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. If onset of recovery does not follow within hours or few days (5-7d ?) of Intensive Care, Critical Illness often becomes prolonged and organ systems support is frequently needed for several weeks, months.

**ACUTE (early) PHASE**
- 5-7 days

**CHRONIC (late) PHASE**
- ICU dependency potentially lethal
- Time: weeks, months

**DYNAMIC DISEASE**
- * Genetic predisposition
- * Risk factors
- * Underlying diseases

**Injury**
- First HIT

**Septic complications**
- New acute phases on a chronic phase
- Second HIT

**Sepsis Clock**
- >25%
- <25%
INFECTION
(bacteria, fungi, viruses, toxins)

- Surgery/trauma/burns
- Hematoma/venous thrombosis
- Miocardial/pulmonary infarction
- Transplant rejection
- Pancreatitis
- Erythroderma

- Thyroid storm
- Acute adrenal insufficiency

SIRS
Systemic Inflammatory Response Syndrome

CARS
Compensatory Anti-inflammatory Response Syndrome
(systemic host response)

Interpreting the microbiological findings
- Distinguishing colonization from infection
- Prior antibiotic therapy
- Correctly identifying unfamiliar organisms
- Determining the significance of mixed culture results
- Interpreting 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

Different diseases
Different pathways

- Different underlying conditions
- Different genetic predispositions
- Different anatomic sites of infections
- Different micro-organisms with varying virulence and quantity
- Wide range of host inflammatory and immunologic capabilities

J. Carlet et al.
Sepsis: time to reconsider the concept
Crit Care Med 2008;36:964-966

Avoidable
Not avoidable
1. Community Sepsis
2. Human “induced” sepsis
3. ICU Sepsis
   - Sepsis born in ICU
   - Wrong Diagnosis
   - Wrong Therapy
   - Wrong Support

The problem of sepsis in the field

TO DIE BY SEPSIS
TO DIE WITH SEPSIS
- Avoidable deaths
- Unavoidable deaths

Avoidable deaths
Unavoidable deaths
Complaint severe infection ignored infection

Community severe infection
ignored infection

Different Diseases
Comorbidities

AGE +
<table>
<thead>
<tr>
<th>Definition</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Systemic inflammatory</td>
<td>Two or more of the following:</td>
</tr>
<tr>
<td>response syndrome</td>
<td>- Body temperature &gt;38.5°C or &lt;35.0°C</td>
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<tr>
<td></td>
<td>- Heart rate &gt;90 beats per minute</td>
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<td>- Respiratory rate &gt;20 breaths per minute or arterial CO₂ tension &lt;32 mm Hg or need for mechanical ventilation</td>
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<td>- White blood cell count &gt;12,000/mm³ or &lt;4,000/mm³ or immature forms &gt;10%</td>
</tr>
<tr>
<td>Sepsis</td>
<td>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—e.g., ruptured bowel with free air or bowel contents found in abdomen at surgery, wound with purulent discharge)</td>
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<tr>
<td>Severe sepsis</td>
<td>Sepsis and at least one sign of organ hypoperfusion or organ dysfunction:</td>
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<tr>
<td></td>
<td>- Areas of mottled skin</td>
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<td>- Capillary refilling time ≥ 3 s</td>
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<td>- Urinary output &lt;0.5 mL/kg for at least 1 h or renal replacement therapy</td>
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<td>- Lactates &gt;2 mmol/L</td>
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<td>- Abrupt change in mental status or abnormal electroencephalogram</td>
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<td>- Platelet counts &lt;100,000/mL or disseminated intravascular coagulation</td>
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<td>- Acute lung injury—acute respiratory distress syndrome</td>
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<td></td>
<td>- Cardiac dysfunction (echocardiography)</td>
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<tr>
<td>Septic shock</td>
<td>Severe sepsis and one of:</td>
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<td>- Systemic mean blood pressure &lt;60 mm Hg (&lt;80 mm Hg if previous hypertension) after 20–30 mL/kg starch or 40–50 mL/kg serum saline, or pulmonary capillary wedge pressure between 12 and 20 mm Hg</td>
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<td>- Need for dopamine &gt;5 μg/kg per min or norepinephrine or epinephrine &lt;0.25 μg/kg per min to maintain mean blood pressure above 60 mm Hg (80 mm Hg if previous hypertension)</td>
</tr>
<tr>
<td>Refractory septic shock</td>
<td>Need for dopamine &gt;15 μg/kg per min or norepinephrine or epinephrine &gt;0.25 μg/kg per min to maintain mean blood pressure above 60 mm Hg (80 mm Hg if previous hypertension)</td>
</tr>
</tbody>
</table>
The Sepsis Continuum

- 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/MOFS

DEATH

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.

- **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⁻¹m⁻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⁻¹h⁻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 (platelet count < 100,000/µl)
  - Hyperbilirubinemia (plasma total bilirubin > 4 mg/dl or 70 mmol/l)

- **Tissue perfusion parameters**
  - Hyperlactatemia (> 3 mmol/l)
  - Decreased capillary refill or mottling

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**DIAGNOSTIC CRITERIA FOR SEPSIS 2001 SCCM/ESICM/ACCP/ATS/SIS**

International Sepsis Definitions Conference

## Simplified Organ Failure Assessment
### SOFA Score

<table>
<thead>
<tr>
<th>Organ system /Score</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tbody>
<tr>
<td>CNS GCS</td>
<td>13-14</td>
<td>10-12</td>
<td>6-9</td>
<td>&lt;6</td>
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<tr>
<td>RESPIRATORY SYSTEM</td>
<td>&lt; 400</td>
<td>&lt; 300</td>
<td>&lt; 200 with support</td>
<td>&lt; 100</td>
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<tr>
<td>Pa/FiO₂ (mmHg)</td>
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<td>LIVER</td>
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<tr>
<td>Bilirubin (mg/dl)</td>
<td>1,2-1,9</td>
<td>2,0-5,9</td>
<td>6,0-11,9</td>
<td>&gt;12</td>
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<td>COAGULATION</td>
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<tr>
<td>Platelets (10³/mm³)</td>
<td>&lt; 150</td>
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<td>CARDIOVASCULAR</td>
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<tr>
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<td>Dopa &lt; 5 o Dobutamin</td>
<td>Dopa &gt; 5 o Adr &lt; 0,1 o Noradr &lt; 0,1</td>
<td>Dopa &gt; 15 Adr &gt; 0,1 Noradr &gt; 0,1</td>
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**TIME IS ORGAN**

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

Newton’s PRINCIPIA

"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; 24:1125-1128
Early diagnosis of Sepsis

It has been estimated that as many as 60% of critically ill patients develop SIRS manifested by tachycardia, tachypnea, fever and/or leukocytosis.

<table>
<thead>
<tr>
<th>Is there a living infection?</th>
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<tr>
<td>• History</td>
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<td>• Examination</td>
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<td>• Clinical diagnosis of suspected living infection</td>
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<tr>
<td>• Biomarkers (procalcitonin, endotoxin) Septifast/VYOO</td>
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<tr>
<td>• Clinical diagnosis of probable living infection</td>
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<tr>
<td>• Appropriate cultures</td>
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<tr>
<td>(always before antibiotics)</td>
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</table>

6 hours BUNDLE

• Clinical diagnosis of certain living infection

Is there a living infection?

The first 6 hours

24/48 hrs

The problem of the early diagnosis of a living infection
ALGORITHM FOR SYSTEMATIC EVALUATION OF NONNEUTROPENIC PATIENTS WITH SUSPECTED SEPSIS

Intensive Care Med 2001; 27:S10-S32
Techniques for laboratory detection of bloodstream infections

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

Detection of amplicons

- Amplification of the 16S or 23S rRNA gene and 18S rRNA gene (fungi)

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”

Dynamic time-course of the inflammatory response during Sepsis

Causative Agents:
- BACTERIA
- TRAUMA
- SHOCK

Epithelial cells
- Contact system (e.g., kinins)

Endothelial cells
- Pro-inflammatory Cytokines + Chemokines
- ROS production
- Enzyme release
- Tissue Factor expression

PMN

Macrophages

Pro-inflammatory response
- Vascular permeability
- Bacterial killing
- DIC
- Tachypnea
- Fever
- Leukocytosis
- Tachycardia
- Peripheral resistance

Hyperreactive immune response
- Edema
- Tissue damage
- Organ failure
- Leukocytopenia
- Shutdown of neutrophils
- Susceptibility to infection

Hyporeactive immune response
- Susceptibility to infection

Intensity of inflammatory response

Time
Pathogen Associated Molecular Patterns

PAMPs of Gram-positive and Gram-negative Bacteria

Gram - positive Bacteria

Staphylococcus aureus

PM

Lipoprotein Lipopeptides

DNA-CpG Oligomers

Peptidoglycan (Murein)

Turnover

Lipoteichoic Acid

Release

Gram - negative Bacteria

Escherichia coli

PM

OM

Endotoxin
(Lipopolysaccharide)

Bacterial Death (Antibiotics, C')

Shedding /Blebbing
Gram negative bacteria

Lipopolysaccharide

CpGDNA

Flagellin

Peptidoglycan

Lipoteichoic acid

Specific signal

PAMPs

PRRs

Pattern Recognition Receptor

Gram positive bacteria

RESPONSE 1

RESPONSE 2
Toll-like receptor ligands

- PGN
- Lipopeptides
- Lipoproteins
- Zymosan
- LPS
- LTA
- HSP60
- Flagellin
- CpG DNA

CD14

CD14

TIR domain

TLR2

TLR4

TLR5

TLR9

MyD88

IRAK

TRAF6

NFκB activation

TNF-α

Toll-like receptor ligands
PROINFLAMMATORY AND ANTI-INFLAMMATORY EVENTS DURING SEPSIS

Excessive systemic inflammation

Fulminant sepsis
Early mortality

Immunoparalysis

Nosocomial infections
Late mortality

Days

Excess cytokine release
Compensatory anti-inflammatory response

Proinflammatory cytokine release

IL-10
sTNF\(\alpha\)R type 1-2
sIL-1R type 2
IL-1ra

Tom van der Poll Lancet Infectious Diseases 2001; 1: 165-174
Proinflammatory and anti-inflammatory mechanisms during localised and systemic infection

Localised infection
Local inflammation contributes to antibacterial defence

Compartimentalization

Impaired bacterial clearance

Proinflammatory cytokines
Eicosanoids
Neutrophil products
Complement products
Coagulation

Compensatory anti-inflammatory mechanisms
Anti-inflammatory cytokines
Soluble inhibitors
Hyporesponsiveness of immune cells
Stress hormones

Reduction of systemic toxicity

Fulminant sepsis
Systemic inflammation contributes to lethality

Tom van der Poll Lancet Infectious Diseases 2001; 1: 165-174
Dynamic of the septic inflammatory response
The immunologic response to sepsis over time

SIRS
CARS

HMGB1

- Death
- TNF
- IL-1β

LPS Hours Days

Enterocytes

Endothelial cells

Regulation of fibrinolysis

Pro-inflammatory cytokines and chemokines

Vascular permeability

Bacterial translocation

Neutrophil adherence

Ethyl pyruvate

INOS

NO

INOS

NO

NO

NO

NO

HMGB1

MCP-1

IL-8

TNF-α

IL-1α

IL-1β

MIP-1α

IL-8

TNF-α

IL-1α

IL-1β

HMGB1

Maturation of immune cells

Migration to sites of injury

Release of cytokines and other inflammatory mediators

Activated macrophages or other immune cells

Secreted from stressed cells

Damaged or dying cells
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.
**Cell-mediated Immunity**

- **Viruses, some intracellular microbes** (Listeria, Trypanosoma)
- **Intracellular microbes**
  - IFNγ activation
  - IL-12, IL-18
  - IL-2, IFNγ activation
  - TNFα, ROI, RNI

**Extracellular microbes**

- **Th1 activation**
  - Tc-NK cell
  - LAK cell

**Humoral Immunity**

- **Ig class switch:** IgG
  - Neutralization of virions, toxins
  - Numerous pathogens

- **Ig class switch:** IgE
  - Mast cell, basophil, eosinophil
  - Helminths

- **Ig class switch:** IgA
  - Mucosa
  - Helminths

**Function**

- **FUNCTION**
  - Dendritic Cell
  - Th0
  - IL-12, IL-18
  - IL-10

- **PROTECTION**
  - Viruses, some intracellular microbes
  - Intracellular microbes
  - Extracellular microbes
  - All microbes, viruses
  - Extracellular microbes, virions, helminths
  - Humoral immunity
  - Cell-mediated immunity
  - Plasmacell
  - B cell maturation

- **Humoral Immunity**
  - IgG-IgM-IgA
  - IL-5, IL-6, IL-9, IL-10, IL-13
  - Eosinophil activation
The response to pathogens, involving “cross-talk” among many immune cells, including Macrophages, Dendritic Cells and CD4 T cells
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; 170:1435-1444
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

Daniel G Remick. The American Journal of Pathology 2007; 170:1435-1444
From bacteria to disease

Barred lines = inhibition  Arrows = activation and consequences

Temporal development of sepsis induced fluctuations on immune response

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

Different Septic Phenotypes

Healthy person with meningococcemia
Elderly patient with malnutrition and diverticulitis
Patient with diabetes, chronic renal failure and pneumonia

IMMUNE STATUS
- Hypoimmune
- Normal
- Hyperimmune

12345 6 78 days

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
The initial immune response is hyperinflammatory, but the response rapidly progresses to hypoinflammatory.
INSULT (e.g. Sepsis, Trauma)

- ENDOCRINE DOWNREGULATION
- SYSTEMIC INFLAMMATION
- EARLY HYPOXIA
- MITOCHONDRIAL PROTEIN DOWNEXPRESSION
- BIOENERGETIC “FAILURE”
- METABOLIC “SHUTDOWN”
- BIOCHEMICAL/FUNCTIONAL ABNORMALITIES CHARACTERISTIC OF MOF
- MITOCHONDRIAL RECOVERY/REPAIR (BIOGENESIS)

Early appropriate adequate antibiotics

EARLY RESUSCITATION (EGDT)
- Glycaemic control Antioxidants °
  - glutathione, manganese, superoxide dismutase
- Substrates: succinate quercetin, coenzyme Q10 L-canevanine
- Hypothermia
- Hydrogen sulphide
- Nitric oxide (low dose)
- Anabolic hormones
- Resuscitation promoters

RESTORATION OF ENERGY SUPPLY & METABOLISM
RESOLUTION OF ORGAN FAILURE

Recovery

Experimental therapies
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

THE MICROCIRCULATION IS ONE OF THE MOTORS OF SEPSIS
Acute phase

Stress hormones with associated increase in mitochondrial and metabolic activity

- ACTH
- Cortisol
- Cathecol
- Vasopressin
- Glucagon
- GH

Insulin resistance

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

Mitochondrial dysfunction

Mitochondrial respiration is increased (12-16h)

Mitochondrial respiration is decreased

Mitoptosis

Apoptosis

Phenoptosis

The defect is principally functional rather than structural. This perceived failure of organs might instead be a potentially protective, reactive, adaptive mechanism.

Overwhelming external insult

Death

Metabolism

Time
Severe sepsis onset

Antibiotics
Source control
Haemodynamic Resuscitation
Respiratory support

APACHE II, SAPS II, TISS
SOFA, RISSC, DIC Score,
Procalcitonin, SaO2, ScvO2,
PvO2, BE, lactate, ACTH test,
Cortisol, Thyroxine, T3, glycaemia

Multiparametric monitoring
Microbiological cultures

ED
Must Protocol
Referral to ICU

Severe sepsis onset

ED
Must Protocol
Referral to ICU

Acute Phase

24 48 72 96

Day 5/7

Recovery Phase
Rehabilitation program

ICU

Hibernation phase
Immunoparalysis Phase

Mitochondrial dysfunction

Apoptosis

Phenoptosis
Uncoupling

Death

Strict control of glycemia

Antibiotics
Source control
Haemodynamic Resuscitation
Respiratory support

Haemodynamic Resuscitation
* if refractory shock:
  low dose steroids
  * APC for 96 hs
  if no risk of bleeding

Checking suitability of antibiotics
Surgical relook if needed
Early Diagnosis

- **Microbiology**
  - Pathogenesis of Sepsis and Septic Shock
    - Nidus of Infection
      - Blood Stream Invasion by Microbes or their Products
    - Early Diagnosis
      - Host Defenses Activated
        - Anti-Inflammatory
          - Low dose glucocorticoids
        - APC
        - Insulin therapy
        - ?
      - Cell Activation and Inflammatory Mediator Release
        - Shock and Multiple Organ Failure
          - Recovery or Death
        - Supportive treatment
          - Fluid resuscitation
          - Vasopressor administration
          - Inotropic support
          - EGDT

- **Laboratory**

- **Examples**
  - Sites of Infection
    - Abscess
    - Appendicitis
    - Cellulitis
    - Cholecystitis
    - Diverticulitis
    - Empyema
    - Endocarditis

- **Microbes and microbial products**
  - Bacteremia
  - Endotoxin
  - Exotoxins
  - Peptidoglycans

- **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 Cells**
  - Endothelium
  - Epithelium
  - Neutrophils
  - Monocytes
  - Macrophages
  - Lymphocytes

- **Inflammatory Mediators**
  - Complement
  - Kinins
  - Coagulation
  - Cytokines
  - Chemokines
  - Reactive O2 species
  - Nitric oxide
  - Proteases
  - Eicosanoids
  - Platelet activating factor

- **Hemodynamic Effects**
  - Vasodilation
  - Hypotension
  - Myocardial depression

- **Inflammatory Tissue Damage**
  - Diffuse endothelial injury
  - Fibrin and microemboli deposition
  - Tissue Hypoxia
  - Immune Suppression
  - Apoptosis / Cell Necrosis
Therapeutic approach

Interventions aimed at decreasing mortality

Surviving Sepsis Campaign: The Bundles

Eliminate infection
- Diagnosis
- Antibiotics
- Source Control

Reduce systemic reaction
- EGDT
- Steroids
- Insulin (glucose control)
- rhAPC (Xigris)

Support organs
- Ventilation
  - Low Tidal Volume
- CRRT

Specific therapy

Adjunctive therapy

Supportive therapy

Crit Care Med 2004; 32:858–873
Overall approach to severe sepsis patients

**Recognition & Immediate Resuscitation**

- Oxygen therapy / Ventilatory support
- Haemodynamics & Fluid Therapy
- Identify & Treat Infection
- Metabolic support (Insulin & steroids)
- Activated Protein C

**Take microbiology specimens**

- Immediate broad spectrum antibiotics
- Assess for surgery / drainage
- Identify pathogen
- Narrow spectrum if possible

**Supportive care**

- Infection control
- DVT prophylaxis
- Nutrition
- Stress ulcer prophylaxis
- Renal Replacement Therapy
- Good Practice Basics
Principles of treatment in Septic Shock

**CPFA + Current treatment**
- Sodium selenite 1000µg as a 30min bolus followed by 14 daily continuous infusion of 1000µg IV
- Simvastatin 40mg/die
- De-escalation therapy + IgM-enriched ivIg in case of Gram-negative
- ENT, OXEPA + 0.35g/kg/d IV and 30g/d ent. glutamine

**Surgical relook if needed**
- Checking suitability of antibiotics and of possible narrowing spectrum
- Nitroglycerin 2mg/h
- Respiratory support
- Antibiotics (Broad spectrum) Surgical cure if needed
- Fluid challenges
- Vasopressors if patient remains hypotensive
- Non-refractory septic shock
- Refractory septic shock
- Adrenocorticotropic hormone test Start low-dose steroids

**6 hours**
- Shock onset
- Referral to intensive care unit

**24 hours**
- Consider introducing activated protein C for 96 h if no risk of bleeding and no clinical improvement

**4 days**
- Beyond intensive care unit Rehabilitation programme

**5 days**
- De-escalation therapy

**14 days**
- 4-48 h
- Day 5
- Day 7
- 7 days

**5 days**
- Normal adrenal function
- Stop steroids
- Stop steroids
- Consider weaning from vasopressors and other life supportive therapies
Unfortunately, at present, we cannot rapidly measure the patient’s ability to produce an appropriate inflammatory response, as opposed to an excessive or inadequate response.

**Immunological competence**
- HLA-DR+ monocytes
- TNF/IL-12, IL-10, IL-10/TNFα
- Th1/Th2
- CD-13/CD14

**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
The importance of Immuno-monitoring

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

HOW TO IDENTIFY SYSTEMIC SEPSIS-INDUCED IMMUNOPARALYSIS
Guillaume Monneret Advances in Sepsis 2005; 4: 42-9
Changes in HLA-DR expression on monocytes from patients with 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, △).

- 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)
- γδ T lymphocytes
- Other (including B, CD8, NK)

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

*p<0.05 vs. nonsurvivors, **p<0.001 vs. nonsurvivors.
Ab: antibodies; HLA-DR: human leukocyte antigen type DR. Reproduced with permission from [49].
SEPSIS

Cytokines

- Low levels of ATIII
- Impaired function of Protein C system
- Insufficient TFPI

Generation of thrombin mediated by tissue factor

Tissue Factor +factor VIIa

Factor IXa (+factor VIII) → Factor IXa (+factor VIII) → Factor IIa (thrombin)

Fibrinogen → Fibrin

Impairment of anticoagulation pathways

- Suppression of fibrinolysis
  - By PAI-1
  - Plasminogen Activators

Formation of Fibrin

Inadequate removal of Fibrin

Thrombosis of small and midsize vessels

Plasminogen

PAI-1
## MONITORING OF COAGULATION PARAMETERS

### Global and dynamic

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

### DIC SCORE

1. Risk assessment: does the patient have an underlying disorder known to be associated with DICT (yes = 2, no = 0)

<table>
<thead>
<tr>
<th>Platelet Count</th>
<th>PT</th>
<th>Prolongation of Fibrin related markers</th>
<th>Risky = 1</th>
<th>Normal = 0</th>
<th>Failure = 1</th>
<th>Normal = 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;100x10^9/L</td>
<td>&gt;20 s</td>
<td>&gt;3</td>
<td>Risky = 1</td>
<td>Normal = 0</td>
<td>Failure = 1</td>
<td>Normal = 0</td>
</tr>
<tr>
<td>&gt;100x10^9/L</td>
<td>&gt;20 s</td>
<td>&gt;3</td>
<td>Risky = 1</td>
<td>Normal = 0</td>
<td>Failure = 1</td>
<td>Normal = 0</td>
</tr>
</tbody>
</table>

2. Major criteria

3. Specific criteria

4. Calculate score:
THE HOSPITAL ORGANISATION MUST CHANGE
THE EXTENDED ROLE OF THE INTENSIVIST
THE NEW ROLE OF THE ED PHYSICIAN
THE OUTREACH TEAM

FIELD
severe infection, sepsis, severe sepsis, septic shock

EMERGENCY DEPARTMENT
severe infection sepsis

Sepsis Resuscitation Bundle
severe sepsis septic shock

Sepsis Management Bundle
severe sepsis septic shock

COMBINED ICU

Source control

Operating theatre
Source control

Severe infection sepsis

Sepsis Resuscitation Bundle
severe sepsis septic shock

Recovery room

Severe sepsis septic shock

WARD

Sepsis Resuscitation Bundle

Outreach team

Severe sepsis septic shock

CRITICAL AREA
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 is not surprising, given the poor understanding of pathological mechanisms underlying this disease at the molecular and cellular levels

  - Markenson JA Worldwide trends in the socio-economic impact and long term prognosis of RA Semin Arthritis Rheum 1991; 21(suppl 1):4-12
Rheumatoid Arthritis is regarded as a systemic autoimmune disease 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 effector cells leads to the formation of pannus tissue that subsequently degrades bone (leading to erosions) and cartilage (leading to thinning and defects).

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

<table>
<thead>
<tr>
<th></th>
<th>Infliximab (Remicade*)</th>
<th>Etanercept (Enbrel*)</th>
<th>Adalimumab (Humira*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year of FDA approval</td>
<td>1998</td>
<td>1998</td>
<td>2002</td>
</tr>
<tr>
<td>Molecular description</td>
<td>Chimeric monoclonal antibody derived from mouse-human antibodies</td>
<td>Monoclonal antibody derived from human antibodies</td>
<td>Monoclonal antibody derived from human antibodies</td>
</tr>
<tr>
<td>Mechanism(s) of action</td>
<td>Binds to TNF-α and inhibits it from binding with its receptor; induces apoptosis of monocytes and other TNF-α-expressing cells</td>
<td>“Decoy” receptor for TNF-α</td>
<td>Binds to TNF-α and inhibits it from binding with its receptor; lyases surface TNF expressing cells in vitro in the presence of complement</td>
</tr>
<tr>
<td>Usual dosage/route of administration$^{1}$</td>
<td>Induction doses of 3 mg/kg IV at 0, 2, and 6 wk, followed by 3–10 mg/kg IV every 8 wk</td>
<td>25 mg SC twice weekly</td>
<td>40 mg SC every 2 wk</td>
</tr>
<tr>
<td>Mean terminal half-life</td>
<td>10 days</td>
<td>4 days</td>
<td>14 days</td>
</tr>
</tbody>
</table>

Abbreviations: IV = intravenous; SC = subcutaneously.

$^{1}$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(II-1Ra)**
**Efalizumab (RAPTIVA Genentech) anticor**

• *Klinkhoff A Biological agents for rheumatoid arthritis Drugs 2004; 64:1267-1283*
<table>
<thead>
<tr>
<th>Drug properties</th>
<th>Infliximab</th>
<th>Etanercept</th>
<th>Adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structure</strong></td>
<td>Mouse human chimeric IgG1k anti-TNFα monoclonal antibody</td>
<td>Two p75 TNFα soluble receptors fused to the Fc portion of IgG1</td>
<td>Fully humanized IgG1k anti-TNFα monoclonal antibody</td>
</tr>
<tr>
<td><strong>Target</strong></td>
<td>TNFα</td>
<td>TNFα; lymphotoxin</td>
<td>TNFα</td>
</tr>
<tr>
<td><strong>Affinity</strong></td>
<td>Soluble and transmembrane TNFα</td>
<td>Soluble TNFα</td>
<td>Soluble and transmembrane TNFα</td>
</tr>
<tr>
<td><strong>Immune actions</strong></td>
<td>Monocyte and T cell apoptosis, lysis of TNF expressing cells</td>
<td>Antiapoptotic agent, possible long term effects on monocytes, no lysis of TNF expressing cells</td>
<td>Possible effects on apoptosis, monocytes and natural killer cells, lysis of TNF expressing cells</td>
</tr>
<tr>
<td><strong>Half life (d)</strong></td>
<td>8.0-9.5</td>
<td>4.0-5.0</td>
<td>12.0-14.0</td>
</tr>
<tr>
<td><strong>Dosing/route</strong></td>
<td>Every 15-60 d/intravenous</td>
<td>Every 3-4 d to every week/subcutaneous</td>
<td>Every 7-14 d/subcutaneous</td>
</tr>
<tr>
<td><strong>Dosing regimen</strong></td>
<td>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</td>
<td>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</td>
<td>RA,PsA,AS 40mg semimonthly RA patients not taking MTX can increase dose to 40 mg/wk</td>
</tr>
<tr>
<td><strong>Duration of therapy</strong></td>
<td>Usually protracted</td>
<td>Usually protracted</td>
<td>Usually protracted</td>
</tr>
<tr>
<td><strong>Indications</strong></td>
<td>RA,PsA,AS,CD,UC,PP</td>
<td>RA,PsA,AS,JRA,PP</td>
<td>RA,PsA,AS,CD</td>
</tr>
</tbody>
</table>
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

- Klareskog L et al Global safety and efficacy of up to 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
- Demyelinating diseases
- Lupus-like syndromes/ANA formation
- CHF
- Immunogenicity
- Infusion/injection reactions

Focus on the “Big 3”

ANA = antinuclear antibody; CHF = congestive heart failure.
**Serious Infection Rates in RA Clinical Trials**

<table>
<thead>
<tr>
<th></th>
<th>Etanercept*</th>
<th>Infliximab*</th>
<th>Adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>PYs of Exposure</td>
<td>8336</td>
<td>2458</td>
<td>4670</td>
</tr>
<tr>
<td><strong>Incidence Per 100 PYs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF Antagonist</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Placebo</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

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

*Includes clinical trials pre-approval and post-approval; 4.9 after receiving per MedDRA database.

**Serious Infections in Early RA Clinical Trials**

- **Adalimumab**
  - 4.35
  - 4.32
  - MTX Alone: 4.29
  - MTX: 3.93
  - 3 mg/kg + MTX: 2.87

- **Etanercept**
  - 0.7
  - 2.9
  - 1.6
  - 3

- **Infliximab**
  - 6.4

MTX = methotrexate; NA = not available.


**Serious Infections in Long-standing RA Clinical Trials**

- **Adalimumab**
  - 4.9
  - 4.2
  - EU
  - 5.8
  - EU

- **Etanercept**
  - 6

- **Infliximab**
  - 6

**Serious Infectious Events (SIE) With TNF Inhibitors**

<table>
<thead>
<tr>
<th>SIE Rates From Package Inserts</th>
<th>TNF Inhibitor</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Etanercept</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Infliximab</td>
<td>5.3%</td>
<td>3.4%</td>
</tr>
</tbody>
</table>

EU = European Union data; SIE = serious infectious event.


**Incidence of Serious Infections in Patients With RA**

British Society of Rheumatology–Biologics Registry (5952 Patients)

**Rate of Serious Infections**

- Nonbiologic DMARDs
- ETN
- IFX
- ADA

**Incidence Rate Ratio (IRR) ± 95% CI of Serious Infections**

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

**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, 1.29)
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, 1.50)
Smoking | 1.63 (1.46, 1.83)


**Selected Serious Infections in Elderly RA Patients**

Hazard Ratios for Hospitalized Infection*

<table>
<thead>
<tr>
<th></th>
<th>Age, gender</th>
<th>Multivariate</th>
<th>Propensity score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted HR</td>
<td>Adjusted HR</td>
<td>Adjusted HR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF antagonist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1.4 (0.7–2.9)</td>
<td>0.9 (0.41–1.9)</td>
<td>0.7 (0.3–1.9)</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>1.0 (0.5–2.1)</td>
<td>1.2 (0.6–2.3)</td>
<td>1.3 (0.6–2.7)</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>1.0 (0.3–4.3)</td>
<td>1.0 (0.3–4.3)</td>
<td>1.1 (0.2–4.8)</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2.4 (1.3–4.2)</td>
<td>2.1 (1.2–3.7)</td>
<td>1.9 (1.1–3.5)</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>2.9 (1.8–4.5)</td>
<td>2.6 (1.6–4.1)</td>
<td>2.5 (1.6–4.0)</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>1.5 (0.6–4.1)</td>
<td>1.4 (0.5–3.7)</td>
<td>1.3 (0.5–3.5)</td>
</tr>
</tbody>
</table>

*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 1990–2003
  - IFX 45%, ETN 40%, ADA 15%
  - 14,940 hospitalization RA patients
- 367 infection hospitalizations in 7776 PY on TNF inhibitor
  - TNF 47 per 100 PY
- Infection risk increased in 1st year (RR 1.43)
- Predictors of infection risk: age, HAQ, DMARDs, comorbidities

**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

TB = tuberculosis.

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

<table>
<thead>
<tr>
<th>Region</th>
<th>Pre-screening era</th>
<th>Post-screening era</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>1.31</td>
<td>0.33</td>
</tr>
<tr>
<td>North America</td>
<td>0.06</td>
<td></td>
</tr>
</tbody>
</table>

Combined 0.27

*Through April 15, 2005. Data from RA clinical trials with adalimumab, including OLEs, and ACT and ReAct.

Tuberculosis: Postmarketing Safety Data for TNF Antagonists in RA

<table>
<thead>
<tr>
<th></th>
<th>Etanercept1</th>
<th>Infliximab1</th>
<th>Adalimumab2 (US only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time period</td>
<td>12/03</td>
<td>10/03</td>
<td>12/02-12/04</td>
</tr>
<tr>
<td>Number of patients treated</td>
<td>236,000</td>
<td>277,000</td>
<td>NA</td>
</tr>
<tr>
<td>Exposure (patient-years)</td>
<td>423,000</td>
<td>466,000</td>
<td>55,384</td>
</tr>
<tr>
<td>Number of TB reports</td>
<td>38</td>
<td>242</td>
<td>11</td>
</tr>
<tr>
<td>Geography (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>26</td>
<td>98</td>
<td>11</td>
</tr>
<tr>
<td>Non-USA</td>
<td>12</td>
<td>152</td>
<td>-</td>
</tr>
<tr>
<td>Characteristics (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td>34</td>
<td>30-45</td>
<td>73</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>16</td>
<td>-</td>
<td>27</td>
</tr>
<tr>
<td>Events per 100 patient-years</td>
<td>0.01</td>
<td>0.05</td>
<td>0.02</td>
</tr>
</tbody>
</table>


Tuberculina 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

- Anti-TNF-α therapy has been associated with the reactivation of tuberculosis, again raising concerns that infections may pose a significant threat
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 (3594 PY) vs MTX 2933 (4846 PY)

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

**Results**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>PY</th>
<th>DM</th>
<th>COPD</th>
<th>Pred</th>
<th>Infect</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF</td>
<td>2393</td>
<td>3594</td>
<td>8%</td>
<td>8%</td>
<td>56%</td>
<td>2.7%</td>
</tr>
<tr>
<td>MTX</td>
<td>2933</td>
<td>4846</td>
<td>10%</td>
<td>9%</td>
<td>56%</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

**Conclude**
Multivariate relative risk of bacterial infection in TNF-inhibitor-treated RA = 1.9 (1.5–2.8), risk was greatest in 1–6 mos. RR 4.2 (2.0–8.6)

---

Infections in RA Patients Treated With 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**

<table>
<thead>
<tr>
<th></th>
<th>Etanercept</th>
<th>Infliximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>All infections</td>
<td>2.3 1.4–3.9</td>
<td>3.0 1.8–5.1</td>
</tr>
<tr>
<td>Serious infections</td>
<td>2.1 0.9–5.4</td>
<td>2.1 0.8–5.5</td>
</tr>
</tbody>
</table>

---

Serious Infections With Anti-TNF Treatment

<table>
<thead>
<tr>
<th>Observational RA Population</th>
<th>Rate/100 PY</th>
<th>Adjusted Relative Rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>RABBIT: Listing et al. Arthritis Rheum 2005</td>
<td>6.3</td>
<td>2.2</td>
</tr>
<tr>
<td>BSRE: Dixon et al. Arthritis Rheum 2006</td>
<td>5.3</td>
<td>1.0</td>
</tr>
<tr>
<td>ARTIS: A. Asking et al. Ann Rheum Dis 2007</td>
<td>5.4*</td>
<td>1.4</td>
</tr>
<tr>
<td>Curtis JR et al. Arthritis Rheum 2007</td>
<td>2.9†</td>
<td>1.9</td>
</tr>
<tr>
<td>Schneeweiss S et al. Arthritis Rheum 2007</td>
<td>2.2</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*Compared with MTX-treated or DMARD-treated patients with RA.
†Compared with MTX treatment alone.
Courtesy of J. Curtis, MD

---

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

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

- 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 use in light of the reports on reactivation of tuberculosis

**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**

- 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**
- 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)**

**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
<table>
<thead>
<tr>
<th><strong>BRS GUIDELINES FOR ANTI-TNFα THERAPY</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active disease</strong></td>
</tr>
<tr>
<td><strong>Pretreatment</strong></td>
</tr>
<tr>
<td><strong>Exclusion</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Withdrawal</strong></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
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 F. 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 pathogens 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-threatening 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.
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

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

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.
†Ifliximab, ≤3 mg/kg every 4 weeks, or adalimumab, 20 mg/wk.
‡Ifliximab, ≥6 mg/kg every 8 weeks, or adalimumab, 40 mg every other week.

Effect of Anti-TNF Antibody on Occurrence of 1 or More Malignancies or Serious Infections in Patients 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*

<table>
<thead>
<tr>
<th></th>
<th>DMARD</th>
<th>Anti-TNF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person-years</td>
<td>1,352</td>
<td>9,868</td>
</tr>
<tr>
<td>Person-years per person, median (IQR)</td>
<td>0.94 (0.48-1.43)</td>
<td>1.26 (0.75-1.96)</td>
</tr>
<tr>
<td>Nº of infections</td>
<td>56</td>
<td>525</td>
</tr>
<tr>
<td>Rate of infections/1,000 person-years (95% CI)</td>
<td>41.4 (31.4-53.5)</td>
<td>53.2 (48.9-57.8)</td>
</tr>
<tr>
<td>Incidence rate ratio (IRR) overall</td>
<td>Referent</td>
<td>1.28 (0.94-1.76)</td>
</tr>
<tr>
<td>Adjusted for age and sex</td>
<td>Referent</td>
<td>1.47 (1.07-2.01)</td>
</tr>
<tr>
<td>Adjusted for age, sex, disease severity, comorbidity, extrarticular manifestations, steroid use and smoking</td>
<td>Referent</td>
<td>1.03 (0.68-1.57)</td>
</tr>
</tbody>
</table>
# Rates of all serious infections, by drugs

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

<table>
<thead>
<tr>
<th></th>
<th>DMARD</th>
<th>Etanercept</th>
<th>Infliximab</th>
<th>Adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person-years</td>
<td>1,352</td>
<td>4,075</td>
<td>4,618</td>
<td>1,175</td>
</tr>
<tr>
<td>Nº of infections</td>
<td>56</td>
<td>209</td>
<td>255</td>
<td>61</td>
</tr>
<tr>
<td>Rate of infections/1,000 person-years (95%CI)</td>
<td>41.4(31.4-53.5)</td>
<td>51.3(44.7-58.5)</td>
<td>55.2(48.8-62.2)</td>
<td>51.9(39.9-66.2)</td>
</tr>
<tr>
<td>Adjusted Incidence Rate Ratio (IRR) For age, sex, disease severity, comorbidity, extrarticular manifestations, stroid use and smoking</td>
<td>Referent</td>
<td>0.97(0.63-1.50)</td>
<td>1.04(0.68-1.61)</td>
<td>1.07(0.67-1.72)</td>
</tr>
</tbody>
</table>
The frequency of serious skin and soft tissue infections was increased in anti-TNF treated patients.

<table>
<thead>
<tr>
<th>Site</th>
<th>DMARD</th>
<th>anti.-TNF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nº</td>
<td>Incidence rate/1,000 person-years</td>
</tr>
<tr>
<td>LRTI</td>
<td>36</td>
<td>26.6(18.7-36.7)</td>
</tr>
<tr>
<td>Skin and soft tissue</td>
<td>4</td>
<td>3.0(0.8-7.6)</td>
</tr>
<tr>
<td>Bone and joint</td>
<td>4</td>
<td>3.0(0.8-7.6)</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>3</td>
<td>2.2(0.5-6.5)</td>
</tr>
</tbody>
</table>
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
<table>
<thead>
<tr>
<th>Patient age/sex</th>
<th>Ethnicity</th>
<th>Organism</th>
<th>Site of infection</th>
<th>Treatment</th>
<th>Months from treatment start date</th>
</tr>
</thead>
<tbody>
<tr>
<td>59/F</td>
<td>Caucasian</td>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Cervical lymph node</td>
<td>Infliximab</td>
<td>7</td>
</tr>
<tr>
<td>74/F</td>
<td>Caucasian</td>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Colon</td>
<td>Infliximab</td>
<td>3</td>
</tr>
<tr>
<td>47/M</td>
<td>Caucasian</td>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Omentum</td>
<td>Infliximab</td>
<td>2</td>
</tr>
<tr>
<td>47/M</td>
<td>Caucasian</td>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Pleura</td>
<td>Infliximab</td>
<td>3</td>
</tr>
<tr>
<td>66/F</td>
<td>Caucasian</td>
<td><em>Mycobacterium tuberculosis</em></td>
<td>LRT</td>
<td>Infliximab</td>
<td>16</td>
</tr>
<tr>
<td>77/F</td>
<td>Caucasian</td>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Posterior pharyngeal wall</td>
<td>Adalimumab</td>
<td>11</td>
</tr>
<tr>
<td>50/F</td>
<td>Pakistani</td>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Cervical lymph node</td>
<td>Infliximab</td>
<td>4</td>
</tr>
<tr>
<td>71/M</td>
<td>Caucasian</td>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Meninges</td>
<td>Etanercept</td>
<td>2</td>
</tr>
<tr>
<td>66/F</td>
<td>African Caribbean</td>
<td><em>Mycobacterium tuberculosis</em></td>
<td>LRT</td>
<td>Etanercept</td>
<td>9</td>
</tr>
<tr>
<td>63/F</td>
<td>Not known</td>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Meninges</td>
<td>Infliximab</td>
<td>3</td>
</tr>
<tr>
<td>59/M</td>
<td>Caucasian</td>
<td><em>Legionella pneumophila</em></td>
<td>LRT</td>
<td>Infliximab</td>
<td>32</td>
</tr>
<tr>
<td>49/M</td>
<td>Caucasian</td>
<td><em>Legionella pneumophila</em></td>
<td>LRT</td>
<td>Infliximab</td>
<td>4</td>
</tr>
<tr>
<td>47/M</td>
<td>Caucasian</td>
<td><em>Listeria monocytogenes</em></td>
<td>Meninges</td>
<td>Infliximab</td>
<td>2</td>
</tr>
<tr>
<td>67/M</td>
<td>Caucasian</td>
<td><em>Listeria monocytogenes</em></td>
<td>Joint</td>
<td>Etanercept</td>
<td>0</td>
</tr>
<tr>
<td>60/F</td>
<td>Caucasian</td>
<td><em>Listeria monocytogenes</em></td>
<td>Joint</td>
<td>Adalimumab</td>
<td>14</td>
</tr>
<tr>
<td>63/F</td>
<td>Caucasian</td>
<td><em>Mycobacterium fortuitum</em></td>
<td>LRT</td>
<td>Etanercept</td>
<td>4</td>
</tr>
<tr>
<td>80/F</td>
<td>Caucasian</td>
<td><em>Salmonella sp</em></td>
<td>Bowel and joint</td>
<td>Etanercept</td>
<td>9</td>
</tr>
<tr>
<td>57/F</td>
<td>Caucasian</td>
<td><em>Salmonella sp</em></td>
<td>Joint</td>
<td>Infliximab</td>
<td>27</td>
</tr>
<tr>
<td>54/F</td>
<td>Caucasian</td>
<td><em>Salmonella sp</em></td>
<td>Bowel</td>
<td>Etanercept</td>
<td>2</td>
</tr>
</tbody>
</table>
# Suggested screening tests for potential infectious complications among TNFα antagonists recipients

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

<table>
<thead>
<tr>
<th>Infection</th>
<th>Recommended screening</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tuberculosis</strong></td>
<td>PPD at baseline* and every 12 months; baseline chest radiograph</td>
</tr>
<tr>
<td><strong>Histoplasmosis</strong></td>
<td>Consider chest radiograph and urine histoplasmin antigen testing at baseline</td>
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<tr>
<td></td>
<td>Consider follow up urine antigen testing every 3-4 months for patients who live in endemic areas</td>
</tr>
<tr>
<td><strong>Coccidioidomycosis</strong></td>
<td>Chest radiograph and serologic testing with IgM and IgG test at baseline</td>
</tr>
<tr>
<td></td>
<td>Consider follow up testing every 3-4 months for patients who live in endemic areas</td>
</tr>
<tr>
<td><strong>Cryptococcus</strong></td>
<td>No data</td>
</tr>
<tr>
<td><strong>Listeria</strong></td>
<td>Patient education regarding food preparation and safety</td>
</tr>
</tbody>
</table>

- 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 promptly 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

# Fungal Infections associated with anti-TNFα therapy


<table>
<thead>
<tr>
<th>Infectious agents</th>
<th>Infliximab</th>
<th>Etanercept</th>
<th>Adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillus species (n=64) 2-23%</td>
<td>48</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Zygomycetes (n=4)</td>
<td>3</td>
<td>NC</td>
<td>1</td>
</tr>
<tr>
<td>Candida species (n=64) 2-23%</td>
<td>54</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Cryptococcus species (n=28)</td>
<td>17</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Blastomyces species (n=2)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Coccidioides species (N=29)</td>
<td>27</td>
<td>2</td>
<td>NC</td>
</tr>
<tr>
<td>Histoplasma species (n=84 1-30%)</td>
<td>72</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Sporothrix species (n=1)</td>
<td>1</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Prototheca species (n=1)</td>
<td>1</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Tinea or pityriasis versicolor (n=6)</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>226 (80%)</strong></td>
<td><strong>44 (16%)</strong></td>
<td><strong>11 (4%)</strong></td>
</tr>
</tbody>
</table>

ND = no data available; NC = no cases identified
Infections associated with TNF-α antagonists

- Fungal infections associated with infliximab occurred a median of 55 days (IQR 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 male
- 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 fulminant 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

- 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 (e.g., histoplasmosis, coccidioidomycosis)
- High risk outdoor activities (e.g., spelunking)
- Construction
<table>
<thead>
<tr>
<th>Case report</th>
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<tbody>
<tr>
<td>Necrotising fasciitis in a patient receiving infliximab for rheumatoid arthritis</td>
<td><em>Chan ATY et al Postgrad Med J 2002;78:47-48</em></td>
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<tr>
<td>2 Case reports</td>
<td></td>
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<tr>
<td>Case report</td>
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<tr>
<td>Severe Pneumonia</td>
<td><em>Nancy F Crum et al Medicine 2005; 84:291-302</em></td>
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<td></td>
</tr>
<tr>
<td>Sepsis of the prosthesis</td>
<td><em>M.Fernandez-Castro et al Rheumatology 2005; 44:1076-1077</em></td>
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</table>

**ALL 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.

Spleen abscess

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

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

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.
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-TNFα agents should be tailored, an in-depth discussion with the patient about the risks and benefits of anti-TNF therapy is essential.
• 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 hosts with normal immune systems
The normal stress response maintains immune integrity.

60-100% of these patients develop sepsis.

Immunosuppressants can inhibit the ability to kill infection.

Immune recovery
- Witholding of immunesuppressants
- Use of GM-CSF

Again tolerates hemodynamic stress and infection.

Nosocomial sepsis

Critical illness stress-induced immunosuppression (CRISIS)
Rational immune phenotype-directed therapeutic strategies in patients with critical illness stress induced immunesuppression

<table>
<thead>
<tr>
<th>Immunophenotype thresholds</th>
<th>Therapeutic approach</th>
</tr>
</thead>
</table>
| Absolute neutrophil count < 500 cells/mm³ | A. Stop chemotherapy  
B. Administer empiric antimicrobial therapy for neutropenic fever  
C. Administer G-CSF, GM-CSF or WC infusion for neutropenic sepsis |
| Absolute lymphocyte count < 1,000 cells/mm³ | A. Stop dexamethasone, dopamine, cyclosporine A  
B. Administer prophylactic/empiric antiviral, anti-fungal therapies  
C. Replenish zinc, selenium, glutamine |
| Hypogammaglobulinemia (igG < 500mg/dl) | A. Give IVIG q three weeks or IVIGM |

Monocyte deactivation  
HLA-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/m²/day over 12h
Patient with RA

Patient education
Family doctor education
ED education
Rapid access to the hospital

Recurrence

DMARDs

Biologic therapy

PREVENTION OF SEPSIS AND RIGHT INTENSIVE CARE OF SEPSIS, SEVERE SEPSIS AND SEPTIC SHOCK IN THE FLEXIBLE ICU

Screening tests
Assessment of the risk of tuberculosis
Latent tuberculosis infection?

Vaccination

BUNDLES OF SEVERE SEPSIS AND SEPTIC SHOCK
6 hours and 24 hours

CRP
PCT
IL-6
TNFα
IL-10
IL-10/TNFα
Cultures
PCR
WBC
HLA-DR

CRP
PCT
IL-6
TNFα
IL-10
IL-10/TNFα
Cultures
PCR
WBC
HLA-DR

CRP
PCT
IL-6
TNFα
IL-10
IL-10/TNFα
Cultures
PCR
WBC
HLA-DR

CRP
PCT
IL-6
TNFα
IL-10
IL-10/TNFα
Cultures
PCR
WBC
HLA-DR

CRP
PCT
IL-6
TNFα
IL-10
IL-10/TNFα
Cultures
PCR
WBC
HLA-DR

Biologic therapy

Signs and Symptoms of Infection

CRP
PCT
IL-6
TNFα
IL-10
IL-10/TNFα
Cultures
PCR
WBC
HLA-DR

CRP
PCT
IL-6
TNFα
IL-10
IL-10/TNFα
Cultures
PCR
WBC
HLA-DR

CRP
PCT
IL-6
TNFα
IL-10
IL-10/TNFα
Cultures
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WBC
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PCR
WBC
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CRP
PCT
IL-6
TNFα
IL-10
IL-10/TNFα
Cultures
PCR
WBC
HLA-DR

CRP
PCT
IL-6
TNFα
IL-10
IL-10/TNFα
Cultures
PCR
WBC
HLA-DR

• Withholding of immune suppressant
• Administer early appropriate empiric antimicrobial therapy and
• Remove the nidus of infection
• Administer GM-CSF (?)
• Replenish zinc, selenium, glutamine

Rapid access to ED

Call Intensivist

If diagnosis of SEVERE SEPSIS
Call Intensivist

If diagnosis of SEPTIC SHOCK

Ward Care

BSR guidelines
NICE guidelines

24hrs
48hrs
72hrs
96hrs
120hrs

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

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 10⁹/L, neutrophils 13.99 x 10⁹/L and PLTs 295 x 10⁹/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 peripherally 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
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 abdominal 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.
Figure 2 Surgical specimen consisting of the spleen with an abscess on the posterior aspect.

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.

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.
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/mm³ 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, erythromycin, 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 equipped 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.
Case reports

- Further therapy included increased PEEP (> 20 mbar), prone positioning, antibiotic therapy with cefotiam and clarithromycin and CVVH for acute renal failure
- When a penicillin susceptible 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 on 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 pericarditis in a patient with RA treated with etanercept and methotrexate


• 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 abdominal pain and started vomiting
• Her vital signs on presentation 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 presumptive diagnosis of ruptured abdominal aortic aneurysm or anterior myocardial infarction 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 of 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 symptoms 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, PaCO2 27 mmHg, bicarbonate 5 mmol/L BE 28 mmol/L, PaO2 83 mmHg, oxygen saturation 85% on 12L O2 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.
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 withdrawn 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.
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 prosthetic 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 of prednisone, the DAS score being 2.70.

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

- **Learning Points**
- The decision to treat this patient with infliximab was difficult, due to the high risk of reactivation of a putative 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 a latent infection in the prosthetic material with anti-TNFα therapy is essential.
- The use of anti-TNFα agents should be tailored, an in-depth discussion with the patient about the risks and benefits of anti-TNF therapy is essential.