Advances in antibiotics usage in ICU

Introduction

- Intensive care unit (ICU) patients are particularly likely to have or develop infection
- Immunosuppression associated with critical illness and the large number of invasive devices used in these patients.
- Management can be challenging for various reasons including

1. Delayed diagnosis
2. Difficulties
3. Identifying causative microorganisms
4. The high prevalence of antibiotic-resistant strains.

Rello J et al. Adv Ther. 2017; 34(11): 2393–2411

Delay in diagnosis

- The diagnosis of infection in critically ill patients and identification of causative microorganisms and their antibiotic susceptibilities can be a challenge.
- Early appropriate antibiotic therapy is associated with improved outcomes.
- Accurate, rapid diagnosis is important.
- C-reactive protein and procalcitonin are suggested to help diagnosis or to rule out infection.

Rello J et al. Adv Ther. 2017; 34(11): 2393–2411

Preference of combination therapy over monotherapy

- Empirical combination therapy covering common organisms causing community-acquired pneumonia improves survival
- Patients with CAP requiring ICU admission should initially receive a combination of empirical antimicrobial agents covering common causative organisms.

Rello J et al. Adv Ther. 2017; 34(11): 2393–2411

Antibiotic therapy –empiric treatment

- Antibiotics should be administered as an empiric therapy soon as possible once infection is identified.
- There is a debate regarding the potential benefits of combination versus monotherapy in the empiric management of infection in critically ill patients.
- In current guidelines, combination therapy is suggested for:

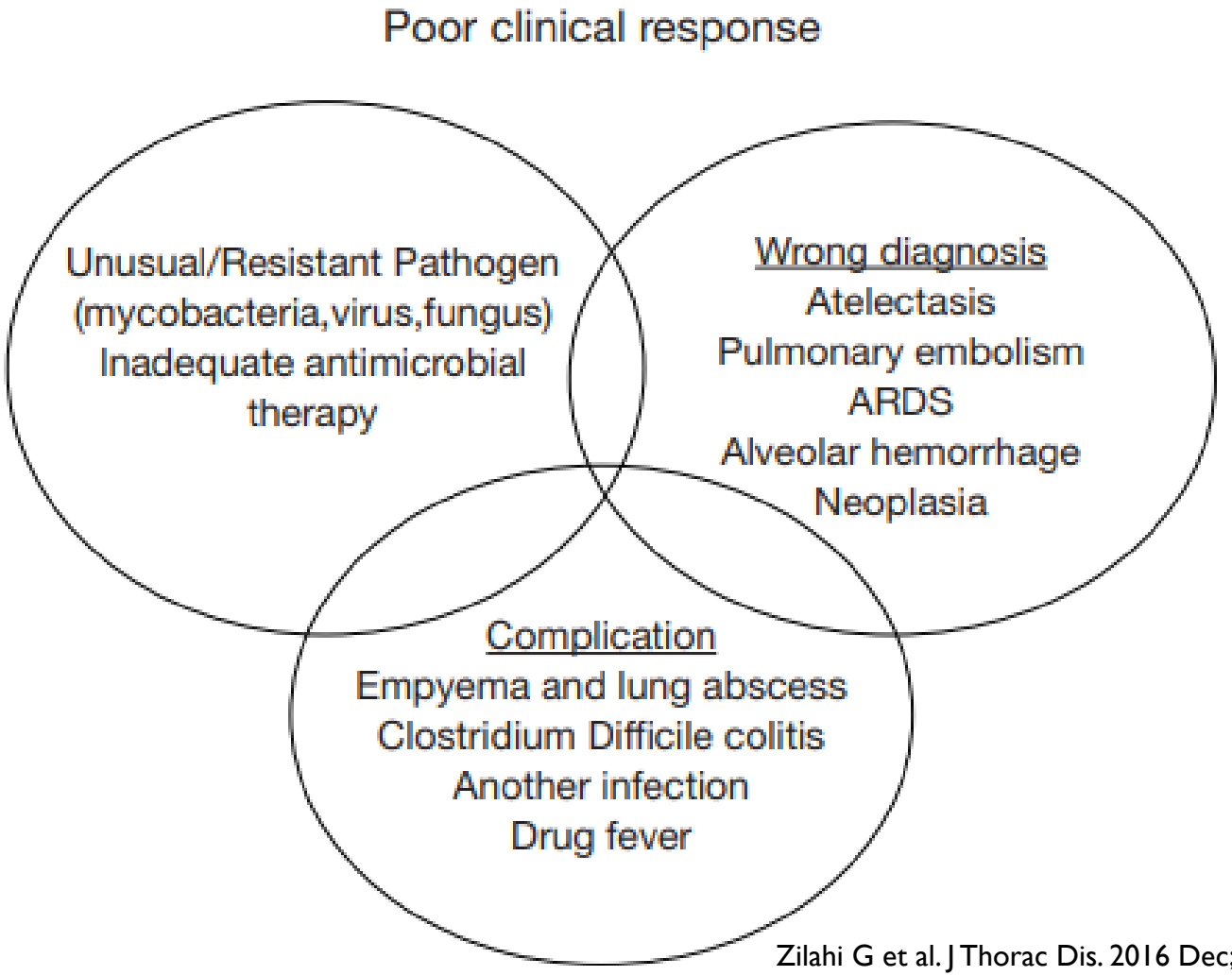
i. neutropenic patients with sepsis

ii. patients with infections caused by MDR pathogens

iii. patients with severe respiratory infections and septic shock

Rello J et al. Adv Ther. 2017; 34(11): 2393–2411

Common situations with poor clinical response to antibiotics



Zilahi G et al. J Thorac Dis. 2016 Dec;8(12):3774-3780

Main threats of antibiotic resistance profile and last treatment resorts

Microorganisms	Threats	Last resort
Enterococcus spp.	XDR (Van^R)	Daptomycin, tigecycline
Staphylococcus aureus	XDR	Gly, Ceft, Caz/Avb, Cft/Taz
Klebsiella pneumoniae	XDR ($C3G^R$, Cbp^R)	Colistin, tigecycline
Acinetobacter baumannii	PDR^R	Colistin, tigecycline
Pseudomonas aeruginosa	PDR^R	Colistin
Enterobacter spp.	XDR	Colistin, tigecycline
Escherichia coli	XDR ($C3G^R$, Cbp^R)	Colistin

XDR, extremely-drug resistant; PDR, pan-drug resistant; C3G, third generation cephalosporins; Cbp, carbapenems; Gly, glycopeptides; Ceft, ceftaroline; Caz/Avb, ceftazidime plus avibactam; Cft/Taz, ceftolozane plus tazobactam.

Pons MJ et al. J Emerg Crit Care Med 2019;3(5): 1-12

“COMMUNITY ACQUIRED PNEUMONIA”

COMMUNITY-ACQUIRED PNEUMONIA

Common causes of community-acquired pneumonia in intensive care unit (ICU)

- Streptococcus Pneumoniae
- Gram-negative Bacilli (Including Klebsiella, Haemophilus Influenzae),
- Atypical Organisms (Mycoplasma Pneumoniae)
- Viruses (Including Influenza)
- Pseudomonas Aeruginosa In Patients With Structural Lung Disease.
- Less Common : Staphylococcus Aureus, Legionella, And Mycobacterium
- Tuberculosis.

Khilnani GC et al. Indian J Crit Care Med. 2019; 23(1):S1-S63

Risk factors for MDR Community-acquired Pneumonia

- Age > 65 years
- Antimicrobial therapy in the pre-ceding 3 months
- High frequency of antibiotic resistance in the community
- Hospitalization for ≥ 48 hours in the preceding 3 months
- Home infusion therapy including antibiotics, home wound care, chronic dialysis within 1 month,
- Family member with MDR pathogen
- Ongoing immunosuppressive treatment.

Antibiotics Initiation in Patients with CAP

- Early initiation of antibiotics has been associated with a reduction in all-cause mortality in community-acquiredpneumonia, including severe pneumonia with sepsis or septic shock
- Appropriate antimicrobial therapy should be initiated as early as possible preferably within the first hour.

Empirical antibiotic therapy in CAP

- Empirical therapy covering common etiologic organisms should be initiated for severe CAP requiring ICU admission
- Investigations including the culture of respiratory secretions (sputum, endotracheal aspirate), blood cultures
- Urinary antigen testing for Pneumococcus and Legionella
- Bronchoscopic BAL or protected specimen brush samples or polymerase chain reaction (PCR) for viral etiology performed for diagnosis on a case by case basis

Recommendations for combination therapy in Community acquired pneumonia

- Patients with CAP requiring ICU admission to initially receive a combination of empirical antimicrobial agents covering common causative organisms.
- For patients with severe CAP a combination of beta-lactams along with macrolides is better as compared to beta-lactam fluoroquinolone combination
- CAP requiring ICU admission, a non-pseudomonal beta-lactam (cefotaxime, ceftriaxone, or amoxicillin-clavulanic acid) plus a macrolide (azithromycin or clarithromycin) to be preferred with no risk factors for Pseudomonas aeruginosa infection

Recommendations for combination therapy in Community acquired pneumonia

- For penicillin-allergic patients, a respiratory fluoroquinolone (levofloxacin, moxifloxacin or ciprofloxacin) and Aztreonam may be used.
- If macrolides cannot be used, a fluoroquinolone may be used if there is no clinical suspicion of tuberculosis, after sending sputum or endotracheal aspirate for AFB and Genexpert

Risk Factors For Infection With Pseudomonas Aeruginosa

- Chronic Pulmonary Disease (Copd, Asthma, Bronchiectasis)
- Frequent Systemic Corticosteroid Use
- Prior Antibiotic Therapy
- Old Age
- Immunocompromised States
- Enteral Tube Feeding
- Cerebrovascular Or Cardiovascular Disease

Empirical therapy

- In P. aeruginosa infection, antipneumococcal, antipseudomonal antibiotic (like Ceftazidime, Cefoperazone, Piperacillin-tazobactam, Cefoperazone–sulbactam, Imipenem, Meropenem or Cefepime) to be used .
- Combination therapy to be considered with the addition of aminoglycosides or antipseudomonal fluoroquinolones (e.g., ciprofloxacin)

MRSA Cover for the Empiric Regimen for CAP in ICU

- **Risk factors for MRSA in cap in icu**
- Close contact with MRSA carrier or patient
- Influenza,
- Prisoners,
- Professional athletes,
- Army recruits,
- Men having sex with men
- Intravenous (iv) drug abusers,
- Regular sauna users
- Recent antibiotic use

Recommendations for MRSA Cover to the Empiric Regimen for CAP in ICU

- If MRSA is a consideration, empiric vancomycin or teicoplanin to be added to the regimen.

- Linezolid to be used for vancomycin intolerant patients, vancomycin-resistant Staphylococcus aureus (VRSA), or patients with renal failure.

Recommendations for Anaerobic Cover be Added to the Empiric Antibiotic Regimen for CAP in ICU

- **Risk factors for aspiration pneumonia in patients admitted with cap in icu**
- Dysphagia
- Altered sensorium
- Coma
- Witnessed aspiration
- Putrid discharge
- The presence of lung abscess, empyema or necrotizing pneumonia

Recommendations for Anaerobic Cover be Added to the Empiric Antibiotic Regimen for CAP in ICU

- **Commonly prescribed empirical antibiotics for cap in icu**
- Ampicillin-sulbactam
- Amoxicillin-clavulanic acid
- Piperacillin-tazobactam
- Carbapenems have excellent anaerobic coverage.
- Clindamycin and moxifloxacin are effective against aspiration and lung abscess caused by anaerobic organisms.
- Lung abscess and necrotizing pneumonia may require prolonged treatment up to 4 to 6 weeks

Optimal Duration of Antibiotics for CAP in ICU

- Patients with CAP requiring ICU admission to receive antibiotics for 7 to 10 days
- Patients with CAP due to Pseudomonas or aspiration pneumonia to be treated for 14 days.
- Necrotizing pneumonia due to Gram Negative Bacilli, MRSA or anaerobes also require treatment for 14 to 21 days
- Duration of treatment to be individualized according to causative organism, response, the severity of disease and complications.
- Procalcitonin levels can be used along with clinical judgment for de-escalation of antibiotics in CAP in ICU in patients treated beyond 5 to 7 days

“Ventilator Associated Pneumonia”

Causes

- Aerobic gram-negative bacilli, such as acinetobacter baumannii, klebsiella pneumoniae, pseudomonas aeruginosa,
- Gram-positive cocci (staphylococcus aureus).
- Gram-negative organisms are the most common etiologic agents (acinetobacter, klebsiella and pseudomonas)

Risk Factors for MDR Pathogens in VAP in ICU

- Age >60 years
- Duration of mechanical ventilation ≥ 7 days
- Prior antibiotic use within 3 months,
- The presence of severe sepsis or septic shock at the time of VAP
- ARDS preceding VAP
- Renal replacement therapy before VAP and systemic corticosteroid therapy.

Empiric Antibiotic Therapy for VAP in ICU

- Piperacillin-tazobactam
- Cefepime
- Levofloxacin
- Imipenem
- Meropenem
- Among antimicrobial agents, carbapenems have a higher chance of clinical cure than non-carbapenems.
- For treatment of VAP due to MRSA, glycopeptides and linezolid have similar clinical success
- Linezolid may be associated with a higher chance of thrombocytopenia and gastrointestinal adverse events

Recommedations for Empiric Antibiotic Therapy for VAP in ICU

- Patients not at high risk of MDR pathogens, with a low prevalence of MRSA (<15%) ,and resistant gram-negative organisms(10%) single antibiotic active against both MSSA and Pseudomonas is preferred over combination antibiotic.
- Patients not at high risk of MDR pathogens with a high prevalence of resistant gram-negative organisms (>15%) but low prevalence of MRSA (
- Patients at high risk of MDR pathogens or are in ICU with a high prevalence of MRSA (> 15%) and resistant gram-negative organisms (> 10%), an agent active against MRSA and at least two agents active against gram-negative organisms including P. aeruginosa is recommended.

Recommedations for Empiric Antibiotic Therapy for VAP in ICU

- Colistin is not recommended for routine use as an empirical agent in VAP. It can be used with high prevalence of carbapenem-resistant Enterobacteriaceae.
- Areas with high endemicity of tuberculosis, use of linezolid may be restricted unless no suitable alternative is available.
- Fluoroquinolones and aminoglyosides to be cautiously used as monotherapy in VAP in our country as well as in other areas with high endemicity of tuberculosis

Antipseudomonal Drugs for VAP in ICU

- **Risk factors**
- Prior use of antibiotics (most consistent association),
- Prolonged duration of mechanical ventilation
- Chronic obstructive pulmonary disease

Recommendations for Antipseudomonal Drugs for VAP in ICU

- Empiric treatment to be given to cover Pseudomonas if there are risk factors for MDR Pseudomonas infection
- In ICUs where gram-negative isolate resistance rate is low (<10 %) and patients have no risk factors for antimicrobial resistance, one antipseudomonal antibiotic may be given
- In ICUs where gram-negative isolate resistance rate is high (> 10 %), two anti-pseudomonal antibiotics from a different class to be given

Duration of Antibiotic Treatment for HAP/VAP recommendations

- Short course (7-8 days) of antibiotic therapy to be used in the case of VAP with good clinical response to therapy
- Longer duration (14 days) of antibiotic therapy to be considered:
- In VAP caused by Nonfermenting Gram-negative bacilli
- Associated with severe immunodeficiency
- Structural lung disease (COPD, bronchiectasis, and interstitial lung disease),
- Empyema
- Lung abscess
- Necrotizing pneumonia
- Inappropriate initial antimicrobial therapy

Anaerobic Cover for VAP

- **Risk factors for VAP**
- Due to anaerobes
- Altered consciousness,
- Aspiration pneumonitis and
- High simplified acute physiology score

Recommendations for Anaerobic Cover for VAP

- Empirical antibiotic regimen for VAP to not include coverage for anaerobic organisms routinely
- In the presence of risk factors for VAP due to anaerobic pathogens, anaerobic antimicrobial coverage to be added in an empirical regimen
- clindamycin or metronidazole to be added to empirical antibiotics regimen for VAP, if it does not include carbapenems (meropenem or imipenem) or piperacillin-tazobactam in the ongoing empirical regimen.

Atypical organisms in VAP

- Risk factors for VAP due to Atypical organisms like Legionella
- Legionella colonization in hospital water supply
- Prolonged use of corticosteroids
- Cytotoxic chemotherapy
- Elderly
- Chronic renal failure
- Previous antibiotic use
- Granulocytopenia
- Poor Glasgow coma score.

Recommendations for Atypical Cover for VAP

- Empirical antibiotic regimen for VAP to not include coverage for atypical organisms routinely.
- In the presence of risk factors for VAP due to atypical bacterial pathogens, atypical antimicrobial coverage to be added to the empirical regimen
- The preferred atypical coverage in combination antibiotics regimen is fluoroquinolones (levofloxacin or moxifloxacin) or macrolides (azithromycin or clarithromycin).
- Serum procalcitonin may be used to guide the de-escalation of antibiotics in VAP when the anticipated duration of therapy is >7 to 8 days

Approach to non responding VAP

- **Factors associated with treatment failure in VAP**
- Host factors (advanced age, immunosuppressed, chronic lung disease, ventilator dependence)
- Bacterial factors (drug-resistant pathogens, opportunistic pathogens)
- Therapeutic factors (inappropriate antibiotics, delayed initiation of therapy, insufficient duration of therapy, suboptimal dosing, inadequate local concentration of drugs)
- Complications of initial VAP episodes (lung abscess, empyema)
- Other non-pulmonary infections or non-infectious mimics of pneumonia.

Approach to non responding VAP

- Re-evaluation at 48 to 72 hours after the initial diagnosis of VAP.
- Evaluation of treatment response for VAP to be on the basis of clinical, laboratory, radiograph and microbiological result.
- Non-responding VAP to be evaluated for

1. noninfectious mimics of pneumonia
2. unsuspected or drug-resistant pathogens,
3. extrapulmonary sites of infection
4. complications of pneumonia or its therapy
5. diagnostic testing to be directed to causes

“CATHETER RELATED BLOODSTREAM INFECTIONS(CRBSI)”

Incidence of catheter related bloodstream infections

- The global incidence of CC ranges from 1.4 to 19.4 % , CRBSI incidence ranges from 2.4 to 12.5 %.
- The incidence of CC is higher in Indian ICUs ranging from 18 % to as high as 59%, whereas the incidence of CRBSI is up to 16.1 per 1000 catheter days.

Risk factors for catheter related bloodstream infections

- Longer indwelling catheter duration
- Immunosuppression
- diabetes mellitus
- sepsis at the time of insertion
- multi-lumen catheters
- APACHE >23.
- APACHE at admission, renal failure, central venous catheterization, and steroid therapy are important risk factors for fungal CRBSI

Organisms Causing CRBSI and their Antibiotic Susceptibility

- Most common

1. Coagulase-negative staphylococci (CONS)
2. S. aureus
3. Enterococcus
4. Candida species

- Staphylococcus aureus and Coagulase Negatibe Staphylococci are methicillin resistant ranging from 11 to 87%.
- increased incidence of CRBSI due to gram-negative organisms (ESBL producers) and candida especially the non-albicans candida.

Empiric Antibiotics for CRBSI

- Empirical antibiotic regimen for CRBSI to include coverage for both gram-positive and gram-negative organisms (2A)
- Vancomycin or teicoplanin is the recommended first line drug for the empiric treatment of CRBSI for MRSA and MR-CONS ,linezolid and daptomycin are good alternative agents
- Empiric coverage for gram-negative bacilli to include a fourth-generation cephalosporin, a carbapenem, or a β-lactam/β-lactamase inhibitor combination, with or without an aminoglycoside
- An echinocandin or fluconazole to be used as empirical antifungal agents for the treatment of suspected central line-associated candidemia.

Recommendations for duration of antibiotic therapy for CRBSI

- Minimum 2 weeks antibiotics to be given for uncomplicated and 4 to 6 weeks for complicated Staphylococcus aureus CRBSI and infective endocarditis
- Minimum 7 days of antibiotics to be given for gram-negative CRBSI
- Five to seven days antibiotics are recommended for CONS bacteremia
- For suspected fungal CRBSI, antifungal therapy for at least 14 days is recommended

“URINARY AND UROGENITAL SEPSIS IN ICU”

URINARY AND UROGENITAL SEPSIS

- The most common organism causing UTI in ICU are gram-negative bacteria (E. coli, Klebsiella) and fungi (especially Candida).
- Risk factors for UTI in ICU include:
- Duration of catheterization
- Length of ICU stay
- Prior antibiotic use
- Higher disease severity score
- Female gender.

Empirical Antimicrobials for Treating UTI in ICU

- Aminoglycosides, beta-lactams along with a beta-lactamase inhibitor as well as carbapenems and fosfomycin have good efficacy in catheter-associated UTI
- The initial choice of antibiotics to cover for ESBL producing gram-negative organisms and includes aminoglycosides, beta-lactam along with a beta-lactamase inhibitor or carbapenems
- In the initial empirical regimen for UTI, antibiotics against gram-positive organisms are not recommended
- In appropriate clinical settings, antifungals to be considered in the empirical regimen

“ACUTE INFECTIVE DIARRHEA, ANTIBIOTIC INDUCED DIARRHEA, AND CLOSTRIDIUM DIFFICILE ASSOCIATED DIARRHEA”

Acute Infective Diarrhea

- The incidence of diarrhea in the ICU ranges from 12.9 to 38%.
- Majority of the cases of diarrhea in ICU are noninfectious in etiology.
- Clostridium difficile is responsible for the majority of infectious cases of diarrhea.
- Empirical use of metronidazole in patients with diarrhea due to Clostridium difficile in ICU setting results in significant symptomatic improvement.

Risk factors for the development of Clostridium difficile infection include

- Prior antibiotic therapy
- advanced age
- Prolonged ICU/hospital stay
- immunosuppression,
- proton pump inhibitors,
- enteral feeding.
- Cephalosporins, clindamycin, fluoroquinolones, carbapenems, and penicillin derivatives are the commonly implicated antibiotics for Clostridium difficile associated Diarrhoea

Recommended Treatment for Clostridium Difficile Infections

- Metronidazole is the first line treatment of mild to moderate Clostridium Difficile Infections
- Oral vancomycin as the first line treatment of microbiologically proven severe CDI and recurrent CDI.
- Addition of vancomycin to a patient with microbiologically proven CDI/CDAD if the patient is already on metronidazole or has no clinical response to metronidazole within 3 to 4 days
- Fecal microbiota transplantation as an alternate treatment of recurrent CDI infection
- Implicated antibiotics to be discontinued as soon as clinically feasible

“ABDOMINAL INFECTIONS IN ICU”

Acute Pancreatitis and Infected Pancreatic Necrosis

- The incidence of pancreatic infection following acute pancreatitis ranges from 12 to 37%.
- Presence of pancreatic necrosis of >50% is a major risk factor for pancreatic infection following acute pancreatitis.
- Primary organ failure predicts the development of infective pancreatic infection in patients with acute pancreatitis.

Acute Pancreatitis and Infected Pancreatic Necrosis

- Gram-negative organisms are the most common organisms isolated from infected pancreatic necrosis following acute pancreatitis in Indian patients.
- Prophylactic antibiotic use has been associated with increased risk of infection with gram-positive organisms.
- Resistance to carbapenems, beta-lactam/beta-lactamase inhibitors and quinolones in gram-negative organisms however sensitivity to colistin and tigecycline is maintained

Empirical Antibiotics of Choice for Treatment of Pancreatic Infection Following Acute Pancreatitis

- Routine use of prophylactic antibiotics to prevent pancreatic infection following acute pancreatitis of any severity is not recommended
- Carbapenems
- Piperacillin -tazobactam
- Cefoperazone - sulbactam (2A).
- In patients not responding to above antibiotics, colistin to be added to the empirical regimen.
- Patients not responding to antibiotics to undergo necrosectomy and drainage

BILIARY SEPSIS

Acute cholangitis

- The incidence of acute cholangitis varies with underlying etiology and ranges from 0.2 to 10%.
- Risk factors:

1. Cholelithiasis
2. Choledocholithiasis
3. benign and malignant common bile duct (CBD) strictures
4. CBD interventions and stenting

Acute cholangitis

- **<u>Risk factors for multidrug drug resistant organisms causing acute cholangitis</u>**

1. An indwelling biliary stent,
2. Malignant biliary obstruction,
3. Previous hospitalization
4. Antibiotic use within 90 days.

Empirical Antibiotic Regimen for Acute Cholangitis

- Empirical antibiotic therapy to be guided by the severity of the cholangitis, susceptibility patterns, biliary penetration of antibiotics and previous antibiotic exposure
- Beta -lactam/beta-lactamase inhibitor (such as cefoperazone-sulbactam or piperacillin/tazobactam)
- carbapenems (imipenem/ meropenem) as monotherapy in patients with moderate to severe cholangitis
- Antibiotic duration for 4–7 days in patients of acute cholangitis after adequate source control
- Biliary drainage to be considered in all patients with cholangitis in addition to empirical antibiotic therapy

LIVER ABSCESS

- Amoebic liver abscess is the most common cause of liver abscess in Indian setup.
- The incidence of pyogenic liver abscess varies from 2.3 to 446 per 100000 hospital admissions per year.
- Gram-negative organisms (E. coli and Klebsiella) are the most common organisms causing a pyogenic liver abscess.

Risk factors for pyogenic liver abscess

- Diabetes mellitus
- Older age
- Male gender
- Biliary diseases
- Biliary procedures
- Alcoholism
- Malignancy
- Intraabdominal infection
- Cystic lesions in the liver.

Empirical Antibiotics for liver Abscess

- Metronidazole is an initial antibiotic of choice in patients with an amoebic liver abscess , antibiotic treatment to be given for 10–14 days
- Needle aspiration of amoebic liver abscess is recommended

a) in patients with lack of clinical improvement in 48 to 72 hours
b) left lobe abscess,
c) abscess more than 5 to 10 cm
d) thin rim of liver tissue around the abscess

Pyogenic liver abscess

- Beta-lactam/Beta-lactamase inhibitors with metronidazole in patients with pyogenic liver abscess for a duration of 2 to 4 weeks
- Carbapenems in case of infection with ESBL producing organisms or melioidosis

“PERITONITIS”

Risk factors for Peritonitis

- Primary Peritonitis:

1. Decompensated cirrhosis
2. Nephrotic syndrome
3. Peritoneal dialysis

- Secondary peritonitis:

1. Intra-abdominal organ perforation
2. Post-intra-abdominal surgery
3. Trauma

Risk factors for Peritonitis

- Tertiary peritonitis

a) Longer ICU stay
b) Emergency surgery on hospital admission
c) Total parenteral nutrition
d) Stomach, duodenum as primary infection site

Empirical Antibiotics for Peritonitis

- Third -generation cephalosporins (such as cefotaxime and ceftriaxone) for 7 to 10 days in patients with primary peritonitis (2A)
- Beta-lactam/Beta-lactamase inhibitor or carbapenems with an anaerobic cover (using metronidazole) for the treatment of secondary peritonitis
- For secondary ndary peritonitis antibiotic treatment is required for 4 days after an adequate source control.

CNS INFECTIONS

Community-acquired Meningitis

- The incidence of community-acquired pyogenic meningitis ranges from 2 to 7.40 per lakh population.
- The common causative organisms include Streptococcus pneumoniae, Neisseria meningitides, Haemophilus influenzae, and Listeria monocytogenes.
- Other causative organisms are Staphylococcus species, gram negative bacilli, Pseudomonas, and Acinetobacter.

Risk factors for Community-acquired Meningitis

- Otitis media
- Elderly population
- Depressed immune status
- Prior use of antibiotics

Empirical Antibiotics for Community-acquired Meningitis

- Third-generation cephalosporin (preferably ceftriaxone) plus vancomycin as empirical antibiotics of choice for community-acquired meningitis
- Ampicillin or amoxicillin if age >50 years
- If beta-lactams are contraindicated,chloramphenicol plus vancomycin as antibiotic of choice, and to add cotrimoxazole, if age >50 years
- Ciprofloxacin or aztreonam plus vancomycin as alternative regimen and to add cotrimoxazole if age greater than 50 years .

Duration of antibiotics treatment for for Community-acquired Meningitis

- 10 to 14 days for Streptococcus pneumoniae
- 14 to 21 days for Streptococcus agalactiae
- 7 days for Neisseria meningitides or Haemophilus influenzae
- 21 days for aerobic gram-negative bacilli
- 21 days or more for Listeria monocytogenes
- If no microorganism is identified, treatment to be given for at least 10 to 14 days

Nosocomial Meningitis - post ventricular drain or catheter meningitis

- The incidence of post ventricular drain or catheter meningitis ranges from 2 to 27%.
- Common organisms are Coagulase negative staphylococcus (especially Staphylococcus epidermidis), Staphylococcus aureus, Acinetobacter, Pseudomonas, and Enterobacteriaceae.
- **Risk factors**

a) repeated catheterization,
b) higher catheter duration,
c) CSF sampling
d) presence of concomitant systemic infection
e) surgical technique i.e., subcutaneously tunneled extraventricular drain (EVD), Rickham reservoir with percutaneous CSF drainage.

Nosocomial Meningitis- post craniotomy or post neurosurgery meningitis

- The incidence is 0.02% to 9.5%.
- Organisms - Staphylococcus aureus, coagulase-negative staphylococci (especially S. epidermidis), Enterobacteriaceae, Acinetobacter and Pseudomonas.
- Risk factors:

a) CSF leak
b) External ventricular **drain**
c) Longer duration of drainage
d) Multiple operations
e) Lack of antibiotic prophylaxis and emergency surgery

Nosocomial Meningitis

- **Post-neuroaxial blockade meningitis :** The incidence is 0.2 per 10000

viridans streptococci and Staphylococcus aureus are common organisms.

Exogenous inoculation is the main risk factor.

- **Post head trauma meningitis :** incidence ranges from 1.39% to 2%

CONS, and Enterobacteriaceae as common microbes

Risk factors: prolonged hospitalization, insertion of the lumbar and ventricular drain.

- **Post internal ventricular drain infection :** incidence ranges from 5.9 to 15.2%.

Causative organisms are CONS, Staphylococcus aureus, gram-negative bacilli, group D streptococci, and Propionibacterium acnes.

Risk factors- CSF leak, single gloves use and a number of times shunt exposed to breached surgical gloves.

Empirical Antibiotics for Nosocomial Meningitis

- Vancomycin plus cefepime or ceftazidime or meropenem as empirical antibiotics of choice for nosocomial meningitis
- Colistin may be given if the incidence of CRE or drugresistant Acinetobacter is high in the specific unit
- If beta-lactams are contraindicated, aztreonam or ciprofloxacin.
- Intraventricular/intrathecal antibiotics to be considered if infection responds poorly to appropriate systemic antibiotics clinically or microbiologically

Brain abscess

- The incidence of brain abscess ranges from 1.3 to 2.6 cases per lakh population.
- Most commonly involved micro organisms include Streptococcus (especially S. viridans), Staphylococcus (especially S. aureus), gram-negative bacilli, anaerobes (Bacteroides, PeptoStreptococcus, Fusobacterium), Pseudomonas and H. influenzae.
- Polymicrobial etiology accounts for 23 to 26% cases.

Risk factors for brain abscess

- Otitis media
- Sinusitis
- Head trauma
- Congenital heart diseases
- Hematogenous spread
- Surgery
- Immunocompromised status
- Pulmonary disease
- Meningitis
- Odontogenic infections

Empirical Antibiotics for Brain Abscess

- 3rd generation cephalosporins plus metronidazole as the empirical antibiotic of choice for brain abscess, adding vancomycin if a high likelihood of MRSA
- Vancomycin plus ciprofloxacin if beta-lactams are contraindicated
- Aztreonam if ciprofloxacin cannot be given or contraindicated.
- Minimum 4 weeks of therapy, duration may be extended according to clinic-radiological response irrespective of aspiration or excision of the abscess

SKIN AND SOFT TISSUE INFECTIONS

- Risk factors:

a) Older age
b) Diabetes mellitus
c) Obesity
d) Malignancy
e) Cirrhosis
f) Longer ICU stay

SKIN AND SOFT TISSUE INFECTIONS

- Gram-positive organisms (Staphylococcus aureus) are the most common organism responsible for the SSTIs.
- E. coli and Pseudomonas are common among gram-negative organisms.
- MRSA and ESBL producing gram-negative organisms are the most common causative agents for SSTIs in ICU.
- Monomicrobial necrotizing fasciitis is commonly caused by Streptococcus pyogenes
- polymicrobial necrotizing fasciitis is caused by mixed coliforms, anaerobes, and staphylococci.

Empirical Antibiotics for SSTI

- For moderate non-purulent SSTI- intravenous penicillin or clindamycin are the first choice of antibiotics
- Severe non-purulent SSTI - a combination of piperacillin-tazobactam along with coverage for MRSA (vancomycin, teicoplanin, daptomycin or linezolid).
- For severe purulent SSTI, incision and drainage followed by empiric antibiotics including piperacillintazobactam, along with MRSA coverage (vancomycin, teicoplanin, daptomycin or linezolid)
- Penicillin plus clindamycin is recommended for monomicrobial necrotizing infection caused by Streptococcus pyogenes or clostridial species.
- For polymicrobial necrotizing fasciitis, a combination of piperacillin-tazobactam, fluoroquinolone, and clindamycin is recommended.

Duration of antibiotic treatment

- Severe nonpurulent SSTIs should be treated with at least 5 days of antibiotics.
- Severe SSTIs with organ dysfunction should be treated with a prolonged course of antibiotics of 2-3 weeks duration.

SEPSIS

Sepsis

- Sepsis is one of the most common causes of morbidity among hospitalized patients in the intensive care unit.
- 2016 Sepsis-3 conference defined sepsis as a "life-threatening organ dysfunction caused by a deregulated host response to infection".
- Septic shock as a "subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality'

Rello J et al. Adv Ther. 2017; 34(11): 2393–2411

Prevalence of sepsis

- The incidence and prevalence of sepsis have increased globally over the last years.
- The Global Burden of Disease described infection as the cause of death of more than 10 million people per year
- Sepsis affects between 3 and 10 per 1,000 people annually in high-income countries.

Genga KR et al. J Innate Immun 2017;9:441–455

Prevalence of sepsis in India

- Sepsis remains the most important cause of multi organ dysfunction syndrome (MODS)
- Over the last decade, sepsis has become more common and deadly to the society.
- Mortality rate of sepsis ranges from 30- 40%.
- Incidence and in-hospital mortality rate of severe sepsis in india - 16.45% and 65% respectively.

Dash L et al. Int J Res Med Sci. 2018;6(6):1927-1933

Clinical Diagnosis of sepsis

- The current recommendation for identifying both sepsis and septic shock is the use of the SOFA score [Sequential (Sepsis-Related) Organ Failure Assessment]
- SOFA score includes-

a) Altered level of consciousness, defined as a Glasgow Coma Scale score ≤ 13.

b) Systolic blood pressure ≤ 100 mmHg.

c) Respiratory rate ≥ 22 rpm.

Rello J et al. Adv Ther. 2017; 34(11): 2393–2411

Sequential Organ Failure Assessment Score for Sepsis

Table Sequential [Sepsis-Related] Organ Failure Assessment Score

System	Score 0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

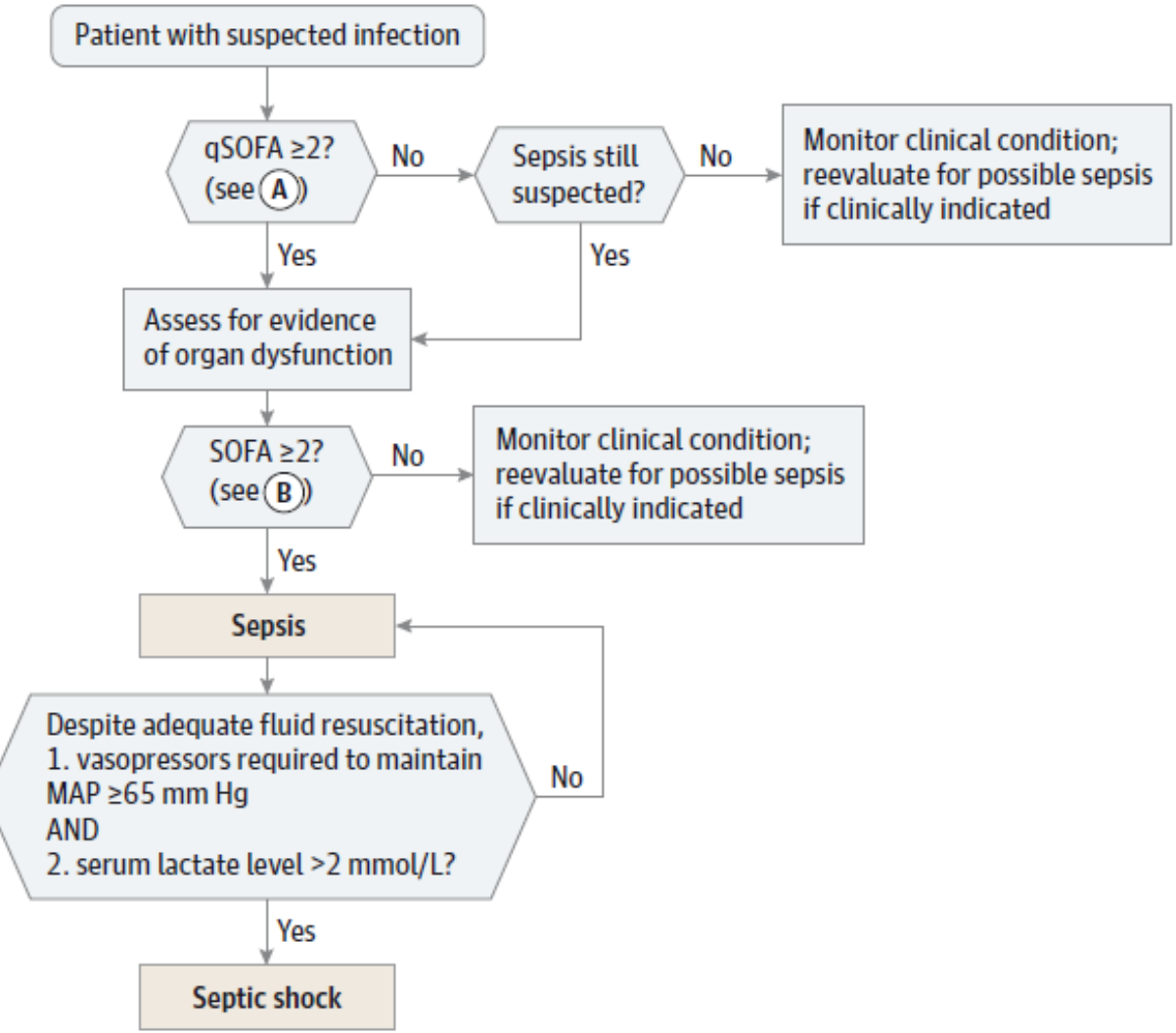
Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

Singer M et al. . JAMA 2016;315:801–810.

Clinical Criteria Identifying Patients With Sepsis and Septic Shock



A qSOFA Variables

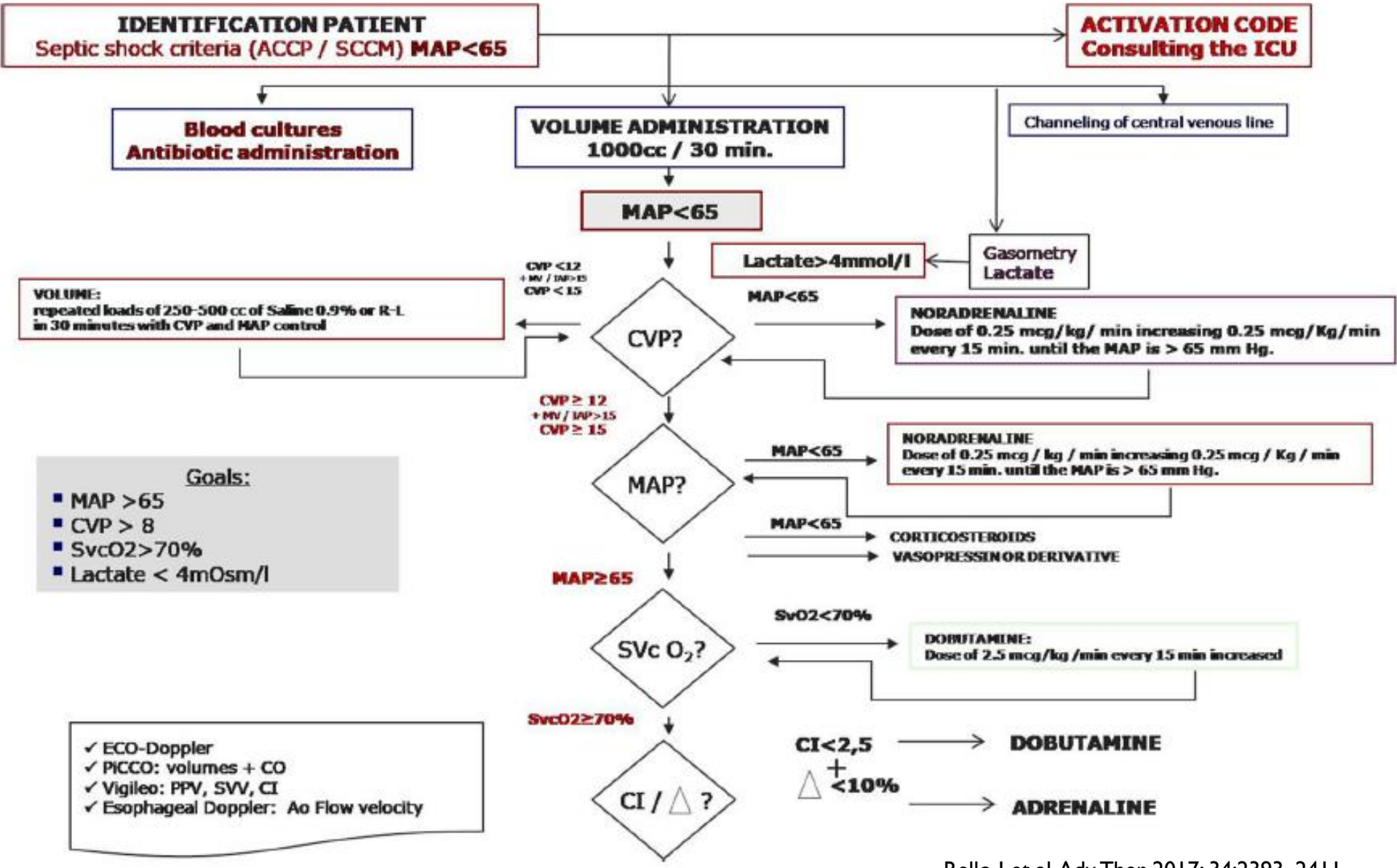
- Respiratory rate
- Mental status
- Systolic blood pressure

B SOFA Variables

- PaO_2/FiO_2 ratio
- Glasgow Coma Scale score
- Mean arterial pressure
- Administration of vasopressors with type and dose rate of infusion
- Serum creatinine or urine output
- Bilirubin
- Platelet count

Singer M et al. JAMA 2016;315:801–810.

Initial treatment of sepsis



Rello J et al. Adv Ther. 2017; 34:2393–2411

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SEPSIS OF UNKNOWN CAUSE

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Empirical Treatment for Sepsis of Unknown Cause

- Combination of ceftriaxone and doxycycline or macrolide for community-acquired sepsis of unknown origin in ICU
- Combination of beta-lactam/beta-lactamase inhibitor and a fluoroquinolone or aminoglycoside for nosocomial sepsis of unknown origin in ICU
- Empiric therapy should provide antimicrobial activity against the most likely pathogens based upon clinical features along with local patterns of infection and resistance.
- Duration of therapy is 7 to 10 days, though longer courses may be appropriate in patients with slow response

Risk Factors for Invasive Fungal Infections

- Surgery
- Total parenteral nutrition
- Renal replacement therapy
- Cardiopulmonary bypass > 120 minutes
- Diabetes mellitus
- Central venous catheters
- Urinary catheters
- Candida colonisation with colonization index > 0.5
- Use of broad-spectrum antibiotics
- Acute renal failure
- Mechanical ventilation > 3 days and APACHE II score >16

Empirical Antifungals in Non-neutropenic Patients

- Routine use of empirical antifungals in non-neutropenic patients in ICU is not recommend
- Empirical antifungals is considered in critically ill patients with a high risk of invasive fungal infections.
- Fluconazole or caspofungin as preferred empirical antifungal agents in non-neutropenic ICU patients at risk for invasive fungal infection
- Caspofungin is preferred in areas with high prevalence of fluconazole resistance
- Micafungin or anidulafungin may be used as alternative agents
- Recommended duration of empirical antifungal therapy is 2 weeks

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Antibiotic Stewardship

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Essential Strategies of Antibiotic Stewardship

- Antibiotic stewardship programs in hospitalized patients are associated with a reduction in a number of antibiotic days, duration of hospital stay.
- Antibiotic stewardship requires a multidisciplinary approach with integration of infectious disease physician, a microbiologist with logistic and financial support from hospital.
- Providing feedback to the treating team improves adherence

Essential Strategies of Antibiotic Stewardship

- Both enablement and restrictive strategies are useful in improving adherence to antibiotic stewardship programs, combination of both the methods and have shown additive effects
- Restrictive strategies give immediate results.
- Enablement practices are more resource intensive.

Role of Antibiotic Cycling

- Studies show significant heterogeneity in terms of site of study, a method of cycling and confounders like simultaneous infection control measures being employed.
- Evidence of benefit of antibiotic cycling is lacking, with few studies demonstrating a reduction in colonization though mortality and length of hospital stay remain unchanged.
- Antibiotic cycling should not be used as a method of antibiotic stewardship program

Intravenous to Oral switch

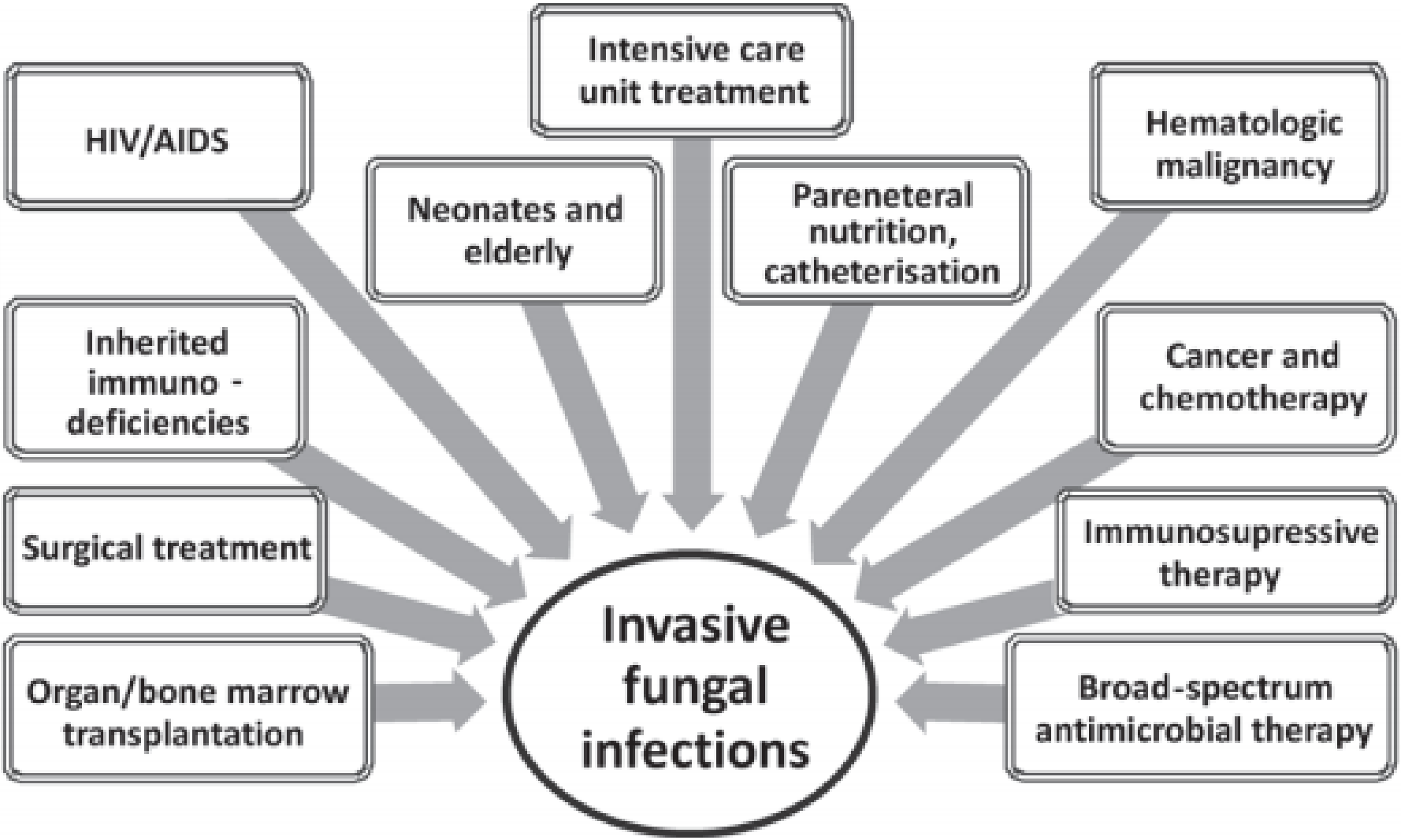
- Early intravenous to the oral transition of antibiotics reduce hospital length of stay and cost of care.
- There is no increase in mortality or other adverse events when this is done after assessing which patients can be safely transitioned to oral therapy.

Antibiotic De-escalation

- Pooled results from observational studies show significant reduction in antibiotic exposure days and ICU length of stay.
- Antibiotic de-escalation algorithm based on serial procalcitonin measurements has been shown to reduce mortality, length of ICU stay, the total duration of antibiotic days and health care costs.

FUNGAL INFECTIONS IN ICU

Risk factors for invasive fungal infections



Kuleta JK et al. Acta Biochim Pol. 2015;62(3):339-51

Rapid Diagnostic Tests for Invasive Fungal Infections

Test	Application	Sensitivity %	Specificity %	Limitations
β-D-glucan	*Candida* spp. and *Aspergillus*	57–97	56–93	False-positive: glucan -contaminated tubes/gauze, cellulose-containing dialysis membranes/filters, contaminated albumin/IVIG with fungal elements, gram-positive infections, gut inflammation, some antibiotics (amoxicillin-clavulanic acid) Controversy surrounding optimal cutoff value
Mannan antigen/ Anti-mannan antibody	*Candida* spp. only	Mannan: 58 Anti-mannan: 59 Combination: 83	Mannan: 93 Anti-mannan: 83 Combination: 86	Positive results occur later in disease course Sensitivity varies depending on species Best results when used together Cutoff value unclear
Nucleic-acid PCR	All species, but only available currently for *Candida* spp.	96	97	Using test too early may decrease sensitivity Unavailable for many organisms
Galactomannan	*Aspergillus* and some other molds	Serum: 71 BAL: 76–88	Serum: 89 BAL: 87–100	False-positive: β-lactams, Plasma-Lyte Not as sensitive in non-neutropenic patients

IVIG = intravenous immunoglobulin; PCR = polymerase chain reaction.

Leon C et al. Intensive Care Med.2014;40(6):808-19.

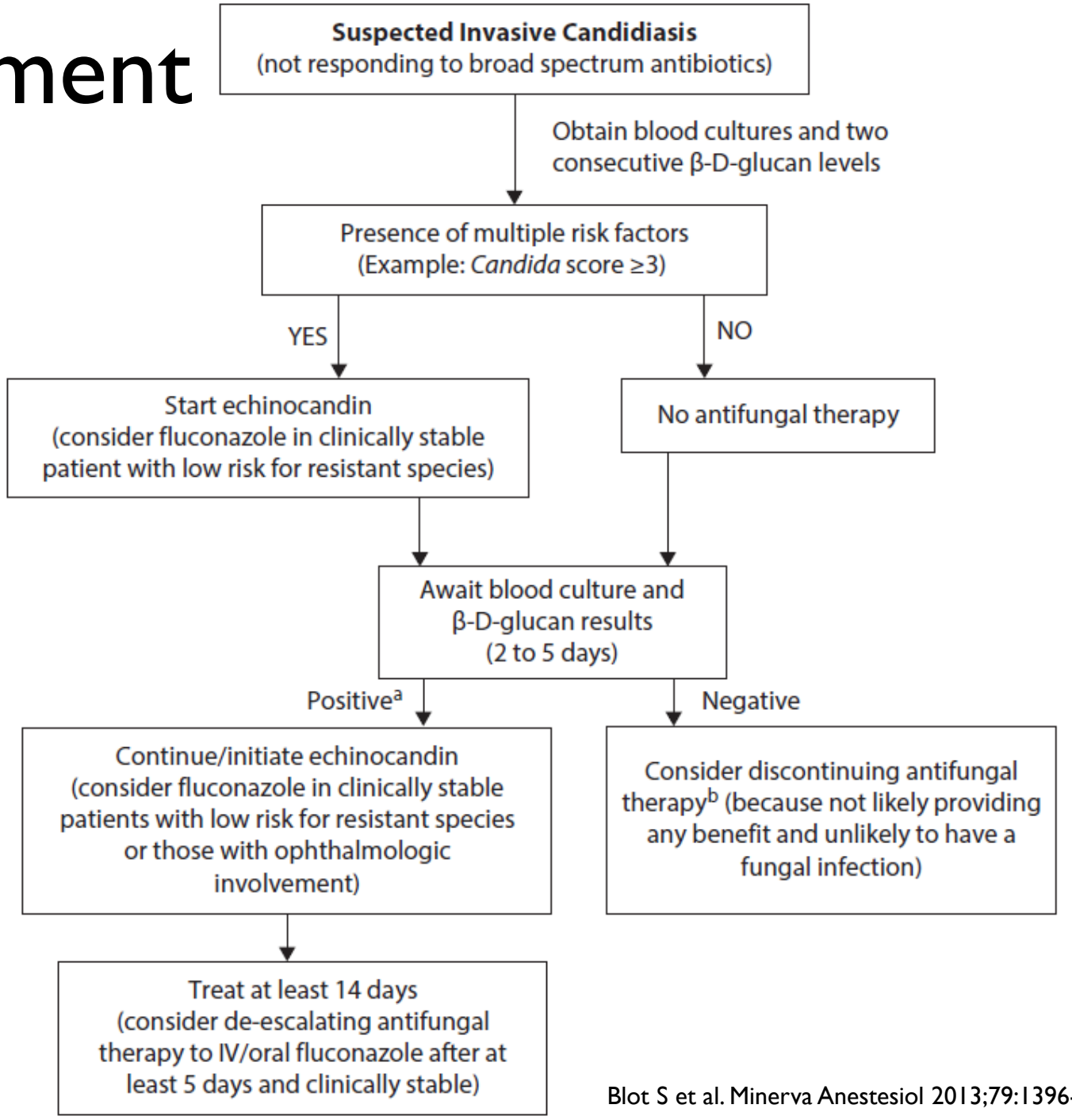
Resistance mechanism of antifungals

Drug Class	Site of Action	Resistance Mechanism	Implications
Azoles	Inhibit lanosterol-14α-demethylase ERG11 Candida CYP51 Aspergillus	Up-regulation of efflux pumps ABC transporters/CDR1,CDR2 genes TAC1 transcription factors Up-regulation of efflux pumps MFS transporters/MDR1 gene MRR1 transcription factors ERG11 and CYP51 mutations ERG11 and CYP51 overexpression ERG3 inactivation Biofilm formation Increase in cell wall chitin content	Decrease drug entry into cell (all azoles) Decrease drug entry into cell (fluconazole) Decrease binding affinity, increase MIC Counteract drug effects Ergosterol replaced by another sterol (cross-resistance all azoles) Inhibit drug penetration Increase tolerance to drug
Echinocandins	Inhibit Fksp catalytic subunit of (1,3)-β-D-glucan synthase	FKS1 and FKS2 mutations Increase in cell wall chitin content	Alter catalytic capacity, increase MIC (cross-resistance to entire class) Increase tolerance to drug, paradoxical growth May correlate better with response to therapy than actual MIC
Polyenes	Bind ergosterol Induce oxidative stress	ERG2, ERG3, ERG5, ERG6, ERG11mutations Increase in anti-oxidative enzymes Alteration in production of free radicals	Decrease ergosterol biosynthesis Decrease oxidative stress

ABC = ATP-binding cassette; MFS = major facilitator superfamily

Leon C et al. Intensive Care Med.2014;40(6):808-19.

Treatment



Blot S et al. Minerva Anestesiol 2013;79:1396-405

Summary

- Management of infection in critically ill patients is an evolving challenge, in part because of the ever-present threat of MDR strains.
- Adequate antibiotic treatment is crucial to optimize survival rates.
- Therapeutic drug monitoring is likely to be more widely used in the future.
- Antibiotic choices and durations need to be individualized for patient according to specific patient characteristics, disease severity, likely infecting organisms, and resistance patterns