LSU Health SHREVEPORT

SEPSIS AND ANTIMICROBIAL STEWARDSHIP

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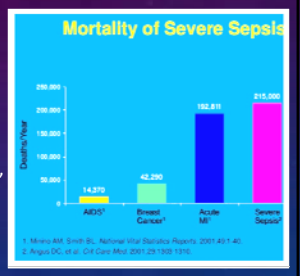
OBJECTIVES

1. Describe the signs and symptoms of sepsis.
2. Discuss laboratory tests that will help diagnose sepsis and monitor treatment.
3. Identify the role of the laboratory in detecting antimicrobial resistance and antimicrobial stewardship.

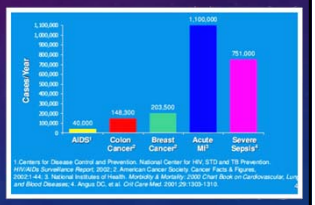
SEPSIS

- >2 million hospitalizations
- 500,000 treated in US EDs
- 45% ICU admissions
- 3rd leading cause of death, morbidity, expense
- ~ $20,000 dollars cost per case
- ~ 5% of healthcare > 20 billion $
- > 8 times as likely to die in hospital
- Prompt recognition and early treatment



INCREASING INCIDENCE OF SEPSIS

- Aging population
- More comorbidities
- Better recognition
- Reimbursement-favorable coding
- Immunosuppression
- Invasive procedures
- Spread of multi-drug-resistant pathogens

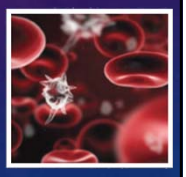


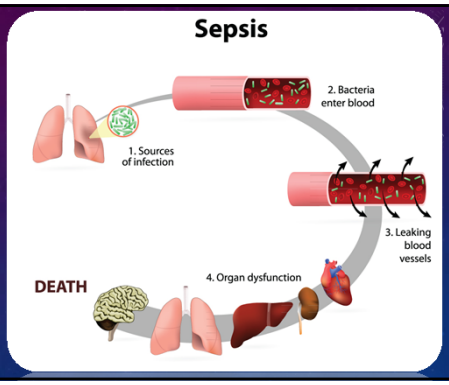
HOW SEPSIS PATIENTS ENTER HEALTHCARE PATHWAYS

- 70% enter through ED
  - Majority of deaths
  - Do not present with severe form
- 25% become septic in ICU
- 7.6% ↑ mortality for each hour of delayed antimicrobials

SEPSIS

- Response to infection causes organ dysfunction
- Septic shock—tissue hypoperfusion with vasopressor-requiring hypotension and elevated lactate levels
- 1/3-1/2 of deaths of hospitalized patients
- Complicated clinical challenge
- Early recognition and management of infection, hemodynamic issues, and other organ dysfunctions





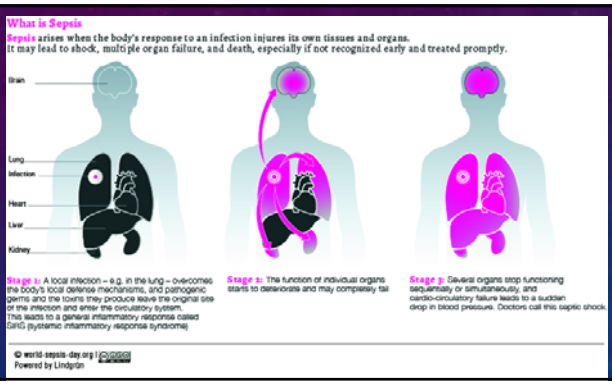
INCREASING INCIDENCE

- More susceptible to sepsis
- Severe burn or physical trauma
- More time in healthcare facility: 7 of 10 recently used
- Consequence of advanced care
- 299,992 in 2009 to 333,965 in 2012 (11% increase)
- 3800 to 4600 per 100,000 admissions

S. Elfeky et al. / Journal of Critical Care 39 (2017) 48–55

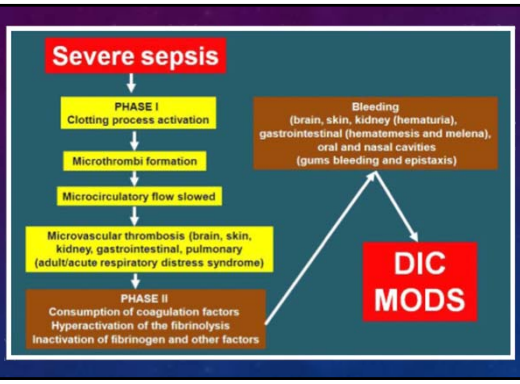
NEW DEFINITIONS ALIGNED WITH CLINICAL USE

- Infection: Routine infection without organ dysfunction
- Sepsis: progresses to organ dysfunction
- Septic Shock: Sepsis requiring vasopressors with lactate > 2 mmol/L--profound circulatory, cellular, and metabolic abnormalities
- Life-threatening organ dysfunction caused by a dysregulated host response to infection
- Mortality ~20%



PATHOLOGY OF SEPTIC SHOCK

- Complex interaction of proinflammatory, anti-inflammatory, activated complement system, and coagulation mediators
- Trigger host response with detector and signaling markers
- Proinflammatory signalers--tumor necrosis factor and IL-1 and -6
- Anti-inflammatory markers--IL-4, -10, and -11 and soluble tumor necrosis factor receptors
- Vascular tone instability-- of vasopress depletion
- Adrenal insufficiency
- Nitric oxide enhancement of vasodilation
- Leads to organ failure



PATHOLOGY OF SEPTIC SHOCK

- IL–15 promotes sepsis by maintaining NK cell numbers and integrity
- Mice missing gene for IL–15:
  - Improved survival
  - Reduced hypothermia
  - Less proinflammatory cytokine production
- Administering IL–15 superagonist to the mice regenerated NK and CD8+ T cells and re–established the mortality of septic shock

Journal of Immunology

HEMODYNAMIC EFFECTS OF SEPTIC SHOCK

- ↓peripheral resistance with ↑ cardiac output and tachycardia in early stages
  - May be found in anaphylaxis, pancreatitis, spinal injury
- Later stages --hypovolemic shock with ↑ vascular resistance, ↓cardiac output and cooler peripheral extremities

SEPSIS LEADING CAUSE OF EARLY READMISSIONS IN THE U.S.

- Unplanned 30-day readmissions common in U.S.
- 1 in 4 -- recurrent life-threatening infection
- 12.2% of > 1.1 million 30-day readmissions
- Cost > heart failure (6.7%), heart attack (1.3%), COPD (4.6%), and pneumonia (5%)

	National Readmission Data			Weighted Proportion of Cases in the United States	
	No. of All Index Admissions Readmitted Within 30 Days	Estimated Mean Length of Stay (95% CI), d	Estimated Mean Cost per Readmission (95% CI), $	Percentage of Index Admissions Readmitted Within 30 Days (95% CI)	Percentage of Total Estimated Cost of All Readmissions (95% CI)
Admissions associated with 30 d readmission	1,187,697	6.4 (6.4-6.5)	8,242 (8,225-8,258)	NA	100.0
Sensitivity analyses					
Sepsis	**89,800**	**7.6 (7.6-7.7)**	**10,828 (10,760-10,897)**	**7.3 (7.1-7.5)**	**9.1 (8.8-9.4)**
Acute Myocardial Infarction (AMI)	21,281	6.0 (5.9-6.1)	9,530 (9,408-9,654)	1.8 (1.7-1.8)	2.0 (1.9-2.1)
Heart Failure (HF)	236,636	6.5 (6.5-6.5)	9,248 (9,211-9,285)	20.0 (19.6-20.4)	22.1 (21.6-22.6)
Pneumonia	130,904	6.9 (6.9-7.0)	9,749 (9,700-9,797)	11.1 (10.9-11.4)	12.5 (12.2-12.8)
Chronic Obstructive Pulmonary Disease (COPD)	201,867	6.3 (6.3-6.4)	8,677 (8,641-8,713)	17.4 (17-17.7)	17.2 (16.7-17.7)

Mayer FB, Talisa VB, Balakumar V, et al. J Am Med Assoc. 2017. Epub ahead of print

CHARACTERISTICS

- 46% discharged from urban teaching hospital
- >30% from lower-income bracket
- 63% white (74.4% in the 2010 US census)
- 67.53 years (54.3-79.5)
- 65% Medicare

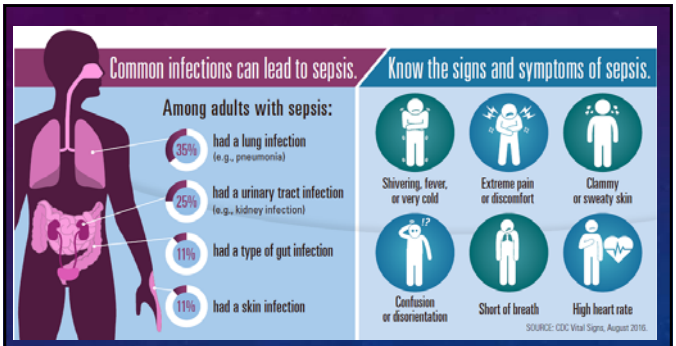
ELEVATED RISK FOR POST DISCHARGE MORBIDITY/MORTALITY

- Multiple comorbidities, organ system failures, surgical needs
- 25,443,292 admissions with complete information--most common comorbidities
  - hypertension (54.2%)
  - renal disorders (65.3%)
  - diabetes (32.4%)
  - pulmonary disease (27.4%)
  - neurologic disorders (19.2%)

S. Elfeky et al. / Journal of Critical Care 39 (2017) 48–55

SURVIVORS

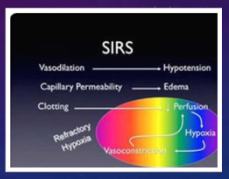
- Long-term physical, psychological, and cognitive disabilities
- ½ as likely discharged home
- 2 X more likely--short-term acute care hospital
- 3 X more likely--skilled outpatient facility



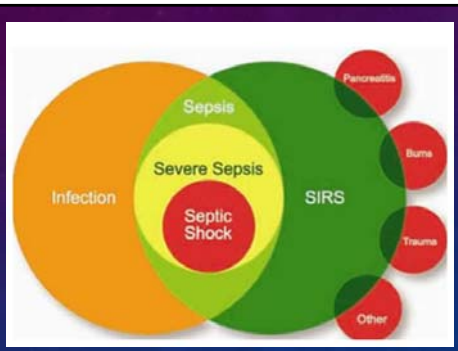
SYMPTOMS: PROGNOSIS

- Abnormal mental status
- Capillary refill time
- Skin mottling
- Temperature variation
- Prognostic for severe organ dysfunction

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS)



- Basis of sepsis
- A continuum
- Deadly
- Resuscitate while diagnosing
- May be met by many conditions
- Anaphylaxis, gastrointestinal emergency, pulmonary disease, metabolic abnormality, toxin ingestion/withdrawal, vasculitis, and spinal injury



SIRS

- Diagnostic if 2 of 4 SIRS criteria are met

Systemic Inflammatory Response Syndrome (SIRS)		
Criteria	**Metric**	**Comment**
Temperature	> 100.4° F (> 38.0°C) or < 96.8°F (< 36.0°C)	Either hyperthermia or hypothermia is a SIRS criteria
Heart rate	> 90 beats per minute	Only tachycardia
Respiratory rate	> 20 breaths per minute	If the patient is mechanically ventilated, $PaCO_2$ < 32 mmHg
White blood count	> 12,000/mm^3 or < 4,000/mm^3 or > 10% immature forms	Any one of these parameters is sufficient for this category


The Third International Consensus Definitions for Sepsis ar
Septic Shock (Sepsis-3)

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Assessment of Clinical Criteria for Sepsis

For t International Consensus Definitions for Sepsis and

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Sep Developing a New Definition and Assessing New Clinical Criteria for Septic Shock

For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

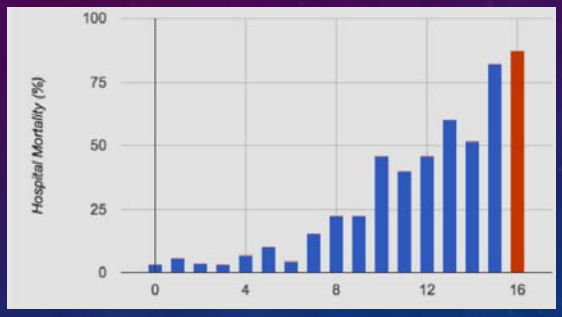
SEQUENTIAL ORGAN FAILURE ASSESSMENT (SOFA)

- Daily assigns 1-4 points to 6 organ systems
- Level of dysfunction
- Score of 2 points or more associated with in-hospital mortality >10%

SOFA SCORE

SOFA score	1	2	3	4
Respiration PaO_2/FiO_2 mm Hg	< 400	< 300	< 200 with respiratory support	< 100 with respiratory support
Coagulation Platelets x $10^3/mm^3$	< 150	< 100	< 50	< 20
Liver Bilirubin, mg/dL (μmol/L)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	> 12.0 (> 204)
Cardiovascular Hypotension[a]	MAP < 70 mm Hg	Dopamine ≤ 5 or Dobutamine (any dose)	Dopamine < 5 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1	Dopamine > 1.5 or epinephrine > 0.1 or norepinephrine > 0.1
Central Nervous System Glasgow coma score	13–14	10–12	6–9	< 6
Renal Creatinine, mg/dL (μmol/L) or urine output	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440) or < 500 mL/day	> 5.0 (> 440) or < 200 mL/day

[a] adrenergic agents administered for at least one hour (doses given are in μg/kg · min)



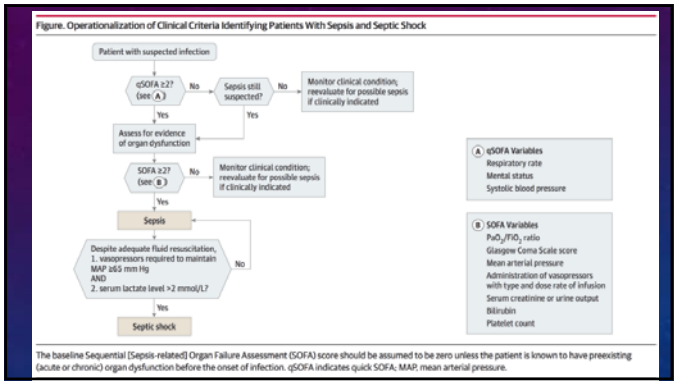
90% Mortality Rate

QUICK SEQUENTIAL ORGAN FAILURE ASSESSMENT (qSOFA) SCORE

- Third International Consensus Definitions Task Force
- Altered mental status, fast respiratory rate, low blood pressure
- No blood tests
- 2 of 3 criteria considered likely to be septic
- Score of 2 points or more associated with in-hospital mortality >10%

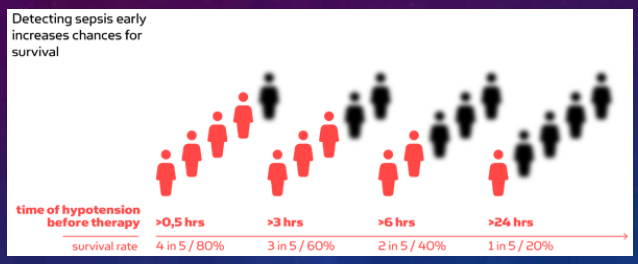
q SOFA SCORE

- 3 parameters:
- Systolic blood pressure of 100 mm Hg or less (1 point)
- Glasgow Coma Scale score of less than 15 (1 point)
- Respiratory rate of 22/min or more (1 point)
- Correlated well with patients outside of ICU



CHALLENGE OF DIAGNOSIS

- Sepsis and SIRS closely mimic each other
- Sepsis = SIRS + infection
  - Microbial verification of pathogen requires time
  - 40% of sepsis patients culture-negative
- Culture-negative sepsis vs. noninfectious SIRS ?



184,875 PATIENTS FROM 182 ICUS IN ANZ

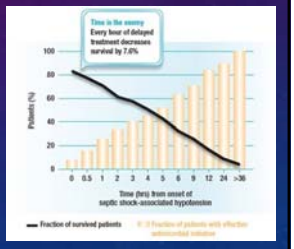
Scoring System	In-Hospital Mortality	Composite of In-Hospital Mortality and Length of ICU Stay
SOFA	0.753	0.736
qSOFA	0.607	0.606
SIRS	0.607	0.609

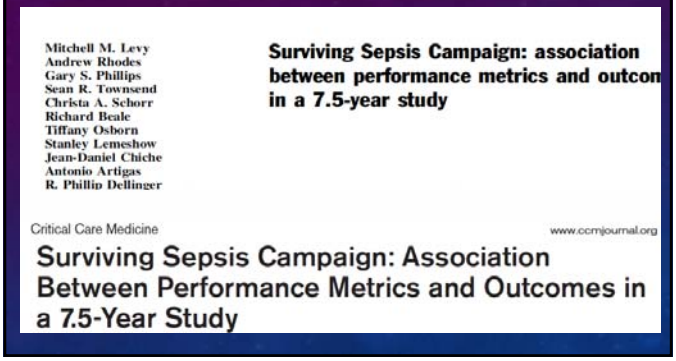
"These findings suggest that SIRS criteria and qSOFA may have limited utility for predicting mortality in an ICU setting," Dr Raith and his colleagues explain

JAMA (2017;317:290-300)

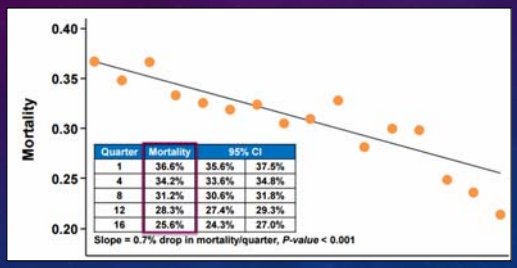
SURVIVING SEPSIS CAMPAIGN: REDUCING SEPSIS MORTALITY

- Collaboration with IHI
- Facilitate adoption of guidelines
- Develop "change bundles"
- Hospitals advised to develop sepsis performance improvement programs





SSC MORTALITY: PARTICIPATION EFFECT



Quarter	Mortality	95% CI	
1	36.6%	35.6%	37.5%
4	34.2%	33.6%	34.8%
8	31.2%	30.6%	31.8%
12	28.3%	27.4%	29.3%
16	25.6%	24.3%	27.0%

Levy MM, Rhodes A, Phillips GS, et al. Crit Care Med. 2015;43:3-12.

TO BE COMPLETED WITHIN 3 HOURS OF TIME OF PRESENTATION

1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30ml/kg cystalloid for hypotension or lactate ≥ 4mmo/L

TO BE COMPLETED WITHIN 6 HOURS OF TIME OF PRESENTATION:

5. Apply vasopressors to maintain a mean arterial pressure ≥ 65 mmHg
6. In persistent hypotension (MAP < 65 mmHg) or initial lactate was ≥ 4 mmol/L, re-assess volume status and tissue perfusion
7. Re-measure lactate if initial lactate elevated

MANAGING INFECTION

- Antibiotics: broad-spectrum IV antimicrobials for all likely pathogens within 1 hour after sepsis recognition (strong recommendation; moderate quality of evidence [QOE])
- Source control: Obtain anatomic source control as rapidly as is practical (best practice statement [BPS])
- Antibiotic stewardship: Assess patients daily for de-escalation of antimicrobials; narrow therapy based on cultures and/or clinical improvement (BPS)

RED BLOOD CELL TRANSFUSIONS

- Typically reserved hemoglobin level ≤7 g/dL
- Exceptions--suspicion of concurrent hemorrhagic shock or active myocardial ischemia
- Multicenter RTC of 998 patients with septic shock—no difference in 28 day mortality between patients who were transfused when the hemoglobin was ≤7 g/dL (restrictive strategy) and patients who were transfused when the hemoglobin was ≤9 g/dL (liberal strategy)
- Restrictive strategy = 50 % fewer transfusions without adverse effect on rate of ischemic events

SEPSIS IMPROVEMENT PROCESSES

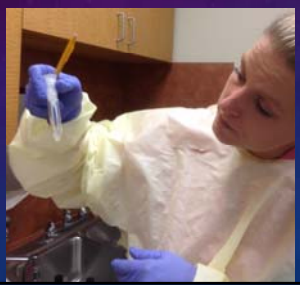
- Universal response and treatment algorithm
- Septic Alert Response System to coordinate initial management
- Defined Responsibilities by role
- One RTC of 1341, 1600 (ARISE), 2160 (ProMISe) = no mortality difference

BUNDLE COMPLIANCE VS. ALL OBSERVED MORTALITY

VITAMIN C?

- Reported to reduce deaths
- Given with steroids
- Not proven with RCTs
- NIH grant to study with blinded RCT

ROLE OF THE LABORATORY IN IMPROVING SEPSIS CARE



CHARACTERISTIC OF AN IDEAL BIOMARKER

- Specific to the tissue or condition of interest
- Released before or during the disease: Early detection useful in predicting mortality and helpful monitoring therapy
- Released in reasonable quantities: highly sensitive to detect in early phase
- Can be detected in blood
- Technically easy to perform, rapid TAT (<60 minutes), quantitative, cost effective

LOW SPECIFICITY

- Most current laboratory biomarkers also elevated in other inflammatory conditions (SIRS)
- Majority performed only when clinician already suspects
- At this point, sepsis protocol, including broad spectrum antibiotics, will be implemented anyway,
- Further improvements in patient outcomes unlikely
- Cost constraints prevent the widespread utilization prior to clinical suspicion

CURRENTLY PROPOSED BIOMARKERS

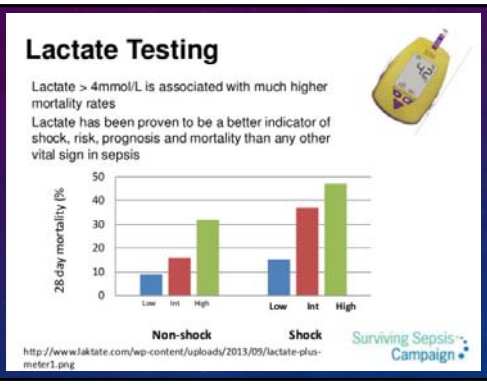
- FDA-approved: procalcitonin
- Non-specific for sepsis:
  - Lactate
  - C-reactive protein
  - D-dimer
  - Proadrenomedullin
  - Myocardial biomarkers
  - Neutrophil antigen expression
  - Microbial detection using molecular techniques

LAB STUDIES NOT SPECIFIC

- ↑ WBC with left shift—any physiological stress
- Fibrin split products, fibrinogen, and a coagulation panel
- Leukopenia and thrombocytopenia
- CRP ↑ any inflammatory state
- Lactic acid
- Procalcitonin promising but takes time

LACTATE

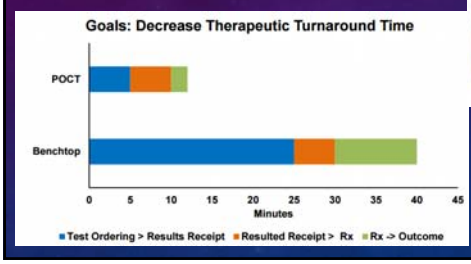
- Marker for organ failure
- Product of cell metabolism that can accumulate in hypoxia
- Strongly associated with poor outcome and high mortality
- Serial measures useful monitoring treatment
- Monitoring clearance predicts morbidity and mortality
- May be ordered with arterial blood gases
- Lactate above 8 mM/L for 2 hr = 90% mortality



INTERPRETATION OF LACTATE

Physiologic state	Serum lactate level
Normal	0.5 – 1 mmol/L
Stressed, but no tissue hypoxia	< 2 mmol/L
Lactic acidosis	> 4 mmol/L

POINT-OF-CARE TESTING (POCT)



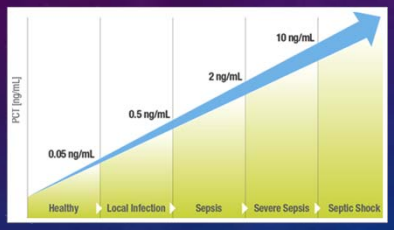
LACTATE LIMITATIONS

- Increase indicates sepsis, heart attack, severe congested heart failure, kidney failure, uncontrolled diabetes, and trauma
- Detects decreased oxygen or blood flow
  - Pulmonary edema
  - Anemia
- Reveals need for excess oxygen
  - Liver disease
  - AIDS
  - Leukemia

PROCALICITONIN (PCT)

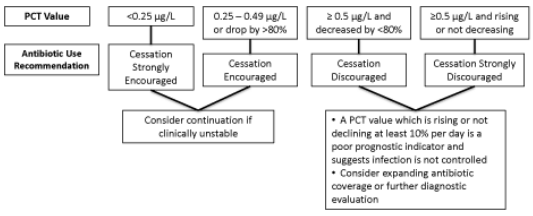
- Elevated in invasive bacterial infection
- Produced by many tissues, not just cells at local infection site
- Best in 1st day of symptoms
- Antimicrobial de-escalation
- Limitations:
  - Not specific to infection
  - Not useful in diagnosis or prognosis with single cutoff

PCT INTERPRETATION



- **Less than 0.5 ng/mL** — Low risk for progression to severe sepsis and/or septic shock
- **Between 0.5 and 2 ng/mL** — Sepsis should be considered
- **Greater than 2 ng/mL** — High risk for progression to severe sepsis and/or septic shock

Sepsis Follow PCT Antibiotic Use Algorithm



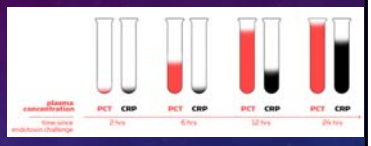
PROCALCITONIN RISKS

- False positive results--unnecessary treatment with antibiotics
- False negative results--may delay selection of therapy
- "Healthcare providers should not rely solely on PCT test results" FDA

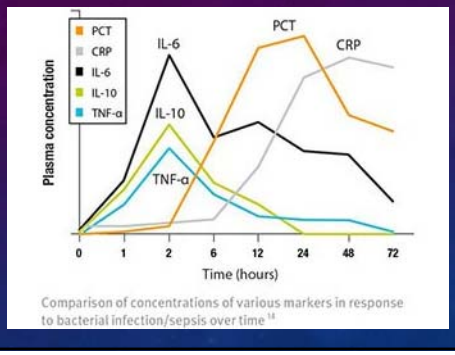
OTHER USES OF PROCALCITONIN

- Distinguish between viral and bacterial meningitis
- Detect/rule out bacterial pneumonia
- Determine if tissue damage due to trauma or surgery or viral illness also has secondary bacterial infection
- Monitor effectiveness of antimicrobial treatment

C-REACTIVE PROTEIN (CRP)



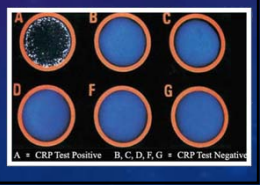
- Acute phase reactant
- Not specific
- Mediocre marker for sepsis diagnosis and prognosis
- Serial measurements confirm adequacy of antimicrobial therapy
- Detects fungal infection and PID



Comparison of concentrations of various markers in response to bacterial infection/sepsis over time[14]

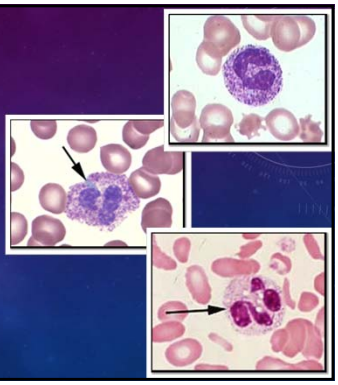
C-REACTIVE PROTEIN

- Monitors flare-ups in autoimmune disease
  - Lupus
  - Vasculitis
  - Inflammatory bowel disease
  - Arthritis
- May indicate further testing needed



CBC AND DIFF

- Lack sensitivity and specificity
- WBCs, ANC and IG
- Toxic granulation
- Dohle bodies
- Cytoplasmic vacuolization



BLOOD CULTURES

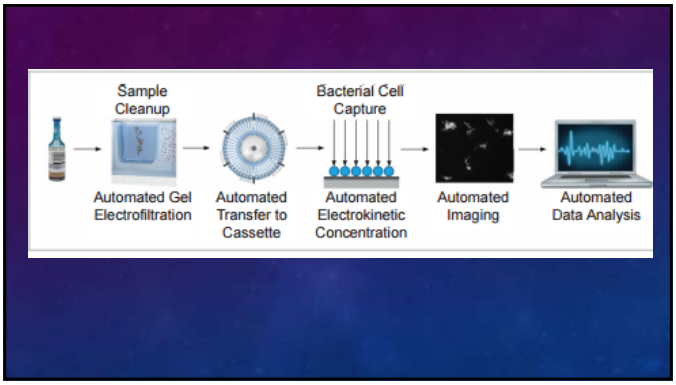
- ~ 40% culture negative
- *Staphylococcus aureus, Escherichia coli (E. coli)*, and some types of *Streptococcus*

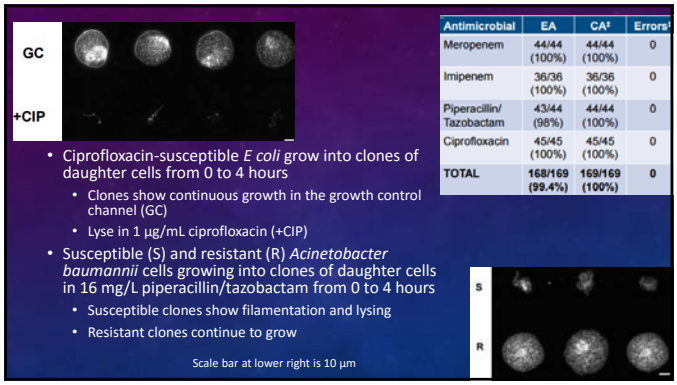
WHEN TO DRAW BLOOD CULTURES

- Major criteria
  - Suspicion of endocarditis
  - Temperature >39.4°C (102.9°F) & chills
  - Indwelling catheter
- Minor criteria
  - Temperature 38.3°C–39.3°C (100.9–102.7°F)
  - Age ≥65 years
  - Chills, vomiting
  - Systolic BP ≤ 90 mm Hg
  - WBC ≥ 18,000/µL
  - Creatinine ≥ 2 mg/dL

PHENOTEST BC KIT

- Can identify 14 different species of bacteria or two species of yeast
- From a positive blood culture in about 1.5 hrs
- 6.5 hours delivers antibiotic susceptibility
- Detects 2 indicators of antibiotic resistance
- 95% of the time
- Can have false positives





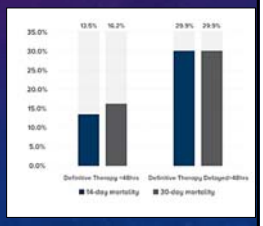
- Ciprofloxacin-susceptible *E coli* grow into clones of daughter cells from 0 to 4 hours
  - Clones show continuous growth in the growth control channel (GC)
  - Lyse in 1 µg/mL ciprofloxacin (+CIP)
- Susceptible (S) and resistant (R) *Acinetobacter baumannii* cells growing into clones of daughter cells in 16 mg/L piperacillin/tazobactam from 0 to 4 hours
  - Susceptible clones show filamentation and lysing
  - Resistant clones continue to grow

Scale bar at lower right is 10 µm

Antimicrobial	EA	CA[2]	Errors[1]
Meropenem	44/44 (100%)	44/44 (100%)	0
Imipenem	36/36 (100%)	36/36 (100%)	0
Piperacillin/ Tazobactam	43/44 (98%)	44/44 (100%)	0
Ciprofloxacin	45/45 (100%)	45/45 (100%)	0
TOTAL	**168/169 (99.4%)**	**169/169 (100%)**	**0**

IMPACT OF TIME TO DEFINITIVE THERAPY ON MORTALITY

- Empiric therapy inadequate in up to 25% of patients with bloodstream infections (BSIs)
- Shortening the time from empiric to optimal therapy requires susceptibility results with the MIC for 52% of patients with BSIs



FUNGAL TESTS

- Invasive candida or aspergillus = circulating antigens, metabolites
- Beta-D-glucan in the cell wall of many fungi
  - Not specific for candida but useful adjunct to BCs; 50% sensitive, 99% specific
  - 78-81% of 107 with proven candidiasis had positive results
- Galactomannan antigen = *Aspergillus* cell walls and others
  - EIA on serum
  - Metaanalysis 4000 patients 71% sensitive, 89% specific—hematological malignancies
- T2Candida FDA approved NAAT
- Anti-mannan antibodies

MULTIMARKER APPROACH

- PASS Study: PCT, when used as a single marker, failed to provide useful information
- Best panel of biomarkers for diagnosis of sepsis or prediction of developing septic shock is likely to include both pro-inflammatory and anti-inflammatory markers

Biomarker	Sepsis Diagnosis or Prognosis (AUC)[1-3]	Effective Biomarker Guided Treatment
Lactate	0.82	Yes – CMS, SSC, Sepsis-3
C-reactive protein (CRP)	0.73	-
Procalcitonin (PCT)	0.71–0.89	No – Multicenter trial[4]
Interleukin 6 (IL-6)	0.51–0.86	-
Soluble urokinase plasminogen activator receptor (suPAR)	0.62–0.79	-
Pro-adrenomedullin	0.72	-
Presepsin	0.74–0.82	-
Soluble triggering receptor expressed on myeloid cells (sTREM)	0.87	-

1. Khater WS, Salah-Eldeen NN, Khater MS, et al. Eur J Microbiol Immunol. 2016 ;6(3):78–85.
2. 2. Yang Y, Xie J, Guo F, et al. Ann Intensive Care. 2016;6:51.
3. 3. Fan SL, Miller NS, Lee D, et al. Clin Chim Acta. 2016;460:203-10.
4. 4. Bloos F, Trips E, Nierhaus A, et al. JAMA Intern Med. 2016; 76(9):1266-76.

CONCLUSION

- Time is tissue
- Education is vital
- POCT can be utilized to improve TAT
- POCT can improve compliance
- Education + POCT can reduce sepsis mortality

PREVENTION

- Vaccination programs
- Prevent infections
  - Clean scrapes and wounds
  - Wash hands
- Chronic disease management
- Appropriate use of antibiotics
- CDC developing tracking systems to measure impact of successful interventions

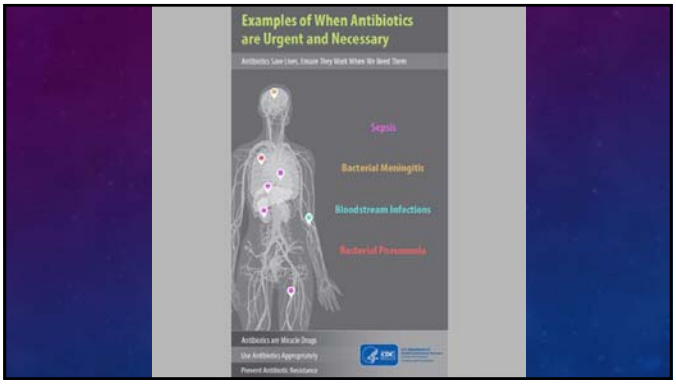
ANTIMICROBIAL STEWARDSHIP

STUDIES HAVE SHOWN THAT PHYSICIANS IN HOSPITALS OFTEN PRESCRIBE UNNECESSARY ANTIMICROBIALS, THEREBY RAISING THE RISK FOR NOSOCOMIAL INFECTIONS FROM ANTIBIOTIC-RESISTANT BACTERIA.

ANTIMICROBIAL STEWARDSHIP

- 2 million infected resistant bugs
- 23,000 deaths estimated by CDC
- Most important strategy
- Optimize treatment
- 50% of antimicrobial use inappropriate
- Reduce adverse events

Pathogen and Antibiotic Exposure	Increased Risk
Carbapenem Resistant Enterobactericeae and Carbapenems	15 fold 1
ESBL producing organisms and Cephalosoprins	6- 29 fold 3,4



INAPPROPRIATE USE

- Given when they are not needed
- Continued when they are no longer necessary
- Given at the wrong dose
- Broad spectrum agents are used to treat very susceptible bacteria
- The wrong antibiotic is given to treat an infection

C DIFF

- Antibiotic exposure single most important risk factor for the development of *Clostridium difficile* associated disease
  - Up to 85% of patients with CDAD have antibiotic exposure in the 28 days before infection
- Hospital-acquired, hospital-onset: 165,000 cases, $1.3 billion in excess costs, and 9,000 deaths annually
- Hospital-acquired, post-discharge (up to 4 weeks): 50,000 cases, $0.3 billion in excess costs, and 3,000 deaths annually
- Nursing home-onset: 263,000 cases, $2.2 billion in excess costs, and 16,500 deaths annually

CORE ELEMENTS

- Leadership commitment
- Accountability
- Drug expertise
- Action
- Tracking
- Reporting
- Education

ANTIMICROBIAL STEWARDSHIP

- ↓ antimicrobial resistance and in-hospital infections
- Prescribers –involved in understanding consequences
- Resistance—consequence of selective pressures
- Reducing pressures by judicious administration
- Facilitate return of susceptible bacteria
- Prevent or slow pace of emergence of resistant strains

CDC RECOMMENDATIONS

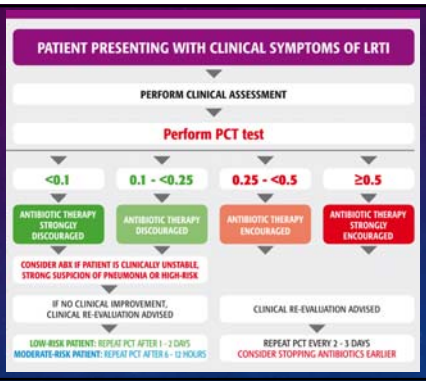
- Evidence-based diagnostic criteria and treatment recommendations
- Delay prescribing or watchful waiting
- Provide communications skills training for clinicians
  - When antibiotics are and are not needed
  - Potential harms of antibiotic treatment
- Require explicit written justification in medical record for nonrecommended prescribing
- Provide support for clinical decisions
- Use call centers, nurse hotlines, or pharmacist consultations to prevent unnecessary visits

RESTRICTIVE INTERVENTIONS

- Selective reporting of laboratory susceptibilities
- Formulary restriction
- Requiring expert authorization for therapeutic substitution
- Automatic stop orders

ENABLING MEASURES

- Improving the quality of prescribing
- Advice and feedback to help physicians make more targeted prescribing decisions
- ↑ appropriate decision making
- Only patients likely to benefit receive them
- Alter physician behavior



COCHRANE REVIEW CONCLUDES IT WORKS

- "High-certainty evidence" interventions effective in safely reducing unnecessary antibiotic use in hospitalized
- Studies published up to January 2015 comparing antimicrobial stewardship interventions with standard practice in hospitalized patients receiving acute care including elective surgery
- Outcomes: effectiveness on antibiotic prescribing and patient safety
- 221 studies (58 randomized controlled trials [RCTs]; 163 non-RCTs)

RESULTS

- More patients were treated according to prescribing policies based on 29 RCTs (n=23,394; high certainty evidence)
- Interventions decreased antibiotic duration by 1.95 days --high-certainty evidence
- Moderate-certainty evidence that intervention: probably decreased length of hospital stay by 1.12 days
- Did not increase mortality (based on 28 RCTs; n=15,827)
- Both enabling and restricting interventions were independently associated with increased antibiotic policy compliance
- More research needed on unintended consequences of restrictive interventions-- 7 studies suggested delays in treatment

CONCLUSIONS OF COCHRANE REVIEW

- Future research
  - Examine factors that impede or expedite the implementation
  - Explore unintended consequences of restrictive interventions
- More studies not warranted to test the overall value of intervention vs placebo with respect to improving prescribing practices
- 2016 national study showed that 39% of US hospitals have antimicrobial stewardship programs
- Proportion varies widely between states
  - 7% in Vermont
  - 58% in California

CUTTING FLUOROQUINOLONE USE MAY BE KEY TO QUELLING C. DIFF OUTBREAKS

- UK fought *C. diff* by avoiding clindamycin and cephalosporins and minimize use of fluoroquinolone, carbapenem and aminopenicillin
- Along with improved infection prevention and control measures
- Fluoroquinolone use was reduced by 50%, while *C. difficile* infections fell by 80%

Lancet Infect Dis 2017

OUTPATIENT ANTIBIOTIC STEWARDSHIP

- 60% of U.S. antibiotic expenditures received in outpatient settings
- 20% of pediatric visits and 10% of adult visits result in AB prescriptions
- Prevent avoidable adverse events resulting from antibiotics

OUTPATIENT PRESCRIPTIONS 2013

Provider specialty	# antibiotic prescriptions (millions)	Antibiotic prescriptions per provider, rate
Primary Care Physicians	121.7	512
Physician Assistants & Nurse Practitioners	48.4	279
Dentistry	24.5	200
Surgical Specialties	20.3	228
Emergency Medicine	14.3	441
Dermatology	7.9	700
Obstetrics/Gynecology	6.8	182
Other	24.7	119
All Providers	268.6	295

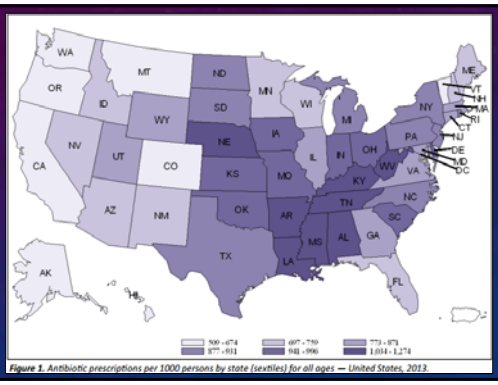
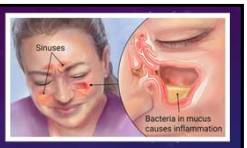


Figure 1. Antibiotic prescriptions per 1000 persons by state (sextiles) for all ages — United States, 2013.

Common Condition: What's got you sick?	Common Cause			Are antibiotics needed?
	Bacteria	Bacteria or Virus	Virus	
Strep throat	✓			Yes
Whooping cough	✓			Yes
Urinary tract infection	✓			Yes
Sinus infection		✓		Maybe
Middle ear infection		✓		Maybe
Bronchitis/chest cold (in otherwise healthy children and adults)*		✓		No
Common cold/runny nose			✓	No
Sore throat (except strep)			✓	No
Flu			✓	No

* In some cases, acute bronchitis is caused by bacteria, but even in these cases antibiotics still do not help.

ACUTE RHINOSINUSITIS



- About 1 out of 8 adults (12%) in 2012 reported receiving a diagnosis of rhinosinusitis in the previous 12 months
- >30 million diagnoses
- 90–98% viral
- Antibiotics not guaranteed to help even if the causative agent is bacterial

ACUTE RHINOSINUSITIS

- Diagnose bacterial rhinosinusitis based on:
  - **Severe (>3-4 days),** such as a fever ≥39°C (102°F) and purulent nasal discharge or facial pain
  - **Persistent (>10 days) without improvement**, such as nasal discharge or daytime cough
  - **Worsening (3-4 days)** such as worsening or new onset fever, daytime cough, or nasal discharge after initial improvement of a viral upper respiratory infections (URI) lasting 5-6 days
- Sinus radiographs not routinely recommended

ACUTE RHINOSINUSITIS

- If bacterial infection is established:
  - Watchful waiting for uncomplicated cases
  - Amoxicillin or amoxicillin/clavulanate is first-line therapy
  - Macrolides such as azithromycin not recommended due to high levels of *Streptococcus pneumoniae* antibiotic resistance (~40%)
  - For penicillin-allergic patients, doxycycline or a respiratory fluoroquinolone (levofloxacin or moxifloxacin)

ACUTE UNCOMPLICATED BRONCHITIS

- Cough most common symptom for adult patients visit their PCP
- Acute bronchitis most common diagnosis in these patients
- Evaluation should focus on ruling out pneumonia
- Colored sputum does not indicate bacterial infection
- For most cases, chest radiography not indicated

ACUTE UNCOMPLICATED BRONCHITIS

- Routine treatment with antibiotics not recommended, regardless of cough duration
  - Cough suppressants (codeine, dextromethorphan)
  - First-generation antihistamines (diphenhydramine)
  - Decongestants (phenylephrine)
  - Beta agonists (albuterol)

COMMON COLD OR NON-SPECIFIC UPPER RESPIRATORY TRACT INFECTION

- 3rd most frequent diagnosis in office visits
- Most adults experience 2-4 colds annually
- At least 200 viral causes
- No antimicrobials
- Symptomatic Tx

UNCOMPLICATED CYSTITIS

- Most common infection in women
- Usually *E.coli*
- Nitrites and leukocyte esterase in urine most accurate
- Nitrofurantoin, trimethoprim/sulfamethoxazole (TMP-SMX, where local resistance is <20%), and fosfomycin appropriate first-line agents

OTITIS MEDIA

- Acute otitis externa: usually treated with antibiotic ear drops
- Effusion: usually goes away on its own and does not benefit from antibiotics
- Acute: no antibiotics in many cases because immune system can fight off infection without antibiotics

CONCLUSION

- Best practices evolving
- Integration of IT
- Diagnostic lab testing
- Optimizing antibiotic use