

Sepsis

Reuben Ramphal M.D.
Division of Infectious Diseases
University Of Florida

Occurrence of Severe Sepsis

- Annual incidence: ~750,000 cases in US
- 2.26 cases per 100 hospital discharges
- 51.1% received ICU care and 17.3% received IMC care
- Incidence and mortality increased with age
- Case fatality rate: 28%
- Economic burden
 - \$22,100 per case
 - ~\$16.7 billion nationally

Angus DC et al. 2001. Crit Care Med 29:1303-1310.

Reference Diseases

- Incidence in US (cases per 100,000)
 - AIDS¹ 17
 - Colon and rectal cancer² 48
 - Breast cancer² 112
 - Congestive heart failure³ ~196
 - Severe sepsis⁴ ~300
- Number of deaths in US each year
 - Acute myocardial infarction⁵ 218,000
 - Severe sepsis⁴ 215,000

¹Centers for Disease Control and Prevention. 2000. Incidence rate for 1999.

²American Cancer Society. 2001. Incidence rate for 1993-1997.

³Angus DC et al. 2001. Crit Care Med 29:1303-1310.

⁴Angus DC et al. 2001. Crit Care Med 29:1303-1310.

⁵National Center for Health Statistics. 2001.

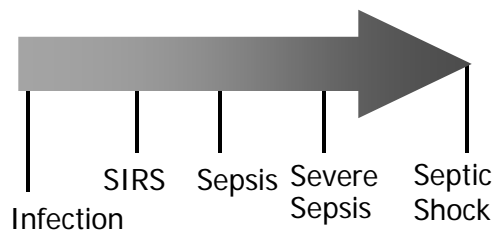
Sepsis on the Rise

- Incidence projected to rise to 1.0 million cases annually in US during the next decade
 - Aging population
 - Increased awareness and diagnosis
 - Immunocompromised patients
 - Invasive procedures
 - Resistant pathogens

Angus DC et al. 2001. Crit Care Med 29:1303-1310.

Balk RA. 2000. Crit Care Clin 16(2):179-191

Definitions



Systemic Inflammatory Response Syndrome

- Systemic Inflammatory Response Syndrome (SIRS)
 - ≥ 2 of the following:
 - Temp > 38°C or < 36°C
 - Heart rate > 90 bpm
 - Respiratory rate > 20 bpm
 - WBC > 12,000, < 4,000 or bands > 10%

Bone, et al. 1992. Chest 101:1644-1655

Sepsis

- Sepsis
 - SIRS + infection
- Severe sepsis
 - Sepsis with organ dysfunction, hypoperfusion or hypotension
- Septic Shock
 - Sepsis with hypotension and perfusion abnormalities despite adequate volume replacement

Bone, et al. 1992. Chest 101:1644-1655

Mortality from Sepsis Martin NEJM 2003

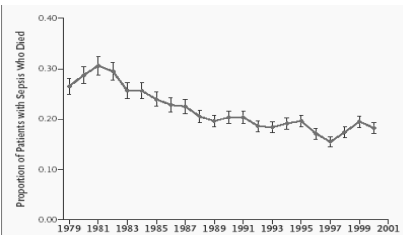


Figure 4. Overall In-Hospital Mortality Rate among Patients Hospitalized for Sepsis, 1979–2000. Mortality averaged 27.8 percent during the first six years of the study and 17.9 percent during the last six years. The I bars represent the standard error.

Changes in the Causes of Sepsis Martin NEJM 2003

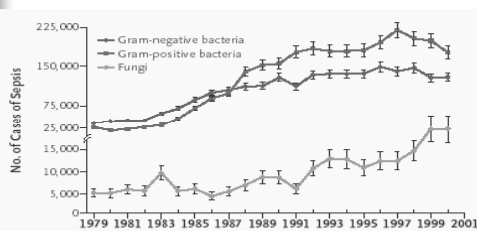


Figure 3. Numbers of Cases of Sepsis in the United States, According to the Causative Organism, 1979–2000. Points represent the number of cases for the given year, and I bars the standard error.

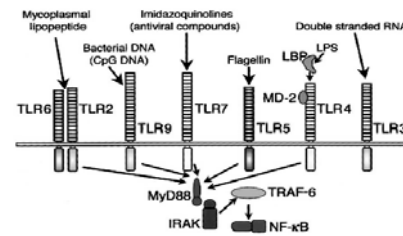
Pathogenesis of Sepsis

- Interaction of specific Pathogen associated molecular patterns (PAMPs--microbial ligands) on organisms with specific receptors Toll like receptors (Tlrs) on animal cells
- PAMPs
 - Highly conserved parts of microbial molecules
- Sepsis also caused by Interactions of super antigens with T- cells e.g. **Some staphylococcal and streptococcal toxins**

Innate Immune response → Sepsis

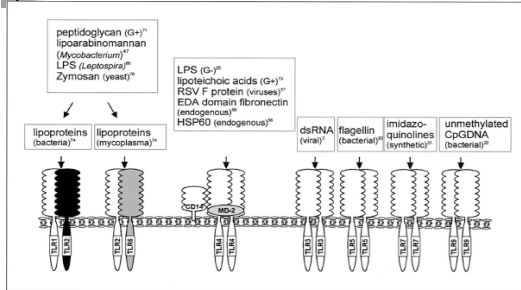
- Interaction of a PAMP with a Tlr results in a cellular cascade which leads to activation of innate immune mechanisms
 - Message sent to nucleus resulting in transcription of repressed genes
 - Antimicrobial peptide synthesis and release
 - Beginning of a specific adaptive antibody response
 - Release of Mediators of inflammation
 - Normally protective but some type of dysregulation leads to signs of SEPSIS

Microbial Ligands Recognized by TLR family

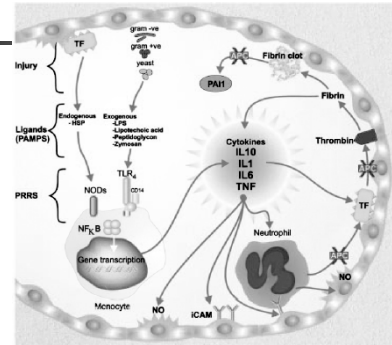


Akira and Hashino, Osaka University JID 2003

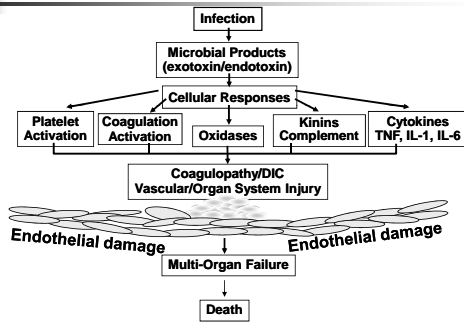
Microbial Ligands and Tlr recognition



Synthesis and release of effector molecules



Pathogenesis of Severe Sepsis



Clinical effects of dysregulation of innate immune responses

- Clinical sepsis
 - Fever
 - Hypoperfusion
 - Hypotension → Shock
 - Clotting → Disseminated intravascular coagulation
 - Renal failure
 - Cardiac depression
 - Central nervous system depression
 - Acute respiratory Distress syndrome

Most effective therapies

- Early recognition of preshock- tachynea leading to respiratory alkalosis
 - Low Pco₂, pH >7.45
- Lots of Fluids-crystalloid or colloid
- Antibiotics
- Effective antibiotics
- Timely administration of Effective antibiotics

Effect of antibiotics on Survival from sepsis

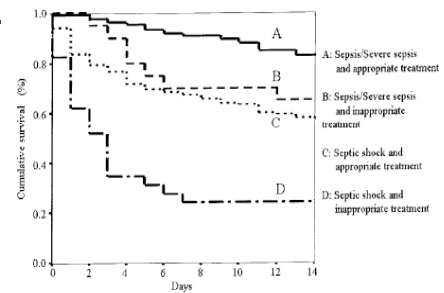


FIGURE 2. Survival rate according to the presence of shock and empiric antibiotic treatment (log-rank test, $p < 0.001$).

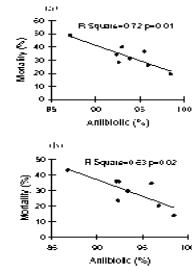
Independent risk factors for mortality for 136 patients with *Pseudomonas aeruginosa* bacteremia.

Risk factor	OR (95% CI)	P
Ineffective definitive antibiotic treatment	11.68 (2.5154.38)	.002
Ineffective empirical antibiotic treatment	4.61 (1.1818.09)	.028
Presentation with septic shock	45.37 (10.19201.93)	<.001
Pneumonia	11.43 (2.6050.19)	.001
Increasing APACHE II score	1.31 (1.151.50)	<.001

NOTE. Multivariate analysis using logistic regression model.
^a Per 1 point increase in score.

Pseudomonas aeruginosa Bacteremia: Risk Factors for Mortality and Influence of Delayed Receipt of Effective Antimicrobial Therapy on Clinical Outcome
 Cheol-In Kang et al Clin Inf Dis Oct 03

Timing of Antibiotic administration and mortality Due Sepsis

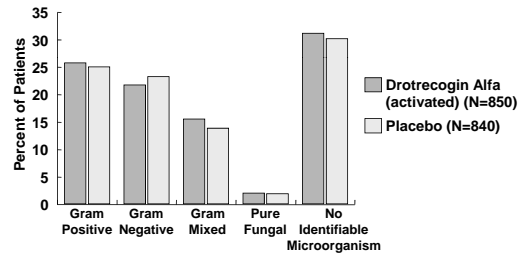


Relationship between mortality rate and antibiotic use. This plot displays the mortality rate versus whether an antibiotic was given within 24 hours after sepsis onset in the eight centers. The results were significant for (a) all patients (n=1028) and (b) for the subgroup (n=924) after excluding those with a 'do not resuscitate' order (n=104).

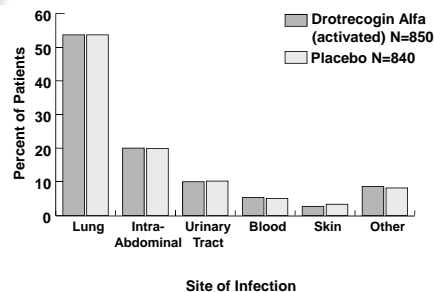
What constitutes adequate antibiotic therapy in Sepsis

- Site of Infection if known helps to limit choices ie-intraabdominal, or necrotizing soft tissue infection need for anaerobic coverage.
- Lung most common site of documented infection
- Resistance picture in hospital if hospital acquired and in the community if community acquired
- Generally Gram positive and Gram negative coverage

Baseline Microbiology from a large Septic shock study



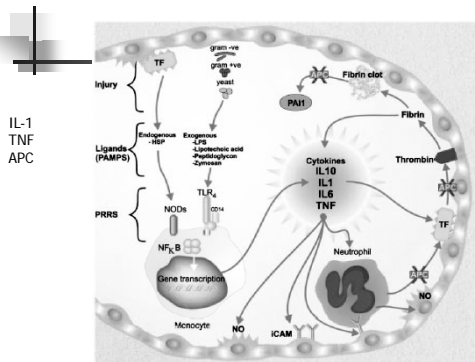
Primary Sites of Infection in a recent large study of Septic shock



Antibiotic Choices

- Given the world wide resistance issues the most effective antibiotic choices to cover gram negatives would be
 - Fourth generation cephalosporins ± aminoglycoside
 - Carbapenems ± aminoglycoside
 - Pip-Tazobactam + an aminoglycoside
- If the incidence of MRSA is high add an anti Staphylococcal agent --Vanco, Teicoplanin

Effector mechanism based non antibiotic adjuncts to therapy



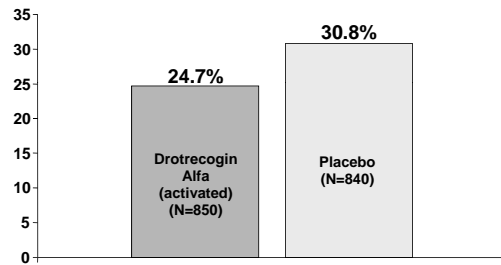
Nonantibiotic therapy of septic shock and sepsis

TABLE 7. Randomized controlled trials of immunotherapy in sepsis and septic shock*

Type of trial	No. of trials	Total no. of patients	Mortality (%) in patients receiving:	
			Placebo	Therapy
Anti-endotoxin	4	2,010	35	35
Anti-IL-1R	3	1,898	35	31
Anti-bradykinin	2	755	36	39
Anti-PAF	2	870	50	45
Anti-TNF	8	4,132	41	40
Soluble TNF-R	2	688	38	40
NSAIDS	3	514	40	37
Steroids	9	1,267	35	39
Activated protein C	1	1,690	31	25
All studies	33	13,824	38	37

Agent	Statistically Significant Reduction in Mortality	Patients with Adrenal Insufficiency benefit from Corticosteroids*
Non steroidal antiinflammatory drugs	No	
Corticosteroids	Unresolved	
Anti endotoxin	No	
Anti TNF	No	
TNF receptor antagonist	No	
IL-1 receptor antagonist	No	
PAF antagonist	No	
Activated protein C	Yes	

Drotrecogin Alfa (Activated ProteinC) Reduced 28-Day All-Cause Mortality



Optimum therapy of sepsis

- Antibiotics remain the most critical choice to be made
 - TIMELY, EFFECTIVE, BROAD SPECTRUM
 - Resistance issues need to be kept in mind
 - Modify antibiotics when organism is known
 - A large number of patients with the sepsis syndrome will not have an organism cultured
- Agents designed to neutralize the biologic actions of the inflammatory response may be additive, but it will likely require multiple agents