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# PROCALCITONIN:

*Contributing to improved clinical decision making*

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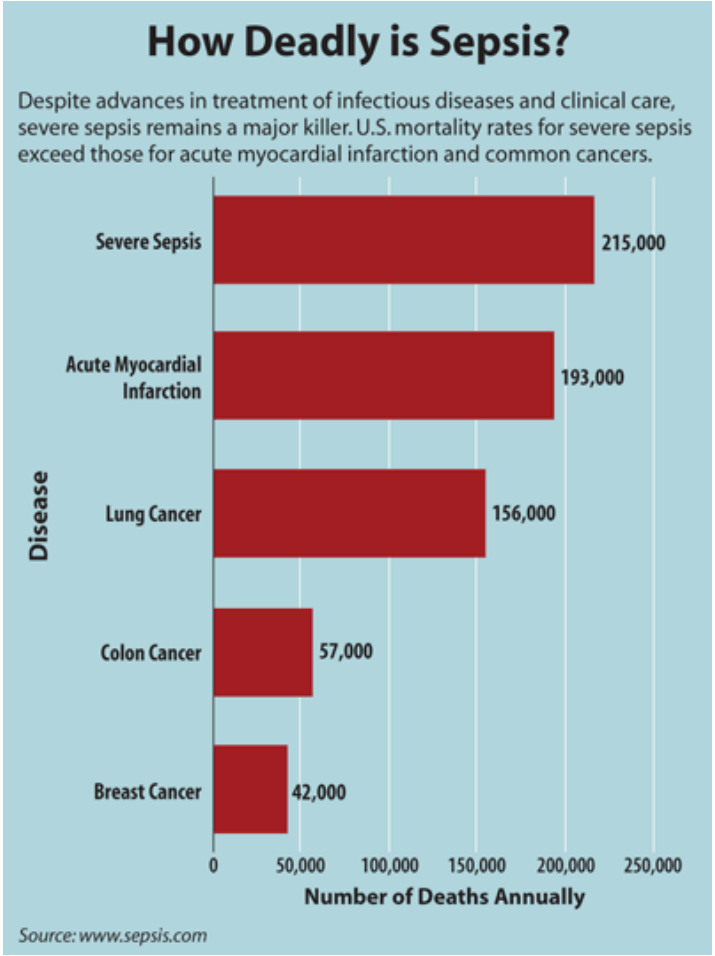
Sepsis/Sepsis Biomarkers/Procalcitonin

# Major Cause of Morbidity & Mortality World Wide

- ***10th leading*** cause of death overall
- More than ***750,000 cases*** of in US annually
- Mortality was ***8 x higher*** than other reasons for hospitalization
- *Sepsis* ***survivors live only ½ as long as predicted age***

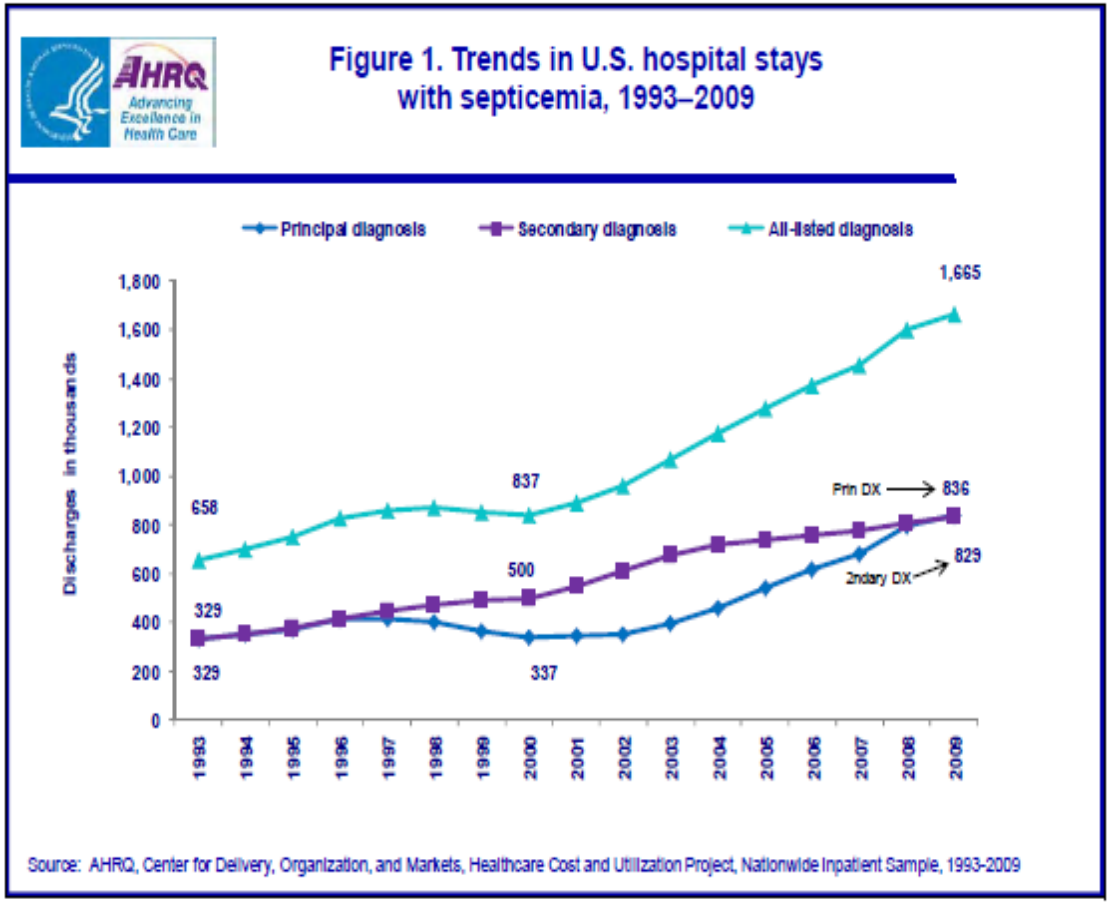



Angus D et al., Crit Care. 2001. Jul29(7): 1303-10
Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project. Statistical Brief #122. 2011

# AHRQ: Sepsis Admissions are on the Rise

AHRQ's Nationwide Inpatient Sample 2000-2009

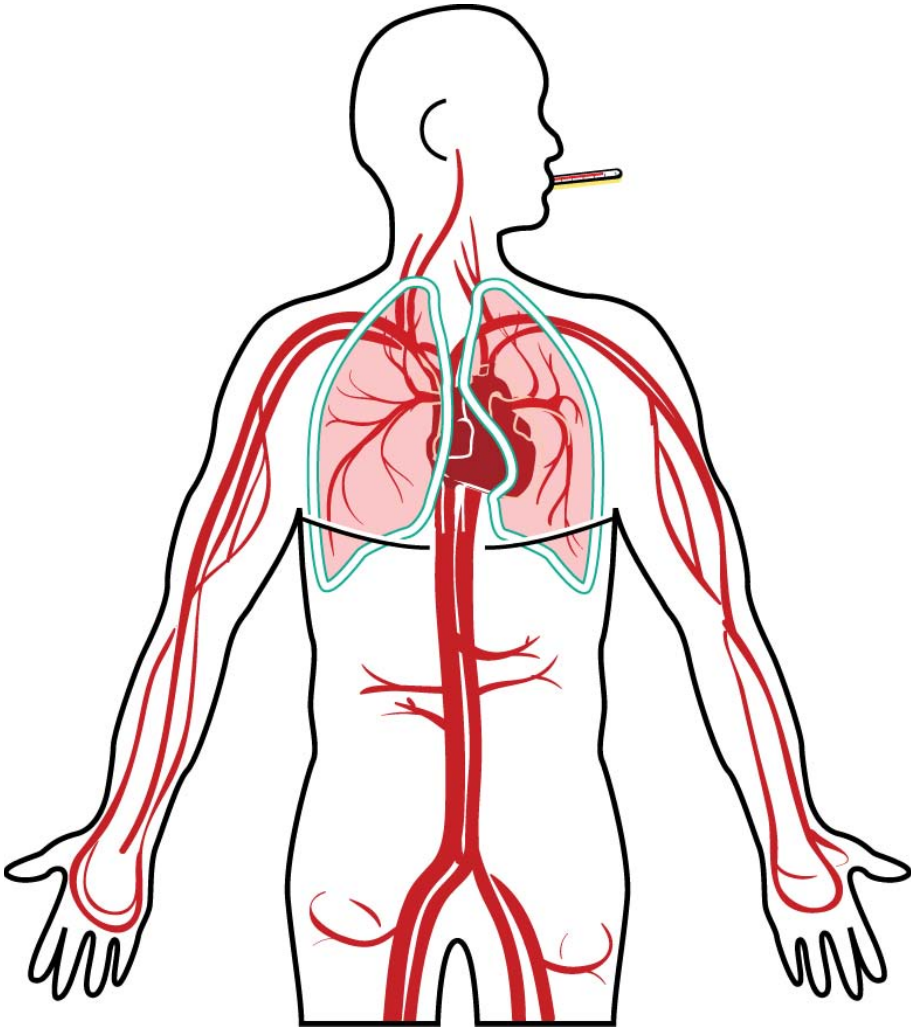
- Hospital stays with a ***principal*** diagnosis of septicemia increased ***146%***
- ***Secondary*** diagnosis increased by ***66%***, as determined by a search of.



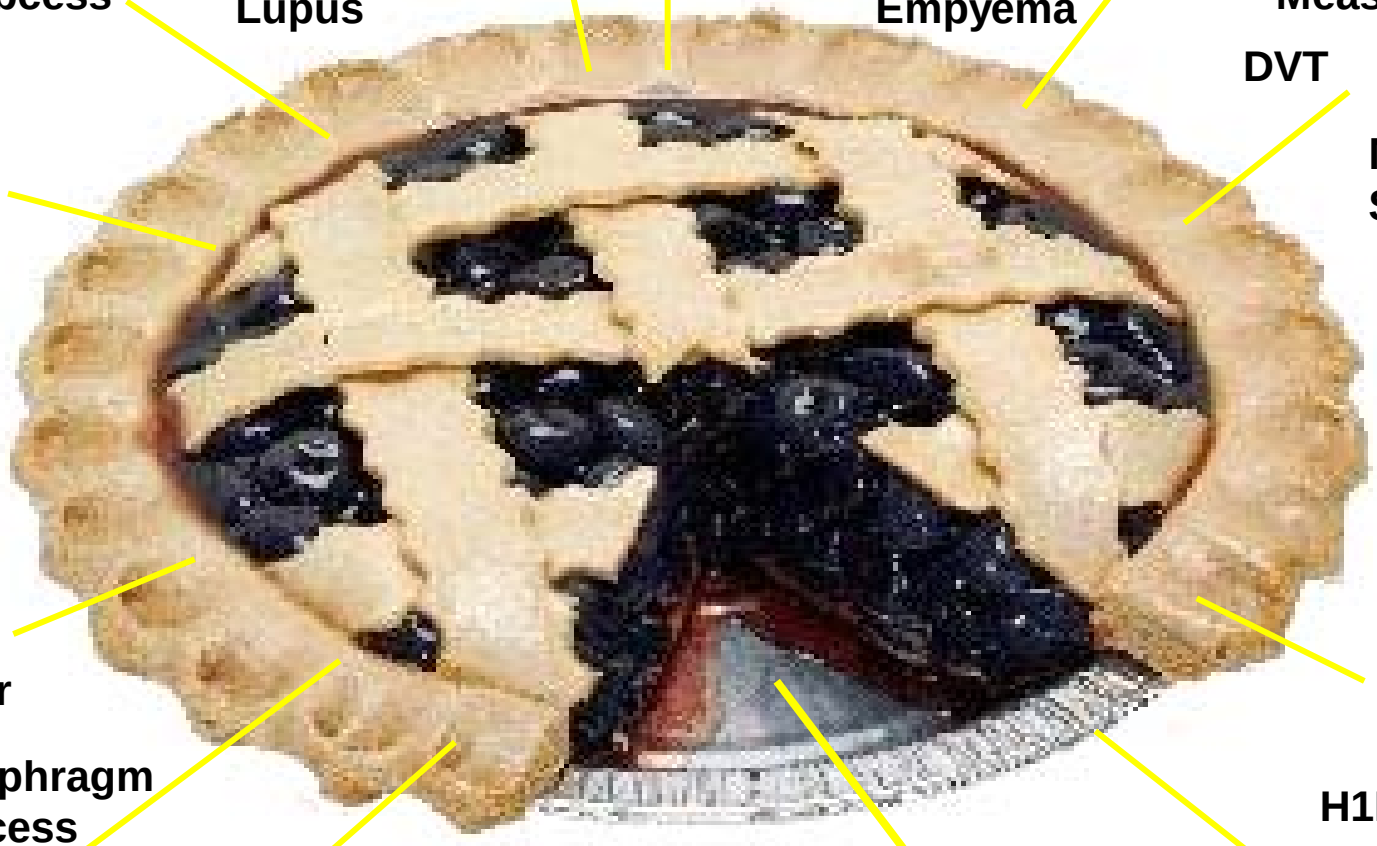

Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project. Statistical Brief #122. 2011

# SIRS Criteria

- Clinical Manifestations defined by ACCP/SCCM:
  - Temperature > 38°C or < 36°C.
  - Heart rate > 90 bpm.
  - Respiratory rate:
    - >20 breaths/min.
    - $paCO_2$ < 32 mm Hg.
  - WBC > 12,000/$mm^3$, < 4,000/$mm^3$, or >10% immature (band) forms.
  - New onset confusion.
  - Blood glucose > 150 in absence of diabetes.



Bone RC, *et al*. Chest 1992 Jun;101(6):1644-55.




# Influenza

# Making the Diagnosis

- Tachycardia – 718 possibilities
- Tachypnea - 371 possibilities
- Increased/Decreased Temperature – 1380 possibilities
- Increased/Decreased WBC – 350 possibilities

**541 possible diagnosis with 2 or more of the criteria!!!**

# Possible Diagnoses

- 3-Quinuclidinyl Benzilate/Weapons (QNB/BZ) agent Aberrancy/supraventricular tachycardia Abortion, septic Abscess pathophysiology Abscess, abdominal, visceral Abscess, cervical gland Abscess, dentoalveolar Abscess, gallbladder/pericholecystic Abscess, intracranial Abscess, intraperitoneal, RL quadrant Abscess, ischiorectal Abscess, lesser sac Abscess, liver Abscess, myocardium Abscess, orbital Abscess, palmar space Abscess, parapharyngeal Abscess, perianal/pararectal Abscess, periapical Abscess, renal Abscess, retroperitoneal Abscess, retropharyngeal Abscess, subcutaneous Abscess, submammary Abscess, submastoid/Bezold's abscess Abscess, subphrenic Acidosis Acidosis, metabolic Acute **gastric acid/aspiration syndrome** Acute infection Acute inflammatory reaction Acute **Lymphoblastic/lymphocytic leukemia**, Acute mountain sickness/high altitude Addison's disease (chronic adrenal ins) Adrenal hemorrhage/apoplexy Adrenal insufficiency, acute Agent 15/Weapons agent exposure Alcohol induced hypoglycemia Alcohol intoxication, acute Alcohol withdrawal Alcohol/Ethanol ingestion/intake Alcoholism, chronic Allergic, Collagen, Auto-Immune Disorders Alveolar hypoventilation/extrapulmonary Amanita muscarina/atropinoid toxicity (fly agaric) Amebic (Naegleria) meningoencephalitis Amniotic fluid embolism Amphetamine (Adderall) Administration/Toxicity/ingest Amphetamine/Speed toxidrome/Acute Anaphylaxis, generalized Anatomic, Foreign Body, Structural Disorders Anorexia nervosa Anticholinergics (Belladonna/Atropine) toxidrome Anticholinergics/Spasmolytics Administration/Toxicity Antihistamine Administration/Toxicity/effect Anxiety Anxiety disorder Anxiety, acute Aortic regurgitation, acute Aortitis, bacterial Apathetic thyroid crisis Appendicitis Appendix abscess Arsenic poisoning/Acute ingestion Arsenic trioxide (Trisenox) Administration/Toxicity Arteriosclerotic, Vascular, Venous Disorders Arteritis, giant cell/non-cranial Arthritis, gonococcal Arthritis, pyogenic/septic Aspergillosis, disseminated Aspergillosis, invasive pulmonary type Asphyxia/suffocation Aspirin (Acetylsalicylic acid) Administration/Toxicity Asplenic status/bacteremia (capsule) Asthma Atelectasis, pulmonary Atropine Administration/Toxicity/injection Atropine/homatropine/parasympatholytic Atypical Hemolytic Uremic Syndrome Atypical mycobacteria, disseminated Autonomic/regulatory disorder Avian influenza (H5N1) in human/zoonosis Bacteremia/Septicemia Bacteremia/Septicemia, gram positive Bacterial acute illness Bacterial endocarditis, subacute Bacterial endocarditis/acute Bacterial overwhelming sepsis Bacterial tracheitis Barbiturate overdose Barbiturate withdrawal Belladona-like plant alkaloid poisoning Belladonna tincture/elixir Administration/Toxicity Belladonna/Nightshade herbal/intake Biochemical Disorders Black widow spider bite Blackwater fever Blastomycosis, disseminated Brain abscess Breast abscess Brodie's abscess Bronchiectasis Bronchiolitis Bronchitis, acute Bronchodilator Drug Administration/Toxicity Brucellosis Cadmium fumes/inhalation/toxicity Campylobacter enterocolitis Candidiasis, pulmonary Carbon monoxide poisoning/exposure Carcinoma lung squamous cell/large cell Carcinoma, bronchogenic Cardiogenic shock Cardiomyopathy Carrington's pulmonary eosinophilia Cellulitis Cellulitis, chronic pelvic Cellulitis, dissecting, of scalp Cellulitis, orbital Cellulitis, pelvic, acute Cellulitis, periurethral, male Cellulitis/lower extremities Cellulitis/pinna Chickenpox pneumonia Chlamydia/pneumonia/TWAR agent Chloral hydrate (Noctec) Administration/Toxicity Chlorpromazine (Thorazine) Administration/Toxicity Cholangitis, ascending Cholecystitis without gallstones Coca plant/intake Cocaine abuse/intoxication Coccidioidomycosis, disseminated **Colorado tick fever** Congenital, Developmental Disorders Congestive heart failure Contaminated blood transfusion/bacteria Corticosteroid Administration/Toxicity Crack (free base cocaine) usage/ingestion Cushing's disease/Syndrome Cyanide/Hydrogen cyanide exposure/poisoning Cytomegalic infection, disseminated Cytomegalic pneumonia Decompression sickness Deficiency Disorders Dehydration Dehydration and fever Delirium tremens Dengue fever Dengue hemorrhagic fever Dextroamphetamine (Dexedrine) Administration/Toxicity Diabetic autonomic neuropathy syndrome Diabetic ketoacidosis/coma Diethylene Glycol poisoning Diphenhydramine (Benadryl) Administration/Toxicity Diphtheria myocarditis/toxicity Dissecting aortic aneurysm Disseminated intravascular coagulopathy Diverticulitis/perforated Diverticulitis/phlegmon/abscess Dressler's syndrome Drowning/Near- drowning Drug Induced Arteritis (Cocaine-Speed) Drug induced Hypoglycemia. **Ecstasy** drug/MDMA/MethylenedioxyMA Ectopic pregnancy Electromagnetic, Physics, trauma, Radiation Causes Emphysema/**COPD**/Chronic lung disease Emphysematous cholecystitis Empyema Encephalitis Encephalitis, California Encephalitis, Eastern equine Encephalitis, equine, Venezuelan Encephalitis, Japanese B Encephalitis, Murray valley Encephalitis, post viral Encephalitis, powassan Encephalitis, St Louis B Encephalitis, viral Encephalitis, Western equine Endocarditis, infective Endocarditis, right heart Endocrine gland disorder Endometritis, acute Eosinophilic Pneumonia prolonged/Chronic Ephedra/Herbal ecstacy (Ephedrine) high dose/abuse Epididymitis, acute Epinephrine (Adrenalin) Administration/Toxicity Erysipelas Esophageal Rupture/Boerhaave Syndrome Ethylene glycol [Antifreeze] ingestion Evan's syndrome (AHA/Immune TP) Factitious thyrotoxicosis Fat embolism Fever Fever Unknown Origin Fistula, Aortocoduodenal (Aorticoenteric) Functional, Physiologic Variant Disorders Gas gangrene Gastrointestinal bleeding Gingiva, abscess Glanders abscess Goodpasture's syndrome Gout/acute polyarticular syndrome Gouty attack, acute/podagra Gram negative (e coli) meningitis Gram negative septicemia/endotoxemia Granulomatous, Inflammatory Disorders Group B Strep Neonatal Sepsis Hanta virus/Navaho disease Hashimoto's thyrotoxic variant Heart disorders Heat exhaustion/prostration Heat stroke Heirarchical Major Groups Hemolysis acute Hemolytic anemia, autoimmune Hemolytic-uremic syndrome Hemophilus influenzae infection Hemorrhagic fever, Argentinian/Junin Hemorrhagic fever, Bolivian/Machupo Hemorrhagic fever, Brazilian/Sabia Hemorrhagic fever, Crimea-Congo Hemorrhagic pancreatitis, necrotizing Hemothorax Henbane plant poisoning Hepatic abscess, pyogenic Hepatitis, alcoholic Hereditary, Familial, Genetic Disorders Heroin/opiate withdrawal High altitude pulmonary edema High output heart failure Histoplasmosis, disseminated Histoplasmosis, pulmonary Hot environment/exposure Hypersensitivity angiitis Hypersensitivity pneumonitis/alveolitis Hyperserotoninemia/serotonin syndrome Hyperthermia Hyperthyroid status Hypoglycemia **Hypoglycemia**, diabetic/treatment Hypoglycemia, factitious Hypoglycemia, functional Hypoglycemia, reactive diabetic Hypoplastic left heart syndrome Hypothalamic lesion Hypovolemic shock Hypoxia Hypoxia, systemic, chronic Hypoxic environment Iatrogenic, Self Induced Disorders Idiopathic Anaphylactoid Reactions/Recurrent Infections **Influenza** Influenza pneumonia Intraperitoneal abscess Iron intoxication, **acute Jerusalem cherry plant poisoning** Jimsonweed/Jamestown weed poisoning Juvenile rheumatoid arthritis/Stills d Kawasaki disease Klebsiella pneumonia Kyasanur forest disease Lacrimal gland infection/abscess Lassa fever Legionaires disease Lemierre's Disease Leptospiral meningitis Leptospirosis Ictohemorrhagica Leptospirosis/severe (Weils) type Leukemia, acute Leukemic/lymphocytic lung infiltrate Lingula pneumonia Listeria meningitis Listeria monocytogenes/listeriosis Lithium toxicity/overdose Loeffler's Eosinophilic Pneumonitis, acute/PIE LSD ingestion/intoxication Lung abscess Malaria Malignant hyperthermia Mallory Weiss syndrome(esophageal tear) Manic delerium Marituba fever Mastitis, puerperal Mastoiditis, zygomatic Measles (rubeola) Measles pneumonia/viral giant cell Meckel's acute diverticulitis Mediastinal abscess Medication/drugs Mediteranean spotted fever Mediterranean fever, periodic Melioidosis Meningitis Meningitis Bacterial Meningitis, Hemophilus Meningitis, pneumococcal Meningitis, staphylococcus aureus Meningococcal arthritis Meningococcal meningitis Meningococcemia/meningococcus Meningococcus/chronic Metabolic, Storage Disorders Metal fume fever Metastatic staphylococcus abscess synd Methamphetamine/Speed/Amphetamine chronic/abuse Methemoglobin inducing/poisons Methylphenidate (Ritalin) Administration/Toxicity Middle lobe pneumonia Monkshood/Aconite herbal/intake Monoamine oxidase inhibitor Administration/Toxicity Monoamine oxidase inhibitor crisis Monocytic leukemia, acute Muscle abscess Mushroom/Amanita Phalloides poisoning Mushroom/Belladonna-like poisoning Mushroom/Fly agaric/Pantherina/Muscarin Myelodysplasia/Myelodysplastic Syndrome Myelogenous leukemia, chronic Myelogenous/Blastic Leukemia, Acute **Myocardial infarction**, acute Myocarditis, acute Myocarditis, bacterial Myocarditis, trichinosis Myocarditis, viral Necrotizing alveolitis/Pneumonia Necrotizing fasciitis/mixed Neonatal chlamydial pneumonia Neonatal Graves/thyrotoxicosis disease Neonatal pneumonia, bacterial Nephritis, allergic interstitial, acute Neuroleptic malignant syndrome Neuropathy, autonomic Newborn Sepsis Syndrome Nicotine/patch (Nicotrol) application/gum-lozenge Nicotine/tobacco intake/poisoning Nocardiosis, pulmonary Omentum abscess Organ Poisoning (Intoxication) Osteomyelitis Osteomyelitis, vertebral Osteomyelitis/petrous bone/Petrositis Ovarian abscess/Tubo-ovarian abscess Pancreas abscess Pancreatitis, acute Panic attacks/Anxiety disorder Paraquat poisoning Paroxysmal Cold Hemoglobinuria Pathophysiologic Pelvic abscess Pelvic inflammatory disease Pelvic thrombophlebitis Penis cellulitis **Perforated duodenal ulcer** Perforated viscus Perforated/ruptured esophagus Perforation of GI tract Pericarditis Pericarditis, acute Pericarditis, purulent Pericarditis, viral, acute benign Perinephric abscess Periorbital cellulitis Peritonitis, acute Peritonsillar abscess Pharyngitis, acute septic Phencyclidine (Angel dust) intoxication Phenothiazines Administration/Toxicity Pheochromocytoma Phlebotomus fever Pit viper snakebite Pittsburgh pneumonia agent disease/PPA Plague meningitis Plague, bubonic Plague, pneumonic Plant botanical/alkaloid poisoning Plant poisoning Plasmodia vivax/malariae/ovale Plasmodium falciparum malaria Pneumocystis Jiroveci/Carinii Pneumonia (PCP) Pneumonia Pneumonia of newborn Pneumonia, abscessing staphylococcal Pneumonia, acute lobar Pneumonia, aspiration Pneumonia, bacterial Pneumonia, chlamydia Pneumonia, cryptococcal Pneumonia, gram-negative type Pneumonia, hemophilus influenza Pneumonia, lipoid/hydrocarbon Pneumonia, mycoplasma Pneumonia, pneumococcal Pneumonia, psuedomonas Pneumonia, staphylococcal Pneumonia, unresolved Pneumonia, viral Pneumonia/Bronchopneumonia Pneumonitis, collagen vascular disease Poisoning (Specific Agent) Polyarteritis nodosa Polyarteritis nodosa, infantile Popliteal Abscess Porphyria, acute intermittent Postural hypotension Potato poisoning/solanaceous alkaloid Pregnancy Prostate abscess Psittacosis/ornithosis Psoas abscess Puerperal pelvic cellulitis/sepsis Pulmonary anthrax Pulmonary edema Pulmonary edema, left vent. acute **Pulmonary edema**, noncardiac Pulmonary embolism Pulmonary infarction Pyelonephritis (acute) Pyogenic Ankle Arthritis Pyogenic Elbow Arthritis Pyogenic Hip Arthritis Pyogenic Knee Arthritis Pyogenic Sternoclavicular Arthritis Pyogenic Wrist Arthritis Q fever Rabies Reference to Organ System Reiters Syndrome Relapsing fever (Borrelia) Relational, Mental, Psychiatric Disorders Renal arteritis Renal failure, acute Respiratory distress (adult) syndrome Respiratory distress (newborn) syndrome Retroperitoneal hematoma Retroperitoneal hemorrhage Rheumatic arthritis/acute Rheumatic carditis, active Rheumatic fever Rheumatoid arteritis/vasculitis Rheumatoid arthritis Rickettsial disease Rickettsialpox Rift Valley fever Right sided diverticulitis Right-sided bacterial endocarditis Rocky mountain spotted fever Sacroiliac pyogenic arthritis Salicylate intoxication/overdose Salmonella infection Salmonella/enteric fever/septicemia Sarcoidosis, pulmonary Scarlet fever Scopolamine Administration/Toxicity Scorpion sting Scurvy, infantile Sepsis Sepsis encephalopathy/elderly Sepsis, overwhelming Septic Acromioclavicular Arthritis/Pyogenic Septic shock Septicemia, pseudomonas Severe Acute Respiratory Syndrome/SARS Shigella enteritis(bacillary dysentery) Shock Sialadenitis Smoke inhalation Snakebite (rattlesnake/pit viper type) Solanaceous alkaloid poisoning Spinal epidural abscess Splenic abscess Splenic infarct Staphylococcus aureus/CA-MRSA virulent PVL gene Status epilepticus Stevens-Johnson syndrome Stomach abscess Streptoccus bovis infection/bacteremia Streptococcal pharyngitis, beta type A Streptococcal septicemia Streptococcosis syndrome Streptococcus pyogenes pneumonia Streptococcus, beta hemolytic Stress/Emotional/Physical Subhepatic/gallbladder bed abscess Submaxillary gland infection/abscess Surgical, Procedure Complication **Swine-Avian influenza** (epizootic) Sympathomimetics Administration/Toxicity T3 thyrotoxicosis Tamponade, cardiac Testis, abscess Tetanus Tetanus, neonatal Theophylline (Elixophyllin/Theodur) adm Thermo-regulatory defect/inadequacy Thigh cellulitis Thromboembolic disease Thrombophlebitis, deep vein Thrombotic thrombocytopenic purpura Thyroid Administration/Toxicity Thyroiditis, purulent acute Thyrotoxic crisis Thyrotoxicosis (Graves disease) Thyrotoxicosis/exogenous Thyroxin/Levothyroxin (T4/Synthroid) ad Tonsil, abscess Tonsillitis/exudative, acute Toxic megacolon Toxic shock syndrome **Transfusion reaction**, febrile Transfusion reaction, hemolytic Transfusion Related Acute Lung Injury/TRALI syndrome Trauma Causes Tricyclic antidepressant Administration/Toxicity Tricyclic overdose Tri-iodothyronine(T3) (Cytomel) Administration/Toxicity Tuberculosis peritonitis Tuberculosis pulmonary Tuberculosis, disseminated Tuberculosis, miliary hepatic Tuberculosis, pericardial Tularemia Tularemia meningitis Tularemia pneumonia Typhoid fever Typhus, acute/epidemic Typhus, murine Urinary tract infection Urosepsis/septicemia Usage, Degenerative, Necrosis, Age Related Disorders Vegetative, Autonomic, Endocrine Disorders Viral acute illness/Viremia Viral hemorrhagic fevers Water hemlock poisoning Wegeners granulomatosis West Nile fever/encephalitis Yellow fever

# Diagnostic Accuracy of SIRS Criteria

- **Critical Care - Zhao (2012):**
  - *The diagnostic performances of the two definitions range from modest to good*
- **Critical Care – De Kruif (2010):**
  - *"Clinician judgment" of sepsis correct 73% of time*
- **AJCCM – Harbarth (2001):**
  - *Clinicians' clinical diagnosis of sepsis were correct 77% of time*

Zhao H et al., *Crit Care Med.* 2012 Jun;40(6):1700-6
De Kruif et al., *Crit Care Med*. 2010 Feb;38(2):457-63
Harbarth et al., *Amer J Crit Care Med*. 2001 Aug 1;164(3):396-402.

# Importance of Focused Antimicrobial Use

- Worldwide, drug-resistant organisms are increasing
  - *C.difficile*, *MRSA*, *Acinetobacter* species, *Klebsiella pneumoniae* carbapenemase-producing organisms
- Well documented causal relationship between antimicrobial misuse and the emergence of antimicrobial – resistance.
  - Overuse of antibiotics increases costs.
  - Unchecked antibiotic consumption increases risks of drug-related adverse events.
- Antimicrobial agent development is on the decline
- Lower respiratory tract infections (LTRI)
  - Most frequent indication for antibiotic prescriptions in the Northwestern hemisphere
  - 75% of patients are treated with antibiotics
  - Predominantly viral origin of infection

Bartlett; Clin Infect Dis. (2011) 53 (suppl 1): S4-S7

# SIRS Criteria

- Clinical Manifestations defined by ACCP/SCCM:
  - Temperature > 38°C or < 36°C.
  - Heart rate > 90 bpm.
  - Respiratory rate:
    - >20 breaths/min.
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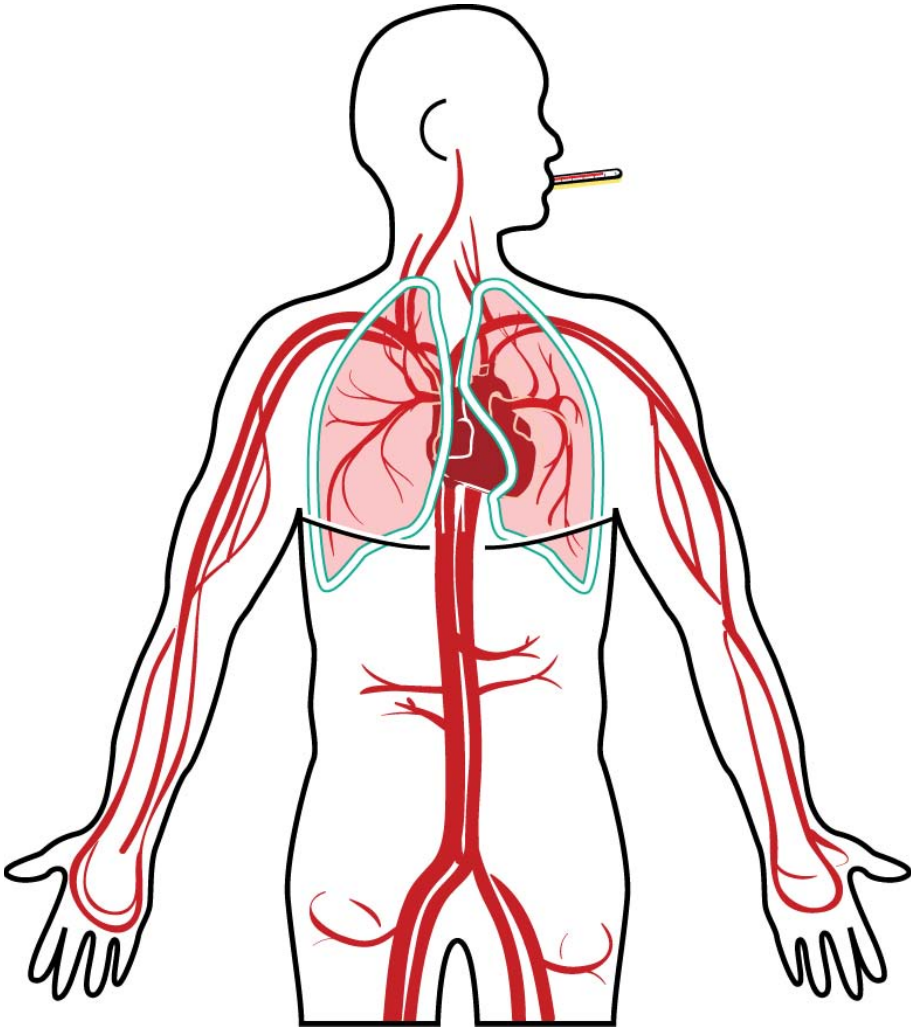
  - WBC > 12,000/$mm^3$, < 4,000/$mm^3$, or >10% immature (band) forms.
  - New onset confusion.
  - Blood glucose > 150 in absence of diabetes.



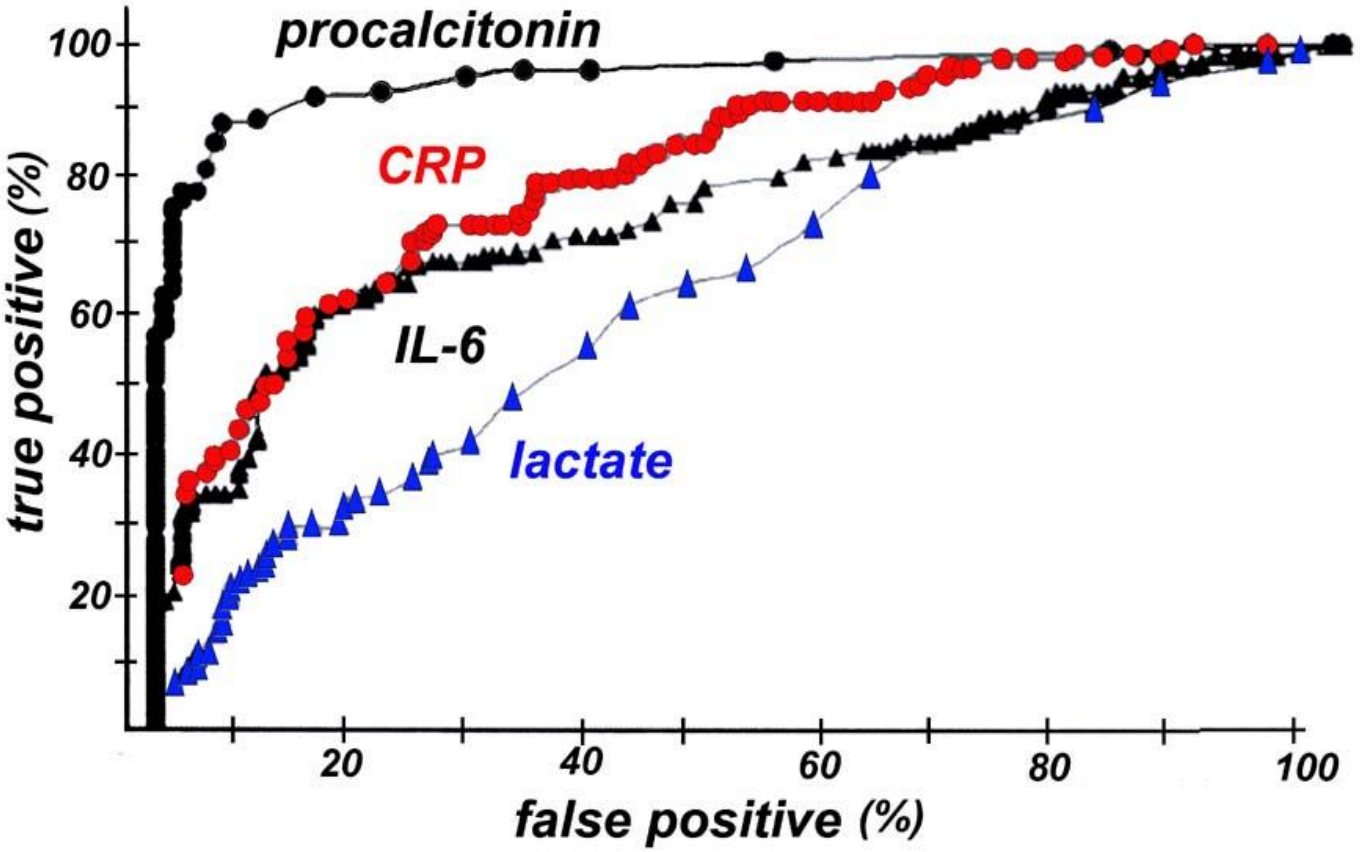
Bone RC, *et al*. Chest 1992 Jun;101(6):1644-55.

# SIRS/Sepsis/Severe Sepsis/Septic Shock

- Sepsis is SIRS plus a known or suspected infection. (27% mortality)
- Severe Sepsis is sepsis associated with organ dysfunction, hypoperfusion, or hypotension. (32% mortality)
- Septic Shock is sepsis-induced hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities. (54%)
  - May include:
    - Lactic acidosis.
    - Oliguria.
    - An acute alteration in mental status.
    - Others.


Bone RC, *et al*. Chest 1992 Jun;101(6):1644-55.

# Plasma Markers for Diagnosis of Sepsis



# PCT

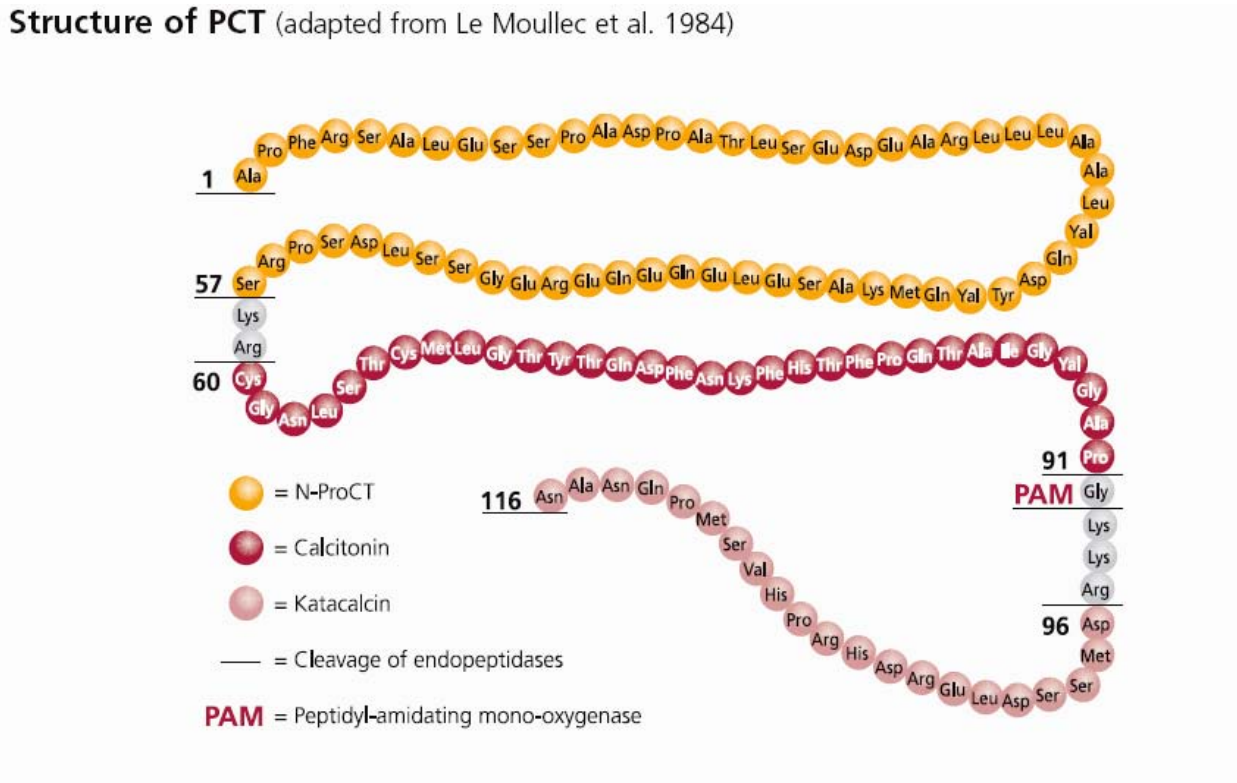
What is PCT

Secretion in healthy vs. sick

Expression

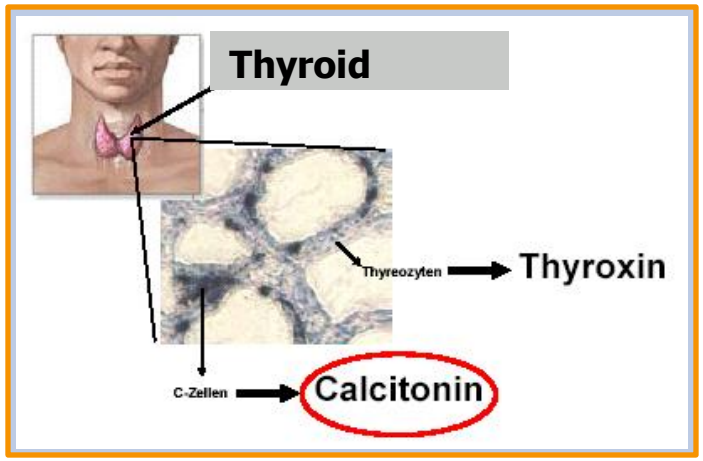
Kinetics

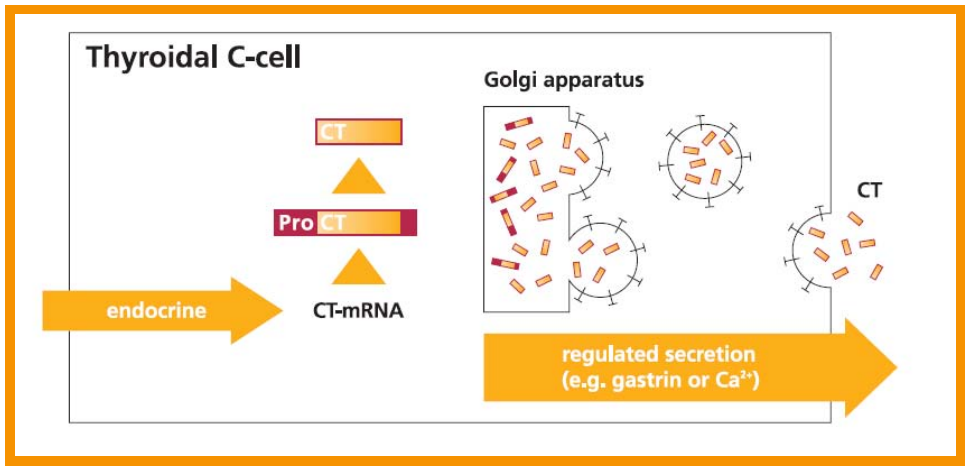
# Procalcitonin (PCT)



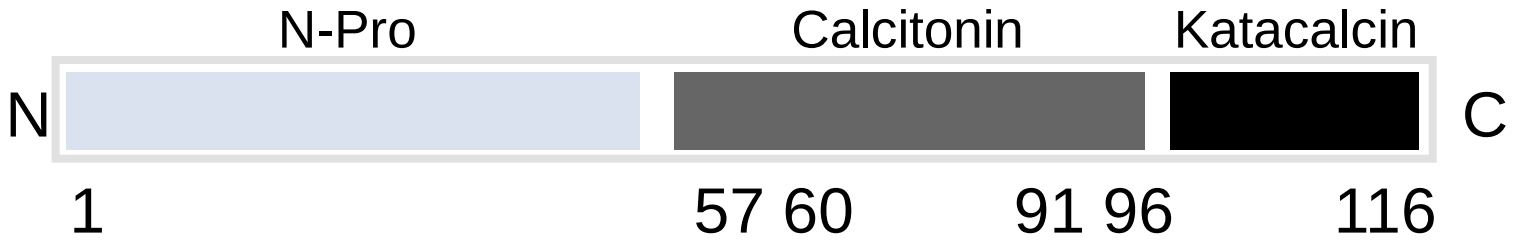

- Propeptide of the hormonal active calcitonin (116 AA; 12.3 kD)
- Specifically induced by bacterial infections
- Low levels in viral infections or autoimmune disorders

# Procalcitonin – Precursor to Calcitonin




After P. Linscheid, Endocrinology 2003



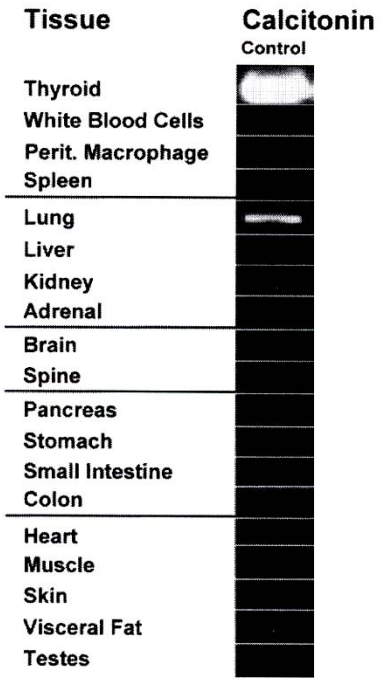

**LOW PCT values** in the blood of healthy persons: 95% have measurement of 0.1ng/ml or less**

Morgenthaler N. et al., Clin Lab 2002, 48: 263-270

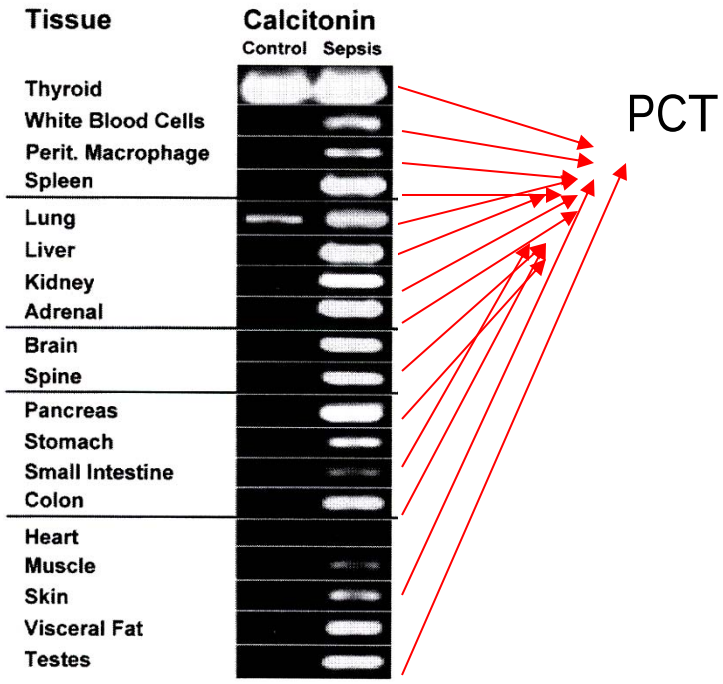
# Expression

Calcitonin in healthy persons

PCT in bacterial infection

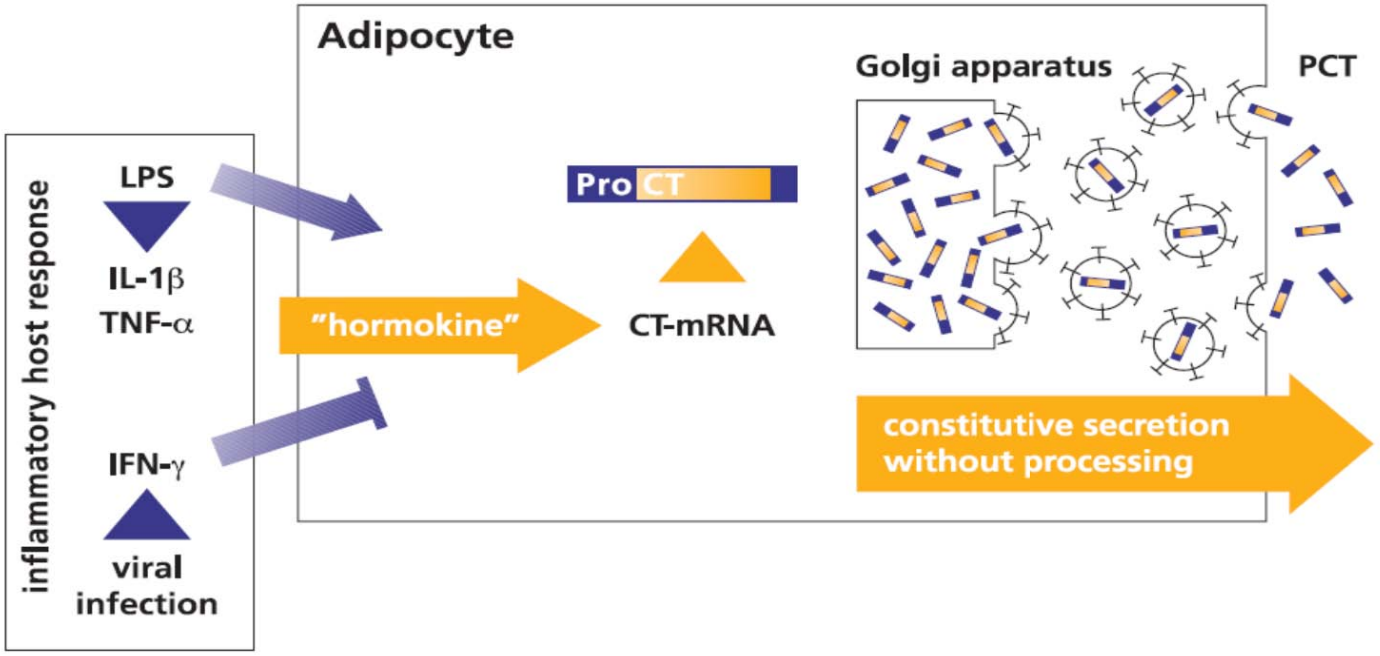



Calcitonin




Muller B, *et al*. J Clin Endocrinol Metab 2001 Jan;86(1):396-404.

# Bacterial Specificity

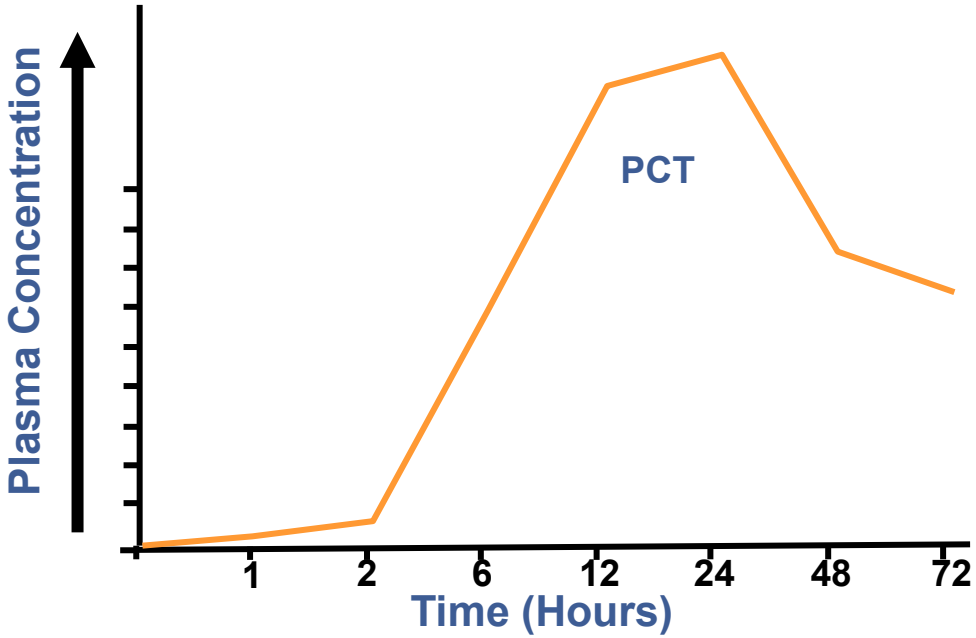



**Alternative synthesis of PCT**

- Bacterial toxins (gram+/-) and cytokines stimulate production of PCT in all parenchymal tissues
- PCT is immediately released into bloodstream
- This process can be blocked during viral infections

Chris-Crain, M. et al., Current Infect. Dis. Reports (2007) 9:233-240

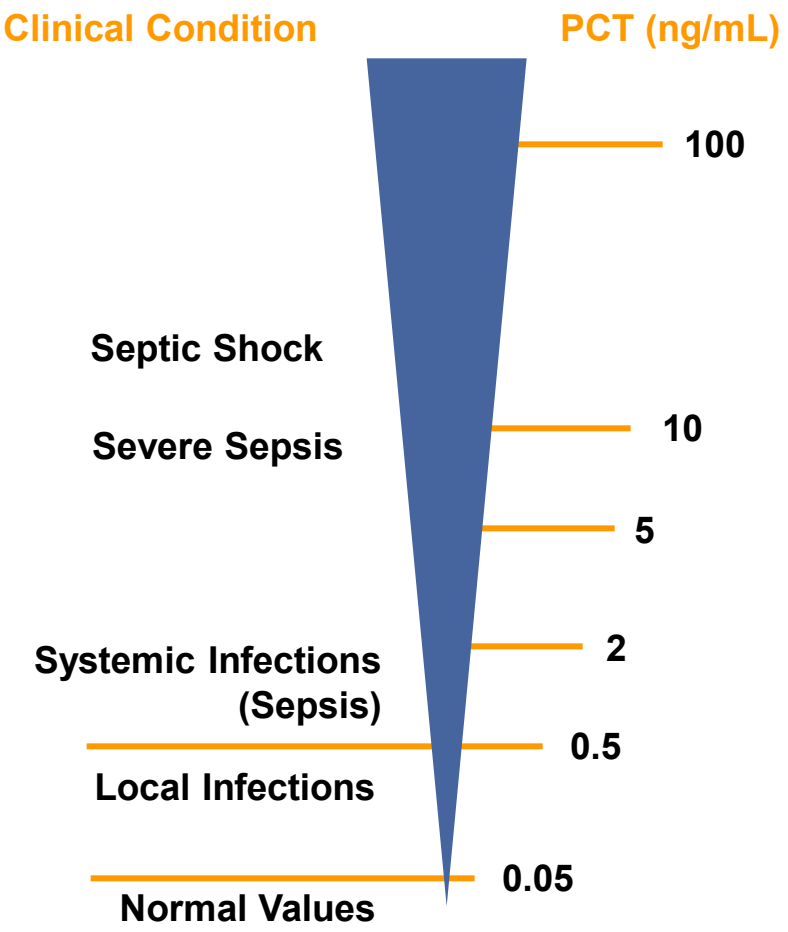
# PCT Kinetics




- Rapid kinetics: rises 3h after bacterial invasion
- Peak: 6-12h
- Half-life: ~ 24h

*Brunkhort FM et al., Intens. Care Med (1998) 24: 888-892*
*Dandona P. ed al., J. of Endocrineologiy and Metabolism. (1994). 79: 5*

# Procalcitonin Interpretation




- **No "universal" cut-off**
- **PCT cut-offs depend on the general clinical situation of the patient**

*Harbarth S et al. AJRCC Med. 2001;164:396-402.*
*Meisner M et al. Crit Care. 1999, 3:45-50.*
*Krüger S et al. Eur Respir J. 2008;31: 349–55.*

# Potential Limitations of PCT

**Low PCT levels in the presence of bacterial infection may occur:**

- Early in the course of infection
- Sub acute Endocarditis
- Localized infections

# Potential Limitations of PCT

- Newborn < 48hr - increased PCT values (physiological peak)
  - On 3rd day after birth, normal adult reference ranges apply
- Primary inflammation syndrome following trauma: multiple trauma, extensive burns, major surgery (cardiac, transplant, abdominal)
  - Rapid decrease (half-life 24hr) in the absence of bacterial infection
- Medullary C-cell cancers of the thyroid, pulmonary small-cell carcinoma and bronchial carcinoma
- Prolonged circulatory failure (eg: cardiogenic shock, hemorrhagic shock, thermal shock)
- Treatments that can cause a cytokine storm e.g. OKT3, anti-lymphocyte globulins, etc.

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# PCT in the Emergency Department

# PCT in the Emergency Department

- PCT:
  - ED staff often examining patient in earliest hours of disease progression.[1]
  - Helps improve estimation risk of severe sepsis and of mortality.[1]
  - Sensitivity and specificity over 80%.[1]
  - NPV 92% or higher.[2]
- If start is delayed 24 to 48 hours, therapy significantly less effective.[1]
- Several medical conditions are very similar to sepsis.
- There are also several common diseases that can cause sepsis.
  - Peritonitis, pneumonia, pyelonephritis/urinary tract infections, soft tissue infections, gastroenteritis, meningitis, aspiration, and limited bacteremia.

1 Meisner M "Procalcitonin – Biochemistry and Clinical Diagnosis" 2010 UNI-MED Verlag AG Bremen – London – Boston.
2 Riedel S, *et al*. Am J Clin Pathol 2011 Feb;135(2):182-9.

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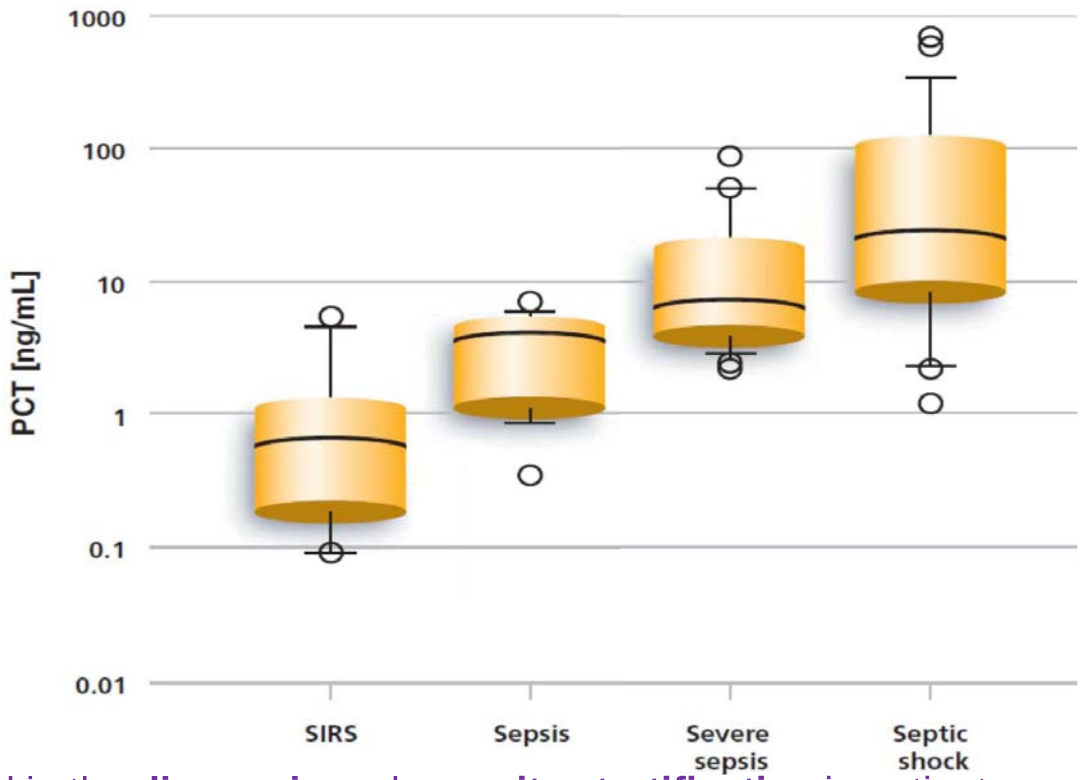
# PCT in the Intensive Care Unit

# PCT in the Intensive Care Unit

- Gray Zone = Delayed diagnosis and treatment of an infection, compared with excess antibiotic use, multi-drug resistance and increased costs.[1]
- Unmet need for clinical or laboratory tools to distinguish between SIRS and the various forms of sepsis.[2]
- PCT:
  - Early production.[3]
  - Sharp increases.[3]
  - More sensitive to resolution of infection.[3]
  - Correlates with host response to microbial infection.[4]
- Guidelines recommended that serum PCT levels could be employed as an adjunctive diagnostic tool for discriminating infection as the cause for fever or sepsis presentations.[5]


1 Tsangaris I *et al*. A BMC Infect Dis 2009 Dec 22;9:213.
2 Harbarth S *et al*. Am J Respir Crit Care Med 2001 Aug 1;164(3):396-402.
3 Castelli GP *et al*. Crit Care Med 2009 Jun;37(6):1845-9.
4 Simon L *et al*. Clin Infect Dis 2004 Jul 15;39(2):206-17.
5 O'Grady NP *et al*. Crit Care Med 2008 Apr;36(4):1330-49.

# Adding PCT results to clinical assessment improves the accuracy of the early clinical diagnosis of sepsis

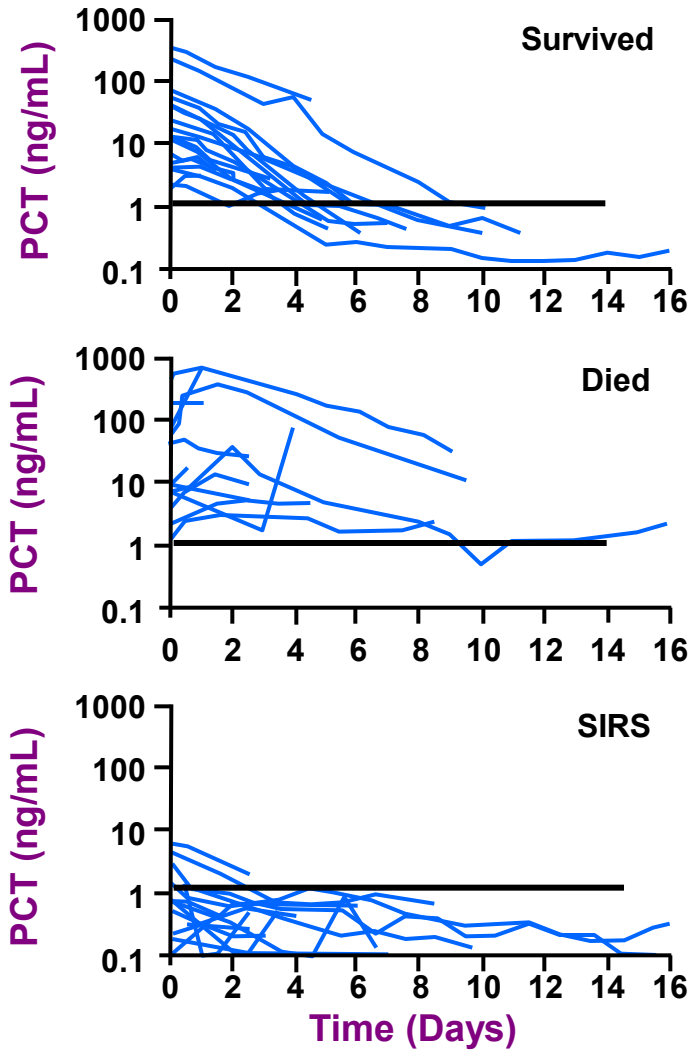



- **PCT** can aid in the **diagnosis** and **severity stratification** in patients suspected of sepsis, severe sepsis, and septic shock.
- **Clinical symptoms** of sepsis and other noninfectious disease conditions are often similar
- **In multiple studies,** PCT has demonstrated a high sensitivity and specificity for the differentiation of sepsis from SIRS (Systemic Inflammatory Response Syndrome)
- **PCT levels** can be useful for the management of patients after surgery or transplant and in peritonitis



Harbarth S et al. Am J Respir Crit Care Med 2001, 164: 396-402 ; Meisner M et al., Critical Care 1999, 3(1): 45-50 ; Krüger S. et al., Eur Respir J 2008; 31: 349–355

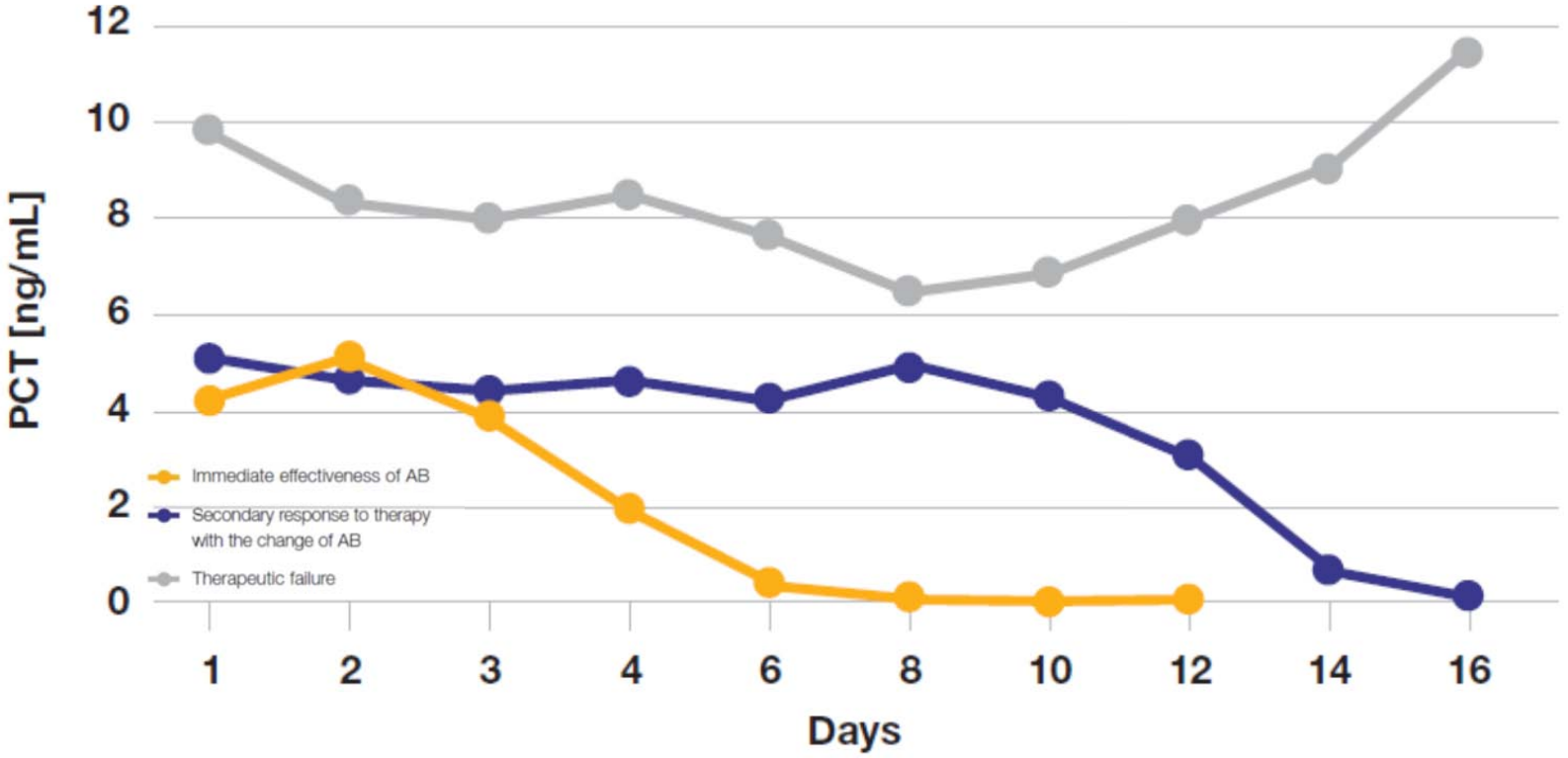
# PCT correlation to Patient Prognosis




- In sepsis initial PCT values > 1 ng/ml
- Rapid decline to PCT values< 1 ng/ml associated with good prognosis
- No or slow decline, not getting < 1 ng/ml associated with poor prognosis
- In SIRS no or only short-time increase > 1 ng/ml

*Harbarth S et al. Am J Respir Crit Care Med. 2001;164:396-402.*

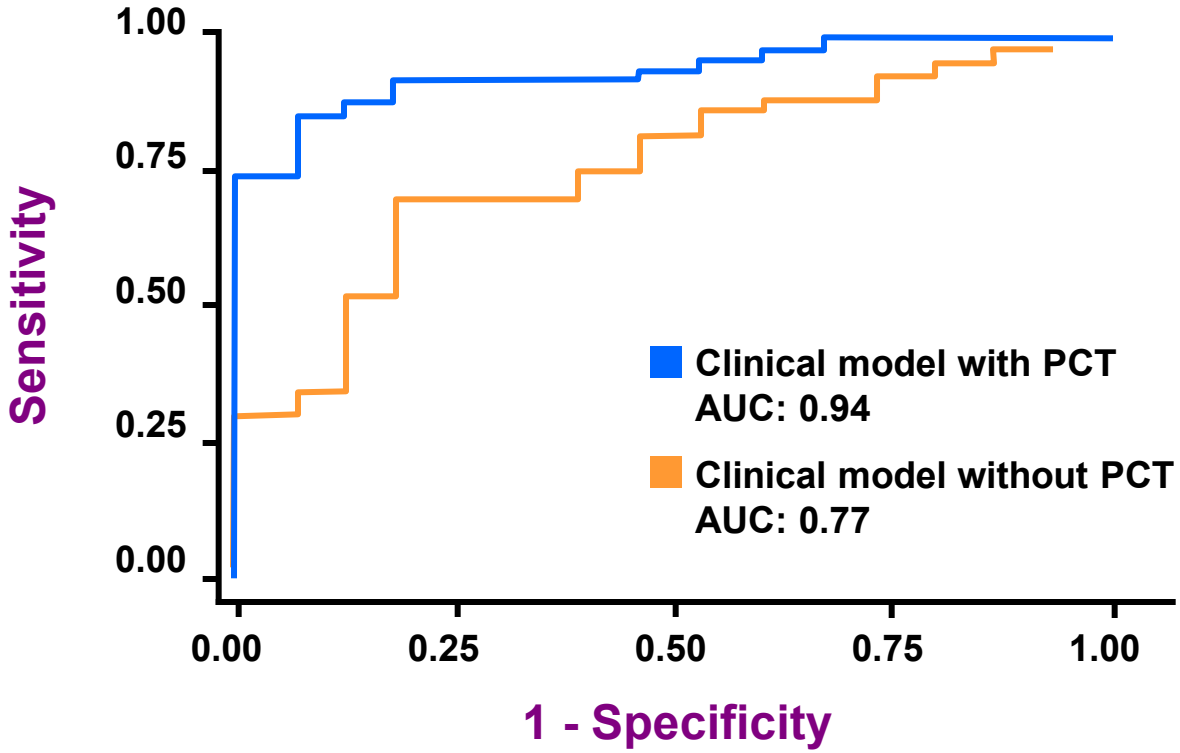
# Serial measurement of PCT provides a clearer picture of the patient's response to antibiotic treatment.




- **Decreasing PCT levels** in patients with sepsis indicate effective treatment of the underlying infection
- **Persistently elevated PCT levels** indicate a possible treatment failure
- **When integrated into the management of septic patients,** PCT can help clinicians to manage septic patients more efficiently

Stueber, F. University of Bonn, Lecture at ISICEM, Brussels 2001

# PCT shown to improve Accuracy of Clinical Diagnosis




**IL-6, IL-8 or CRP without impact on accuracy of clinical diagnosis**

*Harbarth S. AJRCCM 2001*

Harbarth S et al. *Am J Respir Crit Care Med.* 2001;164:396-402.

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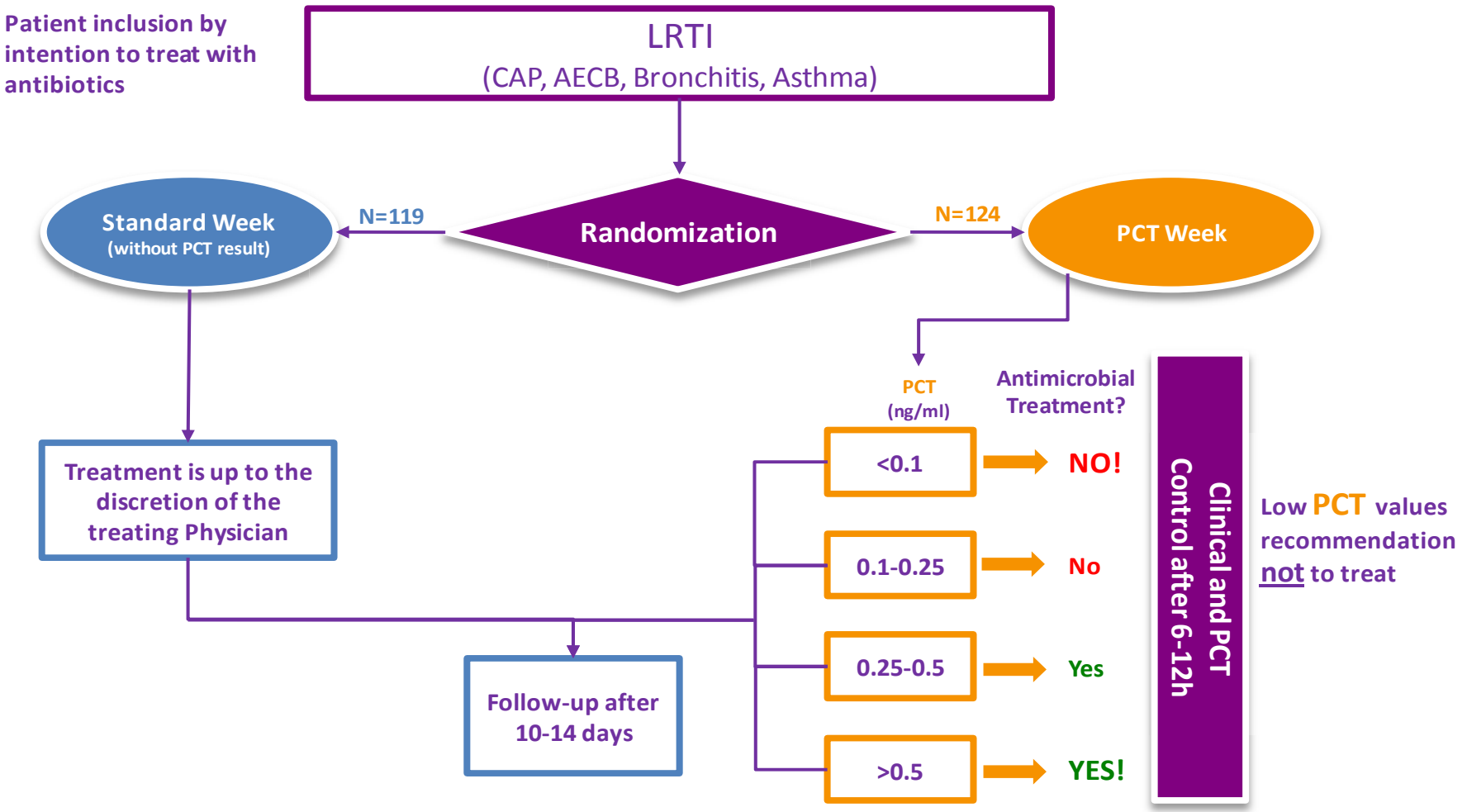
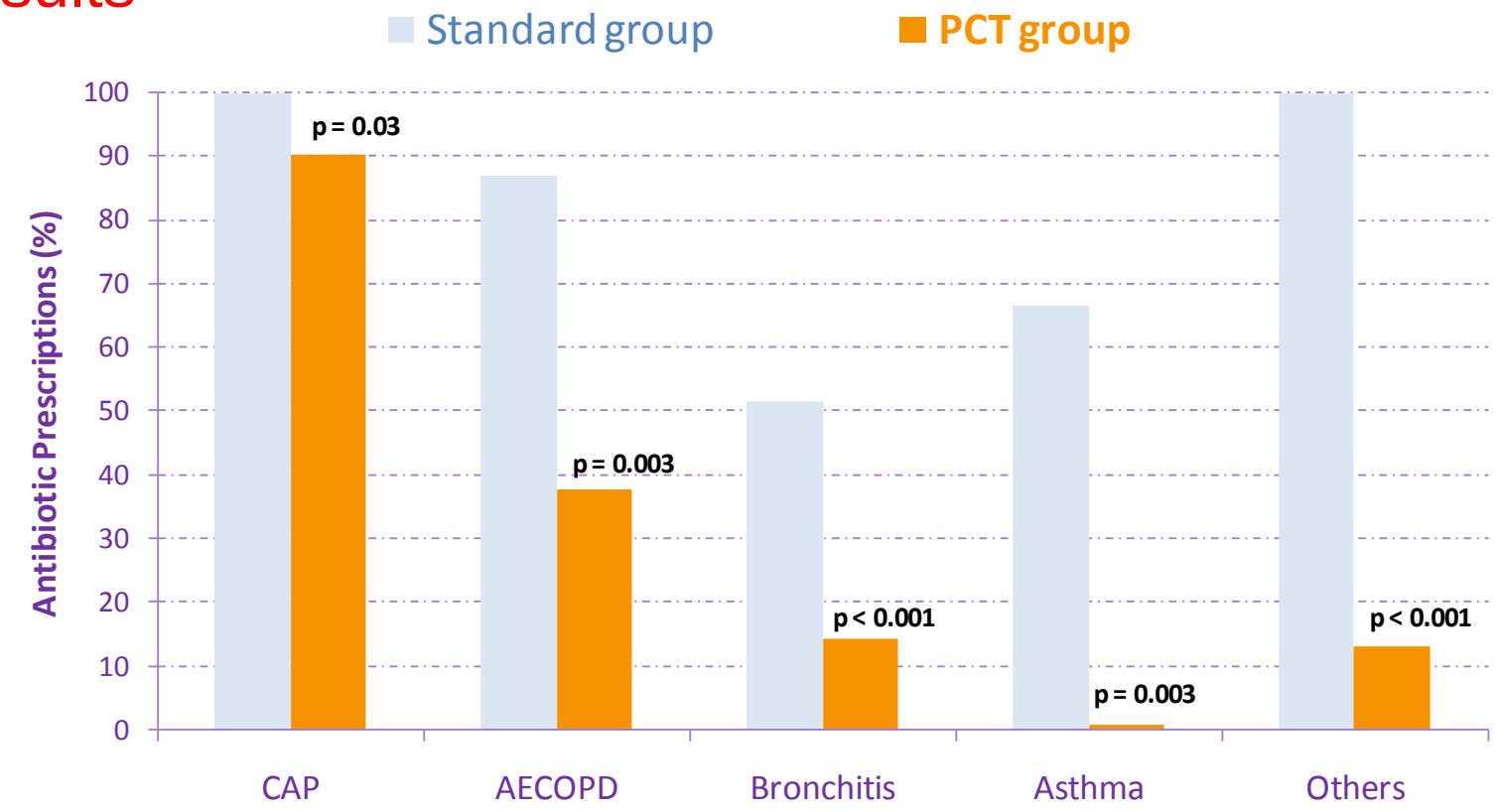
# PCT in Abx Stewardship

# Effect of Procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomized, single-blinded interventional trial: Study Design




Christ-Crain et al., Lancet 2004, 363(9409) : 600-607

# Effect of Procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomized, single-blinded interventional trial: Study Results




**Key Takeaways:** Reduction of antibiotic prescription by ~50%. No difference in outcomes.

| | Admittance | Hospital LOS | Outcome | Mortality |
|---|---|---|---|---|
| Control (n=119) | 74 | 11 | 64 | 3 |
| PCT Group (n=124) | 80 | 11 | 65 | 3 |



Christ-Crain et al., Lancet 2004, 363(9409) : 600-607

# ProHosp – *JAMA* 2009 (Schuetz et al)

***Effect of Procalcitonin-Based Guidelines vs. Standard Guidelines on Antibiotic Use in Lower Respiratory Tract Infections: The ProHOSP Randomized Controlled Trial***

*Journal of the American Medical Association.* 2009;302(10):1059-1066

**Objective:**

- **Examine whether a PCT algorithm can reduce antibiotic exposure without increasing the risk for serious adverse outcomes.**

# ProHosp: Overview

- **Unnecessary antibiotic use**
  - Contributes to increasing bacterial resistance
  - Increases medical costs and the risks of drug-related adverse events
- **Lower respiratory tract infections (LTRI)**
  - Most frequent indication for antibiotic prescriptions in the Northwestern hemisphere
  - 75% of patients are treated with antibiotics
  - Predominantly viral origin of infection
- **Procalcitonin (PCT) algorithm**
  - Reduced antibiotic use in patients with LTRIs without negative impact on outcomes (non-inferiority)

**Schuetz P et al. *J Am Med Assoc*. 2009;302(10):1059-66.**

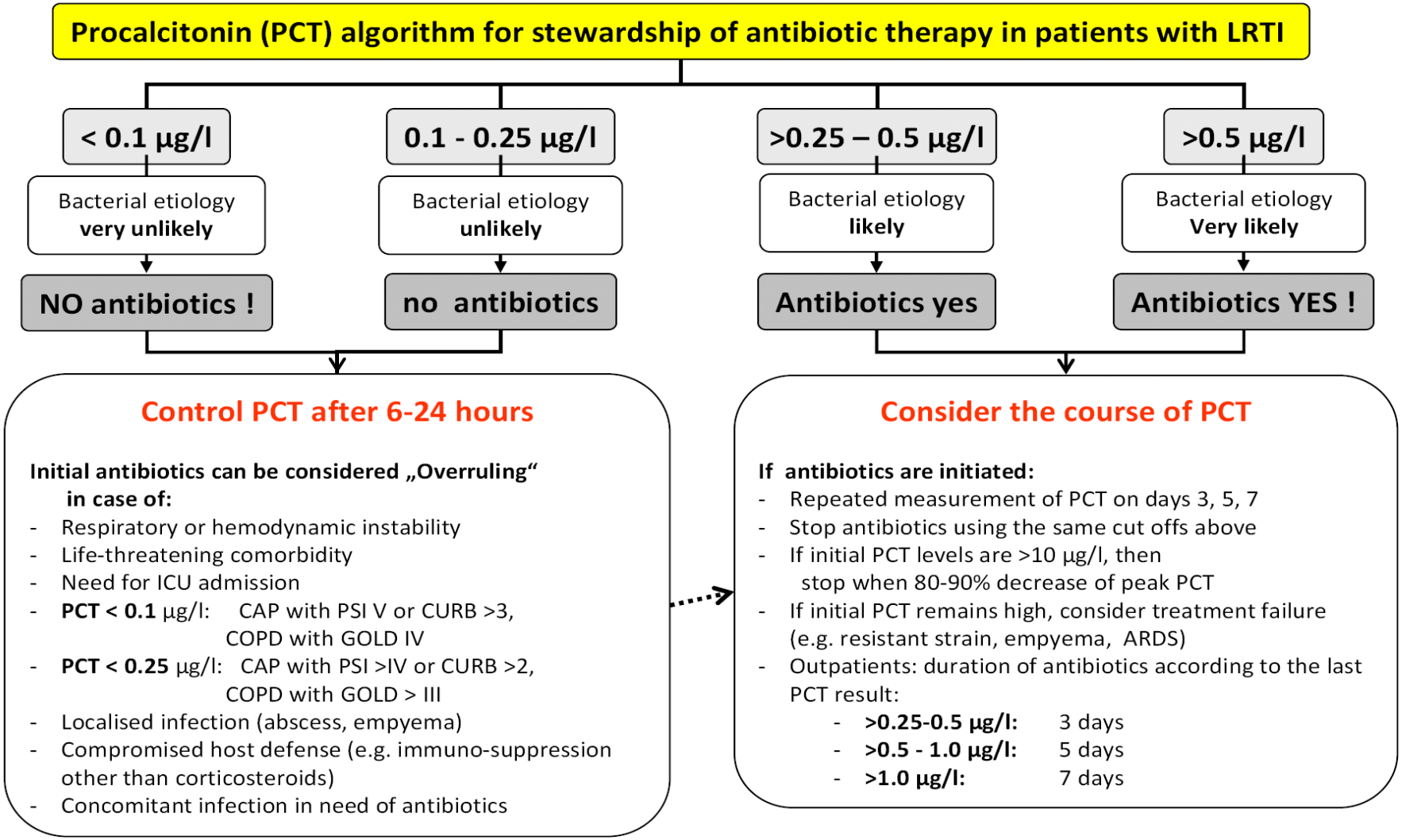
# ProHosp - Study Design

## Multicenter, non-inferiority, randomized controlled trial

- **Patients**
  - 1381 patients with LRTI randomized to administration of antibiotics based on PCT algorithm
  - Cutoff ranges for initiating or stopping antibiotics (PCT group) or standard guidelines (control)
  - 6 academic/non-academic ED
- **Outcome Measure**
  - Composite adverse outcomes of
    - Death,
    - All Cause ICU admission
    - Disease-specific complications,
    - Recurrence/Relapse within 30 days
  - Antibiotic exposure and adverse effects from antibiotics

Schuetz P et al. *J Am Med Assoc*. 2009;302(10):1059-66.

# ProHosp – *JAMA* 2009 (Schuetz et al)



# ProHosp: Primary Endpoint (Safety)

## Overall Adverse Oucome (30 days)

**PCT 15.4% vs. Control 18.9%, RD -3.5,%**

- **Death**
  - 5.1 % vs. 4.8%,
    - Risk Difference 0.3%
- **All cause ICU admission**
  - 6.4% vs. 8.7%,
    - Risk Difference -2.3%
- **Disease-specific complications**
  - 2.5% vs. 2.0%,
    - Risk Difference 0.5%,
- **Recurrance/Readmission**
  - 3.7% vs. 6.5%,
    - Risk Difference -2.8%

- ***The95% CI for the risk difference excludes an excess risk in the PCT group of 7.5% or more satisfying the pre-defined noninferiority citerion.***

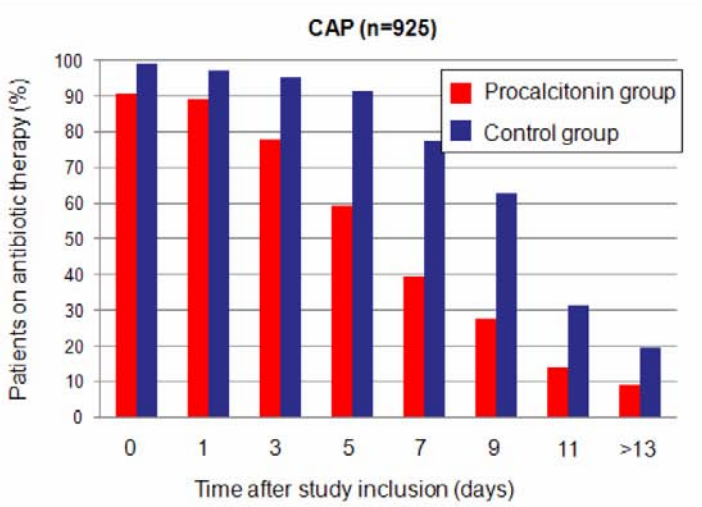


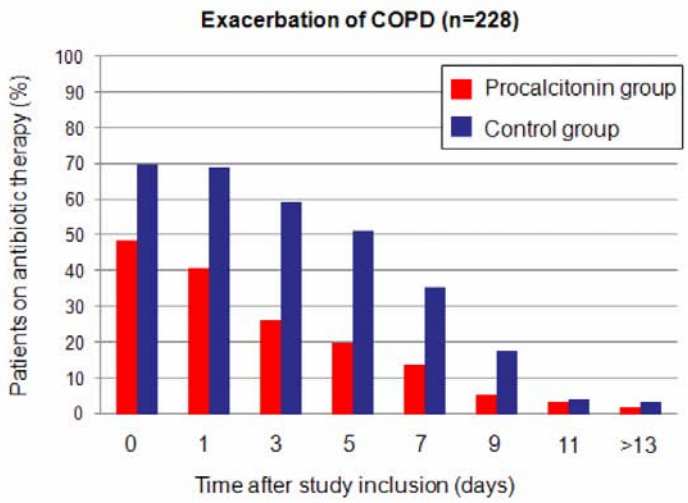
*Schütz et al., JAMA.2009;302(10):1059-66*

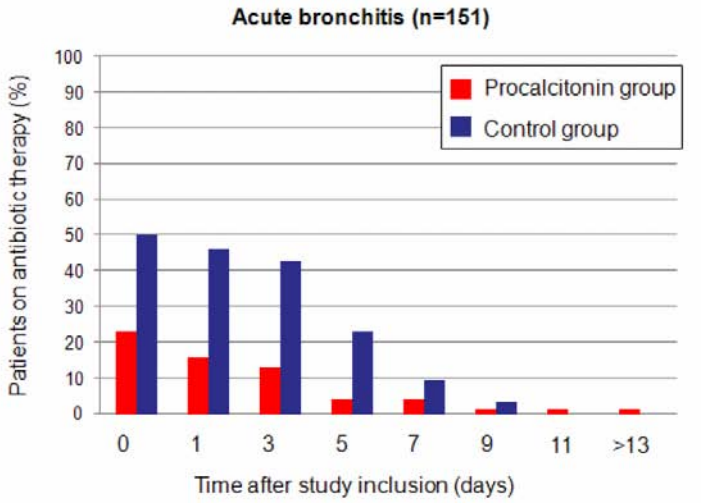
# Results: Secondary Endpoint (Superiority)

**Reduction of Abx exposure in subgroups of patients:**

- CAP ⇒ 32.4% reduction,
- AECOPD ⇒ 50.4% reduction,
- Acute bronchitis ⇒ 65.0% reduction




*Schütz et al., JAMA.2009;302(10):1059-66*

# Summary of Results

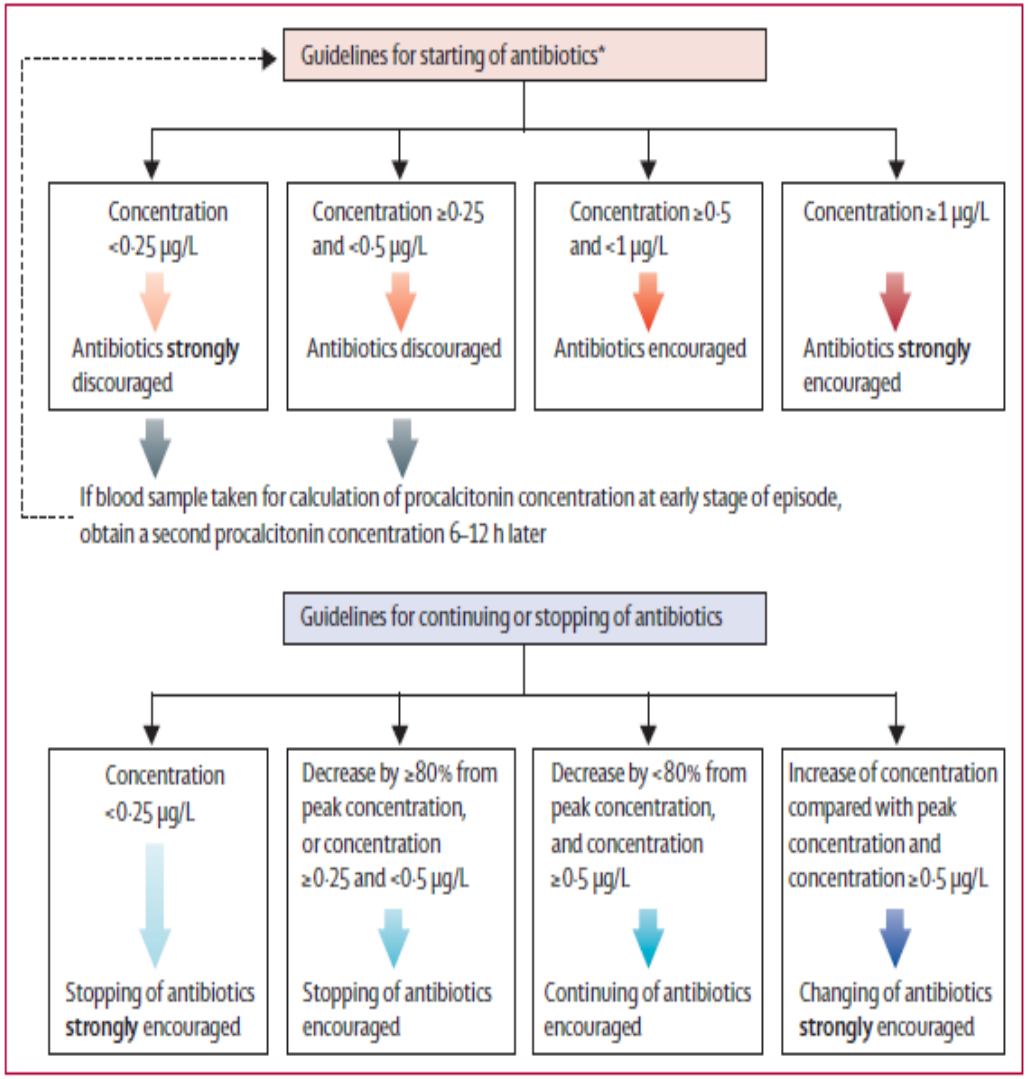
- PCT guided algorithm in patients presenting to the ED with LRTI, compared to conventional guided practices resulted in:
  - Similar rates of adverse outcomes (non-inferiority)
  - Mean antibiotic exposure was significantly lower
  - Antibiotic-associated adverse effects were significantly lower

*Schütz et al., JAMA.2009;302(10):1059-66*

# ProRATA –Lancet 2010 (Bouadma et al.,)

- The prospective, parallel-group open-label
- 5 MICU, 2 SICU
  - 5 university hospitals
  - Suspected bacterial infection
  - N=621

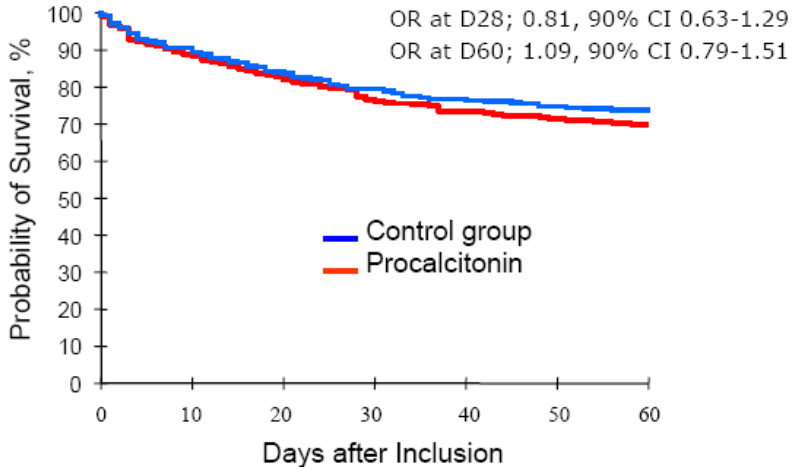
- Exclusion
  - <18 years
  - Pregnancy
  - ICU LOS < 3days
  - BMT
  - Chemotherapy induced neutropenia
  - Infections were long-team treatment is recommended




Bouadma L, *et al*. Lancet 2010 Feb 6;375(9713):463-74.

# ProRATA: Primary Endpoints

- Mortality at 28 and 60 days (non-inferiority)
  - non-inferiority safety margin of 10%
- Number of days without antibiotics by day 28 (superiority)




| Primary Endpoints | PCT Group (n=307) | Control Group (n=314) | Between group absolute difference | P value |
|---|---|---|---|---|
| 28-day mortality | 65 (21.2%) | 64 (20.4%) | 0.8% | NA |
| 60-day mortality | 92 (30.0%) | 82 (26.1%) | 3.8% | NA |
| # days without antibiotics | 14.3 (9.1) | 11.6 (8.2) | 2.7% | <0.0001 |

Bouadma L, *et al*. Lancet 2010 Feb 6;375(9713):463-74.

# ProRATA: Secondary Endpoints

| Endpoint | PCT Group (n=307) | Control Group (n=314) | P value |
|---|---|---|---|
| Relapse (%) | 20 (6.5) | 16 (5.1) | 0.45 |
| Superinfection (%) | 106 (34.5) | 97 (30.9) | 0.29 |
| Days without MV (%) | 16.2 (11.1) | 16.9 (10.9) | 0.47 |
| ICU LOS, d | 15.9 (16.1) | 14.4 (14.1) | 0.23 |
| Hospital LOS, d | 26.1 (19.3) | 26.4 (18.3) | 0.87 |
| Multi-resistant bacteria | 55 (17.9) | 52 (16.6) | 0.67 |
| **AB exposure/1,000 days** | **663** | **812** | **0.0001** |

***No significant difference between number and type of organ dysfunctions*

Bouadma L, *et al*. Lancet 2010 Feb 6;375(9713):463-74.

# ProRATA: Summary of results

- In ICU patients studied in this trial, a strategy of PCT guidance for AB treatment compared with standard guidelines was
  - Non-inferior regarding 28 and 60 days all cause mortality
  - Superior, enabling more days alive at 28d without antibiotics

Bouadma L, *et al*. Lancet 2010 Feb 6;375(9713):463-74.

# Antibiotic Stewardship Studies(n=4241)

| Authors | Study name | Research question | Setting | n= | Mortality Control vs PCT group | AB exposure Control vs PCT | Relative AB reduction |
|---|---|---|---|---|---|---|---|
| *Christ-Crain et al,* | **ProRESP** | Reduction of antibiotic prescription for LRTI in the ED? | ED, single center | *243* | 4/119 (3.4%) vs 4/124 (3.2%) | 10.7 vs 4.8* | 55.1% |
| *Christ-Crain et al,* | **ProCAP** | Reduction of antibiotic exposure in CAP in ED and hospital? | ED and hospital, single center | *302* | 20/151 (13.2%) vs 18/151 (11.9%) | 12.9 vs 5.7* | 55.8% |
| *Stolz et al,* | **ProCOLD** | Reduction of antibiotic exposure in COPD exacerbation over 6 month? | ED, single center | *208* | 9/106 (8.5%) vs 5/102 (4.9%) | 7.0 vs 3.7* | 47.1% |
| *Briel et al,* | **PARTI** | Safety & reduction of antibiotic exposure in upper and lower RTI? | Primary Care, multicenter | *458* | 1/232 (0.4%) vs 0/226 (0%) | 6.8 vs 1.5* | 77.9% |
| *Nobre et al,* | **"ProSEP"** | Reduction of antibiotic exposure in septis in the ICU ? | ICU , single center | *79* | 8/39 (20.5%) vs 8/40 (20%) | 9.5 vs 6** | 36.8% |
| *Schuetz et al,* | **ProHOSP** | Safety & feasability in LRTI in a multicenter setting? | ED and hospital, multicenter | *1359* | 33/671 (4.9%) vs 34/688 (4.9%) | 8.7 vs 5.7* | 34.5% |
| *Stolz et al,* | **ProVAP** | Reduction of antibiotic exposure in VAP in differnt ICUs ? | ICU, multicenter | *101* | 12/50 (24%) vs 8/51 (15.7%) | 9.5 vs 13*** | 26.9% |
| *Kristoffersen et al,* | **1-PCT** | Reduction of antibiotic exposure for LRTI in Denmark? | ED and hospital, single center | *210* | 1/107 (0.9%) vs 2/103 (1.9%) | 6.8 vs 5.1* | 25.0% |
| *Hochreiter et al,* | **ProSICU** | Guiding antibiotic therapy with PCT in a surgical ICU? | Surgical ICU, single center | *110* | 14/53 (26.4%) vs 15/57 (26.3%) | 7.9 vs 5.9* | 25.3% |
| *Bouadma et al,* | **ProRATA** | Reduction of antibiotic exposure for sepsis in different french ICUs ? | ICU , multicenter | *621* | 64/314 (20.4%) vs 65/307 (21.2%) | 11.6 vs 14.3*** | 18.9% |
| *Burckhardt et all* | **"PARTI Germany"** | Safety & reduction of only initial PCT measurement in primary care? | Primary Care, multicenter | *550* | 0/275 (0%) vs 0/275 (0%) | 36.7% vs 21.5%**** | 42.0% |
| | **Total** | | | ***4241*** | **166/2117 (7.8%) vs 159/2124 (7.5%)** | | |

*mean; **median; ***antibiotic –free days, ****initial prescription of AB; AB; antibiotic; ED emergency department, ICU intensive care unit, CAP community-acquired pneumonia, COPD chronic obstructive pulmonary disease, VAP ventilator associated pneumonia



*Schuetz P, Expert Rev Anti Infect Ther. 2010 May;8(5):575-87.*

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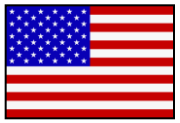
- **PCT Supported by…**

# Procalcitonin in Practice Guidelines



## ACCM/IDSA 2008

Guidelines for evaluation of ***new fever in critically ill adult patients***:

- **Use of Adjunctive Markers for the Evaluation of Fever**
  - Procalcitonin level elevations of >0.5 ng/mL occur within 2–3 hrs of onset, with higher levels observed along the continuum from systemic inflammatory response (0.6 –2.0 ng/mL), severe sepsis (2–10 ng/mL), and septic shock (>10 ng/mL).
  - Most importantly, viral infections, recent surgery, and chronic inflammatory states are not associated with an increment in procalcitonin levels.

- **Recommendation for Using Biomarkers to Determine the Cause of Fever**
  - Serum **procalcitonin levels** and endotoxin activity assay can be employed **as an adjunctive diagnostic tool for discriminating infection as the cause for fever or sepsis presentations** (level 2).
    - Level 2 : “reasonably justifiable by available scientific evidence and strongly supported by expert critical care opinion”

*O”Grady NP et.al., Crit Care Med 2008; 36:1330-1349; ** Dellinger et.al., Crit Care Med 2008; 36:296-327

# Procalcitonin in Practice Guidelines

## SCCM 2012

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock

- **Antimicrobial Therapy**
  - Antimicrobial therapy within **1 hr** of septic shock (1B) or severe sepsis (1C) recognition
  - Antimicrobial regimen should be reassessed **daily** for potential de-escalation (1B)
    - *Use of **low PCT** or similar biomarkers to assist in the **discontinuation of empiric antibiotics** in patients who initially appeared septic, but have no subsequent evidence of infection (2C)*

- *Weak recommendation in favor of an intervention indicates judgment that the desirable effects of adherence to a recommendations probably will outweigh the undesirable effects. Panel is not confident about the benefit vs. downside or they are closely balanced.*
  - *Weak recommendation "we suggest"*

Dellinger R et al., Crit Care Med. 2013. 41:2 580-637.