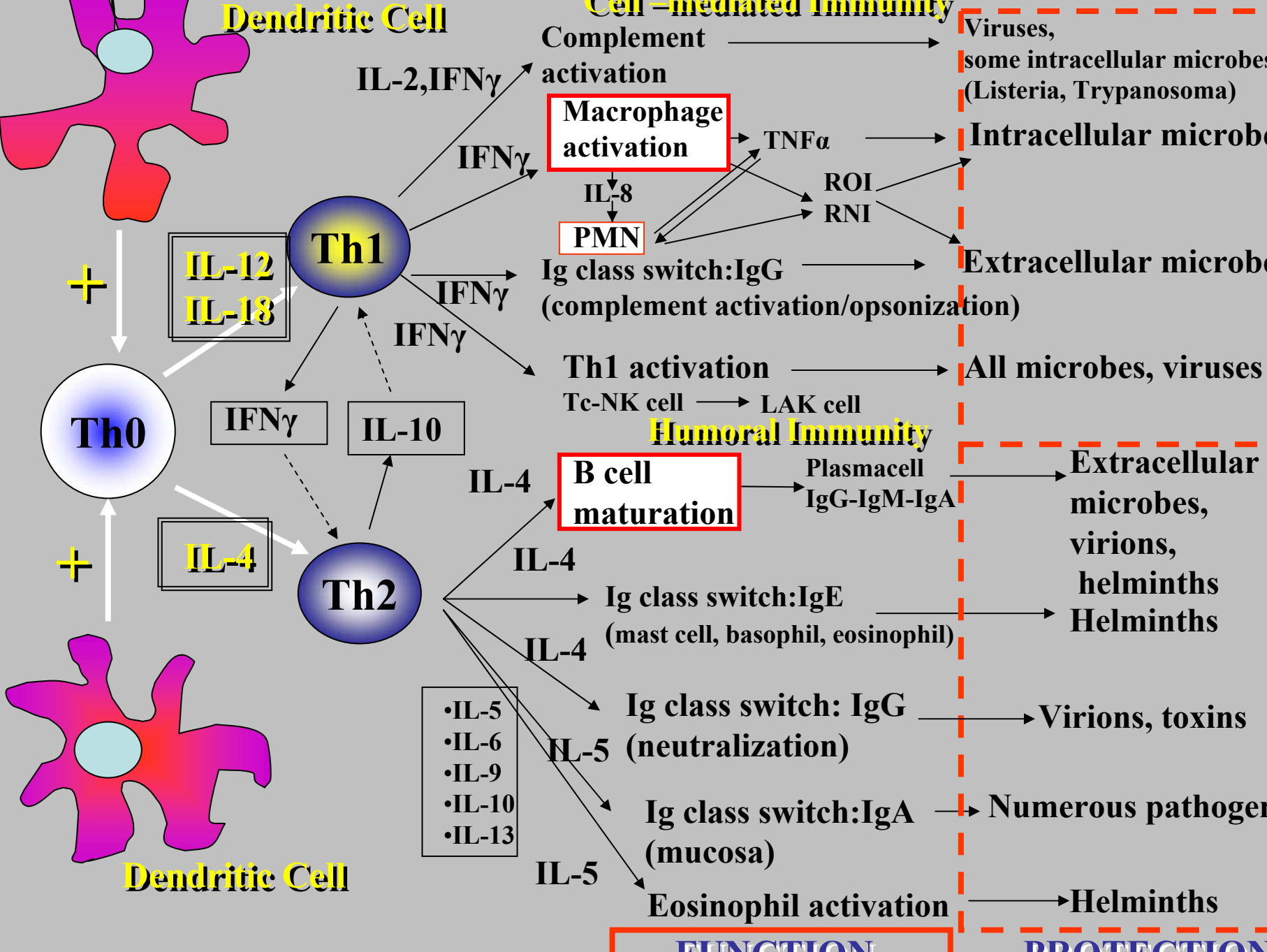
"Deactivated" monocyte:

- Decreased inflammatory cytokine production
- NF-kB subunits = p50:p50 homodimers
- Increased TLR inhibitors (e.g., IRAK-M)
- Reduced HLA-DR expression

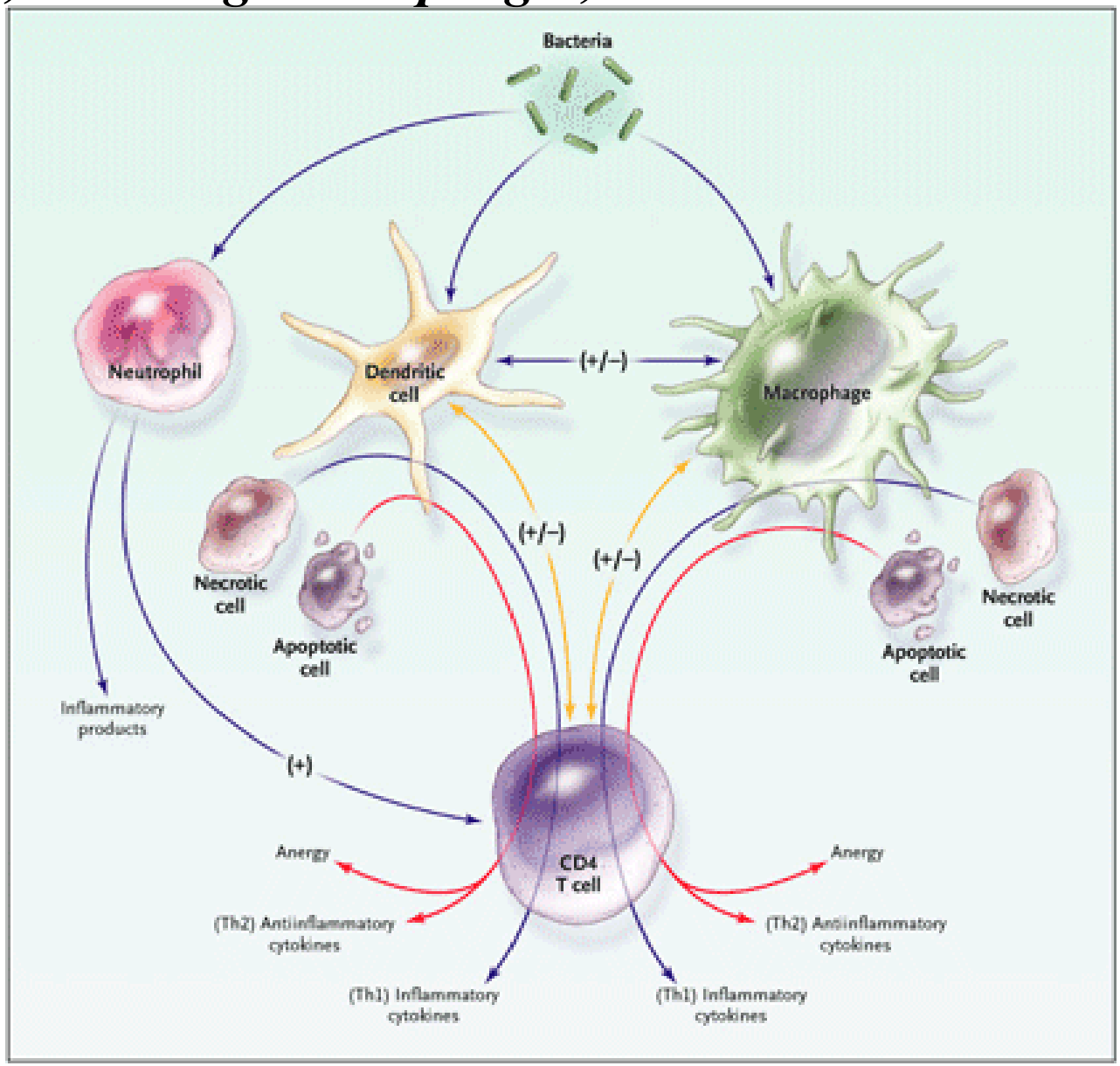


Lymphocyte:

- Apoptotic loss


Dendritic Cell
Cell –mediated Immunity
Complement activation
Viruses, some intracellular microbes (Listeria, Trypanosoma)
IL-2,IFNγ
Macrophage activation
TNFα
Intracellular microbe
IFNγ
IL-8
ROI
RNI
PMN
Th1
IL-12
IL-18
Ig class switch:IgG
(complement activation/opsonization)
Extracellular microbe
IFNγ
IFNγ
Th1 activation
All microbes, viruses
Tc-NK cell
LAK cell
Th0
IFNγ
IL-10
Humoral Immunity
IL-4
B cell maturation
Plasmacell
IgG-IgM-IgA
Extracellular microbes, virions, helminths
IL-4
IL-4
Th2
Ig class switch:IgE
(mast cell, basophil, eosinophil)
Helminths
IL-4
Ig class switch: IgG
(neutralization)
Virions, toxins
•IL-5
•IL-6
•IL-9
•IL-10
•IL-13
IL-5
Ig class switch:IgA
(mucosa)
Numerous pathogen
IL-5
Eosinophil activation
Helminths
Dendritic Cell
FUNCTION
PROTECTION

he response to pathogens, involving "cross-talk" among many
mmune cells, including Macrophages, Dendritic Cells and CD4 T cell



Potential Mechanisms of Immune Suppression in Patients with Sepsis.*

Shift from an inflammatory (Th1) to an antiinflammatory (Th2) response

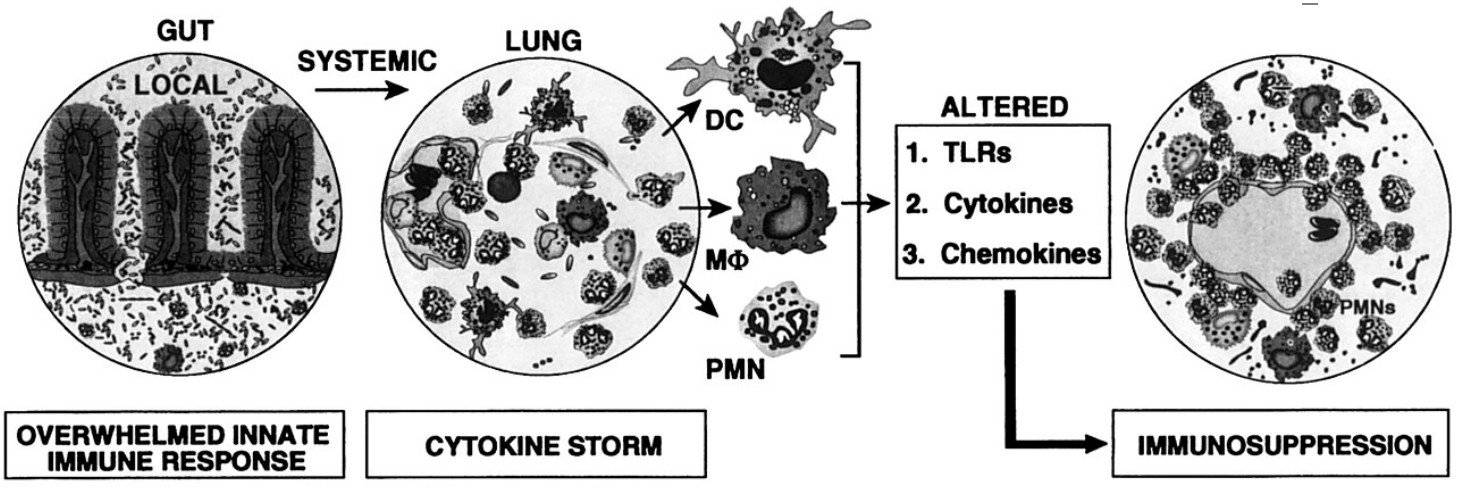
Anergy

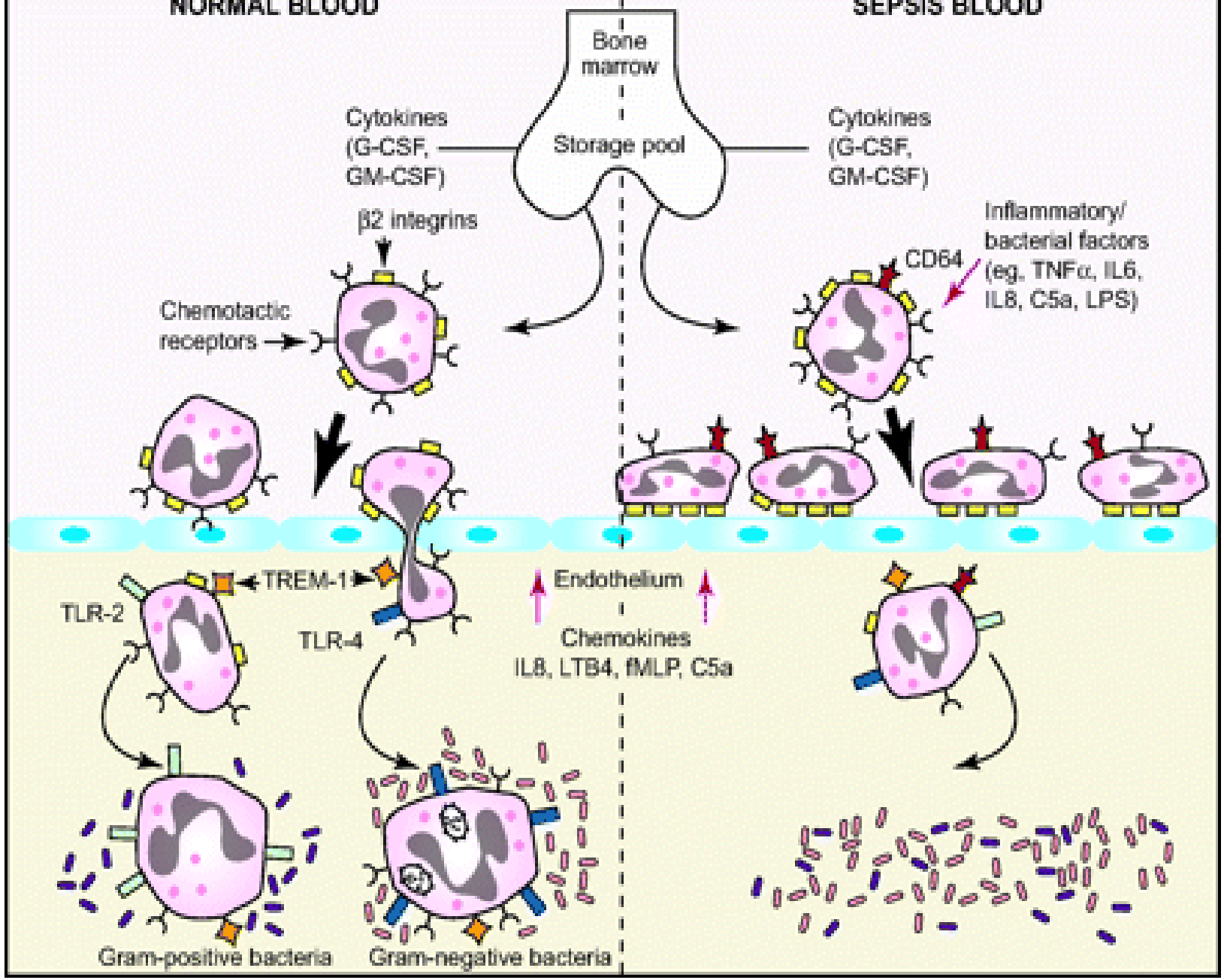
Apoptosis-induced loss of CD4 T cells, B cells, and dendritic cells

Loss of macrophage expression of major-histocompatibility-complex class II and costimulatory molecules

Immunosuppressive effect of apoptotic cells

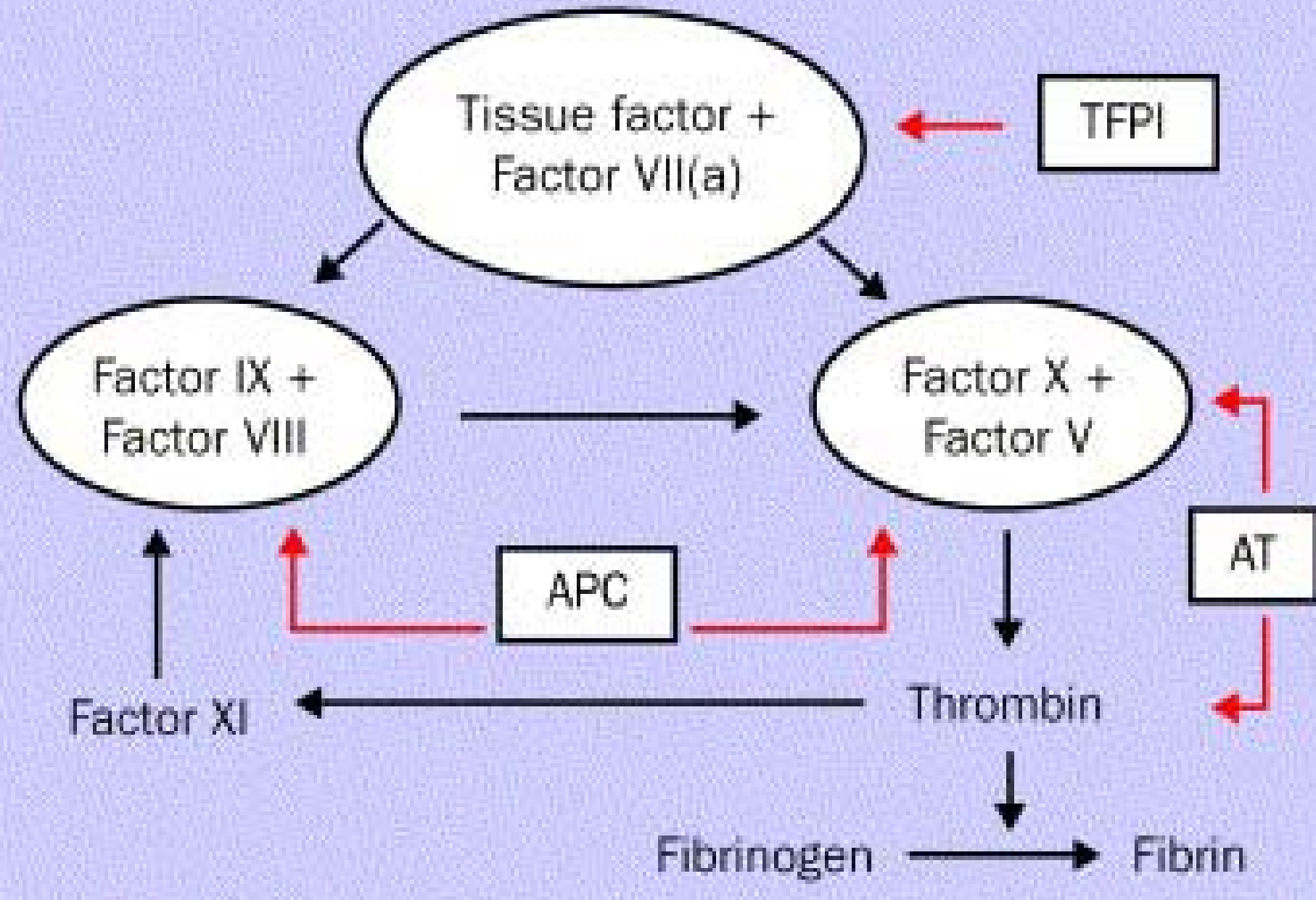
* Th1 denotes type 1 helper T cell, and Th2 type 2 helper T cell.

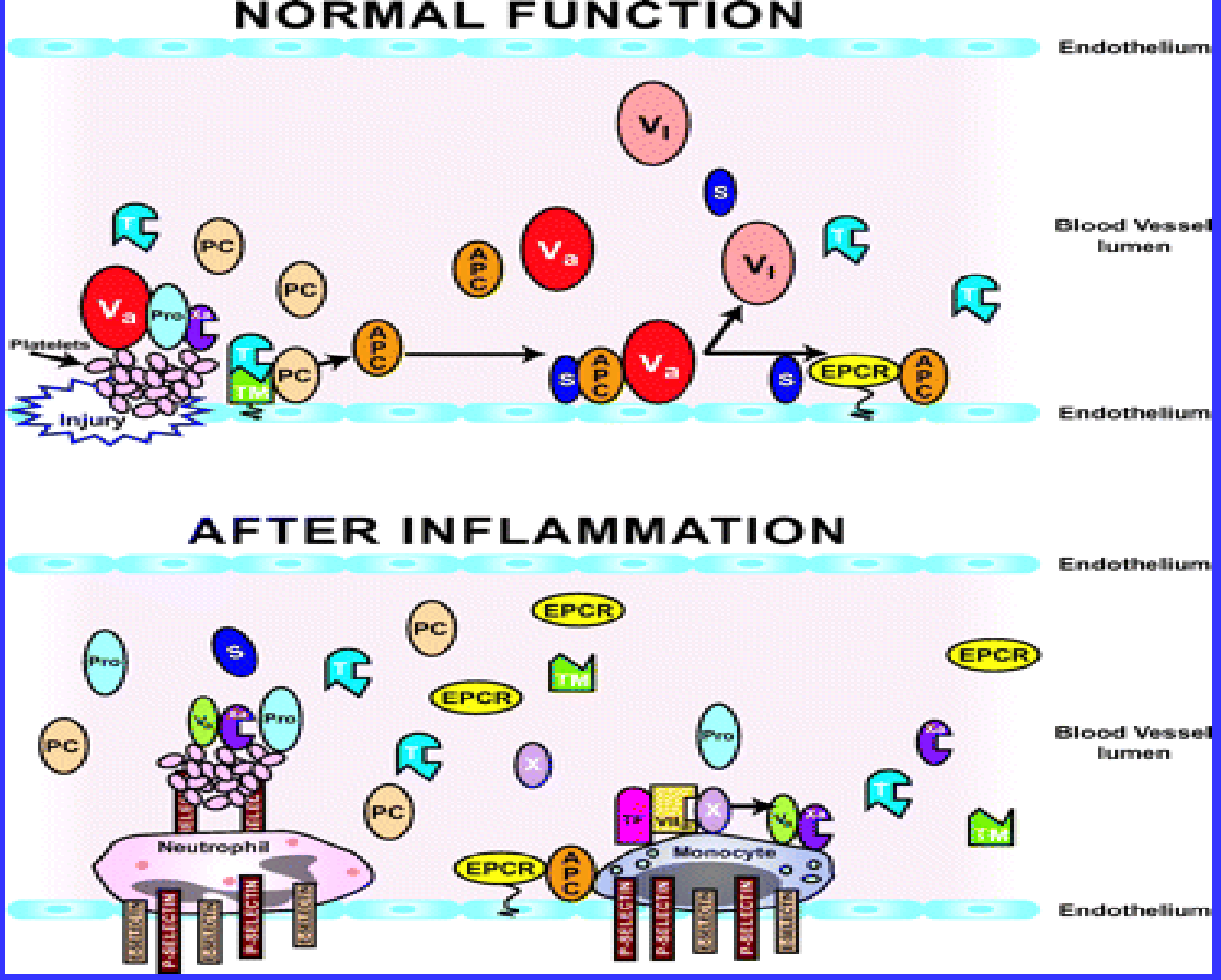




Daniel G Remick The American Journal of Pathology 2007; 170:1435-144

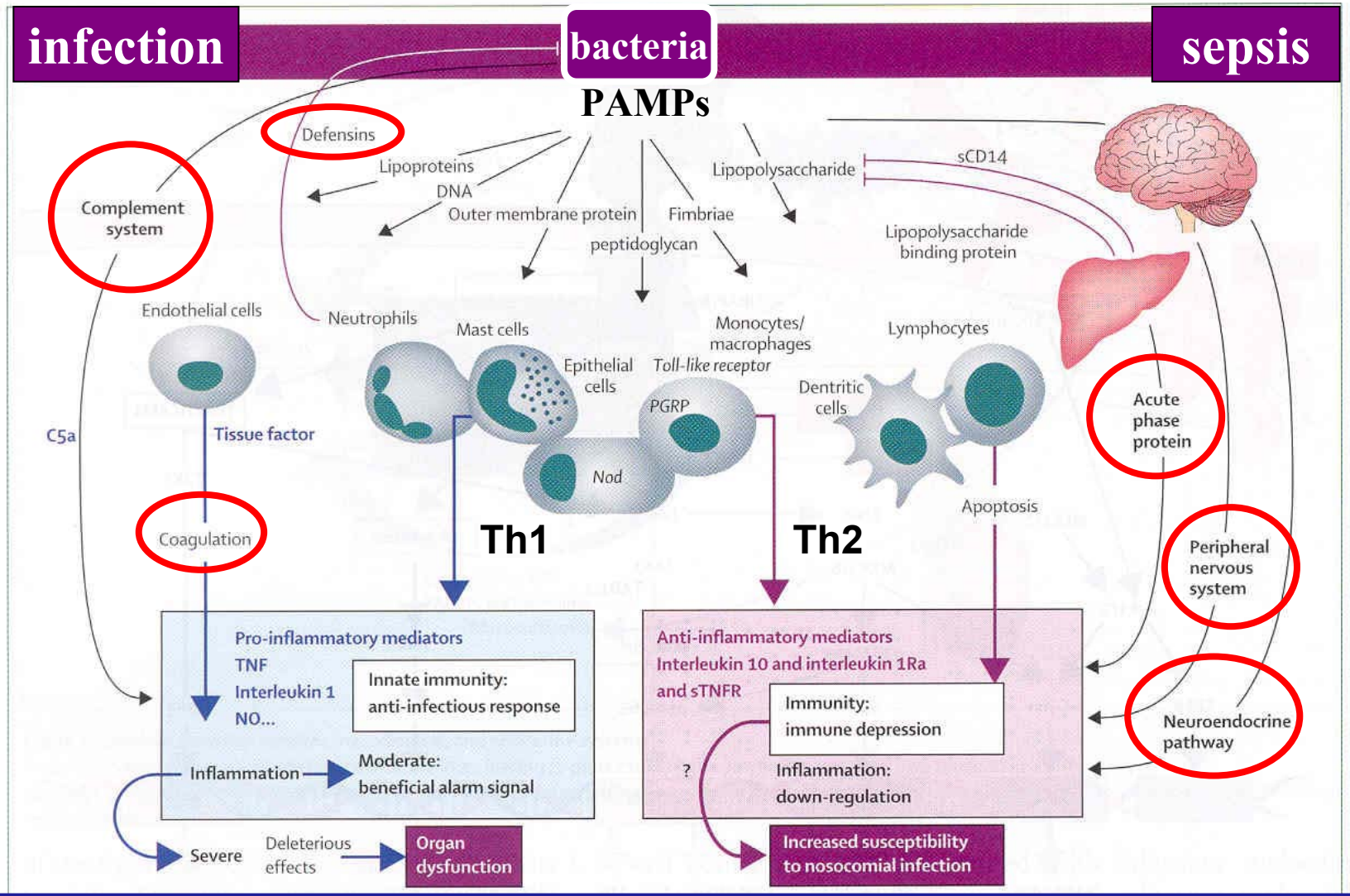
Coagulation and anticoagulation. TF, expressed on the surface of activated monocytes and endothelial cells, initiates activation of coagulation in response to a bacterial infection



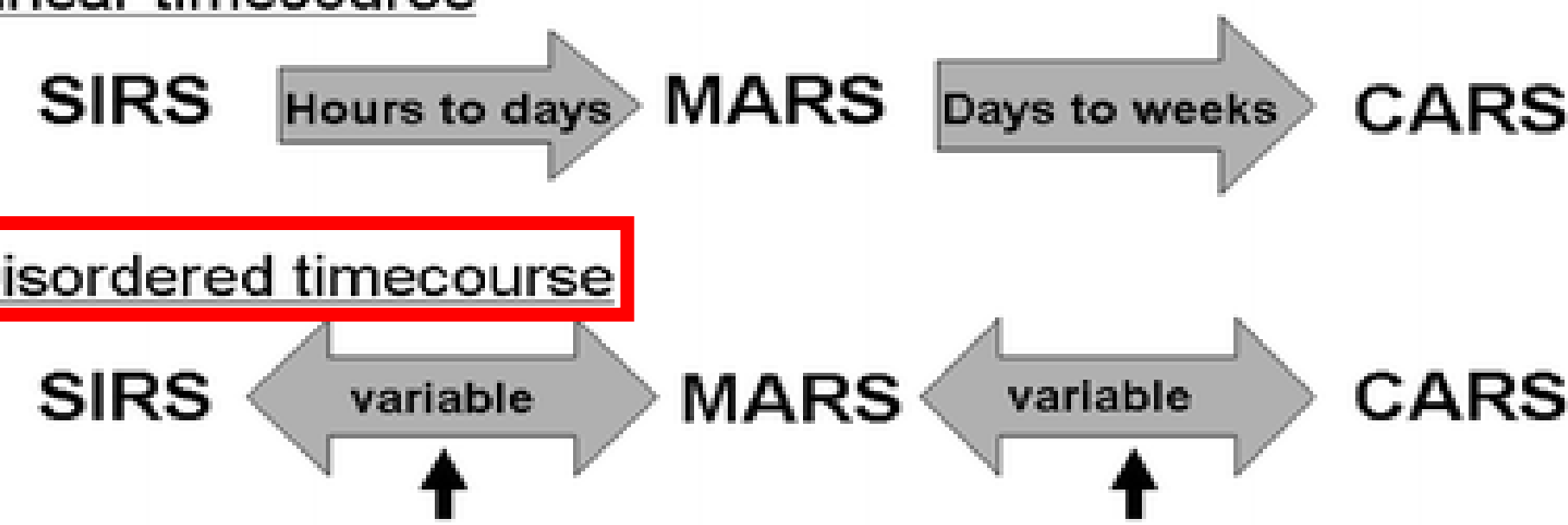


Control of coagulation in normal and inflamed vasculature

Annane D et al "Septic Shock" Lancet 2005; 365: 63-78



From bacteria to disease

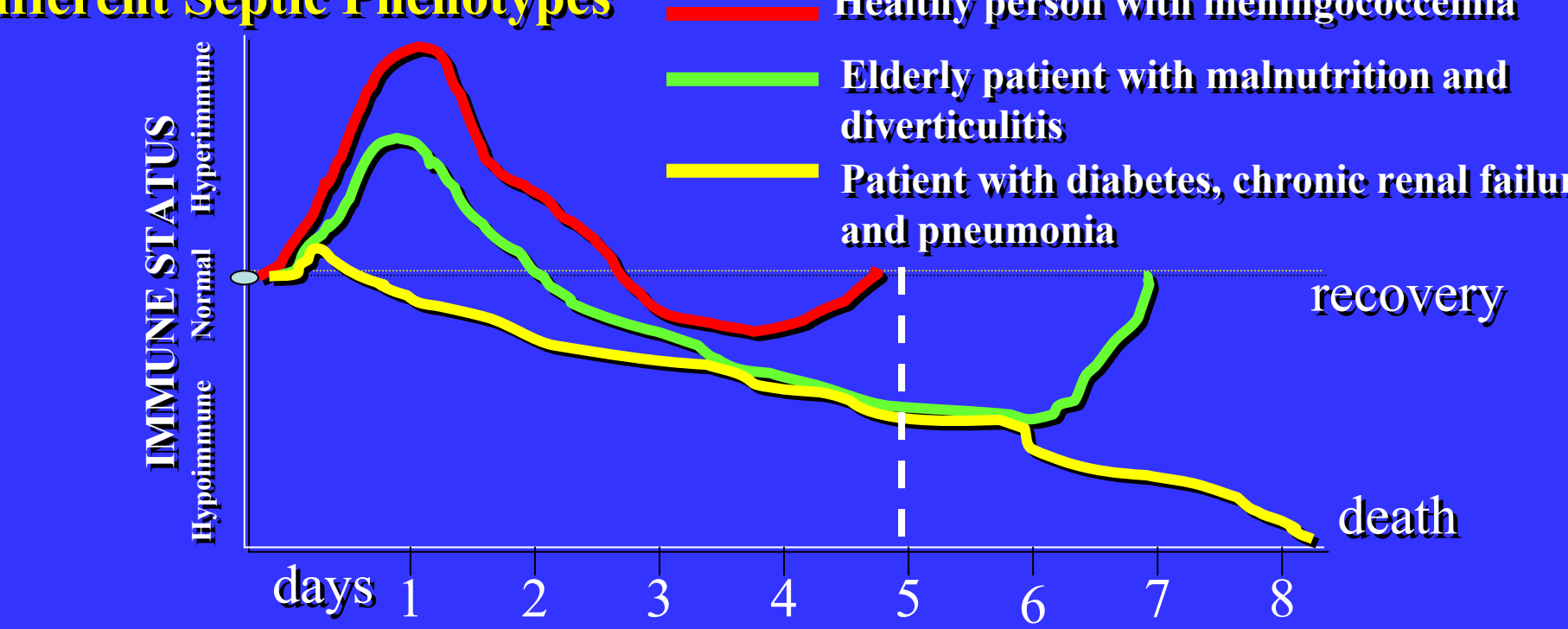


Modulating factors:

- Infection (recurrent)
- Surgery
- Medications (antibiotics, steroids, blood products, etc.)
- Underlying immune status
- Genetic predisposition
- Comorbid conditions (e.g., diabetes)
- Transfusion of blood products

Temporal development of sepsis induced fluctuations on immune response

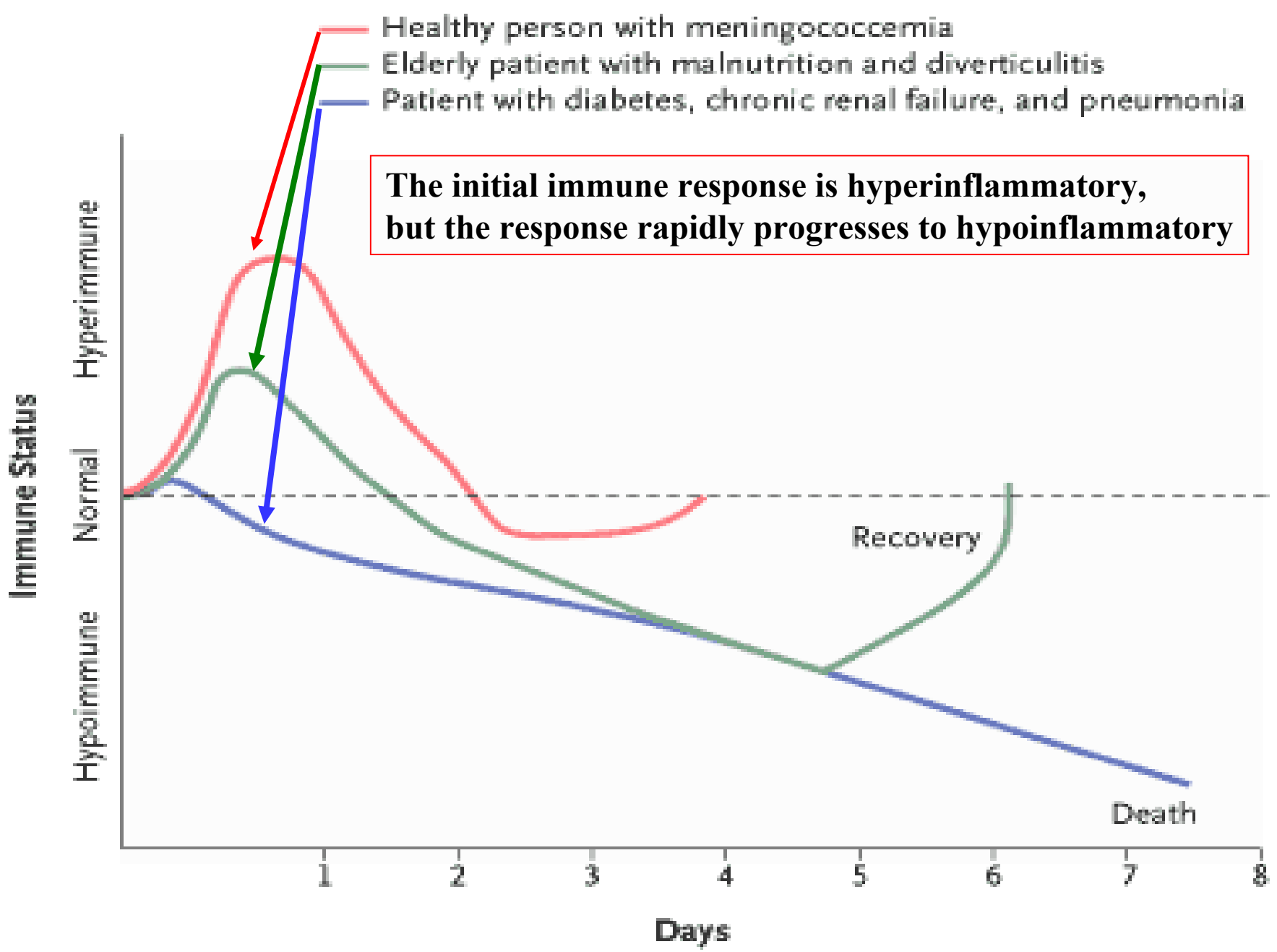
In the clinical setting , multiple factors , will tilt the balance toward one end of the spectrum or the other



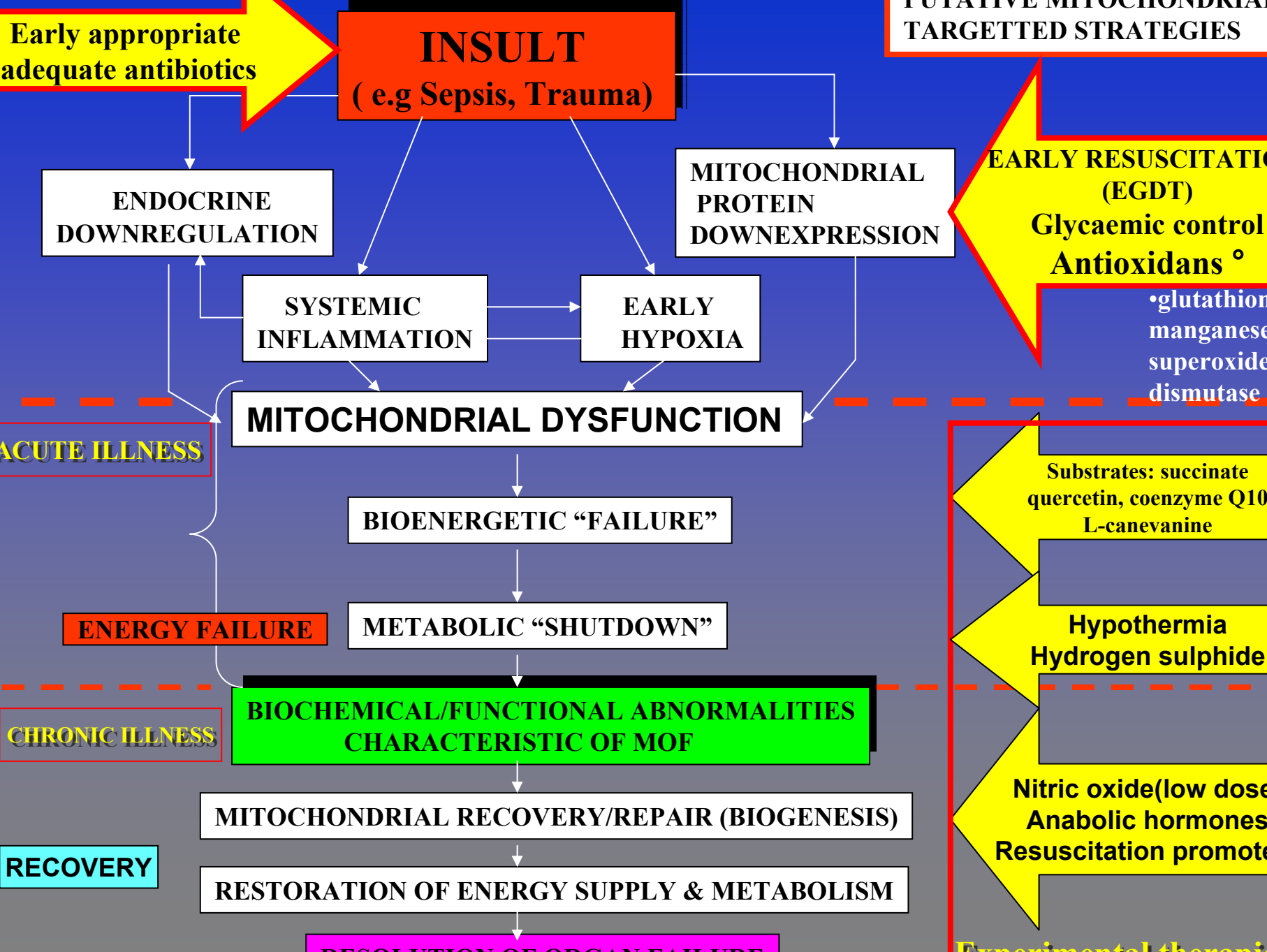
THE HETEROGENEITY

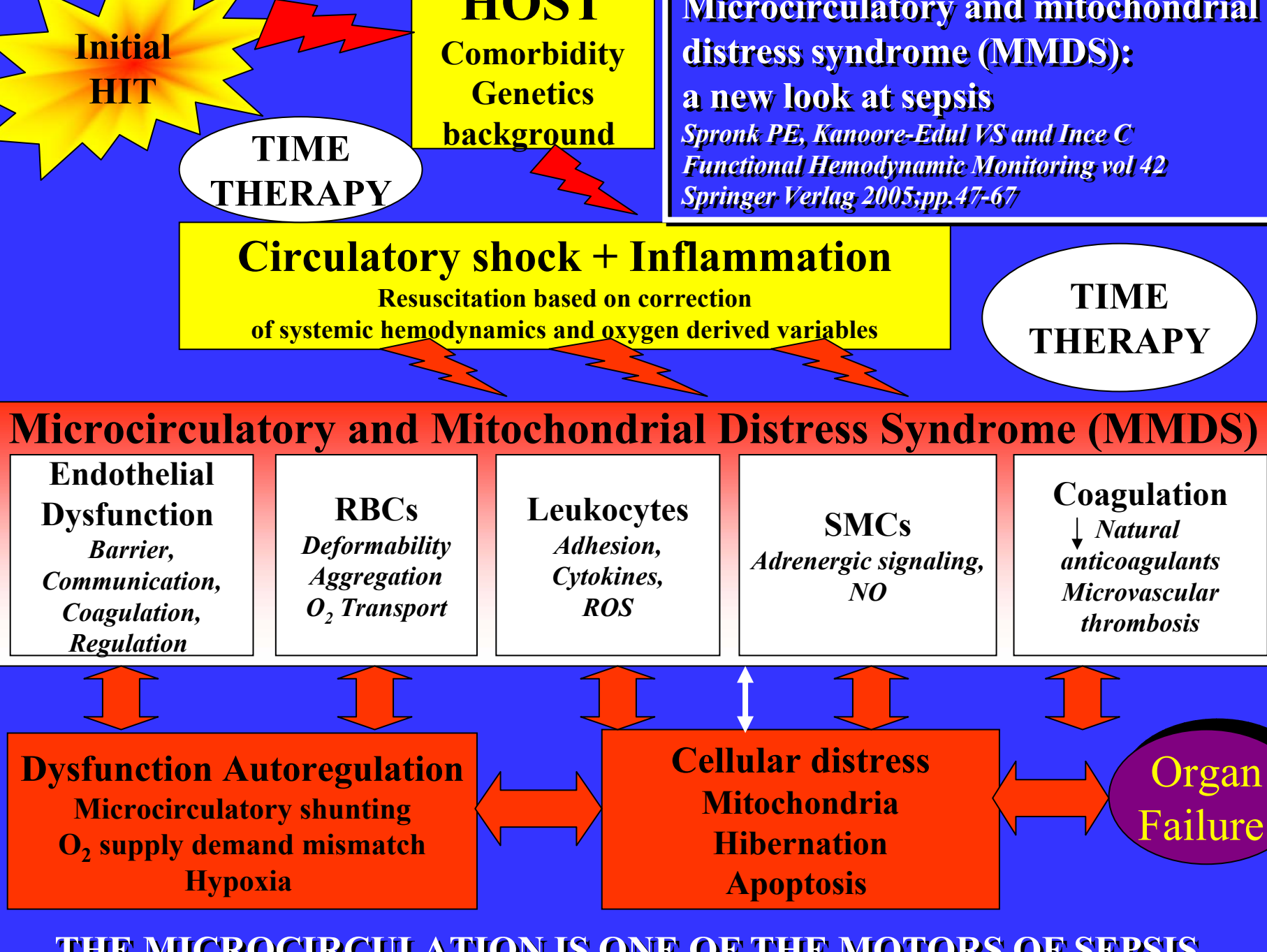
The individual response is determined by many factors, including:

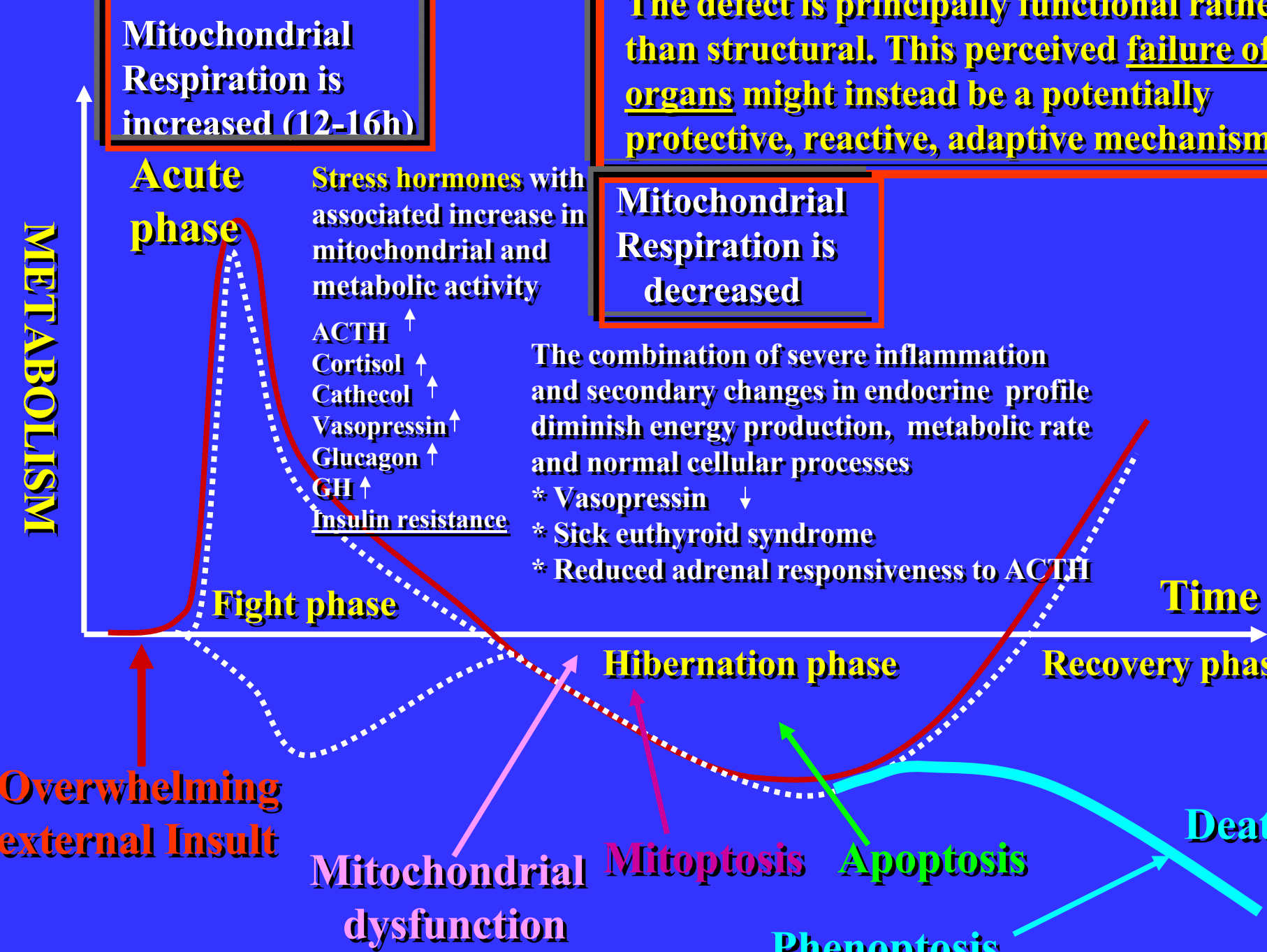
- **The virulence of the organism**
- **The size of the inoculum**
- **The patient's coexisting conditions**
- **The age**
- **The polymorphisms in genes for cytokines**

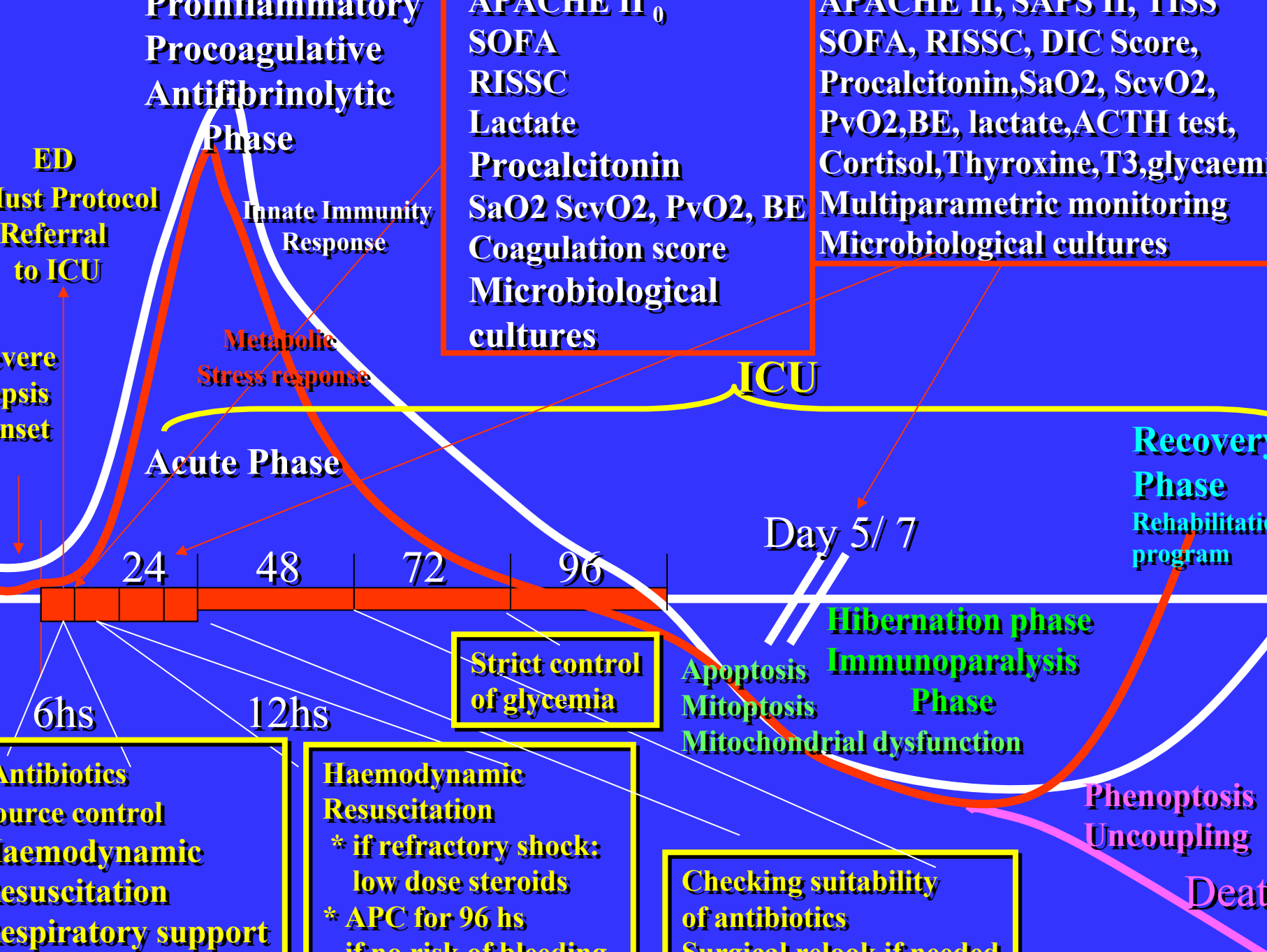


...Pathophysiology and Treatment of Sepsis. RS Hotchkiss and IE Karl N Engl J Med 2003;348:138-


Early appropriate adequate antibiotics
INSULT
(e.g Sepsis, Trauma)
PUTATIVE MITOCHONDRIA
TARGETTED STRATEGIES
ENDOCRINE DOWNREGULATION
MITOCHONDRIAL PROTEIN DOWNEXPRESSION
EARLY RESUSCITATIO
(EGDT)
Glycaemic control
Antioxidans °
•glutathion
manganese
superoxide
dismutase
SYSTEMIC INFLAMMATION
EARLY HYPOXIA
MITOCHONDRIAL DYSFUNCTION
ACUTE ILLNESS
BIOENERGETIC "FAILURE"
Substrates: succinate
quercetin, coenzyme Q10
L-canevanine
ENERGY FAILURE
METABOLIC "SHUTDOWN"
Hypothermia
Hydrogen sulphide
CHRONIC ILLNESS
BIOCHEMICAL/FUNCTIONAL ABNORMALITIES CHARACTERISTIC OF MOF
Nitric oxide(low dose
Anabolic hormones
Resuscitation promote
MITOCHONDRIAL RECOVERY/REPAIR (BIOGENESIS)
RECOVERY
RESTORATION OF ENERGY SUPPLY & METABOLISM
Experimental therapi


Initial HIT
HOST
Comorbidity
Genetics
background
TIME
THERAPY
Microcirculatory and mitochondrial distress syndrome (MMDS): a new look at sepsis
Spronk PE, Kanoore-Edul VS and Ince C
Functional Hemodynamic Monitoring vol 42
Springer Verlag 2005;pp.47-67
Circulatory shock + Inflammation
Resuscitation based on correction
of systemic hemodynamics and oxygen derived variables
TIME
THERAPY
Microcirculatory and Mitochondrial Distress Syndrome (MMDS)
Endothelial Dysfunction
Barrier, Communication, Coagulation, Regulation
RBCs
Deformability
Aggregation
O_2 Transport
Leukocytes
Adhesion, Cytokines, ROS
SMCs
Adrenergic signaling, NO
Coagulation
↓ Natural anticoagulants
Microvascular thrombosis
Dysfunction Autoregulation
Microcirculatory shunting
O_2 supply demand mismatch
Hypoxia
Cellular distress
Mitochondria
Hibernation
Apoptosis
Organ Failure
THE MICROCIRCULATION IS ONE OF THE MOTORS OF SEPSIS


Mitochondrial Respiration is increased (12-16h)
The defect is principally functional rathe
than structural. This perceived failure of
organs might instead be a potentially
protective, reactive, adaptive mechanism
Acute phase
Stress hormones with associated increase in mitochondrial and metabolic activity
ACTH
Cortisol
Cathecol
Vasopressin
Glucagon
GH
Insulin resistance
Mitochondrial Respiration is decreased
The combination of severe inflammation and secondary changes in endocrine profile diminish energy production, metabolic rate and normal cellular processes
* Vasopressin
* Sick euthyroid syndrome
* Reduced adrenal responsiveness to ACTH
METABOLISM
Time
Fight phase
Hibernation phase
Recovery phas
Overwhelming external Insult
Mitochondrial dysfunction
Mitoptosis
Apoptosis
Deat
Phenoptosis


Proinflammatory
Procoagulative
Antifibrinolytic
Phase
ED
lust Protocol
Referral
to ICU
vere
psis
nset
Innate Immunity
Response
Metabolic
Stress response
APACHE II 0
SOFA
RISSC
Lactate
Procalcitonin
SaO2 ScvO2, PvO2, BE
Coagulation score
Microbiological
cultures
APACHE II, SAPS II, TISS
SOFA, RISSC, DIC Score,
Procalcitonin,SaO2, ScvO2,
PvO2,BE, lactate,ACTH test,
Cortisol,Thyroxine,T3,glycaem
Multiparametric monitoring
Microbiological cultures
ICU
Acute Phase
Recovery
Phase
Rehabilitati
program
Day 5/ 7
24
48
72
96
6hs
12hs
Strict control
of glycemia
Apoptosis
Mitoptosis
Mitochondrial dysfunction
Hibernation phase
Immunoparalysis
Phase
Phenoptosis
Uncoupling
Deat
ntibiotics
ource control
aemodynamic
esuscitation
espiratory support
Haemodynamic
Resuscitation
* if refractory shock:
low dose steroids
* APC for 96 hs
Checking suitability
of antibiotics

Pathogenesis of Sepsis and Septic Shock

Examples

Sites of Infection

Abscess	Fasciitis
Appendicitis	IV catheter
Cellulitis	Meningitis
Cholecystitis	Peritonitis
Diverticulitis	Pneumonia
Empyema	Pyelonephritis
Endocarditis	Sinusitis

Nidus of Infection

Standard Therapy

Drain site of infection

Early antibiotic therapy often empiric and based on likely pathogens and susceptibilities

Microbes and microbial products

Bacteremia	Mannans
Endotoxin	Glucans
Exotoxins	Bacterial DNA
Petidoglycans	

Blood Stream Invasion by Microbes or their Products

Early Diagnosis

MICROBIOLOGY

Humoral Microbial Receptors

C reactive protein
Serum amyloid
Mannose binding protein
Lipopolysaccharide binding proteins
Complement

Cellular Microbial Receptors

Toll-Like Receptors
CD14
Scavenger receptors I, II
Complement receptors
Mannose receptors

Host Defenses Activated

Anti-Inflammatory
Low dose glucocorticoids ?
APC
Insulin therapy

Host Cells

Endothelium
Epithelium
Neutrophils
Monocytes
Macrophages
Lymphocytes

Inflammatory Mediators

Complement
Kinins
Coagulation
Cytokines
Chemokines
Reactive O2 species
Nitric oxide
Proteases
Eicosanoids
Platelet activating factor

Cell Activation and Inflammatory Mediator Release

LABORATORY

Hemodynamic Effects

Vasodilation
Hypotension
Myocardial depression

Inflammatory Tissue Damage

Diffuse endothelial injury
Fibrin and microemboli deposition
Tissue Hypoxia
Immune Suppression
Apoptosis / Cell Necrosis

Shock and Multiple Organ Failure

Supportive treatment
Fluid resuscitation
Vasopressor administration
Inotropic support
EGDT

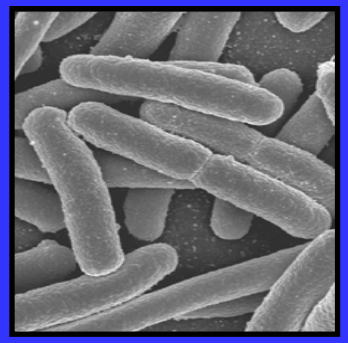
EARLY treatme 6hrs bund

Therapeutic approach

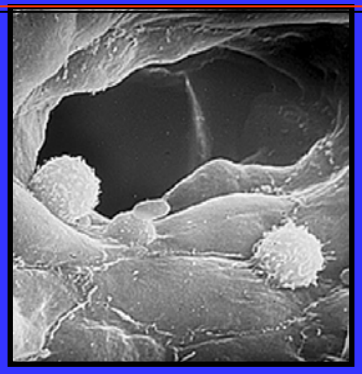
interventions aimed at decreasing mortality

Surviving Sepsis Campaign : *The Bundles*

Infection



Systemic inflammatory response



Endothelial Dysfunction

Cell activation

Multi-organ dysfunction

Eliminate infection

- DIAGNOSIS
- Antibiotics
- Source Control

Specific therapy

Reduce systemic reaction

- EGDT
- Steroids
- Insulin (glucose control)
- rhAPC (Xigris)

Adjunctive therapy

Support organs

- Ventilation

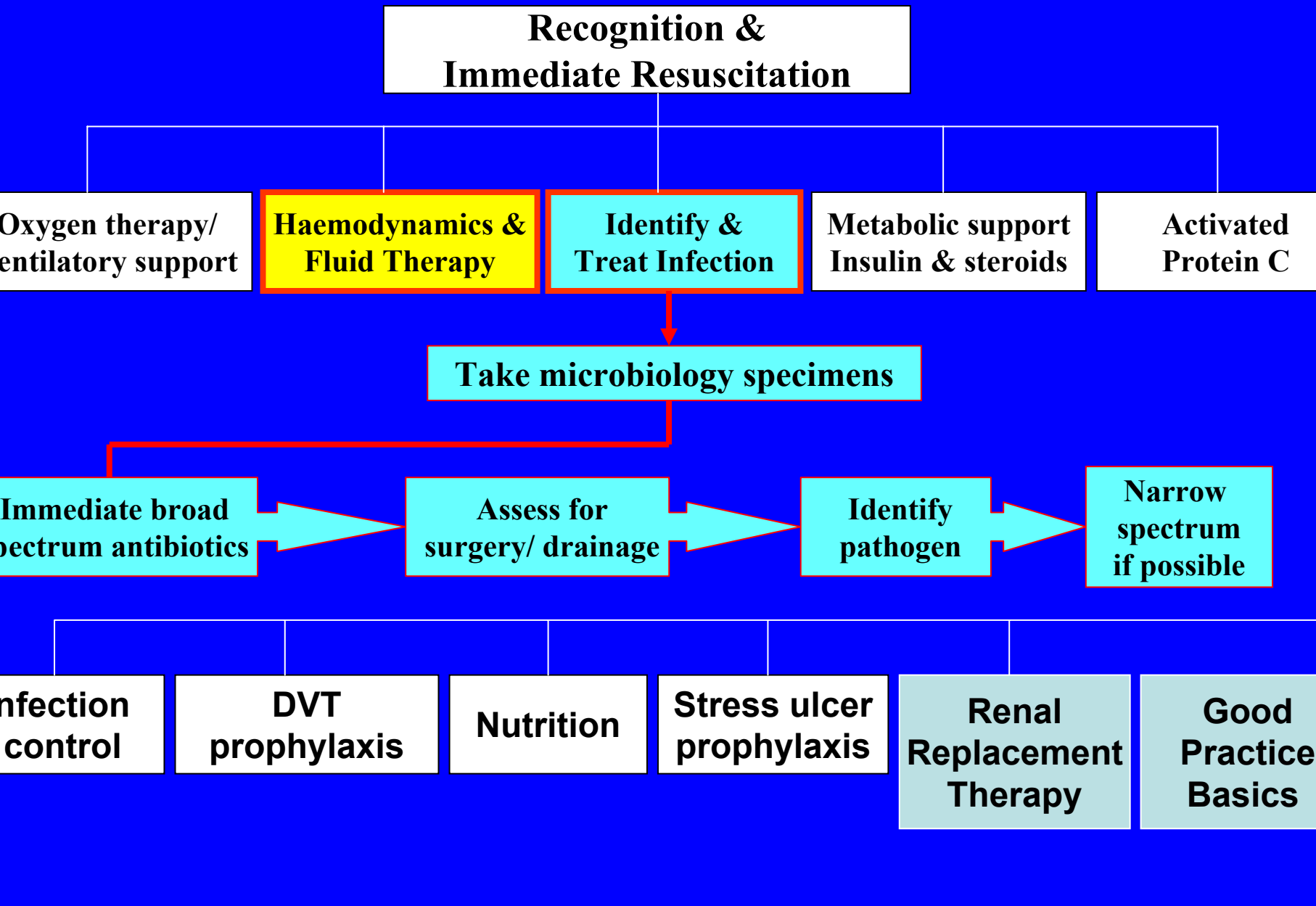
Low Tidal Volume

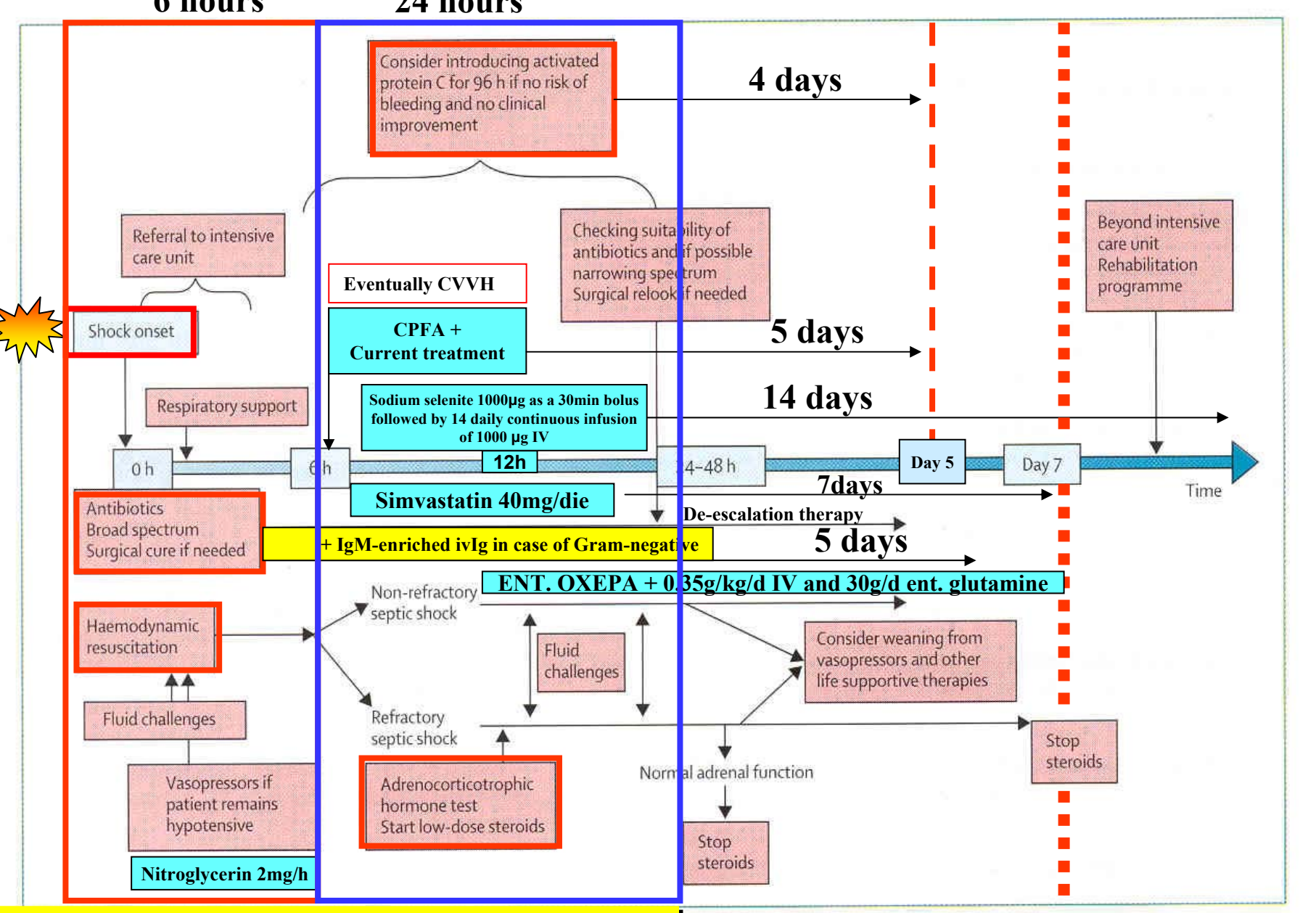
- CRRT

Supportive therapy

Crit Care Med 2004; 32:858–873

Overall approach to severe sepsis patients





Principles of treatment in Septic Shock

IMMUNOLOGICAL MONITORING

nfortunately, at present, we cannot rapidly measure the patient's ability to produce ppropriate inflammatory response, as opposed to an excessive or inadequate respon

Immunological competence

HLA-DR+monocytes, TNF/IL-12, IL-10, IL-10/TNFα

CD-13/CD14HLA-DR Th1/Th2

Inflammation

TNF,IL-6,IL-8 plasmatic,

IL-8(BAL), CRP

MBL and EndoCab

Infection

Procalcitonin

Neopterin

TREM-1

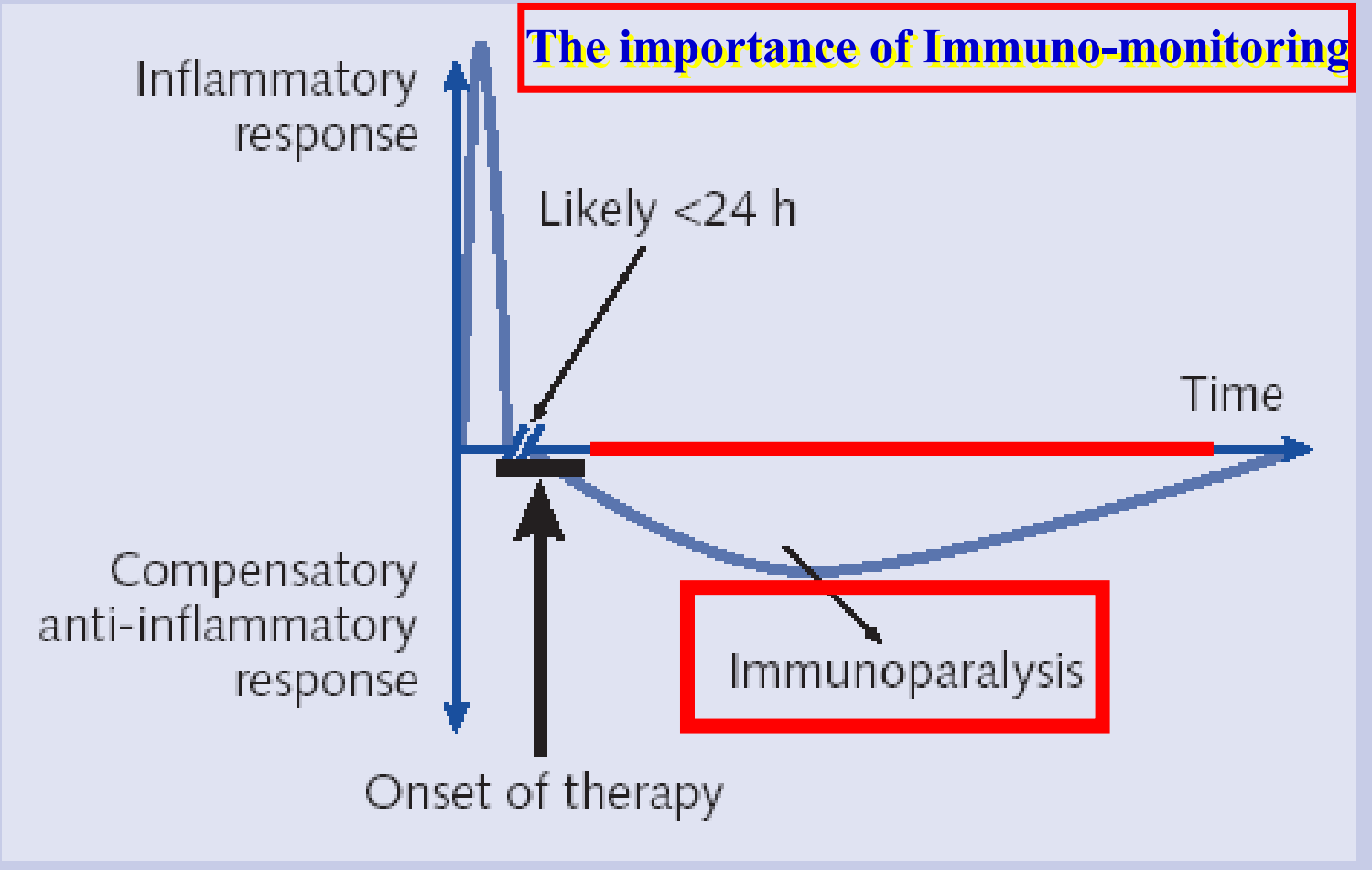
Septi Fast

Tissue injury

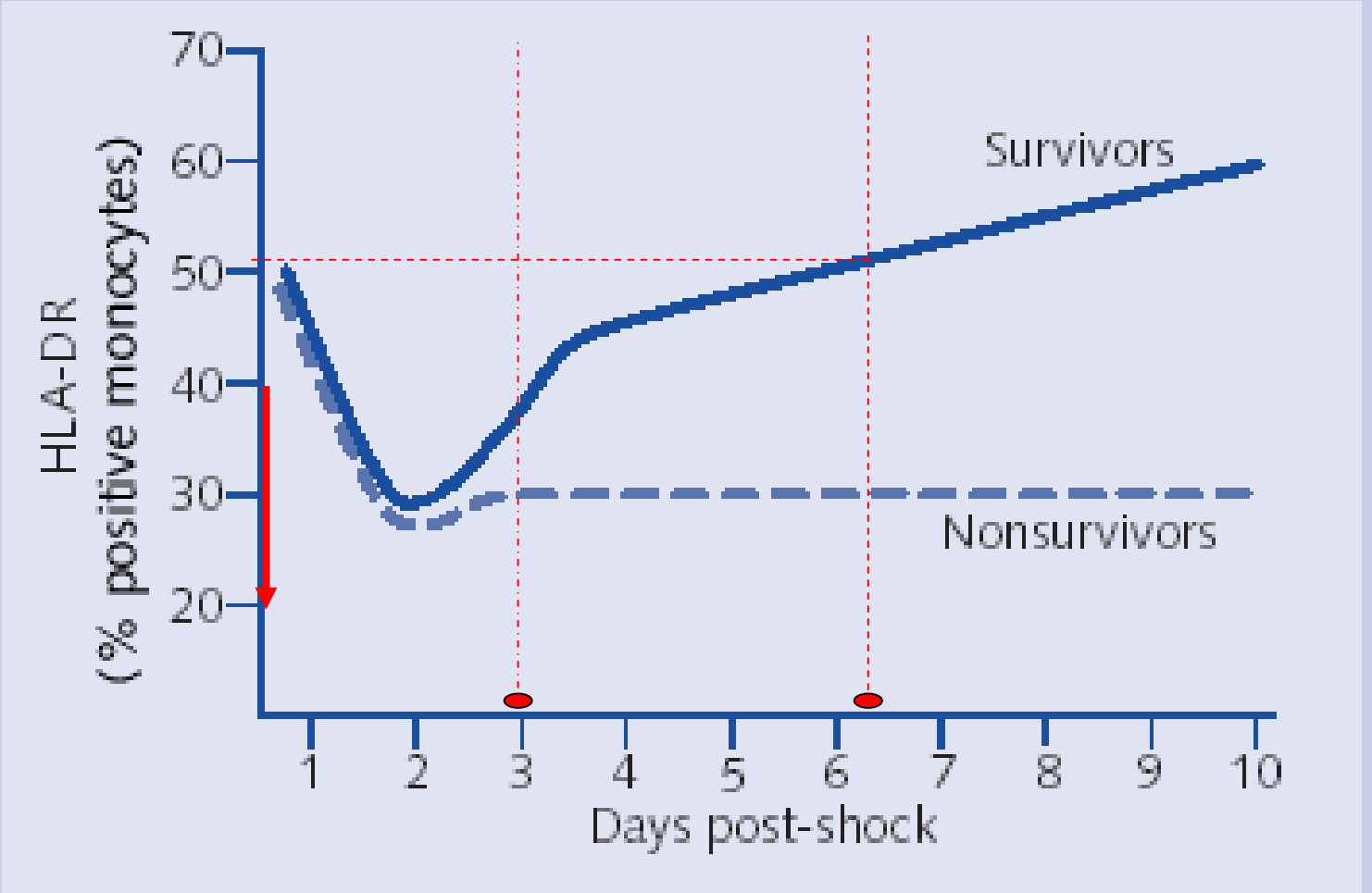
IL-6, E-Selectin (plasmatic)

s-Thrombomodulin,s-VWF

Simplified description of the pro- and anti-inflammatory responses after septic shock. At the onset of therapy most patients are already immunoparalyzed and anti-inflammatory drugs may be deleterious.



Schematic representation of monocyte HLA-DR expression in patients with septic shock over time



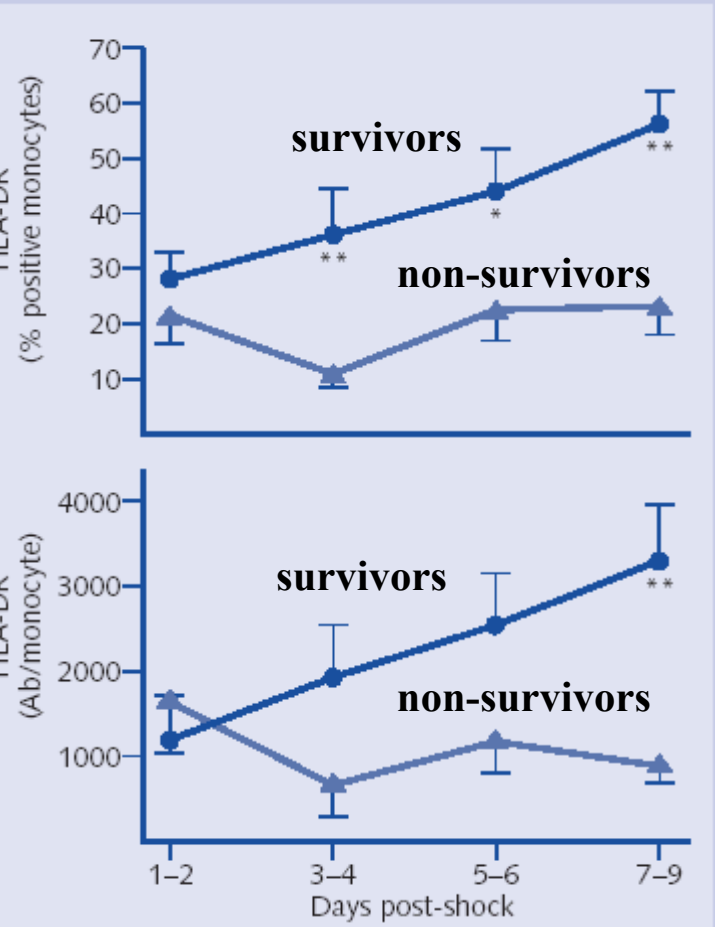
HLA-DR: human leukocyte antigen type DR.

HOW TO IDENTIFY SYSTEMIC SEPSIS-INDUCED IMMUNOPARALYSIS

Guillermo Monneret Advances in Sepsis 2005; 4: 42-9

Changes in HLA-DR expression on monocytes from patientswith septic shock.

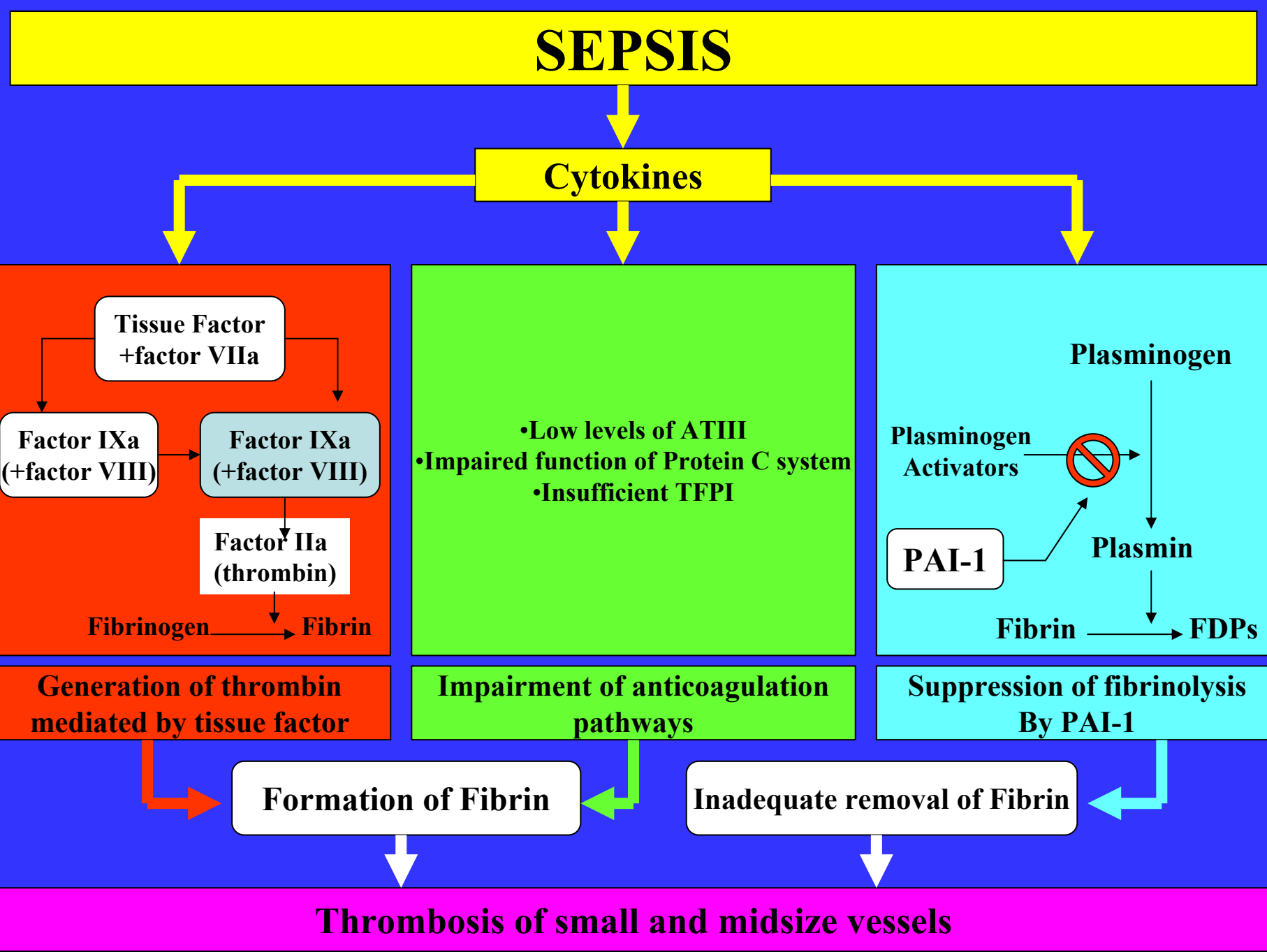
Results are expressed as the mean percentage of monocytes expressing HLA-DR (top) and as the number of antibodies bound per cell (bottom) in patients who survived (n= 22, ●) or died (n=16, △)



<0.05 vs. nonsurvivors; **p<0.001 vs. nonsurvivors.
antibodies; HLA-DR: human leukocyte antigen type DR.

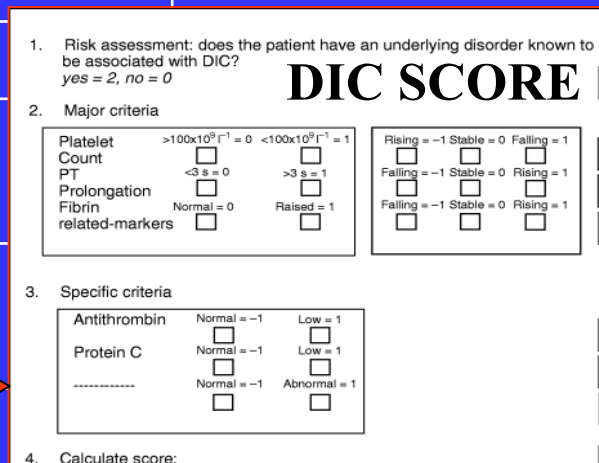
- TNF-α
- Whole blood TNF-α response to LPS
- IL-6
- IL-10
- IL-10/TNF-α
- Total lymphocytes
- CD3 T lymphocytes
- CD4 T lymphocytes
- CD4CD25 (Treg)
- CD4CD25
- γδ Tlymphocytes
- Other (including B, CD8,NK)

Guillaume Monneret Advances in Sepsis 2005; 4: 42

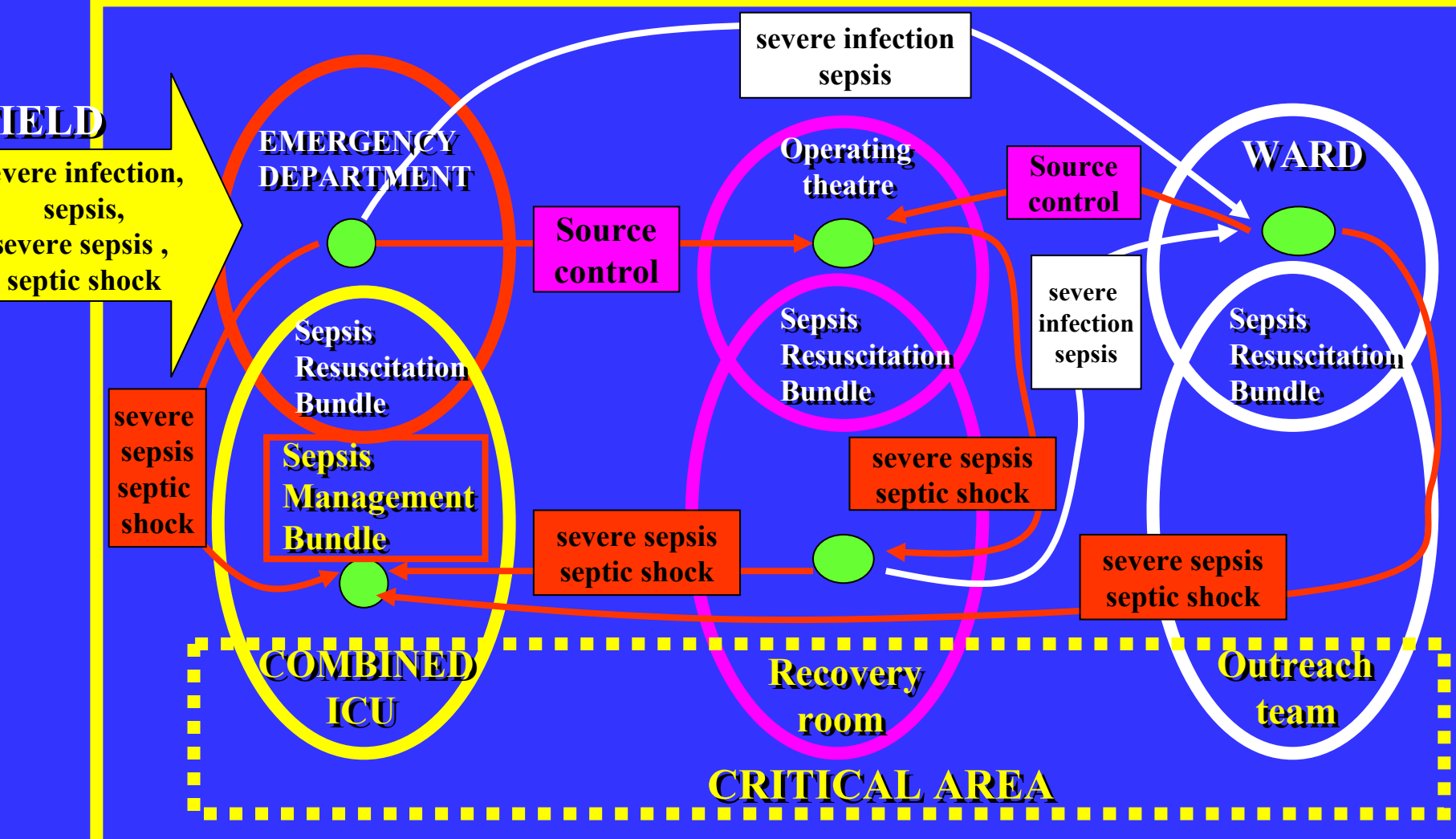

SEPSIS
Cytokines
Tissue Factor
+factor VIIa
Factor IXa
(+factor VIII)
Factor IXa
(+factor VIII)
Factor IIa
(thrombin)
Fibrinogen
Fibrin
•Low levels of ATIII
•Impaired function of Protein C system
•Insufficient TFPI
Plasminogen
Plasminogen
Activators
PAI-1
Plasmin
Fibrin
FDPs
Generation of thrombin
mediated by tissue factor
Impairment of anticoagulation
pathways
Suppression of fibrinolysis
By PAI-1
Formation of Fibrin
Inadequate removal of Fibrin
Thrombosis of small and midsize vessels

MONITORING OF COAGULATION PARAMETERS
global and dynamic

lobal coagulation arameters	Turn-over coagulation parameters	Endothelial function	Platelets function
PT	*FM	*levels of soluble Thrombomodulin	*platelets aggregation with PRP
APTT	*TAT	*levels of Von Willebrand factor and Von Willebrand CAB	*PFA-100(ADP)
TT	*F1+2	*endothelial protein C receptor (ECPR)	*plasmatic levels of PF-4
ATIII	*D-dimers	*activated Protein C	*plasmatic levels of Beta-TG
Fibrinogen	*tPA	*protein S	
platelets count	Antigen/activity *PAP	*C4bBP	
TEG	Antigen/activity *PAI-1	*AT antigen	
ROTEM			



THE HOSPITAL ORGANISATION MUST CHANGE
THE EXTENDED ROLE OF THE INTENSIVIST
THE NEW ROLE OF THE ED PHYSICIAN
THE OUTREACH TEAM



Biologic therapy in clinical practice: enthusiasm must be tempered by caution

Rheumatoid Arthritis (RA) is a major cause of disability and is associated with significant mortality in its own right

The effects of therapy with traditional Disease-Modifying-Anti-Rheumatic Drugs (DMARDs) on outcomes have previously left much to be desired. This i not surprising, given the poor understanding of pathological mechanisms underlying this disease at the molecular and cellular levels

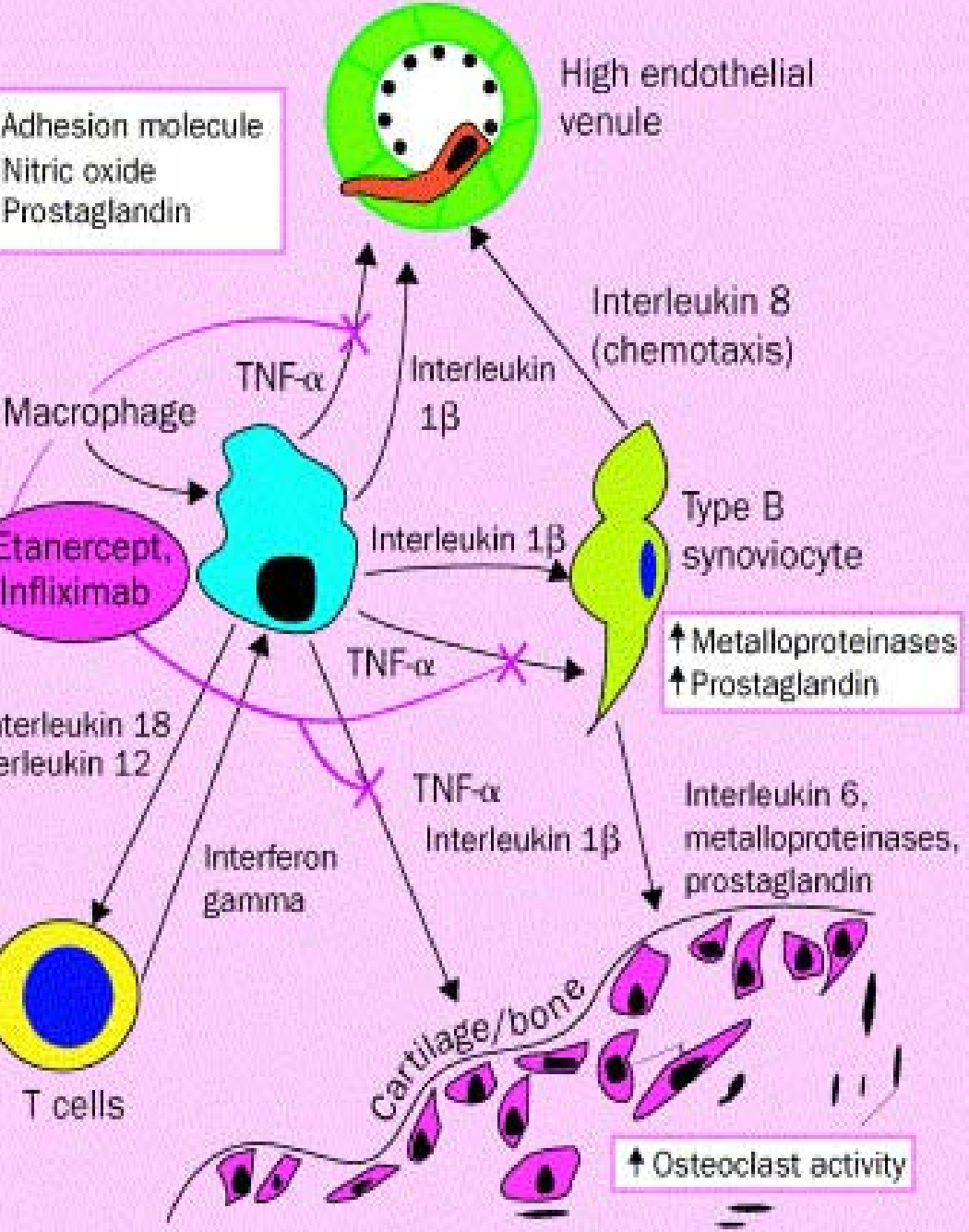
Prior P et al. Causes of death in RA Brit J Rheumatol 1984; 23:2-9

Vandenbroucke JP et al Survival and cause of death in RA: a 25 year prospective followup J Rheumatol 1984; 11:158-61

Mitchell DM et al Survival, prognosis and causes of death in RA Arthritis Rheum 1986; 29:706-14

Markenson JA Worldwide trends in the socio-economic impact and long term prognosis o RA Semin Arthritis Rheum 1991; 21(supll 1):4-12

Wolfe F et al. The mortality of RA 1994;37:481-94



Rheumatoid Arthritis is regarde as a systemic autoimmune diseas characterized by inflammation and subsequent destruction of joints.

In the traditional view, the inflammatory process starts in the synovial tissue, where an interaction of immunoglobulins mediators of inflammation and progressively specialized effecto cells leads to the formation of pannus tissue that subsequently degrades bone (leading to erosions) and cartilage (leading to thinning and defects)

Dinarello C, Moldawer L. *Proinflammatory and Anti-inflammatory Cytokines in Rheumatoid Arthritis: A Primer for Clinicians.* 3rd ed. Thousand Oaks, Ca,

Biologic therapy in clinical practice: enthusiasm must be tempered by caution

Drugs currently licensed for use in RA that inhibit these inflammatory molecules - etanercept, infliximab, adalimumab (TNF-α) and anakinra (IL-1β) – have been shown clearly to be effective in reducing disease activity

The efficacy of the anti-tumor necrosis factor α(TNF-α) agents infliximab, etanercept and adalimumab in the treatment of rheumatoid arthritis (RA) (to reduce disease activity and progression of joint damage) has been demonstrated in large scal trials

The success in clinical trials is the more impressive given that the have tended to be used in patients who had previously failed to respond to a number of conventional DMARDs

Maini R et al . Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) vs placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999; 354: 1932-9

Lipsky PE et al Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti –tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study group. N Engl J Med 2000; 343: 1594-602

Weinblatt ME et al A trial of etanercept , a recombinant tumor necrosis factor receptor :Fc fusion protein, in patien with rheumatoid arthritis receiving methotrexate . N Engl J Med 1999; 340: 253-9

Moreland LW et al Etanercept therapy in rheumatoid arthritis. A randomized controled trial. Ann Intern Med 1999

	Infliximab (Remicade*)	Etanercept (Enbrel*)	Adalimumab (Humira*)
Year of FDA approval	1998	1998	2002
Molecular description	Chimeric monoclonal antibody derived from mouse-human antibodies	Monoclonal antibody derived from human antibodies	Monoclonal antibody derived from human antibodies
Mechanism(s) of action	Binds to TNF-α and inhibits it from binding with its receptor; induces apoptosis of monocytes and other TNF-α-expressing cells	''Decoy'' receptor for TNF-α	Binds to TNF-α and inhibits it from binding with its receptor; lyses surface TNF expressing cells *in vitro* in the presence of complemen
Usual dosage/route of administration†	Induction doses of 3 mg/kg IV at 0, 2, and 6 wk, followed by 3–10 mg/kg IV every 8 wk	25 mg SC twice weekly	40 mg SC every 2 wk
Mean terminal half-life	10 days	4 days	14 days

Abbreviations: IV = intravenous; SC = subcutaneously.
*See Introduction for manufacturer information.
†Dosage may vary by disease and clinical response to therapy.

Infliximab (REMICADE Schering-Plough)
Etanercept (ENBREL Wyeth)
Adalimumab (HUMIRA Abbott)
Anakinra (KINERET Amgen) recombinant form of the antagonist receptor of IL-1(IL-1Ra)
Efalizumab (RAPTIVA Genentech) anticor

Klinkhoff A Biological agents for rheumatoid arthritis Drugs 2004; 64:1267-1283

Properties of currently available anti-TNFα agents

	TNF-α inhibitor		
rug properties	Infliximab	Etanercept	Adalimimab
ructure	Mouse human chimeric IgG1k anti-TNFα monoclonal antibody	Two p75 TNFα soluble receptors fused to the Fc portion of IgG1	Fully humanized IgG1k antiTNFα monoclonal antibody
rget	TNFα	TNFα; lymphotoxinα	TNFα
finity	Soluble and transmembrane TNFα	Soluble TNFα	Soluble and transmembrane TNFα
mune actions	Monocyte and T cell apoptosis, lysis of TNF expressing cells	Antiapoptotic agent, possible long term effects on monocytes, no lysis of TNF expressing cells	Possible effects on apoptosis, monocytes and natural killer cells, lysis of TNF expressing cells
lf life (d)	8.0-9.5	4.0-5.0	12.0-14.0
sing/route	Every 15-60 d/intravenous	Every 3-4 d to every week/subcutaneous	Every 7-14 d/subcutaneous
sing regimen	RA (with MTX) Induction:3mg/kg at 0,2,6wk Maintenance:3mg/kg every 8wk If response incomplete, dose can be adjusted as high as 10mg/kg every 4 wk PsA (with or without MTX)AS,PP Induction: 5mg/kg at 0,2,6 wk Maintenance:5mg/kg every 8 wk CD,UC Induction:5mg/kg at 0,2,6 wk Maintenance:5mg/kg every 8 wk	RA,PsA,AS 50 mg/wk If two 25-mg injections are chosen, they can be given 3-4 d apart JRA 0.8mg/kg weekly up to 50 mg PP 50 mg semiweekly	RA,PsA,AS 40mg semimonthly RA patients not taking MTX can increase dose to 40 mg/wk CD Induction : 160mg at 0 wk (single dose or two 80mg doses daily Maintenance: 40mg every other w starting at wk 4
ration of erapy	Usually protracted	Usually protracted	Usually protracted

Biologic therapy in clinical practice: enthusiasm must be tempered by caution

Pro-inflammatory cytokines have not evolved merely to cause RA

They are essential components of physiological homeostasis and the immune system in particular, with important roles in defence against infections and tumours

One can therefore predict that the chronic inhibition of these cytokines, which appears to be required for effective therapy in RA , might result in an increased incidence of infections or tumours in some patients

Such potential adverse effects have been investigated carefully in the various clinical trials but not found to be a particular problem

Lipsky PE et al Infliximab and methotrexate in the treatment of RA. Anti-TNFα trial in RA with concomitant therap study group NEngl J med 2000;343:1594-602

Bathon JM et al A comparison of etanercept and methotrexate in patients with early RA N Engl J Med 2000;343:1586-93

Klareskog L et al Global safety and efficacy of up of five years of etanercept (enbrel) therapy in RA Arthritis Rheum 2001; 44(suppl):S77

Kavanaugh A et al Long term follow up of patients treated with remicade (Infliximab) in clinical trials Arthritis Rheum 2001;44(suppl):S81

Major Safety Issues Associated With Biologic Therapy in RA

- Infections and serious infections
- Tuberculosis/opportunistic infections
- Lymphoma and other malignancies

Focus on the "Big 3"

- Demyelinating diseases
- Lupus-like syndromes/ANA formation
- CHF
- Immunogenicity
- Infusion/injection reactions

THE BIG 3

ANA = antinuclear antibody; CHF = congestive heart failure.

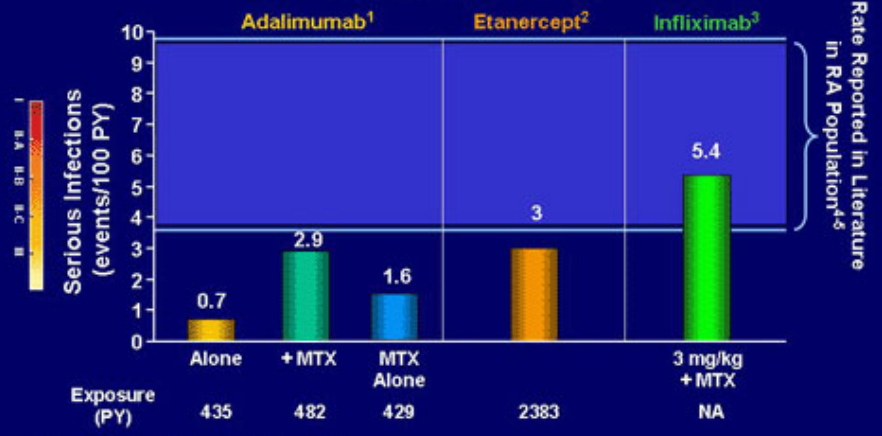
Serious Infection Rates in RA Clinical Trials

	Etanercept*	Infliximab*	Adalimumab
PYs of Exposure	8336	2458	4870
	Incidence Per 100 PYs		
TNF Antagonist	4	3	4†
Placebo	4	3	2

Serious infection rates have been similar to rates in patients receiving placebo and have been stable over time

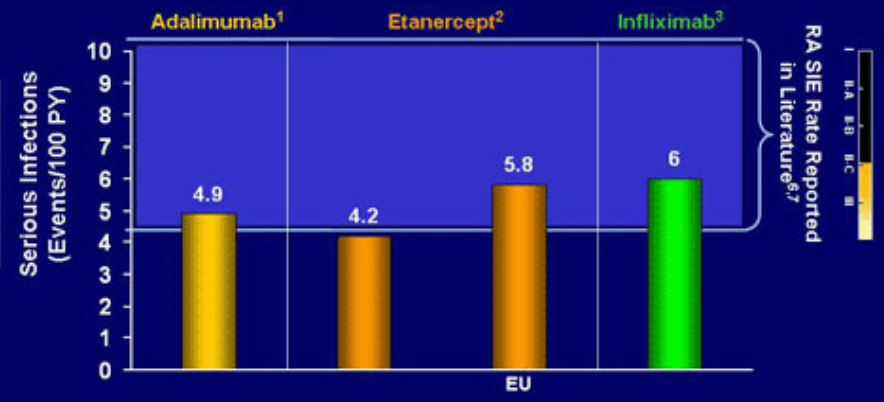
ludes clinical trials pre-approval and post-approval; †4.9 after recoding per MedDRA database.
= patient-years; TNF = tumor necrosis factor.
sented at FDA Arthritis Advisory Committee Meeting, March 2003; Kavanaugh A, et al. *Clin Exp Rheumatol.* 3;21:S203-8.

Serious Infections in Early RA Clinical Trials



MTX = methotrexate; NA = not available.
1. Schiff MH, et al. Presented at: EULAR Annual Meeting; June 8-11, 2005; Vienna, Austria; 2. Lebwohl, et Presented at: 63rd Annual Meeting of AAD; February 18-22, 2005; New Orleans, LA; 3. Conservative est. assuming 54-wk drug exposure for all pts (ie, 21 infections in 386 PY exposure) St Claire E, et al. *Arthritis Rheum.* 2004;50:3432-43; 4. Singh G, et al. *Arthritis Rheum.* 1999;42:S242; 5. Doran M, et al. *Arthritis Rhe* 2002;46:2287-2293.

Serious Infections in Long-standing RA Clinical Trials



= European Union data; SIE = serious infectious event.
Schiff MH, et al. Presented at: EULAR Annual Meeting; June 8-11, 2005; Vienna, Austria. 2. Lebwohl, et al. sented at: 63rd Annual Meeting of AAD; February 18-22, 2005; New Orleans, LA; 3. FDA Safety Review line) accessed 2003; 4. Emery P, et al. *Arthritis Rheum.* 2006;54:1390-1400; 5. Genovese MC, et al. sented at: ACR; November 10-15, 2006; Washington, DC. Abstract 498. 6. Singh G, et al. *Arthritis Rheum.*

Serious Infectious Events (SIE) With TNF Inhibitors

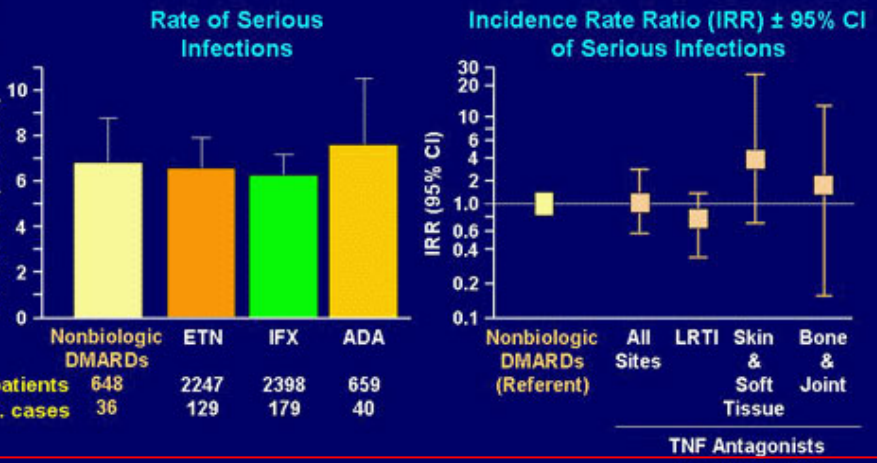
Summary From Pivotal Trials

SIE Rates From Package Inserts	TNF Inhibitor	Placebo
Adalimumab	2%	1%
Etanercept	1%	1%
Infliximab	5.3%	3.4%

HUMIRA (adalimumab) [package insert]. Abbott Park, IL; Abbott Laboratories; 2008; ENBREL (etanercept) [package insert]. Thousand Oaks, CA; Immunex Corporation; 2006; REMICADE

Incidence of Serious Infections in Patients With RA

British Society of Rheumatology–Biologics Registry (5952 Patients)



No difference in the rates of serious infections between patients receiving TNF antagonists and patients receiving traditional DMARDs

= adalimumab; ETN = etanercept; IFX = infliximab; LRTI = lower respiratory tract infection.

n W, et al. *Arthritis Rheum*. 2005;52:S738. Abstract 1990; Dixon W, et al. *Arthritis Rheum*. 2006;54:2368-76.

Risk of Infections With TNF Blockers: CORRONA Database

- 5596 RA patients (6,17 PY)
- 3012 on TNF (2722 PY) 54%
- IFX 48%, ETN 40%, ADA 12%

Variable	Adjusted RR (95% CI)
TNF Blocker	1.16 (1.06, 1.28)
ACR Functional Class > 2	1.32 (1.19, 1.48)
Erosion	1.16 (1.04,1.28)
Diabetes	1.27 (1.08, 1.50)
Lung disease	1.37 (1.18, 1.58)
Smoking	1.63 (1.46, 1.83)

Maury E, et al. *Arthritis Rheum*. 2005;52:S547 [Abstract 1453].

Selected Serious Infections in Elderly RA Patients

Hazard Ratios for Hospitalized Infection*

	Age, gender Adjusted HR	Multivariate Adjusted HR	Propensity score Adjusted HR
TNF antagonist			
Pneumonia	1.4 (0.7–2.9)	0.9 (0.41–1.9)	0.7 (0.3–1.9)
Bacteremia	1.0 (0.5–2.1)	1.2 (0.6–2.3)	1.3 (0.6–2.7)
Osteomyelitis	1.0 (0.3–4.3)	1.0 (0.3–4.3)	1.1 (02–4.8)
Glucocorticoids			
Pneumonia	2.4 (1.3–4.2)	2.1 (1.2–3.7)	1.9 (1.1–3.5)
Bacteremia	2.9 (1.8–4.5)	2.6 (1.6–4.1)	2.5 (1.6–4.0)
Osteomyelitis	1.5 (0.6–4.1)	1.4 (0.5–3.7)	1.3 (0.5–3.5)

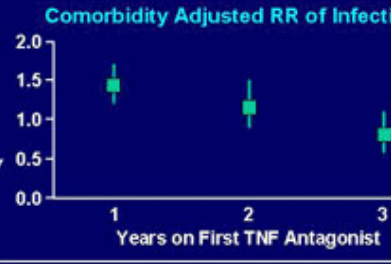
*HR compared with MTX initiation (alone or in combination)

Conclusions:

- No increased risk in infections in patients on anti-TNF compared to MTX
- Prednisone use confers significant, dose-related risk of infection

TNF-Antagonist Treatment and Risk of Hospitalization for Infection

- ARTIS database in Sweden
  - 4167 biologic-treated RA pts 1999–2003
    - IFX 64%, ETN 40%, ADA 13%, 56% prednisone, 70% DMARDs
  - 44,946 hospitalized RA patients
- 367 infection hospitalizations in 7776 PY on TNF inhibitor
  - TNF = 4.7 per 100 PY
- Infection risk increased in 1st year (RR 1.43)
- Predictors of infection risk: age, HAQ, DMARDs, comorbidities



	RR (age/sex/propensity score-matched)
Infections	1.63 (1.28–2.07
COPD	1.52 (0.96–2.42
Diabetes	1.43 (0.94–2.18
CVD	1.61 (1.24–2.07
MTX	0.91 (0.69–1.20
Other DMARDs	1.45 (1.0–2.12)

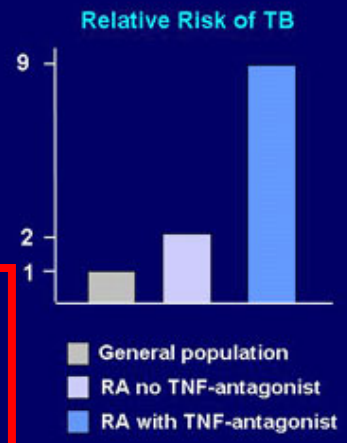
Conclusion:

- 30% increased risk of infection on anti-TNF was only seen in 1st year
- No increase in mortality
- Risk decreases with duration of treatment (RR = 0.82 after 2 yrs)

HAQ = health assessment questionnaire

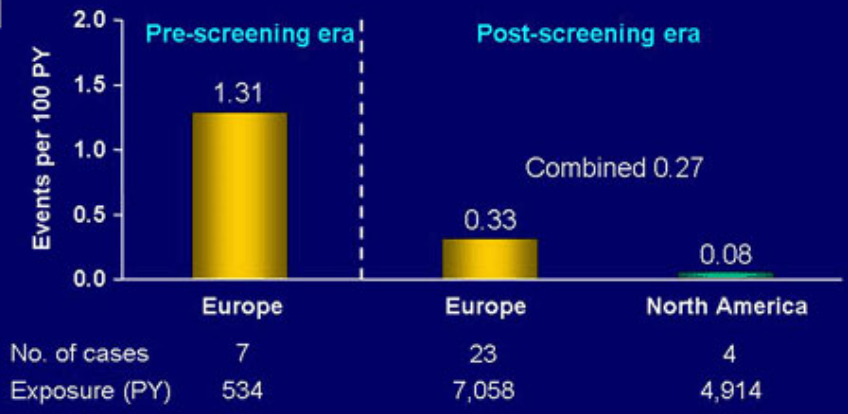
TB Risk and TNF Antagonists in RA

- RA Swedish database
  - 1999-2001
    No screening for latent TB
  - 31,185 patients (2500 anti-TNF)
  - Patients with RA have 2-fold increase of TB
  - The above risk is magnified 4-fold with the addition of anti-TNF medication
  - Both etanercept and infliximab increased risk



= tuberculosis.
ling J, et al. *Arthritis Rheum*. 2005;52:1986-92.

TB Rates Pre- and Post-Screening in Adalimumab RA Clinical Trials*



*Through April 15, 2005. Data from RA clinical trials with adalimumab, including OLEs, and ACT and ReA
Schiff MH, et al. *Ann Rheum Dis*. 2006;65:889-894.

Tuberculosis: Postmarketing Safety Data for TNF Antagonists in RA

	Etanercept[1]	Infliximab[1]	Adalimumab[2] (US only)
Time period	→ 12/03	→ 10/03	12/02–12/04
Number of patients treated	230,000	277,000	NA
Exposure (patient-years)	423,000	466,000	55,384
Number of TB reports	38	242	11
Geography (n)			
USA	26	90	11
Non-USA	12	152	—
Characteristics (%)			
Extrapulmonary	34	30–45	73
Miliary	16	–	27
Events per 100 patient-years	0.01	0.05	0.02

Keystone EC. *J Rheumatol*. 2005;32:8-12.

Tuberculin Skin Testing Options: 2 > 1 > 5 > 3 > 4

2. PPD now; come back Monday to you (96 hrs)
1. Come back on Monday and place PPD
5. Start TNF inhibitor now; do PPD at next visit (~3 mo)
3. PPD now; go to Doc-in-Box near home in 48–72 hrs
4. PPD now; patient will call you Saturday with results

Best → Worst

- The best/most accurate PPD is one placed and read by you, the health care professional
- Studies show PPD reactivity is reliable for a week
- Alternatively effective when read by another health care worker
- Patient-reported findings are VERY unreliable

Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-α therapy

On the basis of these data, it was assumed that the incidence and severity of infections were not markedly increased under treatment with these agents when compared with other data on infections in RA

Prior P et al Cause of death in rheumatoid arthritis Br J rheumatol 1984; 23:92-9

Van den Borne et al No increased risk of malignancies and mortality in cyclosporin-A treated patient with rheumatoid arthritis. Arthritis Rheum 1998; 41:1930-7

Doran MF et al Frequency of infection in patients with rheumatoid arthritis compared with controls: a population based study . Arthritis Rheum 2002; 46:2287-93

Anti-TNF-α therapy has been associated with the reactivation of tuberculosis, again raising concerns that infections may pose a significant threat

Keane J et al Tuberculosis associated with infliximab, a tumor necrosis factor alpha neutralizing agent . N Engl J Med 2001; 345: 1098-104

Risk of serious bacterial infections among RA patients exposed to TNFα antagonists

Jeffrey R Curtis et al Arthritis and Rheumatism 2007; 56: 1125-1133

The multivariate adjusted risk of hospitalization with a physician confirmed definite bacterial infection was ~2-fold higher overall and 4-fold higher in the first 6 months among patients receiving TNFα antagonists versus those receiving MTX alone

RA patients were at increased risk of serious infections, irrespective of the method used to define an infectious outcome

Older age, diabetes mellitus and preexisting pulmonary disease place patients at particular risk

Patients and physicians should vigilantly monitor for signs of infection when using TNFα antagonists, particularly shortly after treatment initiation

Serious Bacterial Infections Occur Early With TNF Antagonist Use

Goal

Determine risk of serious bacterial infections in TNF-inhibitor-treated patients with RA from a large health care cohort

N

Health organization database cohort of patients with RA
TNF 2393 (3894 PY) vs MTX 2933 (4846 PY)

Patients/ Measures

RA: Female 73%, median F/U 17 mo, Dx of RA and serious bacterial infections (ICD9 codes x2), confirmed by trained nurse chart review and 2 infectious disease MDs

Results

	N	PY	DM	COPD	Pred	Infect
TNF	2393	3894	8%	8%	56%	2.7%
MTX	2933	4846	10%	9%	56%	2.0%

Conclude

Multivariate relative risk of bacterial infection in TNF-inhibitor-treated RA = 1.9 (1.3–2.8); risk was greatest in 1st 6 mos. RR 4.2 (2.0–8.8)

rtis J, et al. *Arthritis Rheum.* 2007;56:1125-33.

CURTIS J

Infliximab or Etanercept: Data From the RABBIT Study

- Patients with RA enrolled in German Society of Rheumatology Biologics Registry
- 1459 patients from May 2001 until Sept 2003;
  - ETN (n = 512), IFX (n = 346), control RA DMARD patients (n = 601)
- Risk of infection adjusted for disease activity (higher in anti-TNF treated)

Relative risk (RR) of infections compared to control

	Etanercept		Infliximab	
	Adjusted RR	95% CI	Adjusted RR	95% CI
All infections	2.3	1.4–3.9	3.0	1.8–5.1
Serious infections	2.1	0.9–5.4	2.1	0.8–5.5

Listing J, et al. *Arthritis Rheum.* 2005;52:3403-12.

LISTING J

Serious Infections With Anti-TNF Treatment

Frequency of Serious Infections in Anti-TNF-treated Patients

bservational RA Population	Rate/100 PY	Adjusted Relative Rate*
ABBIT: Listing et al. *Arthritis Rheum* 2005	6.3	2.2
SRBR: Dixon et al. *Arthritis Rheum* 2006	5.3	1.0
RTIS: Askling et al. *Ann Rheum Dis* 2007	5.4*	1.4
urtis JR, et al. *Arthritis Rheum* 2007	2.9†	1.9
chneeweiss S, et al. *Arthritis Rheum* 2007	2.2	1.0

mpared with MTX-treated or DMARD-treated patients with RA.
ompared with MTX treatment alone.

RA and Serious Infections

- Infection is a major cause of morbidity and mortality
- The best predictor of serious infection events (SIE) and infectious deaths is:
  - RA severity/disease activity
  - Corticosteroid therapy
  - Comorbid diseases: CHF, CRF, IDDM, COPD, etc.
  - Skin infection, role of skin breakdown in SIE
  - Joint surgery
- Contributory role of DMARDs [MTX, Au, LEF] has NOT been established

SIE: Is There a Difference Between RCTs and Observational Studies of RA?

	Randomized, Controlled Trials	Observational
Patient selection	Very severe RA only	Varied, no restrictions; more comorbidities and drugs
Steroid use	Stable, limited to low dose	No restrictions
Comorbidities	Excluded	Common (> 50%)
Is there a significant risk of SIE with TNF inhibitor use?	No	Yes/small

Biologic therapy in clinical practice: enthusiasm must be tempered by caution

Recently, etanercept and infliximab have been subjected to scrutiny by the National Institute of Clinical Excellence (NICE) in the UK

Its appraisal recommended that these drugs could be used in refractory RA, following strict guidelines drawn up by the British Society for Rheumatologists(BSR)

The approval by NICE means that the use of these drugs will increase significantly and this is most welcome

Nevertheless, the more widespread availability of such drugs will have implications for the workload and working practice of those who use them

Controlled trials have shown no overall increase in the risk of serious sepsis with these agents

Postmarketing surveillance has identified an increased risk of reactivation of tuberculosis in patients taking infliximab and has led to new guidelines to prevent this

NICE technology appraisal guidance N°36 . Guidance on the use of etanercept and infliximab for the treatment RA. London NICE 2002

British Society for Rheumatology. Guidelines for prescribing TNF blockers in adults with RA. Report of a working party of the BSR London BSR 2000

Keane J et al Tuberculosis associated with infliximab , a TNFα neutralizing agent N Engl J Med 2001;343:1098-104

Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-α therapy

In addition to the existing warnings of potential infections under etanercept and infliximab contained in the package insert, in the case of the latter the FDA-USA requested the addition of a black box with recommendations concerning tuberculosis

Postmarketing surveys have not revealed significant problems with serious infections under anti-TNF-α therapy

The Committee on Safety of Medicine (UK) advises caution with infliximab us in light of the reports on reactivation of tuberculosis

Committee on Safety on Medicines . Current Problems in Pharmacovigilance 2001; 27:7

Rheumatologists are aware of these risks and screen patients for sepsis prior to starting the drugs, especially tuberculosis and monitor patients for sepsis before each drug is given

Keane J et al Tuberculosis associated with infliximab, a tumor necrosis factor alpha neutralizing agent . N Engl J Med 2001; 345: 1098-104

Gomez-Reino JJ et al Treatment of rheumatoid arthritis with tumour necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active surveillance report. Arthritis Rheum 2003; 48: 2122-7

Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-α therapy

Patients with a predisposition to infection or chronic infection are ineligible for anti-TNF-α therapy

The British Society of Rheumatology has drawn up guidelines for these issues

GUIDELINES FOR PRESCRIBING TNF-α BLOCKERS IN ADULTS WITH RHEUMATOID ARTHRITIS

Report of a Working Party of the British Society for Rheumatology

First edition 2nd April 2001

UPDATE ON THE BRITISH SOCIETY FOR RHEUMATOLOGY GUIDELINES FOR PRESCRIBING TNFα BLOCKERS IN ADULTS WITH RHEUMATOID ARTHRITIS (UPDATE OF PREVIOUS GUIDELINES OF APRIL 2001)

Ledingham J et al Rheumatology 2005; 44: 157-163

UPDATING THE BRITISH SOCIETY FOR RHEUMATOLOGY GUIDELINES FOR ANTI-TUMOUR NECROSIS FACTOR THERAPY IN ADULT RHEUMATOID ARTHRITIS (AGAIN)

Deighton CM et al Editorial Rheumatology 2006; 45: 649-652

BRS GUIDELINES FOR ANTI-TNFα THERAPY

Active disease	Disease Activity Score DAS > 5.1
Pretreatment	Failure of at least two DMARDs after adequate trial
Exclusion	•Pregancy or breast feeding •Active infection •High risk of infection (various identified •Malignancy or premalignancy
Withdrawal	•Adverse events •Lack of effect, DAS not improved by > 1.2 at >3 months

Infections associated with TNF-α antagonists

Clinical experience suggests that infection in general is an even greater cause for concern when these drugs are used in the general patient population

One of the striking features it has been noted is the rapidity of the onset of the infection

TNF-α plays an essential role in the immune-mediated response to infection, especially intracellular pathogens

Data supporting the association between TNF-α blockers and infection include

CASE REPORTS

EPIDEMIOLOGIC STUDIES (meta-analysis etc.)

ANALOGOUS RESULTS FROM ANIMAL MODELS

Nancy E. Crum Medicine 2005; 84:291-302

Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-α therapy

S. Kroesen and colleagues reviewed patient charts and records of the Infectious Disease Unit for serious infections in patients with RA in the 2 years preceding anti-TNF-α therapy and during therapy

Serious infections affected 18.3% of patients treated with infliximab or etanercept, the rates of serious infections in these patients are approximately twice as high as those reported in the efficacy studies or registered in postmarketing surveys

The incidence was 0.181 per anti-TNF-α treatment year versus 0.008 in the 2 years preceding anti-TNF-α therapy

In several cases, only a few signs or symptoms indicated the severity of developing infections , including Sepsis

Kroesen S et al Rheumatology 2003; 42: 617-621

Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-α therapy

Patient and physician awareness must be tuned to recognize that the course of infections may be fulminant and that every effort must be made to clarify even slight alterations in well-being

(patients with RA, especially RA of long duration, have a record of fatigue and recurrent episodes of reduced well-being. They are used to managing these conditions without seeking medical attention. Likewise, physicians may be desensitized to potential warning signs)

This is necessary because clinical and laboratory signs may be blunted by TNF-α blockade and by concomitant immunosuppressive medications

A well-informed patient

A physician highly suspicious of infectious complications

Rapid access to hospital

Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-α therapy

Certain common features in the reported case series indicate how to identify infections early

1. a rise in the CPR level, in which case an infection must be ruled out immediately
   a. PCT
   b. PCR (SeptiFast)
   c. cultures
2. positive blood cultures or synovial fluid cultures with pathogen of low pathogenicity (e.g. coagulase-negative staphylococci) must be taken seriously even though the patient's well-being is not or only slightly affected and laboratory results are normal
3. once symptoms become clinically overt Severe Sepsis must be anticipated and rapid deterioration averted

Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-α therapy

Considering the total number of treatments currently applied and the potential for a widening of indications for the use of anti-TNF-α agents , it is strongly recommended that institutions using these therapies provide safeguards 24 hours a day 7 days a week

Patient education is essential and may benefit from a structured programme

Finally, the question of immunization before the initiation of anti-TNF-α therapy must be considered (additional strategies for the prevention)

A well-informed patient, a physician highly suspicious of infectious complications and rapid access to health care (rapid identification and pre-emptive therapy of infections) will make it possible to take advantage of this new treatment option while minimizing potentially life-threating complications

«Kroesen S et al Rheumatology 2003; 42: 617-621

Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies

Systematic review and meta-analysis of rare harmful effects in RCTs

JAMA 2006; 295: 2275-2285

Tim Bongartz and colleagues calculated a pooled odds ratio (Mantel-Haenszel methods with a continuity correction designed for sparse data) for malignancies and serious infections (infection that requires antimicrobial therapy and/or hospitalization) in anti-TNF treated patients versus placebo patients

They estimated effects for high and low doses separately

The pooled odds ratio for malignancy was 3.3 (95% CI 1.2-9.1) and for serious infection was 2.0 (95% CI 1.3-3.1)

Malignancies were significantly more common in patients treated with higher doses compared with patients who received lower doses of anti-TNF antibodies. For patients treated with anti-TNF antibodies in the included trials, the number needed to harm was 154 (95% CI 91-500) for one additional malignancy with a treatment period of 6 to 12 months.

For serious infections, the number needed to harm was 69 (95% CI 39-125) within a treatment period of 3 to 12 months

Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies

Systematic review and meta-analysis of rare harmful effects in RCTs

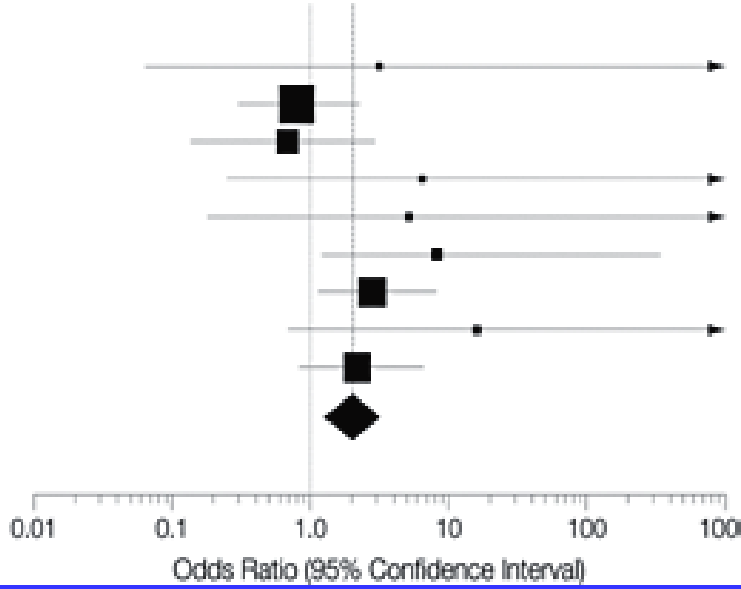
Tim Bongartz et al JAMA 2006; 295:2275-2285

There is evidence of an increased risk of serious infections and a dose-dependent increased risk of malignancies in patients with rheumatoid arthritis treated with anti-TNF antibody therapy

The formal meta-analysis with pooled sparse events data from randomized controlled trials serves as a tool to assess harmful drug effects

Source	Anti-TNF	Placebo	Odds Ratio (95% Confidence Interval)
Maini et al,[32] 1998	2/87	0/14	3.13 (0.06-Infinity)
Lipsky et al,[9] 2000	21/342	7/86	0.76 (0.30-2.18)
Furst et al,[8] 2003	4/318	6/318	0.66 (0.14-2.83)
Van de Putte et al,[10] 2003	4/214	0/70	6.33 (0.30-Infinity)
Weinblatt et al,[11] 2003	3/209	0/62	4.93 (0.19-Infinity)
Keystone et al,[6] 2004	16/419	1/200	7.90 (1.21-332.96)
St Clair et al,[7] 2004	40/749	6/291	2.68 (1.11-7.81)
Van de Putte et al,[33] 2004	11/434	0/110	15.34 (0.71-Infinity)
Westhovens et al,[34] 2004	25/721	6/361	2.13 (0.84-6.39)
Total	126/3493	26/1512	2.01 (1.31-3.09)

Test for overall effect:
Mantel-Haenszel $\chi^2 = 9.1$; $P = .002$



Effect of Anti-TNF Antibody Therapy vs Control Therapy on Occurrence of 1 or More Serious Infections in Patients With Rheumatoid Arthritis

Table 4. Effect of Anti-TNF Antibody on Occurrence of 1 or More Malignancies or Serious Infections in Patients With Rheumatoid Arthritis, Stratified by Dose Group

Adverse Event	Odds Ratio (95% Confidence Interval)*			
	All Doses of Anti-TNF Antibody Therapy vs Placebo	Low-Dose Anti-TNF Antibody Therapy vs Placebo†	High-Dose Anti-TNF Antibody Therapy vs Placebo‡	High-Dose‡ vs Low-Dose† Anti-TNF Antibody Therapy
≥1 Malignancy	3.3 (1.2-9.1)	1.4 (0.3-5.7)	4.3 (1.6-11.8)	3.4 (1.4-8.2)
≥1 Serious infection	2.0 (1.3-3.1)	1.8 (1.1-3.1)	2.3 (1.5-3.6)	1.4 (1.0-2.0)

Abbreviation: TNF, tumor necrosis factor.
*Pooled odds ratio based on a fixed-effects Mantel-Haenszel model for the all-doses estimate and based on high-dose/low-dose stratification.
†Infliximab, ≤3 mg/kg every 4 weeks, or adalimumab, 20 mg/wk.
‡Infliximab, ≥6 mg/kg every 8 weeks, or adalimumab, 40 mg every other week.

ffect of Anti-TNF Antibody on Occurrence of 1 or More Malignancies or Serious Infections in Patien With Rheumatoid Arthritis, Stratified by Dose Group

Rates of serious infection, including site-specific and bacterial intracellular infection in RA patients receiving anti-TNF therapy

In patients with active RA , anti-TNF therapy was not associated with increased risk of overall serious infection compared with DMARD treatment, after adjustment for baseline risk

There was no difference in infection risk between the 3 main anti-TNF drugs [etanercept – adjusted IRR 0.97 (0.63-1.50), infliximab - adjusted IRR 1.04 (0.68-1.61), adalimumab – adjusted IRR 1.07(0.67-1.72)

Dixon WG et al Arthritis and Rheumatism 2006; 54: 2368-2376

Rates of all serious infections

Dixon WG et al Arthritis and Rheumatism 2006; 54: 2368-2376

	DMARD	Anti-TNF
erson-years	1,352	9,868
erson-years per erson,median (IQR)	0.94 (0.48-1.43)	1.26(0.75-1.96
° of infections	56	525
ate of infections/1,000 erson-years (95%CI)	41.4 (31.4-53.5)	53.2 (48.9-57.8)
ncidence rate ratio (IRR) verall	Referent	1.28 (0.94-1.76)
djusted for age and sex	Referent	1.47 (1.07-2.01
djusted for age, sex , isease severity, omorbidity, extrarticular anifestations, steroid use nd smoking	Referent	1.03 (0.68-1.57)

Rates of all serious infections, by drugs

Dixon WG et al Arthritis and Rheumatism 2006; 54: 2368-2376

	DMARD	Etanercept	Infliximab	Adalimumab
erson-years	1,352	4,075	4,618	1,175
° of infections	56	209	255	61
ate of infections/1,000 erson-years (95%CI)	41.4(31.4-53.5)	51.3(44.7-58.5)	55.2(48.8-62.2)	51.9(39.9-66.2
djusted Incidence ate Ratio (IRR) or age, sex, disease everity, comorbidity, xtrarticular anifestations, stroid use nd smoking	Referent	0.97(0.63-1.50)	1.04(0.68-1.61)	1.07(0.67-1.72

Rate of site-specific infections

The frequency of serious skin and soft tissue infections was increased in anti-TNF treated patients

	DMARD		anti.-TNF		
te	N°	Incidence rate/ 1,000 person-years	N°	Incidence rate/ 1,000 person-years	Adjusted IRR (95%CI) Incidence rate rati
RTI	36	26.6(18.7-36.7)	203	20.6(17.9-23.6)	0.77(0.46-1.31)
kin and soft ssue	4	3.0(0.8-7.6)	118	12.0(9.9-14.3)	4.28(1.06-17.17)
one and joint	4	3.0(0.8-7.6)	68	6.9(5.4-8.7)	1.12(0.32-3.88)
rinary tract	3	2.2(0.5-6.5)	45	4.6(3.3-6.1)	1.70(0.32-9.03)

Rates of serious infection, including site-specific and bacterial intracellular infection in RA patients receiving anti-TNF therapy

In contrast , the rate of serious skin and soft tissue infections was increased suggesting an important physiologic role of TNF in host defense in the skin and soft tissues beyond that in other tissues

19 serious bacterial intracellular infections occurred, exclusively in patients in the anti-TNF treated cohort

Dixon WG et al Arthritis and Rheumatism 2006; 54: 2368-2376

Details of bacterial intracellular infections

tient e/sex	Ethnicity	Organism	Site of infection	Treatment	Months from treatment start dat
/F	Caucasian	*Mycobacterium tuberculosis*	Cervical lymph node	Infliximab	7
/F	Caucasian	*Mycobacterium tuberculosis*	Colon	Infliximab	3
/M	Caucasian	*Mycobacterium tuberculosis*	Omentum	Infliximab	2
/M	Caucasian	*Mycobacterium tuberculosis*	Pleura	Infliximab	3
/F	Caucasian	*Mycobacterium tuberculosis*	LRT	Infliximab	16
/F	Caucasian	*Mycobacterium tuberculosis*	Posterior pharingeal wall	Adalimumab	11
/F	Pakistani	*Mycobacterium tuberculosis*	Cervical lymph node	Infliximab	4
/M	Caucasian	*Mycobacterium tuberculosis*	Meninges	Etanercept	2
/F	African Caribbean	*Mycobacterium tuberculosis*	LRT	Etanercept	9
/F	Not known	*Mycobacterium tuberculosis*	Meninges	Infliximab	3
/M	Caucasian	*Legionella pneumophila*	LRT	Infliximab	32
/M	Caucasian	*Legionella pneumophila*	LRT	Infliximab	4
/M	Caucasian	*Listeria monocytogenes*	Meninges	Infliximab	2
/M	Caucasian	*Listeria monocytogenes*	Joint	Etanercept	0
/F	Caucasian	*Listeria monocytogenes*	Joint	Adalimumab	14
/F	Caucasian	*Mycobacterium fortuitum*	LRT	Etanercept	4
/F	Caucasian	*Salmonella sp*	Bowel and joint	Etanercept	9
/F	Caucasian	*Salmonella sp*	Joint	Infliximab	27

Suggested screening tests for potential infectious complications among TNFα antagonists recipients

Nancy F Crum et al Medicine 2005; 84:291-302

nfection	Recommended screening
uberculosis	PPD at baseline* and every 12 months; baseline chest radiograph
listoplasmosis	Consider chest radiograph and urine histoplasmin antigentesting at baseline Consider follow up urine antigen testing every 3-4 months for patients who live in endemic areas
Coccidioidomycosis	Chest radiograph and serologic testing with igM and IgG test at baseline Consider follow up testing every 3-4 months for patients who live in endemic areas
Cryptococcus	No data
isteria	Patient education regarding food preparation and safety

- Consider 2-step testing for initial PPD
& patients who currently live or have resided in endemic locations

Infections associated with TNF-α antagonists

Nancy F Crum et al Medicine 2005; 84:291-302

Since most complications arise within the first 3 months of infliximab therapy , frequent patient follow up during this time period is critical

All febrile or novel illnesses should be proptly evaluated

The exact data on the risk of infection remain limited, as most reports involve single cases or data collected by passive surveillance from the Adverse Event Reporting System Database

Prospective studies to assess the risk of infections among TNFα antagonist recipients are necessary to develop evidence-based consensus guidelines

Physicians are encouraged to report all infectious complications that occur during TNFα inhibitor therapy to the FDA's MEDWATCH SYSTEM (available at http://www.fda.gov/medwatch)

Infections associated with TNF-α antagonists

A deep relationship with the microbiologist

Disseminated Tuberculosis

Atypical Mycobacterium species **(Mycobacterium avium , leprae)**

Streptococcus pneumoniae **(pneumonia)**

Staphylococcus aureus **(MSSA, MRSA) (necrotizing fasciitis, septic arthritis)**

Moraxella catharralis **(septic arthritis)**

Listeriosis (listeria monocytogenes Gram + : meningoencephalitis)

Legionellosis (Legionella pneumophila Gram – : pneumonia)

Salmonella, Toxoplasma, Bartonella, Leishmania, Nocardia, Microsporidium

Viral infections: varicella , cytomegalovirus, herpes simplex molluscum contagiosum

Infections associated with TNF-α antagonists

A deep relationship with the microbiologist expert in fungi

Coccidioidomycosis (ENDEMIC FUNGUS -coccidioides immitis is a dimorphic endemic fungus)

Histoplasmosis (ENDEMIC FUNGUS - histoplasma capsulatum the most common endemic mycosis in the United States)

Sporotrichosis (ENDEMIC FUNGUS)

Aspergillosis (MOLDS- Aspergillus species : ubiquitous environmental fungi)

Zygomycosis (Zygomycetes species)

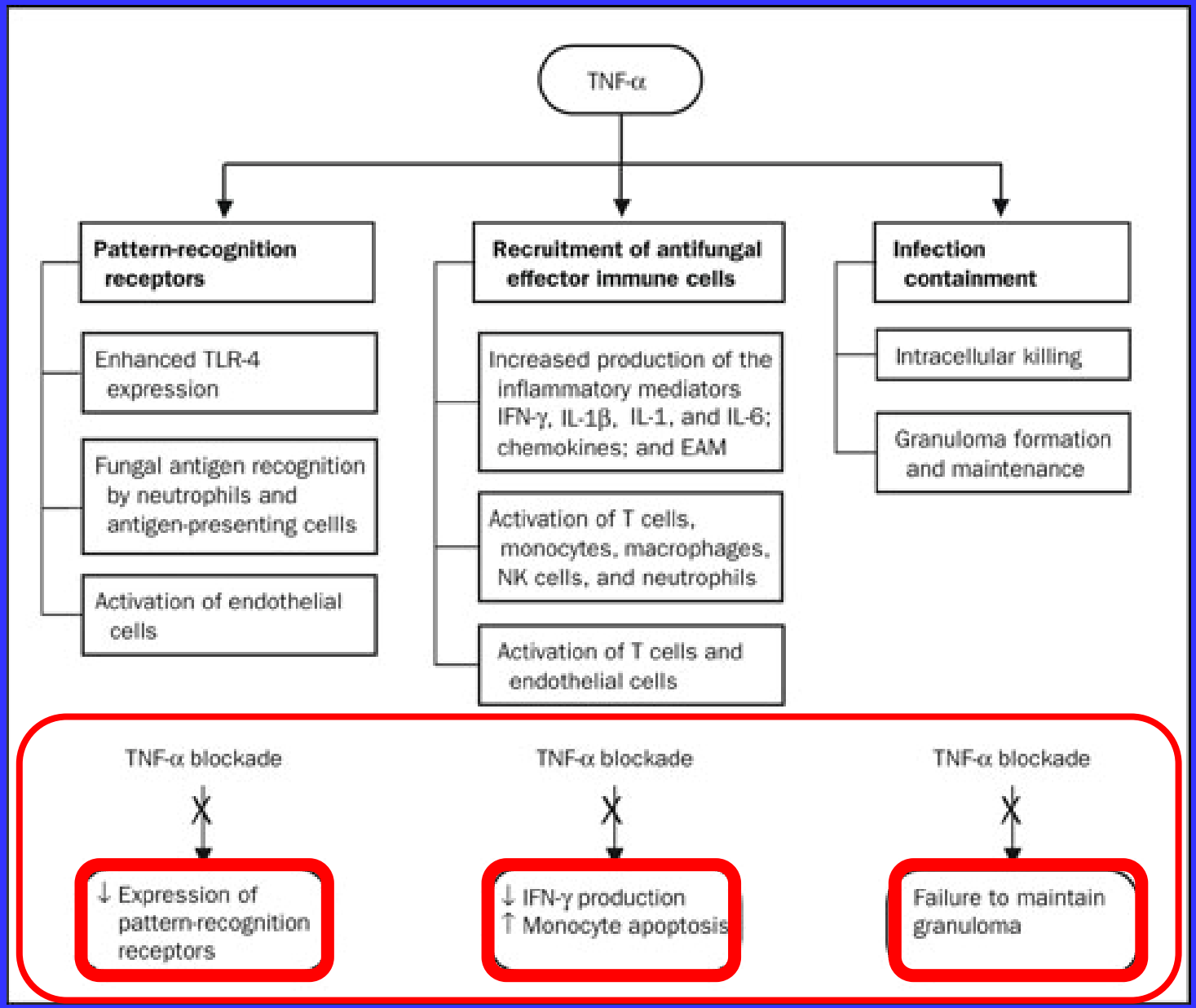
Candidiasis (YEASTS - Candida species –Candida glabrata)

Cryptococcosis (YEASTS - Cryptococcus neoformans is an encapsulated fungus)

Tinea and Pityriasis versicolor infections

Pneumocystis carinii (jiroveci) Pneumonia (PCP)

Fungal Infections Complicating TNF-α Blockade Therapy



Setinos Tsiodras et al. Mayo Clin Proc 2008;83:181-194

Fungal Infections associated with anti-TNFα therapy

Sotiros Tsiodras et al. Mayo Clin Proc.2008;83:181-194

nfectious agents	Infliximab	Etanercept	Adalimumab
spergillus species (n=64) 2- 23%	48	14	2
ygomycetes (n=4)	3	NC	1
andida species (n=64) 2-23%	54	9	1
ryptococcus species (n=28)	17	10	1
lastomyces species (n=2)	ND	ND	ND
occidioides species (N=29)	27	2	NC
istoplasma species (n=84 1- 30%	72	8	4
porothrix species (n=1)	1	NC	NC
rototheca species (n=1)	1	NC	NC
inea or pityriasis versicolor =6)	3	1	2
otal	226 (80%)	44 (16%)	11 (4%)

ND = no data available; NC = no cases identified

Infections associated with TNF-α antagonists

Sotiros Tsiodras et al. Mayo Clin Proc.2008;83:181-194

Fungal infections associated with infliximab occurred a median of 55 days (IQ
15-140 days) after initiation of therapy and 3 infusions of the medication (IQR
2-5)

Fungal infections associated with etanercept occurred a median of 144 days
(IQR 46-240 days) after initiation of therapy

The median age of patients was 58 years (IQR 44-68 years) and 62% were mal

Use of at least 1 other immunosuppressant medication, typically a systemic
corticosteroid, was reported during the course of the fungal infection in 102
(98%) of the 104 patients for whom data were available

PNEUMONIA was the most common pattern of infection

Of the 90 (32%) of 281 cases for which outcome information was available , 29
fatalities (32%) were recorded

A high index of suspicion in patients treated with TNFα antagonists is
recommended because the course of such infections can be serious or fulminan
and rapid access to health care should be provided

Surveillance of IFIs complicating TNFα blockade and other biologic therapies is warranted through well organized prospective patient registries

High risk conditions for invasive fungal infections after TNF-α blockade

Sotiros Tsiodras et al. Mayo Clin Proc.2008;83:181-194

- Graft vs host disease (severe neutropenia)
- History of invasive aspergillosis or other mold infections
- Colonization with pathogenic fungi
- Environmental exposure
- High risk travel in endemic area (eg, histoplasmosis, coccidioidomycosis)
- High risk outdoor activities (eg, spelunking)
- Construction

Case report

Necrotising fasciitis in a patient receiving infliximab for rheumatoid arthritis

Chan ATY et al Postgrad Med J 2002;78:47-48

2 Case reports

Life threatening intra-abdominal sepsis in patients on anti-TNFα therapy

Goode S et al Gut 2005 doi:10.1136/gut.2005.085449

Case report

Severe Pneumonia

Nancy F Crum et al Medicine 2005; 84:291-302

Case report

Lethal ARDS during anti-TNFα therapy for rheumatoid arthritis

Christian Zimmer et al Clin Rheumatol 2006; 25:430-432

Case reports

Purulent pericarditis in a patient with RA treated with etanercept and MTX

David D Sweet et al Can JEmerg Med 2007;9:40-2

Case report

Sepsis of the prosthesis

M.Fernandez-Castro et al Rheumatology 2005; 44:1076-1077

J.J. CASES OF SEVERE SEPSIS AND SEPTIC SHOCK ADMITTED TO THE ICU

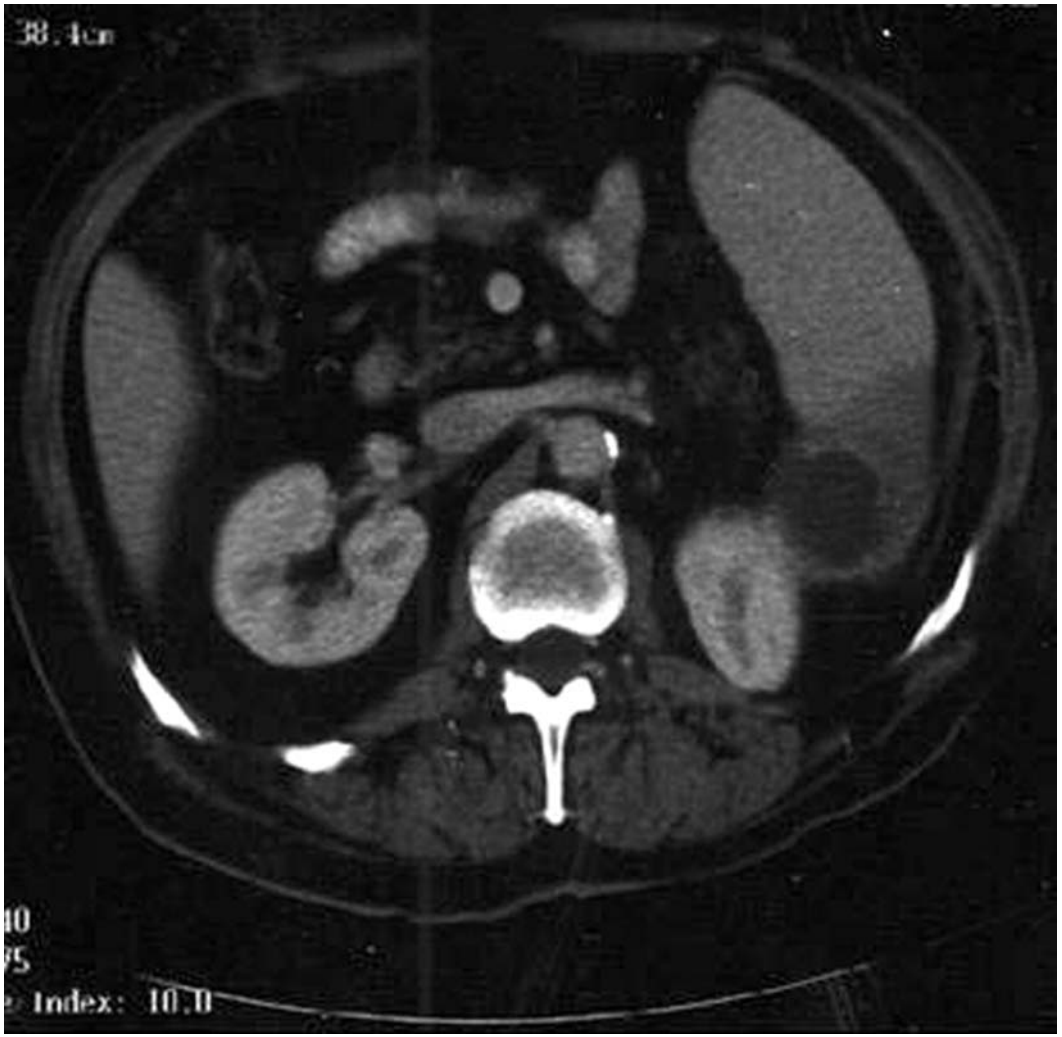
Case reports

Learning points

- Anti-TNFα agents are useful in reducing disease activity and joint destruction in RA
- Overall the data from drug trials shows that infliximab is safe when used appropriately
- The use of infliximab is associated with the risk of severe sepsis and septic shock
- The absence of pyrexia or other signs of infection does not exclude the possibility of sepsis in patients treated with infliximab
- Report all adverse events with the use of anti-TNFα agents

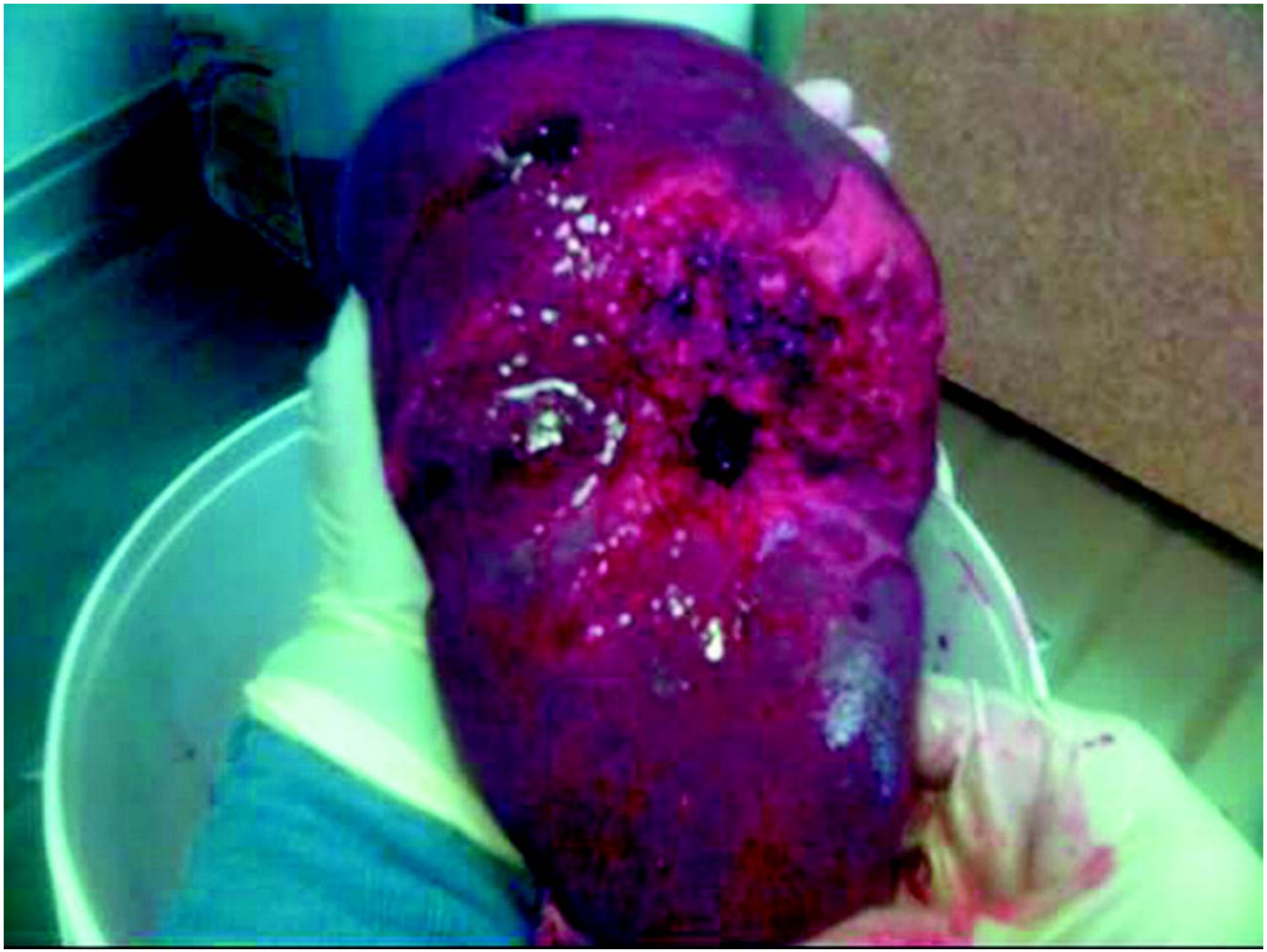
Figure 1 Computed tomography. Expansile predominantly cystic mass located within an area of hypodensity in the posterior pole of the spleen.

pleen abscess



Goode, S et al. Gut 2006;55:590-591

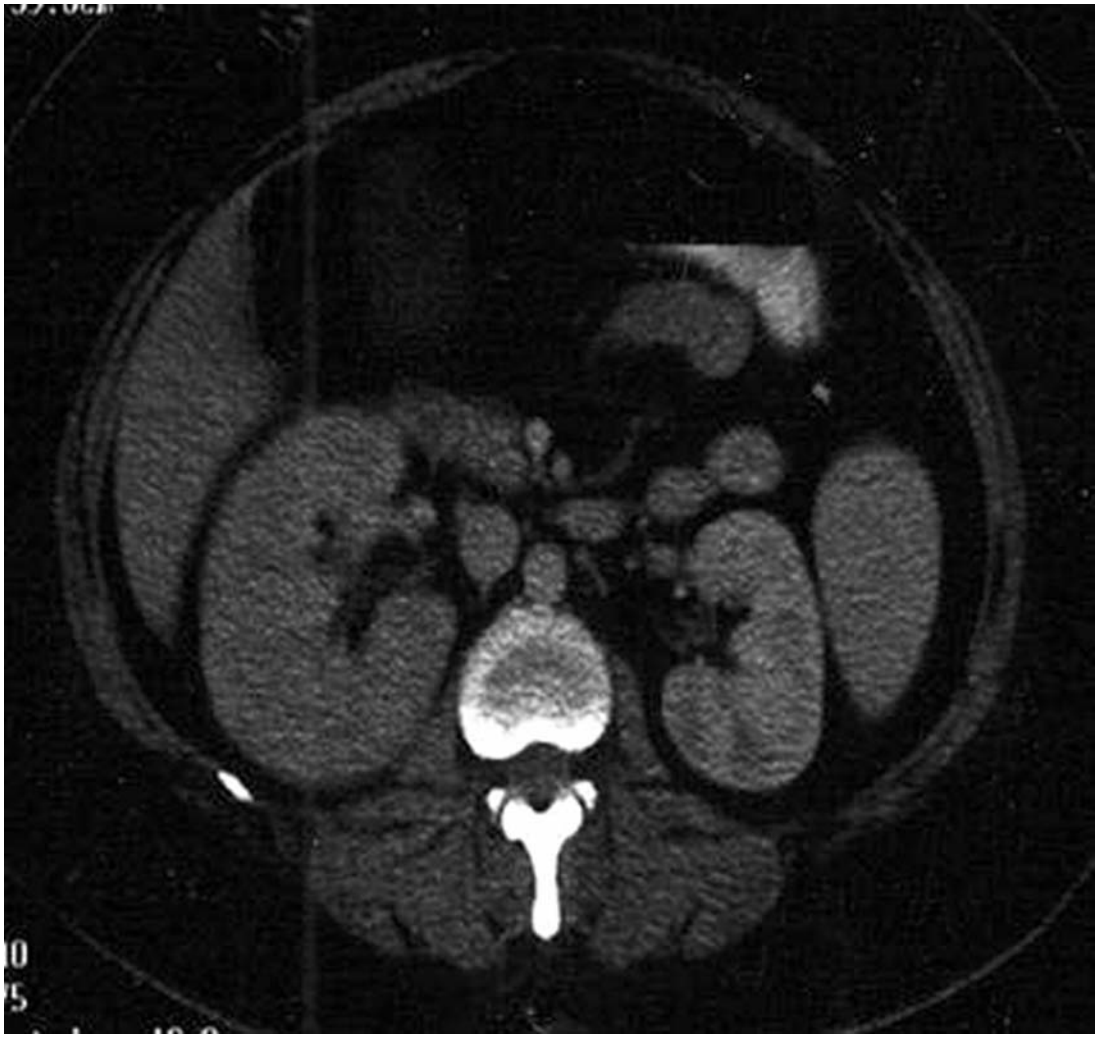
Figure 2 Surgical specimen consisting of the spleen with an abscess on the posterior aspect.



Goode, S et al. Gut 2006;55:590-591

Figure 3 Computed tomography. Expanded non-enhancing right kidney consistent with pyelonephritis.

Urosepsis



Goode, S et al. Gut 2006;55:590-591

Case reports

Learning points

The patients could have an important delay in initial diagnoses

This may have resulted in a worse outcome or even death

The patients who have received anti-TNFα therapy and develop a non specific abdominal pain should proceed to urgent abdominal ultrasound or CT scan to exclude significant intra-abdominal sepsis

A further concern is that anti-TNFα drugs may diminish the acute phase response, so that significant sepsis may not always have dramatic or acute presentations. This may lull the attending doctor into a false sense of security

Doctors who encounter patients on anti-TNFα therapy need to be aware of the possible complications

They should be treated as if they are significantly immunocompromised, and non specific symptoms such as abdominal pain need to be investigated intensively

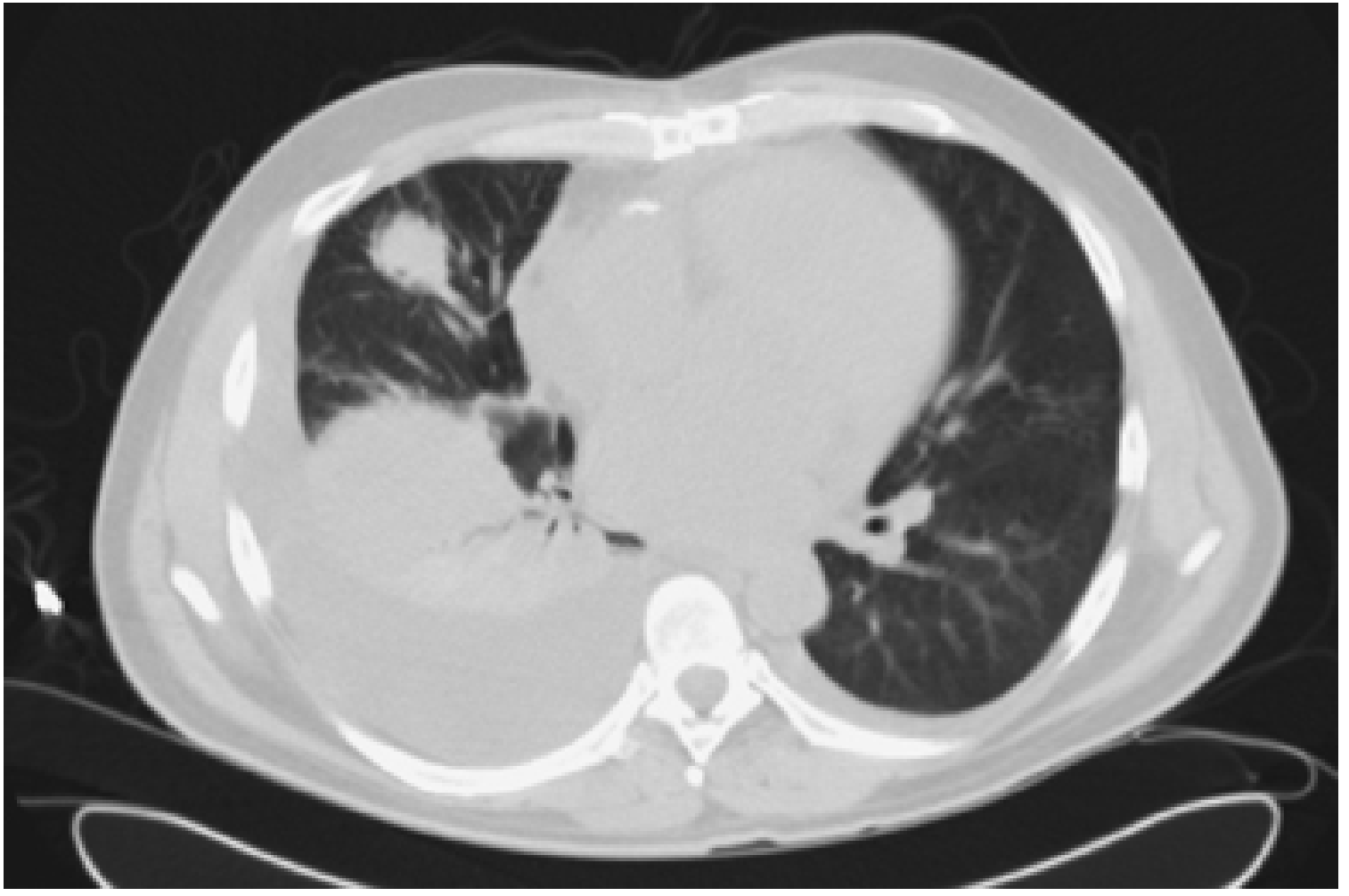
Case reports

Learning points

The risk of bacterial infections with typical organisms such as Streptococcus, staphylococcus and moraxella may be increased among TNFα inhibitor recipients

Infections such as pneumonia, abscess, cellulitis and sinusitis have been noted; severe infections, including necrotizing fasciitis and septic arthritis have also been reported

It is noteworthy that the occurrence of these bacterial infections is often unrelated to the exact time of TNFα blockade; patients appear to remain at risk for the duration of immunesuppression. This is in contrast to the TB or histoplasmosis experience, possibly because the latter are more often reactivated infections

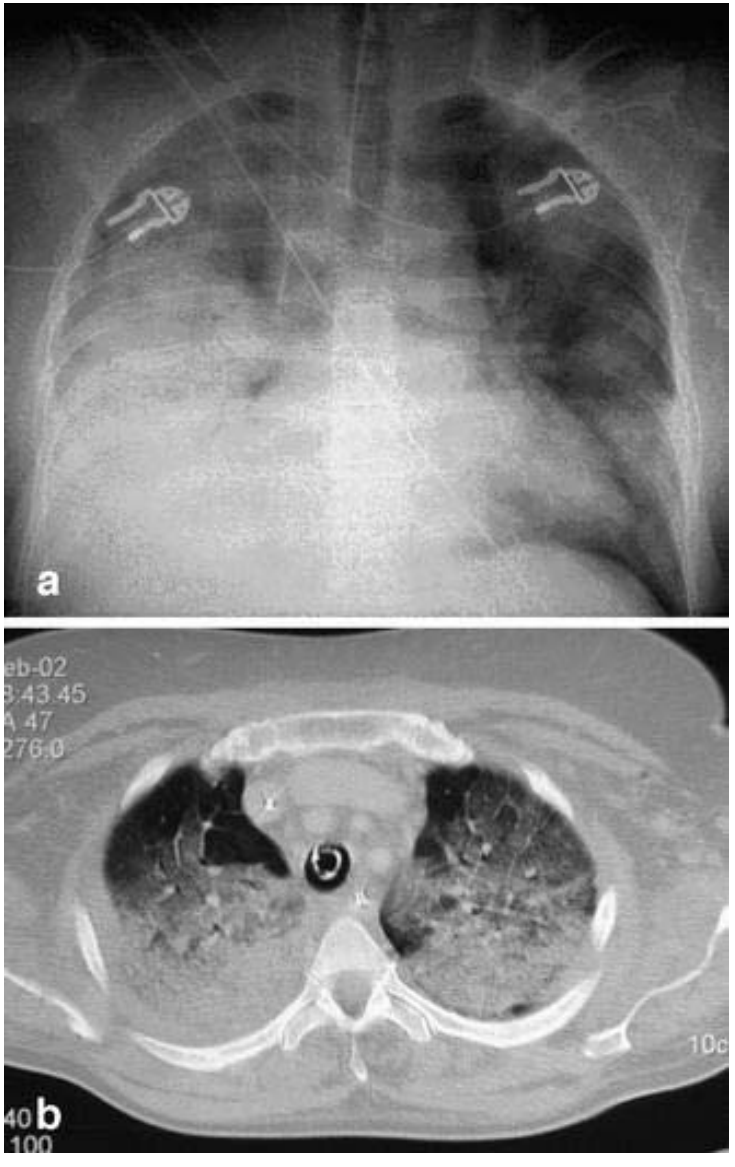


Case reports

Learning points

Infections in patients with anti-TNFα therapy, particularly when combined with other immunosuppressants, might be more severe

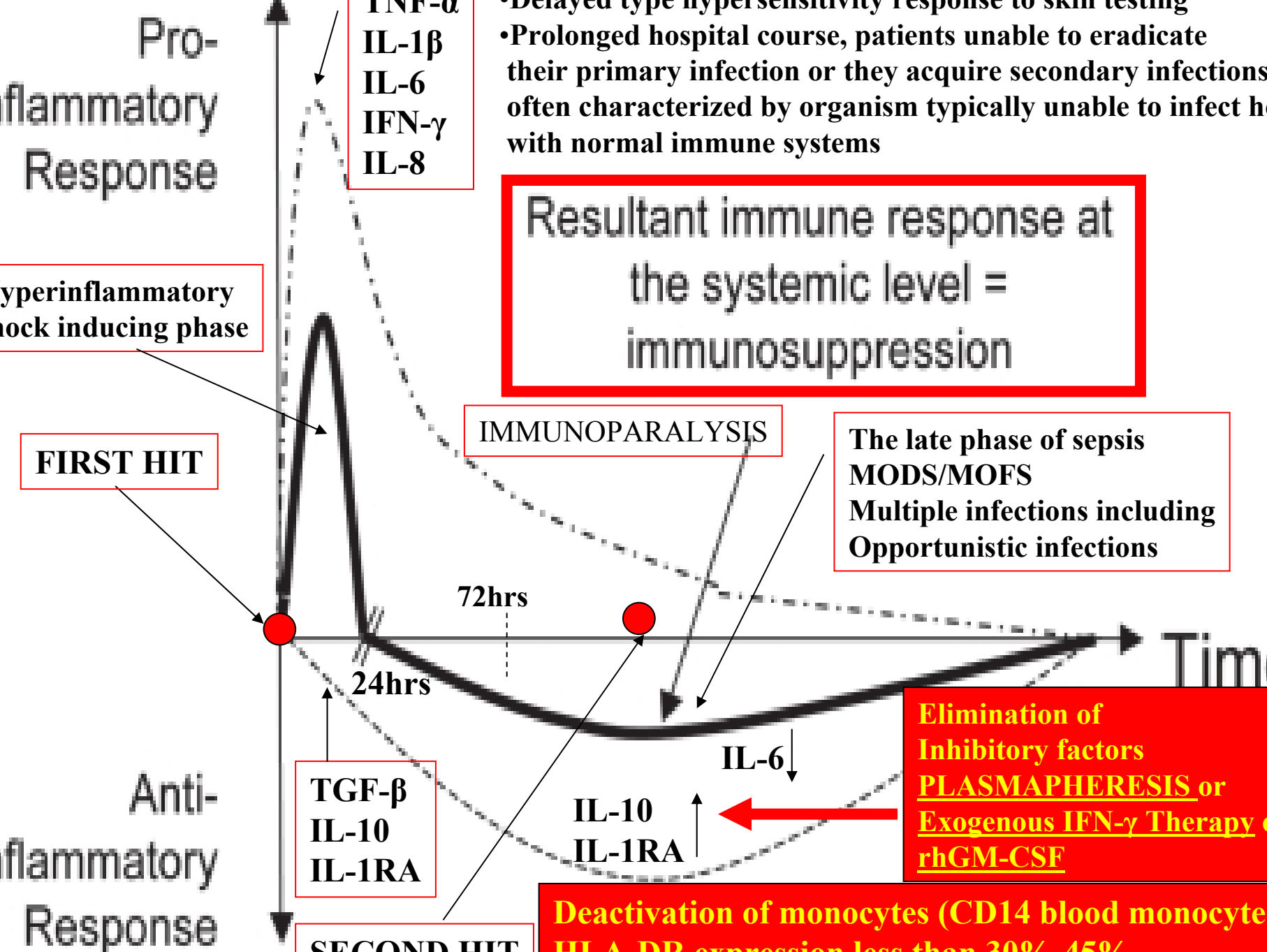
Accordingly, any signs of pulmonary infection should be regarded as very serious, as fulminant pneumonia with ARDS and severe sepsis may develop within 24 hours

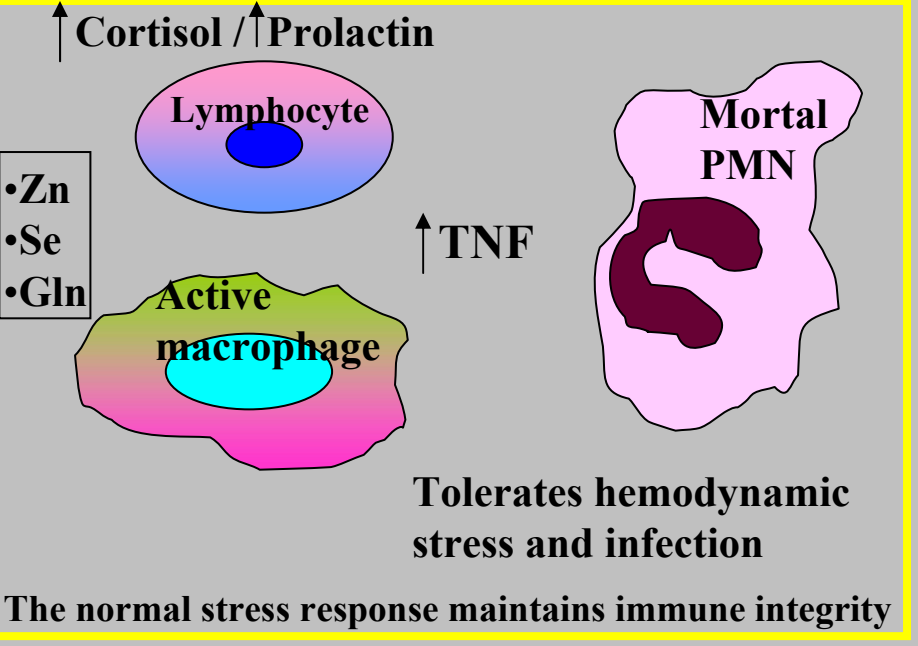

a
b

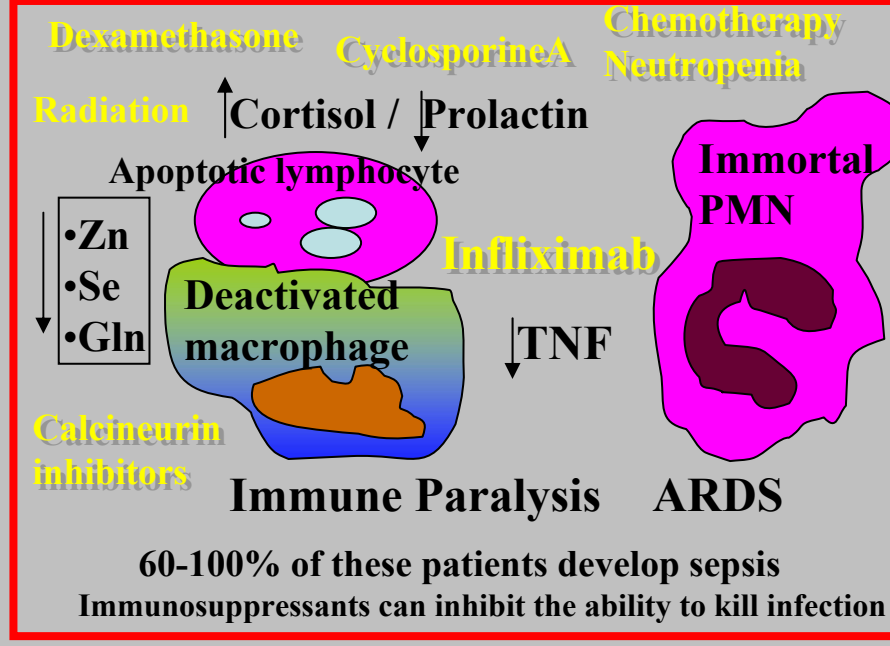
Case reports

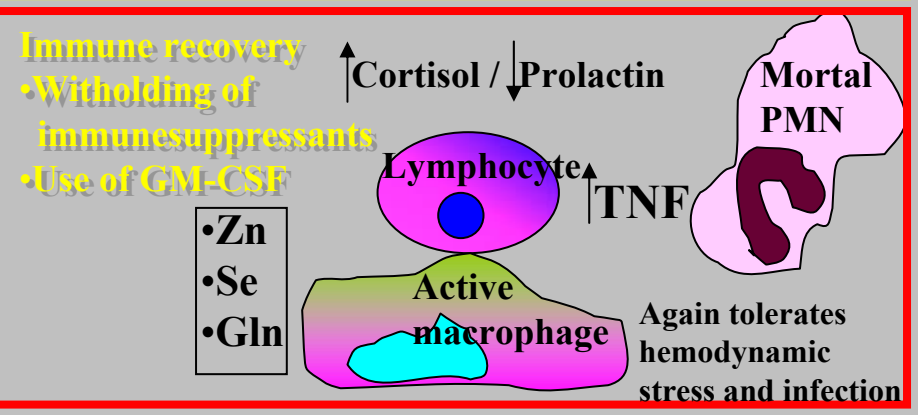
Learning Points

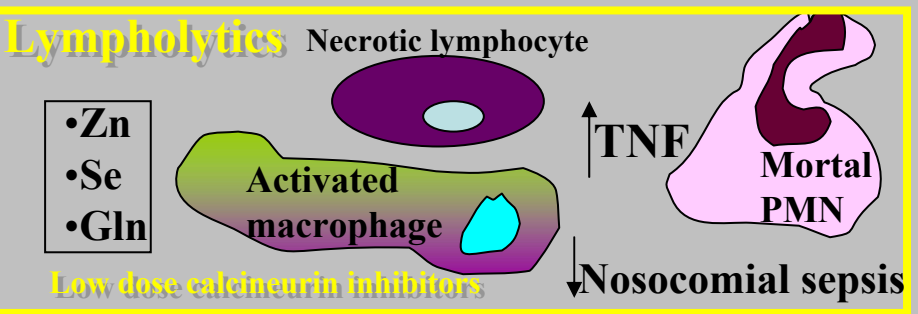
- The decision to treat a patient with a prosthesis with infliximab is difficult, due to the high risk of reactivation of a putative latent infection in the prosthetic joint, since the synthetic material is not removed
- The high activity of the disease , despite aggressive treatment with non biological agents, could require additional therapeutic options
- More information about the true risk of reactivation of a latent infection in the prosthetic material with anti-TNFα therapy is essential
- The use of anti-TNFαagents should be tailored, an in-depth discussion with the patient about the risks and benefits of anti-TNF therapy is essential

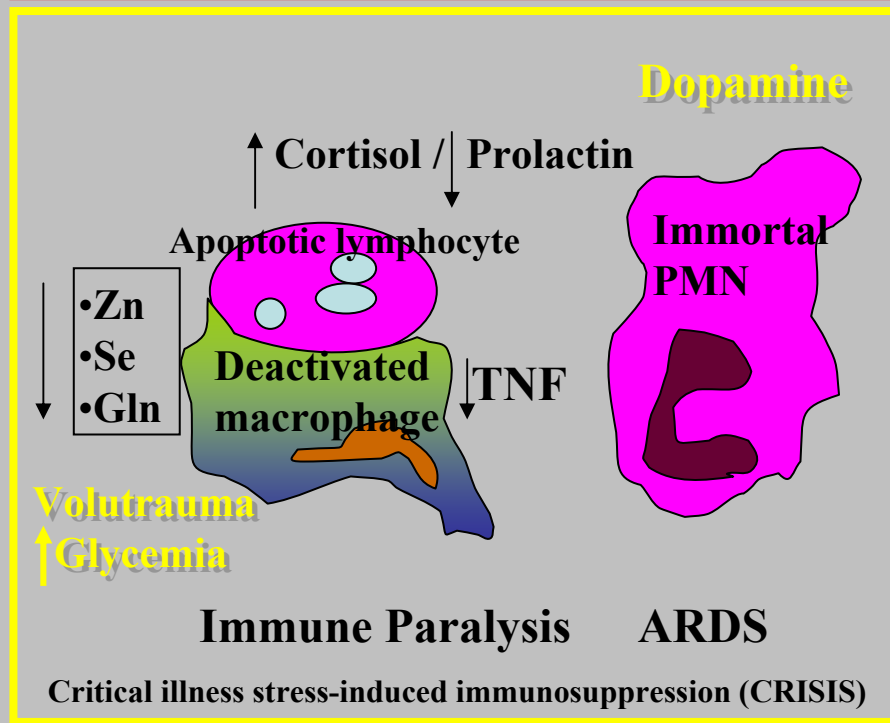

Pro-
flammatory
Response
TNF-α
IL-1β
IL-6
IFN-γ
IL-8
•Delayed type hypersensitivity response to skin testing
•Prolonged hospital course, patients unable to eradicate their primary infection or they acquire secondary infections often characterized by organism typically unable to infect h with normal immune systems
Resultant immune response at the systemic level = immunosuppression
yperinflammatory
ock inducing phase
FIRST HIT
IMMUNOPARALYSIS
The late phase of sepsis
MODS/MOFS
Multiple infections including
Opportunistic infections
72hrs
24hrs
Tim
IL-6
Elimination of
Inhibitory factors
PLASMAPHERESIS or
Exogenous IFN-γ Therapy
rhGM-CSF
Anti-
flammatory
Response
TGF-β
IL-10
IL-1RA
IL-10
IL-1RA
Deactivation of monocytes (CD14 blood monocyte
SECOND HIT


Cortisol / Prolactin
Lymphocyte
•Zn
•Se
•Gln
TNF
Active macrophage
Mortal PMN
Tolerates hemodynamic stress and infection
The normal stress response maintains immune integrity


Dexamethasone
CyclosporineA
Chemotherapy
Neutropenia
Radiation
Cortisol / Prolactin
Apoptotic lymphocyte
•Zn
•Se
•Gln
Deactivated macrophage
Infliximab
TNF
Immortal PMN
Calcineurin inhibitors
Immune Paralysis
ARDS
60-100% of these patients develop sepsis
Immunosuppressants can inhibit the ability to kill infection

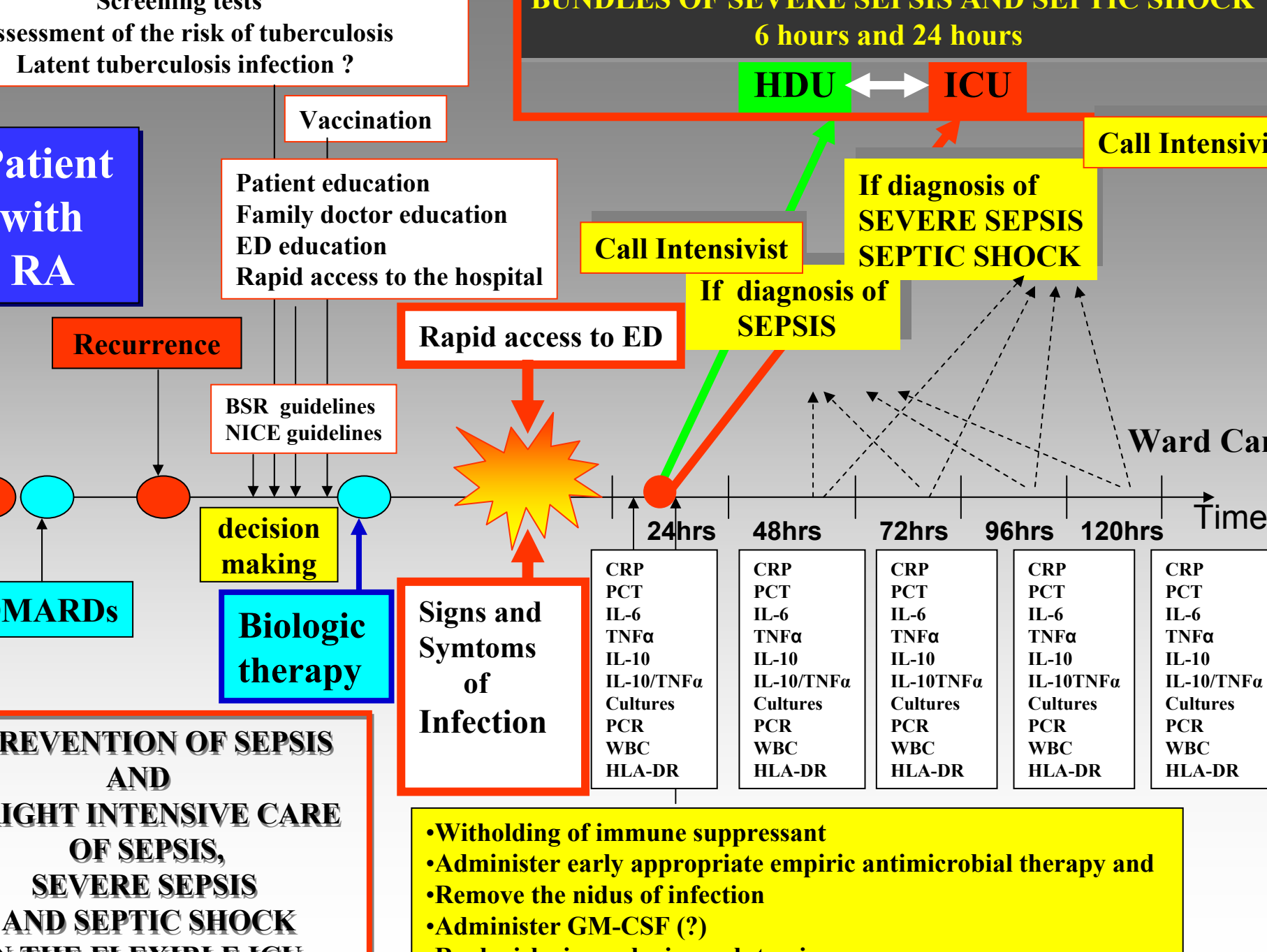

Immune recovery
•Witholding of immunesuppressants
•Use of GM-CSF
Cortisol / Prolactin
Mortal PMN
Lymphocyte
TNF
•Zn
•Se
•Gln
Active macrophage
Again tolerates hemodynamic stress and infection

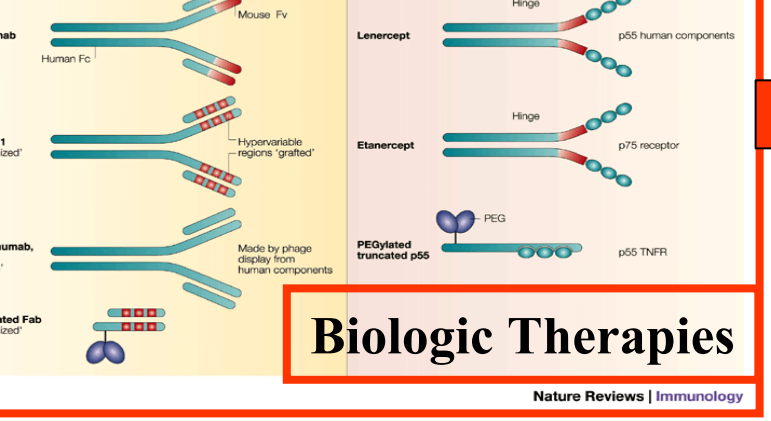

Lympholytics
Necrotic lymphocyte
•Zn
•Se
•Gln
Activated macrophage
TNF
Mortal PMN
Nosocomial sepsis
Low dose calcineurin inhibitors


Dopamine
Cortisol / Prolactin
Apoptotic lymphocyte
•Zn
•Se
•Gln
Deactivated macrophage
TNF
Immortal PMN
Volutrauma
Glycemia
Immune Paralysis
ARDS
Critical illness stress-induced immunosuppression (CRISIS)

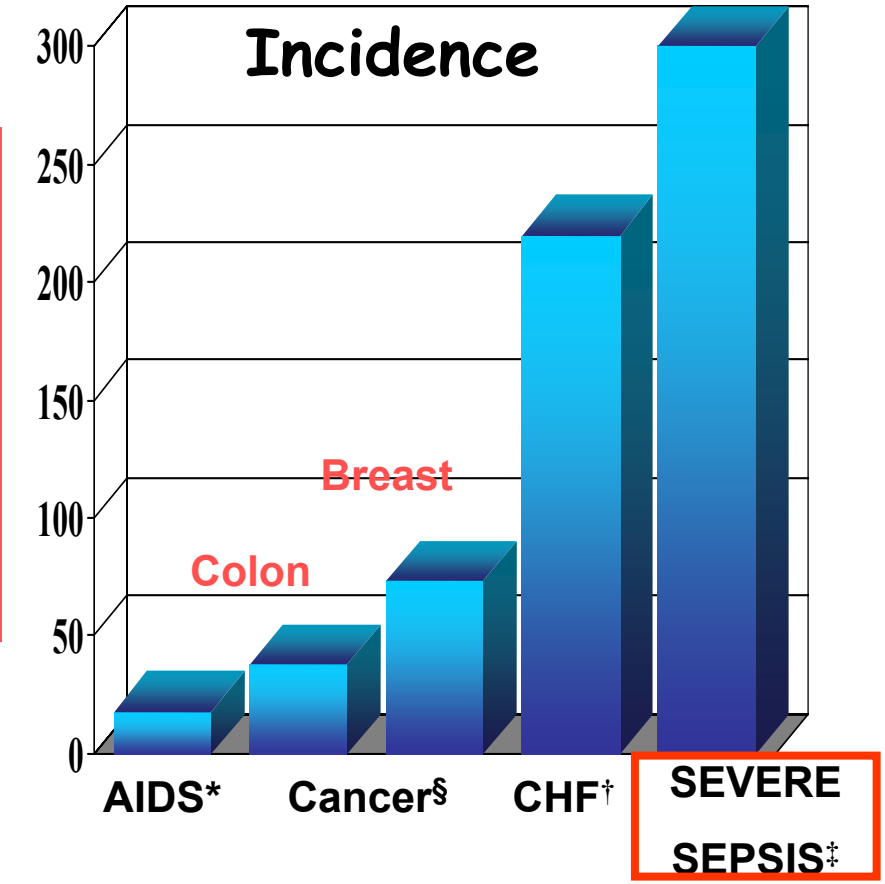
Rational immune phenotype-directed therapeutic strategies in patients with critical illness stress induced immunesuppression

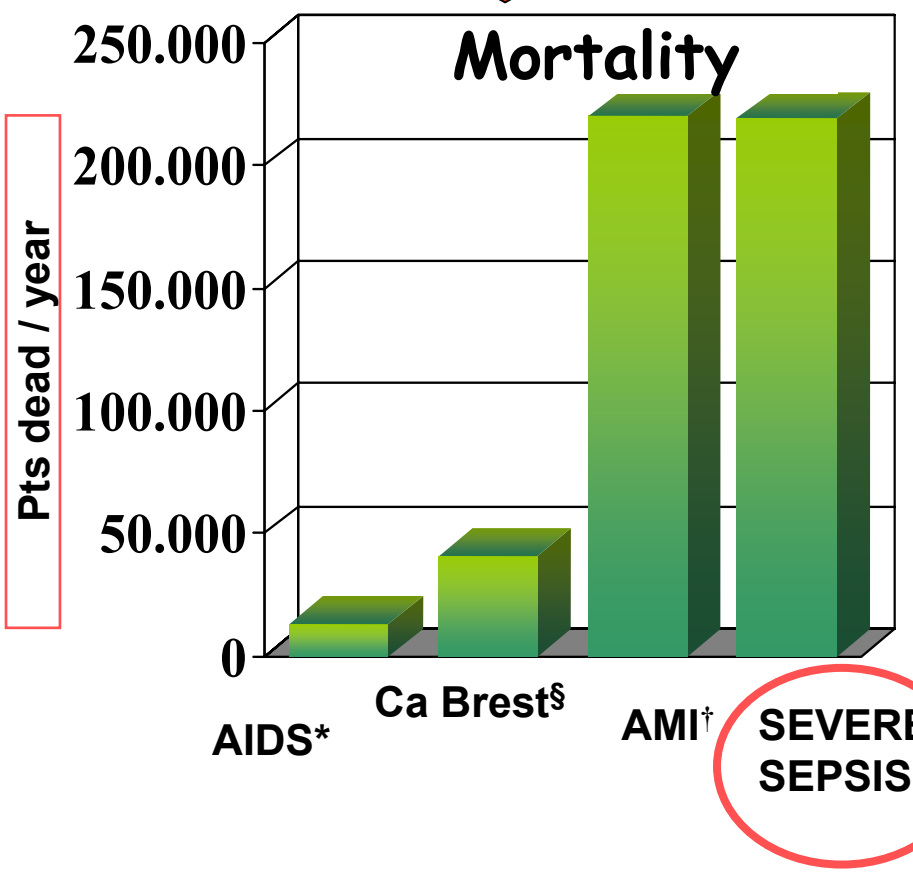
mmunophenotype thresholds	Therapeutic approach
bsolute neutrophil count < 500 cells/mm^3	A. Stop chemotherapy B. Administer empiric antimicrobial therapy for neutropenic fever C. Administer G-CSF,GM-CSF or WC infusion for neutropenic sepsis
bsolute lymphocyte count < 1,000cells/mm^3	A. Stop dexamethasone, dopamine, cyclosporine A B. Administer prophylactic/empiric ant viral, anti-fungal therapies C. Replenish zinc, selenium, glutamine
ypogammaglobulinemia (igG < 500mg/dl)	A. Give IVIG q three weeks or IVIGM
lonocyte deactivation LA-DR <30% or 8,000 to 12,000 molecules/cell; Whole blood TNFα response to LPS < 200 pg/ml	A. Stop dopamine, dexamethasone, calcineurin inhibitors, infliximab B. Replenish zinc, selenium, glutamine C. Apply appropriate antibiotic therapy and remove the nidus of infection D. Give GM-CSF 125μg/m^2/day over 12


Screening tests
ssessment of the risk of tuberculosis
Latent tuberculosis infection ?
BUNDLES OF SEVERE SEPSIS AND SEPTIC SHOCK
6 hours and 24 hours
HDU
ICU
Call Intensivi
Vaccination
Patient education
Family doctor education
ED education
Rapid access to the hospital
atient with RA
Recurrence
Call Intensivist
If diagnosis of SEVERE SEPSIS SEPTIC SHOCK
If diagnosis of SEPSIS
Rapid access to ED
BSR guidelines
NICE guidelines
Ward Ca
decision making
MARDs
Biologic therapy
Signs and Symtoms of Infection
24hrs
48hrs
72hrs
96hrs
120hrs
Time
CRP
PCT
IL-6
TNFα
IL-10
IL-10/TNFα
Cultures
PCR
WBC
HLA-DR
REVENTION OF SEPSIS AND
IGHT INTENSIVE CARE OF SEPSIS, SEVERE SEPSIS AND SEPTIC SHOCK
•Witholding of immune suppressant
•Administer early appropriate empiric antimicrobial therapy and
•Remove the nidus of infection
•Administer GM-CSF (?)



SEVERE SEPSIS:
a neglected disease
the septic patient has no appeal
and is of no interest to the media





†National Center for Health Statistics, 2001. §American Cancer Society, 2001. *American Heart

Case reports

Necrotising fasciitis in a patient receiving infliximab for rheumatoid arthritis

Chan ATY et al Postgrad Med J 2002;78:47-48

A 54 year old man with a 12 year history of seropositive RA presented to the outpatient clinic with a 3 day history of painful , confluent , erythematous pustular rash over his trunk and limbs

He had felt generally unwell with lethargy and loss of appetite, he denied any fever or night sweats

He had various disease modifying antirheumatoid drugs that failed to induce remission

His severe RA resulted in a left hip replacement , which was subsequently revised twice due to prosthesis failure.

Infliximab was started (3mg/kg- at baseline, two four and eight weeks , then repeated every eight weeks

He remained on intramuscular methotrexate (10mg/week)

Case reports

On examination he was apyrexial (temperature 36.5°C)

Pulse 90 beats/min , BP 124/72 mmHg

There was no lymphadenopathy

Examination of his respiratory and abdominal systems was unremarkable

Neurologically, there was a reduced power in his left leg (grade 4/5) due to pain . There was no active synovitis

A skin biopsy of the rash showed an acute pustular dermatitis secondary to a drug reaction

HB 13 g/dl, White cell count 14.82 x 10^9/L , neutrophils 13.99 x 10^9/L and PLTs 295 x $10^{9/L}$

A clotting screen gave a PT 27 seconds, APTT 38 seconds and fibrinogen 9.33g/L

Urea and electrolyte concentrations were normal and plasma glucose 6.1 mmol/L

Chest radiography was normal

Blood culture and skin swabs were taken

Case reports

Five hours after the hospital admission he became light headed and collapsed

He was tachycardic (140/min) and perpherally shut down but had a blood pressure of 120/70 mmHg

He remained apyrexial at 36.9°C

His left leg had become very tense painful and swollen

He had a metabolic acidosis with a pH of 7.21 and bicarbonate of 12.9 mmol/L

He was transferred to the ICU

Case reports

In the ICU he had worsening acidosis and hyperkalaemia (potassium 6.02 mmol/L)

Further investigations showed a Hb of 3g/dl, white cell count 2.04 x 10^9/L, platelets 70 x 10^9/L, PT 34 seconds, APTT 50 seconds, fibrinogen 5.87 g/L and raised D-Dimer of 11.4 mg/L

These findings were consistent with a DIC

All his biochemical and haematological abnormalities were treated appropriately

He required inotropes, vasopressors and intubation

There was marked necrosis of his adductor compartment and fascia of his left thigh on exploration

He underwent debridement of his necrotic muscles but this was hampered by recurrent cardiac arrests

Despite resuscitation effort , he died

His blood cultures and skin swabs grew haemolytic group A streptococcus. The isolation of this bacterium together with necrosis of subcutaneous tissue and severe systemic illness (sudden death, shock, DIC and MODS) conforms to the case of necrotising fasciitis

Case reports

Learning points

- Anti-TNFα agents are useful in reducing disease activity and joint destruction in RA
- Overall the data from drug trials shows that infliximab is safe when used appropriately
- The use of infliximab is associated with the risk of severe sepsis and septic shock
- The absence of pyrexia or other signs of infection does not exclude the possibility of sepsis in patients treated with infliximab
- Report all adverse events with the use of anti-TNFα agents

Case reports

Life threatening intra-abdominal sepsis in patients on anti-TNFα therapy

Goode S et al Gut 2005 doi:10.1136/gut.2005.085449

A 60 year old male with psoriatic arthritis resistant to treatment had benefit from etanercept for six months

In rheumatology outpatients he complained of a two week history of admoninal pain

On examination he was tender in the left upper quadrant with a palpable mass

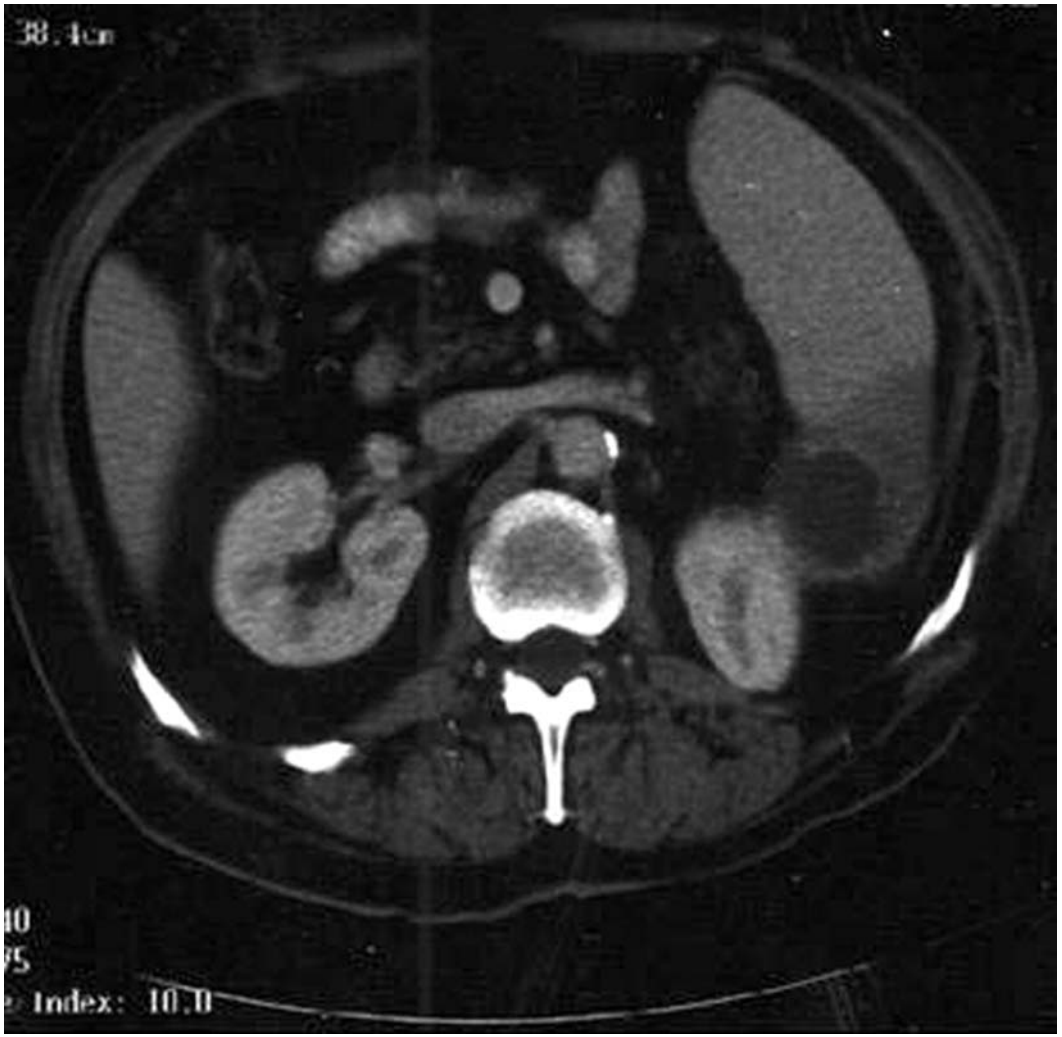
A contrast enhanced computed tomography (CT) scan demonstrated a large multilocular splenic abscess with subcapsular extension

Blood cultures grew staphylococcus aureus

Conservative treatment with high dose intravenous antibiotics, initially with cefuroxime, metronidazole and gentamicin on microbiological advice, had no effect

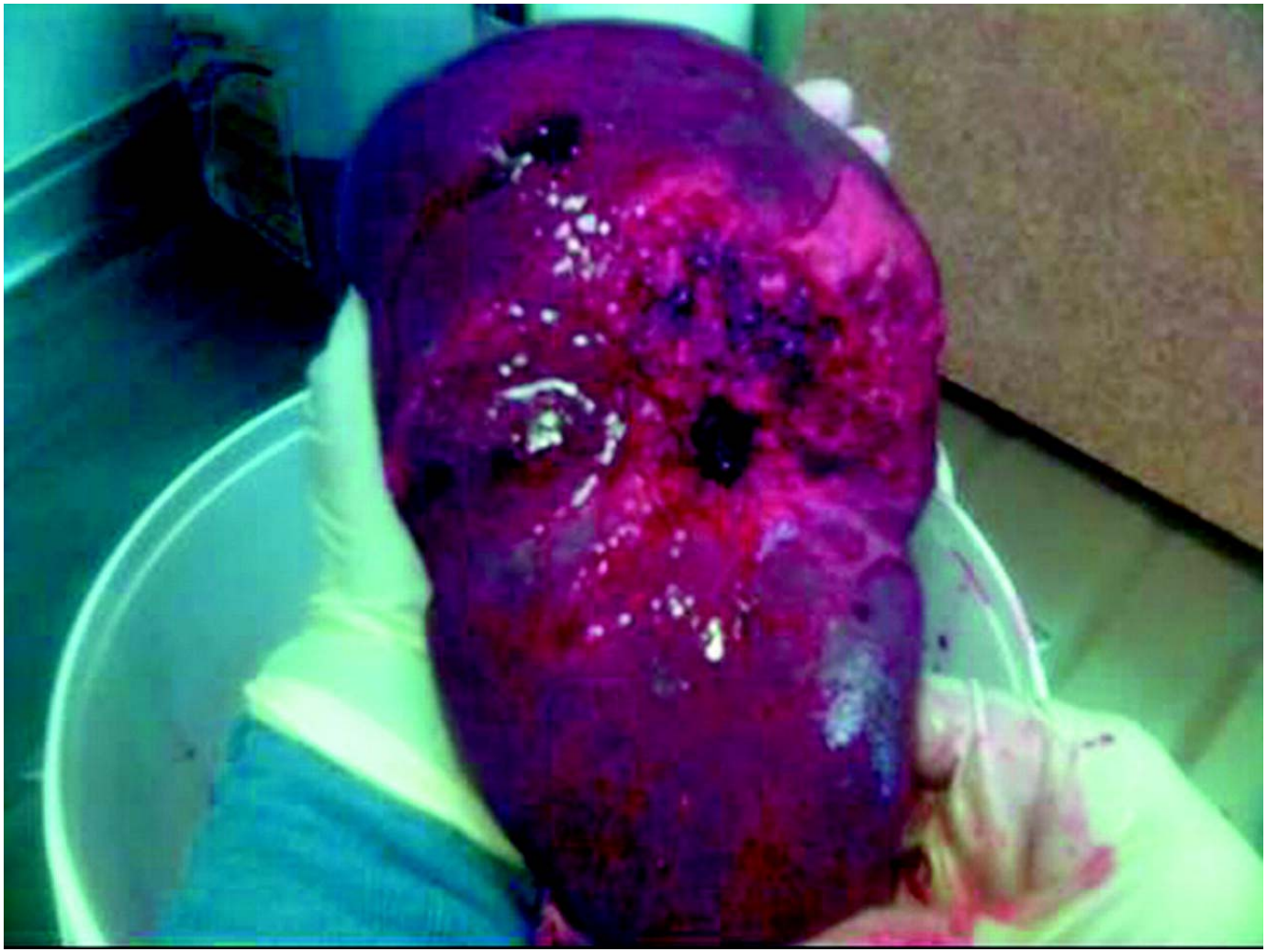
The patient became increasingly septic and after one week of conservative therapy he proceeded to laparatomy and splenectomy. Postoperatively he developed a severe sepsis requiring ICU admission

Figure 1 Computed tomography. Expansile predominantly cystic mass located within an area of hypodensity in the posterior pole of the spleen.



Goode, S et al. Gut 2006;55:590-591

Figure 2 Surgical specimen consisting of the spleen with an abscess on the posterior aspect.



Goode, S et al. Gut 2006;55:590-591

Case reports

In the ICU the patient developed a septic shock requiring fluids, vasopressors and inotropes, intubation and mechanical ventilation for five days

Histopathology of the spleen showed multiple splenic abscesses that grew staphylococcus aureus

The patient made a full recovery

He has received no further etanercept and has no evidence of a flare up of his arthritis six months postoperatively

He was given prophylactic low dose penicillin and anti-pneumococcal vaccination

Case reports

A 40 year old female presented via Emergency Department with three day history of abdominal pain and rigors

She had been treated with infliximab for six weeks for severe RA resistant to other therapies

On examination she had pyrexia of 39.2°C with right upper quadrant tenderness

She deteriorated with a worsening sepsis and metabolic acidosis and required admission to ICU

Case reports

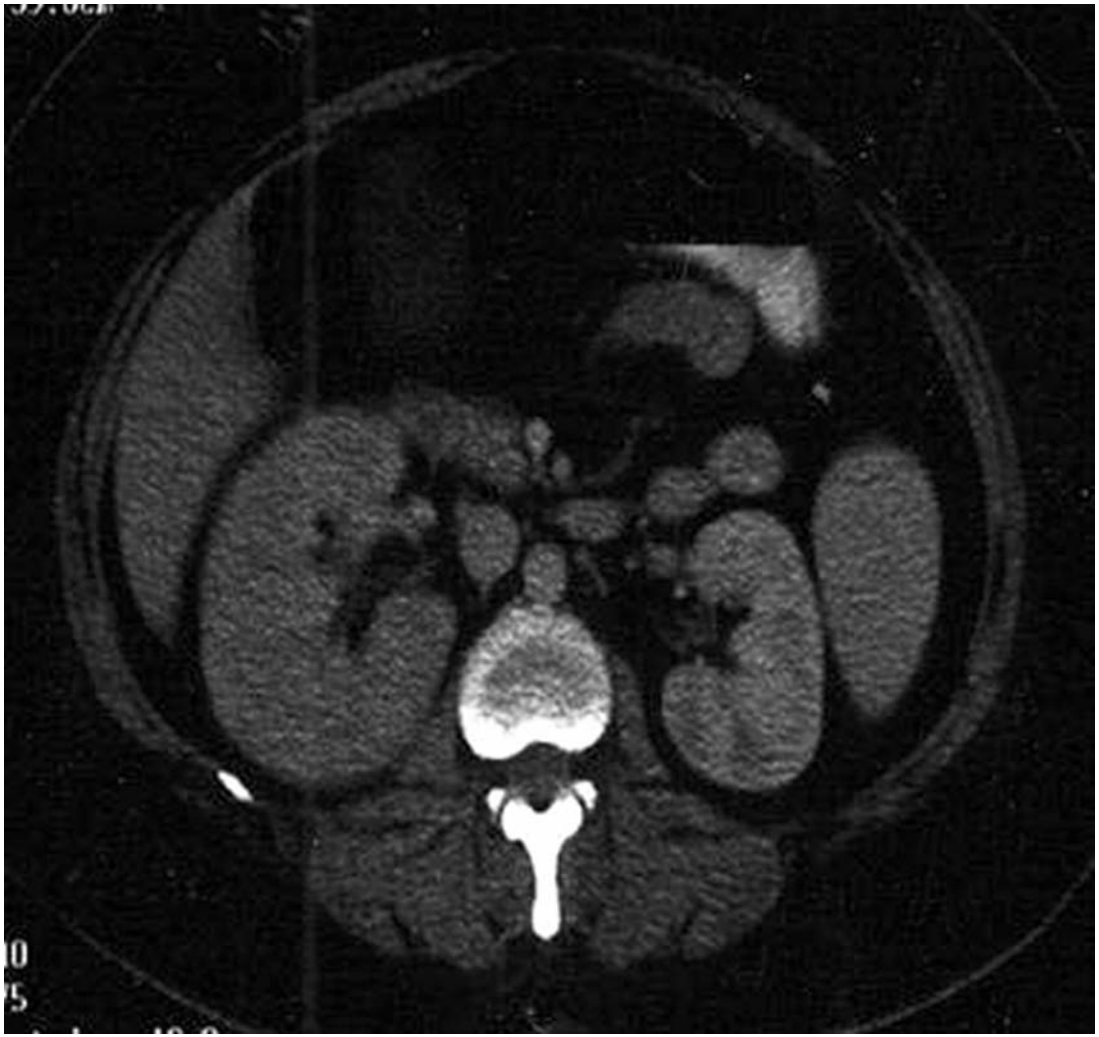
In the ICU she had an haemodynamic support with fluids, inotropes and vasopressors, and a respiratory support with intubation and mechanical ventilation

Once stabilised, a CT scan of her abdomen demonstrated a large right sided hydronephrosis

Urine cultures were negative but blood cultures grew escherichia coli

After 48 hours of intravenous cefuroxime and gentamicin she improved and was discharged to the ward

Figure 3 Computed tomography. Expanded non-enhancing right kidney consistent with pyelonephritis.



Goode, S et al. Gut 2006;55:590-591

Case reports

Learning points

The patients presented here had delay in initial diagnoses

This may have resulted in a worse outcome or even death

We suggest that patients who have received anti-TNFα therapy and develop a non specific abdominal pain should proceed to urgent abdominal ultrasound or CT scan to exclude significant intra-abdominal sepsis

A further concern is that anti-TNFα drugs may diminish the acute phase response, so that significant sepsis may not always have dramatic or acute presentations. This may lull the attending doctor into a false sense of security

Doctors who encounter patients on anti-TNFα therapy need to be aware of the possible complications

They should be treated as if they are significantly immunocompromised, and non specific symptoms such as abdominal pain need to be investigated intensively

Case reports

Nancy F Crum et al Infections associated with TNFα antagonists

Medicine 2005; 84:291-302

A 47 year old white woman with a history of RA, non insulin dependent diabetes mellitus and Sjogren syndrome arrived to the Emergency Department with fever , chills and generalized weakness

The patient had been receiving etanercept for 1 month

Her temperature was 39.9°C, pulse 140, blood pressure 90/60, respiratory rate 24 and pulse oxymetry 88%

There were no focal abnormalities except joint changes consistent with RA

The WBC was 21,300/mm^3 with 56% neutrophils and 22% bands, creatinine 1.5 mg/dl, bicarbonate 15 mmol/l and glucose 191 mg/dl

The patient was admitted to the ICU

Case reports

In the ICU the patient was treated with intravenous fluids, oxygen and empiric antibiotics

Chest radiography revealed a left lower pneumonia

3 of 4 blood cultures were positive for Streptococcus pneumoniae sensitive to penicillin, erythtomycin, levofloxacin, vancomycin and trimethoprim-sulphamethoxazole

She was treated with intravenous penicillin and discharged after 7 days to complete a course of oral amoxicillin

The patient completely recovered and etanercept was restarted 2 months later

A pneumococcal vaccination was administered before the TNFα blocker restarted

Case reports

Learning points

The risk of bacterial infections with typical organisms such as Streptococcus, staphylococcus and moraxella may be increased among TNFα inhibitor recipients

Infections such as pneumonia, abscess, cellulitis and sinusitis have been noted; severe infections, including necrotizing fasciitis and septic arthritis have also been reported

It is noteworthy that the occurrence of these bacterial infections is often unrelated to the exact time of TNFα blockade; patients appear to remain at risk for the duration of immunesuppression. This is in contrast to the TB or histoplasmosis experience, possibly because the latter are more often reactivated infections

Case reports

Lethal ARDS during anti-TNFα therapy for rheumatoid arthritis

Christian Zimmer et al Clin Rheumatol 2006; 25:430-432

A 56 year old woman (70Kg, 162 cm) with a long history of rapidly progressive seropositive RA had been treated with etanercept (Enbrel 25 mg s.c. twice a week) for two years

In addition, she received methotrexate (Methotrexat 15 mg/week p.o.) and prednyliden (Decortilen 3mg/day p.o.)

After 2 days of muscle weakness, fatigue and cough producing reddish brown sputum, she received ciprofloxacin (500 mg p.o. twice a day) by her general practitioner but , 1 day later, was admitted to a hospital

On admission, she presented with severe dyspnoea and bilateral opacities on chest x ray , increased CRP (326mg/L) impaired renal function (serum creatinine 3.2 mg/dl) and oliguria and leukopenia

She was immediately transferred to the ICU

Case reports

In the ICU she was immediately intubated and antibiotic treatment was started with ceftriaxon, ciprofloxacin, erythromycin and fluconazol. However despite fluid resuscitation she required high dose norepinephrine (0.2 µg/kg/min) and developed an ARDS (paO2/FiO2 100 mmHg)

The patient was transported with a specially equpped ambulance in a more equipped ICU for an advanced ARDS therapy

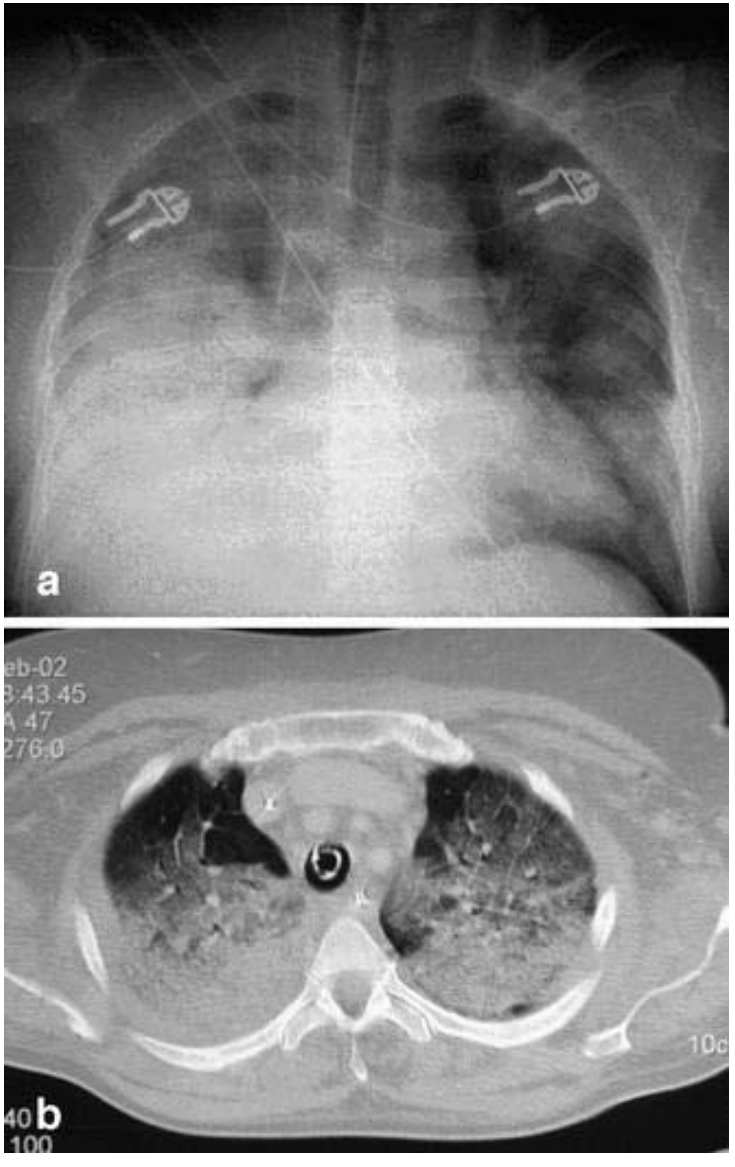
Despite aggressive ventilation with pure oxygen and a PEEP of 17 mbar, both gas exchange (PaO2 79.5 mmHg, PaCO2 46.5 mmHg) and acidosis (pH 7.10) worsened

Very high dosages of NE (1.4 µg/kg/min) were required continuously for counteracting severe hypotension

Pulmonary artery hypertension (mean PAP 36 mmHg) was also present, and transesophageal echocardiography revealed right heart loading

A chest CT scan confirmed widespread consolidation of both lungs

The simplified acute physiologic score was 46 indicating multiple organ failure within 1 day of hospitalisation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Case reports

Further therapy included increased PEEP (> 20 mbar), prone positioning, antibiotic therapy with cefotiam and clarythromycin and CVVH for acute renal failure

When a penicillin suspectible Streptococcus pneumoniae was identified in BAL fluid, penicillin G was added

While gas exchange improved gradually and FiO2 could be decreased to 0.6, pulmonary hypertension remained unresponsive to any treatment, including inhaled NO and iloprost

During the next 5 days , vasopressors and oxygen demand remained unaltered

Blood cultures positive for Escherichia coli and Candida krusei o day 5 after admission evoked a change to imipenem, gentamicin and amphotericine B

The patient died of overwhelming septic shock 13 days following admission

Case reports

Learning points

Infections in patients with anti-TNFα therapy, particularly when combined with other immunosuppressants, might be more severe

Accordingly, any signs of pulmonary infection should be regarded as very serious, as fulminant pneumonia with ARDS and severe sepsis may develop within 24 hours

Case reports

Purulent pericarditiitis in a patient with RA treated with etanercept and methotrexate

David D Sweet et al Can JEmerg Med 2007;9:40-2

After a day of golf, a 71 year old woman presented to a local resort clinic complaining of lower back pain with radiation to the right leg

While at the clinic she developed extreme abdiominal pain and started vomiting

Her vital signs on presentatrion to the clinic were: 92 beats/min, blood pressure 140/85 mmHg, respiratory rate 18 breaths/min and oxygen saturation 99% on room air

She was afebrile, but pale and diaphoretic with cool extremities

Her chest, precordial and abdominal exams were all normal and she had normal femoral pulses

The chest x ray was normal

The ECG revealed Q waves in the anterior leads

A presumtive diagnosis of ruptured abdominal aortic aneurysm or anterior myocardial infaction was made and she was flown by helicopter to a tertiary emergency department

Case reports

On arrival at the ED, the patient was restless, distressed and complaining of extreme abdominal pain

Vital signs at this time revealed a blood pressure of 103/60 mmHg HR of 95 beats/min, RR of 30 breath /min, pulse oxymetry saturation of 93% on 12 liters/min of oxygen and a temperature o 37.5°C

She was pale and diaphoretic with cool extremities but the remainder of her clinical examination was normal apart from a distended, diffusely tender abdomen with neither point tenderness nor peritoneal signs

Pulsus paradoxus was not assessed

She had no specific signs or symtoms that would identify a focus of infection or a bacterial portal of entry

A bedside portable ultrasound showed intraperitoneal free fluid a thickened gallbladder wall, without evidence of stones or biliary dilation and no aortic aneurysm

An incidental small pericardial effusion was noted

Case reports

Portable A-P chest x ray was unremarkable and the ECG showed generalized low amplitude and an anterior infarct of undetermined age

Arterial blood gases revealed a profound metabolic acidosis with inadequate respiratory compensation; pH 6.90 , $PaCO_2$ 27 mmHg ,bicarbonate 5 mmol/L BE 28 mmol/L , PaO_2 83 mmHg , oxygen saturation 85% on 12L O_2 by mask

The initial Hb, platelets, electrolytes , glucose , CK, troponin , INR and aPTT were all within normal limits

White blood cell count was 24.0 with 6.88 polymorphs and 9.61 bands

There was a severe anion gap acidosis with a lactate of 12.3 mmol/l

The creatitine was elevated at 178 mmol/l , but the urea was normal at 6.2 mmol/l

Case reports

The past medical history of this patient was remarkable for a 13 year history that was controlled by both methotrexate for 11 years and etanercept twice weekly for 2 years

The patient had a history of hypercholesterolemia, hypertension and a remote history of psoriasis

Her other medications included atenolol, clonidine , estradiol , refecoxib (Vioxx) and ASA

Her only known allergy was to sulfa

Case reports

In the ED , she developed progressive respiratory failure and shock, requiring intubation and admission to the ICU

Following intubation she was fluid resuscitated and started on broad spectrum antibiotics

20 minutes post intubation she suffered pulseless electrical activity cardiac arrest, received epinephrine and atropine

Spontaneous circulation returned after 2 minutes of cardiac compressions and she was started on a dopamine infusion and sent for abdominal CT scan

This showed free fluid in the abdomen and pelvis with a thick walled gallbladder, perpancreatic, pararenal and mesenteric fat stranding, bilateral pleural effusions and mild to moderate sized pericardial effusion

Case reports

Despite several liters of IV fluid, a dopamine infusion and repeated boluses of phenylephrine, the patient remained hemodynamically unstable requiring intermittent boluses of epinephrine to maintain blood pressure

At this time, the possibility of cardiac tamponade was considered and ED ultrasound guided pericardiocentesis was performed

A total of 75 ml of cloudy, brown fluid was withdrrawn and sent for gram stain and culture

The patient stabilized

Gram's stain of the pericardial fluid showed 4+ polymorphs with gram-positive cocci and cultures later identified methicillin sensitive Staphylococcus aureus

The patient's course in hospital included prolonged respiratory failure , septic shock and renal failure requiring dialysis

Following a 1 month stay in the ICU , she was transferred to the ward and discharged from hospital

The patient was advised to discontinue TNFα antagonist agents and remain on the lowest possible dose of prednisone to control her RA

Case reports

M.Fernandez-Castro et al Rheumatology 2005; 44:1076-1077

A 59 year old woman with long lasting, severe , erosive and seropositive rheumatoid arthritis

Despite treatment with several DMARDs , the disease remained active and structural damage progressed

A prosthetic joint was implanted in the right knee in august

In november , she was diagnosed with sepsis of the prosthetic joint with penicillin sensitive Staphylococcus aureus isolated from the synovial fluid culture

She was treated with intravenous cefazolin for 3 weeks and extensive surgical debridment without removing the prostetic joint

An oral 6 month course of ciprofloxacin and rifampicin was completed

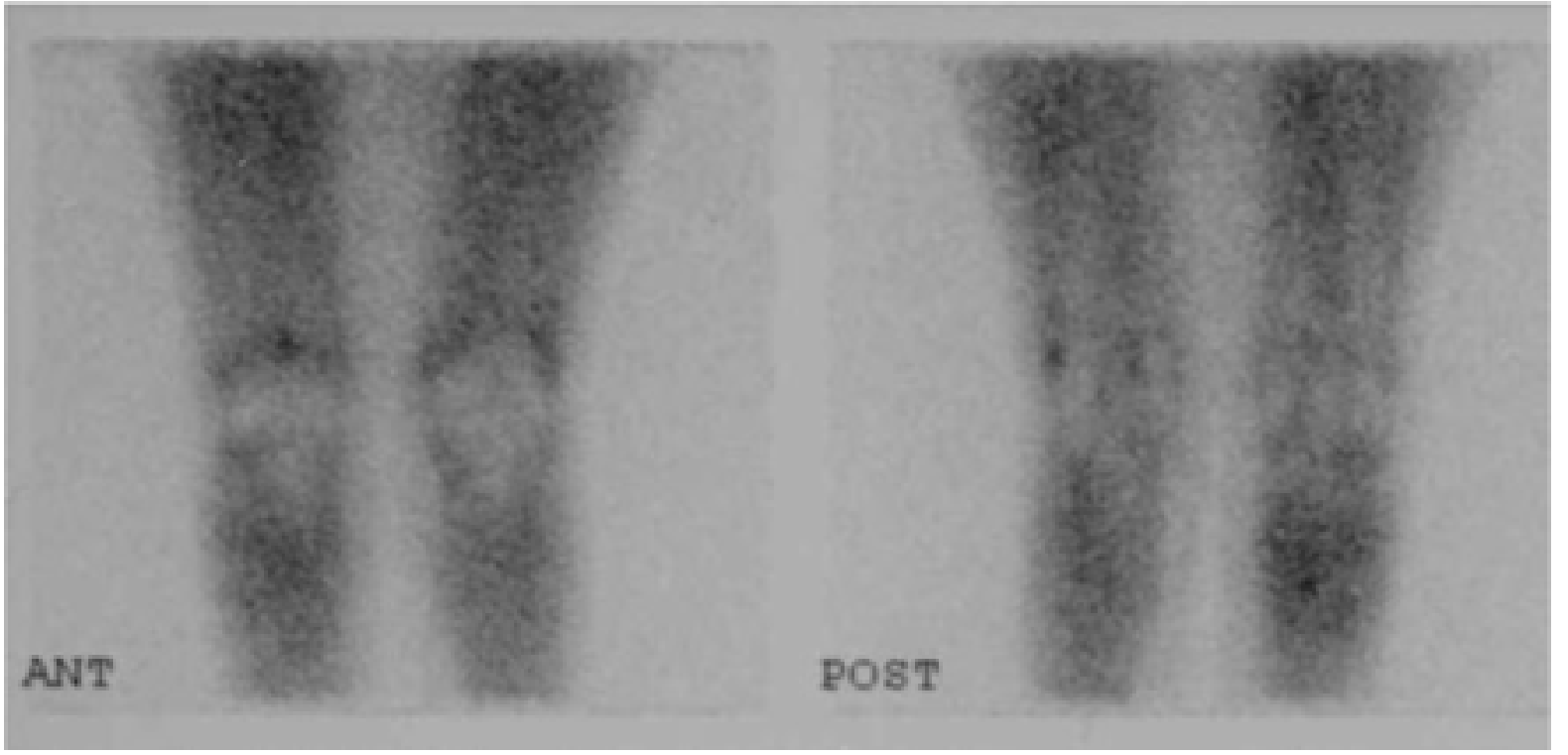
Case reports

In february of the following year , despite the treatment with leflunomide , celecoxib and low dose prednisone, the disease remained active with a DAS of 7.28

After an in depth discussion about the risk of reactivation of the sepsis of the prosthetic joint, the patient accepted the treatment with infliximab

Three years later , the activity of RA is well controlled with 3mg/kg every 8 weeks of infliximab and 5mg/day o prednisone, the DAS score being 2.70

The right knee is asymptomatic and gallium scintigraphy is not suggestive of infection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Case reports

Learning Points

The decision to treat this patient with infliximab was difficult, due to the high risk of reactivation of a putativ latent infection in the prosthetic joint, since the synthetic material was not removed

But, the high activity of the disease , despite aggressive treatment with non biological agents, required additional therapeutic options

More information about the true risk of reactivation of latent infection in the prosthetic material with anti-TNFα therapy is essential

The use of anti-TNFαagents should be tailored, an in-depth discussion with the patient about the risks and benefits of anti-TNF therapy is essential