EMPICRIC ANTIMICROBIAL THERAPY

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Ignaz Philipp Semmelweis, a Hungarian physician, called the “Father of Hand Hygiene”

He made important discovery in 1847.

He proved statistically that the incidence of puerperal fever, also known as childbirth fever could be drastically cut by use of hand washing standards for doctors and nurses in obstetrical clinics.
Learning Objectives:

1. Early Recognition of Sepsis
2. Selection of Appropriate Empiric antimicrobials based on involved Organ System
3. Importance of antimicrobial de-escalation
SEPSIS

Severe sepsis and septic shock are major healthcare problems, affecting millions of people around the world each year, killing one in four (and often more)

In the US, 20% of ICU admissions are related to or complicated by infection

After cardiac disease, sepsis is the second leading cause of death among ICU patients
SEPSIS STEPS

SIRS
- T: >100.4 F
- < 96.8 F
- RR: >20
- HR: >90
- WBC: >12,000
- <4,000
- >10% bands
- PCO2 < 32 mmHg

SEPSIS
2 SIRS

Confirmed or suspected infection

SEVERE SEPSIS
- Sepsis +
- Signs of End Organ Damage
- Hypotension (SBP <90)
- Lactate >4 mmol

SEPTIC SHOCK
Severe Sepsis with persistent:
- Hypotension
- Signs of End Organ Damage
- Lactate >4 mmol

Slide Courtesy Curtis Merritt, DO
The early identification of sepsis and implementation of early evidence based therapies have been documented to improve outcomes and decrease sepsis related mortality.

Reducing the time to diagnosis of severe sepsis is thought to be a critical component of reducing mortality from sepsis-related multiple organ dysfunction.

Similar to polytrauma, acute Myocardial infarction, or stroke, the speed and appropriateness of therapy administered in the initial hours after severe sepsis develops are likely to influence outcome.
SURVIVING SEPSIS CAMPAIGN: INTERNATIONAL GUIDELINES FOR MANAGEMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

Society of Critical Care Medicine and European Society of Intensive Care Medicine.

*Endorsed by IDSA
The Surviving Sepsis Campaign targeted the implementation of a core set ("bundle") of recommendations in hospital environments where change in behavior and clinical impact were measured.

Initial guidelines were in 2004 then updated in 2008, 2012 and more recently 2015.

Application of the SSC sepsis bundles led to sustained, continuous quality improvement in sepsis care and was associated with reduced mortality.
SURVIVING SEPSIS CAMPAIGN BUNDLES (2015)

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 crystalloid for hypotension or lactate ≥4mmol/L

* “Time of presentation” is defined as the time of triage in the emergency department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of severe sepsis or septic shock ascertained through chart review.

TO BE COMPLETED WITHIN 6 HOURS OF TIME OF PRESENTATION:

5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65mmHg
6. In the event of persistent hypotension after initial fluid administration (MAP < 65 mm Hg) or if initial lactate was ≥4 mmol/L, re-assess volume status and tissue perfusion and document findings according to Table 1.
7. Re-measure lactate if initial lactate elevated.
The benefit to society of antibiotics is one of the most important advances in medicine of the 20th century.

Empiric antibiotic therapy: Antibiotics administered without culture documented infection or its susceptibilities.

Selecting appropriate initial antimicrobial therapy improves clinical symptoms more quickly and improves eventual outcome (all cause mortality) compared to inappropriate or delayed antimicrobial therapy.

Unfortunately this has also led to inappropriate overuse of antibiotics thereby creating multi drug resistant bacteria.
Selecting an empiric antimicrobial therapy is typically based on the presumed source of infection, suspected or known organisms, gram stain results and resistance patterns of common pathogens prevalent within the acquisition setting (community acquired vs hospital acquired).
TEN QUESTIONS TO ASK BEFORE SELECTING AN ANTIBIOTIC (REESE AND BETTS)

1. Is an antibiotic indicated?
2. Have appropriate specimen been obtained?
3. What organisms are most likely?
4. What is the best antibiotic for that particular system?
5. Is antibiotic combination indicated?
6. What are the important host factors?
7. What is the best route of administration?
8. What is the appropriate dose?
9. Will initial therapy require modification after culture data?
10. What is the optimal duration of therapy?
FACTORS TO CONSIDER WHEN CHOOSING EMPIRIC ANTIBIOTICS

- Infection Specific Factors
- Host Factors
- Drug Factors
A. **Severity of infection**: – influences the route of administration, dose, number of antibiotics

- **Oral** – for infections that are mild, or for those that are significantly improved after initial IV antibiotic.

- **IV** – used for infections that are serious or life-threatening. They provide high peaks with hopefully greater potential for diffusion into tissue rendered ischemic by the acute process.
INFECTION-SPECIFIC FACTORS

B: **Site Of infection**: - The organ system involved will strongly influence the decision about whether coverage will be directed against Gram positive, gram negative, or anaerobic organisms.

- Also influences the antibiotic and dose, since adequate concentrations of the drug must reach the site of infection for efficacy (e.g meningitis, endocarditis)

C. **Infecting organism**: - Site of acquisition of the infection (community versus hospital, nursing home) will influence the decision to empirically cover for multi drug resistant organisms.
HOST FACTORS

- Patient-specific characteristics should be considered in every patient in whom antimicrobial therapy will be instituted
- Special risks: e.g. immunosuppressed, neutropenic, transplant patients etc
- Renal and hepatic function: will affect dosages and choice of antibiotics.
- Age
- Allergies
- Concomitant drug therapy
- Pregnancy/ lactating
DRUG FACTORS

- The individual characteristics of each antibiotic must be considered when selecting the most appropriate agent:

1. Bacteriostatic – antimicrobial agents that inhibit the growth of susceptible bacteria and rely on host defenses to help kill the bacteria and subsequently eradicate the infection

2. Bactericidal – antimicrobial agents that kill susceptible bacteria in the absence of host defenses

3. In vitro spectrum of activity and current susceptibilities – Always consider antibiogram (local, national or regional)

4. Pharmacokinetics (tissue penetration, route of elimination)

5. Side Effects
CASE #1

25 y/o male with no PMHx presents in December with HA, fever, stiff neck. No seizures, paralysis or change in mental status. CT head is negative. LP is performed. CSF cell count with neutrophilic pleocytosis. Gram stain with no organisms. Working Dx is Acute Bacterial Meningitis.
BACTERIAL MENINGITIS

Factors to Consider:
- Age (<50)
- Medical Hx

Organism:
- Streptococcus Pneumoniae
- N. Meningitidis

Empiric Antibiotics :
- Vancomycin
- 3rd generation cephalosporin
52 y/o male with no PMHx presents in December with HA, fever, stiff neck. No seizures, paralysis or change in mental status CT head is negative. LP is performed. CSF cell count with neutrophilic pleocytosis. Gram stain with no organisms. Working Dx is Acute Bacterial Meningitis.
BACTERIAL MENINGITIS

Factors to Consider:
- Age (>50)
- Medical Hx

Organisms: (In addition to Strep Pneumo and N meningitidis
- Listeria monocytogenes (8% of cases)

Empiric Abx: (In addition to Vanc and 3rd generation cephalosporin)
- ampicillin
45 y/o male with Hx of CSF shunt presents with HA, fever, stiff neck. LP is performed. CSF cell count with neutrophilic pleocytosis. Gram stain with no organisms. Working Dx is Acute Bacterial Meningitis.
BACTERIAL MENINGITIS

Factors to Consider:
- Post neurosurgical procedure

Organisms:
- CoNS (staph epi)
- Aerobic GNR (e.g. pseudomonas)
- Staph areus
- P. Acnes

Empiric Abx:
- Vanc + pseudomonal cephalosporin (Cefepime or ceftazidime)
- Vanc + meropenem
25 y/o female with no PMHx presents in Southern California in June with a 2 day hx of HA, Fever, stiff neck, bizarre behavior, seizure. CT head nml. LP done. CSF cell count with lymphocytic pleocytosis. Working diagnosis is aseptic meningitis/ meningoencephalitis
Factors (besides age)
- Summer month, location (Southern California)
- Neurological symptoms

Organisms (in Addition to the common bacterial organisms):
- Viruses e.g HSV, West Nile, Enteroviruses (e.g coxsackie), HIV etc

In addition to Vanc/ceftriaxone:
- Acyclovir
CASE #2

- 44 y/o lady with HTN, smoker, no recent antibiotic exposure, no recent travel presents from home in November with fever, productive cough, RLL consolidation, leukocytosis. You decide to admit to regular medical floor. Working diagnosis is Community Acquired pneumonia:
COMMUNITY ACQUIRED PNEUMONIA

Factors to Consider:
- Antibiotic use, Setting for the symptoms (home)
- Comorbidities (smoker)
- Always consider season

Organism:
- Strep pneumonia (most common)
- M. pneumoniae, C. pneumoniae, H. influenzae, Legionella species
- Respiratory viruses including Influenza

Empiric abx
- Beta lactams (e.g Ceftriaxone )+ macrolide (e.g azithromycin)
- Respiratory quinolone (e.g levofloxacin, moxifloxacin)
66 y/o with DM admitted 7 days ago with acute cholecystitis. Now with new onset productive cough, fever, new RLL infiltrates. Working Dx is Hospital acquired pneumonia.
HOSPITAL ACQUIRED PNEUMONIA

Factors to consider:
- Days in the hospital (>5 days in this case = late onset HAP)

Organisms:
- Gram negative Bacteria (e.g. Pseudomonas (including MDRO), klebsiella, acenitobacter
- Staph aureus (especially MRSA)
- Legionella, Strep Pneumo

Empiric Abx:
- Antipseudomonal cephalosporin or carbanepem or beta lactam/lactamase inhibitor or an aminoglycoside
+ Antipseudomonal quinolone
+ Linezolid or vanco
CASE #3

- 45 y/o male with no sig PMHx now admitted from home with RLQ pain, fever, normotensive, leukocytosis. CT abd consistent with perforated appendix with peritonitis:
CA-INTRAABDOMINAL INFECTION

Factors to Consider:
- Onset at home
- Severity of illness (severe in our case due to perforation)

Organisms:
- Enteric GNR (e.g. E.coli, klebsiella, enterobacter etc)
- Enteric Gram positive streptococcus (e.g. viridans strep)
- Anaerobes (mainly Bacteroides)

Empiric Abx:
- Ceftriaxone + metronidazole, Pip/tazo, Ertapenem
- Metronidazole + levofloxacin, or ciprofloxacin
***Empiric coverage for enterococcus is not recommended in Community acquired intra-abd infections

***Empiric coverage for candida albicans is not recommended in Community acquired intra-abd infections

***Avoid Amp/sulbactam due to increase of Community acquired E.coli resistance

***Because of increasing resistance of Escherichia coli to fluoroquinolones, local population susceptibility profiles should be reviewed prior to initiation of quinolones for intrabdominal infections.
80 y/o lady with DM, HTN, COPD admitted to the hospital 3 days ago with HCAP and possible UTI. Now with an acute abdomen, fever, leukocytosis. CT abdomen consistent with SBO with perforation. Working diagnosis is Health Care Associated Complicated Intraabdominal infection:
HA- COMPLICATED INTRAABDOMINAL INFECTION

Organisms (in addition to previously mentioned for community):
- Pseudomonas aeruginosa, ESBL-producing Enterobacteriaceae
- Acinetobacter, or other MDR GNB
- MRSA (consider if the patient is known to be colonized)
- Enterococcus

Empiric Abx:
- Carbapenem (with pseudomonal coverage)
- Pip/tazobactam
- Cefepime + Metronidazole
- Add Vancomycin (if MRSA suspected or *enterococcus)
Empiric anti-enterococcal therapy is recommended for patients with health care–associated intra-abdominal infection, particularly those with postoperative infection, those who have previously received cephalosporins or other antimicrobial agents selecting for Enterococcus species, immunocompromised patients, and those with valvular heart disease or prosthetic intravascular materials.
CASE #4

- 80 y/o lady with DM, HTN, COPD now admitted from NH with a deep foot ulcer that has been present for a week. No recent abx. No Hx of MRSA infections. Ulcer with no discharge. There is surrounding erythema. She is febrile, leukocytosis with a left shift. Working diagnosis is an infected Diabetic foot ulcer (Moderate):
Factors to Consider:
- Duration of the ulcer/severity of infection
- DM
- Previous Abx use, MRSA colonization

Organisms:
- Gram positive organisms (streptocccus, MSSA, +- MRSA)
- Enteric GNRs (E.coli, kleb etc)
- +- Obligate anaerobes

Empiric Abx:
- Amp/sulbactam
- Ceftriaxone, cefazolin
- Moxifloxacin, Ertapenem, Levofloxacin
WHEN TO INCLUDE MRSA COVERAGE IN DIABETIC FOOT INFECTIONS

- The patient has a history of previous MRSA infection or colonization within the past year.

- The local prevalence of MRSA is high enough (~30%) that there is a reasonable probability for an MRSA infection.

- The infection is severe enough that delaying coverage of MRSA empirically would pose an unacceptable risk for treatment failure.

- Empiric Abx for MRSA:
  - Daptomycin, Vancomycin
  - Linezolid, Ceftaroline

** Newer drugs : Tedizolid, Dalbavancin, Oritavancin
WHEN TO INCLUDE PSEUDOMONAL COVERAGE IN DIABETIC FT. INFECTION

- Chronic Ulcer with previous abx use
- Warmer climates
- Severe infection/sepsis

- Empiric Abx
  - Pip/Tazo
  - Cefepime
  - Carbapenem with pseudomonal coverage
  - Aztreonam (in pts with severe PCN allergy)
CASE #5

- 40 y/o obese male with HTN presents with slowly progressing redness on the LLE x 5 days, low grade fever, mild leukocytosis. LLE is red, tender and warm. No pus. No bullae. The redness has some delineated borders and appears to be superficial at least on your exam. Working diagnosis is Cellulitis/erysipelas. You decide to admit and start IV abx.
CELLULITIS

- **Organisms:**
  - Streptococcus species

- **Empiric Abx:**
  - Cefazolin
  - Clindamycin
  - Penicillin G
  - Ceftriaxone
MRSA is an unusual cause of ‘typical’ cellulitis. A prospective study of patients with cellulitis in a medical center with a high incidence of other MRSA-related SSTIs demonstrated that treatment with β-lactams, such as cefazolin or oxacillin, was successful in 96% of patients, suggesting that cellulitis due to MRSA is uncommon and treatment for that organism is usually unnecessary.

However, coverage for MRSA may be prudent in cellulitis associated with penetrating trauma, especially from illicit drug use, purulent drainage, or with concurrent evidence of MRSA infection elsewhere.
60 y/o male with DM, presents with new onset LLE redness, pain, fever and chills. Symptoms started this morning where he had a little cut by the ankle and now the redness has spread upwards to below the knee. On exam, the whole lower leg is red, hot and on your exam you think its involving the deeper tissues. Working diagnosis is Necrotizing fasciitis. You call a surgeon and start abx:
NECROTIZING FASCIITIS

Organisms:
- Streptococcus pyogenes
- CA-MRSA
- Polymicrobial – (Mixed Anaerobic (e.g. clostridium)-aerobic organisms)

Empiric Antibiotics:
- Vanc + Zosyn

*Some experts will add clindamycin while awaiting cultures*
40 y/o obese male with HTN presents with slowly progressing redness on the LLE x 5 days, low grade fever, mild leukocytosis. LLE is red, tender and warm. You also notice some multiple small abscesses in the affected leg. Working diagnosis is purulent SSTI:
PURULENT SSTI

- Organisms:
  - Staph aureus (MSSA and MRSA)

Empiric Abx
- Vancomycin, Daptomycin
- Linezolid, Telavancin
- Ceftaroline

*** Newer abx: Tedilozid, dalbavancin, oritavancin
CASE #6

80 y/o lady with HTN, DM, Chronic foley catheter admitted with fever, chills, R flank pain. U/A with LE/Nitrites/ WBC 80/ 3+ bacteria/RBC. No recent antibiotic use. Patient with leukocytosis with a left shift. Working diagnosis is a complicated UTI
Organisms:
- Enterobactericiae (e.g. E.coli, klebsiella)
- Pseudomonas aeruginosa
- Acinetobacter
- Enterococcus
- ??MRSA

Empiric Antibiotics:
- Ciprofloxacin or Levofloxacin (check local antibiogram)
- Cefepime
- Pip/tazobactam
- Carbapenem with pseudomonal coverage
70 y/o male presents from home with fever of 102, hypotension, tachycardia, tachypnea. Has a rash and leukocytosis with a left shift. He gets intubated in the ED before you can take a hx. You have no obvious source infection:

Empiric abx:

- Vanc + pip/tazo or a pseudomonal carbapenem or a pseudomonal cephalosporin + aminoglycoside
Always remember to deescalate once the Organism(s) has been identified.

Ask for help early if not sure
REFERENCES

- Infectious Disease Society of America guidelines
- Reese and Betts: A Practical Approach To Infectious Diseases, fifth edition
- Surviving Sepsis Campaign guidelines