Antibiotic Stewardship – Rational use of Antibiotics and Antifungal Agents
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ABSTRACT
Antibiotics remain the single biggest weapon that we have in our fight against infections. Sepsis continues to be one of the biggest problems faced by the critically ill children. They are either admitted to the ICU with a new infection or later in their course of illness, acquire an infection termed as nosocomial infection or a hospital acquired infection. There are not very many new antibiotics that are available to fight the bacterial infection. At the same time the microbes are rapidly developing resistance against antibiotics of all classes, seemingly winning this war against infections. Antibiotics are one class of drugs that have the potential to affect the health of not only the patient but also of the entire society over a period of time. The rise of multidrug resistant organisms is a global phenomenon. It is imperative that we cherish and protect the drugs with the goal of preserving them for generations to come. We may be able to do this by exercising antibiotic stewardship. This refers to a set of coordinated strategies to improve the use of antimicrobial medications with the goal of enhancing patient health outcomes, reducing resistance to antibiotics and decreasing unnecessary costs. Antimicrobial stewardship is the responsibility of all physicians. We can each make a difference by exercising discipline in the management of patients. It is imperative that we try to protect the environment of appropriate handling of waste. Hand hygiene, appropriate isolation practices, terminal cleaning are all essential practices to reduce the spread of resistance organism. Selecting the right antimicrobial looks at various aspects of the patient and the drug pharmacokinetics and pharmacodynamics. This article will examine this concept and antibiotic stewardship in general, that makes the difference between success and failure in the treatment of infections and spread of multidrug resistance.

Keywords: Multidrug resistance, nosocomial infections, antibiotic stewardship, Drug resistance, Pediatrics, ICU, infections.
Abbreviations: MRSA: methicillin resistant staph aureus. MDR Multidrug resistance. ESBL Extended spectrum Beta lactamase.

Introduction
Antibiotic stewardship refers to a set of coordinated strategies to improve the use of antimicrobial medications with the goal of enhancing patient health outcomes, reducing resistance to antibiotics and decreasing unnecessary costs.

Empirical Antibiotic therapy
Empiric antibiotics are essential in the management of critically ill patients. Early and adequate therapy has been shown to improve outcomes. The guidelines for time to therapy are as follows: Septic shock: 1 hour from the determination of hypotension, Meningitis: as soon as possible and Community acquired pneumonia: 4 Hours. Prior to starting antibiotic, however, it is important to confirm the presence of infection. High index of suspicion and good clinical judgement is needed in determining the need for anti-infective treatment. Not all patients with fever and elevated white count have infection, similarly not all patients with infections will necessarily have fever. All positive cultures need not be labelled as infection, there may be colonisation. Initiate antibiotic after obtaining all appropriate microbiological specimens, including blood cultures, and if required urine cultures. In case of meningitis
Empiric antibiotic should be started as soon as possible. Lumbar puncture can be performed when it is clinically appropriate. In presence of central venous catheters one peripheral line along with a central line culture is needed. (Some authorities recommend drawing culture from each lumen of the catheter. This may not be practical or economically feasible). If the suspicion for central venous line infection is strong, the device should be removed as soon as feasible.

a) Consider obtaining sepsis biomarkers like procalcitonin & C-reactive protein. Obtain fungal biomarkers if index of suspicion for disseminated fungal infection is high. Early diagnosis and treatment of fungal infection has also been shown to improve outcomes⁶.

b) The optimal therapy for the patient should take into account: Most likely pathogens that need to be covered. Target tissue penetration (respiratory tract, blood stream, CNS etc.). Community versus hospital-associated infection. Recent previous antibiotic prescription. Organisms and its resistance pattern commonly present in the patients community. Patients renal and hepatic function.

c) Need for monotherapy versus combination therapy.

d) Pharmacokinetics and pharmacodynamics of the drug to be used.

Antibiotics are the single biggest weapon that we have in our fight against infections. Sepsis continues to be one of the biggest problems faced by the critically ill patients. They are either admitted to the ICU with an infection or later in their course of illness acquire an infection. There are not very many new antibiotics that are available to fight the bacterial infection. At the same time the microbes are rapidly developing resistance against antibiotics of all class, seemingly winning this war against infections. Antibiotics are one class of drugs that have the potential to affect the health of not only the patient but also of the entire society over a period of time. The rise of multidrug resistant organisms is a global phenomenon. It is imperative that we cherish & protect the drugs with the goal of preserving them for generations to come. We may be able to do this by exercising Antibiotic stewardship¹. This refers to a set of coordinated strategies to improve the use of antimicrobial medications with the goal of enhancing patient health outcomes, reducing resistance to antibiotics and decreasing unnecessary costs. Antimicrobial stewardship is the responsibility of all physicians. We can each make a difference by exercising discipline in the management of patients. It is imperative that we try to protect the environment of appropriate handling of waste. Hand hygiene, appropriate isolation practices, terminal cleaning are all essential practices to reduce the spread of resistance organism. Selecting the right looks at various aspects of the patient and the drug. This article will look at some of this concept that makes the difference between success and failure in the treatment of infection.

Empirical Antibiotic Therapy

Empiric antibiotics are essential in the management of critically ill patients. Early and adequate therapy has been shown to improve outcomes². The guidelines for time to therapy are septic shock 1 hour from the determination of hypotension¹, meningitis as soon as possible⁴ and community acquired pneumonia-4 hours⁵. Prior to starting antibiotic however it is important to confirm the presence of infection. High index of suspicion and good clinical judgement is needed in determining the need for anti-infective treatment. Not all patients with fever and elevated white count have infection, similarly not all patients with infections need to have fever. All positive cultures need not be infection, they may be colonisation. Initiate antibiotic after obtaining all appropriate microbiological specimens, including blood cultures, and if required urine cultures. In case of meningitis empiric antibiotic should be started as soon as possible. Lumbar puncture can be completed when it is clinically appropriate. In presence of central venous catheters one peripheral along with a central line culture is needed. (Some authorities recommend drawing culture from each lumen of the catheter. This may not be practical or economically feasible). If the indications for central venous infection is strong, the device should be removed as soon as feasible.

a) Consider obtaining sepsis biomarkers like procalcitonin and C-reactive protein. Obtain fungal biomarkers if index of suspicion for disseminated fungal infection is high. Early diagnosis and
treatment of fungal infection has also shown to improve outcome.\(^6\)

b) The optimal therapy for the patient should take into account. Most likely pathogens that need to be covered Target tissue penetration (respiratory tract, blood stream, CNS etc.). Community versus hospital-associated infection. Recent previous antibiotic prescription. Organisms and its resistance pattern commonly present in the patients community Patients renal and hepatic function

c) Need for monotherapy versus combination therapy.

d) Pharmacokinetics and pharmacodynamics of the drug to be used.

### Suggestions For Empirical Antibiotic Therapy

<table>
<thead>
<tr>
<th>Situation</th>
<th>Drug</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis without focus-Immunocompetent</td>
<td>Third generation cephalosporin</td>
<td>Consider cefotaxime if liver abnormality is present Ceftazidime if pseudomonas is possible</td>
</tr>
<tr>
<td>Sepsis without focus-Immunosupressed</td>
<td>Piperacillin Tazobactum +/- Vancomycin Carbapenem +/- Vancomycin</td>
<td>Meropenem if CNS infection is suspected Add vancomycinif MRSA is possible.</td>
</tr>
<tr>
<td>Intrabdominal sepsis</td>
<td>Ceftriaxone + a) Metronidazole +/- aminoglycoside b) Carbapenem +/- vancomycin c) Piperacillin Tazobactum +/- vancomycin</td>
<td>Use carbapenem only if there is high chance of ESBL gram negative If chances of MDR gram negative is high as in hospital acquired infections consider adding Tigecycline Antifungal if colon is the focus Tigecycline also covers MRSA and enterococcus</td>
</tr>
<tr>
<td>Community acquired pneumonia</td>
<td>2(^{nd}) generation cephalosporin Amoxicillin + clavulanic acid</td>
<td>Consider Oseltamivir if the influenza is likely</td>
</tr>
<tr>
<td>Community acquired pneumonia with shock</td>
<td>3(^{rd}) generation cephalosporin + Clindamycin or linezolid Consider azithromycin in intubated patients for immunomodulation</td>
<td>A β-lactum agent is bactericidal but does not inhibit the toxin production clindamycin or linezolid although bacteriostatic inhibits toxin production and improves toxic shock. In situations of treating MRSA infection it is important to look for inducible resistance to clindamycin ( D Test ). Some recommend addition of clindamycin due to the Eagle effect due to high inoculum.(^7)</td>
</tr>
<tr>
<td>Ventilator associated pneumonia &lt; 4 days, without hospitalization in 30 days or antibiotics in 15 days</td>
<td>Ceftriaxone/Amoxicillin + clavulanic ± macrolide or ertapenem ± macrolide</td>
<td>Ceftriaxone/amoxicillin + clavulanic ± macrolide or ertapenem ± macrolide</td>
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<tr>
<td>Late onset VAP defined as ventilator LOS &gt; 4 days Pseudomonas Acinetobacterspp, Stenotrophomonas, Klebsiellapneumoniae (ESBL+) MRSA are the common org</td>
<td>Antipseudomonal cephalosporin / carbapenem /beta-lactam/beta-lactamase inhibitor + Antipseudomonal/ fluoroquinolone/aminoglycoside + Tigecycline + carbapenem + sulbactam or Tigecycline + carbapenem + colistin +/- linezolid or vancomycin</td>
<td>- Modify therapy to local antibiogram. - De-escalate as soon as culture results are back-ertapenem, tigecycline do not cover pseudomonas. - Ertapenem is as effective as meropenem as long as the MIC of the organism is &lt; 2(\mu)g/ml(^8) - Do not use tigecycline or colistin alone - Cotrimoxazole is the drug of choice in stenotrophomonas - Colistin combination with rifampicin useful in pan resistant acinetobacter(^9,10).</td>
</tr>
<tr>
<td>Central line associated blood stream infection</td>
<td>Vancomycin + carbapenem +/- echinocandin or fluconazole</td>
<td>Carbapenem may be replaced with any appropriate antibiotic to cover gram negative as per the local antibiogram. Imperative to decide about the need for line and remove the device as soon as feasible</td>
</tr>
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</table>
Carbapenems are drug of choice against ESBL producing gram negative organisms. ESBL producers often tend to have cross resistance to fluoroquinolone and aminoglycoside. Considering that gram negative infections resistant to carbapenems is on the rise it is important to look at other alternatives in an attempt to conserve carbapenams. βeta lactam/βeta lactamase inhibitor such as piperacillin–tazobactam are effective for ESBL producers when susceptibility is proven, especially in urinary and biliary tract infections or when the bacterial inoculum or MIC is low 11.

**PK/PD and Tissue Penetration 12**

Critical to dose optimisation is an understanding of the pharmacokinetics (PK) and pharmacodynamics (PD) of available drugs. PK describes the fate of the drug once administered to a patient, including absorption, distribution, metabolism, and excretion. Volume of distribution (V_d) is the theoretic volume in which the total amount of drug needs to be distributed uniformly to produce the desired concentration of a drug. Hydrophilic antibiotics (e.g., aminoglycosides, beta-lactams, glycopeptides, and colistin) are affected by increased V_d and altered drug clearance. Lipophilic antibiotics (e.g., fluoroquinolone, macrolides, tigecycline) are less susceptible to alterations in V_d but may have altered drug clearance in critically ill patients. Increased capillary permeability, increased cardiac output, reduced serum albumin, augmented renal blood flow and organ failure all influence the volume of distribution (V_d) and drug clearance (Cl) potentially leading to inadequate drug levels and therapeutic failure. Augmented kidney blood flow may occur in many patients with burns, sepsis, febrile neutropenia and hypoalbuminemia. This increased blood flow results in increased creatinine clearance (CLCr), leading to an increased capacity of the kidneys to eliminate hydrophilic molecules. This is called ‘augmented renal clearance’ (ARC) 14. ARC is one of the reason why loading dose is needed while using colistin in patients with MDR gram negative infections. This is a phenomenon that is being increasingly recognised as a reason for failure to respond to treatment in the case of hydrophilic molecules.

Pharmacodynamics PD describes the effect of a drug on the patient or the pathogens 15. The effect of the antibiotic depends on inoculum size, microbial physiology, and resistance mechanisms. The most important PD parameter to consider is the minimal inhibitory concentration (MIC), which is the lowest serum drug concentration that inhibits bacterial growth. Dosing strategies manipulate these parameters for the best antimicrobial activity. The way the drug kills may be categorised in two predominant ways time-dependent killing and concentration-dependent killing 16.

In time-dependent killing, maximum bacterial killing occurs when the drug concentration remains above the minimal inhibitory concentration (MIC). Examples of antibiotics that demonstrate time-dependent killing include β-lactam antibiotics (i.e., penicillins, cephalosporins, carbapenems, and monobactams) and vancomycin.

In concentration-dependent killing, maximum bacterial killing occurs when the peak drug concentration is approximately 10 times the MIC. Examples of agents with concentration-dependent killing are fluoroquinolones and aminoglycosides. Microbial killing continues to occur even when the drug levels in the serum are very low. This phenomenon is called postantibiotic effect (PAE). It is this phenomenon along with the concentration dependent killing that constitutes the basis for once-daily aminoglycoside therapy.
Drug | PD Property | Tactic to enhance killing
---|---|---
Carbapenems, Cephalosporins, Linezolid, Beta lactam | Time-dependent | Maximize duration of exposure with prolonged or continuous infusion
Aminoglycosides, Fluoroquinolones, Ketolides, Metronidazole, Polymixins | Concentration-dependent (with PAE) (achieve Cmax:MIC) > 10 | Maximize peak concentration
Clindamycin, Macrolides, Vancomycin, Colistin | AUC:MIC 24h > 125 AUC:MIC 24h > 400 for MDR pathogens | Maximize drug dosage while avoiding toxicity

**Tissue Penetration**

The site of infection is an important aspect that has to be taken into consideration prior to the prescription\textsuperscript{16}. For example MRSA is treated by vancomycin, linezolid and daptomycin. The choice of agent depends on site of infection and MIC of the organism. Vancomycin has poor penetration into the alveolar epithelium. This problem may be overcome by giving it every 6 hours as a 1 hour infusion or giving it as a continuous infusion while treating a patient with severe MRSA pneumonia. Linezolid has a better penetration into the alveolar epithelium. In adults some studies show better results with linezolid than vancomycin in the treatment of MRSA pneumonia\textsuperscript{19}. Pneumonia is best not treated with daptomycin as it is inactivated by surfactant. In bacteremia due to MRSA daptomycin may be better than vancomycin as the latter is only nominally bactericidal. In situations meningitis due to resistant streptococcus pneumoniae dose of 15mg/Kg of vancomycin administered every six hours is recommended to increase the area under the curve. Colistin levels in bronchial secretions are extremely low even when serum levels are adequate. This makes it essential that appropriate alternative drug or method of administration of colistin is needed while treating ventilator associated pneumonia (VAP). In order to reduce toxicity colistin is combined with Carbapenem. Nebulized colistin has been tried to increase levels of the drug in bronchial secretion.\textsuperscript{20, 21} Enough studies are not there to give firm recommendation of the dose. Tigecycline does not have any urinary excretion hence should not be used in the management of UTI even if there is in vitro sensitivity. Same holds for colistin which has very minimal renal excretion. On the contrary fluoroquinolone have excellent renal excretion and can be used even if it is an ESBL producing organism that is causing a UTI.

**Monotherapy Versus Combination Therapy**

Combination therapy is used principally because a) there is an increased likelihood that the infective pathogen will be susceptible to at least one of the drugs of combination therapy, thereby allowing appropriate initial therapy; b) To prevent resistance especially in organisms like pseudomonas c) possibility of synergy between drugs and hence betterbacterial clearing. d) To produce immunomodulatory effects as in the use of macrolides in ventilated patients with pneumonia. e) To work on a different aspect of the illness like clindamycin or linezolid to reduce toxin production in Toxic Shock Syndrome. Combination therapy has been found to be effective mostly in enterococcus where penicillin or ampicillin is combined with gentamicin or streptomycin.\textsuperscript{22} Combination therapy is often used to improve outcomes such as mortality and duration of ICU stay in patients with MRSA infection. Despite numerous in vitro and in vivo studies there is still confusion regarding this practice. It is best to avoid combination of linezolid plus vancomycin or linezolid plus fluoroquinolone because the combination at best is associated with antibiotic indifference and at worst associated with antagonism.\textsuperscript{22} β-lactam combination with aminoglycoside combinations have been most studied. Meta-analysis of several studies has failed to show any advantage in terms of mortality, bacterial clearance or development of resistance when the combination has been compared with β lactam monotherapy. In addition the combination is associated with nephrotoxicity.\textsuperscript{23} Despite the theoretical advantages, combination therapies have not shown to improve outcomes except in patients with septic shock.\textsuperscript{24} Even here it is best to use combinations only till hemodynamic stability is achieved and then change
over to monotherapy if cultures are negative. Also combination therapy is not very useful when using broad spectrum agents such as carbapenems, β-lactam/β-lactamase inhibitor such as piperacillin-tazobactam, and anti-pseudomonal cephalosporin.²⁴ The potential disadvantages related to combination therapy, such as increased risk for toxicity, higher costs, possible antagonism between specific drug combinations (penicillin and chloramphenicol, linezolid and fluoroquinolone), and selection of resistant strains should always be kept in mind.

Antifungal Agents

Invasive fungal infections are becoming common in the ICU world over. They are generally associated with patients who are on prolonged antibiotics, are immunosuppressed or have had multiple intravascular devices. Invasive fungal infections are associated with greater mortality than bacterial infections²⁵. Time is of as much essence in their treatment as with bacterial infections in critically ill. Increasing use of antifungals is also led to on the rise because of use of. Certain organisms are intrinsically resistant to different agents. Empiric differentiation of fungal and bacterial infection is difficult because clinical signs and symptoms are similar.

In an attempt to enhance appropriate patient selection for empiric antifungal therapy scores have been used. There are often combined with biological marker (β-D glucan, anti mannan antibody, galactomannan) to determine the probability and type of fungal infection. The type of fungus involved determines the empiric coverage.

The most common fungus continues to be candida however the number of non albicans species causing infections have increased. In order to determine the at risk patient for candidemia the colonization index and candida score is commonly used. León and colleagues developed the Candida score based on four risk factors to which numeric values were assigned as follows: total parenteral nutrition-TPN (1 point), multifocal colonization sites (1 point), severe sepsis (2 points), and surgery (1 point). Patients with a score greater than 2.5 were more than 7 times as likely to have proven infection as patients with a Candida Score up to 2.5.²⁶ A prospective multicenter observational study demonstrated that a CandidaScore ≥3 discriminated between colonization and invasive candidiasis in non-neutropenic ICU patients colonized with candidaspp., with a minimum length of ICU stay of 7 days. Colonization index²⁷ is a score that is used to determine the risk of patients for subsequent infections. It is defined as the ratio of the number of body sites colonized with the same strain to the total number of sites cultured²⁷.

Aspergilus is the other fungus that is increasing in incidence due to increasing survival of patients withmalignancy and increasing numbers of patients who are on immunosuppressant therapy. Empirical antifungal treatment is started in a high risk individual after obtaining appropriate cultures and if possible serum biomarkers. The agent that is started will depend on the nature of patient’s illness, local resistance pattern and the organ system that may be affected of the patient.

General Guidelines

In general invasive fungal infection should be suspected and treated early.

a) Invasive candidiasis-Drug of choice is echinocandin and narrow it to fluconazole as soon as possible. Treatment is for 14 days from negative blood cultures²⁸

b) Invasive Aspergillosis- Drug of choice is voriconazole.³⁰ Has hepatotoxicity. Several drugs that are used in immunosuppressed ICU patients can affect drug level.

c) Candiduria generally does not need treatment. Fluconazole is the drug of choice if treatment is needed. Bladder irrigation with amphotericin is no longer recommended

d) Candida pneumonia is rare and diagnosis requires invasive sampling. Most candida isolated from sputum samples or tracheal aspirates often represent upper respiratory tract flora and does not require treatment²⁸

e) Zygomycetes – Liposomal amphotericin is recommended along with surgical debridement.

f) Cryptococcus – Combination therapy is recommended with amphotericin and flucytosine. In vitro studies show antagonism with amphotericin and azole. However variable results have been obtained when voriconazole and amphotericin are combined for invasive aspergillosis.
Summary

Antibiotic stewardship is a concept catching on fairly rapidly with most health care institutions. Infection control teams with infectious disease specialist, microbiologist, infection control nurse are becoming an essential tool in most NABH or JCI accredited institution to monitor antimicrobial therapy and to curb nosocomial infection rates as well as the antimicrobial resistance. Empiric therapy is needed with most appropriate drug for optimal outcome in ICU patients. It is impractical to wait for culture results before starting treatment. Adequate coverage should take into account the nature of the patients illness, comorbid conditions and the local antibiogram. Prior to choosing an agent one also needs to consider the pharmacodynamics and pharmacokinetics of the drug. Combination therapy may be needed in patients with septic shock and if MDR organisms is likely. De-escalation is needed as soon as feasible. Utility of de-escalation is difficult to prove. It can be practiced by reducing the dose of the drug (when appropriate), narrowing the spectrum of coverage and by reducing the number of drugs used to treat the infection. Due to emergence of resistant fungi, the guidelines to treat invasive fungal infection should be diligently followed to prevent further morbidity and mortality.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fungus sensitive</th>
<th>Resistant fungus</th>
<th>Remark</th>
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<tbody>
<tr>
<td>Amphotericin B</td>
<td>Most Candida spp, Cryptococcus neoformans, Histoplasma Blastomycyes, Mucorales, Coccioidoides, Paracoccioidoides, Aspergillus spp, Fusarium spp, Sporothrix schenckii</td>
<td>Trichosporon C. lusitaniae, C. guilliermondii, Zygomycetes, Cryptococcus spp</td>
<td>Fungicidal. Binds to fungal cell membrane, causes leakage of cell content. No dose adjustment needed in renal or liver failure or for renal replacement therapy</td>
</tr>
<tr>
<td>Azole</td>
<td>Depends on the Azole</td>
<td></td>
<td>Inhibit the synthesis of ergosterol by the fungal cell membrane, Three generation of azole are there. All azoles penetrate into CSF and eye well. All have good oral bioavailability, Cause varying extents if GI upset. All inhibit the metabolism of cyclosporine and tacrolimus increasing the drug level</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Most candida spp, Cryptococcus</td>
<td>Candida Krusei, C. glabrata–variably Aspergillus, Zygomycetes</td>
<td>-Only azole with good urinary levels. Metabolized in liver -Dose adjustment needed in renal failure. Useful mainly in patients who are relatively stable. -First line of treatment noneutropenic patients at risk for candidemia without previous exposure to azole. -Do not use if there is history of use of azole in past 30 days. -Significant drug interaction- rifampicin, benzodiazepine, phenytoin decrease drug level</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Aspergillus Candida krusei</td>
<td></td>
<td>No dose adjustment in renal failure. when parenteral treatment used, carrier cyclodextrin gets accumulated and would need dose reduction if creatinine clearance &lt; 50ml/min. Reduction in dose needed in liver failure. Therapeutic drug monitoring of voriconazole levels should be considered in patients in whom aspergillosis is refractory to therapy or drug toxicity is suspected. The recommended trough level of voriconazole is &gt;1 and &lt;5.5 mg/L.</td>
</tr>
<tr>
<td>Echinocandin</td>
<td>Candida spp Aspergillus</td>
<td>Cryptococcus</td>
<td>Caspofungin, Antidulafungin and Micafungin. Inhibit β1,3-D glucan synthesis Useful in patients with hemodynamic instability No penetration in CSF, eye or urine. No dose adjustment needed for renal failure Caspofungin dose to be reduced in moderate liver failure</td>
</tr>
</tbody>
</table>
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Source of Funding: None

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